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Regiocontrolled Synthesis of Pyrazole Derivatives Through 1,3-Dipolar Cycloaddition Reaction And Synthesis of Helicene-Thiourea based and Polymer Supported Soos's Catalyst for Asymmetric Synthesis

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Esame finale anno 2013

Dedication

This dissertation is dedicated to my grandmother Late. Mrs. Girijabai, my father Mr. Zumbar and mother Mrs. Nanda whose encouragement and support have tremendously assisted me in all the struggles throughout my life. This thesis is also dedicated to to my brother Vijay and Ms. Vaishali as well whose constant support encouraged me to achieve this title. I would also like to dedicate this to my uncle Late. Mr. Anil and all family members, friends, relatives and all well wishers who have been with me, for loving, supporting and encouraging me throughout my jouney towards this title.

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Abstract

In first part we have discussed about the pyrazoles, ring fused pyrazoles and their applications. Pyrazole derivatives display a broad spectrum of biological activities. In order to investigate new pyrazole derivatives, we have developed a simple regiocontrolled protocol of 1,3-DC to get ring fused pyrazole derivatives. These pyrazole derivatives were synthesized using 1,3-DC between nitrile imine and various dipolarophiles such as alkynes, cyclic α,β-ketones, lactones, thiocatones and lactums. The reactions were found to be highly regiospecific.

When thio-actylenes were used, the reactions were found to be controlled by the oxidation state of the 'S' to give thienopyrazoles. 'S' in +2 state gives preference to 5-regioisomer and in +6 state gives 4-regioisomer as major one. Reaction was also found to be affected by the use of a lewis acid catalyst like $Sc(OTf)_3$, which leads to form 4-regioisomer as the prevalent isomer. This strategy was further used to synthesize a biologically active thienopyrazole molecule which showed some promising biological activity on nanomolar scale.

When the cyclic α,β-ketones, lactones, thiocatones and lactams were used, reactions were found to be more substrate controlled as well. With small ring size we found the formation of 4-regioisomer as major one with activated dipoles whereas with moderate or larger rings we found prevalence of 5-regioisomer. To demonstrate this reactivity we have developed a theoretical model which describes the trends in this type of reactions. Topological analysis further gave support to our assumption for existence of those theoretical models.

In second part we have discussed about helicene, its properties, synthesis and applications as asymmetric catalyst. Helicenes are interesting carbocyclic compounds that involve ortho-fused ring systems forming a helix. Helicene compounds have numerous applications in modern chemistry, in biological systems and in molecular mechanics. Due to special structural arrangement they are chiral in nature. In this context of chirality, herein we have made an attempt to synthesize the helicene-thiourea based catalyst for asymmetric catalysis. The synthesis involved formation of two key intermediates *viz,* bromo-phenanthrene **5** and a vinyl-naphthalene **10**. The coupling of these two intermediates leads to formation of hexahelicene. We have described a simple route towards helicene synthesis.

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Prior Publications

- J. Z. Chandanshive, B. F. Bonini, D. Gentili, M. F. Fochi, L. Bernardi, M.C. Franchini, "*Regiocontrolled synthesis of ring-fused Thieno[2,3 c]pyrazoles through 1,3-dipolar cycloaddition of nitrile imine with sulfur-based acetylenes", Eur. J. Org. Chem*. **2010**, 6440-6447.
- J. Z. Chandanshive, B. F. Bonini, W. Tiznado, C. A. Escobar, J. Caballero, C. Femoni, M. F. Fochi, M.C. Franchini, "*1,3-dipolar cycloaddition of nitrile imines with cyclic α-β unsaturated ketones: A Regiochemical route to ring-fused pyrazoles", Eur. J. Org. Chem.* **2011**, 4806-4813.
- J. Z. Chandanshive, P. B. Gonzalez, W. Tiznado, B. F. Bonini, J. Caballero, C Femoni, M. C. Franchini, "1,3-Dipolar cycloaddition of nitrile imines with *α-β unsaturated lactones, thiolactones and lactums: Synthesis of ring-fused pyrazoles." Tetrahedron,* **2012,** *68,* 3319-3328.

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List of Abbreviations:

Ac	acetyl
Anhyd	anhydrous
aq	aqueous
Ar	aryl (substituted aromatic ring)
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2,2'-naphthol
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp	boiling point
Bz	benzoyl
br	broad (NMR signal)
*n*Bu	*n*-butyl
$_t$Bu	tertiary butyl
ca	circa(approximately)
CAN	cerium(IV) ammonium nitrate (cericammonium nitrate)
°C	degrees Celcius
cat.	catalytic
Cbz (Z)	benzyloxycarbonyl
conc.	concentrated
d	doublet (NMR signal)
dd	doublet of doublets (NMR signal)
dt	doublet of triplets (NMR signal)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
1,3-DC	1,3-dipolar cycloaddition
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
dr	diastereomeric ratio
DIBAL(DIBAL-H)	diisobutylaluminum hydride

DIPEA(Hünig's base)	diisopropylethylamine
DMAP	*N,N*-4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPA (DIPA)	diisopropylamine
dppf	diphosphinoferrocene
E^+	electrophile (denotes any electrophile in general)
EDC (EDAC)	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride
EDG	electron-donating group
ee	enantiomeric excess
e.g.	exempli gratia (for example)
EI	electron ionization
ESI	electronspray ionization
Et	ethyl
Equiv	equivalent
FT-IR	Fourier transform infra-red
EWG	electron-withdrawing group
FMO	frontier molecular orbital (theory)
δ	chemical shift
g	gram
GC	gas chromatography
GC/MS	gas chromatography/mass spectroscopy
h	hour
hν	irradiation with light
Hgmm	millimeter of mercury (760 Hgmm = 1 atm = 760 Torr)
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoric acid triamide
HMPT	hexamethylphosphorous triamide

HOMO	highest occupied molecular orbital
HPLC	high-pressure (performance) liquid chromatography
Hz	hertz
IPA	isopropyl alcohol
iPr	isopropyl
J	coupling constant (NMR signal)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
liq.	liquid
LUMO	lowest unoccupied molecular orbital
m	multiplet (NMR signal)
m-CPBA	*meta*-chloroperbenzoic acid
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
m/z	mass/charge
Me	methyl
Mes	mesityl
MOM	methoxymethyl
MS	mass spectrometry
MS	molecular sieves
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
o	ortho
Ph	phenyl
p	para
PCC	pyridinium chlorochromate

PMB (MPM)	*p*-methoxybenzyl
ppm	parts per million (NMR signal)
Pr	propyl
Py	pyridine
q	quartet (NMR signal)
rac	racemic
Red-Al	sodium bis(2-methoxyethoxy) aluminum hydride
R_f	retention factor in chromatography

Part – I

Regiocontrolled synthesis of pyrazole derivatives through 1,3-dipolar cycloadditions

Chapter 1

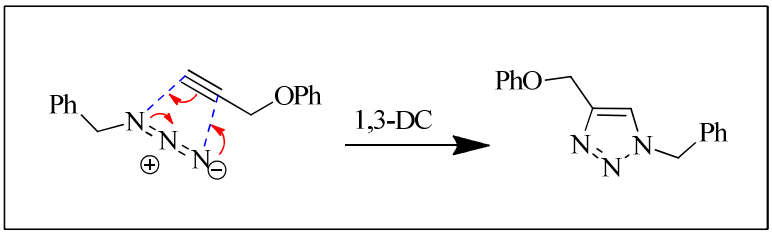
1,3-Dipolar cylcoaddition (DC) reaction and Pyrazoles

1.1 Introduction of 1,3-dipolar cycloadditon reactions:

Cycloaddition is a pericyclic reaction, in which "two or more unsaturated molecules (or parts of the same molecule) combine to form a cyclic adduct in which there is a net reduction of the bond multiplicity."[1] The resulting reaction is a cyclization reaction. Many but not all cycloadditions are concerted. Cycloadditions are usually described by the backbone size of the participants. This would make the Diels-Alder reaction a (4 + 2) cycloaddition, the 1,3-dipolar cycloaddition a (3 + 2) cycloaddition and cyclopropanation of a carbene with an alkene a (2+1) cycloaddition. This type of reaction is non-polar addition reaction.

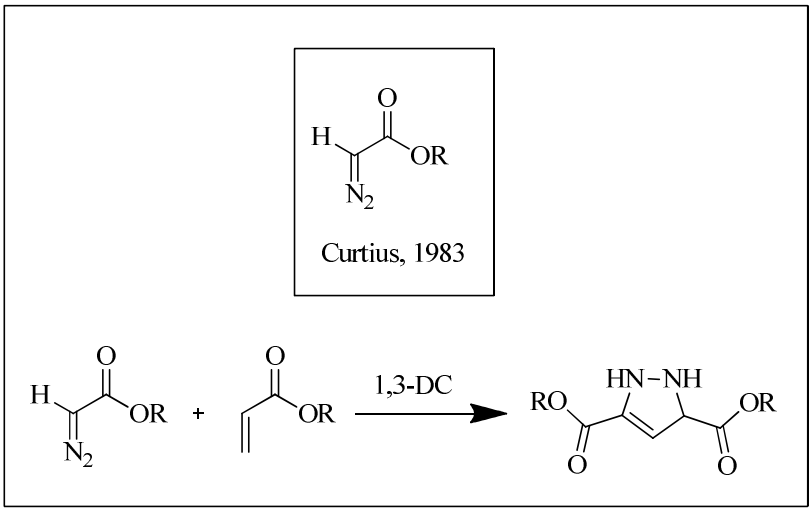
1,3-dipolar cycloaddition reactions are those in which multiple unsaturated compounds combine to form a cyclic addition product. They combine 1,3-dipoles and dipolarophiles to form five-membered rings.[2] The earliest 1,3-dipolar cycloadditions were described in the late 19th century to the early 20th century, following the discovery of 1,3-dipoles. Mechanistic investigation and synthetic applications were established in the 1960s, primarily through the work of Rolf Huisgen.[3a] Hence, the reaction is sometimes referred to as the **Huisgen cycloaddition** which involves the 1,3-dipolar cycloaddition between an organic azide and an alkyne to generate 1,2,3-triazole (**Scheme 1.1**). American chemist K. Barry Sharpless has referred to this cycloaddition as "the cream of the crop" of click chemistry.[3b]Currently, 1,3-dipolar cycloaddition is an important route to the regio- and stereoselective synthesis of five-membered heterocycles and their ring-opened acyclic derivatives.

Scheme 1.1: Huisgen cycloaddition between benzyl azide and (prop-2-yn-1-yloxy)benzene.



The first dipole methyl 2-diazo ester and its 1,3-DC with acrylate ester were discovered by Curtius[3c] and Buchner[3d] in 1880s. The reaction product they found was pyrazoline compound (**Scheme 1.2**).

Scheme1.2: First 1,3-dipole and its 1,3-DC.



This reaction has been developed into very general and useful method for synthesis of five-membered heterocycles and carbocycles.

1.2 1,3-Dipoles and their properties:

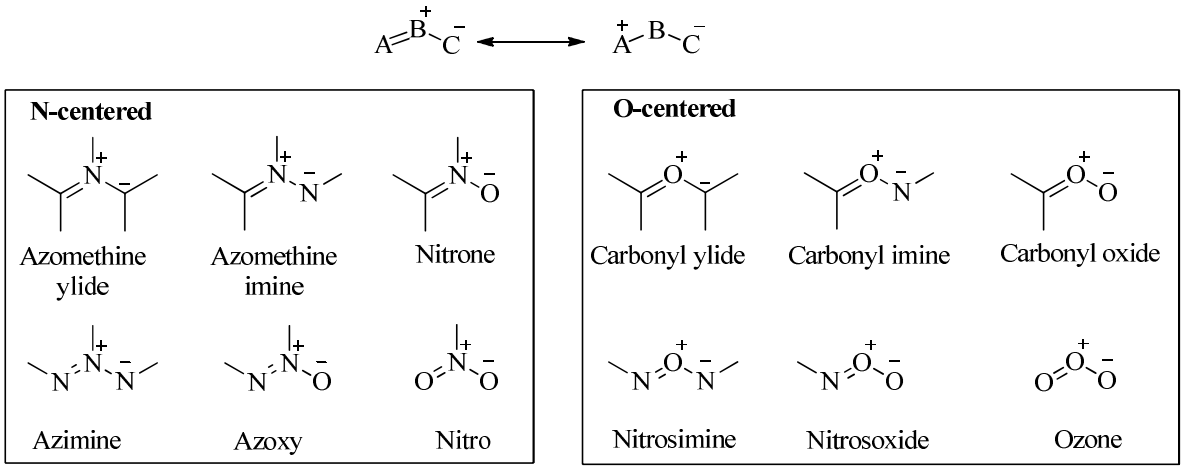
A 1,3-dipole is an organic compound. First 1,3-dipole, diazoacetic acid ester was discovered by Curtius[3b] in 1883 (**Scheme 1.2**). Then it was followed by series of invention of other dipoles *viz.* hydrazine (1887), hydrogen azide, nitrone (1890), nitrile oxide (1894), ozone (1903), nitrile imine (1934), azomethine imine (1958) azomethine ylide (1959), nitrile ylide (1960), carbonyl ylide (1965), azimine (1970) and thiocarbonyl ylide (1976). There are 18 well characterized 1,3-dipoles which forms a base for 1,3-DC reactions.

They are divided into two categories,

1. Allyl anion type
2. Propargyl/allenyl type zwitterionic octet/sextet structures.

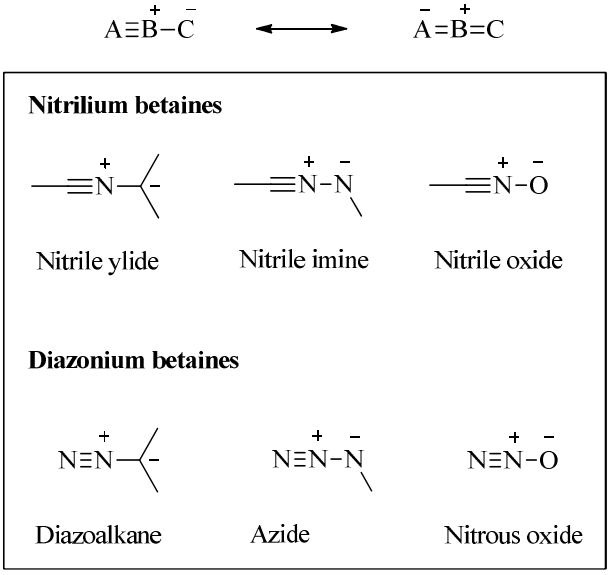
The allyl anion type is bent and has four electrons in three parallel *p*-orbitals perpendicular to the plane of the dipole.[3a] There are a total of 12 allyl-type dipoles (**Figure 1.1**).

Figure 1.1: Allyl anion 1,3-dipoles.



The propargyl/allenyl anion type dipole is normally linear. The central atom is occasionally presented as hypervalent and is limited to nitrogen (**Figure 1.2**). The other dipole atoms can be carbon, oxygen and nitrogen. There are 6 number of propagyl/allenyl-type second-row 1,3-dipoles (which consist of carbon, nitrogen and oxygen centers).

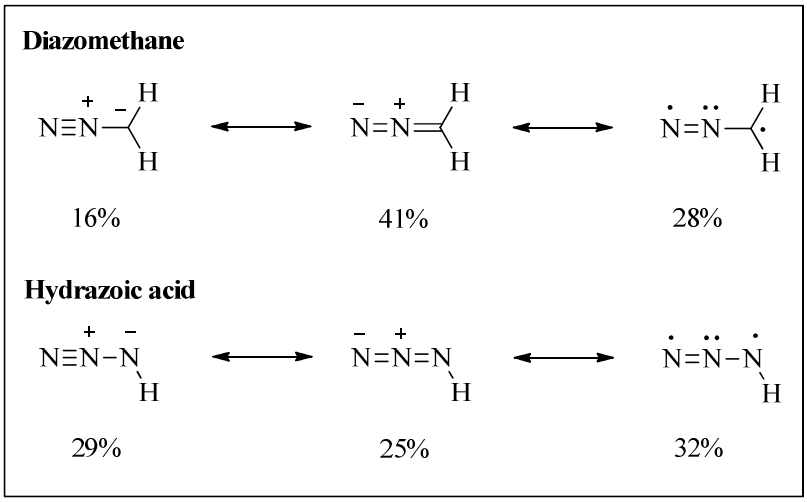
Figure 1.2: Propargyl/allenyl type 1,3-dipoles.



1,3-Dipoles containing higher-row elements such as sulfur or phosphorus are also known, but are utilized less routinely.

Resonance structures can be drawn to delocalize both negative and positive charges onto any terminus of a 1,3-dipole. A more accurate method to describe the electronic distribution on a 1,3-dipole is to assign the major resonance contributor based on experimental or theoretical data, such as dipole moment measurements[4] or computations.[5] For example, diazomethane bears the largest negative character at the terminal nitrogen atom, while hydrazoic acid bears the largest negative character at the internal nitrogen atom (**Scheme 1.3**). This means that the termini of a 1,3-dipole can be treated as both nucleophilic and electrophilic at the same time. The extent of nucleophilicity and electrophilicity at each terminus can be evaluated using the frontier molecular orbitals (FMO), which can be obtained computationally. In general, the atom that carries the largest orbital coefficient in the HOMO acts as the nucleophile, whereas that in the LUMO acts as the electrophile. The most nucleophilic atom is usually, but not always, the most electron-rich atom.[6,7,8]

Scheme 1.3: Major resonance structures for diazomethane and hydrazoic acid.

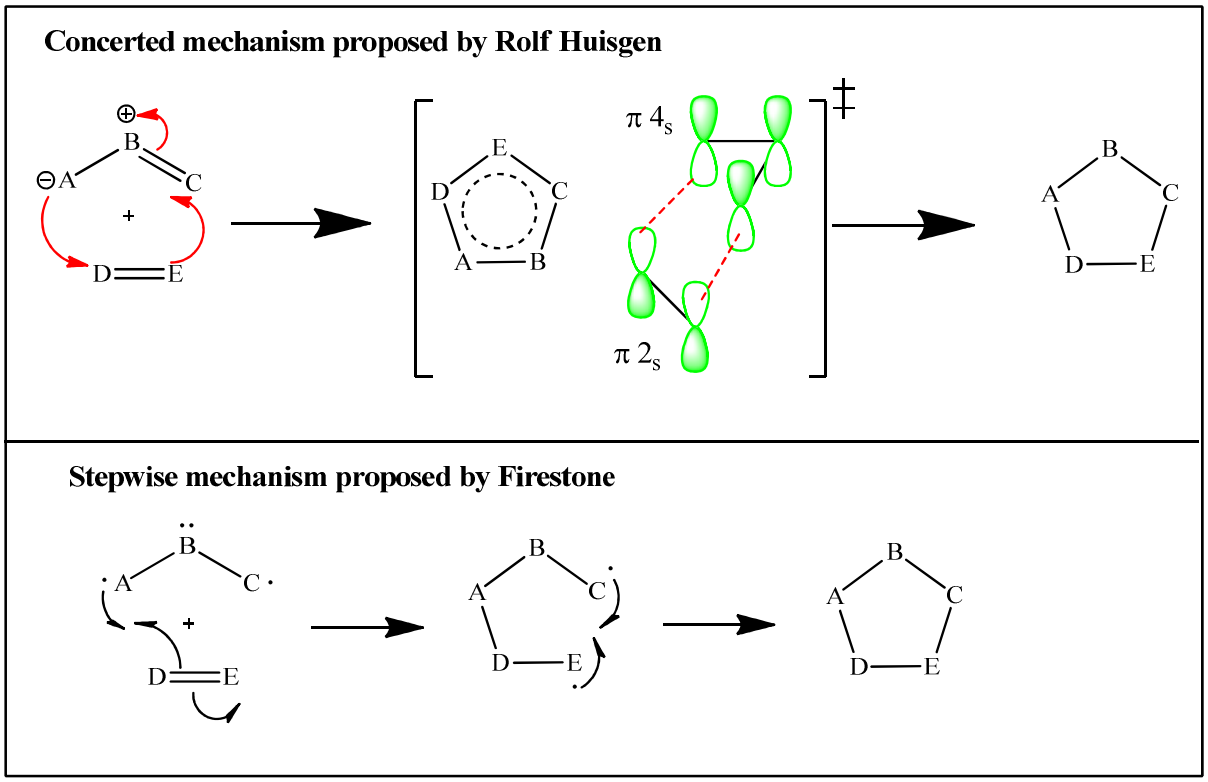


Dipolarophiles display less diversity than dipoles. The most commonly used dipolarophiles are substituted alkenes and alkynes. Double or triple bonds with heteroatoms like carbonyl, iminium and cyano groups can also be dipolarophiles. Other examples of dipolarophiles include fullerenes and nanotubes, which can undergo 1,3-dipolar cycloaddition with azomethine ylide in the Prato reaction.

1.3 Mechanism of 1,3-DC reactions:

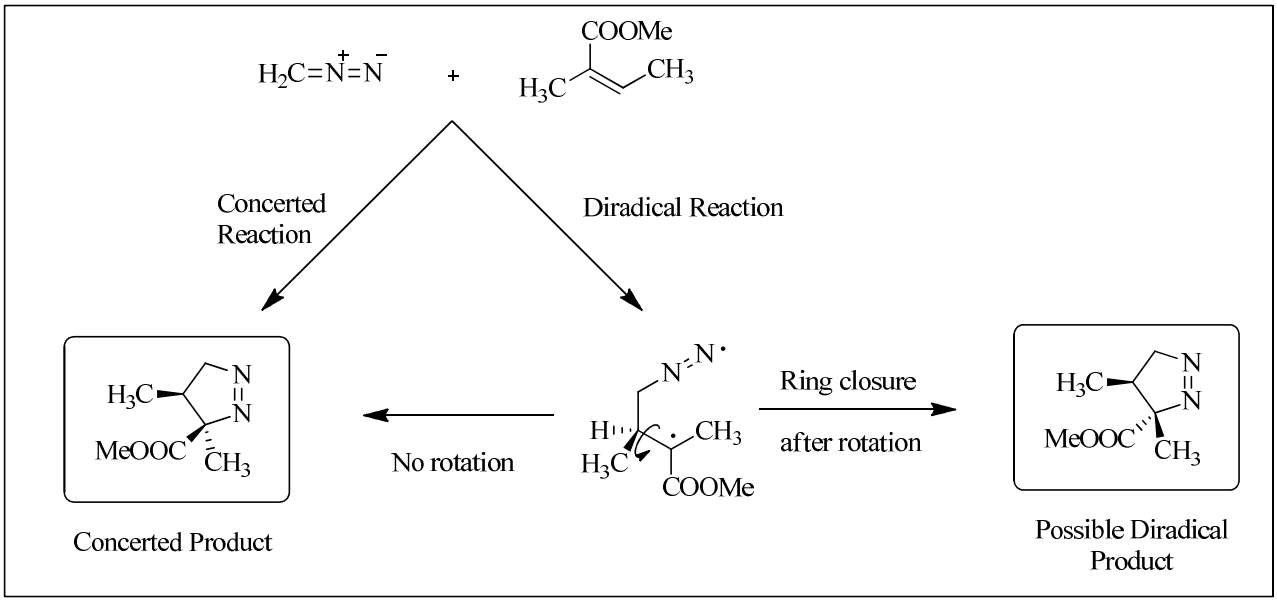
Originally it was thought to have two possible reaction mechanisms for 1,3-DC reactions, first one concerted reaction mechanism proposed by Rolf Huisgen[10] and second one, stepwise reaction mechanism involving diradical intermediate proposed by Firestone[11] (**Scheme 1.4**). In concerted mechanism, 1,3-DC involves 4π electrons from a dipole and 2π electrons from dipolarophile. According to the Woodward-Hoffmann rules,[12] if 1,3-DC reaction proceeds *via* a concerted mechanism, three p_z orbitals of 1,3-dipole and two p_z orbitals of a dipolarophile will combine suprafacially, symbolized as [$\pi\ 4_s + \pi\ 2_s$] to give cycloadduct.

Scheme 1.4: Concerted mechanism by Huisgen and diradical mechanism by Firestone.



During the concerted reaction mechanism the stereochemistry of the reactants could be transferred to the product. For example, the 1,3-DC of diazomethane with (Z)-methyl 2-methylbut-2-enoate gave exclusively the *trans*-pyrazoline (**Scheme 1.5**).[13]

Scheme 1.5: Stereochemistry in 1,3-DC reaction.



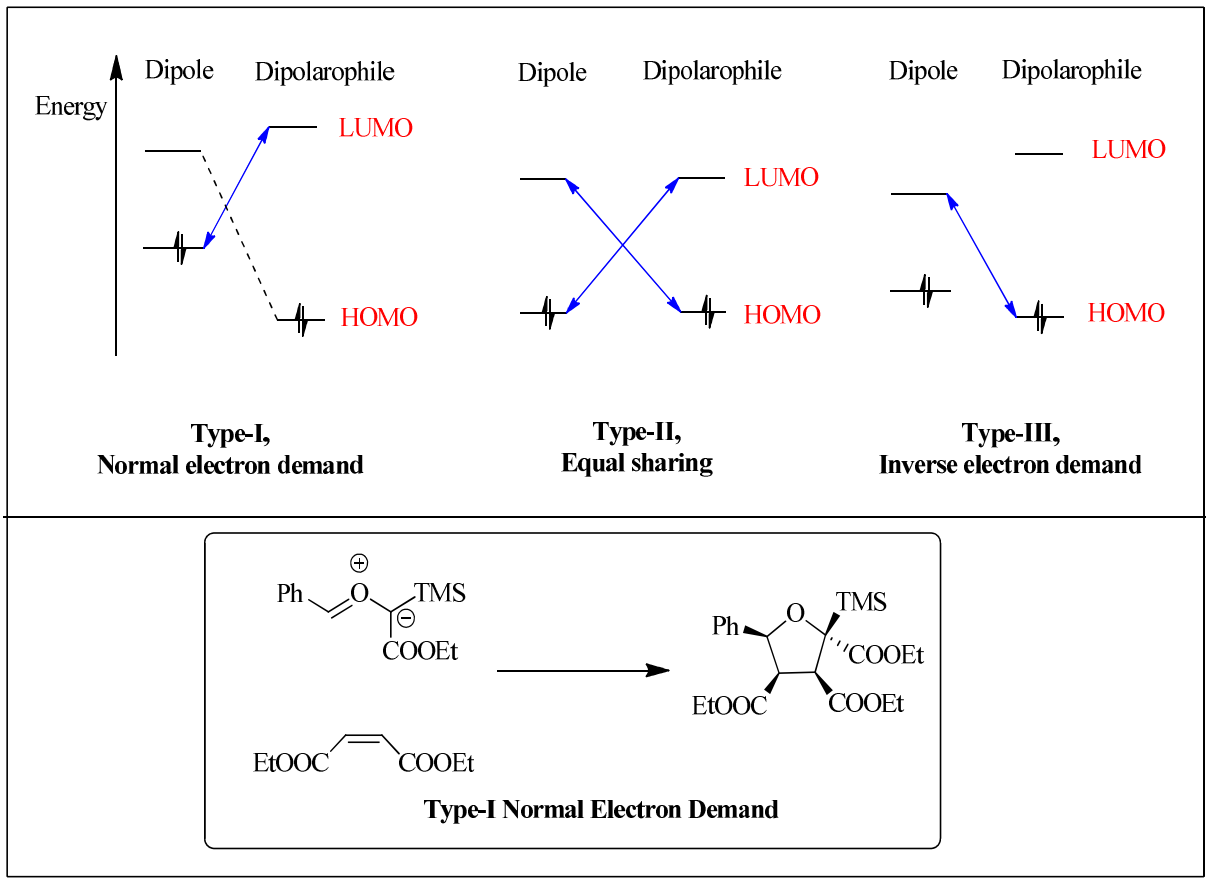
For those step-wise 1,3-DC involving some intermediates, the stereochemical information will be destroyed during these transformations. Therefore, after much debate the concerted mechanism is accepted, which is based on experimental evidances although there are some experimental evidances for the diradical mechanism as in above case (**Scheme 1.5**).[14]

Concerted 1,3-DC can be interpreted by frontier molecular orbital theory (FMO).[15] Based on FMO theory, three types of interactions are possible between the 1,3-dipole and dipolarophile (**Figure 1.3**).

a. **Type-I (Normal electron demand)**: In this type of FMO interaction, highest occupied molecular orbital (HOMO) of the dipole interact with the lowest unoccupied molecular orbital (LUMO) of the dipolarophile. Here the dipole is considered as a nucleophilic dipole. Some *e.g.* of this type includes azomethine ylide, carbonyl ylide, nitrile ylide, azomethine imine, carbonyl imine and diazoalkane. These dipoles add to electrophilic alkenes readily. Electron-withdrawing groups (EWG) on the dipolarophile would accelerate the reaction by lowering the LUMO, while electron-donating groups (EDG) would decelerate the reaction by raising the HOMO (**Figure 1.3**). *e.g.* Without any activation of either component, the reaction between an electron-rich dipole (*e.g.*TMS substituted carbonyl ylides) and an electron-deficient

dipolarophile (*e.g.*,dimethyl maleate)[16] is dominated by the interaction between the dipole HOMO and the dipolarophile LUMO.

Figure 1.3: FMO interaction in 1,3-DC.

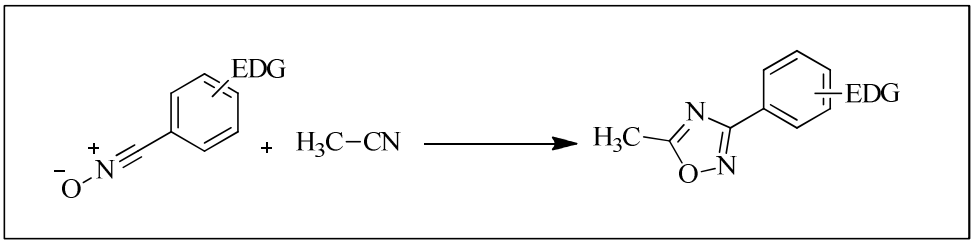


b. **Type –II (Equal sharing)**: In this type HOMO of the dipole can pair with LUMO of the dipolarophile; alternatively, HOMO of the dipolarophile can pair with LUMO of the dipole. This two-way interaction arises because the energy gap in either direction is similar (**Figure 1.3**). A dipole of this class is referred to as a HOMO-LUMO-controlled dipole or an ambiphilic dipole, which includes nitrile imine, nitrone, carbonyl oxide, nitrile oxide and azide. Any substituent on the dipolarophile would accelerate the reaction by lowering the energy gap between the two interacting orbitals i.e. EWG would lower the LUMO while EDG would raise the HOMO.

c. **Type-III (Inverse electron demand)**: These interactions are dominated by the reaction between the HOMO of the dipolarophile and the LUMO of the dipole. The

dipole has a low-lying LUMO which overlaps with HOMO of the dipolarophile. A dipole of this class is referred to as a LUMO-controlled dipole or an electrophilic dipole, which includes nitrous oxide and ozone. EWGs on the dipolarophile decelerate the reaction, while EDGs accelerate the reaction. Reaction between nitrile oxide and acetonitrile gives 1,2,4-oxadiazoles[17] (**Scheme1.6**).

Scheme 1.6: Example of Inverse electron demand. Reaction between nitrile oxide and nitrile.



Even though some cases, like ozonolysis of olefins and addition of nitrile oxides to alkynes,[18] proceed without additional promoters, many more substrate combinations result in no cycloadduct formation when dipole and dipoarophile are simply mixed. To accelerate those reactions, lewis acids like Scandium triflate are often used.

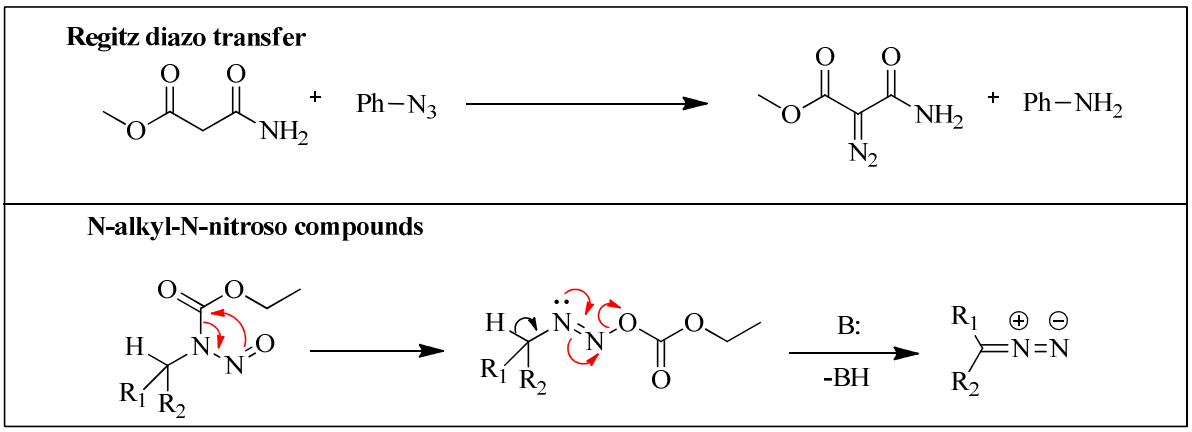
1.4 Diazo dipole properties and synthesis:

Diazo compounds are one of the reagents involved in 1,3-DC reactions for the synthesis of pyrazoles. In 1890's, Buchner[3c] and Pechmann[19] discovered the first [3+2] cycloaddition reaction using diazoacetate and diazomethane as dipole components respectively. After that, diazo compounds as well as azide compounds have been developed to be some of the most useful dipoles in organic synthesis over the past century. Diazo compounds are also used as precursors to carbenes, which are generated by thermolysis or photolysis, for example in the Wolff rearrangement. Certain diazo compounds can couple to form alkenes in a formal carbene dimerization reaction. Here the focus will be on use of diazo compounds as 1,3-dipoles in 1,3-DC reactions to form pyrazoles.

Several laboratory methods exist for synthesis of diazo compounds. Diazo compounds can be obtained by treatment of amine with nitrous acid, electrophilic substitution using diazomethyl compound with acyl halide but the major methods include diazo group transfer from

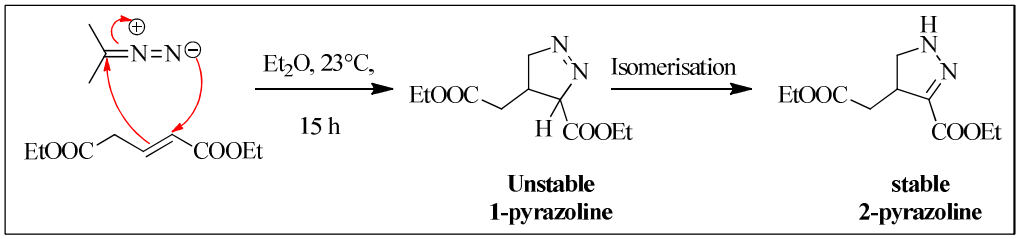
azides (Regitz diazo transfer reaction),[20] dehydrogenation of hydrazones, alkaline cleavage of *N*-alkyl-*N*-nitroso compounds (**scheme1.7**).

Scheme 1.7: Synthesis of diazo compound.



Diazo compounds reacts as 1,3-dipoles in diazoalkane 1,3-dipolar cycloadditions. In this reaction 1,3-dipole like diazomethane reacts with a dipolarophile (an alkene) to form a pyrazoline compound.[21] The reaction product of a cycloaddition between diazomethane and *trans*-diethyl glutaconate is a 1-pyrazoline.[22] This reaction is 100% regioselective because the diazo terminal nitrogen atom binds exclusively to the α-carbon of the ester. The reaction is also a syn addition, and the configuration in the dipolarophile is preserved. The 1-pyrazoline is unstable and isomerizes to the 2-pyrazoline due to favorable conjugation with the ester group (**Scheme 1.8**).

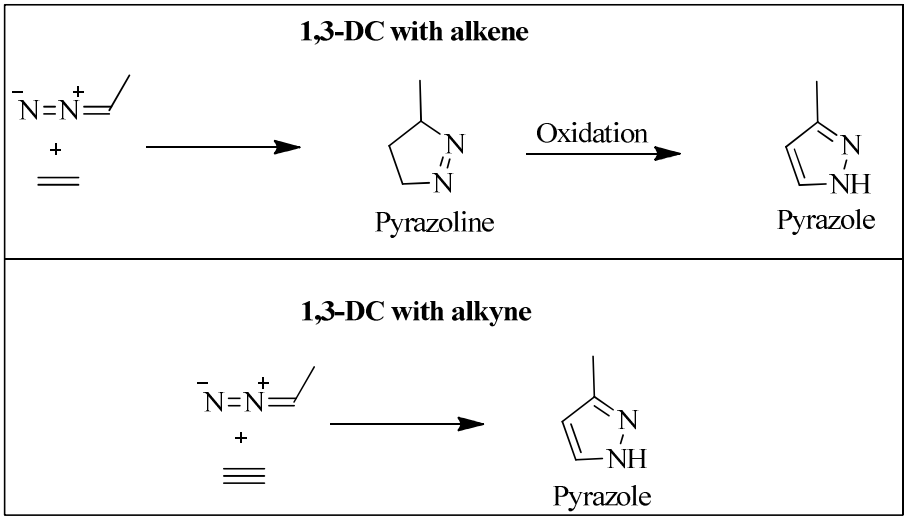
Scheme 1.8: 1,3-DC of diazomethane and *trans*-diethyl glutaconate.



With phenyldiazomethane as the reactant, the regioselectivity is reversed and the reaction is extended further by oxidation of the 2-pyrazoline to the pyrazole.

The utility of 1,3-DC of diazo compounds has been expanded based on the investigation of novel dipolarophiles, such as functionalized carbon-carbon double and triple bonds, carbon-hetereoatom double and triple bonds, and hetereoatom-hetereoatom double and triple bonds.[2] Among these dipolarophiles, alkenes and alkynes have been extensively studied as cycloaddition partners for different types of diazo dipoles. Depending on the substitution of these two cycloaddition partners, the cycloaddition can yield dihydropyrazoles (pyrazolines) or, after 1,2-elimination reaction, pyrazoles, while the treatment of the dipole with alkyne yields directly the pyrazole (**Scheme 1.9**).

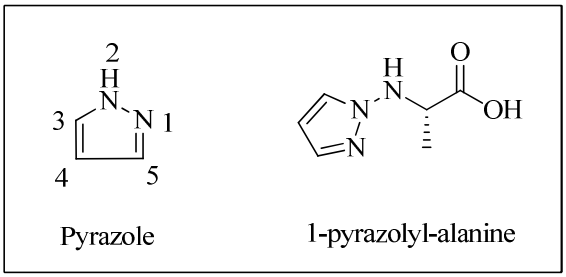
Scheme 1.9: 1,3-DC of diazo compounds.



1.5 Pyrazoles background and properties:

Pyrazole is a 5-membered heterocyclic diazole compound composed of three carbon atoms and two nitrogen atoms in adjacent positions. It is a prevalent scaffold in drug discovery programs. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, even though they are rare in nature. First natural pyrazole, 1-pyrazolyl-alanine was isolated in 1959 from seeds of watermelon[23] (**Figure 1.4**). Pyrazoles constitute an important class of biologically active compounds as they display broad spectrum of biological activities. As they are biologically important, they have applications in agrochemical and pharmaceutical industries as herbicides and active pharmaceuticals.

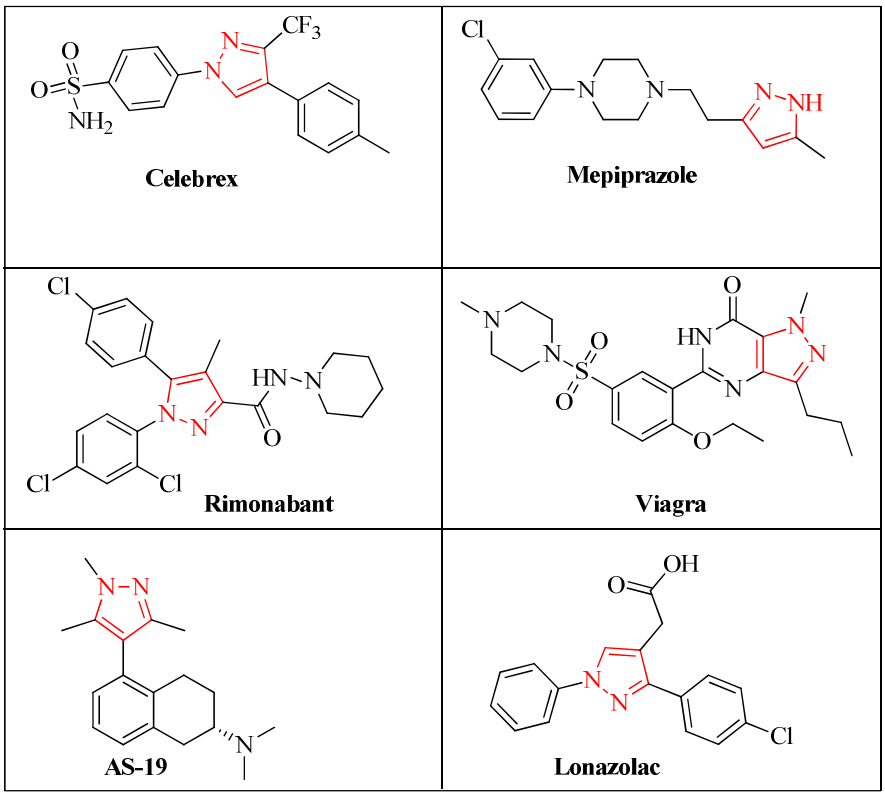
Figure 1.4: Pyrazole and first natural pyrazole 1-pyrazolyl-alanine.



Derivatives of pyrazole are used for their anti-microbial,[24] anti-inflammatory,[25] antipyretic,[26] antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant,[27] antibacterial[28], anticancer,[29] monoamineoxidase inhibiting, antidiabetic and selective enzyme inhibitory activities.[30] The pyrazole ring is present as the core in a variety of leading nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive drugs. It has been found that these compounds have hypoglycemic activity, and are also known as inhibitors and deactivators of liver alcohol dehydrogenase and oxidoreductases.[31] It has been shown in *vivo* that some of the pyrazole derivatives have appreciable antihypertensive activity.[32] These compounds also exhibit properties such as cannabinoid hCB1 and hCB2 receptor, inhibitors of p38 Kinase, CB1 receptor antagonists.[33] The 1-phenylpyrazole motif is present in several drug candidates for treatment of various diseases such as cyclooxygenase-2 (COX-2) inhibitors, IL-1 synthesis inhibitors, and protein kinase inhibitors etc. Similarly a few of the 1, 5 diarylpyrazole derivatives have been shown to exhibit non-nucleoside HIV-1 reverse transcriptase inhibitory activities along with Cox-2 inhibitor.[34a] Several substituted pyrazolo [3, 4-d] pyrimidine derivatives have xanthine oxidase inhibitor activity[34b] like allopurinol which was first synthesized by Robins in 1956 and is still the drug for the treatment of hyperuricemia and gouty arthritic disease.[34c]

Here are some of the representative examples of drugs containing pyrazole motif which are accounted for important biological activity (**Figure 1.5**).

Figure 1.5: Some important drugs containing pyrazole moiety.



1. **Celecoxib (Celebrex):** Celebrex[35] is a sulfa non-steroidal anti-inflammatory drug (NSAID) and selective COX-2 inhibitor used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis and it is marketed by Pfizer.
2. **Viagra:** Sildenafil citrate, sold as Viagra,[36] Revatio and other trade names, is a drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH). It was originally developed by British scientists and then brought to market by the Pfizer.
3. **Lonazonac**: Lonazolac is a non-steroidal anti-inflammatory drug.

4. **Rimonabant** : Also known as SR141716 sold with trade names Acomplia, Bethin, Monaslim, Remonabent, Riobant, Slimona, Rimoslim, Zimulti and Riomont. It is an anorectic antiobesity drug that has been withdrawn from the market. It is an inverse agonist for the cannabinoid receptor CB1.[37] It's main effect is reduction in appetite.

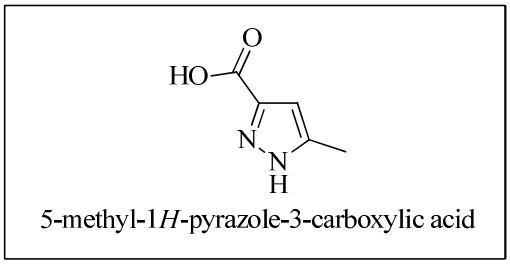
5. **Mepiprazole:** Mepiprazole (Psigodal) is a minor tranquilizer with a phenylpiperazine structure used in Spain for the treatment of anxiety neuroses.[38] It acts as a 5-HT_{2A} and α_1-adrenergic receptor antagonist,[39] and has also been shown to inhibit the reuptake and induce the release of serotonin, dopamine, and norepinephrine to varying extents.[8][9] Similarly to other phenylpiperazines like trazodone, nefazodone, and etoperidone, mepiprazole produces *m*CPP as an active metabolite.[40]

6. **AS-19**: AS-19 is a substance which acts as a potent agonist at the $5HT_7$ receptor, with an IC_{50} of 0.83 nM. It reverses the amnesia induced by drugs such as scopolamine and dizocilpine and improves long term memory acquisition, but inhibits short term memory formation.[41]

Pyrazole derivative as anti-diabetic:

Froesch E.E *et.al.*[42] has reported anti-diabetic activity in the 5-methyl-1*H*-pyrazole-3-carboxylic acid (**Figure 1.6**).

Figure 1.6: Pyrazole derivative as anti-diabetic.

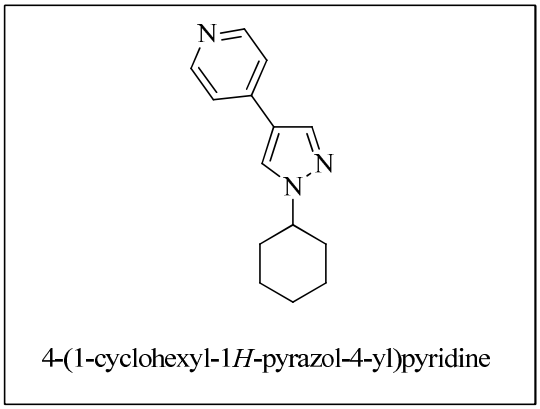


5-methyl-1*H*-pyrazole-3-carboxylic acid

Pyrazole derivative as vasodilator:

Bruner H. R. *et.al.* [43] have reported vasodilator action in 4-(1-cyclohexyl-1H-pyrazol-4-yl)pyridine (**Figure 1.7**).

Figure 1.7: Pyrazole derivative as vasodilator.

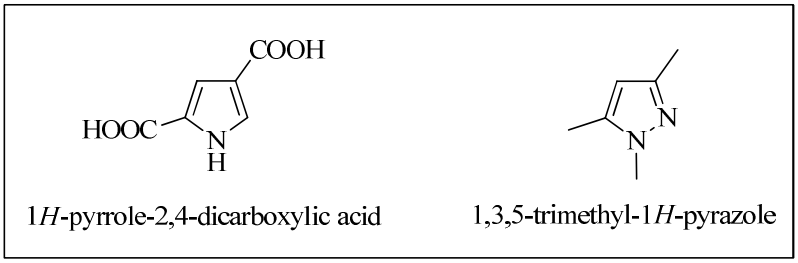


4-(1-cyclohexyl-1*H*-pyrazol-4-yl)pyridine

Pyrazole derivatives as hypoglycemic agents:

Smith D. L. *et. al.*[44] have reported that 1*H*-pyrrole-2,4-dicarboxylic acid and 1,3,5-trimethyl-1*H*-pyrazole exhibited hypoglycemic activity (**Figure 1.8)**.

Figure 1.8: Pyrazole derivatives as hypoglycemic agents.

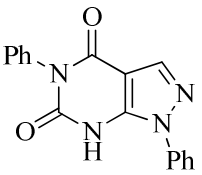


1*H*-pyrrole-2,4-dicarboxylic acid 1,3,5-trimethyl-1*H*-pyrazole

Pyrazole derivative as anti-inflammatory agents:

Sarangan S. *et.al.*[45] have synthesized number of derivatives of pyrazole- (3, 4-d) pyrimidine-4-6-diones (**Figure 1.9**) and reported the screening for C.N.S depression properties and anti-inflammatory activity. It was also reported that some derivatives showed anti-inflammatory properties equivalent to aspirin.

Figure 1.9: Pyrazole derivative as anti-inflammatory agents.

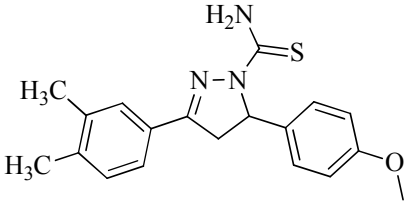


1,5-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

Pyrazole derivative as anti-tumor agent:

Peng-Cheng L.V. *et. al.,*[46] synthesized a series of pyrazole derivatives. Following 1*H*-pyrazole-1-carbothioamide shows high anti-proliferative activity against MCF-70 with IC_{50} 0.08 μM (**Figure 1.10**).

Figure 1.10: Pyrazole derivative as anti-tumor agent.

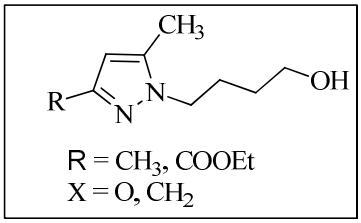


3-(3,4-dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

Pyrazole derivative as anti-microbial agent:

Samaail Radi *et. al.*[47] synthesized pyrazole derivatives, which were found potent for anti-microbial activity (**Figure 1.11**).

Figure 1.11: Pyrazole derivatives as anti-microbial agent.

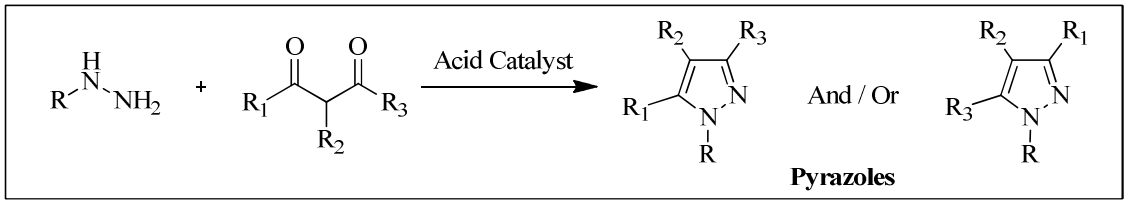


R = CH_3, COOEt
X = O, CH_2

1.6 Pyrazole synthesis:

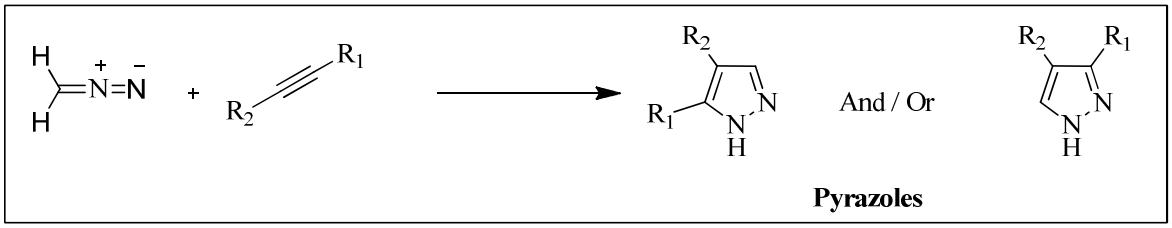
Owing to its biological significance, lot of efforts have been made for synthesis of pyrazoles and its analogues. The name "Pyrazole" was given by L. Knorr. In 1883, L. Knorr synthesized first pyrazole starting from a 1,3-dicarbonyl compound and a hydrazine derivative using a acid catalyst[48] (**Scheme 1.10**).

Scheme 1.10: Knorr synthesis of pyrazole.



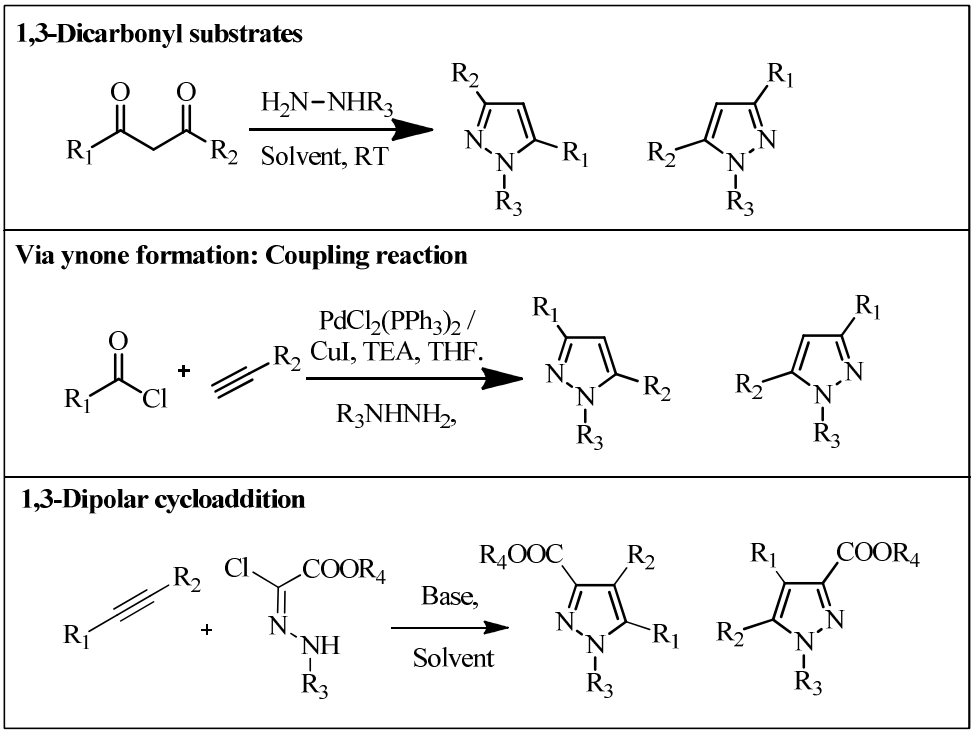
In this reaction depending on the substituents in the starting materials, two regioisomers may or may not form as shown in the above scheme. Following L. Knorr in 1898, German chemist Hans Von Pechmann[49] developed another method for pyrazole synthesis in which he used acetylenes and diazomethane as starting materials (**Scheme 1.11**).

Scheme 1.11: Pyrazole synthesis by Pechmann.



Two general methods are known for the synthesis of pyrazoles. The first method is the standard reaction of hydrazines with 1,3-difunctional substrates such as 1,3-dicarbonyl compounds,[48, 50] ynones[51] or β-aminoacrolein.[52] The second method involves the 1,3-dipolar cycloaddition between alkynes and nitrile imines and it provides a direct access to pyrazoles,[53] but regioisomeric mixtures of pyrazoles are frequently obtained (**Scheme 1.12**). Moreover, during the last years new paths have emerged, like domino C-N coupling/hydroamination of enynes,[54] azacyclization of elaborated structures[55] and direct *N*-arylation of a 1*H*-pyrazole.[56]

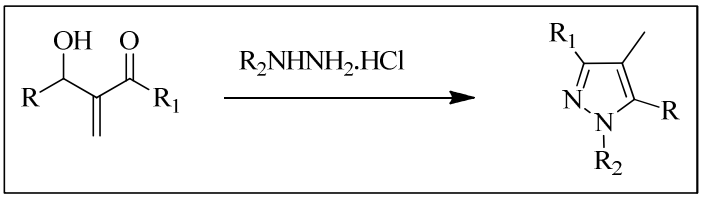
Scheme 1.12: General methods for pyrazole synthesis.



1.7 Recent literature on pyrazole synthesis:

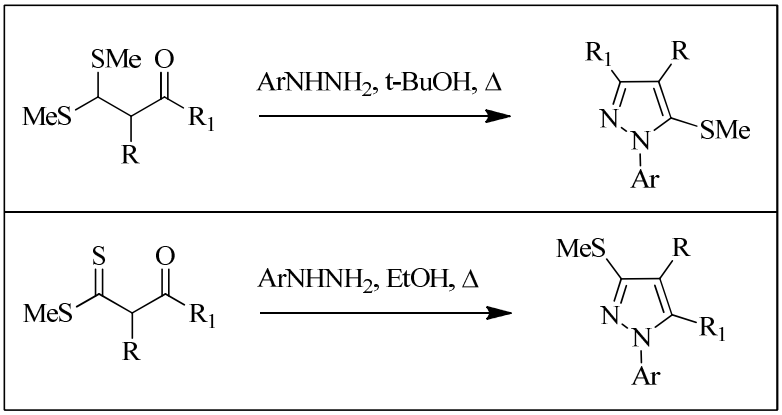
Jae Nyoung Kim *et.al.* reported[57] the expeditious synthesis of 1, 3, 4 trisubstituted pyrazoles from Baylis-Hillman adducts (**Scheme 1.13**).

Scheme 1.13: Synthesis of 1,3,4-trisubstituted pyrazoles.



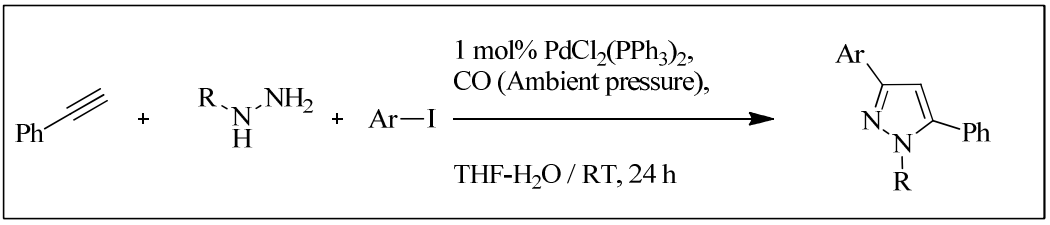
H. Junjappa *et.al.* reported[58] regioselective synthesis of 1-Aryl-3, 4-substituted/ annulated-5-(methyl thio) pyrazoles and 1-Aryl-3-(methyl thio)-4, 5-substituted/annulated pyrazoles (**Scheme 1.14**).

Scheme 1.14: Synthesis of thio-substituted pyrazoles.



A.Mori *et.al.*[59] reported the pyrazole and isoxazole derivatives that are prepared by a palladium-catalyzed four-component coupling of a terminal alkyne, hydrazine (hydroxylamine), carbon monoxide under ambient pressure and an aryl iodide (**Scheme 1.15**).

Scheme 1.15: Synthesis of pyrazole reported by A. Mori *et. al.*



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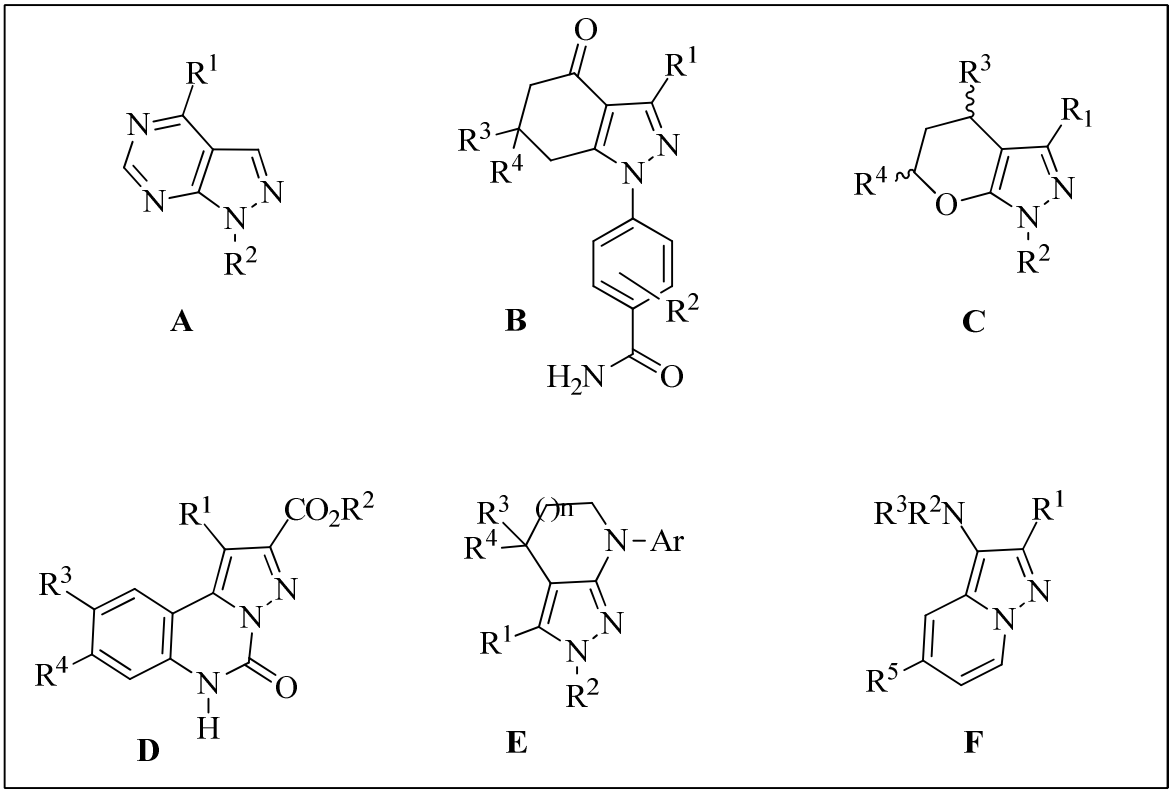
Chapter 2

1,3-DC of nitrile imines with sulfur substituted acetylenes and their application in synthesis of ring-fused thieno[2,3-c]pyrazoles

2.1 Ring-fused pyrzoles properties and their biological importance:

Ring-fused pyrazoles are the compounds in which pyrazole ring is fused with other aromatic or carbocyclic ring forming a bicyclic or multicyclic structure. Synthesis of pyrazoles is well known but when it comes to ring-fused pyrazoles it seems to be challenging from the synthetic point of view. Ring fused pyrazoles are also important biological targets as they display a vast array of biological properties. There exists numerous examples of the ring fused pyrazoles which have shown promising biological activities (**Figure 2.1**).

Figure 2.1: Ring fused pyrazoles.



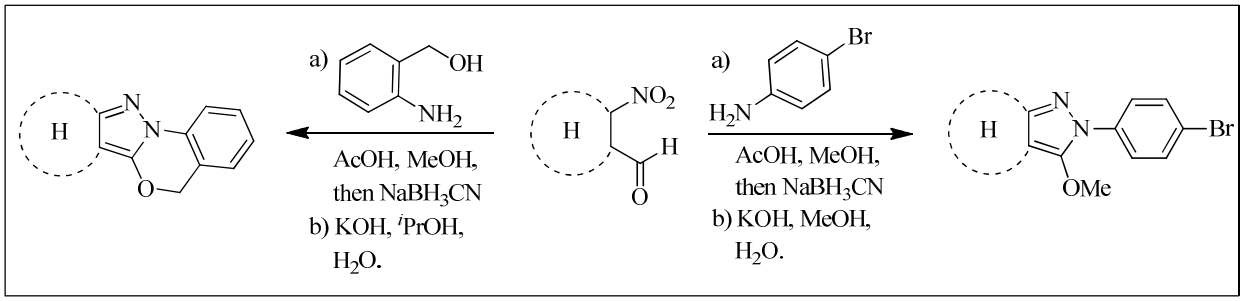
Pyrazolo[3,4-d]pyrimidines of type **A** show inhibition properties towards Src in a cell-free assay, as well as antiproliferative activity towards the epidermoid (A431) and breast cancer (BC-8701) cell line.[1] Pyrazolo-pyrimidines have also been tested in terms of inhibition of Abelson Kinase (Abl) enzymatic activity and antiproliferative properties towards human leukemic cells.[2] Huang *et.al.* recently reported that a novel class of indazol-4-ones of type **B** exhibits low nanomolar antiproliferative potencies across multiple cancer cell lines.[3] 2,3-Dihydropyran[2,3-*c*]pyrazoles of type **C** have been recently obtained through multicomponent microwave-assisted organocatalytic domino Knoevenagel/hetero Diels-Alder reaction and are potential anti-tubercular agents.[4] Pyrazolo[1,5-*C*]quinazolines[5] of type **D** are Gly/NMDA receptor antagonists while pyrazol-piperidines **E** and pyrazol-pyridines **F** are acorticotrophin-releasing-factor (CRF-1) receptor antagonists and very promising for the treatment of depression and anxiety.[6]

In 2007, T. Gharbaoui *et. al.* synthesized series of pyrazole fused-ring derivatives, which showed promising activity as GPR109a agonist activity.[7] F.D Boyer *et.al.* made a novel series of conformationally-restricted oxazolidinones which possess a fused pyrazole ring substituted with various alkyl, aryl and heteroaryl substituents. A number of analogs exhibited potent activity against both Gram-positive and fastidious Gram-negative organisms.[8] Sheriff Rostom, synthesized some indeno[1,2-c]pyrazoles substituted with sulfonamide, thiourea pharmacophores. [9] They found that some of these compounds were cytotoxic and cytostatic. He further evaluated their antitumour activity against broad spectrum of cancer cells. In 2004, L. Bhat *et. al.* synthesized some steroid fused pyrazole derivatives for bile acid transporters (hIBAT and hLBAT). The selected pyrazole fused bile acids were further conjugated with drugs and drug surrogates. The annulated pyrazoles and their drug conjugates showed good affinity for hLBAT as compared to hIBAT, and weak to moderate transport activity in hIBAT expressing oocytes.[10] Fused pyrazole-bearing systems have become well-recognized pharmacophores for numerous Chk1 inhibitors. These aminopyrazole cores have been reported by companies like Agouran Pharmaceuticals,[11a] Abott Laboratories.[11b]

2.2 Recent literature in synthesis of ring fused pyrzoles:

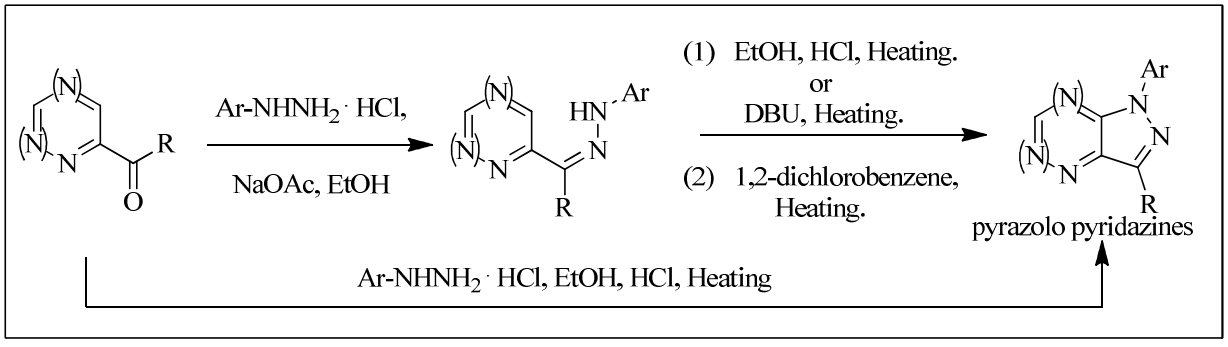
Recently Mark Kruth *et.al.*[12] have reported a facile syntheses of novel benzo- 1,3-dioxolo-, benzothiazolo-, pyrido-, and quinolino-fused 5*H*-benzo[*d*]-pyrazolo[5,1-*b*][1,3]-oxazines and 1*H*-pyrazoles (**Scheme 2.1**) by using an easy and effective *N*,*N*-bond forming heterocyclization reaction. In doing so, the substrate scope of this heterocyclization reaction, which starts with *o*-nitroheterocyclic aldehydes, was expanded to provide several unique heterocyclic compounds for biological screening.

Scheme 2.1: Ring-fused pyrazoles reported by Mark Kruth *et.al.*



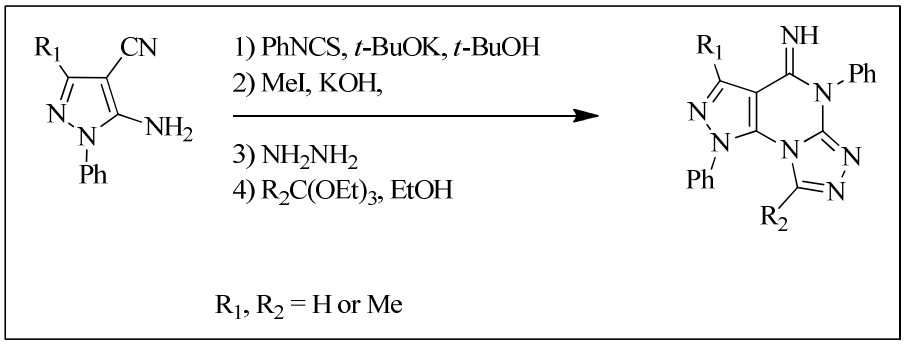
G. Hajós *et.al.*[13] have reported synthesis of pyrazolo[3,4-*b*]pyrazines and pyrazolo[4,3-*c*]pyridazines through ring closing reaction of 2-pyrazinyl and 3-pyridazinylketone arylhydrazones. These arylhydrazones were obtained by treatment of pyrazinyl ketones with aryl hydrazines. The aryl hydrazones were then subjected for the treatment with either EtOH/HCl/heating or DBU/heating followed by heating with 1,2-dichlorobenzene to yield the final compounds (**Scheme 2.2**).

Scheme 2.2: Synthesis of pyrazolo[3,4-*b*]pyrazines and pyrazolo[4,3-*c*]pyridazines.



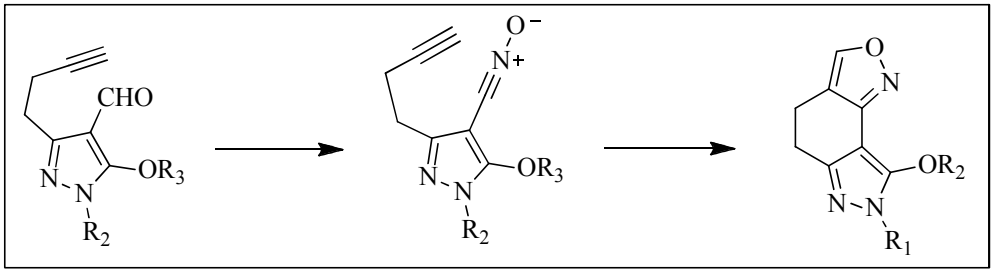
Recently M. Bakavoli *et.al.*[14] have reported synthesis of pyrazolo [4,3-e][1,2,4]triazolo-[4,3a]pyrimidine-4(5*H*)-imines over 4 steps (**Scheme 2.3**). This new route for the synthesis of pyrazolo[4,3-e][1,2,4]triazolo[4,3-a]pyrimidine4(5*H*)-imines has been delineated through heterocyclization of suitably functionalized pyrazoles with phenylisothiocyanate followed by methylation, nucleophilic displacement with hydrazine, and finally cyclocondensation with orthoesters.

Scheme 2.3: Synthesis of pyrazolo [4,3-e][1,2,4]triazolo-[4,3a]pyrimidine-4(5*H*)-imines.



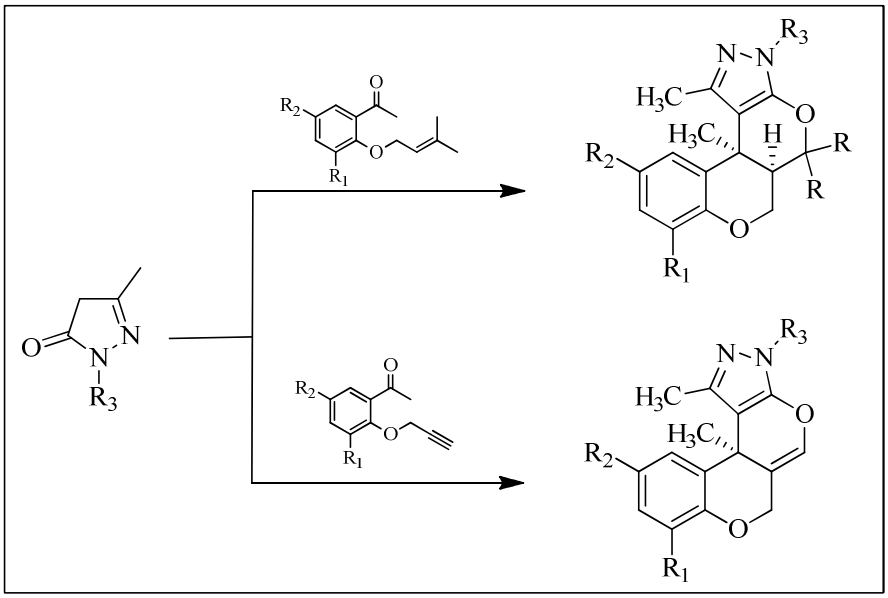
In 1999, M. J. Kurth *et. al.*[15] reported synthesis of pyrazolo[3,4-g] [2,1] dihydrobenzoisoxazole and pyrazolo[3,4-g] [2,1] dihydrobenzoisoxazoline through a intramolecular [3+2] - nitrile oxide cycloaddition. In this synthesis they started with ethyl acetoacetic ester, which was converted to a desired pyrazole derivative over 3 steps. The pyrazole thus obtained was formylated and this aldehyde was then converted to a nitrone which was subjected to an intramolecular [3+2] - nitrile oxide cycloaddition to yield the final ring fused pyrazole (**Scheme 2.4**).

Scheme 2.4: Synthesis of pyrazolo [3,4-*g*] [2,1] dihydrobenzoisoxazol(in)e.



Narsidas J. Parmar *et. al.*[16] have reported synthesis of benzopyran-annulated pyrano[2,3-c]pyrazoles through tetrabutylammonium hydrogen sulfate mediated domino / Knoevenagel-hetero-Diels–Alder reaction (**Scheme 2.5**). Angularly fused pyrazole derivatives are also of biological importance as they exhibit various biological activity specially with the core pyrano[2,3-c]pyrazole.

Scheme 2.5: Synthesis of pyrano[2,3-*c*]pyrazoles.

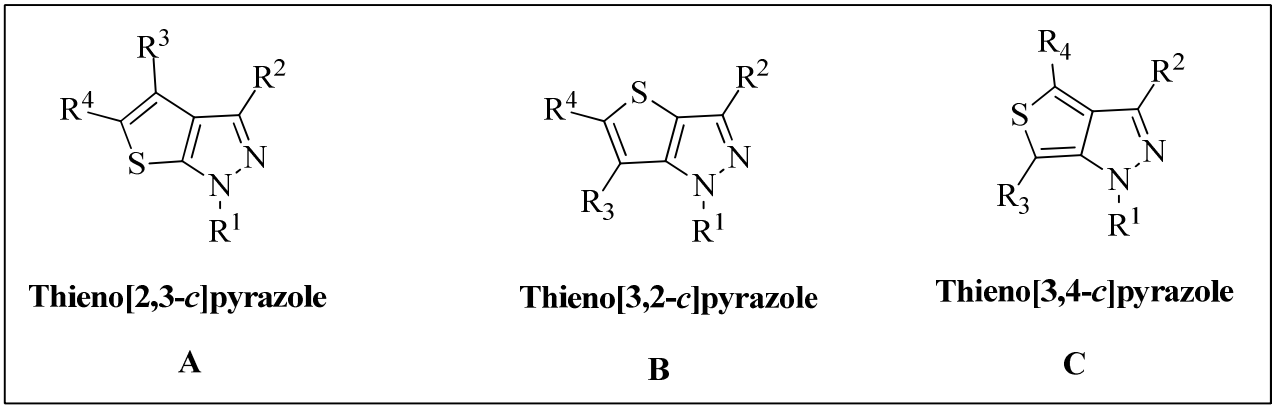


2.3 Thieno-pyrazoles:

As pyrazole containing compounds display a broad spectrum of biological activity, there are numerous systems developed by organic chemists in order to obtain novel pyrazole fused ring compounds. Thieno-pyrazole is one of the classes of these compounds.

Thieno-pyrazoles are the organic compounds in which one or more rings of pyrazole and thiophene are fused to form a single unit. Depending on the position of sulfur atom in the ring with respect to diazo group in pyrazole ring, there are 3 different types of regioisomers **(Figure 2.2)**. These compounds broadly exhibit the kinase inhibitor activity.

Figure 2.2: Structures of thieno[2,3-c]pyrazole, thieno[3,2-c]pyrazole, thieno[3,4-c]pyrazole.



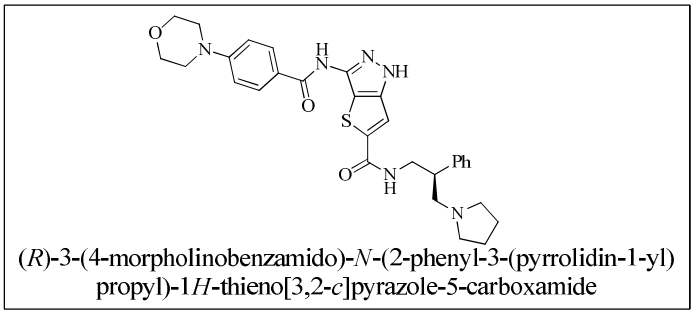
Thieno-pyrazole of type **B** and **C** have been extensively explored, whereas the type **A** is underexplored and scarcely reported in literature.

2.4 Biological activity of thienopyrazoles:

Thieno-pyrazoles of type **A** is used for inhibiting PDE 7 selectively which is responsible for allergy, immunological diseases and inflammatory diseases.[17] Several thienopyrazole analogs have been identified as inhibitors of KDR. Thieno-pyrazoles of type **B** have ability to inhibit the protein kinase ITK (asthma).

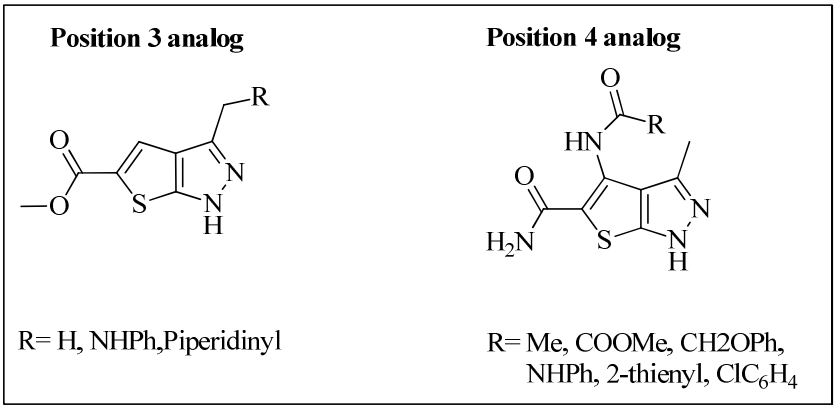
Simona Bindi *et.al.*[18] reported a series of thieno[3,2-c]pyrazoles (type **B**) to demonstrate their activity as a potent inhibitor for aurora kinase. They also discovered a representative compound (**Figure 2.3**), which showed low nanomolar inhibitory activity in the anti-proliferation assay and was able to block the cell cycle in HCT-116 cell line. This compound demonstrated favorable pharmacokinetic properties. It showed good efficacy in the HL-60 tumor model and was able to induce significant TGI.

Figure 2.3: Thieno[3,2-*c*]pyrazole reported by Simona Bindi *et.al.*



In 2006, Irini Akritopoulou-Zanze *et.al.*[19] reported kinase targeted libraries based on thieno[2,3-c]pyrazole (type **A**) scaffold (**Figure 2.4**). Several analogs have been identified as submicro- molar inhibitors of KDR.

Figure 2.4: Thieno[3,2-c]pyrazoles reported by A. Z. Irini *et. al.*



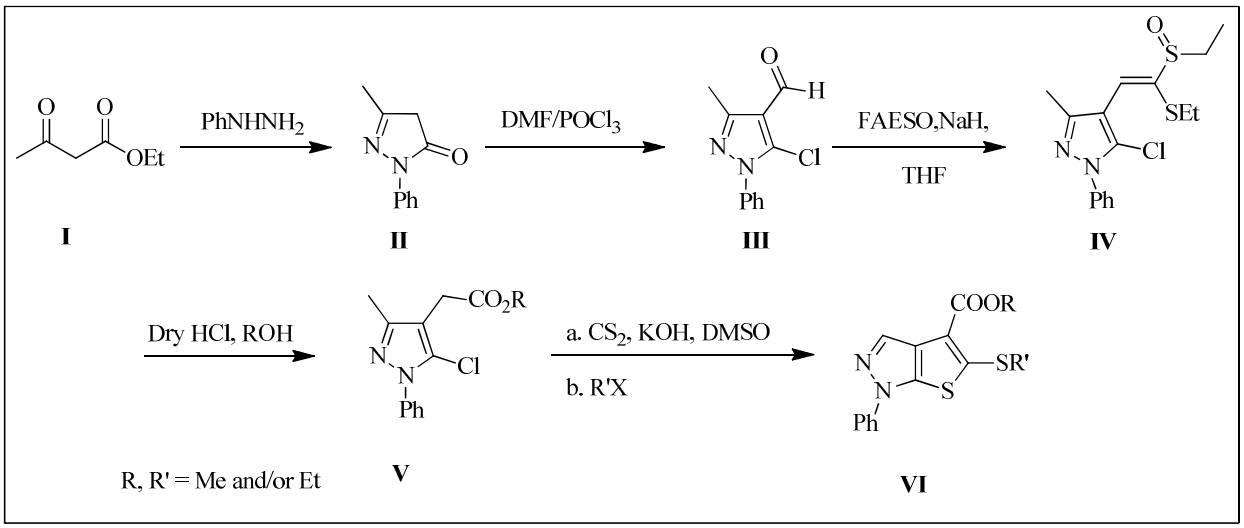
2.5 Recent literature on synthesis of thieno[2,3-c]pyrazoles:

Although thieno[3,2-c]pyrazole (Type **B**) and thieno[3,4-c]pyrazole (type **C**) are important biological targets we are going to focus our attention on synthesis of thieno[2,3-c]pyrazoles as these are interesting biological targets and are scarcely reported in literature.

In 1998, Wang *et.al.*[20] reported synthesis of thieno[2,3-c]pyrazoles starting with ethyl acetoacetate (**Scheme 2.6**). The ethyl acetoacetate ester **I** was treated with phenyl hydrazine to give pyrazolone **II**, which was then chlorinated and followed by formylation using Vilsmeier-Haak reaction to give pyrazolealdehyde **III**. This pyrazolaldehyde **III** was converted to alkene **IV** by Wittig reaction modified by Ogura, which in turn was converted to pyrazolacetate ester **V**

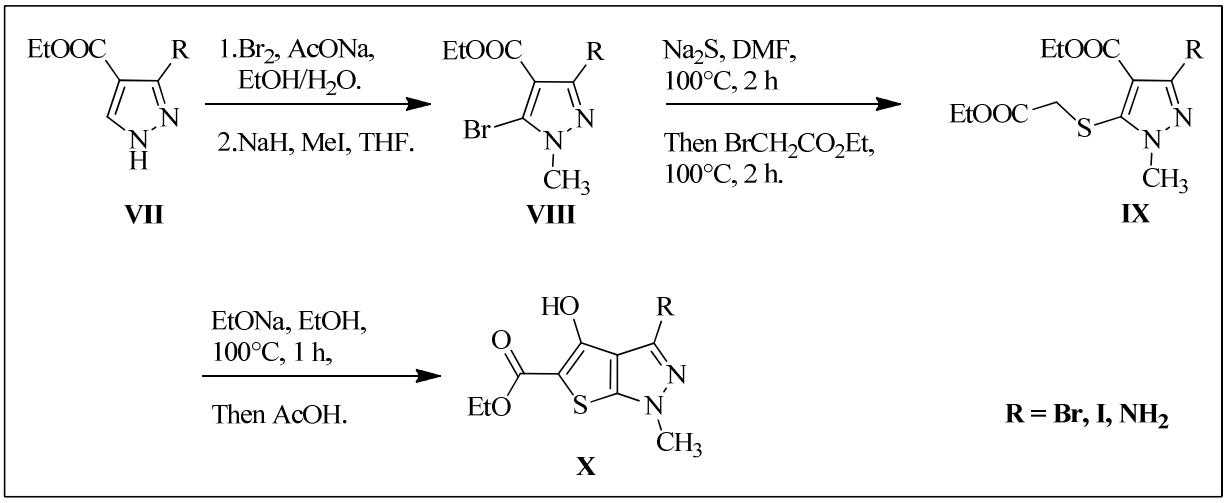
by using dry HCl. This pyrazolacetate ester was then finally treated with CS_2 / KOH followed by R'X to give thieno[2,3-c]pyrazole **VI.**

Scheme 2.6: Synthesis of thieno[2,3-c]pyrazoles reported by Wang *et.al.*



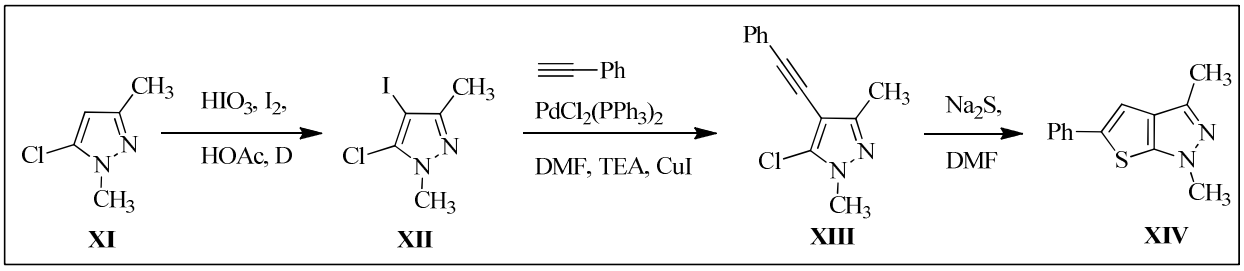
Later in 2008, Mohamed Akssira *et.al.*[21] reported a synthesis of thieno[2,3-c]pyrazoles starting with functionalized pyrazoles (**Scheme 2.7**). Pyrazoloester **VII** was selectively brominated. This bromo-pyrazoloester **VIII** was then treated with disodium sulfide at 100°C in DMF, followed by addition of ethyl bromoacetate to give **IX**. The thio-pyrazoloester **IX** thus obtained was then subjected to base promoted ring closure using sodium ethoxide in ethanol which then subsequently aromatized by addition of acetic acid to yield the final thieno[2,3-c]pyrazole **X**.

Scheme 2.7: Synthesis of thieno[2,3-c]pyrazoles as reported by Akssira *et.al.*



In 2011, Garnet A. Eller *et.al.*[22] devised a new route using sonogashira reaction. In this methodology they also started with functionalized pyrazoles (**Scheme 2.8**). Pyrazole **XI** was iodinated, the iodo-pyrazole **XII**, thus obtained was treated with phenylacetylene to get pyrazole **XIII**. This pyrazole **3** was then treated with disodium sulfide in dimethylformamide to yield desired thieno[2,3-c]pyrazole **XIV**.

Scheme 2.8: Synthesis of thieno[2,3-c]pyrazoles reported by G. A. Eller *et.al.*

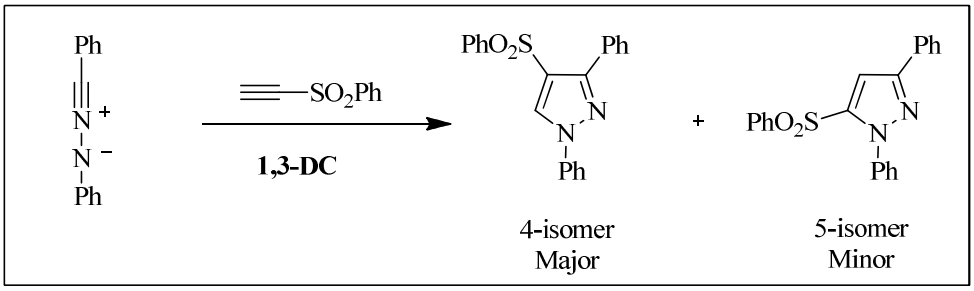


We have recently developed a method for the regiocontrolled synthesis of pyrazoles based on the 1,3-DC of nitrile imines with functionalized acetylenes.[23] As part of our group's ongoing effort[24] directed towards obtaining the pyrazole derivatives as multi-kinases inhibitors we decided to investigate the application of our methodology to the regiocontrolled synthesis of

thieno[2,3-*c*]-pyrazoles **(**Type **A)**, through a 1,3-DC of nitrile imines and sulphur-substituted acetylenes.

Heteroatom-substituted acetylenes have been scarcely studied and reported in 1,3-DC reaction of nitrile imines as 1,3-dipoles. Only Zecchi reported the reaction of *N*-phenyl *C*-phenyl nitrile imine with alkynyl phenyl sulfones with yields in the range 15-71% and with the cycloadduct having the $PhSO_2$ group in position 4 as the predominant or exclusive regioisomer (**Scheme 2.9**), [25] while alkynyl phenyl sulfides have been never investigated in this 1,3-DC. On the other hand, this kind of dipolarophiles, and the possible control of the regiochemistry, could play an important role to install the '*S*' atom in the correct position of the pyrazole ring which after synthetic elaboration can lead to the formation of ring-fused thienopyrazoles.

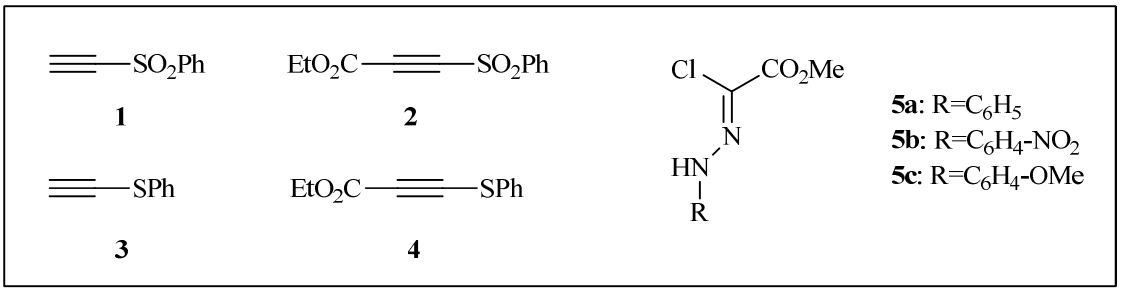
Scheme 2.9: Zecchi's synthesis of pyrazoles.



2.6 Results and discussion:

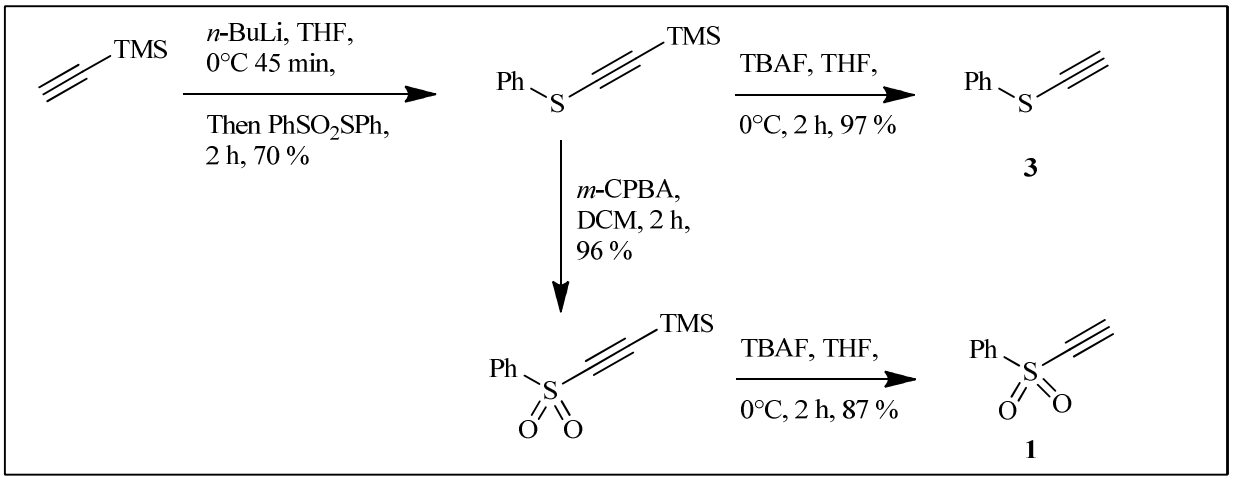
For primary investigation we decided to synthesize mono- **1** and di-functional **2** sulfones containing triple bond to extend Zecchi's result with the more versatile and unreported *C*-carboxymethyl-*N*-aryl-nitrile imines. Moreover, we present herein the sulfur acetylenes **3-4** in their general behaviour in 1,3-DC with nitrile imines derived from **5a-c** (**Figure 2.5**).

Figure 2.5: General sulphur acetylenes and nitrile imines.



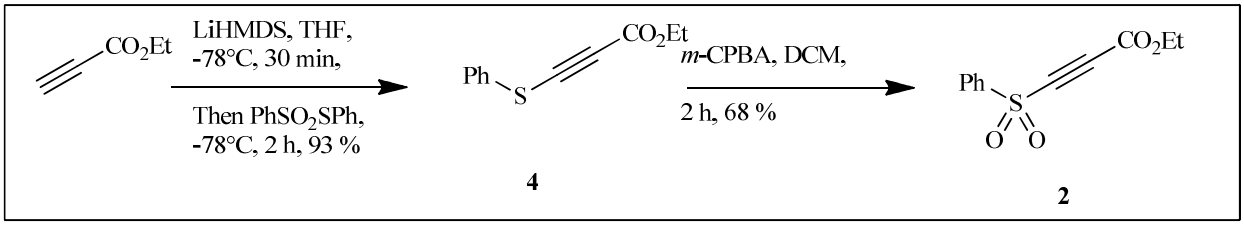
The starting acetylenes **1-4** were readily prepared according to literature procedures. The trimethylsilylethyne was treated with *n*-BuLi followed by treatment with S-Phenyl benzenethiosulfonate to give trimethyl(phenylthioethynyl)silane, which was then treated with tetrabutyl ammonium fluoride (1M solution in THF) to give acetylene **3**. The intermediate trimethyl(phenylthioethynyl)silane was oxidised with *m*-CPBA followed by TMS deprotection using tetrabutyl ammonium fluoride (1M solution in THF) to give acetylene **1** (**Scheme 2.10**).

Scheme 2.10: Synthesis of acetylenes **1** and **2**.



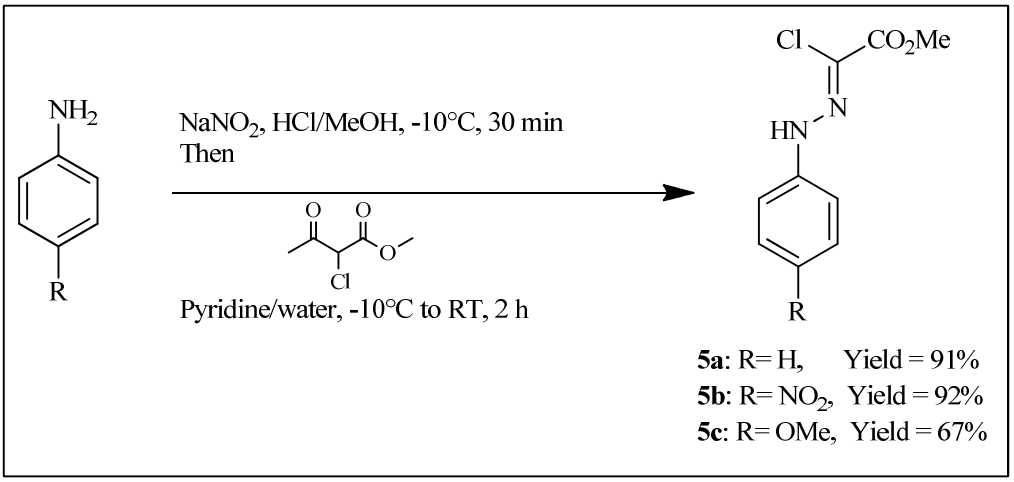
Acetylenes **2** and **4** were prepared in the same manner from ethyl propiolate (**Scheme 2.11**).

Scheme 2.11: Synthesis of acetylene **3** and **4**.



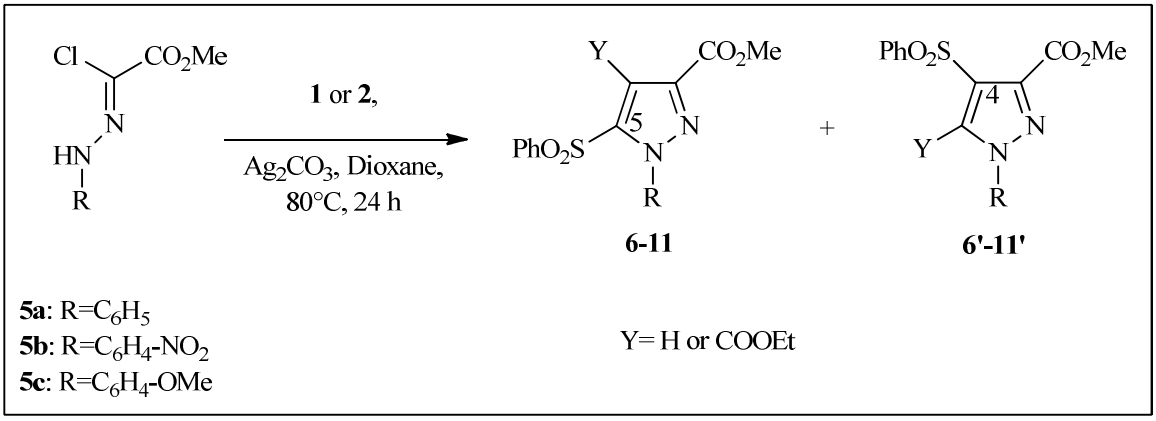
While the selected hydrazonoyl chlorides **5a-c** were prepared from corresponding aromatic amines by treating with nitrous acid forming a diazonium salt which was then treated with methyl 2-chloroacetoacetate to yield the desired hydrazonoyl chloride **5a-c** (**Scheme 2.12**).

Scheme 2.12: Synthesis of hydrazonoyl chlorides **5a-c.**



The cycloadditions of **1** and **2** with the *C*-carboxymethyl-*N*-aryl-nitrile imines derived from **5a-c** were carried out in dry dioxane at 80°C for 24 hours using 2.5 equivalents of Ag_2CO_3, and **1-2** were used in stoichiometric amount with respect to the dipoles with yields ranging from 35 to 63% (**Scheme 2.13**, **Table 2.1**, entries 1-6).

Scheme 2.13: 1,3-DC of sulfone substituted acetylenes **1-2** and nitrile imines **5a-c**.



Cycloadducts **6-6'** were obtained in 35/65 ratio, **7-7'** in 40/60 ratio while **8-8c'** were isolated as balanced mixtures in a 54/46 ratio (entries 1-3). These results of regiochemistry fit with the data obtained for the *N*-phenyl-*C*-phenyl nitrile imines,[25] and are due to the strong electron withdrawing effect of the sulfonyl group which determine a large LUMO coefficient at the β-carbon of the acetylene with a consequent HOMO (dipole)-LUMO (dipolarophile) interaction.

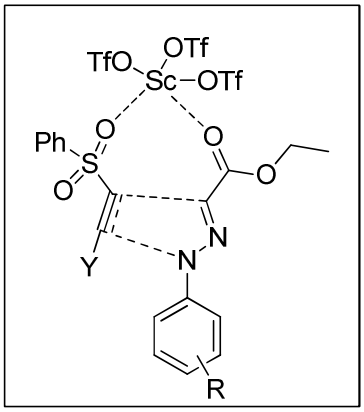
Table 2.1: 1,3-DC of sulfone substituted acetylenes **1-2** and nitrile imines **5a-c**.

Entry	Dipolaro-phile	1,3-Dipole	Y	Cycload-ducts	Yield (%)[a]	Ratio[a]	Yield (%)[b]	Ratio[b]
1	**1**	**5a**	H	**6-6'**	49	35:65	38	12:88
2	**1**	**5b**	H	**7-7'**	35	40:60	34	14:86
3	**1**	**5c**	H	**8-8'**	58	54-46	39	14:86
4	**2**	**5a**	CO_2Et	**9-9'**	63	11-89	72	8:92
5	**2**	**5b**	CO_2Et	**10-10'**	65	20:80	67	15:85
6	**2**	**5c**	CO_2Et	**11-11'**	60	10:90	64	9:91

[a] Without $Sc(OTf)_3$ [b] With 10% $Sc(OTf)_3$.

The same reactions were repeated in the presence of scandium triflate catalyst for a possible control of the regiochemistry.[23] As expected, the amount of the 4-isomer was higher under $Sc(OTf)_3$ catalysis (entries 1-3), the 4-isomer increased to 12:88 for **6-6'** and to 14:86 for **7-7'** and **8-8'**, due to the possibility of a chelate transition state involving the CO_2Me group and the sulfonyl group with scandium catalyst (**Figure 2.6**).[23]

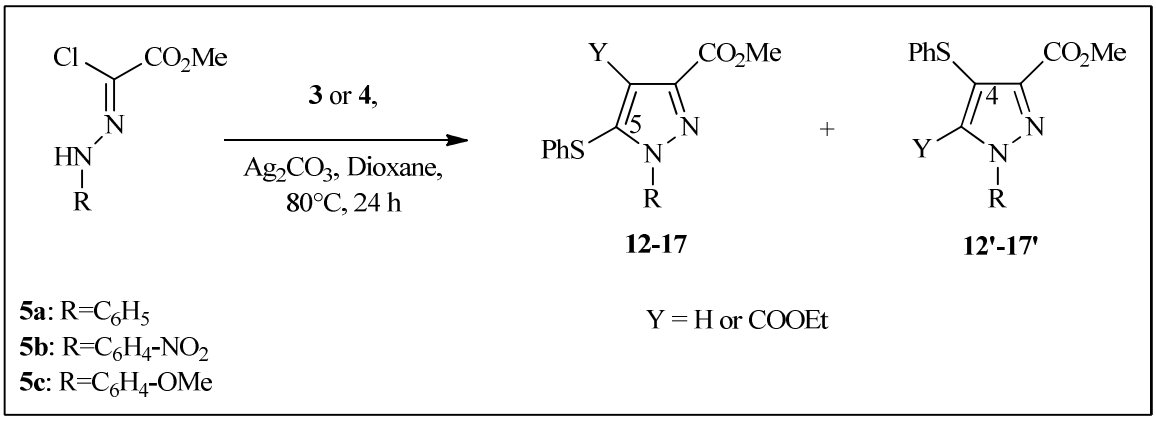
Figure 2.6: Possible mode of chelation of $Sc(OTf)_3$ with 1,3 dipole and acetylene.



Disubstituted-sulfone **2** gave good yields of cycloadducts (60-65%) with a higher quantity of the 4-isomer, ratio 11:89 for **9-9'**, 20:80 for **10-10'** and 10:90 for **11-11'** (entries 4-6 in **Table 2.1**), but in this case no significant improvement was observed in the ratio under scandium catalysis in favour of 4-isomer. This observation shows that this kind of 1,3-DC is substrate-controlled and does not take place under the control of the catalyst. Moving to the PhS-

dipolarophile **3** and **4** a reversal in the regiochemistry in favor of the 5-substituted pyrazoles was observed. The *C*-carboxymethyl-*N*-aryl-nitrile imines derived from **5a-c** with **3** and **4** gave only the regioisomers **12-17** with the PhS- group in position 5 with or without scandium catalysis (**Scheme 2.14**, **Table 2.2**). Satisfactory yields in the range 45-70% were achieved (entries 1-6). These results are in line with results obtained by us in 1,3-NED (normal electron demand) dipolar cycloaddition of nitrile imines with acetylene derivatives.[26]

Scheme 2.14: 1,3-DC of sulfur substituted acetylenes **3-4** and nitrile imines **5a-c**.



The identification of the 5- and the 4-pyrazoles in the cycloadducts **6-8** and **12-14** was done by using ^{1}H-NMR signals taking advantage from the fact that it is known that the CH signal on the C5 for the 4-substituted pyrazole resonates at about 8.0 ppm. This signal was absent in the NMR spectra of our cycloadducts.[23] Furthermore, NOE experiments confirmed the formation of 5-pyrazole. Similar was the case for compounds **9-11** and **15-17**.

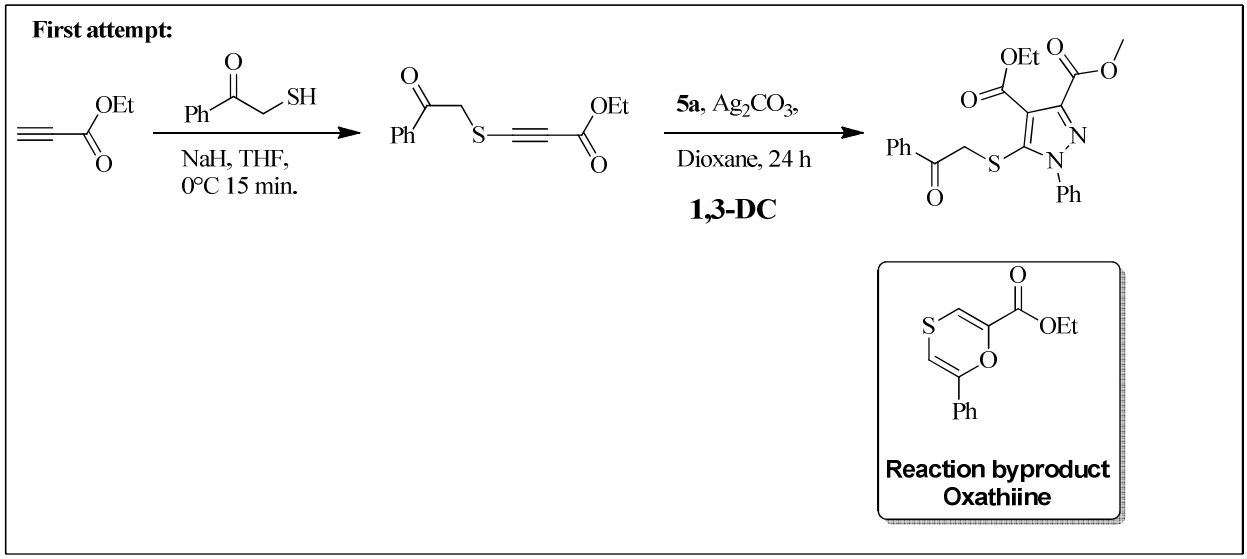
Table 2.2: 1,3-DC of sulfur substituted acetylenes **3-4** and nitrile imines **5a-c**.

Entry	Dipolarophile	1,3-Dipole	Y	Cycloadducts	Yield (%)	Regioisomeric Ratio
1	**3**	**5a**	H	**12-12'**	70	>99:1
2	**3**	**5b**	H	**13-13'**	57	>99:1
3	**3**	**5c**	H	**14-14'**	67	>99:1
4	**4**	**5a**	CO_2Et	**15-15'**	50	>99:1
5	**4**	**5b**	CO_2Et	**16-16'**	45	>99:1
6	**4**	**5c**	CO_2Et	**17-17'**	67	>99:1

From these results we understood that sulphur or sulfone based functionalities controls the regiochemistry in the cycloaddition reaction. The electron-releasing property of the *S* atom together with the electron-withdrawing CO_2Et group bring to a synergistic regiochemical effect that leads exclusively to one regioisomer, in contrast with the behaviour of the SO_2 substituted triple bond. This regiochemistry is correct for the obtaining the ring-fused thienopyrazole of **Type A**.

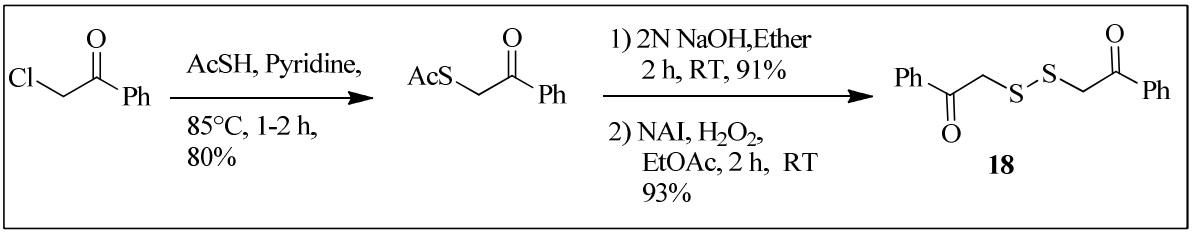
To apply this protocol for synthesis of ring-fused thieno-pyrazole we decided to synthesize properly substituted simple acetylene having a CH_2- group at *α* position to the sulphur atom and on other side of the acetylene a carbonyl group like COOEt, as this was feasible with the literature procedure.[27] For synthesis of this type of acetylene we started with with ethyl propyolate which was then treated with sodium hydride followed by addition of phenacyl mercaptan to yield disubstituted acetylene in good yield. When this disubstituted acetylene was treated with one of the nitrile imine **5a**, the cycloadduct was formed together with a by-product oxathiine in the reaction (S**cheme 2.15**) which was due to presence of highly acidic *H'*s next to S. But when we tried to cyclise this cycloadduct using strong acidic and basic conditions we didn't got any conversion in fact the cycloadduct got degraded.

Scheme 2.15: Synthesis of disubstituted acetylene.



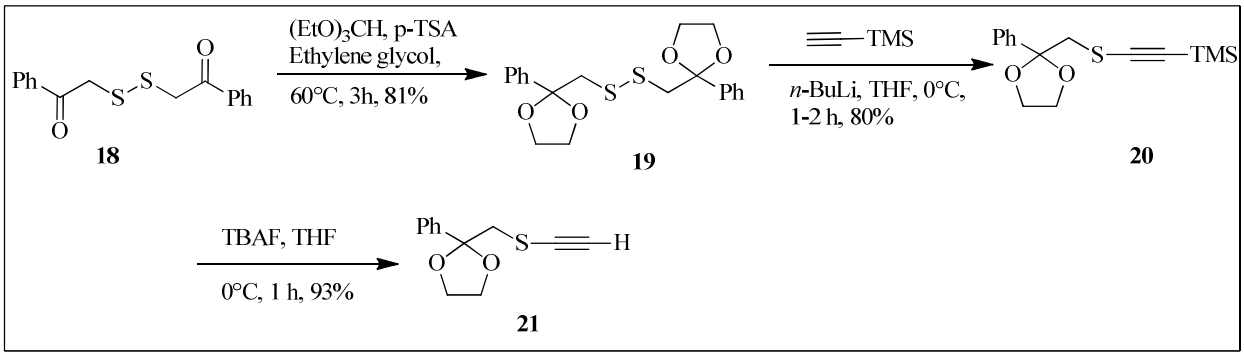
To overcome the fact that ester group was not reacting in the final step we decided to synthesise acetylene containing formyl group and less acidic functionality on S. In order to achieve this we planned to synthesize acetal of phenacyl disulfide. We started with synthesis of diphenacyldisulfide **18**, which was synthisized from readily available phenacyl chloride (**Scheme 2.16**).[27] The phenacyl chloride was treated with thiolacetic acid in pyridine at 85°C for 2 h to yield phenacylthioacetate. This intermediate phenacylthioacetate was then deacylated using 2N NaOH at RT in 91% yield, which was then subjected to dimerisation using NaI / H_2O_2 in ethylacetate to give diphenacyldisulfide **18** with 93% yield.

Scheme 2.16: Synthesis of diphenacyldisulfide.



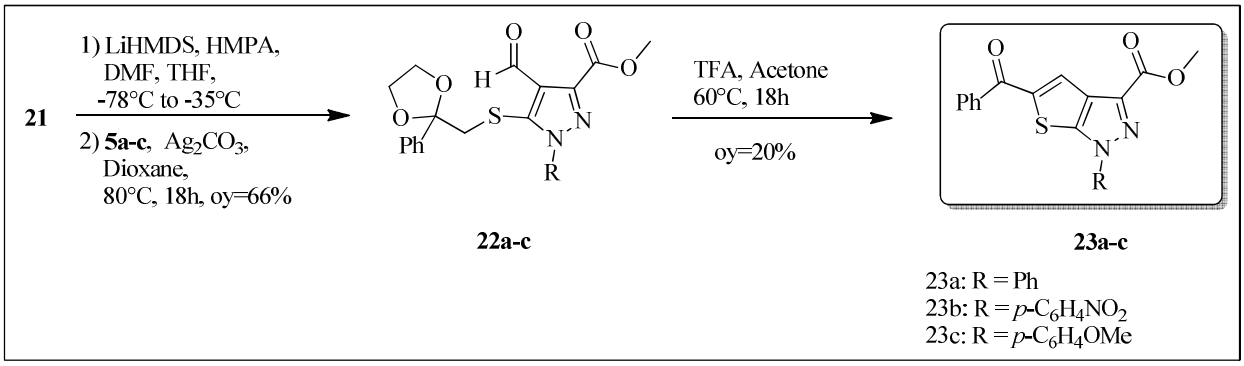
This diphenacyldisulfide **18** was then protected with ethylene glycol to yield dioxolane-disulfide **19** with 81% yield. This dioxolane-disulfide **19** was then treated with TMS acetylene to give S-substituted acetylene, the acetylene **20** was obtained by reaction of **19** with lithium trimethylsilyl acetylene in THF at 0°C in 80% yield. The acetylene 20 was then desilylated using TBAF at 0°C, to give compound **21** in 93% yield (**Scheme 2.17**).

Scheme 2.17: Synthesis of acetylene **21**.



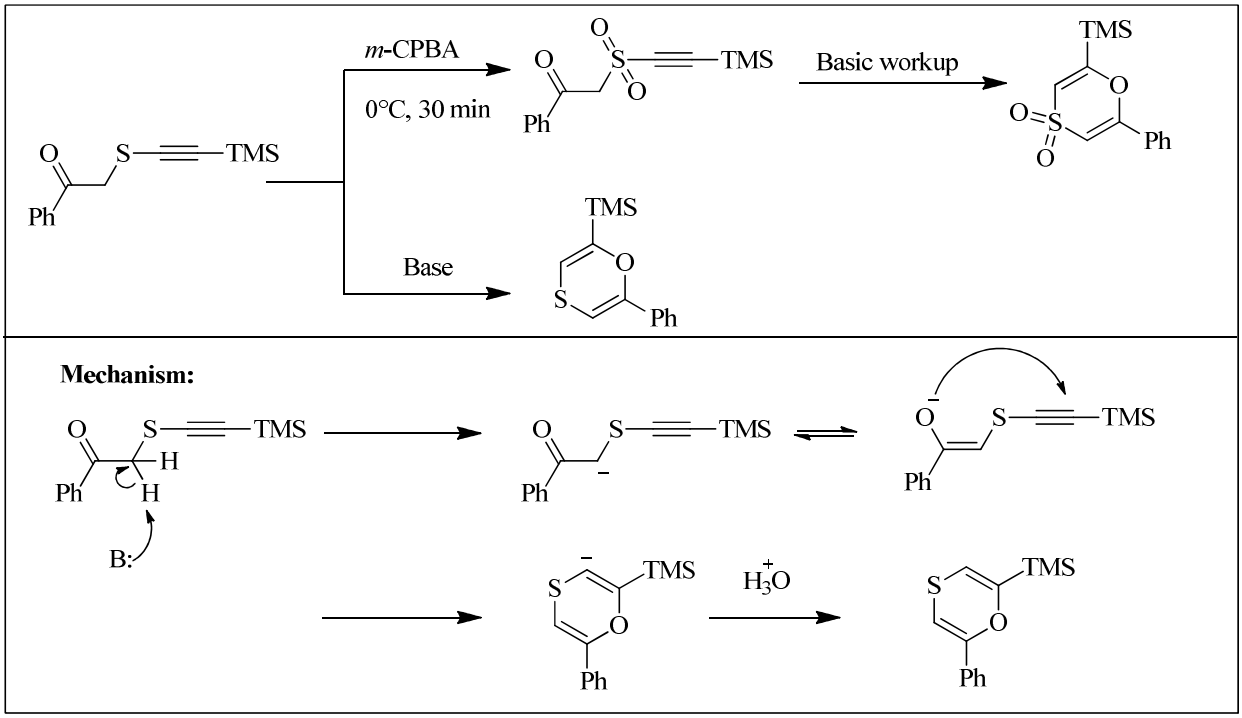
In the acetylene **21** the formyl group was introduced by reaction with LiHMDS in THF at -78°C followed by addition of a mixture of DMF and HMPA (**Scheme 2.18**). The disubstituted acetylene was not isolated but immediately treated with **5a-c** in the usual conditions. The corresponding were obtained in good overall yields, 66% for **22a,** 42% for **22b**, 43% for **22c** and fully characterized after chromatography on silica. Deprotection of the dioxolane in **22** and condensation to the thieno[2,3-*c*]pyrazole **23** was done in one step by reaction with trifluoroacetic acid in acetone in 20% overall yield. Similar results were obtained with using 6M HCl, but overall yields were very pure in the range of 10 to 11%.

Scheme 2.18: General scheme for synthesis of ring-fused thieno[2,3-c]pyrazole **23a-c**.



When we tried to oxidise compound **20** using *m*-CPBA in order to get thieno[3,2-c]pyrazole (**Type B**) we found in was getting oxidised but the on basic workup it was getting cyclised forming a 1,4-oxathiine. This is attributed to the fact that the molecule contains more acidic *H*'s next to carbonyl group making it more acidic which on basic workup gets enolized that subsequently attacks on one of the acetylenic carbon atom preferably forming a 6-membered structure (**Scheme 2.19**) which was also confirmed by ^{1}H-NMR data.

Scheme 2.19: Formation of 1,4-oxathiine.



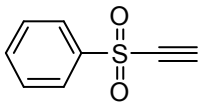
2.7 Conclusion:

In summary, an efficient multi-step synthetic sequence based on a 1,3-DC of *C*-carboxymethyl-*N*-aryl-nitrile imines with sulfur-acetylenes has been developed and this methodology appears suitable for the regiocontrolled synthesis of thieno[2,3-*c*]pyrazoles of type **A**. With a particular interest there is the possible synthetic elaboration of the ester group that would allow the preparation of libraries of potentially active thienopyrazoles. Therefore, applications in medicinal chemistry call for other studies which will be reported in due course.

2.8 Experimental Section:

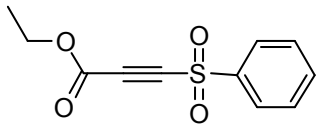
2.8.1 Material and Methods:

^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ or CD_3OD or DMSO-*d6* solutions at 300, 400 and 600 MHz for ^{1}H and 75.46, 100.6 and 150.92 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). *J* values are given in Hz. ^{1}H NMR and ^{13}C NMR spectral assignments were made by DEPT, gCOSY and gHSQC experiments. IR spectra were recorded in solvent as specified. Mass spectra (MS) were obtained with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. High Resolution Mass Spectra (HRMS) were recorded on a micromass LCT spectrometer using electrospray (ES^{+}) ionisation techniques. Reactions were conducted in oven-dried (120°C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under argon. Toluene was distilled from sodium. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with bp 40-60°C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70-230 mesh). Preperative TLC was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified as needed.

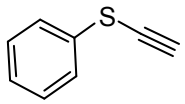


Ethynylsulfonylbenzene (1): To a stirred solution of trimethyl(phenylthioethynyl)silane (0.5 g, 2.4 mmol) in DCM (5 mL) was added solution of *m*-CPBA (77%, 1.34 g, 6.4 mmol) in DCM (5 mL). The reaction was vigorously stirred for 1-2 h. After completion, reaction was cooled to 0 ^{o}C and sat. $NaHCO_3$ solution (15 mL) was added with caution. Then reaction mixture was extracted with DCM (3 x10 mL) and washed with water and brine. The DCM layer was dried on $MgSO_4$ and evaporated. No purification was necessary as almost pure product was obtained as yellow oil (0.55 g, 96% yield). ^{1}H (300MHz, $CDCl_3$): δ 7.97–8.09 (d, J = 6 Hz, 2H), 7.55–7.75 (m, 3H), 0.22–0.25 (s, 9H). This oil (0.55 g, 2.3 mmol) was then dissolved in THF (10 mL) and cooled to ~ 78^{o}C and

then mixed with *n*-Bu_4NF (1 M in THF, 0.7 mL, 0.7 mmol). The reaction was stirred for 2-3 h at same temperature. After completion of reaction sat NH_4Cl solution (15 mL) was added and mixture was extracted with diethyl ether (3 x 10 mL). The combined ether extracts were washed with water (2 x 10 mL) and brine and then dried over anhydrous Na_2SO_4. Ether layer was carefully evaporated in *vacuo* and crude product **1** (0.33 g, 87% yield) was kept as stock solution in diethyl ether (*ca. 20%w/v*) at ~ 4 ^oC. The crude product was used as such for further reactions without purification.

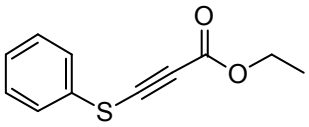


Ethyl-3-(phenylsulfonyl)propiolate (2): To a stirred solution of ethyl-3-(phenylthio)propiolate **4** (0.77 g, 3.7 mmol) in DCM (10 mL) was added a solution of *m*-CPBA (77%, 2.1 g, 9.3 mmol) in DCM (10 mL) and left to react at room temperature for 2 h. Afterwards, the solution was washed with 10% aq. $Na_2S_2O_4$ solution (10 mL) and saturated aq. $NaHCO_3$ solution (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4, evaporated and the crude product was purified by chromatography on silica gel (EtOAc/Light Petroleum 1/5) to yield 0.59 g (68 %) of compound **2** as a yellow oil. ^1H NMR (300 MHz , $CDCl_3$):δ 8.03 (d, J = 7.6 Hz, 2H), 7.76 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 139.6, 135.2, 129.6 (2CH), 127.9 (2CH), 79.7, 78.9, 63.5, 13.7;IR (CCl_4): ν = 3061, 2978, 2532, 1726, 1570, 1472, 1441, 1358, 1238, 1171, 1088 cm^{-1}; $[M+Na]^+$: 261; Anal. Calcd for C11H10O4S: C, 55.45; H, 4.23. Found: C, 55.48; H, 4.25.



Phenylthioacetylene (3): Trimethylsilylethyne (1 g, 10.2 mmol) was dissolved in dry THF (15 mL) at 0^oC. A solution of *n*-BuLi (1.6 M *in Hexane*, 6.4 mL, 10.2 mmol) was then added dropwise with stirring under argon at 0 ^oC. After 45 min. a solution of *S*-Phenyl benzenethiosulfonate (2.3 g, 9.2 mmol) in THF (10 mL) was introduced at 0 ^oC stirring was continued for 2 h and the reaction mixture was then quenched with sat. NH_4Cl solution (20 mL). The reaction mixture was extracted with diethyl ether (3 x 15 mL) and organic layer was washed with water (2 x 15 mL) and brine. The ether layer was then dried over anhydrous Na_2SO_4 and evaporated in *vacuo.* The residue was purified by flash column chromatography using *n*-hexane as eluent to afford yellow oil (1.48 g, 70% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50-7.55 (m, 2H), 7.42-7.49 (t, J = 7.5 Hz, 2H), 7.29-7.38 (tt, J = 7.5 and 1.5

Hz, 1H), 0.36-0.38 (s, 9H). This oil trimethyl(phenylthioethynyl)silane (1 g, 4.8 mmol) was then dissolved in THF (20 mL) and cooled to −78 ^{o}C and then mixed with *n*-Bu_4NF (1M in *THF*, 1.45 mL, 1.4 mmol). The reaction was stirred for 2-3 h at same temperature. After completion sat. NH_4Cl (20 mL) was added and reaction mixture was extracted with diethyl ether (3 x 15 mL). The combined ether extracts were washed with water (2 x 15 mL) and brine and then dried over anhydrous Na_2SO_4. Ether layer was carefully evaporated in *vacuo* and crude product **3** (0.63 g, 97% yield) was kept as stock solution in ether (*ca. 20%w/v*) at -4 ^{o}C. The crude product was used as such for further reactions without purification.

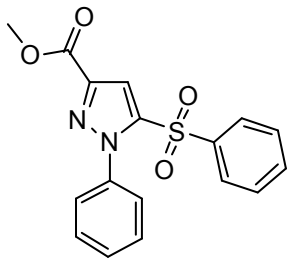


Ethyl-3-(phenylthio)propiolate (4): To a stirred solution of ethyl propiolate (0.4 mL, 4 mmol) in THF (8 mL) at -78 °C was added slowly a solution of lithium bis(trimethylsilyl)amide (1 M in *THF*, 4 mL, 4 mmol). After 30 minutes, a solution of *S*-Phenyl benzenethiosulfonate (1.0 g, 4 mmol) in THF (6 mL) was added at -78 °C and left to react at room temperature for 2 h. After completion of reaction, saturated NH_4Cl solution (10 mL) was added and extracted with diethyl ether (2 x 10 mL), then the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to afford the product **4** as a yellow oil (0.77 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J = 7.9 Hz, 2H), 7.39 (t, J = 7.9 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 129.6 (2CH), 129.5, 127.9, 127.4 (2CH), 91.6, 79.8, 62.0, 14.1; IR (CCl_4): ν = 3066, 2984, 2153, 1709, 1583, 1479, 1444, 1366, 1232, 1037 cm^{-1}; $[M+Na]^+$: 229.

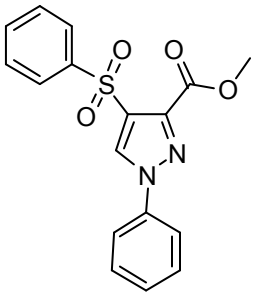
2.8.1 General Procedure for 1,3 dipolar cycloaddition and analysis of cycloadducts:

To a stirred solution of phenylthioacetylene (1 eq.) and 1,3- dipole (1 eq.) in freshly distilled dioxane (5 mL) was added silver carbonate (2.5 eq.) under argon atmosphere. Reaction was heated at reflux for overnight. After completion, reaction mixture was allowed to cool and filtered through bed of celite and washed with DCM (5 mL). The filtrate was then evaporated in *vacuo* to give dark red crude oil. The crude product was purified by column chromatography to give corresponding title compound/s.

Methyl 1-phenyl-5-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (6) and **Methyl 1-phenyl-4-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (6'):** Compounds **6** and **6'** were obtained as a off white solids following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/hexane 2:8).

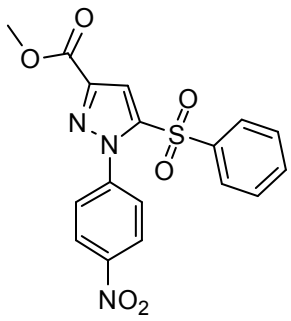


Methyl 1-phenyl-5-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (6): m.p.= 154.8 ^{o}C; ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.57–7.60 (s, 1H), 7.44-7.57 (m, 4H), 7.32–7.42 (quartet, J = 7.9 Hz, 4H), 7.22–7.28 (m, 2H), 3.92–3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 144.0, 142.7, 138.7, 137.6, 134.1, 130.2, 129.0 (2C), 128.6 (2C), 128.1 (2C), 127.1 (2C), 114.6, 52.6; IR (CCl_4): ν = 2955, 1737, 1509, 1328, 1236, 1151, 1067, 816; $[M+H]^+$: 343.



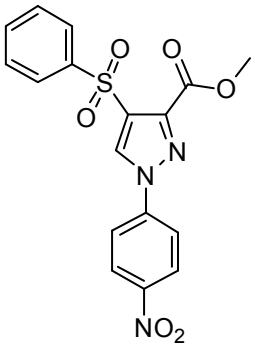
Methyl 1-phenyl-4-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (6'): m.p. = 147.3-148.2 ^{o}C ^{1}H NMR(300 MHz, $CDCl_3$): δ 8.64–8.66 (s, 1H), 8.08–8.14 (d, J = 6 Hz, 2H), 7.70-7.77 (d, J = 6 Hz, 2H), 7.40–7.65 (m, 6H), 3.88–3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 141.1, 140.8, 138.2, 133.3, 133.2, 129.7 (2C), 128.8, 128.6 (2C), 128.1 (2C), 128.3, 120.2 (2C), 52.6; IR (CCl_4): ν = 2955, 1737, 1509, 1328, 1236, 1151, 1067, 816; $[M+H]^+$: 343.

Methyl 1-(4-nitrophenyl)-5-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (7) and **Methyl 1-(4-nitrophenyl)-4-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (7'):** Compounds **7** and **7'** were obtained as a off white solids following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/hexane 2:8).



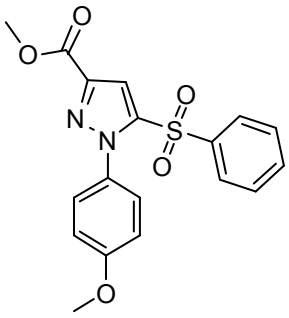
Methyl 1-(4-nitrophenyl)-5-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (7): m.p. = 192.7 ^{o}C; ^{1}H (300 MHz, $CDCl_3$): δ 8.28–8.35 (d, J = 9 Hz, 2H), 7.59–7.71 (m, 4H), 7.42–7.53 (m, 3H), 7.25–7.28 (s, 1H), 3.96–3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ160.7, 148.2, 144.4, 143.8, 142.5, 138.6, 134.7, 129.4 (2C), 128.0 (2C), 127.8 (2C),

124.1 (2C), 115.3, 52.8; IR (CH_2Cl_2): ν = 3970, 2985, 1737, 1531, 1346, 1236; Anal. Calcd for $C_{17}H_{13}N_3O_4S$: C, 52.71; H, 3.38; N, 10.85; O, 24.78; S, 8.28. $[M+H]^+$: 388.

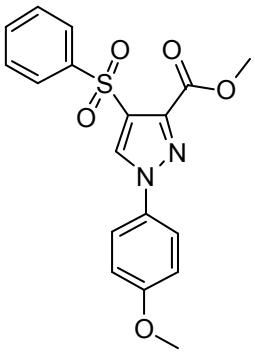


Methyl 1-(4-nitrophenyl)-4-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (7'): m.p.= 218-219.1 ^oC; ^1H NMR(300 MHz, $CDCl_3$): δ 8.75–8.79 (s, 1H), 8.39-8.46 (d, J = 9 Hz, 2H), 8.09–8.15 (d, J= 6 Hz, 2H), 7.96–8.03 (d, J= 9Hz, 2H), 7.52–7.69 (m, 3H), 3.90–3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 147.5, 142.6, 140.7, 133.9, 133.8, 133.8, 129.1, 129.0, 128.6 (2C), 125.7 (2C), 120.5 (2C), 53.0; IR (CH_2Cl_2): ν= 3070, 2985, 1737, 1531, 1346, 1236, 1068. $[M+H]^+$: 388.

Methyl 1-(4-methoxyphenyl)-5-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (8) and **Methyl 1-(4-methoxyphenyl)-4-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (8'):** Compounds **8** and **8'** were obtained as a off white solids following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/hexane 2:8).



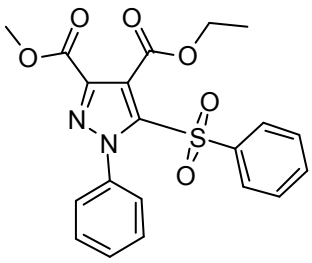
Methyl 1-(4-methoxyphenyl)-5-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (8): m.p.= 121.3 ^oC; ^1H (300 MHz, $CDCl_3$): δ 7.54–7.61 (m, 2H), 7.47–7.53 (m, 2H), 7.34–7.43 (t, J = 7.5 Hz, 2H), 7.12–7.18 (d, J = 9 Hz, 2H), 6.83-6.89 (d, J = 9 Hz, 2H), 3.94–3.97 (s, 3H), 3.86–3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 160.6, 144.0, 142.5, 138.8, 134.0, 130.4, 128.9 (2C), 128.4 (2C) , 128.0 (2C), 114.3, 113.6 (2C), 55.6, 52.5; IR (CCl_4): ν = 2919, 1740, 1550, 1520, 1464, 1330, 1251, 1172, 1069; $[M+H]^+$: 373.



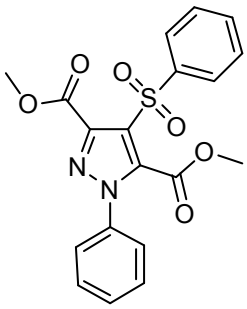
Methyl 1-(4-methoxyphenyl)-4-(phenylsulfonyl)-1H-pyrazole-3-carboxylate (8'): m.p.= 147-148 ^oC; ^1H (300 MHz, $CDCl_3$): δ 8.51–8.55 (s, 1H), 8.07–8.14 (d, J= 6Hz, 2H), 7.51–7.67 (m, 5H), 6.97–7.05 (m, 2H), 3.89–3.90 (s, 3H), 3.86–3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 141.0, 140.8, 133.2, 133.1, 131.7, 128.6 (2C), 128.3, 128.1 (2C), 126.9,

121.9 (2C), 114.7 (2C), 55.7, 52.6; IR (CCl_4): ν = 2919, 1740, 1550, 1520, 1464, 1330, 1251, 1172, 1069; $[M+H]^+$: 373.

4-Ethyl 3-methyl-1-phenyl-5-(phenylsulfonyl)-1H-pyrazole-3,4-dicarboxylate and **5-Ethyl 3-methyl-1-phenyl-4-(phenylsulfonyl)-1H-pyrazole-3,5-dicarboxylate (9** and **9'):** Compound **9/9'** were obtained as a white solids following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/Light Petroleum 3/7). The two regioisomers were further separated by Preperative TLC plates (EtOAc/Light Petroleum 2/3) as yellow oils.

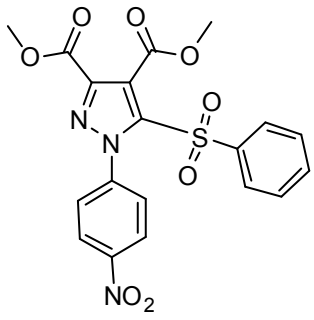


4-Ethyl 3-methyl-1-phenyl-5-(phenylsulfonyl)-1H-pyrazole-3,4-dicarboxylate (9): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.49 (m, 4H), 7.43-7.35 (m, 4H), 7.14 (d, J = 7.8 Hz, 2H), 4.56 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H) ; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.1, 160.4, 141.0, 139.8, 138.8, 137.2, 134.4, 130.6, 129.1 (2CH), 128.7 (2CH), 128.4 (2CH), 127.6 (2CH), 122.7, 62.8, 52.7, 14.0; IR (CCl_4): ν = 2957, 2931, 1745, 1504, 1450, 1331, 1222, 1159 cm^{-1}; $[M+Na]^+$: 437.

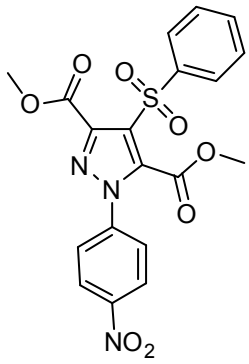


5-Ethyl 3-methyl-1-phenyl-4-(phenylsulfonyl)-1H-pyrazole-3,5-dicarboxylate (9'): ^{1}H NMR (400 MHz, $CDCl_3$,): δ 8.25 (d, J = 8.6 Hz, 2H), 7.67-7.44 (m, 8H), 4.39 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.8, 158.9, 141.6, 140.7, 139.5, 137.8, 133.5, 130.0, 129.4 (2CH), 128.7 (2CH), 128.5 (2CH), 124.7, 124.4 (2CH), 63.7, 52.9, 13.7; IR (CCl_4): ν = 2955, 2928, 1746, 1501, 1447, 1336, 1219, 1163 cm^{-1}; $[M+Na]^+$: 437.

4-Ethyl 3-methyl-1-(4-nitrophenyl)-5-(phenylsulfonyl)-1H-pyrazole-3,4-dicarboxylate and **5-Ethyl 3-methyl-1-(4-nitrophenyl)-4-(phenylsulfonyl)-1H-pyrazole-3,5-dicarboxylate (10** and **10'):** Compound **10/10'** were obtained as white solids following the general procedure for the 1,3-DC and separated by preperative TLC plates (EtOAc/Light Petroleum 2/3).

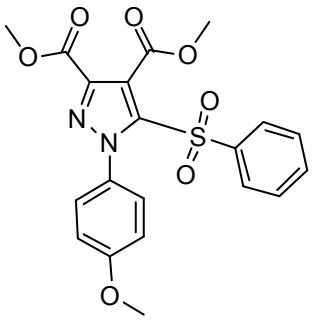


4-Ethyl 3-methyl-1-(4-nitrophenyl)-5-(phenylsulfonyl)-1H-pyrazole-3,4-dicarboxylate (10): m.p. = 195.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 8.9 Hz, 2H), 7.68-7.61 (m, 3H), 7.50-7.40 (m, 4H), 4.54 (q, J = 7.2 Hz, 2H), 3.95 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.5, 159.8, 148.6, 141.9, 141.2, 140.9, 138.6, 134.9, 129.4 (2CH), 128.6 (2CH), 128.1 (2CH), 124.0 (2CH), 123.3, 63.0, 53.0, 14.1; IR ($CHCl_3$): ν = 2955, 2930, 1745, 1615, 1600, 1539, 1505, 1439, 1347, 1223, 1164 cm^{-1}; $[M+Na]^+$: 482.

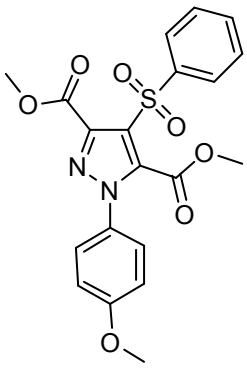


5-Ethyl 3-methyl-1-(4-nitrophenyl)-4-(phenylsulfonyl)-1H-pyrazole-3,5-dicarboxylate (10'): m.p.= 208.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 9.1 Hz, 2H), 8.23 (d, J = 7.7 Hz, 2H), 7.75 (d, J = 9.1 Hz, 2H), 7.68-7.56 (m, 3H), 4.46 (q, J = 7.2 Hz, 2H), 3.95 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.6, 158.8, 148.1, 142.8, 142.4, 140.4, 139.5, 133.8, 128.9 (2CH), 128.6 (2CH), 126.1, 125.0 (2CH), 124.9 (2CH), 64.2, 53.0, 13.7; IR ($CHCl_3$): ν = 2955, 2928, 1747, 1615, 1600, 1537, 1505, 1436, 1345, 1221, 1164 cm^{-1}; $[M+Na]^+$: 482.

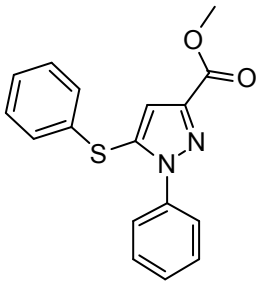
4-Ethyl 3-methyl-1-(4-methoxyphenyl)-5-(phenylsulfonyl)-1H-pyrazole-3,4-dicarboxylate and **5-Ethyl 3-methyl-1-(4-methoxyphenyl)-4-(phenylsulfonyl)-1H-pyrazole-3,5-dicarboxylate (11** and **11'):** Compound **11/11'** were obtained as yellow oils following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/Light Petroleum 3/7). The two regioisomers were further separated by preperative TLC plates (EtOAc/Light Petroleum 2/8).



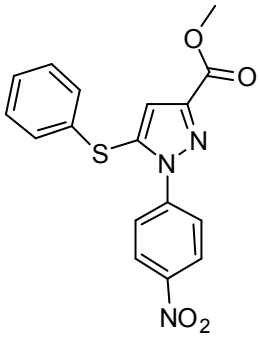
4-Ethyl 3-methyl-1-(4-methoxyphenyl)-5-(phenylsulfonyl)-1H-pyrazole-3,4-dicarboxylate (11): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (t, J = 8.5 Hz, 3H), 7.40 (t, J = 8.0 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.55 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.2, 161.1, 160.4, 146.1, 134.4, 131.9, 129.9, 129.1 (2CH), 128.8 (2CH), 128.6, 128.4 (2CH), 114.7, 113.7 (2CH), 62.7, 55.6, 52.7, 14.1; IR (CCl_4): ν = 2955, 1745, 1510, 1460, 1441, 1340, 1219, 1163 cm^{-1}; $[M+Na]^+$: 467.



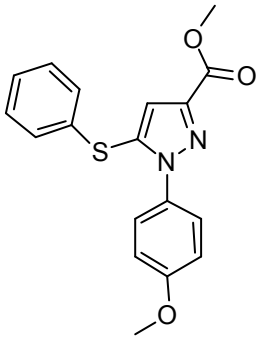
5-Ethyl 3-methyl-1-(4-methoxyphenyl)-4-(phenylsulfonyl)-1H-pyrazole-3,5-dicarboxylate (11'): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 7.8 Hz, 2H), 7.67-7.54 (m, 3H), 7.42 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.85 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 160.6, 159.8, 159.0, 141.2, 140.7, 139.7, 133.5, 130.7, 128.6 (2CH), 128.5 (2CH), 126.0 (2CH), 124.4, 114.4 (2CH), 63.6, 55.6, 52.8, 13.8; IR (CCl_4): ν = 2953, 1743, 1515, 1463, 1444, 1337, 1219, 1163 cm^{-1}; $[M+Na]^+$: 467.



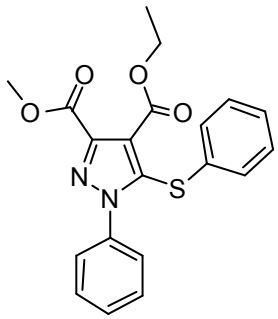
Methyl 1-phenyl-5-(phenylthio)-1H-pyrazole-3-carboxylate (12): Compound **12** was obtained as a light yellow oil following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/hexane 1/9). ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.48-7.60 (m, 5H), 7.30–7.40 (m 4H), 7.22–7.29 (m, 1H), 7.12–7.17 (m, 1H), 4.03–4.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 143.3, 137.9, 134.9, 132.8, 128.9 (2C), 128.7 (2C), 128.2, 128.1 (2C), 126.9, 124.9 (2C), 115.2, 51.5; IR (CCl_4): ν = 2919, 1726,1229,1011; $[M+H]^+$: 311.



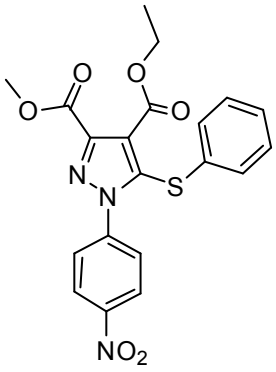
Methyl 1-(4-nitrophenyl)-5-(phenylthio)-1H-pyrazole-3-carboxylate (13): Compound **13** was obtained as a light yellow solid following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/hexane 1/9). m.p.= 89.7-91.1 ^{o}C. ^{1}H (300 MHz, $CDCl_3$): δ 8.36-8.44 (m, 2H), 7.85–7.92 (m, 2H), 7.36–7.42 (m, 3H), 7.24–7.30 (m, 2H), 7.19–7.20 (s, 1H), 4.06–4.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 147.0, 145.0, 143.2, 136.0, 132.5, 129.6 (2C), 129.5 (2C), 127.9, 125.8 (2C), 124.2 (2C), 117.0, 52.5; IR (CCl_4): ν = 2919, 1730,1531, 1345, 1233,1125, 1009, 854 ; $[M+H]^+$: 356.



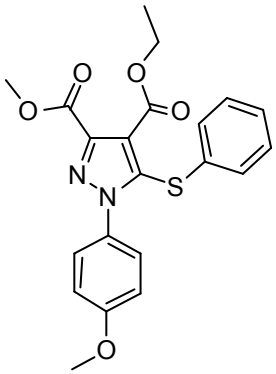
Methyl 1-(4-methoxyphenyl)-5-(phenylthio)-1H-pyrazole-3-carboxylate (14): Compound 14 was obtained as a light yellow solid following the general procedure for the 1,3-DC and separated by column chromatography on silica gel (EtOAc/Light Petroleum 1/9). m.p.= 83.7 ^{o}C; ^{1}H (300 MHz, $CDCl_3$): δ 7.43-7.47 (m, 2H), 7.32–7.40 (m, 3H), 7.23-7.27 (m, 2H), 7.14–7.15 (s, 1H), 6.98–7.04 (m, 2H), 4.04-4.06 (s, 3H), 3.94–3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 160.1, 143.9, 136.0, 133.9, 131.9, 129.8 (2C), 129.6 (2C), 127.7, 127.3 (2C), 115.9, 114.1 (2C), 55.7, 52.3; IR (CCl_4): ν = 2956, 1745, 1726, 1512, 1247, 1225, 1126, 1011; $[M+H]^+$: 341.



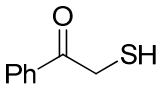
4-Ethyl 3-methyl-1-phenyl-5-(phenylthio)-1H-pyrazole-3,4-dicarboxylate (15): Compound **15** was obtained as a light yellow oil following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/Light Petroleum 1/6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 7.15-7.09 (m, 3H), 7.04-6.99 (m, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.3, 161.5, 142.5, 138.0, 135.7, 133.0, 129.4 (2CH), 129.3, 129.0 (2CH), 128.7 (2CH), 127.3, 126.0 (2CH), 122.3, 61.5, 52.4, 13.8; IR (CCl_4): ν = 3065, 2928, 2843, 1731, 1586, 1498, 1472, 1363, 1285, 1212, 1186 cm^{-1}; $[M+Na]^+$: 405.



4–Ethyl 3-methyl-1-(4-nitrophenyl)-5-(phenylthio)-1H-pyrazole-3,4-dicarboxylate (16): Compound **16** was obtained as a yellow oil following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/Light Petroleum 1/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 9.1 Hz, 2H), 7.64 (d, J = 9.1 Hz, 2H), 7.20-7.16 (m, 3H), 7.06-7.03 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 161.8, 161.1, 147.5, 143.6, 142.7, 136.0, 132.3, 129.4 (2CH), 129.2 (2CH), 127.7 (2CH), 126.6 (2CH), 124.1, 123.5, 61.7, 52.7, 13.9; IR (CCl_4): ν = 3065, 29545, 1734, 1653, 1533, 1347, 1203, 1127, 1079 cm^{-1}; $[M+Na]^+$: 450.

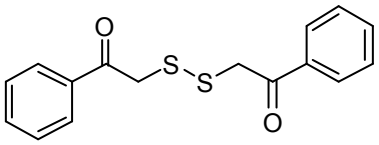


4-ethyl 3-methyl 1-(4-methoxyphenyl)-5-(phenylthio)-1H-pyrazole-3,4-dicarboxylate (17): Compound **14c** was obtained as a white oil following the general procedure for the 1,3-DC and separated by chromatography on silica gel (EtOAc/Light Petroleum 3/7). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.14 (m, 5H), 7.06-7.02 (m, 2H), 6.84 (d, J = 9.0 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 3.80 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.3, 161.5, 160.0, 142.3, 135.7, 133.2, 130.9, 129.3 (2CH), 129.0 (2CH), 127.4 (2CH), 127.2, 122.1, 113.7 (2CH), 61.5, 55.4, 52.4, 13.9; IR (CCl_4): ν = 3063, 2955, 2839, 1734, 1515, 1478, 1365, 1287, 1253, 1212, 1183 cm^{-1}; $[M+Na]^+$: 435.

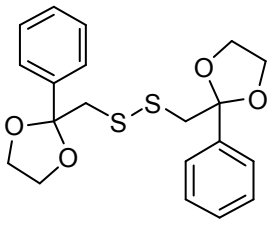


2-mercapto-1-phenylethanone: A solution of thiolacetic acid (5.6 g, 73.6 mmol) in dry pyridine (40 mL) was added to a solution of phenacyl chloride (10 g, 65.0 mmol) and resultant reaction mixture was maintained at 85^{o}C for 1.5-2 h. After cooling to RT, chloroform (200 mL) was added to orange reaction mixture, which was washed with 10% HCl (150 mL), and extracted with 10% NaOH (150 mL). The organic layer was dried over $MgSO_4$, filtered and solvent was evaporated in *vacuo*. The crude product was purified by flash column chromatography using 1-2% EtOAc/hexane as eluent to afford phenacyl thiolacetate (10.2 g, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-8.02 (m, 2H), 7.58-7.64 (tt, J = 6 Hz and 1.5 Hz, 1H), 7.47-7.53 (m, 2H), 4.41 (s, 2H), 2.42 (s, 3H).

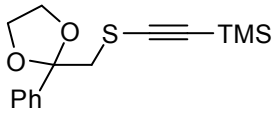
A solution of phenacyl thiolacetate (10.2 g, 52.5 mmol) in ether (60 mL) was stirred vigorously while aq. 2N NaOH solution (58 mL, 120 mmol) was added. This mixture was stirred for 2 h, and then separated. The aqueous layer was cooled to 0 ^{o}C and acidified. This was extracted with DCM (2 x 100 mL). Combined organic layers were dried over $MgSO_4$ and evaporated in *vacuo*. The crude product 2-mercapto-1-phenylethanone was purified by flash column chromatography using 5% EtOAc/hexane as eluent to afford pure product as yellow oil (7.3 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.99 (m, 2H), 7.56-7.63 (m, 1H), 7.45-7.52 (m, 2H), 3.94-3.98 (d, *J*= 8 Hz, 2H), 2.11-2.15 (t, *J* = 8 Hz, 1H).



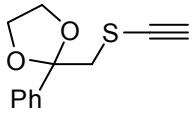
2,2'-disulfanediylbis(1-phenylethanone) (18): To a stirred solution of 2-mercapto-1-phenylethanone (5 g, 32.9 mmol) in EtOAc (30 mL) was added NaI (49.5 mg, 0.33 mmol) and 30% H_2O_2 (3.38 mL, 32.9 mmol) and mixture was stirred at RT for 1 h. Saturated aq. $Na_2S_2O_3$ (100 mL) was then added and resulting mixture was extracted with EtOAc (3 x 50 mL) .The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated in *vacuo*. Crude product was purified with flash column chromatography using 5% EtOAc/Hexane as eluent to get off white solid. (4.65 g, 93% yield).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.99 (d, *J* = 6 Hz, 4H), 7.55-7.63 (tt, *J* = 7.5 and 1.5, 2H), 7.42-7.51 (t, *J* = 7.5, 4H), 4.20 (s, 4H).



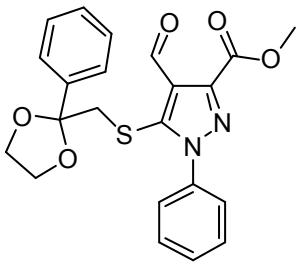
1,2-bis((2-phenyl-1,3-dioxolan-2-yl)methyl)disulfane (19): A solution of 2,2'-disulfanediylbis(1-phenylethanone) **18** (4.65 g, 15.4 mmol), ethylene glycol (5.9 g, 92.4 mmol), triethyl orthoformate (11.58 mL, 61.6 mmol) and PTSA (0.3 g, 1.57 mmol) in toluene was heated to 60^{o}C for 3 h. After completion reaction mixture was cooled and diluted with EtOAc (30 mL) then washed with aq.K_2CO_3 and brine. Organic layer was then dried over anhydrous Mg_2SO_4 and evaporated. The crude solid product was purified by column chromatography using 1-5% EtOAc/hexane to give light yellow solid as product (4.9 g, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.53 (m, 4H), 7.25-7.38 (m, 6H), 4.03-4.18 (m, 4H), 3.77-3.89 (m, 4H), 3.33 (s, 4H).



Trimethyl (((2-phenyl-1,3-dioxolan-2-yl)methylthio)ethynyl)silane (20): Trimethylsilylethyne (0.5 g, 5.1 mmol) was dissolved in dry THF (10 mL) at 0°C. *n*-BuLi solution (1.6 M in *Hexane*, 3.8 mL, 6.1 mmol) was then added dropwise with stirring under argon. After 45 min. a solution of 1,2-bis((2-phenyl-1,3-dioxolan-2-yl)methyl)disulfane (2 g, 6.6 mmol) in THF (20 mL) was introduced at 0°C and stirring was continued for 1-2 h. Then reaction mixture was quenched with sat. NH_4Cl solution (15 mL). The mixture was then extracted with ether (3 x 15 mL) and organic layer was washed with water (2 x 15mL) and brine. The ether layer was then dried dried over anhydrous Mg_2SO_4 and evaporated in *vacuo.* The residue was purified by flash column chromatography using *n*-hexane as eluent to give colourless oil (1.2 g, 80% yield). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.45-7.55 (m, 2H), 7.30-7.44 (m, 3H), 4.02-4.22 (m, 2H), 3.78-3.93 (m, 2H), 3.34 (s, 2H), 0.14 (s, 9H).



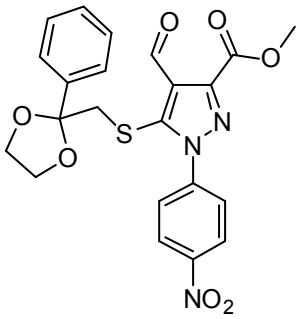
2-(ethynylthiomethyl)-2-phenyl-1,3-dioxolane (21): To a stirred solution of trimethyl(((2-phenyl-1,3-dioxolan-2-yl)methylthio)ethynyl)silane (0.5 g, 1.71 mmol) in THF (10 mL) at 0°C was added dropwise a solution of TBAF-hydrate (0.5 g, 1.91 mmol) dissolved in THF (5 mL). The reaction was then vigorously stirred at 0°C for 1-2 h. After completion, sat. NH_4Cl (15 mL) was added and mixture was extracted with diethyl ether (3 x 10 mL). The combined ether extracts were washed with water (2 x 15 mL) and brine. The ether layer was then dried dried over anhydrous Mg_2SO_4 and evaporated in *vacuo* to give 2-(ethynylthiomethyl)-2-phenyl-1,3-dioxolane as a brown solid (351 mg, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.57 (m, 2H), 7.32-7.44 (m, 3H), 4.17-4.25 (m, 2H), 3.88-3.94 (m, 2H), 3.34 (s, 2H), 2.70 (s, 1H).



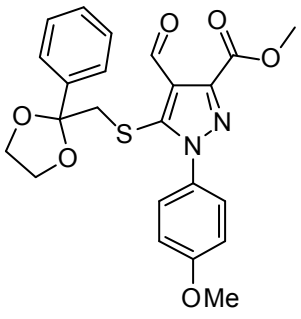
Methyl 4-formyl-1-phenyl-5-((2-phenyl-1,3-dioxolan-2-yl)methylthio)-1H-pyrazole-3-carboxylate (22a): To a solution of 2-(ethynylthiomethyl)-2-phenyl-1,3-dioxolane (0.1 g, 0.43 mmol) in dry THF (5 mL) at ~ 78°C was added dropwise a solution of 1M LiHMDS in THF (0.47 mL, 0.47 mmol) and resulting mixture was stirred for 20 min at same temperature. After 20 min. freshly distilled HMPA (0.37 mL, 2.15 mmol) was added to reaction and reaction was allowed to warm slowly to ~ 35 °C in 2 h. After that reaction was

again cooled to -78 °C and dry DMF (0.06 mL, 0.86 mmol) was added. Reaction was allowed to warm to -35 °C in 2 h and kept at same temperature for further 1.5 h. After that reaction was quenched at -35 °C with sat. NH_4Cl (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined ether extracts were washed with water (2 x 10 mL) and brine. Organic layer was then dried over anhydrous $MgSO_4$ and evaporated in *vacuo.* The crude product was used as it is for further reaction without purification.

Compound **(22a)** was obtained as a light yellow oil following the general procedure for the 1,3-DC and separated by chromatography on silica gel using 10-20% EtOAc/Hexane. Yield: 126 mg, (66% overall yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.66 (m, 5H), 7.16-7.33 (m, 5H), 4.00 (s, 3H), 3.58-3.68 (m, 4H), 3.38 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 162.1, 144.9, 142.5, 140.8, 138.4, 129.7, 129.1, 128.6, 128.4, 126.7, 125.8, 124.8,108.9, 65.4, 52.9, 45.3; $[M+Na]^+$: 447.

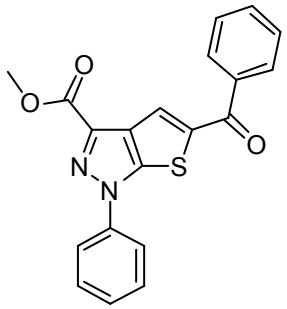


Methyl 4-formyl-1-(4-nitrophenyl)-5-((2-phenyl-1,3-dioxolan-2-yl)methylthio)-1H-pyrazole-3-carboxylate (22b): Compound **(22b)** was obtained as a yellow oil following the general procedure for the 1,3-DC and separated by chromatography on silica gel using 10-20% EtOAc/Hexane. Yield: 60 mg, 42%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.54 (s, 1H), 8.35 – 8.41 (d, J = 9 Hz, 2H), 7.82 – 7.87 (d, J = 9 Hz, 2H), 7.18 – 7.28 (m, 5H), 4.02 – 4.05 (s, 3H), 3.65 – 3.75 (m, 4H), 3.46 – 3.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.0, 161.6, 147.9, 145.6, 143.0, 142.8, 140.3, 128.9, 128.5 (s), 127.4 (s), 125.8 (s), 125.6, 124.4 (s), 108.8, 65.3 (s), 53.1, 45.6; IR (CCl_4): ν= 2956, 1729, 1686, 1598, 1541, 1533, 1347, 1254, 1141, 1011 cm^{-1}; $[M+Na]^+$: 492.

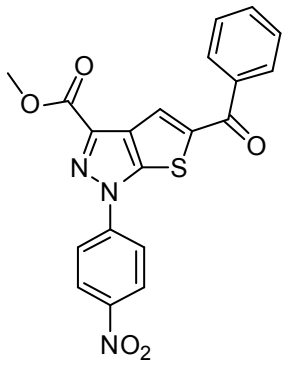


Methyl 4-formyl-1-(4-methoxyphenyl)-5-((2-phenyl-1,3-dioxolan-2-yl)methylthio)-1H-pyrazole-3-carboxylate (22c): Compound **(22c)** was obtained as a yellow oil following the general procedure for the 1,3-DC and separated by chromatography on silica gel using 10-20% EtOAc/Hexane. Yield: 57.7 mg, 43 %;^{1}H NMR (300 MHz, $CDCl_3$): δ 10.53 (s, 1H), 7.44 – 7.48 (d, J = 6 Hz, 2H), 7.21 – 7.25 (m, 5H), 6.97 – 7.02 (d, J = 6 Hz, 2H), 3.99 – 4.02 (s, 3H), 3.87 – 3.89 (s, 3H), 3.62 – 3.72 (m, 4H), 3.36 –

3.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.4, 162.3, 160.5, 144.7, 142.5, 140.8, 131.4, 128.6, 128.4 (s), 127.9 (s), 127.3, 125.8 (s), 114.2 (s), 108.8, 65.4 (s), 55.9, 52.9, 45.1; IR (CCl_4): ν= 3065, 2955, 2892, 1726, 1682, 1612, 1515, 1475, 1253, 1172,1142, 1040 cm^{-1}; $[M+Na]^+$: 477.

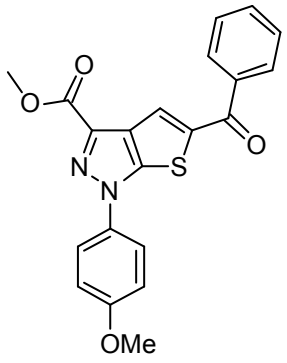


Methyl-5-benzoyl-1-phenyl-1H-thieno[2,3-c]pyrazole-3-carboxylate (23a) : To a stirred solution of **(22a)** (100 mg, 0.23 mmol) in acetone (5mL) was added 30% TFA in water (10 mL). The resulting mixture was then heated at 65°C for overnight. After completion, reaction was cooled to room temperature and then acetone was removed carefully under reduced pressure. The aqueous layer was then extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were washed with water till neutral and then with brine. Organic layer was dried over anhydrous $MgSO_4$ and evaporated in *vacuo* to give crude product. This crude product was then purified by preparative TLC plates to give desired product **(23)** as a off white solid (17 mg, 20% overall yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.97 (m, 4H), 7.87 (s, 1H), 7.62-7.69 (t, *J*=16 Hz, 1H), 7.51-7.62 (quartet, *J*=12 Hz, 4H), 7.37-7.46 (t, *J* = 16 Hz, 1H), 4.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 162.0, 145.6, 144.8, 138.9, 138.0, 137.4, 132.9, 132.1, 130.0, 129.3, 128.9, 127.9, 125.5, 119.3, 52.8. $[M+Na]^+$: 385.



Methyl 5-benzoyl-1-(4-nitrophenyl)-1H-thieno[2,3-c]pyrazole-3-carboxylate (23b): To a stirred solution of **(22b)** (40 mg, 0.08 mmol) in acetone (3mL) was added 50% TFA in water (3 mL). The resulting mixture was then heated at 65 °C for overnight. After completion, reaction was cooled to room temperature and then acetone was removed carefully under reduced pressure. The aqueous layer was then extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water till neutral and then with brine. Organic layer was dried over anhydrous $MgSO_4$ and evaporated in *vacuo* to give crude product. This crude product was then purified by preparative TLC plates to give desired product **(23b)** as a yellow solid (9 mg, 26% yield). m.p.= 223.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 -8-49 (d, *J* = 9 Hz, 2H), 8.09 – 8.13 (d, *J* = 9 Hz, 2H), 7.90 – 7.96 (dt, *J* = 9 and 1.5 Hz, 2H), 7.88 - 7.90 (s, 1H), 7.64 – 7.72 (tt, *J* = 7.5 and 1.5 Hz, 1H),

7.53 – 7.62 (tt, J = 7.5 and 1.5 Hz, 2H), 4.05 – 4.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.3, 161.5, 146.3, 145.9, 145.7, 143.2, 139.5, 137.0, 133.2, 132.8, 129.3 (s), 129.0 (s), 125.9 (s), 125.1, 119.3 (s), 53.1; IR (CCl_4): ν = 2927, 1752, 1727, 1640, 1597, 1532, 1508, 1341, 1285, 1204, 1144, 1085 cm^{-1}; $[M+Na]^+$: 430.



Methyl-5-benzoyl-1-(4-methoxyphenyl)-1H-thieno[2,3-c]pyrazole-3-carboxylate (23c): To a stirred solution of **(22c)** (50 mg, 0.11 mmol) in acetone (3mL) was added 50% TFA in water (3 mL). The resulting mixture was then heated at 65°C for overnight. After completion, reaction was cooled to room temperature and then acetone was removed carefully under reduced pressure. The aqueous layer was then extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water till neutral and then with brine. Organic layer was dried over anhydrous $MgSO_4$ and evaporated in *vacuo* to give crude product. This crude product was then purified by preparative TLC plates to give desired product **(23b)** as a off white solid (10 mg, 23% yield). m.p.= 191.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 -7.93 (d, J = 6 Hz, 2H), 7.84 -7.86 (s, 1H), 7.80 – 7.84 (d, J = 6 Hz, 2H), 7.62 – 7.68 (tt, J = 6 and 1.5 Hz, 1H), 7.52 – 7.58 (t, J = 6 Hz, 2H), 7.05 – 7.09 (d, J = 9 Hz, 2H), 4.00 – 4.03 (s, 3H), 3.87 – 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 162.1, 159.3, 145.4, 144.7, 137.5, 132.8, 132.4, 132.0, 129.3(s), 128.9 (s), 125.6, 123.0, 121.0 (s), 115.1 (s), 55.9, 52.7; IR (CCl_4): ν = 3005, 2954, 2839, 2361, 1748, 1723, 1638, 1543, 1518, 1466, 1392, 1287, 1252, 1204, 1144, 1091 cm^{-1}; $[M+Na]^+$: 415.

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Chapter 3

1,3-Dipolar Cycloaddition of Nitrile Imines with α-β-Unsaturated Cyclic Enones.

3.1 Introduction:

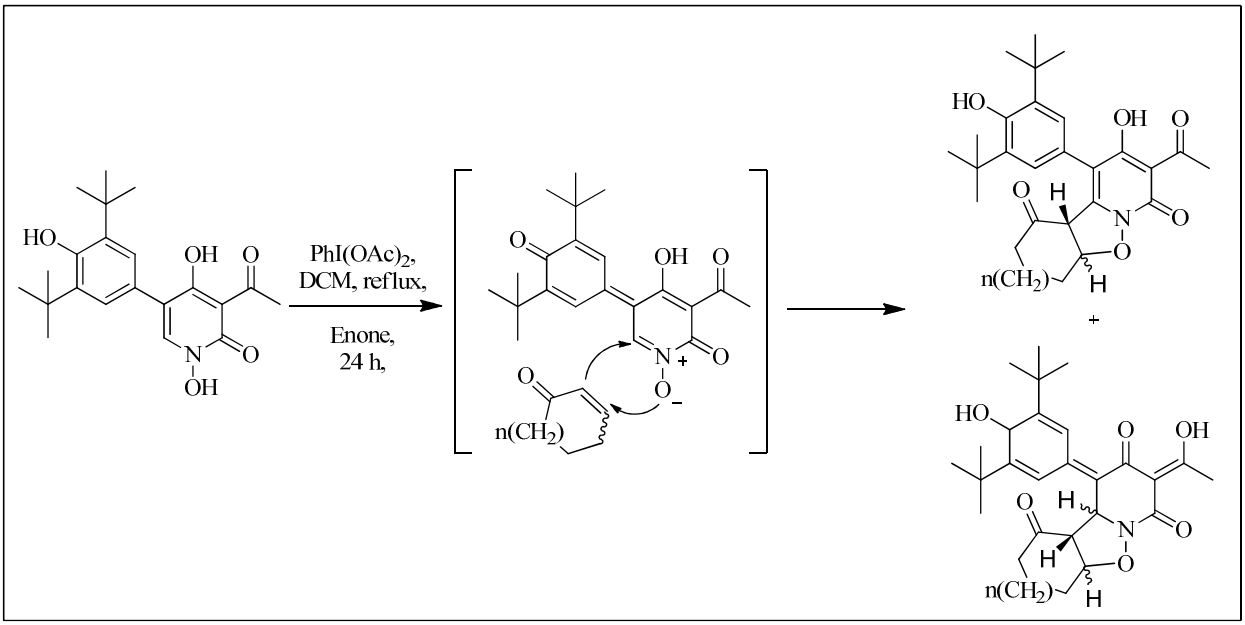
As discussed in earlier chapters, ring-fused pyrazole derivatives displays broad spectrum of biological activities and are synthetically challenging. Much work has been directed towards the design and the synthesis of complex pyrazoles giving particular relevance to the functionalization of the scaffold in different regions and in particular to the synthesis of ring-condensed structures. Indeed, the preparation of pyrazole-fused ring derivatives seems to be very important and challenging from the synthetic point of view. Following our interest in 1,3-DC reaction for direct access to ring-fused pyrazoles, we have developed a protocol through 1,3-DC between cyclic enones and nitrile imines which on further oxidation can lead to the formation of ring-fused pyrazole. This is a direct and simplest route with and advantage of having high regio and stereocontrol in the reaction which is due to the presence of carbonyl group next to the double bond in α- position.

3.2 Recent literature on synthesis and biological importance:

There are few literature references available on cycloaddition reaction of cyclic enones with various 1,3-dipoles. Owing to its importance in synthesis and biological evolution thereafter we decided to investigate a direct and simple route for the synthesis of ring fused pyrazoles starting from various cyclic enones and the nitrile imines.

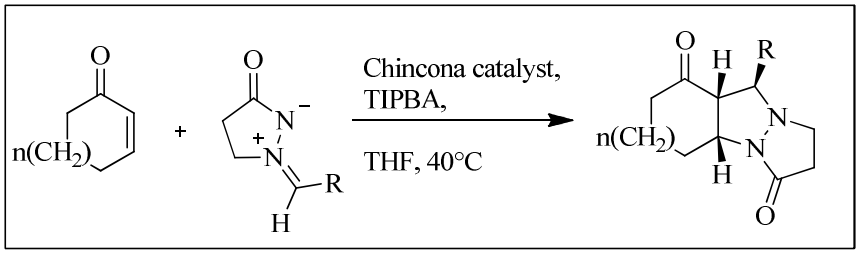
In 2004 Jack Baldwin *et.al.*[1] have reported regio- and stereospecific [3+2] cycloaddition of a nitrone derived from *N*-hydroxy-2-pyridone with medium ring enones which occurred with moderate to good yield. In this they found that these cycloadditions were highly regiocontrolled and the products formed with high retention of alkene geometry (**Sheme 3.1**). They also found that 2-cyclopentenone and 2-cyclohexenone were not reactive in this type of cycloaddition.

Scheme 3.1: Reported work by Jack Baldwin *et.al.*



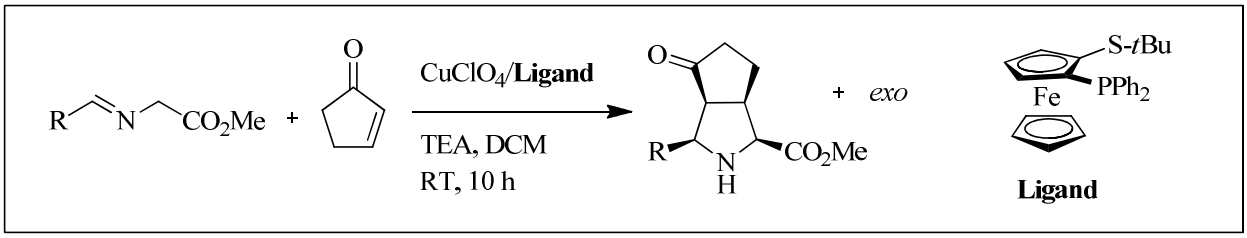
In 2007 Ying-Chun Chen *et.al.*[2] reported a enantioselective 1,3-DC of cyclic enones and a cyclic azomethine imine in the presence of cinchona alkaloids to give a tricyclic product with excellent diastereoselectivity. They have found the additional and synergistic hydrogen bonding interaction of catalyst and 1,3-dipole is essential for enantioselectivity and stereoselectivity in this type of reaction (**Scheme 3.2**).

Scheme 3.2: Enantioselective 1,3-DC of cyclic enones and a cyclic azomethine imine.



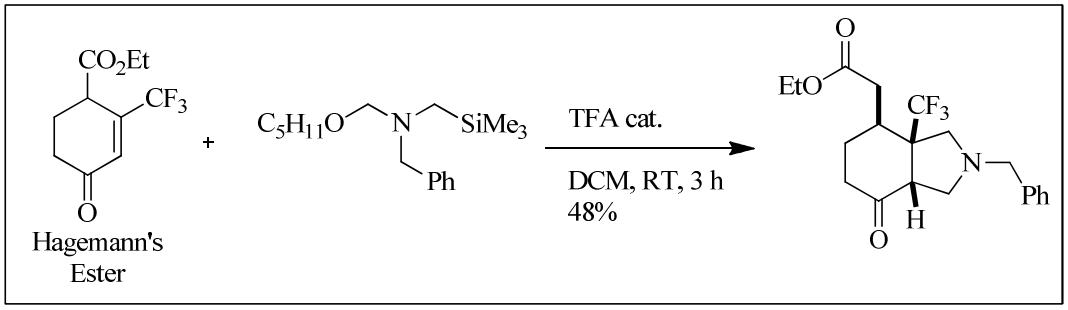
In 2008, Juan Carretero *et.al.*[3] used azomethine ylides in the reaction with cyclic α,β-unsaturated ketones. The reaction of *N*-benzylidene glycine methyl ester with 2-cyclopentenone catalyzed by chiral Cu(I)-Fe-sulphos complexes afforded a bicyclic pyrrolidine with high endo- and enantioselectivity (**Scheme 3.3**), whereas a very low conversion was observed in the reaction with 2-cyclohexenone.

Scheme 3.3: 1,3-DC between azomethine ylide and cyclopentenone.



Furthermore D. Bonnet-Delpon *et.al.*[4] performed the reaction of an azomethine ylide generated from *N*-(trimethylsilylmethyl)-*N*-(pentoxymethyl)-benzylamine with CF_3-substituted 2-cyclohexenone (Hagemann's ester) to give a bicyclic perhydroindolone in moderate yield (**Scheme 3.4**). In this case CF_3 group acts as an activating group in the reaction, which significantly lower the LUMO energy in order to facilitate the cycloaddition reaction.

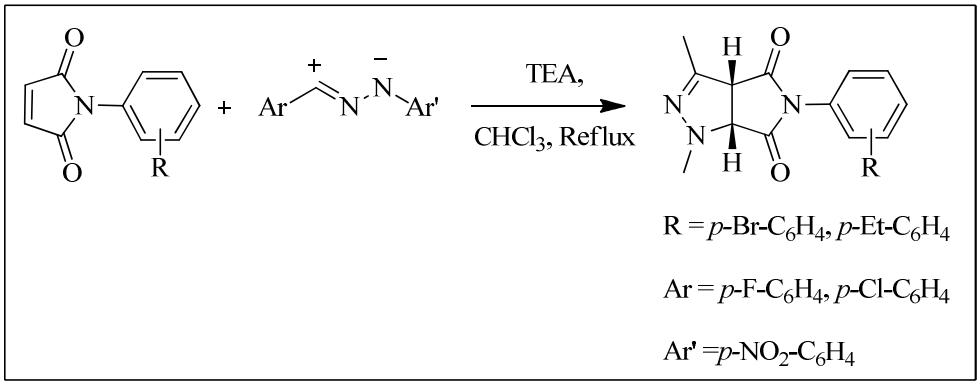
Scheme 3.4: Ring fused perhydroindolone reported by D. Bonnet-Delpon *et.al.*



The reaction of diphenylnitrilimine with cycloalken-2-enone lead to regiomeric mixtures of 4-acyl and 5-acyl derivatives.[5] The synthesis of biologically active pyrrolo[3,4-*c*]pyrazole-4,6-dione derivatives from diarylnitrilimines and *N*-arylmaleimides has been reported by Nada Abunada *et.al.*[6] in 2008 (**Scheme 3.5**). They have tested these compounds for their antimicrobial

activity against gram negative bacteria *Eschercia coli* and gram positive bacteria *Staphylococcus aureus* and antifungal activity against *Asperagillus flavus* and *Candida albicans*.

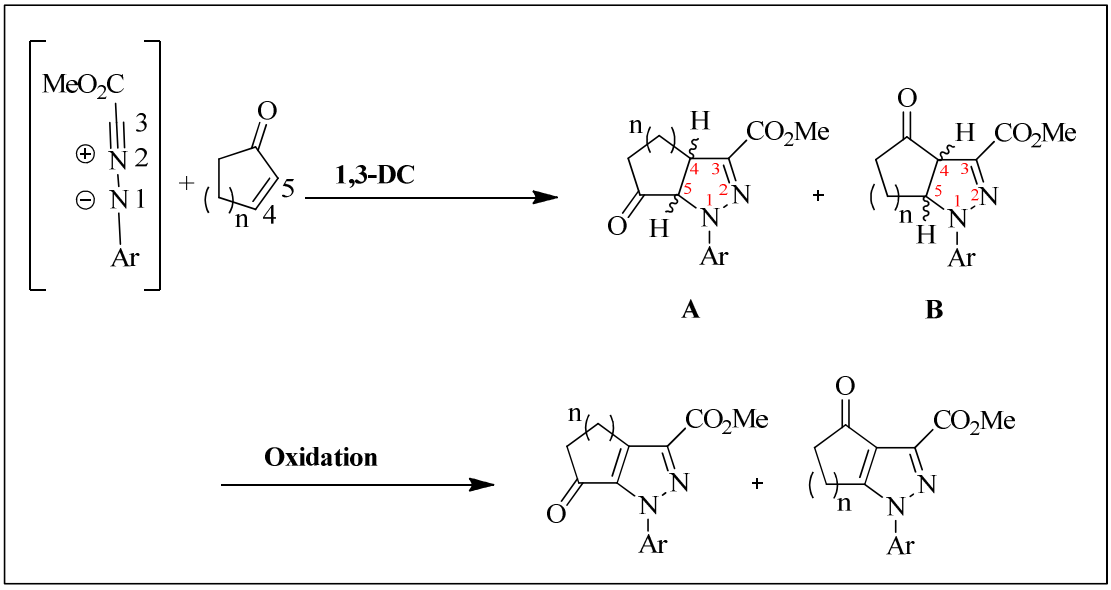
Scheme 3.5: The synthesis of biologically active pyrrolo[3,4-*c*]pyrazole-4,6-dione.



3.3 Present work strategy:

With the aim to extend the scope of nitrile imines cycloaddition for the synthesis of fused heterocycles of pharmaceutical interest, we have tried the 1,3-DC of *C*-carboxymethyl-*N*-aryl-nitrile imines with α,β-unsaturated cyclic enones. The further aromatization of the initially formed fused and strained pyrazolines **A** and **B** *in situ,* would offer a direct method for the synthesis of these bicyclic compounds. (**Figure 3.1**).

Figure 3.1: Generic protocol for obtaining the ring fused pyrazoles.

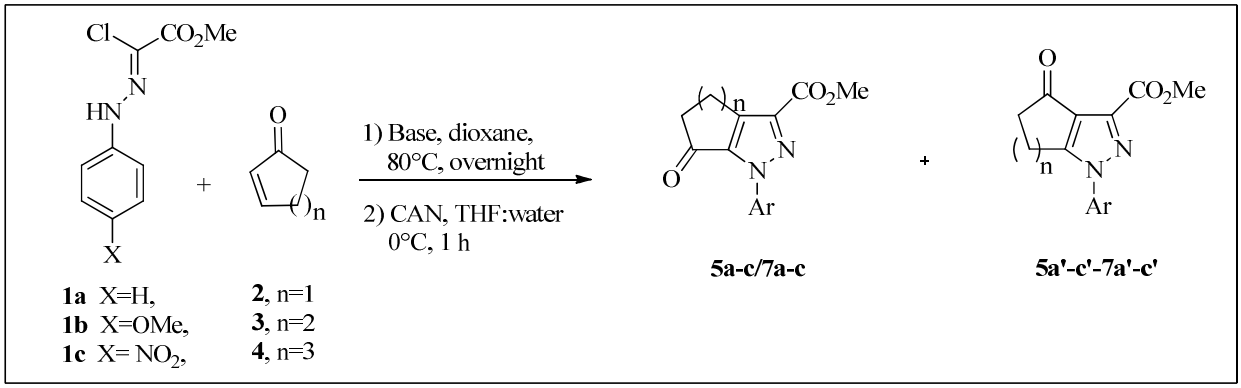


In particular the use of 2-cyclohexenone as dipolarophile would lead directly to the 7-oxo-tetrahydroindazoles, that are scaffolds for the synthesis of more complex 4,5-dihydro-1*H*-pyrazolo [4,3-*h*]quinazolines) which are very promising as kinase inhibitors.[7]

3.4 Result and discussion:

The reaction of 5-, 6-, 7- membered ring enones **2**-**4** with *C*-carboxymethyl-*N*-aryl nitrile imines, generated *in situ* from hydrazonoyl chlorides **1a-c** (**Scheme 3.6**), were carried out in dry dioxane at 80 °C for 18 h, using Ag_2CO_3 or Et_3N (TEA) as bases in order to investigate their influence on the yield and the regioisomeric ratio.

Scheme 3.6: General scheme for the 1,3-dipolar cycloaddition followed by CAN oxidation.



In the literature a different mechanisms for generation of nitrile imines are reported, specifically from hydrazonoyl chlorides in the presence of Ag_2CO_3 or TEA. In the former case the first step is a silver ion promoted dehalogenation to give an intermediate nitrilium- like carbocation,[8] with TEA the deprotonation occurs first followed by the loss of halide ion.[9]

All the reactions were also performed in the presence of catalytic amount of $Sc(OTf)_3$. This Lewis acid was found to affect the regiochemistry of 1,3-DC of nitrile imines with functionalized acetylenes[10] as shown in earlier chapter. In all the reactions GCMS analysis and ^{1}HNMR data revealed a partial aromatization of the initially formed pyrazolines to pyrazoles. For example in the reaction of both cyclohexenone **3** and **1a** with Ag_2CO_3 or TEA about 50% of aromatized product was found at the end of the reaction (entry 4, **Table 3.1**); the reaction of **3** with **1b** gave 90% of aromatization with TEA (entry 5, **Table 3.1**). With cyclic enones **2** and **4** the aromatized product was found in minor amount at the end of the reaction. The aromatization was then completed by treatment of the reaction crude with an oxidizing agent, CAN

(cerium(IV)ammonium nitrate). After purification by column chromatography, the structural assignment of the separated regioisomers **5-7a-c** (5-acyl-pyrazoles) and **5-7a'-c'** (4-acylpyrazoles) was done based on ^{1}HNMR and X-ray analysis. The yield (calculated on separated products) and the regioisomeric ratio of 5-acyl and 4-acyl derivatives in the reaction performed with the two bases and without or with $Sc(OTf)_3$ are reported in **Table 3.1**.

Table 3.1: 1,3-DC of nitrile imines **1a-c** with α,β-Unsaturated Cyclic Enones **2-4**

Sr. No.	Nitrile imine	Cyclic enones	Cycloadducts	Yield (%)		Regioisomeric Ratio		Yield (%)		Regioisomeric Ratio	
				*	**	*	**	***	****	***	****
1	**1a**	**2**	**5a-5a'**	32	14	78:22	76:24	27	43	62:38	70:30
2	**1b**	**2**	**5b-5b'**	49	26	77:23	83:17	43	65	19:81	20:80
3	**1c**	**2**	**5c-5c'**	–	–	–	–				
4	**1a**	**3**	**6a-6a'**	42	19	82:18	99:1	72	60	99:1	99:1
5	**1b**	**3**	**6b-6b'**	65	34	80:20	99:1	88	62	90:10	99:1
6	**1c**	**3**	**6c-6c'**	17	11	60:40	99:1				
7	**1a**	**4**	**7a-7a'**	36	28	99:1	99:1	82	64	86:14	83:17
8	**1b**	**4**	**7b-7b'**	53	38	99:1	99:1	63	69	63:27	79:21
9	**1c**	**4**	**7c-7c'**	–	–	–	–			–	–

[*]: Ag_2CO_3 without $Sc(OTf)_3$ [**] Ag_2CO_3 with $Sc(OTf)_3$ [***]: TEA without $Sc(OTf)_3$ [****] TEA with $Sc(OTf)_3$

Some aspects of this reaction deserve specific comments as outlined from above **Table 3.1**.

1. The reactivity of *C*-carboxymethyl-*N*-*p*-NO_2-phenyl nitrile imine (**1c**) with these alkenes is very low. No cycloadducts are formed with 2-cyclopentenone **2** and 2-cycloheptenone **4** and only 17% yield of a balanced mixture of the adducts **6c-c**' has been obtained with 2-cyclohexenone **3**.
2. The *C*-carboxymethyl-*N*-*p*-OCH_3-phenyl nitrile imine is more reactive than the unsubstituted phenyl analogue and better yields of cycloadducts were obtained by using either Ag_2CO_3 or TEA (compare entries 2, 5, 8 with 1, 4, 7 in **Table3. 1**).
3. As far as the influence of the bases and the size of cyclic enones are concerned, in general better yields were obtained by using TEA as a base and with 6- and 7-membered ring enones. The yields of **6b-b'** and **7a-a'** with TEA were 88% and 82% respectively. The

lower yields obtained with **2** might be the result of an increased tendency for 2-cyclopentenone enolization.

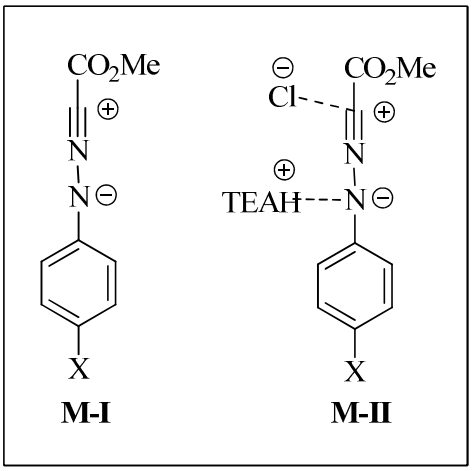
4. 2-Cyclohexenone and 2-cycloheptenone generally exhibit a high degree of regioselectivity with the prevalent formation of 5-acyl derivative: isomeric ratios from 80:20 to 99:1 in the presence of Ag_2CO_3 and from 63:27 to 99:1 with TEA were obtained with nitrile imines originated from **1a** and **1b**.
5. The addition of a catalytic amount of $Sc(OTf)_3$ in the reaction performed by using Ag_2CO_3 increased the ratio 5-acyl / 4-acyl to 99:1 (entries 4-8 **Table 3.1**), but with a drastic reduction of the yields.
6. The influence of $Sc(OTf)_3$ on the isomeric ratio was not so important when TEA was used as a base and the yields of the reaction remained acceptable. A deviant result was found for *p*-MeO-phenyl substituted 1,3-dipole (**1b**) with 2-cyclopentenone in the presence of TEA. In this reaction a ratio 19:81 and 20:80 in favour of the 4-acyl derivative was obtained without and with $Sc(OTf)_3$ respectively.

All these trends can be explained by using a theoretical model (Computational study) by doing some molecular calculations and X-ray studies.

3.4.1 Analysis of the Global and Local Reactivity Indexes at the Ground State of reagents.

The reactivity indexes were evaluated on the dipole and dipolarophile reagents with the aim of describing the experimentally observed regioselectivity. The most interesting effect occurred when an inversion on the regioselectivity was found for *p*-MeO-phenyl substituted 1,3-dipole (**1b**) with 2-cyclopentenone in the presence of TEA. In order to theoretically evaluate the TEA contribution on the regioselectivity, following intermediate conformation that could participate in the reaction was proposed (**Figure 3.2**).

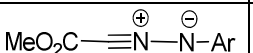
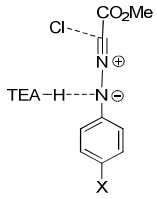
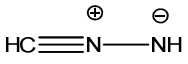
Figure 3.2: Models for the dipoles used in 1,3-dipolar cycloaddition.



In **Table 3.2** the electronic chemical potential μ, chemical hardness η, global electrophilicity index ω, and global nucleophilicity index N are displayed for the dipole and dipolarophile reagents. The electronic chemical potentials, μ, of the dipoles **1a** (-0.1399 a.u.) and **1b** (-0.1293 a.u.) were higher than those for the dipolarophiles, which have values between -0.1409 and -0.1429. Therefore, the charge transference (CT) at these 1,3-DC reactions will take place from the dipole to the dipolarophiles in a normal-electron demand (NED) fashion. On the contrary, in the case of dipole **1c**, the electronic chemical potential (μ = -0.1693a.u.) was lower compared with those found for the dipolarophiles. Therefore, the CT at these 1,3-DC reactions will take place from the dipolarophile to the dipole in an inverse-electron demand (IED) fashion. This change in the reactivity pattern of the *p*-nitro derivative (**1c)** may be responsible for the low reactivity of this system.

In **Table 3.2**, the dipoles are classified as strong electrophiles and the dipolarophiles as moderate electrophiles, according to the absolute scale of electrophilicity based on the ω index reported by Domingo.[11] In this scale the simple nitrilimine (**NI**) is classified as marginal electrophile[11] (ω=0.28 eV), but our calculations at the ground state, using the same level of theory, classify it as moderate electrophile (ω=1.07 eV). The global electrophilicity values predict the charge transfer from dipolarophile to dipole in an IED 1,3-DC reactions, which is in disagreement with the chemical potential μ prediction, but we considered the chemical potential as the index which determines the direction of the electronic flux along the cycloaddition.

Table 3.2: Global properties and global electrophilicity for nitrile imines dipole and cycloalkenones involved in the 1,3-dipolar cycloaddition reactions.

			HOMO	**LUMO**	μ (a.u.)	η (a.u.)	ω (eV)	**N** (a.u)
Dipole		**1a**	-0.2169	-0.0629	-0.1399	0.1541	1.73	0.7831
	**M-I**	**1b**	-0.2018	-0.0568	-0.1293	0.1450	1.57	0.7982
		1c	-0.2394	-0.0991	-0.1693	0.1404	2.78	0.7606
	**M-II**							
		1a	-0.1664	-0.0204	-0.0934	0.1460	0.81	0.8336
		1b	-0.1582	-0.0164	-0.0874	0.1418	0.73	0.8418
		1c	-0.1875	-0.0654	-0.1265	0.1222	1.78	0.8125
		**NI**[a]	-0.2381	-0.0224	-0.1303	0.2158	1.07	0.7618
Dipolarophile								
		2	-0.2376	-0.0443	-0.1409	0.1933	1.40	0.7624
		3	-0.2363	-0.0483	-0.1423	0.1881	1.46	0.7637
		4	-0.2377	-0.0481	-0.1429	0.1897	1.46	0.7623

[a] Values obtained in this work for dipole model of nitril imine used by Domingo.[11]

As we see in **Table 3.2**, the μ and ω indexes properly reflect the substituent effect over the *p*-position at the dipole phenyl group. The electron withdrawing group (EWG), NO_2 increases the global electrophilicty and decreases the chemical potential, and, therefore, increases the electronegativity of the system. On the other hand, the electron donating group (EDG), MeO decreases the global electrophilicty and increases the chemical potential making the system less electronegative. As expected electrophilic (ω) and nucleophilic indexes (N) present inverse reactivity trends (**Table 3.2**). In the case of the dipolarophiles, contrary to what is expected from the bonding strength in the small ring, cyclopentenone **2** is the less reactive in terms of the global electrophilicity compared with the other used dipolarophiles, and all of them are in the range of moderate electrophiles.

Studies of the regioselectivity on Diels Alder (DA) reactions have shown that the analysis of the local electrophilicity, ω_k^+, at the electrophile, together with the analysis of the nucleophilic Fukui functions, f_k^-, at the nucleophile,[12] allows the prediction of the regioselectivity in these competitive cycloadditions. In his work Domingo *et. al.*[13] extended this methodology to describe the regioselectivity of some 1,3-DC. In **Table 3.3** the electrophilic, f_k^+, and nucleophilic, f_k^-, Fukui functions contributions to the respective atomic centres are summarized. The arrows represent the electronic flux directions in the cycloaddition reactions following the chemical potential predictions (μ values in **Table 3.2**).

As is represented in **Figure 3.1**, the interaction between N1 and C3 at the dipole with C5 and C4 at the dipolarophile, respectively, will be favoured to give the experimentally major product, in almost all reactions. As we can see in **Table 3.3** and **Figure 3.2**, the adequate analysis of the corresponding Fukui functions correctly predicts the experimentally observed regioselectivity in these kinds of reactions. As discussed previously, the **1c** dipole will react in an IED fashion. Contrary to **1a** and **1b** dipoles, **1c** will be electrophile in the 1,3 DC reactions. The experimental results showed that this dipole reacts only with cyclohexenone **3** with low yields and with the same regioselectivity as that of other dipoles (**Table 3.1**, entry 6). In **Table 3.2** and **Table 3.3**, we observed that not only the global reactivity changes in **1c** dipole but also the electrophilic local reactivity. Therefore, the final regioselectivity description in terms of these descriptors is in total agreement with the experimental evidence. Additionally, as mentioned in **Table 3.3**, the f_k^+index predicts low reactivity at the **1c** reactive atoms (N1=0.01 and C3=0.09) which accounts for little or null experimental yield when this dipole is used.

Table 3.3: Eletrophilic, f_k^+, and nucleophilic, f_k^-, Fukui functions integrate over the respective atomic centers. The atomic numbers are according to the **Scheme 3.1**.

		Dipole				Dipolarophile		
		1a	**1b**	**1c**	***k***	**2**	**3**	**4**
	f^+	0.12	0.12	0.01		0.24	0.20	0.20
		0.10	0.09	0.06		0.10	0.07	0.04
		0.12	0.11	0.09				
M-I	f^-	0.14	0.12	0.14		0.10	0.10	0.11
		0.00	0.00	0.00		0.05	0.03	0.03
		0.18	0.14	0.17				
M-II	f^-	0.11	0.11	0.14				
		0.00	0.00	0.01				
		0.12	0.12	0.11				

As was previously noted, the activations of dipoles by TEA reverses the regioselectivity when dipole **1b** is used in the reaction. To evaluate the TEA influence in the reactions, the reactivity descriptors were calculated over the intermediate nitrilimine-TEA (M-II in **Scheme 3.2**). The intermediate (M-II) will act as nucleophile against dipolarophiles from chemical potential (μ) prediction (**Table 3.2**). Interestingly, the most nucleophilic intermediate is the corresponding to **1b** dipole (N=0.8418 a.u., **Table 3.2**). Considering that the intermediates (described by model II) have relatively short half-life, it is expected that only the most reactive one is more likely to react with the dipolarophiles, which could justify that only **1b** intermediate reacts. To evaluate the regioselectivity, nucleophilic Fukui functions (f_k^-) were calculated for the intermediates. The total atomic contributions of this function are reported in **Table 3.3**. These values are in disagreement with the experimentally observed regioselectivity. As described in the

computational details, we have evaluated the Fukui functions topologically, obtaining basins (regions) around the maximum of this function with chemical interpretation. **Figure 3.3** shows the Fukui functions basins and their corresponding condensed values. Reactive atom (N1) has two asymmetrical basins, one of them, the less reactive, is protected by the TEA and the other, while the high nucleophilic basin is exposed to possible reactions, i.e. with cyclic enones. Therefore, the analysis of local reactivity in terms of the Fukui function condensed over its own basins, is in total agreement with the observed regioselectivity when **1b** dipole is activated by TEA. Finally, the experimental evidence that the inverse product is only obtained when 2-cyclopentenone is used in the reaction, could be explained by the steric effects of the TEA ethyl substituent when the complex intermediate **M-II** is forming then, only a small dipolarophile will favour the reaction.

Figure 3.3: Local Fukui function prediction of the most probable interaction between **1a** dipole and dipolarophile **2**, using the M-I to the dipole. The same reaction pattern will follows **1b** dipole when react with all the studied dipolarophiles (**Table 3.2** and **Table 3.3**). The Fukui condensed values are placed over its respective basins

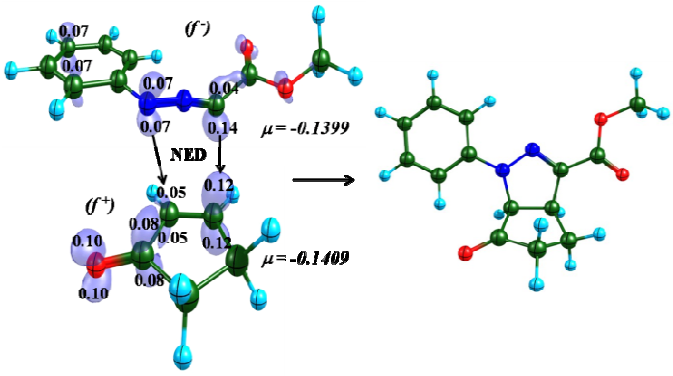
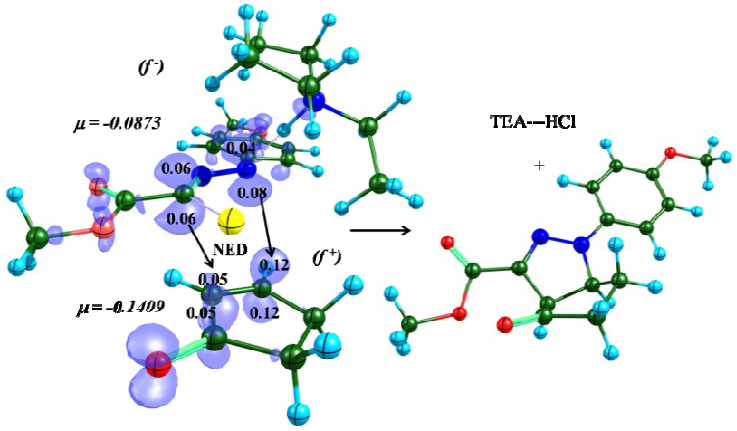


Figure 3.4: Local Fukui function prediction of the most probable interaction between **1b** dipole intermediate (M-II) and dipolarophile **2**, The Fukui condensed values are placed over its respective basins.



3.5 Conclusions:

In conclusion we developed a regiocontrolled one pot synthesis of cycloalkenones fused with pyrazoles through 1,3-dipolar cycloaddition of *C*-carboxymethyl-*N*-aryl nitrilimines and α,β-unsaturated cyclic ketones. The effect of the substituent in para-position of the aryl on the dipole, the size of the dipolarophiles and their effect on yields and regiochemistry have been investigated. These results shows that adequate use of global and local theoretical descriptors of reactivity could give count of the experimental observations in these kind of reactions. To explain the inversion on regioselectivity when **1b** dipole is activated by TEA, we have proposed that an intermediate prior to the dipole formation could be the reactive species, and the use of the topological analysis of the Fukui functions allows a theoretical description of the local reactivity in agreement with the experimental results.

3.6 Experimental Section:

3.6.1 Material and Methods:

^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ or CD_3OD or DMSO-*d6* solutions at 300, 400 and 600 MHz for ^{1}H and 75.46, 100.6 and 150.92 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (δ = 7.26 for ^{1}H and δ = 77.0 for ^{13}C). J values are given in Hz. ^{1}H NMR and ^{13}C NMR spectral assignments were made by DEPT, gCOSY and gHSQC experiments. IR spectra were recorded in solvent as specified. Mass spectra (MS) were obtained with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. High Resolution Mass Spectra (HRMS) were recorded on a micromass LCT spectrometer using electrospray (ES^{+}) ionisation techniques. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Toluene was distilled from sodium. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with bp 40-60°C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70-230 mesh). Preparative thick layer chromatography was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified by distillation as needed.

3.6.2 General Procedure for 1,3 dipolar cycloaddition:

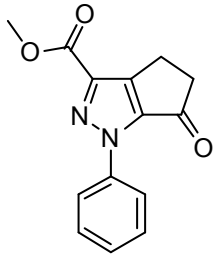
To a stirred solution of alkene (1 eq.) and 1,3-dipole (1 eq.) in freshly distilled dioxane (5 ml) base (2.5 eq.) was added under N_2 atmosphere. Reaction was heated at reflux for overnight. After completion, reaction mixture was allowed to cool and filtered through bed of celite and washed with DCM (5 ml). The filtrate was then evaporated in *vacuo* to give dark red crude oil. The crude product was then dissolved in DCM and washed with water and then with brine. The combined organic layers were dried over $MgSO_4$ and then evaporated in *vacuo* to give the crude product. This crude product was then directly used in next step for oxidation.

3.6.3 General Procedure for CAN oxidation of cycloadducts:

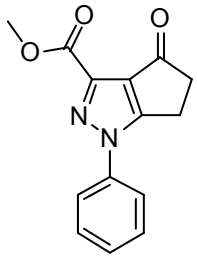
The crude cycloaddition product was suspended in THF:H_2O (1:1, 10 ml) at 0°C. Then cerium (IV) ammonium nitrate (2 eq.) was added slowly in portions. After completion of addition, reaction was allowed to stir at 0°C for further 1-2 h. After completion THF was evaporated at *vacuo* and the aqueous layer was extracted with ethyl acetate (3 x 10 ml). The organic layer was then washed with water (15 ml) and brine. The combined organic layers were dried over $MgSO_4$ and then evaporated in *vacuo*. The crude residue was purified with column chromatography to give the corresponding title compounds.

3.6.4 Analysis of cycloadducts and final compounds:

Methyl 6-oxo-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5a) and **methyl 4-oxo-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5a'):** Compounds **(5a)** and **(5a')** were obtained as solids following the general procedure for 1,3-DC followed by the oxidation with CAN. The two products were separated by column chromatography using 20–30% EtOAc/ Hexane mixture as eluent.

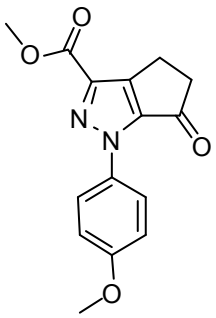


Methyl 6-oxo-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5a): M.P.= 176-177 °C; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 – 3.21 (m, 4H), 3.99 (s, 3H), 7.33 – 7.41 (t, J = 6Hz, 1H), 7.44 – 7.53 (t, J = 6Hz, 2H), 8.08 – 8.14 (d, J = 6Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 19.1, 43.8, 52.5, 121.0 (2C), 128.4, 129.5 (2C), 138.4, 138.8, 144.9, 151.5, 162.0, 188.0; IR (CCl_4): ν = 2955, 2361, 1720, 1592, 1547, 1502, 1254, 1126,1011, 823 cm^{-1}

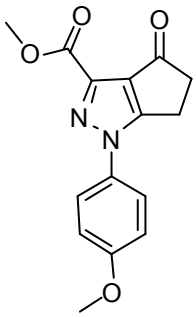


Methyl 4-oxo-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5a'): M.P.= 156-157 °C; Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 – 3.29 (m, 4H), 4.00 (s, 3H), 7.39 – 7.46 (t, J = 7.5Hz, 1H), 7.48 – 7.56 (t, J = 7.5Hz, 2H), 7.69 – 7.74 (d, J = 6Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 22.0, 43.5, 52.9, 121.0 (2C), 128.4, 128.6, 129.9 (2C), 138.4, 138.6, 161.3, 165.3 191.4; IR (CCl_4): ν = 2955, 2361, 1720, 1592, 1547, 1502, 1254, 1126,1011, 823 cm^{-1}

Methyl 1-(4-methoxyphenyl)-6-oxo-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5b) and **methyl 1-(4-methoxyphenyl)-4-oxo-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5b'):** Compounds **(5b)** and **(5b')** were obtained as solids following the general procedure for 1,3-DC followed by the oxidation with CAN. The two products were separated by column chromatography using 20–30% EtOAc/ Hexane mixture as eluent.

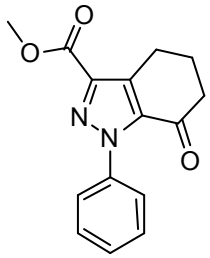


Methyl 1-(4-methoxyphenyl)-6-oxo-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5b): M.P.= 174-175°C; Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ3.06 – 3.21 (m, 4H), 3.84 (s, 3H), 3.97 (s, 3H), 6.92 – 7.02 (d, *J* = 9Hz, 2H), 7.96 – 8.05 (d, *J* = 9Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ19.1, 43.8, 52.6, 55.7, 114.5 (2C), 122.5 (2C), 132.3, 137.9, 144.5, 151.0, 159.8, 162.1, 189.2; IR (CCl_4): ν = 2920, 1677, 1590, 1422, 1323, 1291, 1277, 1181, 1010, 934 cm^{-1}

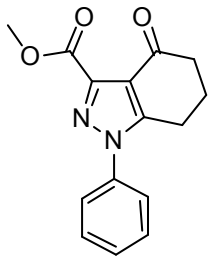


Methyl 1-(4-methoxyphenyl)-4-oxo-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5b'): M.P. = 165-166°C; Brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ3.15 – 3.20 (m, 4H), 3.86 (s, 3H), 4.00 (s, 3H), 6.98 – 7.04 (d, *J* = 9Hz, 2H), 7.57 – 7.63 (d, *J* = 9Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ21.7, 43.5, 52.9, 55.8, 115.0 (2C), 122.8 (2C), 128.0, 131.8, 138.0, 159.7, 161.5, 165.0, 191.4; IR (CCl_4): ν = 2920, 1677, 1590, 1422, 1323, 1291, 1277, 1181, 1010, 934 cm^{-1}.

Methyl 7-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (6a) and **methyl 4-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (6a'):** Compounds **(6a)** and **(6a')** were obtained as solids following the general procedure for 1,3-DC followed by the oxidation with CAN. The two products were separated by column chromatography using 10–30% EtOAc/ Hexane mixture as eluent.

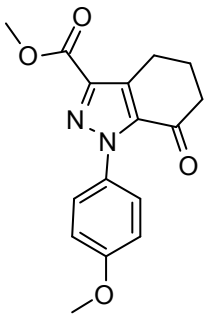


Methyl 7-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (6a): M.P. = 199-200°C; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ2.09 – 2.18 (quintet, *J* = 6Hz, 2H), 2.50 – 2.57 (t, *J* = 6Hz, 2H), 3.05 – 3.11 (t, *J* = 6Hz, 2H), 3.90 (s, 3H), 7.36 – 7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ22.1, 24.3, 39.8, 52.3, 125.8 (2C), 128.8 (2C),129.7, 134.8, 136.4, 139.7, 140.3, 162.7, 188.0; IR (CCl_4): ν = 2954, 1724, 1697, 1548, 1496, 1253, 1202, 1132, 993, 810 cm^{-1}.

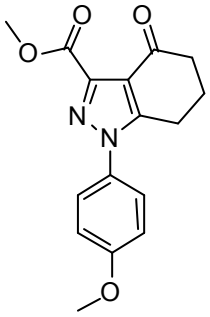


Methyl 4-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (6a'): M.P.= 100-101°C; Brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ2.12 - 2.22 (quintet, *J* = 6Hz, 2H), 2.56 -2.65 (t, *J* = 6Hz, 2H), 2.91 - 2.99 (t, *J* = 6Hz, 2H), 3.98 (s, 3H), 7.45 – 7.54 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ23.4, 23.6, 39.0, 52.9, 119.0, 124.6 (2C), 129.3, 129.7 (2C), 138.2, 142.6, 151.0, 162.3, 191.1; IR (CCl_4): ν = 2954, 1724, 1697, 1548, 1496, 1253, 1202, 1132, 993, 810 cm^{-1}.

Methyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (6b) and **methyl 1-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (6b'):** Compounds **(6b)** and **(6b')** were obtained as solids following the general procedure for 1,3-DC followed by the oxidation with CAN. The two products were separated by column chromatography using 10–30% EtOAc/ Hexane mixture as eluent.

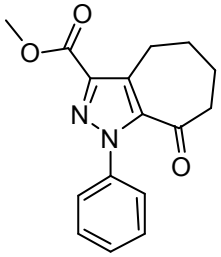


Methyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (6b):M.P. = 144-145°C; Brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ2.14 –2.25 (quintet, *J* = 6Hz, 2H), 2.55 – 2.63 (t, *J* = 6Hz, 2H), 3.10 – 3.17 (t, J = 6Hz, 2H), 3.85 (s, 3H), 3.96 (s, 3H), 6.91 – 6.97 (d, *J* = 6Hz, 2H), 7.38 – 7.43 (d, *J* = 6Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ22.1, 24.3, 39.8, 52.2, 55.7, 113.8 (2C), 127.0 (2C), 132.8, 134.5, 136.3, 139.9, 160.1, 162.6, 188.0; IR (CCl_4): ν = 2954, 1723, 1696, 1548, 1516, 1252, 1203, 1133, 1038, 988 cm^{-1}.

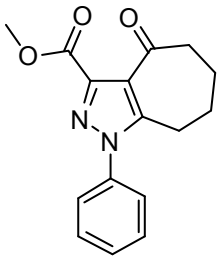


Methyl 1-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (6b'): M.P.= 127-128°C; Brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 – 2.21 (quintet, J = 6Hz, 2H), 2.55 – 2.62 (t, J = 6Hz, 2H), 2.85 – 2.92 (t, J = 6Hz, 2H), 3.86 (s, 3H), 3.97 (s, 3H), 6.97 – 7.02 (d, J = 9Hz, 2H), 7.37 – 7.43 (d, J = 9Hz, 2H); ^{13}C NMR (MHz, $CDCl_3$) δ 23.4 (2C), 39.0, 52.8, 55.8, 114.7 (2C), 118.8, 126.1 (2C), 131.1, 142.2, 151.0, 160.2, 162.3, 191.1; IR (CCl_4): ν = 2954, 1723, 1696, 1548, 1516, 1252, 1203, 1133, 1038, 988 cm^{-1}.

Methyl 8-oxo-1-phenyl-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (7a) and **methyl 4-oxo-1-phenyl-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (7a'):** Compounds **(7a)** and **(7a')** were obtained as solids following the general procedure for 1,3-DC followed by the oxidation with CAN. The two products were separated by column chromatography using 10–30% EtOAc/ Hexane mixture as eluent.

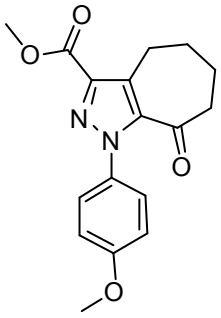


Methyl 8-oxo-1-phenyl-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (7a): M.P.= 205-206°C; White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 – 1.98 (m, 4H), 2.67 – 2.78 (t, J = 6Hz, 2H), 3.19 – 3.29 (t, J = 6Hz, 2H), 3.89 (s, 3H), 7.28 – 7.42 (m, 5 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 22.1, 23.3, 25.7, 43.1, 52.2, 126.0 (2C), 128.9 (2C), 129.0, 131.0, 140.4, 140.6, 140.6, 163.0, 192.7; IR (CCl_4): ν = 2905, 1722, 1686, 1588, 1548, 1320, 1179, 1012 cm^{-1}

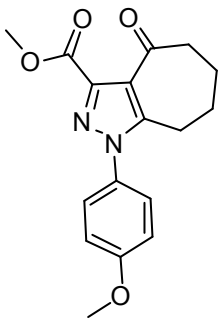


Methyl 4-oxo-1-phenyl-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (7a'): M.P. = 166-167°C; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 – 2.03 (m, 4H), 2.79 – 2.85 (t, J = 6Hz, 2H), 2.88 – 2.94 (t, J = 6Hz, 2H), 3.95 (s, 3H), 7.39 – 7.44 (m, 2H), 7.46 – 7.55 (m, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 1.88 – 2.03 (m, 4H), 2.77 – 2.85 (t, J = 6Hz, 2H), 2.86 – 2.94 (t, J = 6Hz, 2H), 3.93 (s, 3H), 7.37 – 7.44 (m, 2H), 7.45 – 7.55 (m, 3H); IR (CCl_4): ν = 2905, 1722, 1686, 1588, 1548, 1320, 1179, 1012 cm^{-1}

Methyl 1-(4-methoxyphenyl)-8-oxo-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (7b) and **methyl 1-(4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (7b'):** Compounds **(7b)** and **(7b')** were obtained as solids following the general procedure for 1,3-DC followed by the oxidation with CAN. The two products were separated by column chromatography using 10–30% EtOAc/ Hexane mixture as eluent.



Methyl 1-(4-methoxyphenyl)-8-oxo-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (7b):): M.P. = 141-141°C; Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 - 1.99 (m, 4H), 2.69 – 2.78 (t, J = 6Hz, 2H), 3.22 – 3.30 (t, J = 6Hz, 2H), 3.81 (s, 3H), 3.92 (s, 3H), 6.87 – 6.93 (d, J = 9Hz, 2H), 7.21 – 7.27 (d, J = 9Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 22.1, 23.2, 25.6, 43.1, 52.2, 55.7, 114.0 (2C), 127.3 (2C), 130.9, 133.5, 140.3, 140.6, 160.0, 163.0, 192.7; IR (CCl_4): ν = 2952, 1723, 1686, 1516, 1250, 1177, 1126, 833 cm^{-1}.



Methyl 1-(4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (7b'): M.P. = 108-109°C; Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 - 2.01 (m, 4H), 2.77 – 2.89 (m, 4H), 3.86 (s, 3H), 3.94 (s, 3H), 6.96 – 7.01 (d, J = 9 Hz, 2H), 7.29 – 7.34 (d, J = 9 Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 23.1, 25.3, 26.9, 43.7, 52.8, 55.8, 114.7 (2C), 122.7, 127.5 (2C), 131.2, 144.0, 146.7, 160.4, 163.4, 195.9; IR (CCl_4): ν = 2952, 1723, 1686, 1516, 1250, 1177, 1126, 833 cm^{-1}.

3.6.5 Theoretical and computational method:

To rationalize the reactivity of the studied systems we have used some global descriptors of reactivity which have been defined within the context of the density functional theory. The global electrophilicity power measures the capability of a system to acquire electronic charge from the environment, and is calculated by the following simple expression,[14] $\omega = \mu^2/2\eta$, where μ and η are the electronic chemical potential and chemical hardness of the ground state of atoms and molecules, respectively. While μ describes the charge transfer pattern in the system in its ground state geometry, η describes the resistance to this charge transference. Both quantities could be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx \varepsilon_L - \varepsilon_H$, respectively.[15,16] As nucleophilicity (N) descriptor we have used the ionization energy, approached following the Koopmans' theorem[17] and the Kohn-Sham scheme[18] as the negative of the highest occupied molecular orbital (HOMO) energy; but to recover the direct proportionality of the index and nucleophilicity we expressed N as, $N_{(Nu)} = 1 + E_{HOMO}$. A similar expression has been previously successfully used to study the reactivity of captodative ethylenes in polar cycloaddition reactions.[19] As local descriptor of reactivity to evaluate the regioselectivity, we have used the Fukui function; these local quantities were obtained from a topological analysis of the Fukui function, using the same topological tools proposed by Bader almost three decades ago to analyze the gradient field of the electron density to give a definition of an atom in a molecule.[20] For a detailed revision of this methodology see the following references.[21,22]

The molecular geometries have been optimized using the B3LYP density functional method[23] in conjunction with the 6-31G(d) basis set. All electronic structure calculations were done at the same level of theory using the *Gaussian 03* program,[24] the topological analysis of the scalar functions and the calculation of the condensed Fukui function were done with the *DGrid 4.4* set of programs.[25]

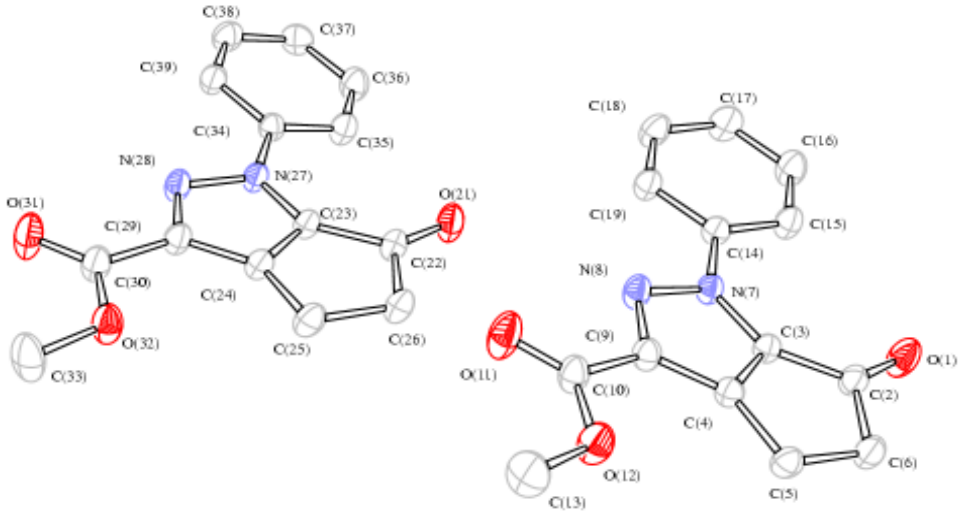
3.7 X-Ray Analyses:

The diffraction experiments were carried out at room temperature (with the exception of compound **6a** for which data were collected at 100 K) and performed on a Bruker ApexII iffractometer equipped with a CCD detector, by using graphite monochromated MoK_α radiation (λ = 0.71073 Å). An empirical absorption correction was applied on all structures by using SADABS.[26] They were solved by using SHELXS-97 and refined by full-matrix least-squares based on F2 using SHELXL-97. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were set geometrically and given fixed isotropic thermal parameters.

3.7.1 X-Ray structure of 5a:

The unit cell of **5a** contains eight molecules, two of which constitute the independent unit. Although being chemically identical, the two are not equivalent from a crystallographic point of view and the analysis of their structural parameters shows that they are, in fact, two conformational isomers, only detectable in the solid state. As a matter of fact, while their bond lengths and angles do not significantly differ, some of the torsion angles considerably diverge (**Table 3.4**). As shown in **Figure 3.5**, if the plane defined by the pyrazolic unit is taken as a reference, in molecule A the 5-member ring is practically coplanar (C(2)-C(3)-N(7)-C(14) = 0.78°) while in molecule B the correspondent torsion angle is 1.74°. More notably, while the phenyl ring in molecule A is slightly rotated counter-clockwise (C(3)-N(7)-C(14)-C(15) = -4.82° and N(8)-N(7)-C(14)-C(19) = -5.44°), in molecule B the rotation is clockwise and much larger (C(23)-N(27)-C(34)-C(35) = 11.80°, N(28)-N(27)-C(34)-C(39) = 11.76°). The same, but to a lesser extent, also happens with the carboxyl groups (N(8)-C(9)-C(10)-O(12) = 178.41 in molecule A, N(28)-C(29)-C(30)-O(32) = 175.66 in molecule B). The solid packing is held only by rather weak intermolecular hydrogen interactions involving the oxygen atoms of the carbonyl groups and the carbon atoms of the 5-member or phenyl rings, with distances varying from 3.055 (O(1)...H-C(13_a)) to 3.611 (O(11)...H-C(13)) Å.

Figure 3.5: Crystal Structure of **5a** with 30% ellipsoid probability (hydrogen atoms have been omitted for clarity).



(A) (B)

Table 3.4: List of the torsion angles for Structure **5a**.

Isomer A atoms				Angles (°)
O(1)	C(2)	C(3)	C(4)	–179.21
O(1)	C(2)	C(3)	N(7)	–0.06
C(6)	C(2)	C(3)	C(4)	–0.08
C(6)	C(2)	C(3)	N(7)	179.06
O(1)	C(2)	C(6)	C(5)	179.61
C(3)	C(2)	C(6)	C(5)	0.43
C(2)	C(3)	C(4)	C(5)	–0.32
C(2)	C(3)	C(4)	C(9)	178.97
N(7)	C(3)	C(4)	C(5)	–179.76
N(7)	C(3)	C(4)	C(9)	–0.47
C(2)	C(3)	N(7)	N(8)	–178.6

Isomer B Atoms				Angles(°)
O(21)	C(22)	C(23)	C(24)	179.23
O(21)	C(22)	C(23)	N(27)	–2.08
C(26)	C(22)	C(23)	C(24)	0.11
C(26)	C(22)	C(23)	N(27)	178.8
O(21)	C(22)	C(26)	C(25)	–179.56
C(23)	C(22)	C(26)	C(25)	–0.4
C(22)	C(23)	C(24)	C(25)	0.23
C(22)	C(23)	C(24)	C(29)	179.78
N(27)	C(23)	C(24)	C(25)	–178.9
N(27)	C(23)	C(24)	C(29)	0.65
C(22)	C(23)	N(27)	N(28)	–179.16

C(2)	C(3)	N(7)	C(14)	0.78
C(4)	C(3)	N(7)	N(8)	0.57
C(4)	C(3)	N(7)	C(14)	179.94
C(3)	C(4)	C(5)	C(6)	0.56
C(9)	C(4)	C(5)	C(6)	–178.34
C(3)	C(4)	C(9)	N(8)	0.23
C(3)	C(4)	C(9)	C(10)	–178.8
C(5)	C(4)	C(9)	N(8)	179.18
C(5)	C(4)	C(9)	C(10)	0.14
C(4)	C(5)	C(6)	C(2)	–0.58
C(3)	N(7)	N(8)	C(9)	–0.41
C(14)	N(7)	N(8)	C(9)	–179.88
C(3)	N(7)	C(14)	C(15)	–4.82
N(8)	N(7)	C(14)	C(15)	174.51
N(8)	N(7)	C(14)	C(19)	–5.44
N(7)	N(8)	C(9)	C(4)	0.11
N(7)	N(8)	C(9)	C(10)	179.26
C(4)	C(9)	C(10)	O(11)	176.6
C(4)	C(9)	C(10)	O(12)	–2.62
N(8)	C(9)	C(10)	O(11)	–2.36
N(8)	C(9)	C(10)	O(12)	178.41
C(9)	C(10)	O(12)	C(13)	178.47
O(11)	C(10)	O(12)	C(13)	–0.76
N(7)	C(14)	C(15)	C(16)	–179.49
C(19)	C(14)	C(15)	C(16)	0.45

C(22)	C(23)	N(27)	C(34)	1.74
C(24)	C(23)	N(27)	N(28)	–0.45
C(24)	C(23)	N(27)	C(34)	–179.55
C(23)	C(24)	C(25	C(26)	–0.46
C(29)	C(24)	C(25)	C(26)	–179.76
C(23)	C(24)	C(29)	N(28)	–0.65
C(23)	C(24)	C(29)	C(30)	177.55
C(25)	C(24)	C(29)	N(28)	178.68
C(25)	C(24)	C(29)	C(30)	–3.11
C(24)	C(25)	C(26)	C(22)	0.51
C(23)	N(27)	N(28)	C(29)	0.04
C(34)	N(27)	N(28)	C(29)	179.26
C(23)	N(27)	C(34)	C(35)	11.8
N(28)	N(27)	C(34)	C(35)	–167.24
N(28)	N(27)	C(34)	C(39)	11.76
N(27)	N(28)	C(29)	C(24)	0.38
N(27)	N(28)	C(29)	C(30)	–178.05
C(24)	C(29)	C(30)	O(31)	178.05
C(24)	C(29)	C(30)	O(32	–2.42
N(28)	C(29)	C(30)	O(31)	–3.87
N(28)	C(29)	C(30)	O(32)	175.66
C(29)	C(30)	O32)	C(33)	–179.64
O31)	C(30)	O32)	C(33)	–0.1
N(27)	C(34)	C(35)	C(36)	177.7
C(39)	C(34)	C(35)	C(36)	–1.28

N(7)	C(14)	C(19)	C(18)	178.64
C(15)	C(14)	C(19)	C(18)	–1.31
C(14)	C(15)	C(16)	C(17)	0.41
C(15)	C(16)	C(17)	C(18)	–0.4
C(16)	C(17)	C(18)	C(19)	–0.47
C(17)	C(18)	C(19)	C(14)	1.32

N(27)	C(34)	C(39)	C(38)	–176.97
C(35)	C(34)	C(39)	C(38)	2.03
C(34)	C(35)	C(36)	C(37)	–0.19
C(35)	C(36)	C(37)	C(38)	0.9
C(36)	C(37)	C(38)	C(39)	–0.14
C(37)	C(38)	C(39)	C(34)	–1.32

3.7.2 X-Ray structure of 5b:

The unit cell of **5b** contains four identical molecules generated by the one constituting the independent unit (**Figure 3.6**). As seen for **5a**, the MeO-substituted phenyl ring is not perfectly coplanar with the pyrazolic fragment but has a torsion angle of -10.55°, probably for steric reasons due to the presence of the methoxy group. The solid packing is held by weak intermolecular hydrogen interactions involving the oxygen atoms of the methoxy and carboxyl groups and the carbon atoms of the methyl groups, whose distances vary from 3.331(1) (O(20)...H-C(21_a)) to 3.543(2) (O(11)...H-C(13_a)) Å, and intermolecular π interactions between the phenyl and the pyrazolic rings. Both drive the solid arrangement in such a way that the molecules are disposed in a parallel fashion, clearly visible along the *b* axis (**Figure 3.7**), and the distance between planes is about 3.41 Å, slightly longer than the one found in the α and β graphite (3.354 Å).

Figure 3.6: Crystal Structure of **5b** with 30% ellipsoid probability (hydrogen atoms have been omitted for clarity).

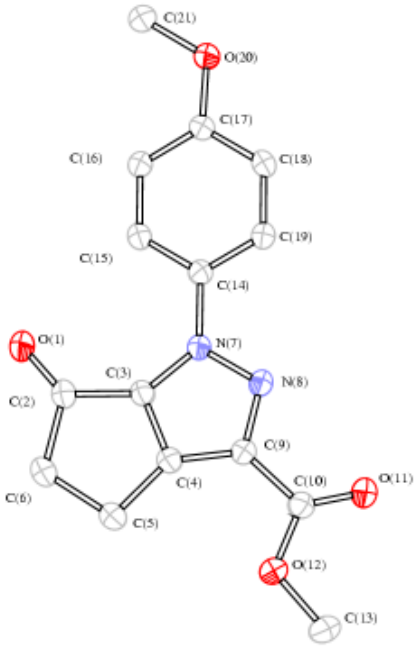
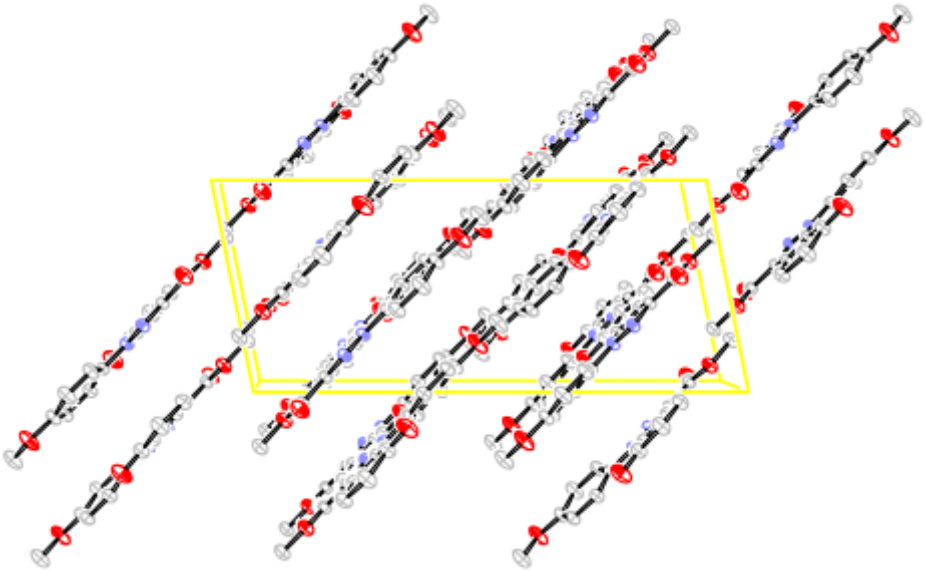


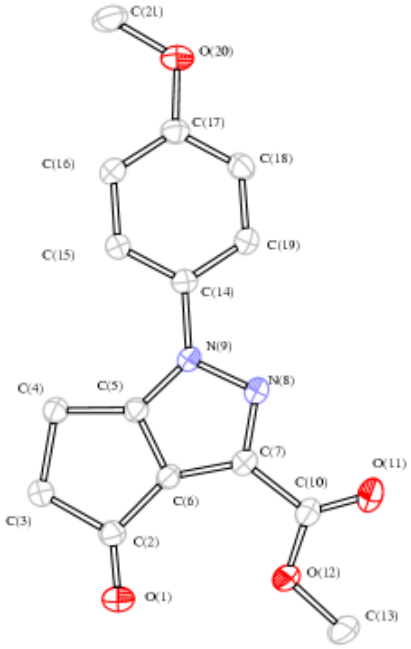
Figure 3.7: Crystal Packing of **5a** viewed along the *b* axis.



3.7.3 X-Ray structure of 5b':

The **5b**' compound crystallizes in a chiral group and the unit cell contains four molecules, while only one constitutes the independent unit. Similarly to the previous structures, there is a torsion angle of 13.18° between the pyrazolic and the phenyl fragments which makes them non co-planar. Again, there are weak intermolecular hydrogen bonds of lengths between 3.161(0) (O(1)...H-C(18_a)) and 3.543 (O(11)...H-C(16_a)) Å within the molecules laying on the same plane, and π interactions between the ones laying on parallel planes (3.55 Å distant), giving the solid state packing the same type of the arrangement than the one seen for **5b'**. Its crystal structure is shown in **Figure 3.8**.

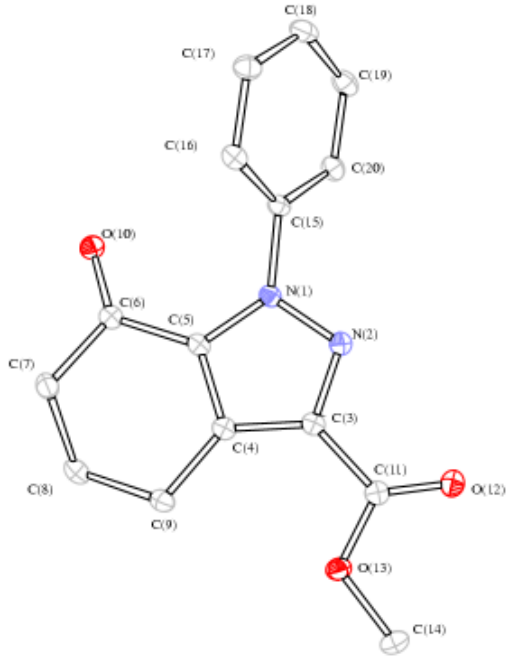
Figure 3.8: Crystal Structure of **5b'** with 30% ellipsoid probability (hydrogen atoms have been omitted for clarity).



3.7.4 X-ray structure of 6a:

The unit cell of **6a** contains four identical molecules generated by the one constituting the independent unit, which is shown in **Figure 3.9**. The phenyl ring is strongly rotated (44.62º) with respect to the plane where the pyrazole ring lies, probably owing to the large steric hindrance of the CO-substituted 6-member ring. As for the hydrogen bonds, the stronger one is 2.976(3) Å long between the oxygen of the carboxyl group, O(10) and the carbon atom of the methyl unit of the neighbour molecule, C(14)_a.

Figure 3.9: Crystal Structure of **6a** with 30% ellipsoid probability (hydrogen atoms have been omitted for clarity).



3.7.5 X-ray structure of 7a:

The unit cell of **7a** contains four molecules and only one in the asymmetric unit, which is shown in **Figure 3.10**. As seen in the structure of **6a**, the phenyl ring is strongly rotated (54.81º) with respect to the plane where the pyrazole ring lies, for the same reason stated above. As for the hydrogen bonds, the stronger one is intermolecular (3.265(1) Å long) and can be found between the oxygen of the CO group on the 7-member ring (O(1)) and one carbon atom of the neighbour phenyl group (C(17_a)).

Figure 3.10: Crystal Structure of **7a** with 30% Ellipsoid probability (hydrogen atoms have been omitted for clarity).

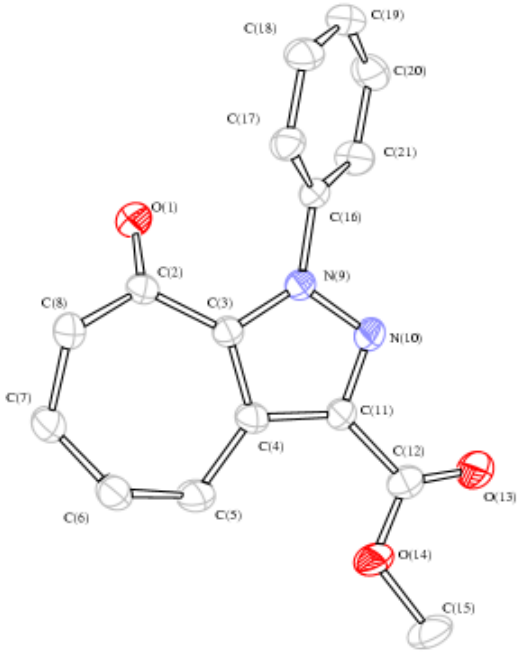


Table 3.5: Summary of Crystal Data for **5a, 5b, 5b', 6a** and **7a**.

Compound	**$C_{15}H_{14}N_2O_3$ (6a)**	**$C_{14}H_{12}N_2O_3$ 5a**	**$C_{15}H_{14}N_2O_4$ 5b**	**$C_{16}H_{16}N_2O_3$ 7a**	**$C_{15}H_{14}N_2O_4$ 5b'**
Fw	270.28	256.26	286.28	284.31	286.28
T, K	97(2)	296(2)	296(2)	296(2)	296(2)
λ, Å	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/c$	$P2_1/n$	$P2_12_12_1$
a, Å	9.9364(18)	10.7675(12)	19.296(3)	9.202(2)	7.0473(5)
b, Å	7.6127(14)	7.1185(8)	8.4029(15)	8.0227(18)	10.7862(8)
c, Å	17.248(3)	31.632(4)	8.4244(15)	18.832(4)	18.1206(14)
α, °	90	90	9	90	90
β, °	95.645(2)	91.4820(10)	101.301(2)	94.205(3)	90
γ, °	90	90	90	90	90
Cell Volume, $Å^3$	1298.3(4)	2423.7(5)	1339.5(4)	1386.5(5)	1377.41(18)
Z	4	8	4	4	4
D_c, g cm^{-3}	1.383	1.405	1.420	1.362	1.381
μ, mm^{-1}	0.098	0.101	0.105	0.095	0.102
F(000)	568	1072	600	600	600
Crystal size, mm	0.25 x 0.20 x 0.15	0.25 x 0.15 x 0.08	0.15 x 0.12 x 0.08	0.25 x 0.20 x 0.10	0.22 x 0.20 x 0.10
θ limits, °	2.37 to 25.00	1.29 to 25.00	1.08 to 25.00	2.17 to 24.98	2.20 to 24.97
Index ranges	$-11 \le h \le 11$, $-9 \le k \le 9$, $-20 \le l \le 20$	$-12 \le h \le 12$, $-8 \le k \le 8$, $-37 \le l \le 37$	$-22 \le h \le 22$, $-9 \le k \le 9$, $-10 \le l \le 10$	$-10 \le h \le 10$, $-9 \le k \le 9$, $-22 \le l \le 22$	$-8 \le h \le 8$, $-12 \le k \le 12$, $-21 \le l \le 21$
Reflections collected	11937	22300	12339	12782	13215

Independent reflections	2287 [R(int) = 0.0225]	4269 [R(int) = 0.0321]	2346 [R(int) = 0.0350]	2438 [R(int) = 0.1668]	2424 [R(int) = 0.0268]
Completeness to θ = 25.00°	99.9 %	99.9 %	100.0 %	99.9 %	100.0 %
Data / restraints / parameters	2287 / 0 / 182	4269 / 0 / 345	2346 / 0 / 193	2438 / 0 / 192	2424 / 0 / 193
Goodness on fit on F^2	1.025	1.029	1.062	0.993	1.065
R_1 ($I > 2\sigma(I)$)	0.0306	0.0393	0.0375	0.0609	0.0303
wR_2 (all data)	0.0777	0.1101	0.1098	0.1606	0.0783
Largest diff. peak and hole, e $Å^{-3}$	0.226 &-0.162	0.167 & -0.187	0.170 & -0.142	0.171 & -0.209	0.151 & -0.131

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Chapter 4

1,3-Dipolar Cycloaddition of Nitrile Imines with α,β-Unsaturated Lactones, Thiolactones and Lactams

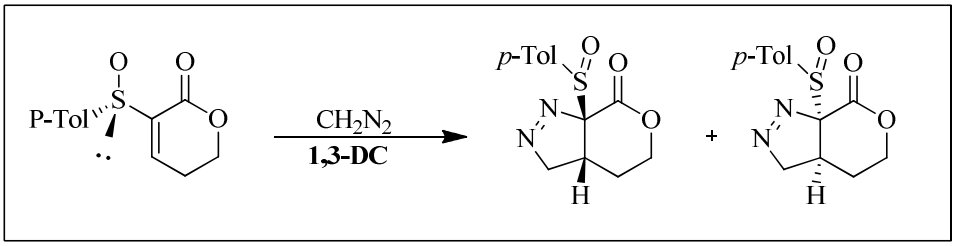
4.1 Introduction and recent literature:

The synthetic utility of the 1,3-dipolar cycloaddition reaction stems from the wide scope and from the relevance of numerous targets achievable by this chemistry[1] especially heterocycles, since many 1,3-dipolar species are readily available and react with a variety of dipolarophiles containing heteroatoms. Pyrazoles fused with lactone, lactum and thiolactone rings are scarcely reported in literature. These bicyclic heterocycles can be important for applications in the agrochemical and pharmaceutical industries. These types of bicyclic systems are still very much challenging by the synthetic point of view.[2]

As shown in earlier chapters, following our interest in the 1,3-DC[3] we have reported the synthesis of pyrazoles using in the 1,3-DC methodology of nitrile imines and functionalized acetylenes,[4a] and we have developed a protocol based on intramolecular cyclization starting from a sulphur-substituted acetylene, to obtain a ring-fused thieno-pyrazole.[4b] Also a regiocontrolled one pot synthesis of cycloalkenones fused with pyrazoles through 1,3-DC of cyclic α,β-unsaturated ketones has been reported by us.[5] On the other hand lactones, lactums and thiolactones have been studied as the dipolarophile. Although few references does exists that uses these compounds as one of the partner element in cycloaddition reaction but 1,3-DC's involving nitrile imine and these dipolarophiles are not that much explored.

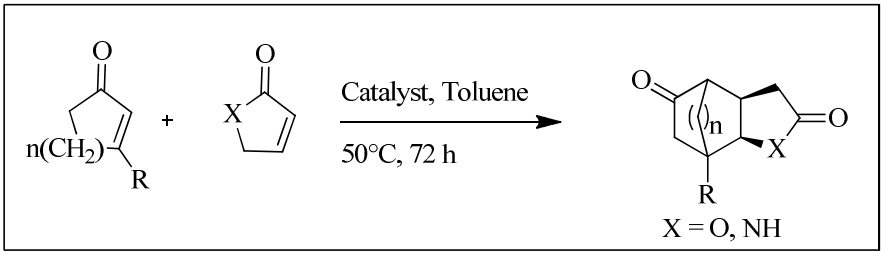
In 2009, G. Ruano *et.al.*[6] have reported a 1,3 dipolar cycloaddition between enatiopure sulfinyllactones as dipolarophile and diazomethane to yield a mixture of isomeric bicyclic pyrazolines (**Scheme 4.1**). The stereochemistry in 1,3-DC was found to be controlled by the presence of lewis acid in the reaction. Use of $Yb(OTf)_3$ was found to be the effective lewis acid in this case. The predominant isomer was found to be with *exo* stereochemistry.

Scheme 4.1: 1,3 DC between sulfinyllactones and diazomethane.



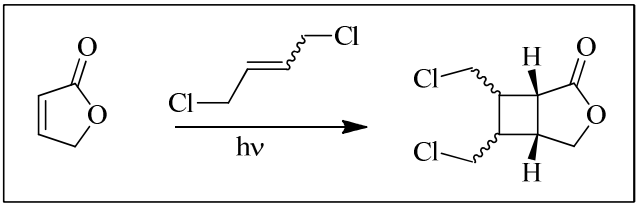
2(5*H*)-Furanone and 1*H*-pyrrol-2(5*H*)-one has attracted considerable attention from organic chemists which is attributed to their frequent occurrence in the biologically active natural and non-natural compounds as a key fragment.[7] Jinzing Ye *et.al.*[8] described use of 2(5*H*)-furanone and 1*H*-pyrrol-2(5*H*)-one for the synthesis of ring fused compounds. In this case they used α,β-unsaturated lactum and α,β-unsaturated lactones and α,β-unsaturated enones in a tandem Michael-Michael type of reaction which was catalysed by using bifuctional thiourea catalyst (**Scheme 4.2**).

Scheme: 4.2: Tandem Michael-Michael reaction involving 2(5*H*)-Furanone and 1*H*-pyrrol-2(5*H*)-one and cyclic α,β-unsaturated enones.



Raman Alibes and Marta Figueredo *et.al.*[9] studied the [2+2] photochemical cycloaddition of 1,4-difunctionalized 2-butenes with 2(5*H*)-furanones. This reaction delivered ring fused 1,2,3,4-tetrasubstituted cyclobutanes (**Scheme 4.3**).

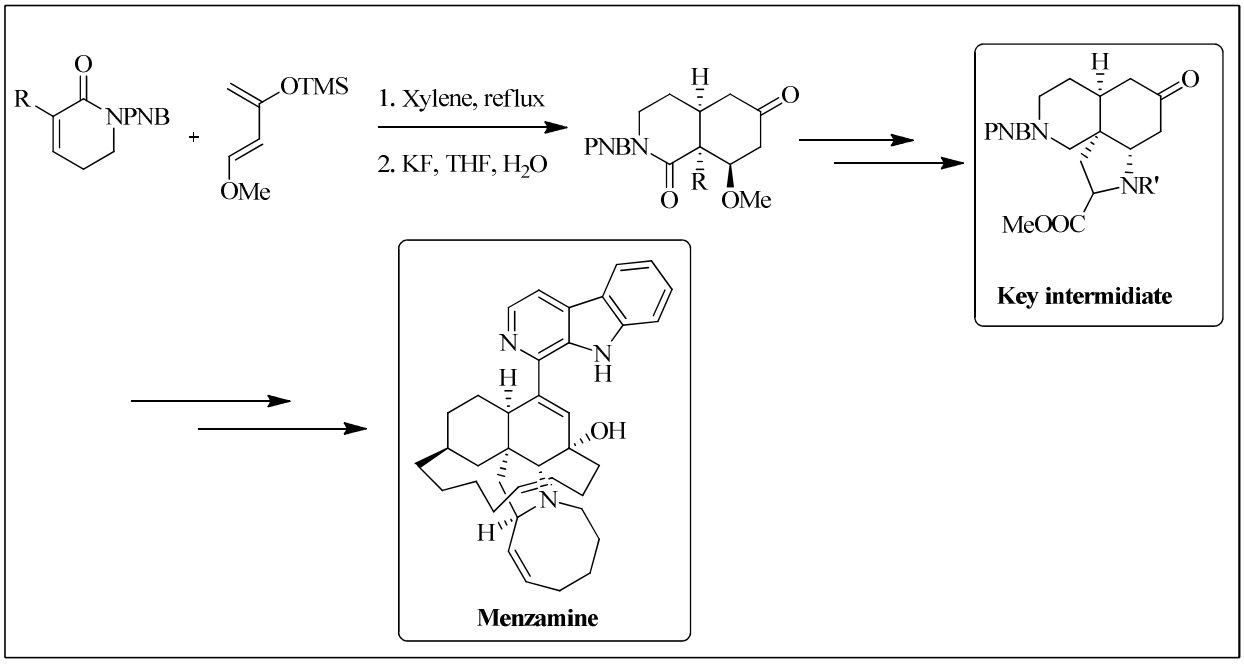
Scheme 4.3: [2+2] photochemical cycloaddition of 1,4-difunctionalized 2-butenes to 2(5*H*)-furanones.



In 1998, Pedro De March *et.al.*[10] used α,β-unsaturated lactones for first time with nitrile ylid. Cycloaddition proceeds effectively with only with electron poor olefins. They discovered methylene-γ-butyrolactone with an exocyclic double bond is the most reactive lactone. In all cases, *exo* adducts were obtained as major or exclusive products.

Another important fragment in biologically active compounds is α,β-unsaturated lactum. Menzamine A, is one of the naturally occurring biologically active compound which acts as a antitumor[11] and antibacterial[12] agent. Tohru Hino *et.al.*[13] in 1992 proposed a synthesis of menzamine A. The core of menzamine A was synthesized by using a Diels-Alder reaction between a α,β-unsaturated lactum and a diene (**Scheme 4.4**).

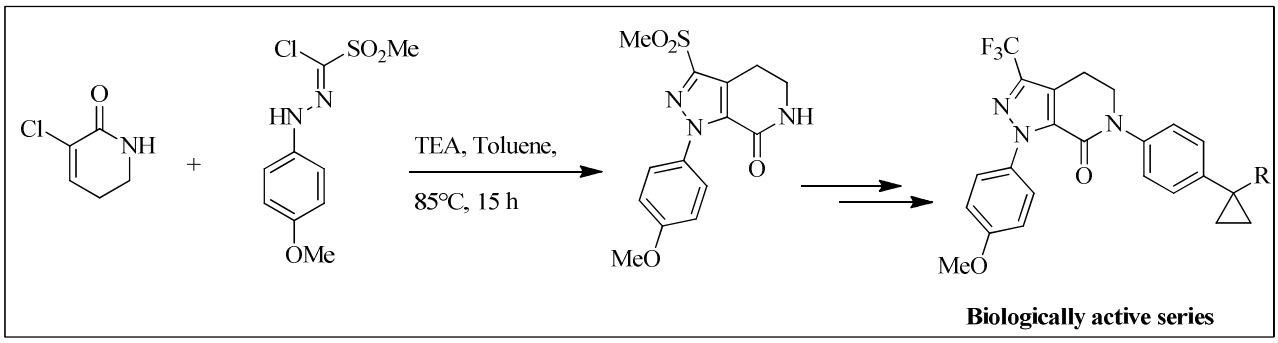
Scheme 4.4: Diels-Alder reaction between a α,β-unsaturated lactum and a diene in synthesis of menzamine A.



Jennifer Qiao *et.al.*[14a] synthesised a library of compounds from 1,3-DC of nitrile imine with 3-chloro-5,6-dihydropyridin-2(1*H*)-one (**Scheme 4.5**). The series of compounds they tested were found FXa inhibitors with high FXa binding affinity (FXa Kof some in the picomolar range) and high anticoagulant activity (PT ECi < 3lM) in vitro. A set of compounds, obtained from optimization of the R group, were orally bioavailable in dog PK studies. Some compounds

obtained in this series were also highly efficacious in the rabbit A-V shunt thrombosis model (E Cd_{50} < 85 nM).

Scheme 4.5: 1,3-DC of nitrile imine with 3-chloro-5,6-dihydropyridin-2(1*H*)-one.

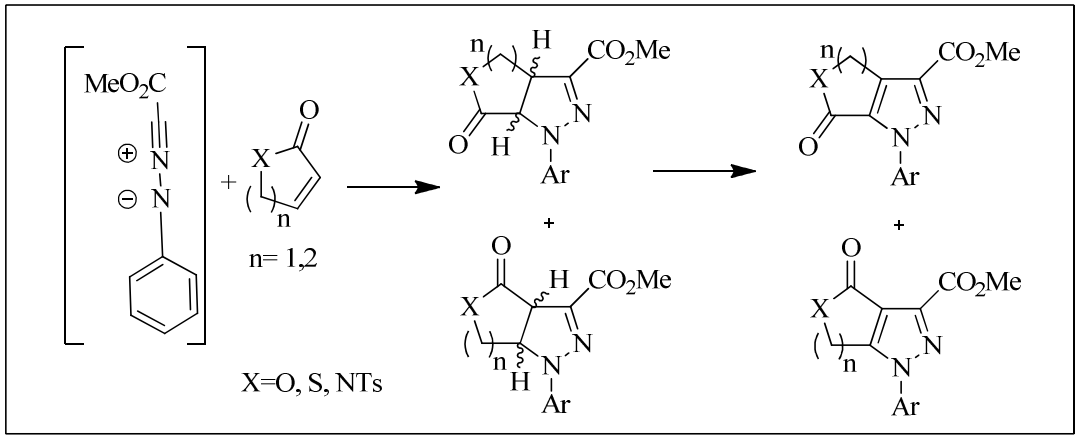


Among the 1,3-DC reactions of α,β-unsaturated lactones an extensive investigation has been dedicated to the reaction with diazoalkanes,[15] chiral and achiral nitrones,[16,15a-b] and nitrile oxides.[17,15a-b] The reaction of α,β unsaturated lactones with nitrile ylids and the cycloaddition of chiral butenolides with azomethine ylids[18,15a] and with azides[19] have also been reported.

No references were found on the 1,3-DC of simple unsaturated lactones and nitrile imines and only the reaction of diphenyl nitrile imine with coumarin or its 3-substituted derivatives has been performed.[20] To our knowledge the use of α,β-unsaturated thiolactones as dipolarophiles in 1,3-DC has not yet been explored. An α,β-unsaturated lactam is a structural motif that is often found in bioactive molecules.[21] The use of such olefins as dipolarophiles in 1,3-DC for the production of bicyclic compounds of biological interest is not very extensive. As a dipole partners the following 1,3-dipoles have been used: diazomethane,[22] nitrones,[23] nitrile oxides[24] and aryl azides.[19] The nitrile imines were the more studied 1,3-dipoles for the synthesis of potent inhibitors of blood coagulation factor Xa (FXa). In this case the starting material was a 6-membered α,β-unsaturated lactam bearing a good leaving group as chlorine or morpholine useful for the aromatization.[14]

The 1,3-DC of nitrile imines with cyclic α,β-unsaturated lactones, thiolactones and lactams could provide, after aromatization of initially formed pyrazoline, a general and direct access to pyrazoles fused with these frameworks (**Figure 4.1**), and indeed the derivatives containing the pyrazole dihydropyridone core are targets of utmost importance in the pharmaceutical industry.[14]

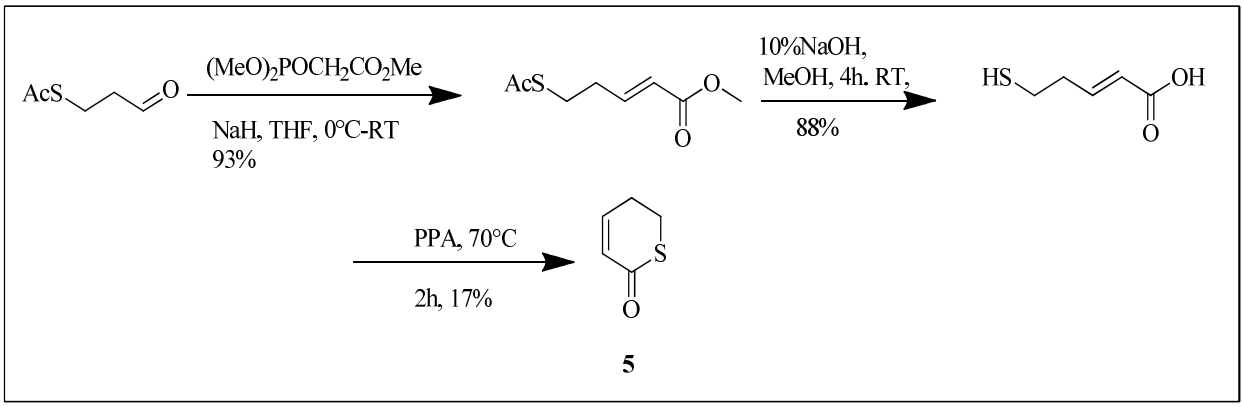
Figure 4.1: General protocol for the synthesis of ring-fused pyrazoles *via* 1,3-DC between nitrile imine and α,β-unsaturated lactones, thiolactones and lactams.



4.2 Result and discussion:

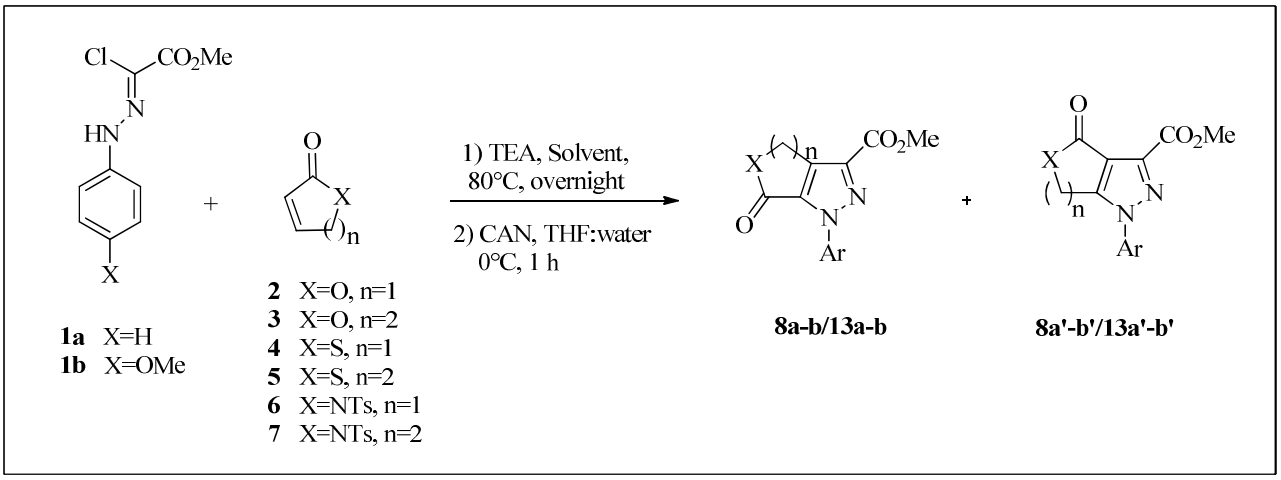
Compounds **2**-**4** were commercially available, while 5,6-dihydro-2*H*-thiopyran-2-one **5**, unknown in the literature, was prepared (**Scheme 4.6**) starting from β-acetylthiopropionaldehyde[25] in a three-steps synthetic protocol. The two *N*-tosyl protected lactams **6** and **7** were prepared according to literature procedures.[26]

Scheme 4.6: Synthesis of 5,6-dihydro-2*H*-thiopyran-2-one **5**.



The **Scheme 4.7** illustrates the synthesis of fused pyrazoles. The reaction of α,β-unsaturated lactones **2**, **3,** thiolactones **4**, **5** and lactams **6**, **7** with *C*-carboxymethyl-*N*-phenyl and *N*-*p*-OCH_3-phenyl nitrile imines,[5] generated "in situ" from hydrazonoyl chlorides **1a**,**b,** was performed in dry dioxane at 80 °C for 18-24 hours, using triethylamine (TEA) for the generation of the nitrile imine. In the case of the lactams toluene was used in order to get better yields.

Scheme 4.7: 1,3-DC of **2-7** with dipoles from **1a-b**.



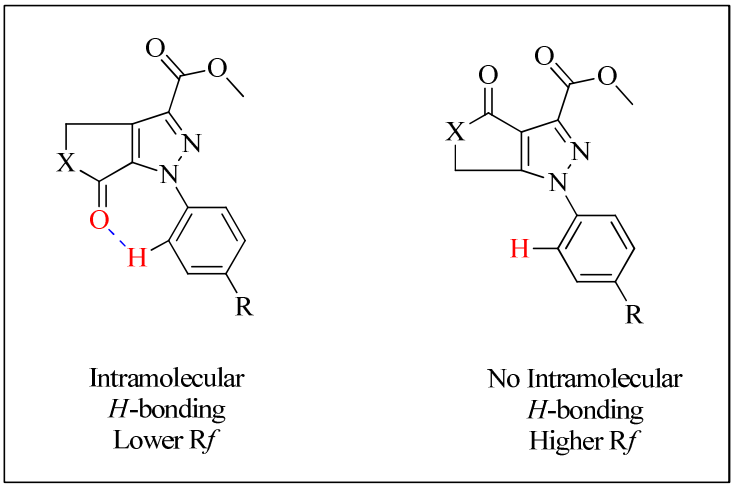
During the cycloaddition a partial aromatization of the initially formed bicyclic pyrazoline was occurred in some cases; the reaction of 6-membered thiolactone **5** with **1a** and **1b** (entries 7 and 8 **Table 4.1**) afforded fully aromatized products in 24 h, while 5-membered thiolactone **4** with both **1a** and **1b** gave about 10 % of aromatization at the end of cycloaddition. The crude cycloadduct was then subjected to oxidation using cerium(IV) ammonium nitrate (CAN) in order to get fully aromatised final pyrazoles. The yield of the products is referred to the sum of the two regioisomers **8a-b/13a-b** (5-acylpyrazoles) and **8a'-b'/-13a'-b'** (4-acylpyrazoles). The lower yields obtained with the dipole from **1a** showed that the *C*-carboxymethyl-*N*-*p*-OCH_3-phenyl nitrile imine is more reactive than the unsubstituted phenyl analogue. Also the size of the ring influenced the yield, lower yields were obtained with 5-membered lactones, thiolactones and lactams and this might result from an increased tendency for the 5-membered ring enolization and from the initially formed strained fused pyrazolines. Same observations were observed in the cycloaddition of these nitrile imines with cyclic α,β-unsaturated ketones.[5]

Table 4.1: 1,3-DC of **2-7** with 1,3-dipoles from **1a-b**.

Entry	1,3-dipole	Dipolarophile	Cycloadducts	Yield %	Ratio **5-acyl/4-acyl**
1	**1a**	**2**	**8a-8a'**	14	70:30
2	**1b**	**2**	**8b-8b'**	31	14:86
3	**1a**	**3**	**9a-9a'**	47	52:48
4	**1b**	**3**	**9b-9b'**	66	87:13
5	**1a**	**4**	**10a-10a'**	21	99:1
6	**1b**	**4**	**10b-10b'**	36	82:18
7	**1a**	**5**	**11a-11a'**	56	81:19
8	**1b**	**5**	**11b-11b'**	77	86:14
9	**1a**	**6**	**12a-12a'**	38	72:28
10	**1b**	**6**	**12b-12b'**	35	61:39
11	**1a**	**7**	**13a-13a'**	74	83:17
12	**1b**	**7**	**13b-13b'**	68	83:17

All the products were characterized by NMR and GCMS analysis. The regioisomeric ratio of 5-acyl/4-acyl pyrazoles was attributed by using ^{1}H-NMR analysis of the purified compounds after complete aromatization. On TLC 5-acyl derivative was found to be non-polar compared to 4-acyl derivative (*Rf* difference was ~ 0.3-0.4). This is probably due to an intramolecular *H*-bonding between the carbonyl of ring and the *H*- of the aromatic ring (**Figure 4.2**).

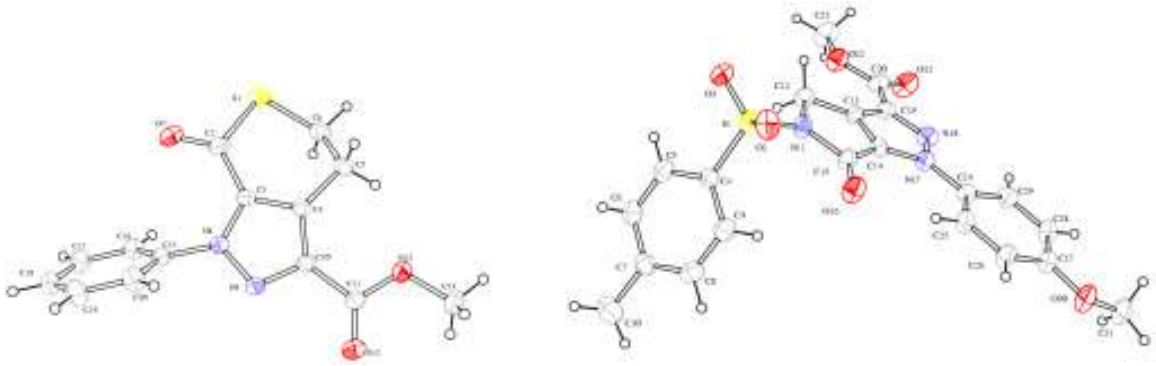
Figure 4.2: Possible mode of intramolecular *H*-bonding in the cycloadducts.



The structural assignment of the regioisomers was based on ^{1}H-NMR signals and X-ray diffraction analyses,[27] for compounds **8b**, **9a'**, **11a**, **12b**, **13a** and **13b.** Other compounds were correlated using the TLC pattern and NMR data. The NMR pattern was a distinguishing factor in aromatic region when the 5-membered lactone, lactum, and thiolactone were involved in the reaction, whereas aliphatic region was the distinguishing factor when 6-memebred lactone, lactum and thiolactones were involved. Incase of reaction between **1b** and **2**, **8b** and **8b'** can be distinguished by NMR signals based on the fact that there might exists an intramolecular H-bonding between the C=O of lactone and H- of aromatic ring, for **8b** the signals are 7.03 and 8.05 ppm and 7.03 and 7.51ppm for **8b'**. Similar observations were found with other compounds whereas for **8a** and **8a'**, the multiplates were observed in aromatic region so they were distinguished by general TLC pattern. Incase of 6-membered lactone, lactum and thiolactone the distinguishing factor was the aliphatic region of the NMR. As to have an intramolecular H-bonding in these compounds, it involves 7-membered ring, which is disfavoured because of the non co-planarity of the 6-membered ring, so we did not observed any significant variations in the aromatic region. In reaction between **1a** and **3**, **9a** has signals 3.31 and 3.98 ppm whereas for **9a'** they are 3.16 and 4.00 ppm for CH_2 next to pyrazole ring respectively on other side aromatic region found to have the same signals. Similar observations were found with other compounds as well.

The X-ray structural data showed that the compounds except **8b** and **12b,** the pyrazole is never coplanar with the the ester function and aryl groups, which is probably due to packing efficiency, and torsion angles going from about -18° to -55° are observed. The compound **8b** is the only one virtually flat, as in **12b** the protective *N*-tosyl group is forced to form a torsion angle of 105.77° with the rest of the molecule, therefore the solid packing of the former is arranged in parallel sheets along the *b* axis (**Figure 4.9**). The crystal structures of two of the major products, **11a** and **12b**, are illustrated in **Figure 4.3** (a) and (b).

Figure 4.3: X-ray structures of the ring-fused pyrazoles **11a** (a) and **12b** (b) (ellipsoids are at 30% probability).

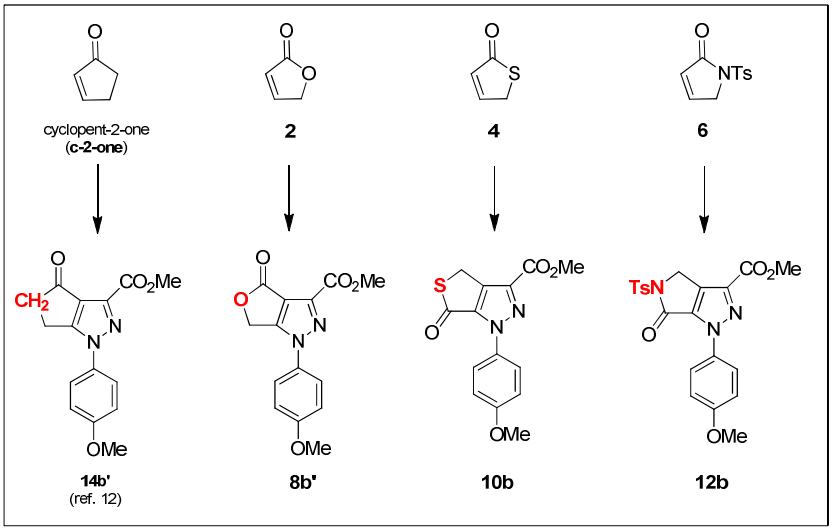


(a) (b)

It appeared from the **Table 4.1** that the nitrile imine from **1a** gave a large prevalence of the 5-acyl derivative with 5-membered lactone **2** (entry 1), thiolactone **4** (entry 5) lactam **6** (entry 9) and with 6-membered thiolactone **5** (entry 7) and lactam **7** (entry 11). A balanced mixture of 5- and 4-acyl derivatives has been obtained with 6-membered lactone **3** (entry 3). The nitrile imine from **1b** gave also the 5-acyl derivative as the major product (entries 4, 6, 8, 10, 12) but a deviant result, with inversion of regiochemistry with the 5-membered lactone **2** (entry 2) was observed. The regioisomeric ratio is influenced by the X moiety and by the nature of the nitrile imine; a very high regioselectivity in favour of the 5-acyl derivative was found when X= S. A ratio up to 99:1 was found with α,β-unsaturated 5- and 6-membered thiolactones. The regioselectivity in favour of the 5-acylderivative, decreased gradually going from lactams (X=N-*p*-Tosyl) to lactones (X= O).

The regiochemical results obtained in the 1,3-DC of 5-membered dipolarophiles with *p*-MeO dipole are summarised in **Figure 4.4**, and are compared with the results obtained previously when cyclopentenone[5] (**c-2-one**) was used as a dinophile.

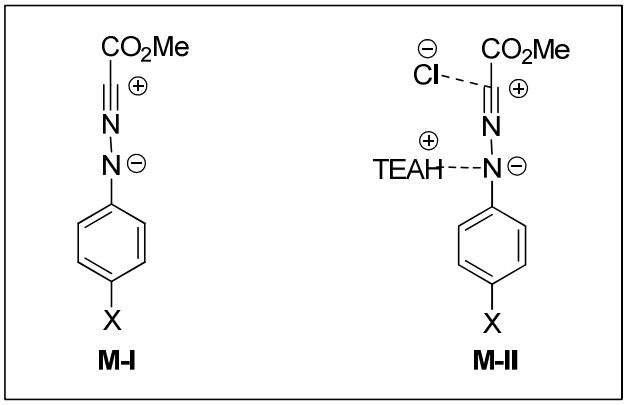
Figure 4.4: Summary of the different regiochemistry obtained from different dipolarophiles **2**, **4**, **6** and **c-2-one** with dipole from **1b**.



4.2.1 Theoretical Analysis:

As was previously discussed there are some intriguing and not obvious regioselectivity trends in the 1,3 DC studied reactions. Inversion of regioselectivity was previously observed in the DC of the nitrile imine from **1b** activated by TEA and 2-cyclopentenone (**c-2-one**). To explain it, an intermediate of the *p*-MeO-dipole with TEA prior to the 1,3-dipole formation as reactive intermediate with **c-2-one** was proposed; this intermediate was labelled as **M-II** to differentiate of the 1,3-dipole which was identified as **M-I** (**Figure 4.5**).[5]

Figure 4.5: Models for the dipoles used in 1,3-dipolar cycloaddition.



4.2.2 Energies analysis:

The 1,3-DC has two reactive channels associated with the formation of 5-acyl and 4-acyl derivatives. In this study we have considered only the first reaction step (see **Figure 4.1**) of the 1,3-dipole (**M-I**) **1b** and the five-member ring dipolarophiles (**c-2-one**, **2**, **4**, **6**) to produce pyrazoline intermediates. Therefore, four transition state (TS) pairs (TS/TS') and the corresponding cycloadducts have been localized and characterized in the potential energy surface (PES).with dipole **1b** (**M-I**) according to **scheme 4.7**. The computed activation barrier energies for **1b** + **c-2-on**e reaction in the formation of 5-acyl (**1b** + **c-2-one**→TS-**14b**) derivatives (7.6 kcal-mol^{-1}) is smaller than the activation barrier involved in the formation of the 4-acyl (**1b** + **2-c-one**→TS-**14b'**) derivative (10.9 kcal-mol^{-1}), as reported in **Table 4.2**. When the dipolarophiles are **2** and **4**, the activation barriers associated to the 5-acyl derivatives are almost 3.3 kcal.mol^{-1} smaller than the barrier energies associated with the 4-acyl derivatives, and when dipolarophile is **6** (X=N-*p*-Tosyl) this barrier difference is lower by 0.9 kcal.mol^{-1}. Therefore, if **1b** (**M-I**) reacts with dipoles: **c-2-one**, **2**, **4** and **6**, the 5-acyl derivative should be the preferred product due to its lower barrier energies compared with the 4-acyl derivatives. In all cases the 5-acyl derivatives are the thermodynamic preferred products (most negative ones) compared with the 4-acyl derivatives. The reactions involving **1a** dipole presents almost the same trend shown by **1b**.

Table 4.2: B3LYP/6-31G(d) total energies (E, in au). Activation, $\Delta E^{\neq}$, and reaction, ΔE^{0}, (in kcal mol^{-1}) energies involved in the formation of the non-aromatized products.

System	*E*
c-2-one	-269.25098
2	-305.18927
4	-628.16360
6	-1104.12910
1a	-607.47671
1b	-721.96653
Ts-14b	-991.29339
Ts-14b’	-991.29217
Ts-8b	-1027.23428
Ts-8b’	-1027.21135
Ts-10a	-1235.71493
Ts-10a’	-1235.71493
Ts-10b	-1350.20369
Ts-10b’	-1350.19100
Ts-12b	-1826.17376
Ts-12b’	-1826.17185

Reactions					$E^{\neq}$	E^{0}
1b + c-2-one	→	Ts-14b	→	14b	7.6	-47.6
		Ts-14b’		14b’	10.9	-46.9
1b + 2	→	Ts-8b	→	8b	6.7	-49.3
		Ts-8b’		8b’	11.4	-34.9
1a + 4	→	Ts-10a	→	10a	7.7	-46.8
		Ts-10a’		10a’	12.2	-38.9
1b + 4	→	Ts-10b	→	10b	7.4	-46.2
		Ts-10b’		10b’	12.0	-38.2
1b + 6	→	Ts-12b	→	12b	6.3	-49.0
		Ts-12b’		12b’	7.2	-47.8

The energies associated with dipole **1a** and dipolarophile **4**, as well as all the other reaction energies, are reported in **Table 4.2**. The PES analysis predicts that in all evaluated reactions the 5-acyl derivatives should be the major regioisomer product if **1b** and **1a** react in their activated dipole form (**M-I**) with all five membered rings dipolarophiles, but as was previously noted, in some specific cases the 4-acyl derivatives are obtained as the major product. Therefore, the **PES** analysis validates our previous hypothesis,[5] that in some cases, intermediate forms previously to the formation of the 1,3 dipole and could be the reactive species against dipolarophiles in the pyrazole synthesis.

4.2.3 Justification of the intermediate form M-II of dipole as reactive species in these 1,3-dipolar cycloadditions:

The analysis of the regioselectivity depending on the experimental conditions allowed us to propose some requirements for the intermediate-dipole **M-II** to be the reactive species in this 1,3-DC: a) the intermediate **M-II** must be sufficiently reactive, clearly the intermediate of the p-MeO-dipole (**1b**) is the most reactive compared to the intermediate of **1a** dipole in terms of the global nucleophilicity index (see **Table 4.3**), b) the dipolarophile should be small due to the sterically protective environment around the reactive region in the intermediate-dipole (surrounding groups and TEA) and because the **M-II** is expected to have a short half-life, then, any reaction involving it, will be kinetically controlled. Summarizing, only dipole-intermediate **1b** (**M-II**) could be the reactive species against small dipolarophiles; among the studied dipolarophiles, when X = -C_2H_4- and –C_3H_6- (with n=1) in our previous work,[5] and X=NTs in the present work, the dipolarophile is too large to react with dipole-intermediate **1b** form, therefore the 1,3-dipole (**M-I**) will be the reactive species. However, when X= O and S (dipolarophiles **2** and **4**), the effect changes as both are comparatively as small as **c-2-one**, which was proposed to react with the dipole-intermediate **M-II** form. The differences in regiochemistry when these two dipolarophiles are used in the reaction will be discussed in the following paragraphs in terms of global and local reactivity descriptors.

4.2.4 Analysis of the global and local reactivity indexes:

To gain more insights about reactivity of these systems we have evaluated some electronic-based reactivity descriptors. In **Table 4.3**, the electronic chemical potential, μ, chemical hardness, η, global electrophilicity index, ω, and global nucleophilicity index, N, are displayed for the dipoles considering both models (**M-I** and **M-II**) and the 5-membered set of dipolarophile reagents. The electronic chemical potential, μ, of the dipoles are higher than those for the dipolarophiles. Therefore, the predicted charge transfer (CT) in these 1,3-DC reactions will take place from the dipole to the dipolarophiles in a normal-electron-demand (NED) fashion.

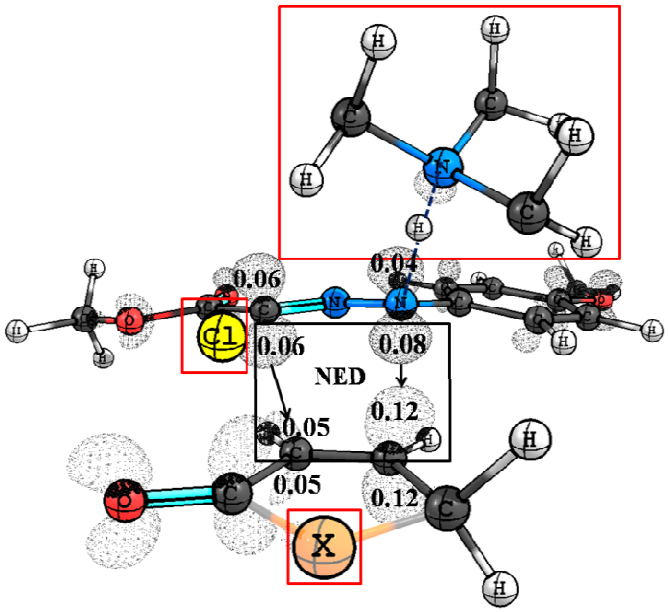
Table 4.3: Global properties and global electrophilicity for nitrile imines dipole and cycloalkenes involved in the 1,3-dipolar cycloaddition reactions.

			HOMO	LUMO	μ (a.u.)	η (a.u.)	ω (eV)	N (a.u.)
Dipole	**M-I**	**1a**	-0.2169	-0.0629	-0.1399	0.1541	1.73	0.7831
		1b	-0.2018	-0.0568	-0.1293	0.1450	1.57	0.7982
	M-II	**1a**	-0.1664	-0.0204	-0.0934	0.1460	0.81	0.8336
		1b	-0.1582	-0.0164	-0.0874	0.1418	0.73	0.8418
Dipolarophile		**c-2-one**	-0.2376	-0.0443	-0.1409	0.1933	1.40	0.7624
		2	-0.2851	-0.0478	-0.1664	0.2373	1.59	0.7149
		4	-0.2539	-0.0575	-0.1557	0.1964	1.68	0.7461
		6	-0.2568	-0.0499	-0.1533	0.2070	1.55	0.7432

The question that remains unanswered is why the regiochemistry with dipolarophile **4** is different from the one with dipolarophile **c-2-one**? **Figure 4.6**, shows the best Fukui predicted interaction between reagents, when **M-II** is proposed in the reactions. The Fukui dipolarophile values correspond to the **c-2-one**; the values for all other dipolarophiles (**2**, **4** and **6**) are almost the same therefore are not reported here. The black square encloses the reactive region, while the regions presenting substituents that could sterically disfavour or favour the reaction are enclosed

in red squares. The terminal methyl groups of TEA have been deleted to allow a better view of the region of interest. The Fukui topological analysis successfully describes the experimentally observed inversion in regioselctivity of dipolarophiles **c-2-one** and **2**, but erroneously predicts that dipolarophile **4** should present the same inversion to give the 4-acyl derivative as the major product.

Figure 4.6: Local Fukui function predictions of the most probable interaction between the dipole from intermediate **1b** (**M-II**) and dipolarophile **c-2-one** (X=CH_2). The same trends are presented when dipoles **2**, **4**, and **6** are used in the simulation. Enclosed in a black square is the reactive region, and enclosed in red squares are the groups that could favour or disfavour the interactions by electrostatic effects.



To explain the different regioselectivity between O and S we propose that repulsive interaction between S and Cl will be higher than repulsive interaction between O and Cl (see **Figure 4.6**) when both reagents interact. This argument is based on the larger size of the S compared to O, therefore the surrounding electronic density in the former will be most polarisable, resulting in a high repulsive interaction with the electronic density around the chloride. This statement needs further analysis and will be addressed using a methodology which allows visualisation of electronic charge density whether excess or deficient around the reactive

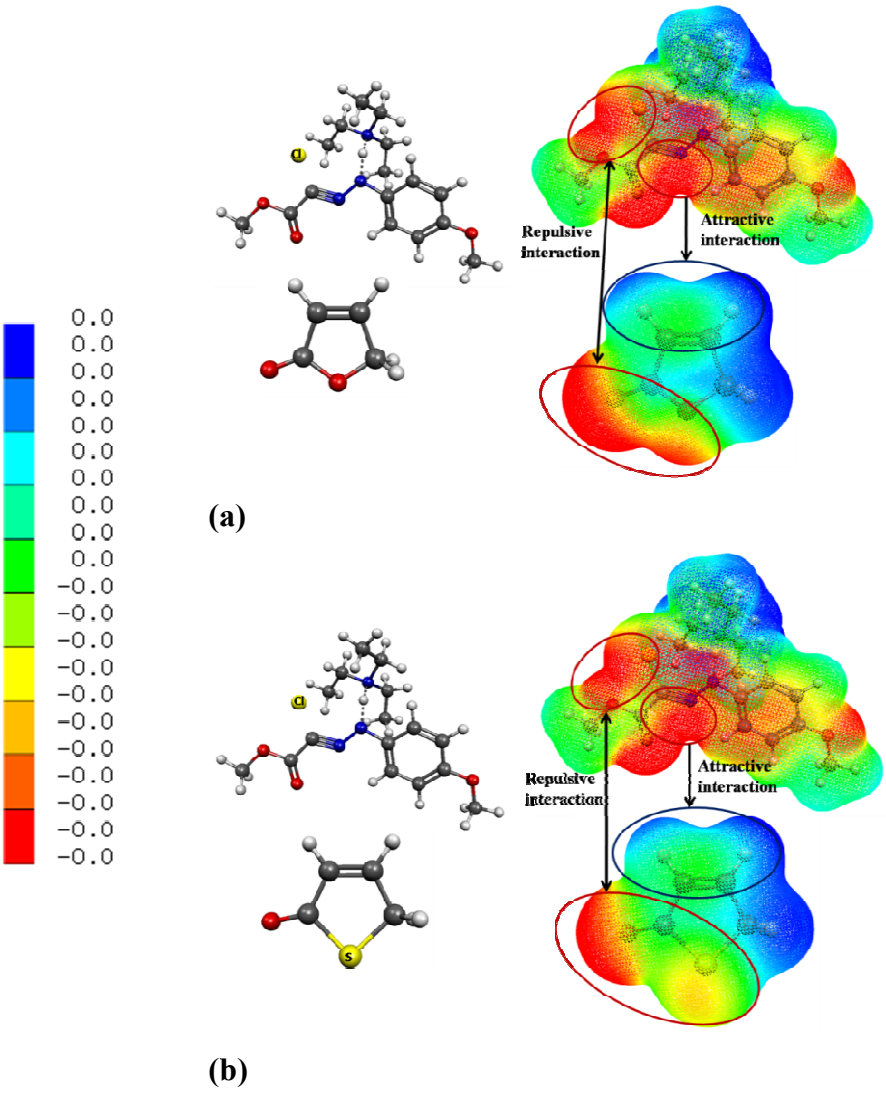
regions of the molecules. This method combines electronic charge density and molecular electrostatic potential values (MEP).

4.2.5 Molecular electrostatic analysis:

To verify the previously proposed hypothesis about repulsive interaction between Cl around the dipole and O or S of the dipolarophiles **2** and **4**, we have calculated the electrostatic potential (V(r)) in both dipolarophiles and in the intermediate reactive species **M-II**, and mapped it over an isodensity surface corresponding to 0.002 a.u. This surface just encloses the Van der Waals volumes of the individual atoms in the molecule and is thus a good representation of the reactive regions around the molecules.[4] The maximum and minimum V(r) values are 0.05 and -0.05 au respectively. Therefore, regions rich in electronic charge density will present negative values of V(r) and regions deficient in electron charge density will present positive values of V(r).

As we can see in **Figure 4.7**, the electronic charge density is concentrated in small regions in dipolarophile **2**, whereas in dipolarophile **4** the electronic charge density is distributed in a large surface around S. The electron charge density in **M-II** remains constant in both the hypothetic reactions and the interaction with dipole **4** (S) should be the most disfavoured by the higher repulsive effects, as indicated in the **Figure 4.6**. This will be the reason why dipole **4** does not react with the intermediate-dipole-**1b** (**M-II**) to produce the 4-acyl derivative, whereas dipole **2** is favoured to react in this form.

Figure 4.7: B3LYP/6-31G(d) 0.002 au isodensity surface with superimposed electrostatic potential for (a) interaction between dipole **1b** (**M-I**) with dipolarophile **2** (X=O) and (b) interaction between dipole **1b** (**M-I**) with dipolarophile **4** (X=S). In both cases, the maximum and minimum potential values are 0.05 and -0,05 au respectively. The molecular structures and the colour scale of the MEP are displayed on the left.



4.2.6: Some insights about isomeric ratio:

Finally, another important experimental result that deserves to be discussed is the higher isomeric ratio in favour of the 5-acylderivative (99:1) for the reaction between **1a** with **4**. From our previously discussed results we summarized some important remarks: only the intermediate dipole **1b** (**M-II**) is enough reactive (higher nucleophilicity) to react against small dipoles, like five-member 2-cyclopentenone and 5-member lactone, which do not present appreciable steric effects; in all other cases the 1,3-dipole **1b** (**M-I**) is expected to be the prevailing reagent, and 1,3-dipole **1a** (**M-I**) should be the unique reagent. Therefore, the product distribution could be analyzed in terms of activation and reaction energies reported in **Table 4.2**. Because the concentration of negative charge around S compared with O is only slightly larger, it is possible to say that in small quantity the intermediate **1b** (**M-II**) could react with **4**, to gives small amounts of the 4-acylderivative, justifying the 82:18 experimental ratio. When the reaction is between **1a** with **4**, the 5-acylderivative is the kinetic and thermodynamic preferred product and there is not the presence of an intermediate reactive form of dipole, which agrees very well with the 99:1 experimental ratios. It is interesting to note that higher regioselectivity of this dipolarophile is in agreement with their higher reactivity (ω=1.68, in **Table 4.3**). Making the same analysis to the reaction with dipolarophile **6**, the 5-acylderivative is only 0.9 and 1.2 kcal/mol kinetically and thermodynamically more favoured than 4-acylderivative, therefore it is reasonable to expect the possible presence of 4-acylderivatives, in agreement with the 72:28 experimental observed ratio.

4.3 Conclusion:

In conclusion, we have developed a simple one-pot two-step method for the regiocontrolled synthesis of pyrazoles fused with lactones, thiolactones and lactams based on the 1,3-DC of nitrile imines with the corresponding α,β-unsaturated dipolarophiles. In all the cases examined the 5-acyl substituted pyrazole is the major product, with ratio 5-acyl/4-acyl up to 99:1, except with the 5-membered α,-β-unsaturated lactone (ratio 5-acyl/4-acyl 14:86). The effect of the substituent in the para-position of the aryl on the dipole, the nature and size of the dipolarophiles and their effect on yields and regiochemistry have been investigated. To rationalize the experimental results a theoretical model including the possibility of reactive intermediate forms of dipole, the size of the dipolarophile and the electrostatic interactions between the reactive forms has been developed.

The reported methodology appears to be suitable for the control of the regiochemistry of this 1,3-DC and could be potentially useful for applications in medicinal chemistry. Computer-assisted syntheses of ring-fused pyrazoles of this type are currently being investigated as multikinase inhibitors.

4.4 Experimental:

4.4.1 Material and Methods:

^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ or CD_3OD or DMSO-d_6 solutions at 300, 400 and 600 MHz for ^{1}H and 75.46, 100.6 and 150.92 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (δ = 7.26 for ^{1}H and δ = 77.0 for 13C). J values are given in Hz. ^{1}H NMR and ^{13}C NMR spectral assignments were made by DEPT, gCOSY and gHSQC experiments. IR spectra were recorded in solvent as specified. Mass spectra (MS) were obtained with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. High Resolution Mass Spectra (HRMS) were recorded on a micromass LCT spectrometer using electrospray (ES^{+}) ionisation techniques. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Toluene was distilled from sodium. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from $_{CaH2}$ prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with bp 40-60°C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70-230 mesh). Preperative TLC was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified as needed.

4.4.2 Synthesis of 5,6-dihydro-2H-thiopyran-2-one (5):

A solution of NaH (0.4 g, 10.0mmol, 60% dispersion in mineral oil) in dry THF (15 ml) was cooled to 0°C and methyl 2-(dimethoxyphosphoryl)acetate (1.68 g, 9.2 mmol) was added slowly for 5 min. The resulting mixture was stirred at 0°C for further 20 min, then S-3-oxopropyl ethanethioate[26] (1 g, 8.4 mmol) dissolved in dry THF was introduced and the resulting mixture was stirred at room temperature for further 1-2 h. After completion, water was added and extracted with EtOAc (3 x 20 ml). Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in *vacuo*. The (E)-methyl 5-(acetylthio)pent-2-enoate (1.4 g, 93 %) was directly used for next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.44-2.54 (qd, J = 7.1

and 1.6 Hz, 2H), 2.98 (t, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 5.87 (dt, *J* = 15.6 and 1.5 Hz, 1H), 6.90 (dt, *J* = 15.6 and 6.54 Hz, 1H).

(E)-methyl 5-(acetylthio)pent-2-enoate (1.4g, 7.4 mmol) was dissolved in MeOH (10 ml) then 10% NaOH (10 ml) was added. The resulting reaction mixture was then stirred at room temperature for overnight. After completion, reaction mixture was extracted with EtOAc (3 x 20 ml). Combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in *vacuo* to give (E)-5-mercaptopent-2-enoic acid (0.87 g, 88 %) as oil which was directly used for next step.

(E)-5-mercaptopent-2-enoic acid (0.8 g, 6.0 mmol) was added to PPA (10 ml) and heated to 70°C for 2 h. After completion, ice water was added to reaction and extracted with DCM (3 x 15 ml). Combined organic layers were washed with water and brine, dried over $MgSO_4$ and evaporated in *vacuo* to give 5,6-dihydro-2H-thiopyran-2-one (**5**) (0.12 g, 17%) as oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57-2.65 (m, 2H), 3.21 (t, *J* = 6.3 Hz, 2H), 6.11 (dt, *J* = 10.8, 1.8 Hz, 1H), 6.91 (dt, *J* = 10.9, 4.8 Hz, 1H).

4.4.3 General Procedure for 1,3 dipolar cycloaddition:

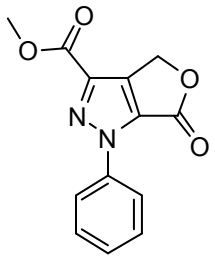
To a stirred solution of dipolarophiles **2-7** (1 eq) and **1a** or **1b** (1 eq. for **2-5** and 2 eq. for **6** and **7**) in freshly distilled dioxane (5 mL for **2-5**) or toluene (5 mL for **6** and **7**) under argon atmosphere was added triethylamine (2.5 eq. for **2-5** and 5 eq. for **6** and **7**). Reaction was heated at 80 °C overnight. After completion, reaction mixture was allowed to cool and filtered through bed of celite and washed with DCM (5 mL). The filtrate was then evaporated in *vacuo* to give dark red crude oil. The crude product was directly used in the oxidation stage.

4.4.4 General Procedure for CAN oxidation of cycloadducts:

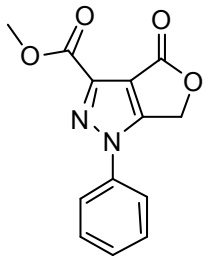
The crude cycloaddition product was suspended in THF:H_2O (6:8, 10 ml) at 0°C. Then cerium (IV) ammonium nitrate (CAN) (2.5 eq.) was added slowly in portions. After completion of addition, reaction was allowed to stirr at 0°C for further 1-2 h. After completion, THF was evaporated at *vacuo* and the aqueous layer was extracted with ethyl acetate (3 x 10 ml). The organic layer was then washed with water (15 ml) and brine. The combined organic layers were dried over $MgSO_4$ and then evaporated in *vacuo*. The crude residue was purified with column chromatography to give the corresponding title compounds.

4.4.5 Cycloadducts and their analysis:

Methyl 6-oxo-1-phenyl-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate and **Methyl 4-oxo-1-phenyl-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate** (**8a** and **8a'**)**:** Compounds **8a** and **8a'** were obtained as a yellow oil following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10-50% EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (50 % EtOAc/hexane).

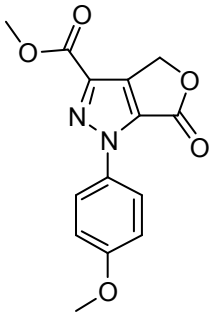


Methyl 6-oxo-1-phenyl-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H), 5.41 (s, 2H), 7.31-8.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9, 65.8, 120.7 (2C), 127.3, 128.9, 129.8 (2C), 136.1, 138.3, 142.5, 158.4, 161.1; $[M]^+$ = 258; IR (CCl_4): ν = 3068, 2953, 1780, 1725, 1576, 1436, 1374, 1276, 1138, 1032, 984 cm^{-1}.

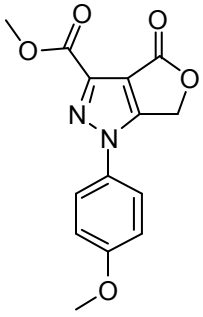


Methyl 4-oxo-1-phenyl-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8a'**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.04 (s, 3H), 5.45 (s, 2H), 7.36-7.78 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.1, 64.1, 119.6 (2C), 125.8, 129.3, 130.3 (2C), 130.6, 137.9, 139.2, 158.2, 160.5; $[M]^+$ = 258; IR (CCl_4): ν = 3068, 2953, 1780, 1725, 1576, 1436, 1374, 1276, 1138, 1032, 984 cm^{-1}.

Methyl 1-(4-methoxyphenyl)-6-oxo-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate and **methyl 1-(4-methoxyphenyl)-4-oxo-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate** (**8b** and **8b'**)**:** Compounds **8b** and **8b'** were obtained as a solid and yellow oil respectively following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10-50 % EtOAc/hexane). The two regioisomers were further separated by preperative TLC plates (50 % EtOAc/hexane).

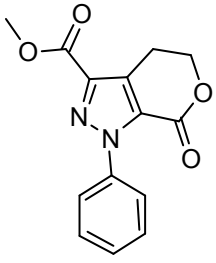


Methyl 1-(4-methoxyphenyl)-6-oxo-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8b**)**:** M.P.= 190-191°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.99 (s, 3H), 5.40 (s, 2H), 7.01 (d, J = 9.1 Hz, 2H), 8.05 (d, J = 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9, 55.8, 65.8, 114.8 (2C), 122.3 (2C), 131.7, 135.4, 135.6, 142.1, 158.6, 160.0, 161.2; $[M]^+$ = 288; IR (CCl_4): ν = 2954, 2909, 2223, 1755, 1720, 1612, 1559, 1505, 1442, 1254, 1119, 1065, 951 cm^{-1}.

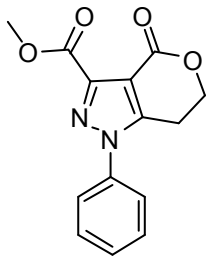


Methyl 1-(4-methoxyphenyl)-4-oxo-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**8b'**)**:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H), 4.04 (s, 3H), 5.39 (s, 2H), 7.03 (d, J = 9.2 Hz, 2H), 7.52 (d, J = 9.2 Hz, 2H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 53.1, 55.9, 63.9, 155.3 (2C), 117.1, 121.3 (2C), 131.2, 138.8, 157.7, 160.0, 160.6, 160.7; $[M]^+$ = 288; IR (CCl_4): ν = 2954, 2909, 2223, 1755, 1720, 1612, 1559, 1505, 1442, 1254, 1119, 1065, 951 cm^{-1}.

Methyl 7-oxo-1-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate and **methyl 4-oxo-1-phenyl-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylate** (**9a** and **9a'**)**:** Compounds **9a** and **9a'** were obtained as solids following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10-50 % EtOAc/hexane). The two regioisomers were further separated by preperative TLC plates (50 % EtOAc/hexane).

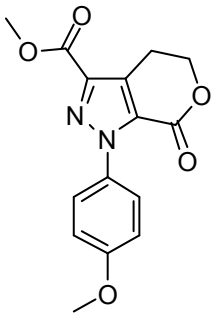


Methyl 7-oxo-1-phenyl-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate (9a): M.P.= 183-184°C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31 (t, J = 6.0 Hz, 2H), 3.98 (s, 3H), 4.64 (t, J = 6.0 Hz, 2H), 7.44-7.63 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 52.5, 69.1, 125.3 (2C), 129.0 (2C), 129.3, 129.6 (2C), 138.8, 139.6, 156.6, 162.1; $[M]^+$ = 272; IR (CCl_4): ν = 2997, 2955, 1751, 1724, 1599, 1509, 1439, 1367, 1265, 1240, 1139,c1101, 1003, 948 cm^{-1}.

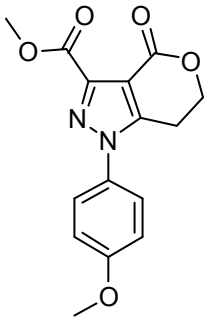


Methyl 4-oxo-1-phenyl-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylate (9a'): M.P.= 141-142 °C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.16 (t, J = 5.9 Hz, 2H), 4.00 (s, 3H), 4.52 (t, J = 5.9 Hz, 2H), 7.46-7.57 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 53.0, 66.4, 110.5, 123.9 (2C), 129.5, 129.9 (2C), 137.6, 144.1, 146.5, 159.5, 161.3; $[M]^+$ = 272; IR (CCl_4): ν = 2997, 2955, 1751, 1724, 1599, 1509, 1439, 1367, 1265, 1240, 1139,c1101, 1003, 948 cm^{-1}.

Methyl 1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate and **methyl 1-(4-methoxyphenyl)-4-oxo-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylate** (**9b** and **9b'**): Compounds **9b** and **9b'** were obtained as solids following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10-50 % EtOAc/hexane). The two regioisomers were further separated by preperative TLC plates (50 % EtOAc/hexane).

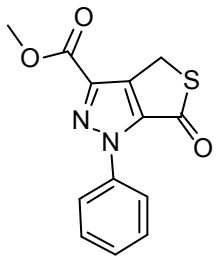


Methyl 1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrano[3,4-c]pyrazole-3-carboxylate (9b): M.P.= 218-219°C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (t, J = 6.1 Hz, 2H), 3.86 (s, 3H), 3.98 (s, 3H), 4.63 (t, J = 6.1 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 52.5, 55.7, 69.1, 114.1 (2C), 126.6 (2C), 129.2, 129.3, 131.9, 139.2, 156.8, 160.4, 162.2; $[M]^+$ = 302; IR (CCl_4): ν = 3000, 2954, 2052, 1755, 1723, 1592, 1559, 1509, 1444, 1391, 1254, 1100, 1065, 951 cm^{-1}.



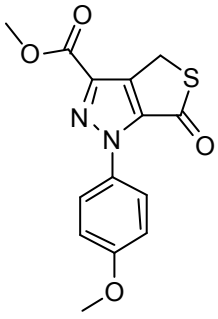
1-(4-methoxyphenyl)-4-oxo-1,4,6,7-tetrahydropyrano[4,3-c]pyrazole-3-carboxylate (**9b'**): M.P.=113-114 °C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (t, J = 6.2 Hz, 2H), 3.86 (s, 3H), 3.99 (s, 3H), 4.51 (t, J = 6.2 Hz, 2H), 7.01 (d, J = 9.3 Hz, 2H), 7.42 (d, J = 9.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 52.9, 55.9, 66.4, 114.9 (2C), 125.4 (2C), 128.2, 130.6, 143.8, 146.5, 159.6, 160.4, 161.4; $[M]^+$ = 302; IR (CCl_4): ν = 3000, 2954, 2052, 1755, 1723, 1592, 1559, 1509, 1444, 1391, 1254, 1100, 1065, 951 cm^{-1}.

Methyl 6-oxo-1-phenyl-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (10a): Compound **10a** was obtained as a solid following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (20 % EtOAc/hexane).

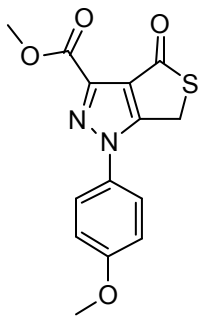


Methyl 6-oxo-1-phenyl-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (**10a**): M.P.= 194°C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H), 4.43 (s, 2H), 7.38-7.53 (m, 3H), 7.79-7.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 52.7, 123.2 (2C), 129.2, 129.4 (2C), 137.8, 138.0, 142.6, 143.2, 161.6, 182.2; $[M]^+$ = 274; IR (CCl_4): ν = 3075, 2957, 2361, 1754, 1721, 1698, 1501, 1464, 1372, 1294, 1202, 1132, 1048, 881cm^{-1}.

Methyl 1-(4-methoxyphenyl)-6-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate and **methyl 1-(4-methoxyphenyl)-4-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate** (**10b** and **10b'**): Compounds **10b** and **10b'** were obtained as a solid and yellow oil respectively following the general procedure for the 1,3-DC followed by the oxidation with CAN and separated by chromatography on silica gel (10-50 % EtOAc/hexane). The two regioisomers were further separated by preperative TLC plates (50 % EtOAc/hexane).

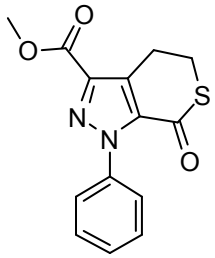


Methyl 1-(4-methoxyphenyl)-6-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (10b): M.P.= 180-181°C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.99 (s, 3H), 4.41 (s, 2H), 6.98 (d, J = 9.1Hz, 2H), 7.72 (d, J = 9.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1, 52.7, 55.8, 114.4 (2C), 124.7(2C), 131.2, 137.4, 142.1, 142.9, 160.2, 161.8, 182.3; $[M]^+$ = 304; IR (CCl_4): ν = 2957, 2361, 1753, 1722, 1698, 1594, 1514, 1439, 1255, 1160, 1132, 1050, 883 cm^{-1}.

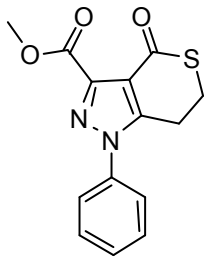


Methyl 1-(4-methoxyphenyl)-4-oxo-4,6-dihydro-1H-thieno[3,4-c]pyrazole-3-carboxylate (10b'): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.00 (s, 3H), 4.35 (s, 2H), 7.03 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 52.9, 55.9, 115.1(2C), 123.8 (2C), 124.9, 130.4, 136.9, 157.8, 160.3, 160.8, 182.7; $[M]^+$ = 304; IR (CCl_4): ν = 2957, 2361, 1753, 1722, 1698, 1594, 1514, 1439, 1292, 1255, 1160, 1132, 1050, 883cm^{-1}.

Methyl 7-oxo-1-phenyl-1,4,5,7-tetrahydrothiopyrano[3,4-c]pyrazole-3-carboxylate and **methyl 4-oxo-1-phenyl-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazole-3-carboxylate** (**11a and 11a'**): Compounds **11a** and **11a'** were obtained as solids following the general procedure for the 1,3-DC and separated by chromatography on silica gel (10-50 % EtOAc/hexane). The two regioisomers were further separated by preperative TLC plates (50 % EtOAc/hexane).



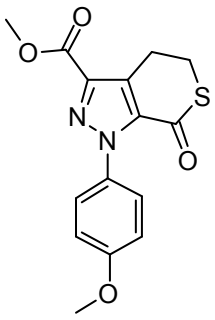
Methyl 7-oxo-1-phenyl-1,4,5,7-tetrahydrothiopyrano[3,4-c]pyrazole-3-carboxylate (11a): M.P.= 206-207°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.35-3.55 (m, 4H), 3.95 (s, 3H), 7.40-7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 31.6, 52.4, 125.8 (2C), 128.9 (2C), 129.6, 131.3, 134.2, 139.7, 140.0, 162.4, 180.9; $[M]^+$ = 288; IR (CCl_4): ν = 3065, 2954, 1747, 1682, 1601, 1566, 1501, 1450, 1263, 1149, 1074, 967, 889 cm^{-1}.



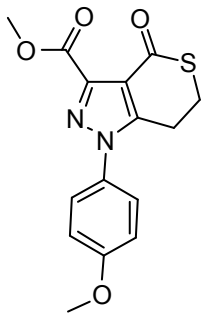
Methyl 4-oxo-1-phenyl-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazole-3-carboxylate (11a'): M.P.= 154-155°C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.16-3.35 (m, 4H), 3.97 (s, 3H), 7.39-7.65 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 29.8, 53.3, 125.1 (2C), 129.7, 129.8 (2C), 137.6, 142.7, 147.8, 162.0, 183.3; $[M]^+$ = 288; IR (CCl_4): ν = 3065, 2954, 1747, 1682, 1601, 1566, 1501, 1450, 1263, 1149, 1074, 967, 889 cm^{-1}.

Methyl 1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-c]pyrazole-3-carboxylate and **methyl 1-(4-methoxyphenyl)-4-oxo-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazole-3-carboxylate** (**11b** and **11b'**): Compounds **11b** and **11b'** were obtained as a solid and yellow oil respectively following the general procedure for the 1,3-DC and separated by

chromatography on silica gel (10-50 % EtOAc/hexane). The two regioisomers were further purified by preperative TLC plates (50 % EtOAc/hexane).

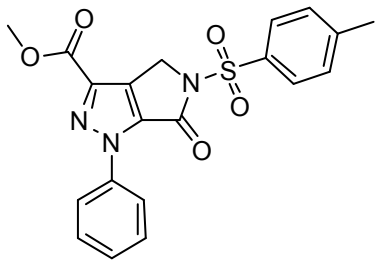


Methyl 1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-c]pyrazole-3-carboxylate (11b): M.P.=201-202 °C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.35-3.53 (m, 4H), 3.83 (s, 3H), 3.95 (s, 3H), 6.92 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 31.6, 52.4, 55.7, 114.0 (2C), 127.0 (2C), 131.1, 132.8, 134.1, 139.7, 160.3, 162.5, 181.0; $[M]^+$ = 318; IR (CCl_4): ν = 3003, 2955, 2837, 1722, 1668, 1593, 1515, 1438, 1250, 1179, 1131, 1038, 891 cm^{-1}.



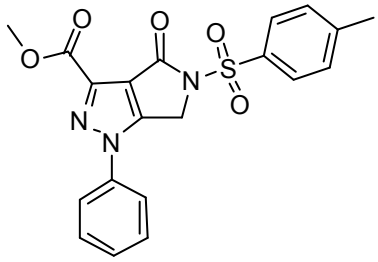
Methyl 1-(4-methoxyphenyl)-4-oxo-1,4,6,7-tetrahydrothiopyrano[4,3-c]pyrazole-3-carboxylate (11b'): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.11-3.16 (m, 4H), 3.87 (s, 3H), 3.97 (s, 3H), 7.01 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 29.7, 53.0, 55.9, 114.9 (2C), 126.5 (2C), 130.5, 142.2, 148.0, 156.1, 160.5, 162.1, 183.3; $[M]^+$ = 318; IR (CCl_4): ν = 3003, 2955, 2837, 1722, 1668, 1593, 1515, 1438, 1250, 1179, 1131, 1038, 891 cm^{-1}.

Methyl 6-oxo-1-phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate and **methyl 4-oxo-1-phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (12a** and **12a'):** Compounds **12a** and **12a'** were obtained as a yellowish solid and yellow foam following the general procedure for the 1,3-DC (in toluene) followed by the oxidation with CAN and separated by chromatography on silica gel (1/9 EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (CH_2Cl_2).



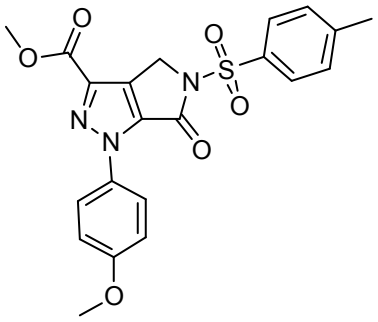
Methyl 6-oxo-1-phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (12a): MP.: 184-189 °C**,** ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 4.00 (s, 3H), 4.96 (s, 2H), 7.32-7.51 (m, 3H), 7.98-8.12 (m, 4H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 22.0, 45.7, 52.7, 121.3, 128.5, 128.9, 129.7, 130.3, 134.8, 135.2, 137.0, 138.2, 145.9, 155.3, 161.2; $[M]^+$ = 411; IR (CCl_4): ν = 2928, 2855, 1741, 1559, 1467, 1177, 1097cm^{-1}.

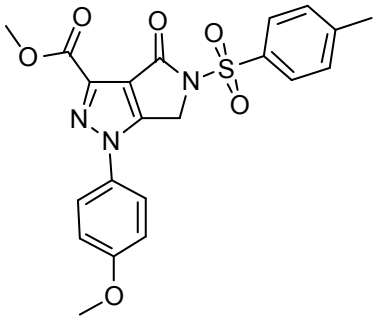


Methyl 4-oxo-1-phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (12a'): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.98 (s, 3H), 5.10 (s, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.45 (tt, *J* = 7.3 and 1.2 Hz, 2H), 7.55 (tt, *J* = 7.3 and 1.7 Hz, 2H), 7.64 (dt, *J* = 7.3 and 1.4 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 45.9, 53.1, 120.1, 120.7, 121.5, 128.6, 129.1, 129.7, 130.1, 130.3, 135.9, 137.9, 145.6, 150.9, 157.6, 160.5; $[M]^+$ = 411; IR (CCl_4): ν = 2928, 2855, 1741, 1559, 1467, 1177, 1097cm^{-1}.

Methyl 1-(4-methoxyphenyl)-6-oxo-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate and **methyl 1-(4-methoxyphenyl)-4-oxo-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (12b** and **12b'):** Compounds **12b** and **12b'** were obtained as a white solid and white foam following the general procedure for the 1,3-DC (in toluene) followed by the oxidation with CAN and separated by chromatography on silica gel (1/9 EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (CH_2Cl_2).

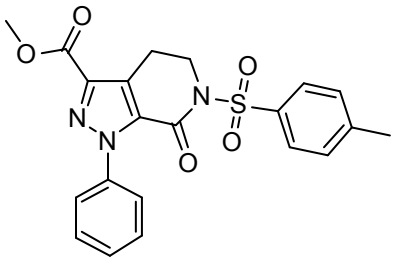


Methyl 1-(4-methoxyphenyl)-6-oxo-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (12b): m.p.: 213-218 °C**,** ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.88 (s,3H), 4.00 (s, 3H), 4.98 (s, 2H), 6.93-9.97 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.94-8.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 45.5, 52.9, 55.8, 114.7, 122.7, 128.5, 130.2, 131.6, 134.4, 135.2, 136.5, 137.2, 145.8, 155.4, 160.0, 161.2; $[M]^+$ = 441, found $[M+23]^+$ = 464; IR (CCl_4): ν = 3071, 2954, 1944, 1725, 1600, 1264, 1098 cm^{-1}.

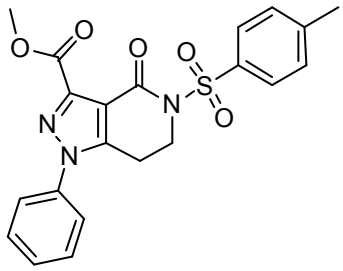


Methyl 1-(4-methoxyphenyl)-4-oxo-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-3-carboxylate (12a'): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 5.04 (s, 2H), 7.03(d, *J* = 8.9 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 45.7, 53.1, 55.9, 115.3, 119.9, 121.9, 128.5, 130.1, 131.2, 135.4, 139.2, 145.6, 150.5, 157.8, 160.0, 160.7; $[M]^+$ = 441; IR (CCl_4): ν = 3071, 2954, 1944, 1725, 1600, 1264, 1098 cm^{-1}.

Methyl 7-oxo-1-phenyl-6-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate and **Methyl 4-oxo-1-phenyl-5-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (13a** and **13a'):** Compounds **13a** and **13a'** were obtained as a white solid and yellow foam following the general procedure for the 1,3-DC (in toluene) followed by the oxidation with CAN and separated by chromatography on silica gel (1/9 EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (CH_2Cl_2).



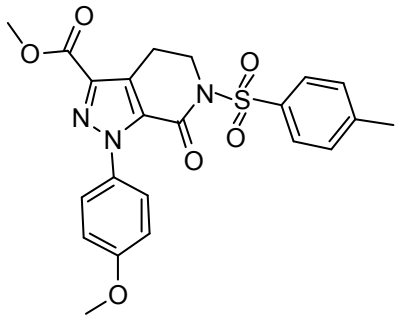
Methyl 7-oxo-1-phenyl-6-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (13a): M.P.: 195-198 °C**,** ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.29 (t, *J* = 6.8 Hz, 3H), 3.95 (s, 3H), 4.34 (t, *J* = 6.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.38-7.41 (m, 5H), 7.89 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.1, 46.8, 52.5, 125.6, 128,7, 128,9 (2C), 129.5, 129.8, 132.1, 136.0, 139.1, 139.4, 145.2, 155.7, 162.2; $[M]^+$ = 425, found $[M+23]^+$ = 448; IR (CCl_4): ν = 2984, 2360, 1710, 1559, 1264, 1174 cm^{-1}.



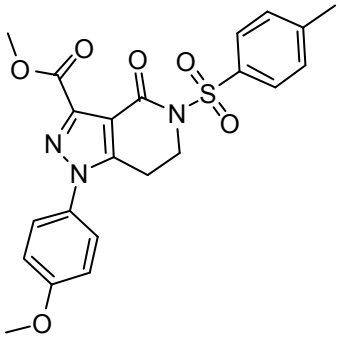
Methyl 4-oxo-1-phenyl-5-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (13a'): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.16 (t, *J* = 6,3 Hz, 3H), 3.95 (s, 3H), 4.29 (t, *J* = 6,3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.44-7.57 (m, 5H), 7.92 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 24.0,

45.1, 53.0, 123.9, 128,8, 129.6, 129.8, 129.9 (2C), 134.0, 136.3, 137.6, 145.0, 146.7, 158.3, 165.6; $[M]^+$ = 425; IR (CCl_4): ν = 2984, 2360, 1710, 1559, 1264, 1174 cm^{-1} .

Methyl 1-(4-methoxyphenyl)-7-oxo-6-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate and **Methyl 1-(4-methoxyphenyl)-4-oxo-5-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (13b** and **13b'):** Compounds **13b** and **13b'** were obtained as a white solid and yellow foam following the general procedure for the 1,3-DC (in toluene) followed by the oxidation with CAN and separated by chromatography on silica gel (1/9 EtOAc/hexane). The two regioisomers were further separated by preparative TLC plates (CH_2Cl_2).



Methyl 1-(4-methoxyphenyl)-7-oxo-6-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (13b): M.P.: 167-172 °C**,** ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.28 (t, *J* = 6,3 Hz, 3H), 3.83 (s, 3H), 3.95 (s, 3H), 4.34 (t, *J* = 6,3 Hz, 2H), 6.89 (d, *J* = 9.1 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 9.1 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.1, 46.952.4, 55.8, 114.1, 126.9, 128.8, 128.9, 129.5, 129.8, 132.0, 132.3, 136.1, 139.1, 145.2, 155.8, 160.3, 162.2; $[M]^+$ = 455, Found $[M+23]^+$ = 478; IR (CCl_4): ν = 2928, 2856, 2360, 1726, 1576, 1516, 1465, 1263 cm^{-1}.



Methyl 1-(4-methoxyphenyl)-4-oxo-5-tosyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (13b'): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.10 (t, *J* = 6,3 Hz, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 4.28 (t, *J* = 6,3 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 9.1 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 23.8, 45.2, 53.1, 55.8, 114.9, 125.7, 128.8, 128.9, 129.5, 130.6, 136.4, 143.8, 144.9, 146.7, 158.4, 160.4, 161.6; $[M]^+$ = 455; IR (CCl_4): ν = 2928, 2856, 2360, 1726, 1576, 1516, 1465, 1263 cm^{-1}.

4.4.6 Theoretical and computational method:

To rationalize the reactivity of the studied systems we have used some global descriptors of reactivity which have been defined within the context of the density functional theory. The global electrophilicity power measures the capability of a system to acquire electronic charge from the environment, and is calculated by the following simple expression,[28] $\omega = (\frac{\mu^2}{2\eta})$, where μ and η are the electronic chemical potential and chemical hardness of the ground state of atoms and molecules, respectively.[29,30] While μ describes the charge transfer pattern in the system in its ground state geometry, η describes the resistance to this charge transference. Both quantities could be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx \varepsilon_L - \varepsilon_H$, respectively. As nucleophilicity (N) descriptor we have used the ionization energy, approached following the Koopmans' theorem[31] and the Kohn-Sham scheme[32] as the negative of the highest occupied molecular orbital (HOMO) energy; but to recover the direct proportionality of the index and nucleophilicity we expressed N as, $N_{(Nu)} = 1 + E_{HOMO}$. A similar expression has been previously successfully used to study the reactivity of captodative ethylenes in polar cycloaddition reactions.[33] As local descriptor of reactivity to evaluate the regioselictivity, we have used the Fukui function; these local quantities were obtained from a topological analysis of the Fukui function, using the same topological tools proposed by Bader almost three decades ago to analyze the gradient field of the electron density to give a definition of an atom in a molecule.[34] For a detailed revision of this methodology see the following references.[35,36] To evaluate the possible electrostatic interactions we have computed the electrostatic potentials on the surfaces of a series of selected systems. For this purpose, we taking the molecular surface to be the 0.002 au contour of the molecule's electronic density ρ(r), as proposed by Bartolotti *et al.*[27] The electrostatic potential V(r) that is produced at any point r by the nuclei and electrons of the molecule is given by:[37]

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r' - r|}$$

Z_A is the charge on nucleous A, located at R_A. Regions where V(r) is negative are attractive to cations and repulsive to anions; regiosn where V(r) is positive are attractive to anions and repulsive to cations. The molecular geometries have been optimized using the B3LYP density functional method[38] in conjunction with the 6-31G(d) basis set.[39] All calculations were carried

out with the *Gaussian 03*suite of programs,[40] the topological analysis of the scalar functions and the calculation of the condensed Fukui function were done with the *DGrid 4.4* set of programs.[41]

4.5 X-ray Analysis:

The diffraction experiments were carried out at room temperature on a Bruker ApexII diffractometer equipped with a CCD detector, by using graphite monochromated MoK_α radiation (λ = 0.71073 Å). An empirical absorption correction was applied on all structures by using SADABS.[42] They were solved by Direct Methods and refined by full-matrix least-squares based on F^2 using SHELXL97.[43] All non-hydrogen atoms were refined anisotropically while hydrogen atoms were set geometrically and given fixed isotropic thermal parameters. Crystal data and details of the data collection and refinement are given in Table 2-SI.

4.5.1 X-ray structures of 8b, 9a', 11a, 12b, 13a and 13b:

The unit cell of **8b** contains four molecules, one of which constitutes the independent unit (**Figure 4.8**). In this case, unlike most of the others that will follow, the pyrazole is practically coplanar with the acyl and the p-methoxy-phenyl groups, the torsion angles being only 1.70(1) (N8-C9-C10-O11) and 1.5381)° (C5-C9-C10-O12) for the former, -4.94(1)° (N8-N7-C14-C19) and -4.69(1)° (C6-N7-C14-C15) for the latter (see Figure 4). As a result the whole molecule is virtually flat and arranges in parallel units in the solid state, as illustrated in **Figure 4.9** (view along the b axis). The packing is held by some intermolecular hydrogen bonds involving the oxygen and nitrogen atoms, whose lengths are comprised between 3.063(1) (O20...H-C13_a) and 3.588(3) Å (N8...H-C4_b).

Figure 4.8: X-ray structure of **8b** (ellypsoids are at 30% probability).

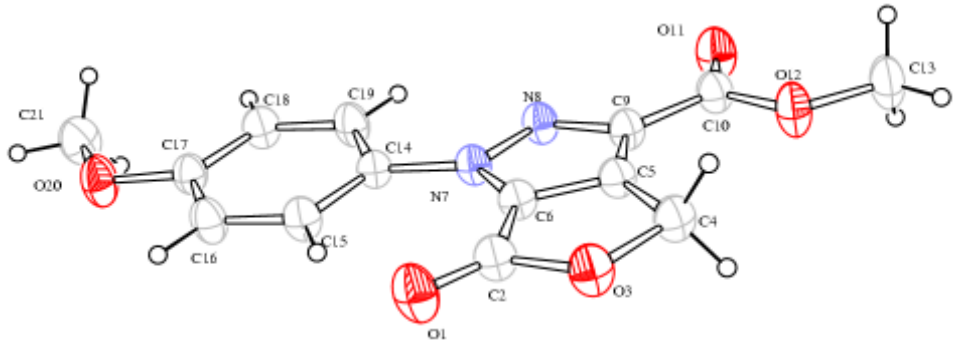
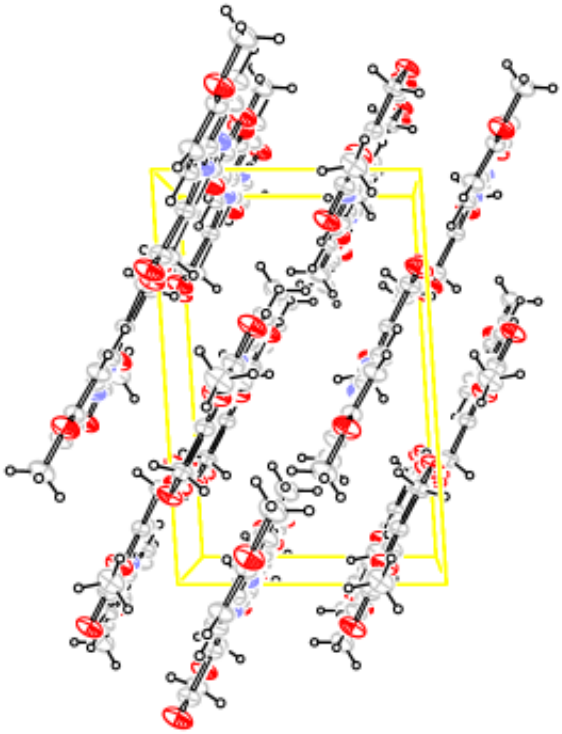
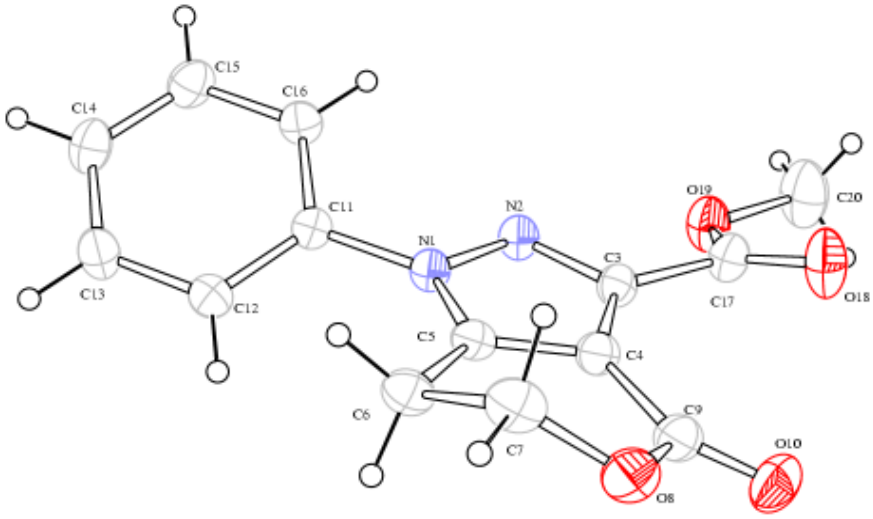


Figure 4.9: Crystal packing of **8b**. View along the *b* axis.



The unit cell of **9a'** contains four molecules, one of which represents the independent unit. As shown in **Figure 4.10**, with respect to the pyrazolic plane both the acyl and phenyl groups are tilted, probably due to packing efficiency, and their torsion angles are -18.20(26)° (C4-C3-C17-O18) and -23.4(2)° (N2-C3-C17-O19) for the acyl, -33.83(23)° (C5-N1-C11-C12) and -30.03(19)° (N2-N1-C11-C16) for the phenyl ring. The solid state packing shows only weak intermolecular hydrogen bonds involving the oxygen and nitrogen atoms, ranging between 3.367(2) (O8...H-C16_a) and 3.562(3) Å (O19...C7_b).

Figure 4.10: Crystal structure of **9a'** (ellypsoids at 30% probability).

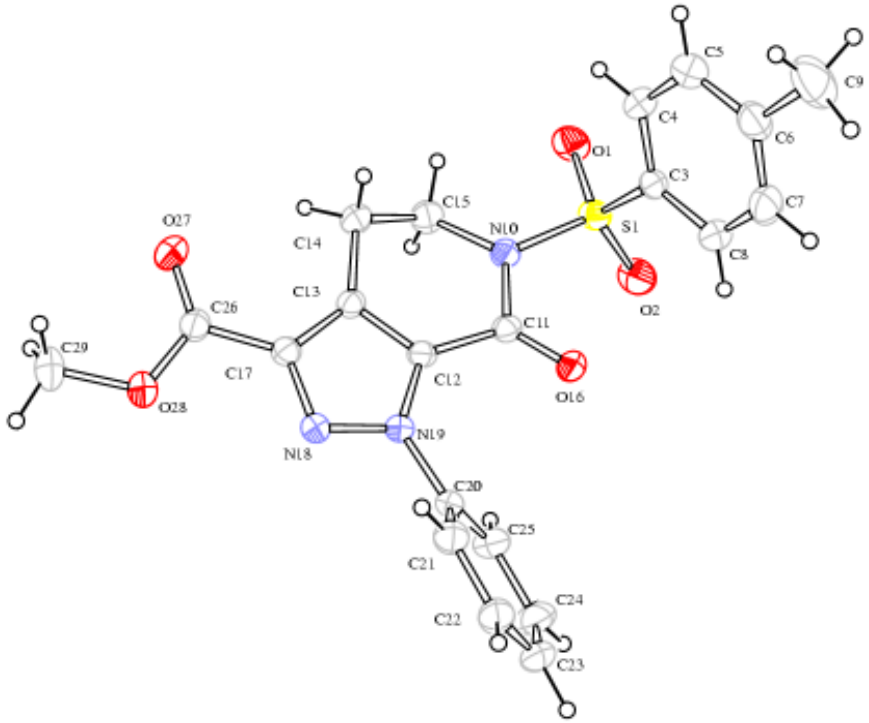


The unit cell of **11a** contains 4 molecules, one of which constitutes the independent unit (see **Figure 4.3 (a)**). Similarly to the previous structure the phenyl ring is tilted with regard to the pyrazole plane by 56.90(1)° (N8-N9-C20-C15) and 53.47(2)° (C3-N8-C15-C20), while the acyl group is nearly coplanar as it only deviates by 3.25° (N9-C10-C11-O12) and 4.94° (C4-C10-C11-O13). The solid state arrangement only shows weak intermolecular hydrogen bonds involving the oxygen atoms, whose distances vary from 3.193(1) (O7...H-C16_a) to 3.507(2) Å (O13...H-C20_b).

The unit cell of **12b** is made of two molecules of which one represents the asymmetric unit (see **Figure 4.3(b)**). Without considering the protective N-tosyl group, whose position is determined by the N1-S1-C4 angle of 105.77°, the rest of the molecule appears almost flat, similarly to what seen for compound **8b**, and the torsion angles between the pyrazole plane and the p-methoxy-phenyl and acyl groups are 2.12(2)° (N18-N17-C24-C29) and 3.43(2) (C14-N17-C24-C25) for the former, 1.27(2)° (N18-C19-C20-O21) and 3.63(2)° (C13-C19-C20-O22) for the latter. The distance of 2.888(1) Å between the oxygen atoms O2 and O16 is close to the sum of their Van der Waals radii (2.80Å). Some intermolecular hydrogen bonds involving both oxygen and nitrogen atoms are present and they vary between 3.047(4) Å (O16...H-C23_a) to 3.581(3) Å (N18...H-C23_b).

The compound **13a** crystallizes in a chiral space group (flack parameter 0.0235) and its unit cell contains four molecules, one of which forms the independent unit (**Figure 4.11**). In the solid state the pyrazolic unit is not coplanar neither with the phenyl ring (torsion angles of -52.49(20)° (N18-N19-C20-C21) and -55.07(24)° (C12-N19-C20-C25)) nor with the acyl group (torsion angles: -11.64(23)° (N18-C17-C26-O28) and -11.15(27)° (C13-C17-C26-O27)), most likely to achieve a more efficient space filling . In terms of connectivity there is an intramolecular Van der Waal's distance of 2.860(2) Å between O2 and O16 and only rather weak intermolecular hydrogen bonds involving O and N atoms, spanning between 3.368(2) (O2...H-C4_a) and 3.511(2) Å (O16...H-C22_b).

Figure 4.11: X-ray structure of **13a** (ellypsoids are at 30% probability).



The crystals of **13b** had a quite low diffraction power and this accounts for a high R(int) value. The unit cell is rather big and contains eight molecules, with just one representing the asymmetric unit (**Figure 4.12**). While the acyl group is laying on the same plane as the pyrazolic unit (the torsion angles are 0.43(3)° (N19-C20-C21-O22) and 4.28(3)° (C14-C20-C21-O23), the p-methoxy-phenyl fragment is heavily rotated, the torsion angles being 45.58(3)° (C15-N18-C25-C30) and 50.30(3)° (N19-N18-C25-C26). As seen for the previous species, the distance of 2.901(1) Å between the oxygen atoms O2 and O17 is close to the sum of their Van der Waal's

radii. In the solid state packing there is one weak intramolecular hydrogen bond of 3.397(1) (O17...H-C5) and some intermolecuar ones involving the oxygen atoms, spanning from 3.204(1) (O17...H-C24_a) to 3.609(1) (O22...H-C9_b).

Figure 4.12: X-ray structure of **13b** (ellypsoids are at 30% probability).

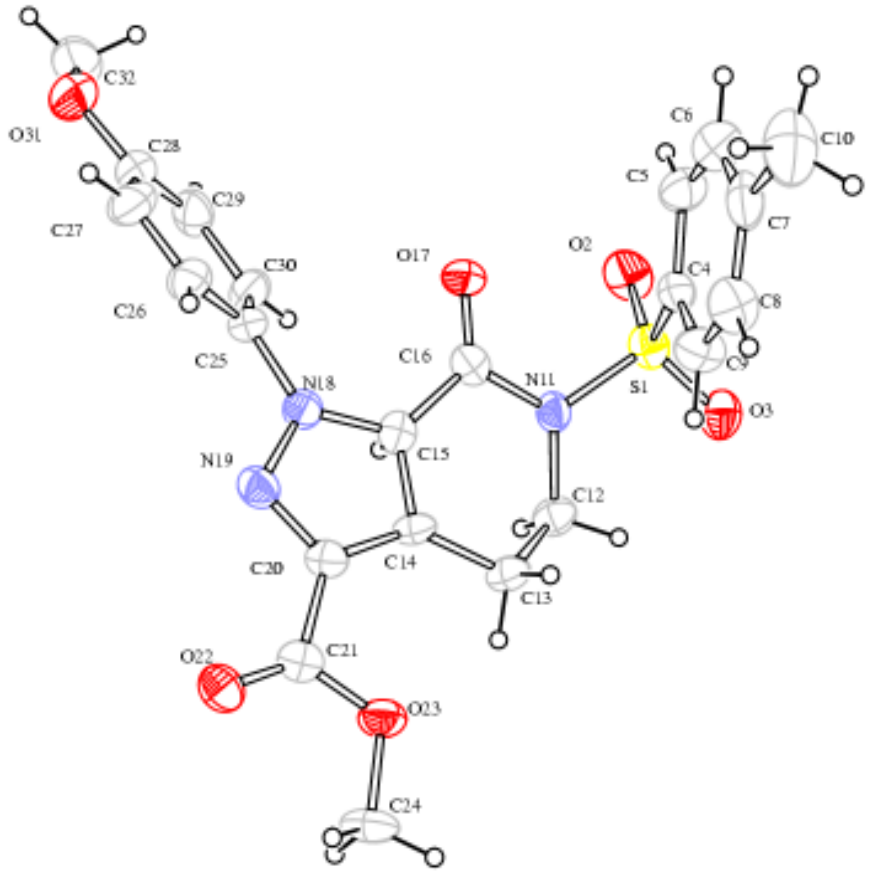


Table 4.4: Summary of Crystal Data for compounds **8b, 9a', 11a, 12b, 13a and 13b.**

Compound	**8b** $C_{14}H_{12}N_2O_5$	**9a'** $C_{14}H_{12}N_2O_4$	**11a** $C_{14}H_{12}N_2O_3S$	**12b** $C_{21}H_{19}N_3O_6S$	**13a** $C_{21}H_{19}N_3O_5S$	**13b** $C_{22}H_{22}N_3O_6S$
Fw	288.26	272.26	288.32	441.45	425.45	456.49
T, K	296(2)	296(2)	296(2)	296(2)	296(2)	296(2)
λ, Å	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic	Orthorhombic	Orthorhombic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P\bar{1}$	$P2_12_12_1$	*P*bca
a, Å	7.8818(9)	11.041(2)	8.9718(16)	7.8255(12)	10.2328(8)	13.864(4)
b, Å	13.6137(16)	16.332(3)	7.9815(14)	9.6341(14)	10.3945(8)	13.094(4)
c, Å	12.1658(15)	7.3439(15)	18.569(3)	13.807(2)	18.5732(14)	23.866(7)
α, °	90	90	90	91.084(2)	90	90
β, °	93.642(2)	101.058(3)	91.571(2)	96.684(2)	90	90
γ, °	90	90	90	105.346(2)	90	90
Cell Volume, $Å^3$	1302.8(3)	1299.7(5)	1329.2(4)	995.7(3)	1975.5(3)	4332(2)
Z	4	4	4	2	4	8
D_c, g cm^{-3}	1.470	1.391	1.441	1.473	1.430	1.400
μ, mm^{-1}	0.114	0.104	0.252	0.209	0.204	0.194
F(000)	600	568	600	460	888	1912
Crystal size, mm	0.20 x 0.18 x 0.15	0.40 x 0.10 x 0.10	0.25 x 0.20 x 0.15	0.25 x 0.20 x 0.18	0.20 x 0.18 x 0.12	0.25 x 0.25 x 0.20
θ limits, °	2.25 to 25.00	1.88 to 24.99	2.19 to 24.99	1.49 to 25.00	2.19 to 24.99	1.71 to 25.00
Index ranges	$-9 \le h \le 9$, $-16 \le k \le 16$, $-14 \le l \le 14$	$-13 \le h \le 13$, $-19 \le k \le 19$, $-8 \le l \le 8$	$-7 \le h \le 10$, $-9 \le k \le 9$, $-21 \le l \le 16$	$-9 \le h \le 9$, $-11 \le k \le 11$, $-16 \le l \le 16$	$-12 \le h \le 12$, $-12 \le k \le 12$, $-22 \le l \le 22$	$-16 \le h \le 16$, $-15 \le k \le 15$, $-28 \le l \le 27$
Reflections collected	12252	12210	5737	9699	17973	29469
Independent	2300 [R(int)	2284 [R(int)	2237 [R(int)	3507 [R(int)	3485 [R(int)	3822 [R(int)

reflections	= 0.0246]	= 0.0339]	= 0.0297]	= 0.0681]	= 0.0199]	= 0.3017]
Completeness to θ = 25.00°	100.0 %	100.0 %	95.3 %	99.7 %	100.0 %	100.0 %
Data / restraints / parameters	2300 / 0 / 193	2284 / 0 / 182	2237 / 0 / 183	3507 / 0 / 283	3485 / 0 / 273	3822 / 0 / 293
Goodness on fit on F^2	1.051	1.026	1.032	1.034	1.050	0.982
R_1 ($I > 2\sigma(I)$)	0.0351	0.0375	0.0355	0.0570	0.0266	0.0698
wR_2 (all data)	0.1047	0.0979	0.0987	0.1424	0.0738	0.2160
Largest diff. peak and hole, e $Å^{-3}$	0.178 and –0.141	0.153 and –0.227	0.171 and –0.264	0.214 and –0.286	0.147 and –0.298	0.306 and –0.298

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Part 2

Synthesis of multifunctional Helicene-thiourea catalyst and its applications in asymmetric synthesis.

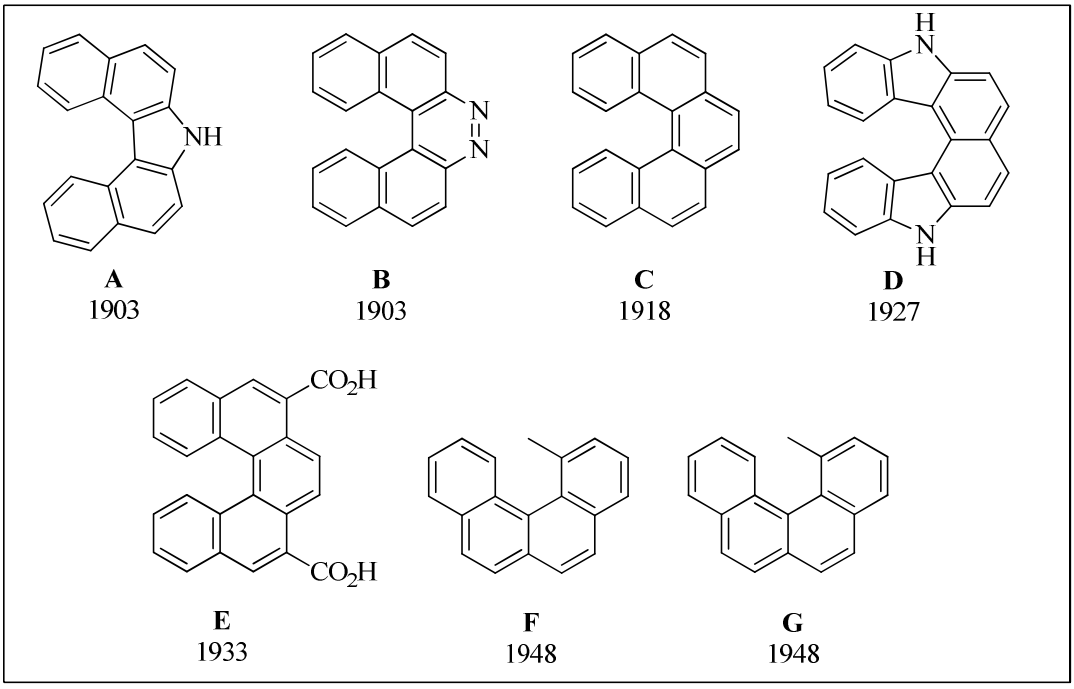
Chapter 5

Synthesis of multifunctional Helicene-thiourea catalyst and its applications in asymmetric synthesis.

5.1 Introduction:

Helicenes are polycyclic aromatic compounds with nonplanar screw-shaped skeletons formed by ortho-fused benzene or other aromatic rings.[1,2] The first helicenes **A** and **B** (**Figure 5.1**) were synthesized by Meisenheimer and Witte in 1903.[3] After then little progress was made towards helicene synthesis. **Figure 5.1** Lists some of the helicene compounds which were discovered before 1950. In 1950 Newmann *et.al.*[4] synthesized [6]-helicene such as **D** in non-racemic form *via* a Friedel-Crafts acylation and managed to resolve the resulting charge transfer complex. After this discovery the helicene chemistry was significantly expanded.

Figure 5.1: Helicenes prepared before 1950.



A 1903 **B** 1903 **C** 1918 **D** 1927

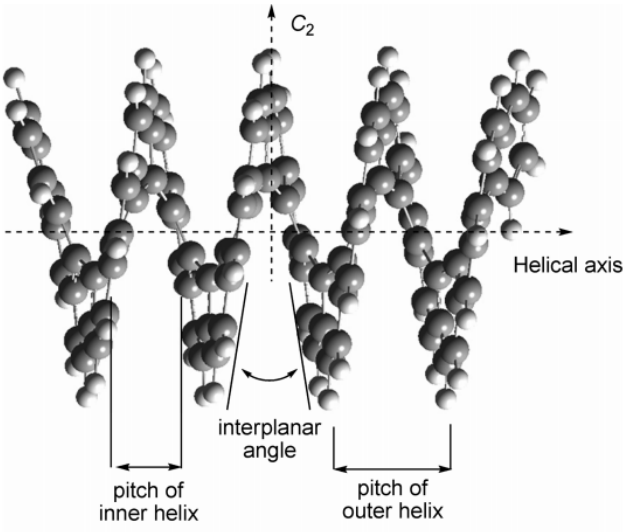
E 1933 **F** 1948 **G** 1948

In the 1990's, the Diels-Alder synthetic approach after Martin's photochemical methods brought another breakthrough in the preparation of helicenes on a large scale.[5] Based on this approach, a large number of helicene derivatives were synthesized.[6] Since the late 1990s, more and more new strategies for the synthesis of helicenes have been developed giving desired helicenes in good yields and enantioselectivity. Typically these methods rely on use of organometallic chemistry.[7]

5.2 Helicene properties:

The defining property of a helicene is its helical structure. Because of the steric hindrance of the terminal rings, helicenes can fold in opposite directions and develope a C_2-symmetry axis along the axis perpendicular to the helical axis (**Figure 5.2**).[8] This property of helicene makes them chiral even though they don't have any asymmetric carbon or chiral centre in it.

Figure 5.2: Ball and stick model of helicene.

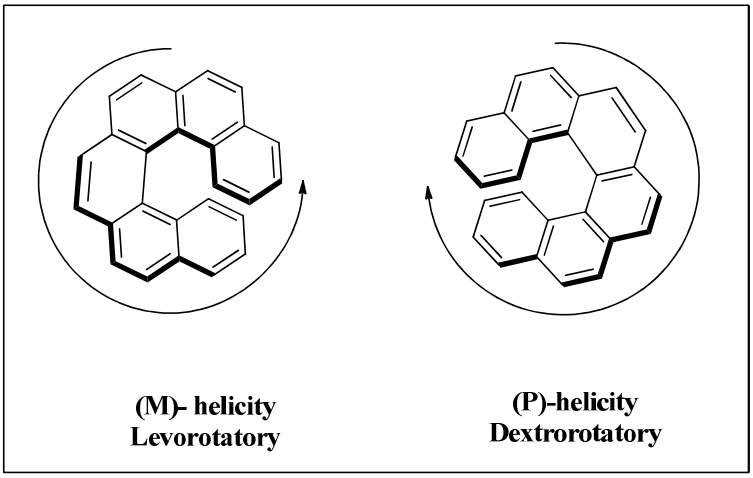


As the number of fused rings increases, the helicene spirals up along the helical axis to form a cylindrical structure with a constant pitch (in both inner and outer helixes).[1d] For helicenes composed of six-membered aromatic rings like benzene, it takes nearly six rings to cover a complete 360° rotation of a screw,[9a] while four thiophene and three benzene units are required for making thiahelicenes.[9b] The interplanar angles (i.e. angle between) of the two terminal rings depend on the lengths of the helicenes and the substituents present. The interplanar angles of carbohelicenes increase as the helicenes are elongated from [4]-helicenes

(26.7˚) to [6]-helicenes (58.5˚) but decrease with further elongation.[10] Thus, even compared with phenacenes, helicenes show a greater departure from planarity. As a result of torsional strain, the bond lengths in the skeleton are different, with different C-C bonds having features of a single bond or a double bond. In comparison with the bond length of benzene (1.393 Å),[11] the average bond length of the C-C bonds in the inner helix is lengthened to about 1.430 Å while the average length of the ones on the periphery are shortened to about 1.360 Å.[1c,d]

Based on helicity, in 1966 Cahn, Ingold and Prelog proposed a IUPAC nomenclature for helicenes and they are denoted as plus or minus. The plus isomer is the one in which the helical twist is clockwise (right handed) and can be designated as "P " while the minus isomer is the one for which the helical twist is anticlockwise (left handed) and desisgnated as "M " (**Figure 5.3**).[12] Furthermore, according to the results of ORD and CD spectroscopy, there is a general relationship between the absolute configuration and the chirality: (P)-helicenes are considered as dextrorotatory, while (M)-helicenes are as levorotatory. [13]

Figure 5.3: Chirality in Helicenes.



The racemization of helicenes is another intriguing property of these annulated systems. For [*n*]-helicenes, the free energy barriers to racemisation increase with *n* and with substitution at the inner helical sites. Thus, the free energy barriers (kcal mol^{-1} at 27 ˚C) for parent [*n*]-helicenes increase in the following order: 24.1 {*n* = 5}, 36.2 {*n* = 6}, 41.7 {*n* = 7}, 42.4 {*n* = 8} and 43.5 {*n* = 9}. Interestingly, introducing two methyl groups at the 1,1'-positions of hexahelicenes, increases the half-life of racemisation ($t_{1/2}$) from 13.4 minutes at 221.7 ˚C, to 444 minutes at

270°C. However, substitution at the 2,2' position did not have a significant effect on racemisation.

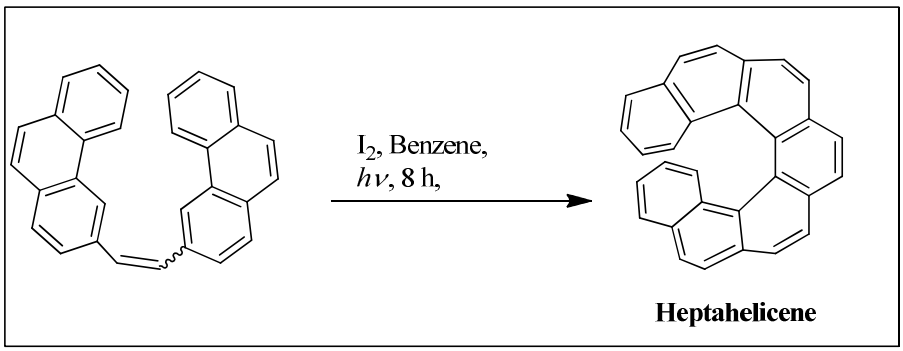
5.3 Helicene recent literature and synthesis:

During the last decade, helicene chemistry has grown to become an interesting field of research owing to the extraordinary optical and electronic properties associated with this type annulated system. The annulation of [*n*]-helicenes affect both the optical and chiral properties of these materials, with larger numbers of aromatic rings (*n*) forming rigid structures which possess large barriers to racemisation, thus, enhancing chirality. There are several methods available to synthesize carbohelicenes. However, an ideal synthetic strategy has not been developed yet as existing methods are having its own limitations. Indeed, the most commonly used method for helicene synthesis is oxidative photocyclisation.

5.3.1 Photocyclisation:

In 1967, Martin *et.al.*[14a] reported the first photoinduced synthesis of heptahelicene (**Scheme 5.1**). Since then, photocyclization has become one of the most important methods for the synthesis of many helicene homologues (from [5]- to [14]helicene) and derivatives, because the stilbene-type precursors can be easily prepared by Wittig olefination and the helicenes can be obtained in relatively few steps.

Scheme 5.1: First synthesis of heptahelicene via photocyclisation.



Photocyclisation is could be carried out in an inert atmosphere or in presence of air. However the two reaction conditions has an effect on both the selectivity and the yield of the reaction. In the presence of air, oxidative photocyclisation also produces side reactions which

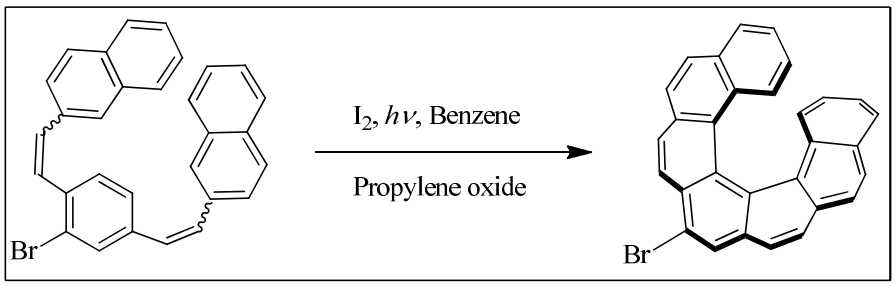
result in further degradation of the reaction product. Similarly, the reactions under inert conditions have some disadvantages like,

1) A stoichiometric amount of iodine is required to affect oxidation;
2) The by-product of this oxidation (HI) reduces double bonds in the presence of light.

In order to overcome these disadvantages, Katz *et.al.*[15] developed a new strategy that uses stoichiometric amount of iodine and excess propylene oxide to destroy reacting the acid (HI) formed during the course of the reaction. In this context propylene oxide prevents the formation of a high concentration of acid which lead to some by-products coming from elimination reactions of pH-sensitive secondary alcohols. This new set of reaction conditions not only enhances the yields greatly compared with the traditional methods for the photocyclization of stilbene, but also prevents photoreduction and photooxidative side reactions of the double bonds. Up to date this has become the standard procedure for the photocyclization of stilbenoid precursors.

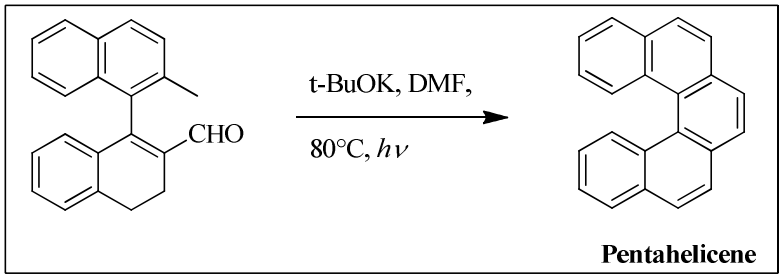
In 1969, in order to optimize the yields and to better direct the cyclization toward the desired regioisomer, Martin *et.al.*[14b] reported the concept of a ‘‘bromine auxiliary’’ for carbohelicene photosyntheses (**Scheme 5.2**). In this context, bromine substituent acts as a directing group for the regioselective formation of the radical species that lead to efficient cyclisation.

Scheme 5.2: The ‘‘bromine auxiliary’’ method for controlling the regioselectivity of photocyclization.



In 2004, de Koning *et.al.*[16] described another type of precursor for the preparation of [5]helicene in good yield (**Scheme 5.3**). The mechanism is believed to involve abstraction of one proton of the methyl group by t-BuOK, followed by transformation into the enolate in aldol reaction which then undergoes photocyclisatoin through isomerization.

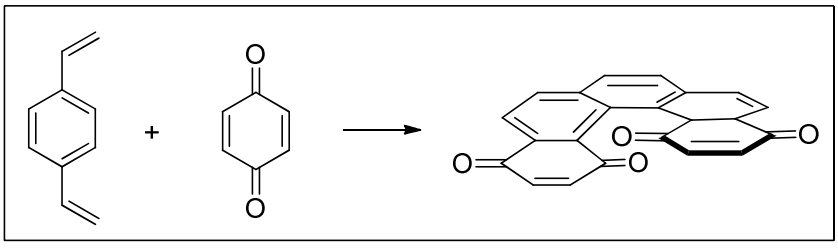
Scheme 5.3: Synthesis of [5]helicene reported by De Koning *et.al.*



5.3.2 Diels-Alder approach:

The problems associated with the photooxidative strategy have led to the advancement of several new methodologies which provide useful alternatives for the synthesis of carbohelicenes. In 1990, Katz and Liu *et.al.*[5] reported a Diels-Alder reaction approach to racemically synthesise [5]-helicene bis-quinone from 1,4-divinylbenzene and benzequinone (**Scheme 5.4**). Interestingly, this paper also reported an enzymatic hydrolysis which enabled the authors to obtain optically pure [5]-helicene bis-quinone. Moreover, the presence of four carbonyl groups in the resulting [5]-helicene allows for convenient functionalization of the terminal rings.

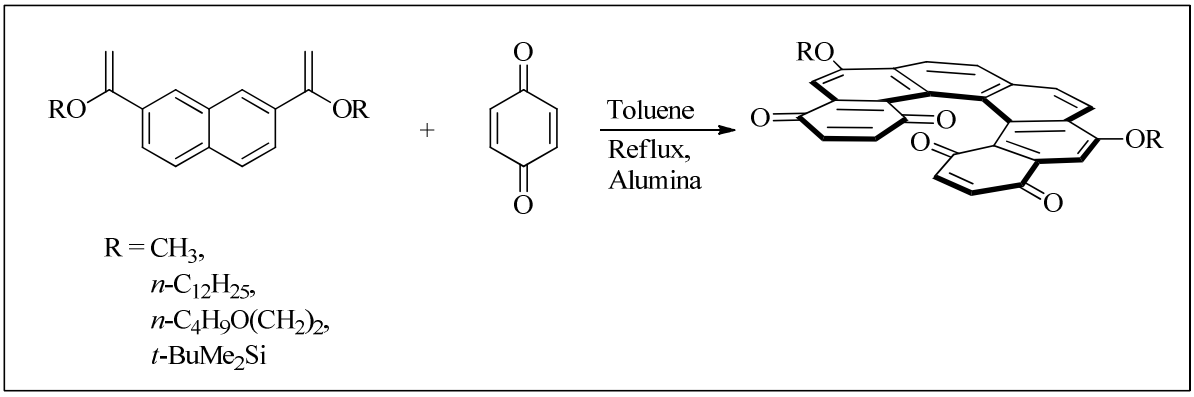
Scheme 5.4: Diels-Alder approach by Katz and Liu *et.al.*



The work carried out by Katz and co-workers in the early 1990's enabled the large scale preparation of helicenes. Although their Diels Alder approach is thought of as a remarkable breakthrough in this field, it yielded rather inert substrates which could not be transformed into more useful materials. Almost immediately after publishing his ground-breaking synthesis of [*5*]-

helicene, Katz and co-workers began investigating routes to more functionalised [*n*]-helicenes. Preliminary results in this area were published in 1992[17] and involved the reaction of acetophenone enol ethers with benzoquinone to yield functionalised [5]- and [6]-helicenes (**Scheme 5.5**). Following this methodology, functionalised [5]- and [7]-helicenes were also synthesised from enol ethers and resulted in good yields. It was observed that further functionalization of the aromatic portion of the enol ether resulted in erosion of yield. The helicene materials obtained from these reactions were resolved, thus, affording them in their non-racemic form.

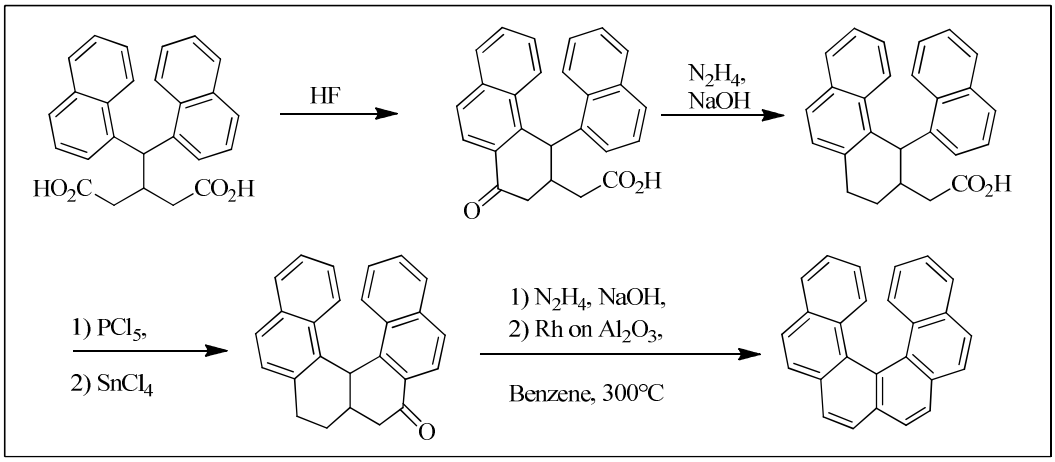
Scheme 5.5: The first synthesis of functionalised [6]-helicenes.



5.3.3 Friedel-Craft type of reactions:

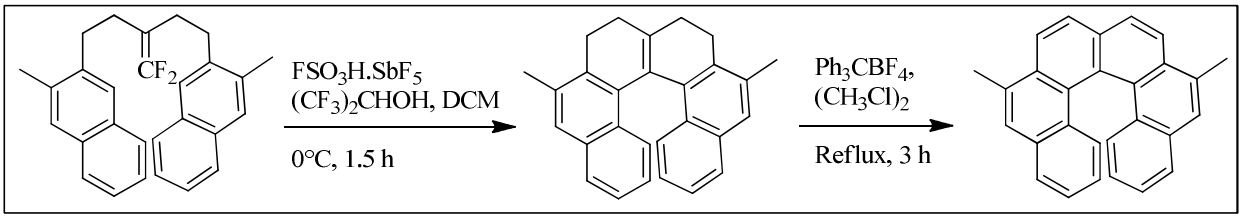
The synthesis of 1,12-dimethylbenzo[c]phanthrene and hexahelicene by double Friedel-Crafts acylation was first reported by Newman *et.al.*[18] As shown in **Scheme 5.6**, the ketoacid prepared by cyclization of malonic acid derivative in the presence of anhydrous hydrogen fluoride was reduced to the carboxylic acid and subsequent acylation was accomplished by stannic chloride. After the reduction of the ketone and a hydrogen transfer reaction over rhodium-on-alumina, the final hexahelicene was obtained in moderate yield.

Scheme 5.6: Work by Newman *et.al.*



Another Friedel-Craft-type cyclisation sequence was described by Ichikawa *et.al.*[19] (**Scheme 5.7**). The presence of two ortho-methyl groups is important to facilitate the domino cyclization. They not only direct the reaction to form a helical structure but also enhance the nucleophilicity of the aromatic moieties. With the help of magic acid ($FSO_3H.SbF_5$) and Ph_3CBF_4, double ring closure and dehydrogenation proceeded efficiently giving 6,11-dimethyl[6]helicene in good yield. This methodology gives direct access to tetracyclic core in one pot.

Scheme 5.7: Friedel-Crafts-type cyclisation by Ichikawa *et.al*.



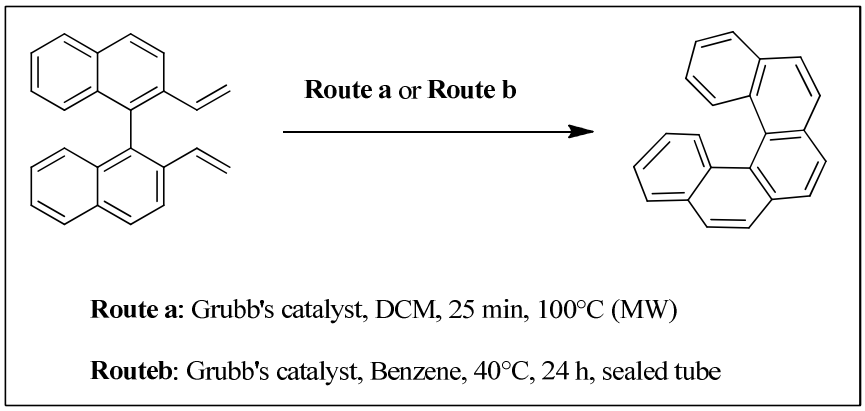
5.3.4 Metal catalysed cyclisations:

Helicenes can be synthesized by metal catalysed cyclisations. Most of the metal catalysed cyclisation reactions involve the use of precious metals. These includs cross-coupling reactions (Pd, Ru), ring-closing metathesis (Ru), [2 + 2 + 2] cycloaddition (Ru), and [2 + 2 + 2] cycloisomerization (Co). These cyclizations are of practical utility not only because of the small number of steps (building several rings in one step), relatively high yields, and good functional group tolerance, but also because such modular synthesis allows construction of a variety of

helicenes (even long helicenes). The [2 + 2 + 2] cycloisomerization, in particular, has been accepted as a general synthetic strategy.

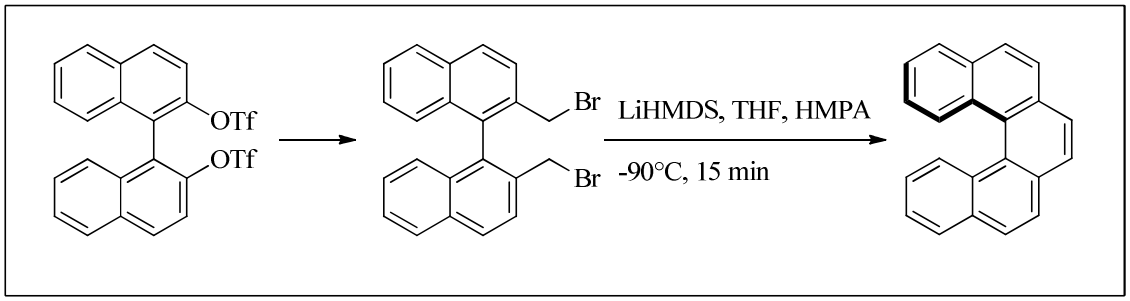
In 2006, Collins *et.al.*[21] reported the synthesis of helicenes in 78-93% yield by the ring-closing olefin metathesis method (**Scheme 5.8**). Two different routes, **a** and **b**, were utilized. Route **a** is very fast (24 min) but requires a high temperature (100°C) which can result in pyrolysis; route **b** occurs under mild conditions (40°C), accommodating the presence of sensitive functional groups, but requires a longer time (24 h). From readily modified 1,1 binaphthyl framework, this method—with good tolerance and high efficiency—was found to be a facile way to prepare substituted [5]-, [6]-, and [7]helicenes.

Scheme 5.8: Ring closing methathesis for synthesis of helicene reported by Collins *et.al.*



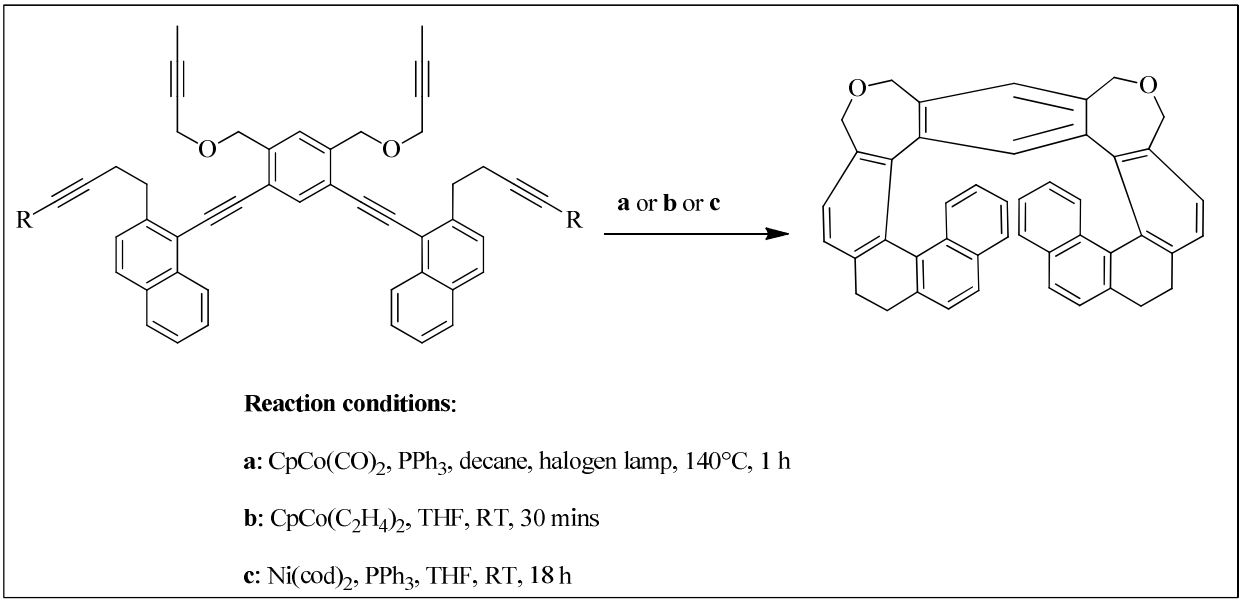
A novel lithium-induced cyclization of tribenzocyclyne was described by Tessier, Youngs *et.al.*[22] in 1996. Gingras and Dubois have reported a synthesis of helicenes via McMurry coupling.[23]The yields in this reactions were not promising. In 1998, they also reported a short and scalable approach to [5]-helicenes, which focused on the coupling of aromatic bis(bromomethyl) moieties in the presence of excess LiHMDS. This 'carbenoid coupling' approach to helicenes was high yielding leading to [5]-helicenes in 3 steps (**Scheme 5.9**).

Scheme 5.9: Carbenoid coupling approach to [5]-helicenes.



In 2009, Sehnal *et.al.*[24] have reported a synthesis of long helicenes by organometallic approach to the derivatives of undecacyclic helicene, which is based on intramolecular [2 + 2 + 2] cycloisomerization of aromatic hexaynes under metal catalysis closing 6 new cycles of a helicene backbone in a single operation (**Scheme 5.10**).They have also developed an asymmetric version involving cobalt- or nickel-catalyzed cyclization to prepare the nonracemic [11]helicene-like derivatives in good diastereomeric purity.

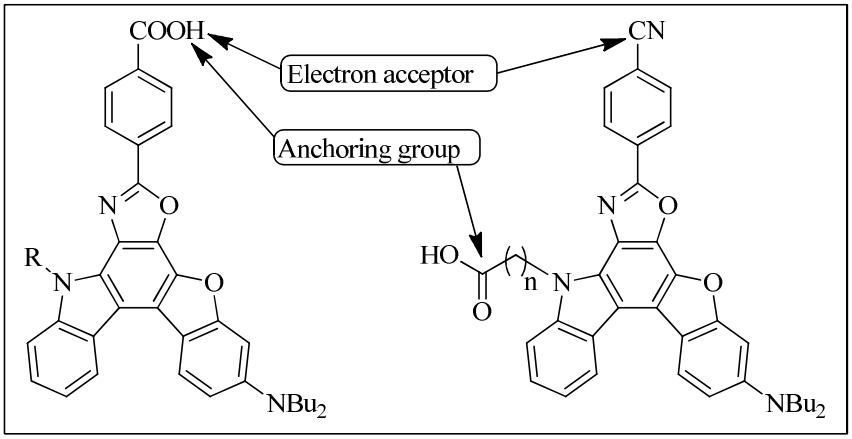
Scheme 5.10: Synthesis of helicenes by intramolecular [2 + 2 + 2] cycloisomerisation.



5.4 Applications of helicenes:

Helicenes as interesting compounds that have numerous potential applications in chemistry. They could be used as molecular machines like molecular ratchet,[25] molecular springs[26] and molecular switches,[27] dyes etc. Recently dye sensitized solar cells (DSSCs) have attracted considerable attention due to their low cost processes, high performance, and ease of production. Gratzel and O'Regan reported the first DSSCs in 1991. Because of the high expense of the Ru dyes involved, several environmentally friendly, easily prepared organic donor-acceptor π–conjugated (D–π–A) dyes have been investigated as alternatives.[28] Harima and co-workers synthesized a series of D–π–A dyes using a heterohelicene as a building block taking advantage of its conjugation framework and helical backbone (**Figure 5.4**).[29]

Figure 5.4: Organic D–π–A dyes.

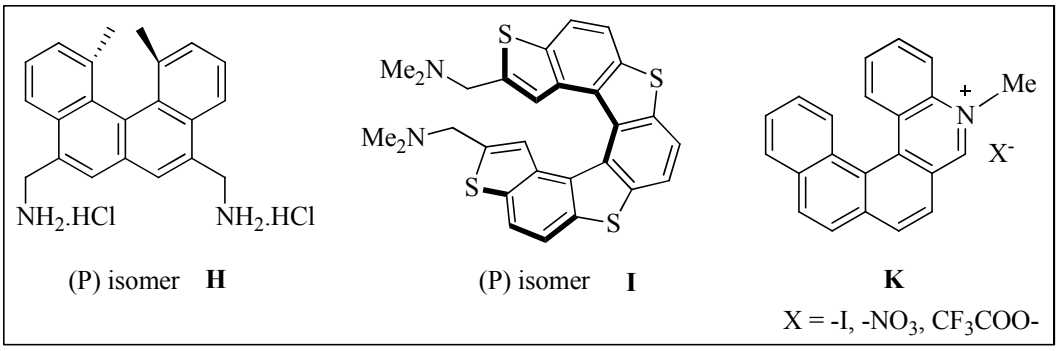


Katz *et.al.* described the first synthesis of two novel ladder polymers bearing heptahelicene connected by nickel salophen units in which the square planar geometry made the π-conjugation extend from the helicenes to the whole polymer.[30] Recently another novel type of ladder polymer forming a one dimensional wire, constructed from fused benzothiophene rings was reported by Nishide *et.al.* [31] Besides the above ladder polymers which have helical skeletons themselves, helicene units can be introduced into macromolecules by either directly synthesizing helicenes or utilizing helicene monomers. Similarly helicenes are used used in molecular recognition techniques.[32]

5.4.1 Biological applications of helicenes:

Telomerase inhibition has been considered as a new method of cancer therapy. Sugiyama and co-workers described the first example using a bridged helicene as a chiral wedge to effectively block the access of telomerase to telomeres by association with higher order G-quadruplex structures.[33] In 2002, Yamaguchi and co-workers first disclosed the chiral recognition between the helicenediamine **H** and B-DNA (**Figure 5.5**).[34] The apparent changes in the UV and CD spectra caused by adding calf thymus DNA to the solutions of (P)- and (M)-730 suggested that DNA-helicene complexes were formed. According to isothermal titration calorimetry, the binding constant of (P)-helicene is slightly larger than that of its enantiomer, whereas the chiral recognition whereby (P)-730 favors right-handed helicity is probably driven by entropy.

Figure 5.5: Helicenes used in biological applications.



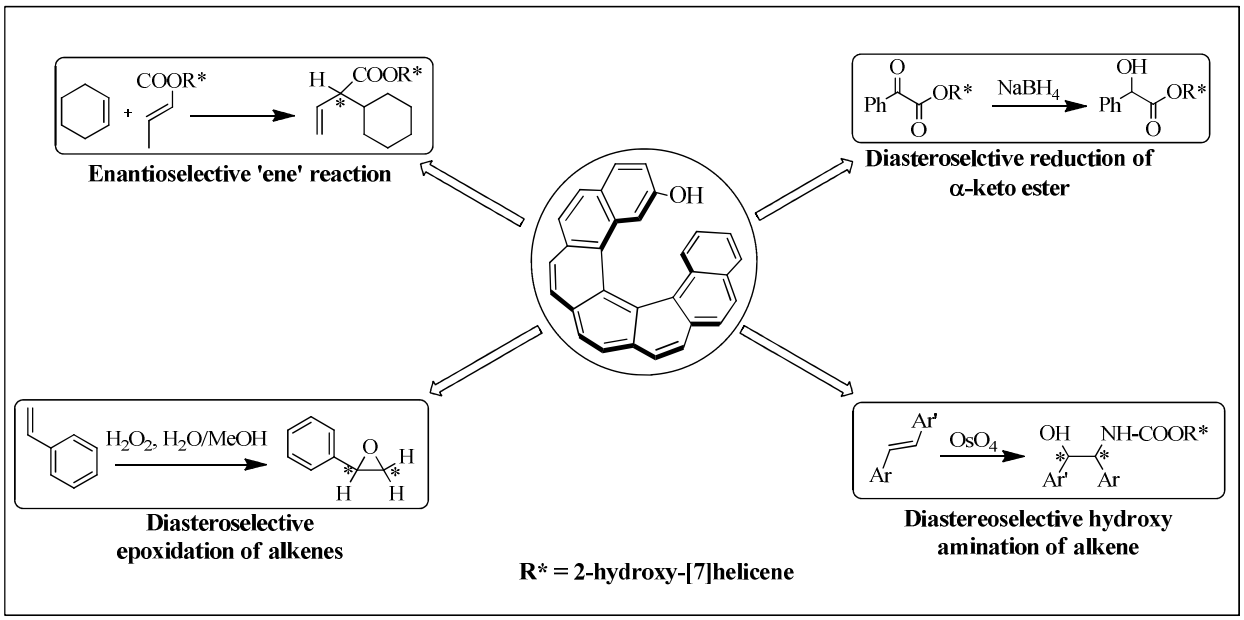
Sugiyama *et.al.*[35] reported that (P)-helicene **I** can bind Z-DNA selectively and convert B-DNA into Z-DNA. Also recently, Latterini *et.al.*[36] reported counterion effects in the binding between helicenes and DNA using the same organic azahelicenium moiety **J** with different anions (I^-, $NO_3^-$and $CF_3CO_2^-$).

5.4.2: Helicenes in asymmetric catalysis:

As helicenes are inherently chiral compounds they can be useful in asymmetric synthesis. As a consequence, helical carbohelicenes of C_2-symmetry were promising candidates for further innovations. Several features would position them favorably with a large chiral polyaromatic template which could favor some efficient and long range chiral inductions and some secondary binding interactions to the substrate by π–stacking. Additionally, reactions at higher temperatures

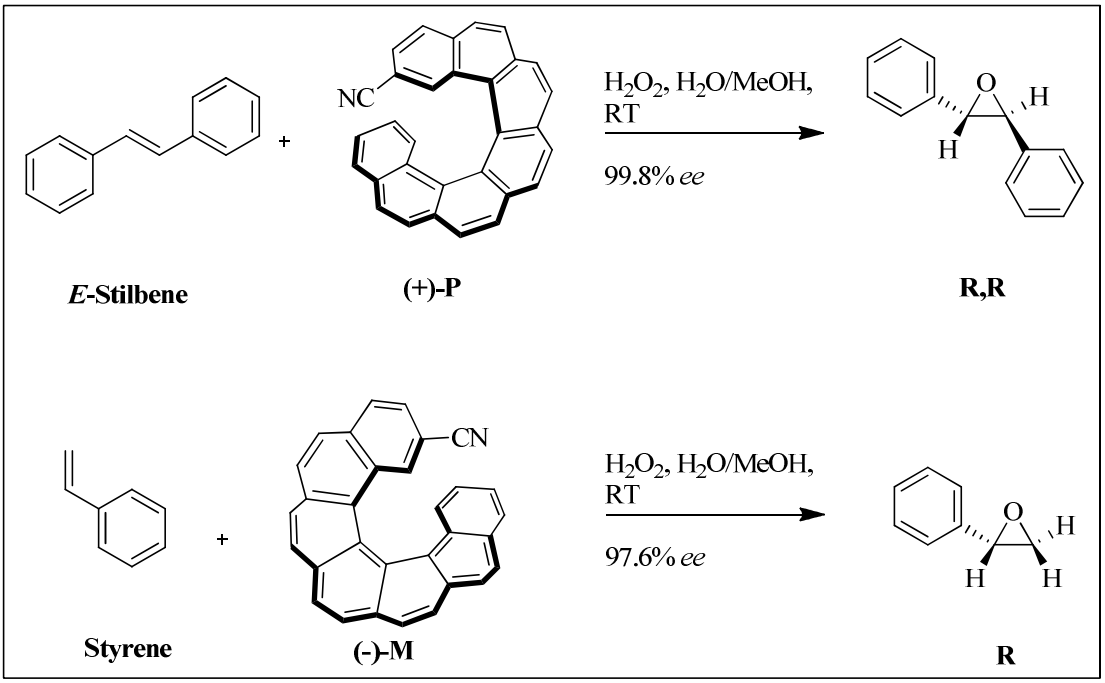
might be possible without racemizing the helicene ligand ([6]helicenes or higher helicenes). It would be an advantage compared to a lower-energy thermal racemization of many binaphthyl ligands.[37] Martin *et.al.* have utilized substituted [7]helicenes as chiral auxiliaries or chiral reagents in five different diastereoselective reactions, including reduction of α-keto esters,[38] hydroxyamination[39] and epoxidation[40] of olefins, synthesis of atrolactic ester,[41] and the ene reaction[42] (**Figure 5.6**).

Figure 5.6: Use of [7]helicenes as chiral auxiliaries or chiral reagent.



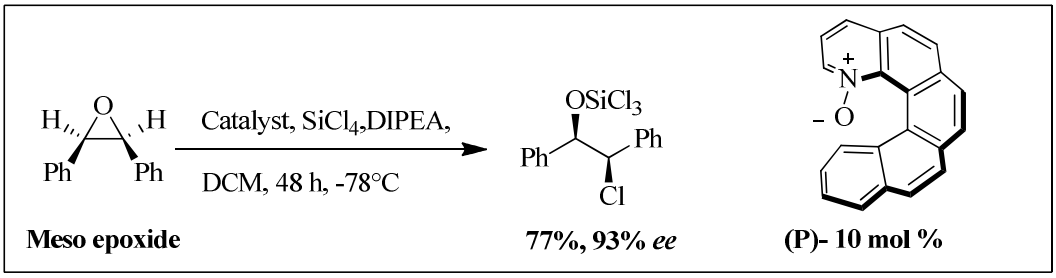
Among the first catalyzed asymmetric reactions involving a carbohelicene a catalytic enantioselective epoxidation of *E*-stilbene with the use of (P)-(+)-2-cyano-[7]helicene in the presence of H_2O_2 (92%; 99.8% ee). Similarly, α-methylstyrene afforded excellent results with (-)-2-cyano-[7]helicene (84%; 97.6% e.e.) [40, 41] (**Scheme 5.11**).

Scheme 5.11: Highly enantioselective epoxidation of *E*-stilbene and styrene.



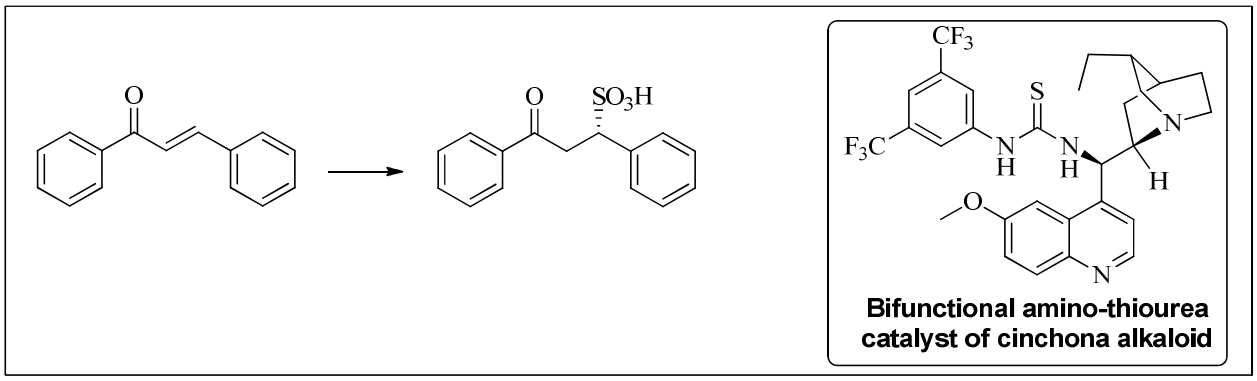
There are numerous examples showing, helicenes as a chiral lingands. Until present the use of helicene as a organocatalyst is not extensively explored. However, a few examples were reported by using a series of 1-aza-helicene *N*-oxides as chiral organocatalysts in heterohelicene chemistry.[42] Aza helicenes were synthesized from a Pd-catalyzed ring closure involving dihalogenated stilbene type substrates and $(Me_3Sn)_2$. *N*-oxidization with *m*-CPBA was achieved and the final helicenes were resolved by chiral HPLC. They were then tested in a catalytic enantioselective desymmetrization of some meso epoxides (**Scheme 5.12**).

Scheme 5.12: Organocatalytic asymmetric desymmetrization of meso epoxides.



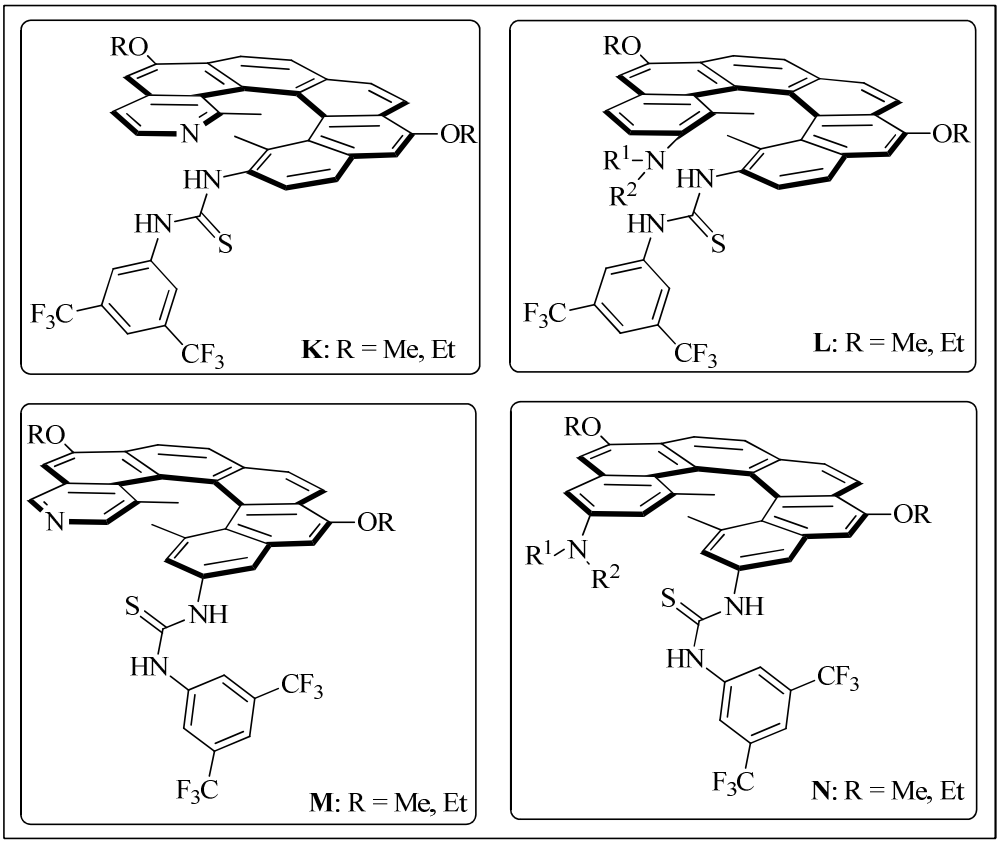
Keeping in mind the catalytic systems involving helicenes have not been explored we decided to synthesize the bifucntional helicene-thiourea catalysts. To the best of our knowledge this type of system has never been applied to any asymmetric synthesis. Recently, we reported the first enantioselective Michael addition of sodium bisulfite to a range of α,β-unsaturated systems (**Scheme 5.13**). Bifunctional aminothiourea derivates of cinchona alkaloids were used to catalyse this reaction. We found that this asymmetric reaction worked best affording products in excellent yields with 90-99% *ee* (for aromatic substrates). The mechanism of this reaction was investigated and we assume that the thiourea moiety is hydrogen bonded to the carbonyl group of the Michael adduct, thus locking it in place. We expect that the amino group belonging to the cinchona alkaloid also plays a key role in the reaction; activating the sodium bisulfite nucleophile and delivering it stereospecifically to one face of the Michael adduct.

Scheme 5.13: Enantioselective Michael addition catalysed by bifunctional aminothiourea catalyst.



We anticipate that aminothiourea derivatives of (*P*)- and (*M*)-[6]- and [7]-helicenes would behave in a similar manner in the organcatalytic reaction to that of aminothiourea derived cinchona alkaloid catalysts. The structures of our first generation helicene based aminothiourea catalysts are outline in **Figure 5.7**. The aminothiourea derivative of [6]-helicene **K** is based on the parent molecule; however, we intend to further substitute this molecule in order to enhance its stability. As only part of the molecule is utilized for organocatalysis the potential exist to further functionalise its backbone and carry out secondary and even tertiary operations there.

Figure 5.7: Proposed helicene-thiourea organocatalyst.

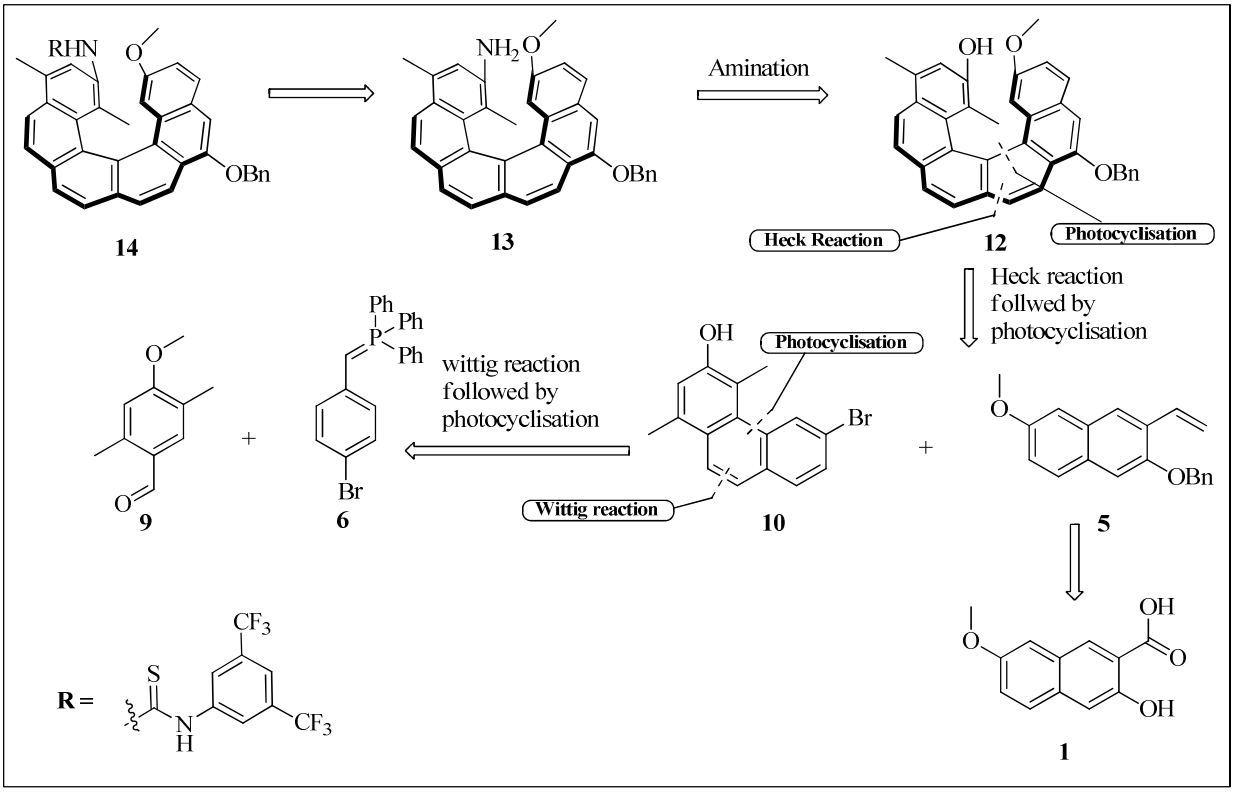


The aminothiourea functionalised [6]-helicenes **K-N** (**Figure 5.7**) are also based on the parent molecule. Again the potential exists to further functionalise this catalyst allowing for stabilization or further participation of the molecule in a secondary or tertiary catalytic cycle. The first catalyst **K** which incorporates the amino functionality into the backbone of the helicene structure can have the potential to bind substrates in a more locked manner, therefore enhancing selectivity. The potential (as with any catalyst/ligand system) exists to tailor these catalysts for specific reactions. Due to the many available binding sites on the helicene backbone, it seems plausible that the catalyst can be substituted in such a manner as to stabilize the intermediates of certain reactions, thus, mimicking nature.

5.5 Retrosynthesis for helicene thiourea catalyst:

Due to structural interest, the catalyst of type **L** was taken in to consideration. The structures **M** and **N** were excluded for the convenience as the catalytic site lie on the periphery of helicene (3,3' position) which can exert very little or negligible catalytic effect on the reaction in consideration. In case of catalyst **K** and **L**, as the catalytic site lie on the core of helicene (2,2' position) they can serve as the catalyst suitable for the primary study. To start we decided to synthesize the catalyst of type **L** as it can be easily accessible. With some structural modifications based on commercially available starting materials we proposed following retrosynthetic pathway (**Scheme 5.14**).

Scheme 5.14: Retrosynthesis for helicene-thiourea catalyst **14**.



In first instance the catalyst **14** can be obtained from 2-aminohexahelicene **13**. The Buchawald-Hartwig cross coupling reaction on triflate derivative of compound **12** with phthalimide followed by phthalimide deprotection of the obtained product will lead to the formation of the 2-aminohexahelicene **13**. The phenanthrene **10** and vinyl-naphthalene **5** can be treated in a heck reaction to get an alkene which can be subjected to the photocyclisation to give

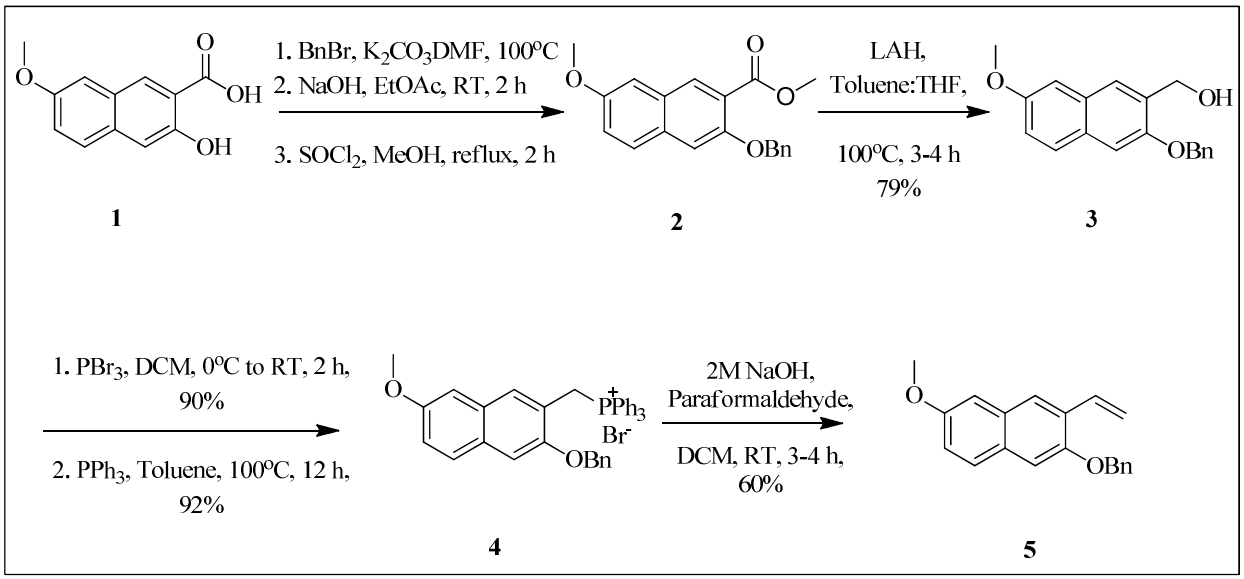
compound **12**. The phenathrene **10** can be synthesized with the classical method of Wittig reaction between **6** and **9** followed by a simple photocyclisation reaction. Whereas the compound **5** can be vinylated by following a sequence of reactions involving esterification of naphthoic acid followed by its reduction, then bromination and Wittig salt formation. The Wittig salt thus obtained, on treatment with paraformaldehyde will lead to formation of vinyl-naphthalene **5**.

5.6 Result and discussion:

In the beginning the plan was to synthesize the helicene derivative bearing two methyl groups at 1,1' positions in the inner helix of helicene (Catalyst **L** in **Figure 5.7**). Then due to difficulties in the synthesis of those properly substituted compounds we decided to synthesize compound **14** bearing only one methyl group in inner helix which is still enough to reduce the recemisation of helicene.

In the synthesis of helicene-thiourea catalyst **14** two building blocks *viz.* vinyl-naphthelene **5** and phenanthrene **10** were the key intermediates. Synthesis of vinyl-naphthalene **5** is outlined in the **Scheme 5.15**. The synthesis was started with the dibenzylation of 3-hydroxy-7-methoxy-2-naphthoic acid **1**.

Scheme 5.15: Synthesis of 2-(benzyloxy)-6-methoxy-3-vinylnaphthalene **5**.

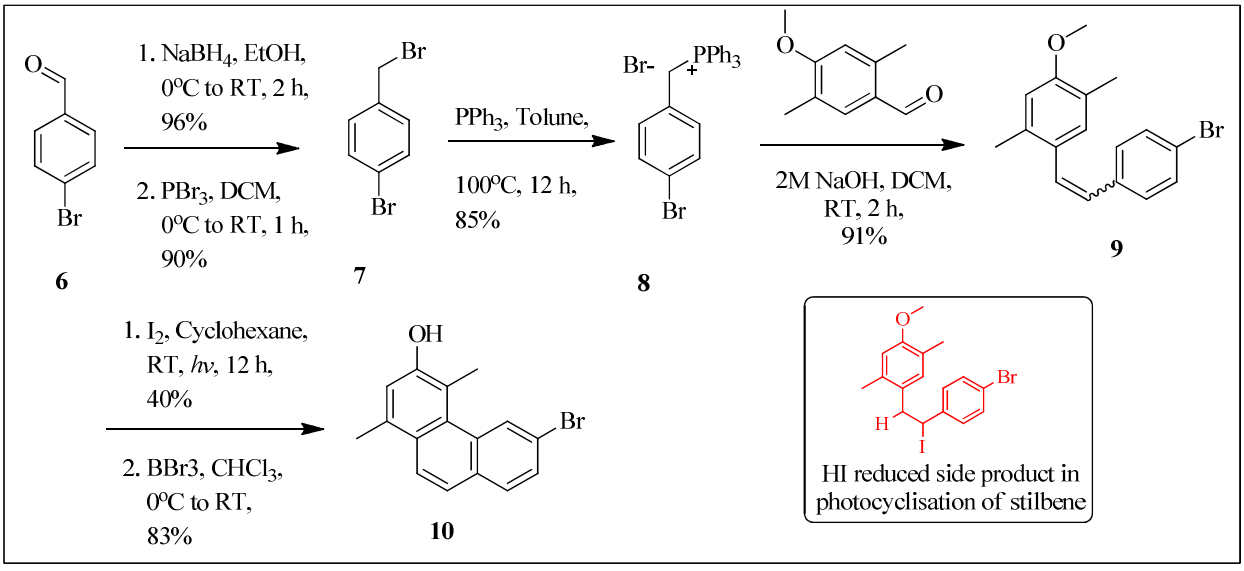


The dibenzylation of 3-hydroxy-7-methoxy-2-naphthoic acid **1** was carried out with benzylbromide, potassium carbonate in dry DMF. The benzyl ester thus obtained was

transesterified by hydrolysis using 2M NaOH followed by the treatment with thionyl chloride in methanol to give methyl ester **2**. The ester was then reduced using LAH in THF:toluene mixture to give (3-(benzyloxy)-7-methoxynaphthalen-2-yl)methanol **3** in 79% yield. The alcohol **3** was then brominated using phosphorus tribromide in dichloromethane to yield bromo-compound in 90% yield which was subsequently converted to a Wittig salt **4** by treatment with triphenyl phosphine in toluene with the yield of 92%. The Wittig reaction between the Wittig salt **4** and paraformaldehyde in presence of 2M NaOH, gave vinyl-naphthalene **5** in 60% yield.

The other intermediate phenanthrene **10** was synthesized from 4-bromobenzaldehyde **6** (**Scheme 5.16**). The 4-bromobenzaldehyde **6** was converted to (4-bromobenzyl)-bromide **7** by reduction using $NaBH_4$/EtOH followed by a treatment with phosphorus tribromide in usual reaction conditions. The (4-bromobenzyl)-bromide **7** was then converted to a Wittig salt **8** using triphenylphosphine in toluene in 85% yield. The Wittig salt **8** was then treated with 4-methoxy-2,5-dimethylbenzaldehyde in presence of 2M NaOH to give stilbene derivative **9** as a cis-trans isomeric mixture in the ratio 40:60 confirmed by ^{1}HNMR. The stilbene derivative **9** thus obtained was subjected to the photocyclisation using I_2 in cyclohexane in 40 % yield. The bromo,methoxy-phenanthrene was then subjected to hydrolysis using borontribromide to give 6-bromo-1,4-dimethylphenanthren-3-ol **10**.

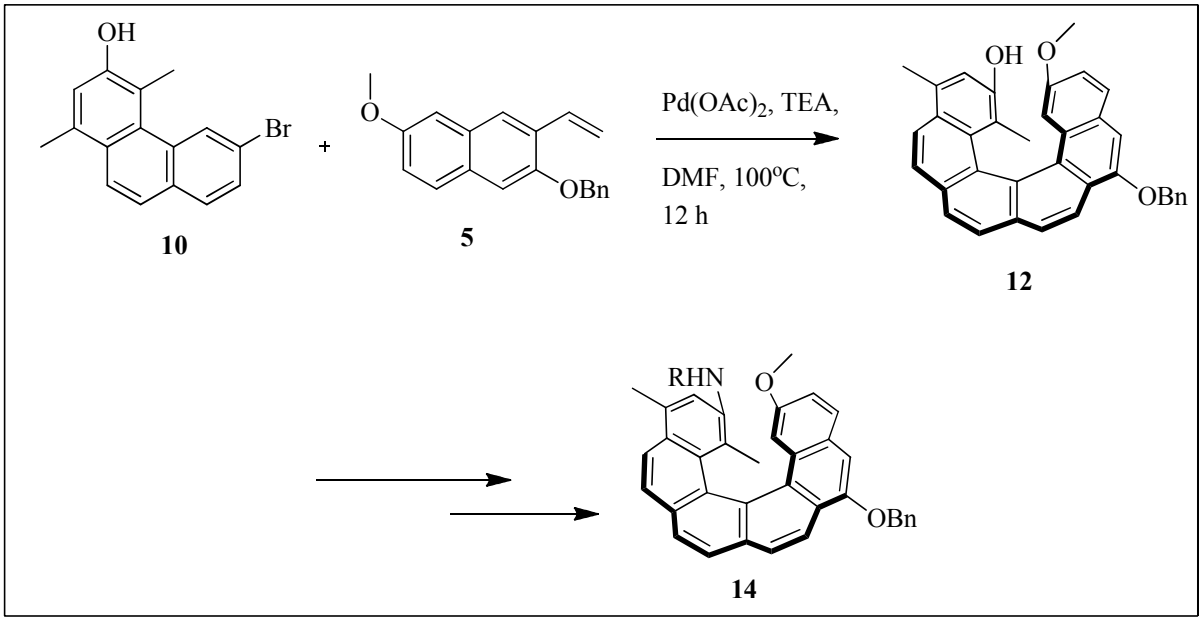
Scheme 5.16: Synthesis of phenanthrene **10**.



During the photocyclisation step we observed the addition/reduction product as well. Attempts of using propylene oxide to overcome formation of side product failed and overall degradation of the product was observed when the reaction was kept for longer times under light whereas the reaction without the use of any additives gave reasonable yield (40%) under normal reaction conditions of photocyclisation together with addition/reduction impurity.

After the synthesis of the two key intermediates (**5** and **10**) the next step was to couple them. They were coupled as shown in **Scheme 5.17**. The coupling was done in presence of $Pd(OAc)_2$ / TEA / DMF at 100°C for overnight. The crude product showed the formation of the coupled product however the yield was very low. This step needs to be optimized. The following sequence is in progress.

Scheme 5.17: Synthesis of helicene-thiourea catalyst **14**.



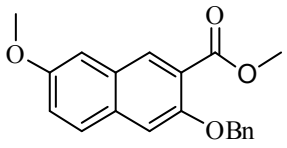
5.7 Conclusion and future work:

In all until now we have developed a route towards the helicene synthesis which can be elaborated for synthesis of diversely substituted helicenes. The final product although not in hand seems to be a promising catalyst for the asymmetric reactions. The next plan will be to finish the synthesis and the application of this novel helicene-thiourea catalyst for the asymmetric reactions. The advancement will be synthetic elaboration for making rest of the model helicen-thiourea catalyst of type **K**, **M**, **N** (**Figure 5.7**) and some more helicene-thiourea derived catalyst from the core of these molecules.

5.8 Experimental:

Material and Methods:

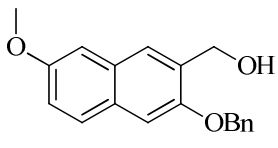
^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ or CD_3OD or DMSO-*d6* solutions at 300, 400 and 600 MHz for ^{1}H and 75.46, 100.6 and 150.92 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). *J* values are given in Hz. ^{1}H NMR and ^{13}C NMR spectral assignments were made by DEPT, gCOSY and gHSQC experiments. IR spectra were recorded in solvent as specified. Mass spectra (MS) were obtained with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. High Resolution Mass Spectra (HRMS) were recorded on a micromass LCT spectrometer using electrospray (ES^{+}) ionisation techniques. Reactions were conducted in oven-dried (120°C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under argon. Toluene was distilled from sodium. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with bp 40-60°C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70-230 mesh). Preperative TLC was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified as needed.



Methyl 3-(benzyloxy)-7-methoxy-2-naphthoate (**2**): To a solution of 3-hydroxy-7-methoxy-2-naphthoic acid **1**(5 g, 21.7 mmol) and K_2CO_3 (9.01 g, 62.2 mmol) in dry DMF (50 mL) was added benzyl bromide (9.29 g, 54.3 mmol). The reaction was then stirred at 100°C overnight. After completion, water was added to reaction mixture and extracted with CHCl3 (2 X 50mL). The organic layer was then washed with water (50 mL), brine and dried in *vacuo* to give benzyl 3-(benzyloxy)-7-methoxy-2-naphthoate as a gray-yellow solid. The crude product was used as it for the next step. Yield: 9.0 g, 98%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (s, 3H), 3.97 (s, 3H), 5.26 (s, 2H), 7.14 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 2.4 and 9.2 Hz, 1H), 7.24 (s, 1H), 7.33 (t, J = 7.44 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.55 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 8.8 Hz, 1H), 8.25 (s, 1H).

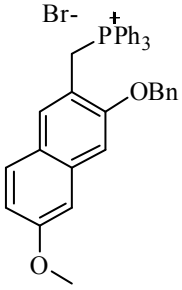
Benzyl 3-(benzyloxy)-7-methoxy-2-naphthoate (7.65 g, 19.22 mmol) was then dissolved in ethanol (50 mL) and 2M NaOH (2 g, 23.1 mmol, 11.5 mL) was added to it. The reaction mixture was stirred at RT for 2 h. After completion, ethanol was partially evaporated at *vacuo* and was extracted with ethyl acetate (3 X 30 mL). Combined organic layer was evaporated in *vacuo* to give brown solid which was recrystallised with absolute ethanol to give 3-(benzyloxy)-7-methoxy-2-naphthoic acid as brown needles. Yield 3.8 g, 64%.

3-(benzyloxy)-7-methoxy-2-naphthoic acid (2.3 g, 7.46 mmol) was then suspended in dry methanol (20 mL) under inert atmosphere and cooled to 0 °C. The solution of thionyl chloride (4.45 g, 37.4 mmol) was then added dropwise and reaction was refluxed for 2-3 h. After completion the reaction was cooled to room temperature and the solvent was evaporated at *vacuo* to give a crude sticky yellow oil which was recrystallised from ethanol to give the final product methyl 3-(benzyloxy)-7-methoxy-2-naphthoate (**2**) as light brown needles. Yield: 1.35 g, 56%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (s, 3H), 5.26 (s, 2H), 7.14 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 9.2 and 2.8 Hz, 1H), 7.24(s, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 7.56 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 9.2 Hz, 1H).



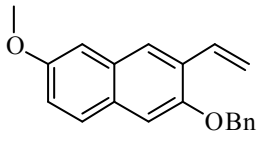
(3-(benzyloxy)-7-methoxynaphthalen-2-yl)methanol (**3**): The solution of methyl 3-(benzyloxy)-7-methoxy-2-naphthoate **2** (1.34 g, 4.17 mmol) in dry THF:toluene (20:10 mL) was cooled to 0 °C under nitrogen and powdered LAH (0.89 g, 23.5 mmol) was slowly added. The reaction was then heated to 100 °C for 3 - 4 h. After completion, reaction was cooled to 0 °C and ethyl acetate (10 mL) was added

slowly. The reaction mixture was then extracted with ethyl acetate (3 X 15 mL). Combined organic layers were washed with water (20 mL) and brine. The organic layer was then evaporated in *vacuo* to give crude oil which was then purified by flash chromatography to give (3-(benzyloxy)-7-methoxynaphthalen-2-yl)methanol **3** as a colorless oil. Yield: 1 g, 82%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (s, 3H), 4.87 (s, 2H), 5.21 (s, 2H), 7.12(s, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.19 (s, 1H), 7.34 – 7.40 (m, 1H), 7.43 (td, J = 0.8 and 7.8 Hz, 2H), 7.48 (d, J = 6.8 Hz, 2H), 7.64 (d, J = 9.2 Hz, 1H), 7.67 (s, 1H).



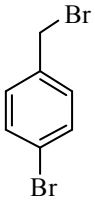
((3-(benzyloxy)-6-methoxynaphthalen-2-yl)methyl)triphenyl phosphonium bromide (**4**): To the solution of (3-(benzyloxy)-7-methoxynaphthalen-2-yl)methanol **3** (1 g, 3.40 mmol) in DCM (10 mL) was added slowly a solution of PBr_3 (2.85 g in 2 mL DCM) at 0 °C and reaction was left for stirring at 0 °C for 2 h. After completion reaction mixture was cooled to 0 °C and sat. $NaHCO_3$ (20 mL) was added slowly. The reaction mixture was then extracted with DCM (3X 10 mL). Combined organic layer was washed with sat. $NaHCO_3$, water, brine and evaporated in *vacuo* to give crude oil which on flash column chromatography gives 2-(benzyloxy)-3-(bromomethyl)-6-methoxynaphthalene as yellow oil. Yield: 1.2, 99 %, ^{1}H NMR ($CDCl_3$, 400 MHz) d 4.76 (s, 3H), 5.25 (s, 2H), 7.14 (dd, J = 2.8 and 8.8 Hz, 1H), 7.17 (s, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 9.2 Hz, 1H), 7.76 (s, 1H).

To the clear solution of 2-(benzyloxy)-3-(bromomethyl)-6-methoxynaphthalene (1.2 g, 3.36 mmol) in dry toluene (10 mL) was added triphenylphosphine (0.89 g, 3.4 mmol). The reaction was then heated overnight at 100°C. After completion the white precipitate was filtered and washed with cold toluene (10 mL). The white precipitate was dried under *vacuo* to give ((3-(benzyloxy)-6-methoxynaphthalen-2-yl)methyl)triphenyl phosphonium bromide **4**. Yield: 1.23, 59 %.



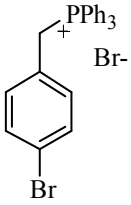
2-(benzyloxy)-6-methoxy-3-vinylnaphthalene (**5**): ((3-(benzyloxy)-7-methoxynaphthalen-2-yl)methyl)bromotriphenyl phosphorane **4** (1.23 g, 1.89 mmol) and paraformaldehyde (0.1 g, 3.33 mmol) were suspended in DCM (15 mL) and to the resulting solution 50% NaOH (0.4 g, 10 mmol) was added dropwise. After stirring the reaction at RT for 2 h, it was extracted with DCM (3 X 10 mL). The combined

organic layer was evaporated in *vacuo* to give a crude oil which was on purification with flash chromatography afforded 2-(benzyloxy)-6-methoxy-3-vinylnaphthalene **5** as a white solid. Yield %, ^{1}H NMR ($CDCl_3$, 400 MHz) d 4.10 (s, 3H), 5.25 (s, 2H), 5.65 (d, J = 12.4 Hz, 1H), 6.15 (d, J = 18.0 Hz, 1H), 7.25(s, 1H), 7.30 (dd, J = 2.8 and 9.2 Hz, 1H), 7.45 (t, J = 9.0 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.58 (t, J = 7.2 Hz, 2H), 7.64 – 7.70 (m, 3H), 7.75 (d, J = 8.8 Hz, 1H), 8.37 (s, 1H).

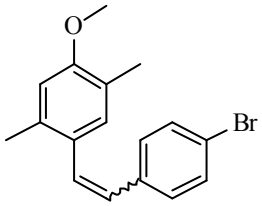


1-Bromo-4-(bromomethyl)benzene (**7**): To a solution of 4-bromobenzaldehyde **6** (1 g, 5.46 mmol) in ethanol (10 mL) was added $NaBH_4$ (0.32 g, 8.2 mmol) at 0 °C. After addition, reaction was slowly warmed and sirred at RT for 2 h. After completion, ethanol was evaporated at rotavapour and the residue was extracted with DCM (3 X 15 mL). The combined organic layer was then dried in *vacuo* to give the 4-bromobenzyl alcohol as white needles. Yield: 934 mg, 92.4%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.65 (s, 2H), 7.24 (d, J = 8.29 Hz, 2H), 7.49 (d, J = 8.24 Hz, 2H).

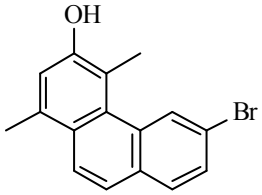
To the solution of 4-bromobenzyl alcohol (934 mg, 4.99 mmol) in DCM (5 mL) was added slowly a solution of PBr_3 (2.70 g, 9.48 mmol, in 5 mL DCM) at 0 °C and reaction was left for stirring at 0 °C for 2 h. After completion reaction mixture was cooled to 0 °C and sat. $NaHCO_3$ (10 mL) was added slowly. The reaction mixture was then extracted with DCM (3 X 10 mL). Combined organic layer was washed with sat. $NaHCO_3$, water, brine and evaporated in *vacuo* to give crude oil which was purified by flash column chromatography to give 1-Bromo-4-(bromomethyl)benzene **7** as a white needles. Yield: 975 mg, 78%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.44 (s, 2H), 7.27 (d, J = 8.40 Hz, 2H), 7.48 (d, J = 8.38 Hz, 2H).



(4-Bromobenzyl)triphenylphosphonium bromide (**8**): To the clear solution of 1-Bromo-4-(bromomethyl)benzene **7** (973 mg, 0.38 mmol) in dry toluene (5 mL) was added triphenylphosphine (1.01g, 0.39 mmol). The reaction was then heated overnight at 100°C. After completion the white precipitate was filtered and washed with cold toluene (5 mL). The white precipitate was dried under *vacuo* to give (4-Bromobenzyl)triphenylphosphonium bromide **8** as a white solid. Yield %, ^{1}H NMR ($CDCl_3$, 400 MHz) d 5.59 (d, J = 15.14 Hz, 2H), 7.03 – 7.13 (m, 2H), 7-14 – 7.25 (m, 2H), 7.54 – 7.67 (m, 6H), 7.70 – 7.86 (m, 9H).

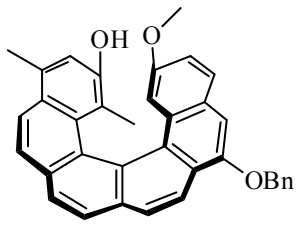


1-(4-Bromostyryl)-4-methoxy-2,5-dimethylbenzene (**9**): (4-Bromobenzyl)triphenylphosphonium bromide **8** (749 mg, 1.46 mmol) and 4-methoxy-2,5-dimethylbenzaldehyde (200 mg, 1.21 mmol) were suspended in chloroform (5 mL) and to the resulting solution 50% NaOH (58.5 mg, 1.46 mmol) was added dropwise. After stirring the reaction at RT for 1 - 2 h, it was extracted with DCM (3 X 5 mL). The combined organic layer was evaporated in *vacuo* to give a crude oil which was on purification with flash chromatography afforded 1-(4-Bromostyryl)-4-methoxy-2,5-dimethylbenzene **9** as a white solid with 60:40 trans:cis ratio. Yield: 290 mg, 75%,



6-Bromo-1,4-dimethylphenanthren-3-ol (**10**): The solution of Iodine (80 mg, 0.63 mmol) and 1-(4-Bromostyryl)-4-methoxy-2,5-dimethylbenzene **9** (100 mg, 0.31 mmol) in cyclohexane was irradiated with light for 12 h at RT. After completion, the solvent was evaporated in vacuo and the residue was directly purified by flash chromatography to give 6-bromo-3-methoxy-1,4-dimethylphenanthrene as a white solid. Yield: 40 mg, 40 %.

6-bromo-3-methoxy-1,4-dimethylphenanthrene (150 mg, 0.49 mmol) was then dissolved in DCM (5 mL) and a solution of BBr_3 (245 mg, 0.98 mmol in DCM) was added dropwise at 0 °C. The reaction was then stirred at RT for 1.5 h. After completion reaction mixture was cooled to 0 °C and cold water was slowly added. The reaction mixture was then extracted with DCM and evaporated in *vacuo*. The crude product was then purified using flash chromatography to give 6-bromo-1,4-dimethylphenanthren-3-ol **10** as a white solid. Yield 70 mg, 49%.



2-(benzyloxy)-14-methoxy-9,12-dimethylhexahelicen-11-ol (**12**): To the solution of 2-(benzyloxy)-6-methoxy-3-vinylnaphthalene **5** (100mg, 0.34 mmol) and 6-bromo-1,4-dimethylphenanthren-3-ol **10** (103 mg, 0.34 mmol) in dry DMF (5 mL) under nitrogen was added triethylamine (52.1 mg, 0.51 mmol) followed by $Pd(OAc)_2$ (7.6 mg, 0.034 mmol). The reaction was then heated at 100 °C overnight. After completion reaction was diluted with ethyl acetate (5 mL) and filtered through a pad of celite. The filtrate was then concentrated at *vacuo* to give crude 2-(benzyloxy)-14-methoxy-9,12-dimethylhexahelicen-11-ol **12** as a brown oil.

5.9 References:

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