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Pyrazoles: Synthetic Strategies and Their biological activity

الطالبات:
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The aim

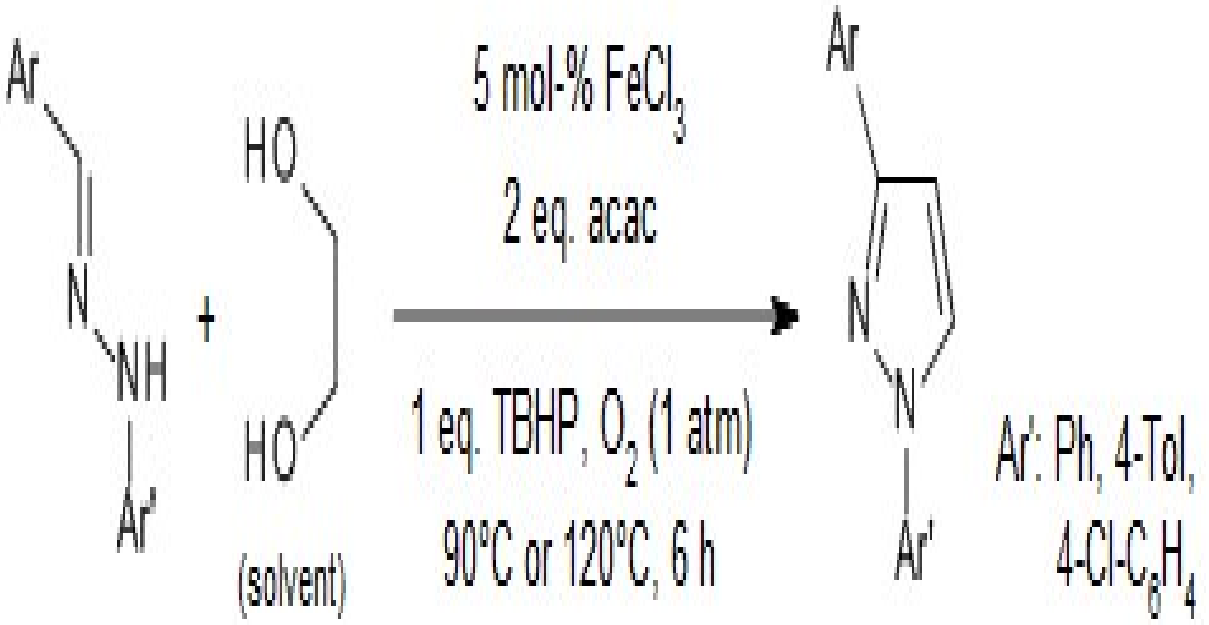
- The aim of this review is to provide an up to date developments in the synthetic strategies, biological activities associated with pyrazole derivatives. Different synthetic methodologies and the diverse pharmacological activities of pyrazole moiety was discussed.

Introduction:

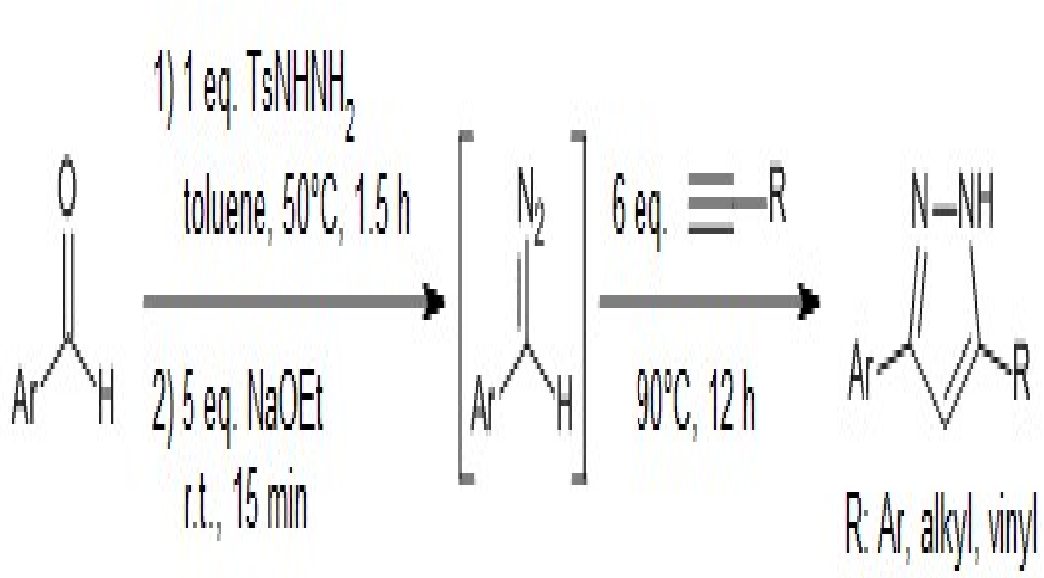
- Pyrazoles are the important members of heterocyclic compounds with two adjacent nitrogens in a five-membered ring system. Among the two nitrogen atoms; one is basic and the other is neutral in nature. These are aromatic molecules due to their planar conjugated ring structures with six delocalized π-electrons. The aromatic nature arises from the four π electrons and the unshared pair of electrons on the –NH nitrogen. The partially reduced forms of pyrazole are named as pyrazolines ; while completely reduced form is pyrazolidine .

❖Methods of preparations :

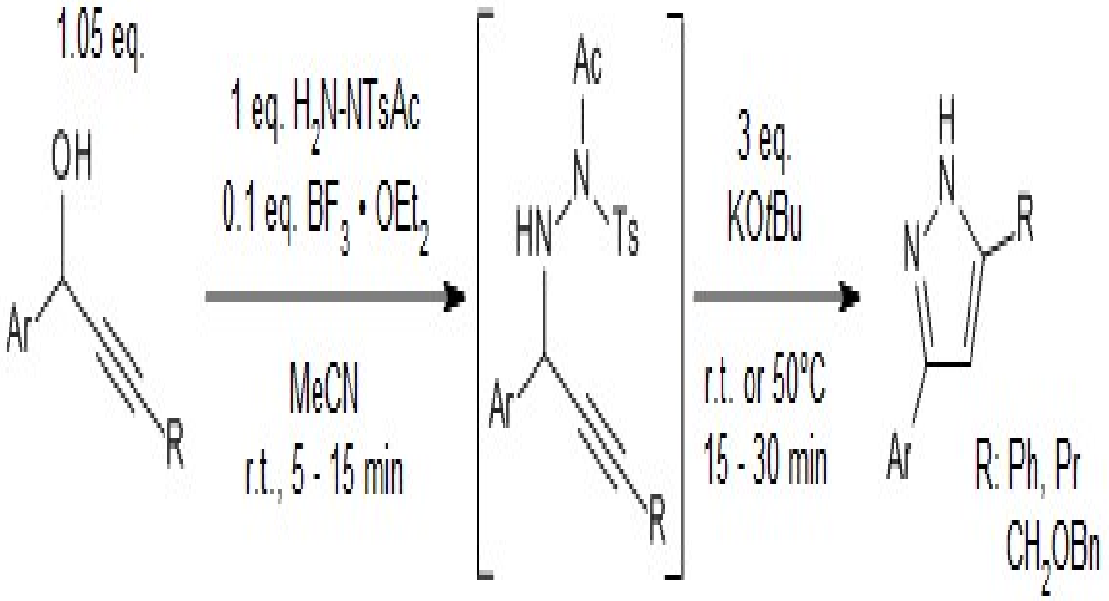
1)



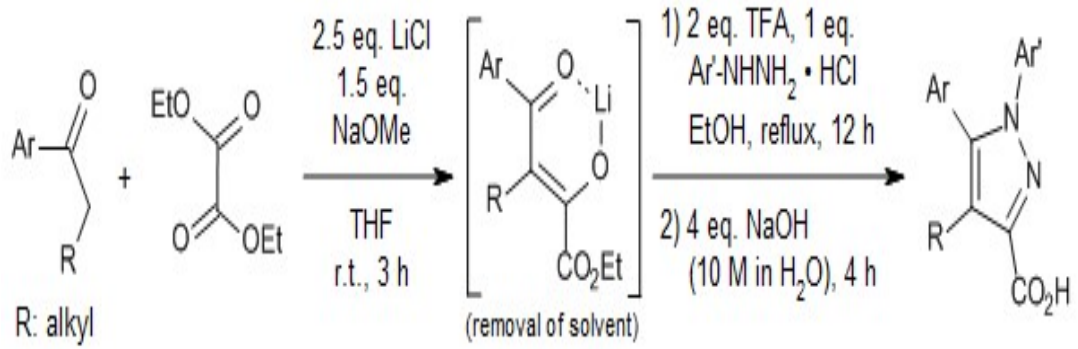
2)


1) 1 eq. TsNHNH2
toluene, 50°C, 1.5 h
2) 5 eq. NaOEt
r.t., 15 min
6 eq.
R
90°C, 12 h
Ar
H
N2
N–NH
R: Ar, alkyl, vinyl

3)


1.05 eq.
OH
Ar
R
1 eq. H2N-NTsAc
0.1 eq. BF3 • OEt2
MeCN
r.t., 5 - 15 min
Ac
N
HN
Ts
Ar
R
3 eq.
KOtBu
r.t. or 50°C
15 - 30 min
H
N
N
R
Ar
R: Ph, Pr
CH2OBn

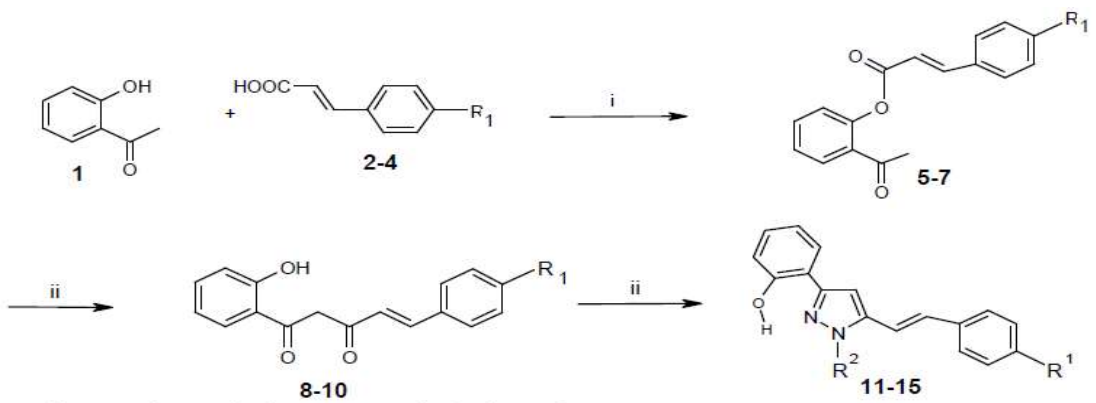
4)


Ar
O
R
+
EtO
O
O
OEt
2.5 eq. LiCl
1.5 eq.
NaOMe
THF
r.t., 3 h
Ar
O
Li
O
R
CO2Et
(removal of solvent)
1) 2 eq. TFA, 1 eq.
Ar'-NHNH2 • HCl
EtOH, reflux, 12 h
2) 4 eq. NaOH
(10 M in H2O), 4 h
Ar
Ar'
N
N
R
CO2H

R: alkyl

Biological activity of azoles:

- The experience in the synthesis of organic compounds, we have decided to devote some attention for the synthesis new substituted pyrazoles in three steps followed by the study of their anti-bacterial and anti-fungal activities.



(11) R_2=Ph ; R_1= Cl, (13) R_2 =H ;R_1=Cl, (15) R_2=Ph; R_1=H
(12) R_2=Ph ; R_1=OCH_3, (14) R_2=H; R_1=H,

[Reagents & Conditions: (i) Pyridine; $POCl_3$, rt. 4 hrs. (ii) Dry pyridine, KOH, rt. 1-2 hrs. (iii) NaOH, Ether, 1h Stirring At 15 ^{0}C.

Sceme-1

Biological activity :

Table-2:Antibacterial activity of pyrazoles

Compound	R_1	R_2	Conc. (µL)	Zone of inhibition (mm) *Xanthomonas campestris*	Zone of inhibition (mm) *Agrobacterium tumafeciens*
11	Cl	Ar	50	5.5	5.4
			100	14.2	11.3
12	OMe	Ar	50	5.6	4.7
			100	11.2	9.1
13	Cl	H	50	6.6	4.2
			100	13.8	10.9
14	H	H	50	6.0	4.3
			100	10.8	7.8
15	H	Ar	50	7.5	4.6
			100	11.6	8.6
Streptomycine			10	15	12

Table-2:Antifungal activity of pyrazoles

Compound	R_1	R_2	Conc. (µL)	Zone of inhibition (mm) *Aspergillus niger*	Zone of inhibition (mm) *Penicillum chrysogenium*
11	Cl	Ar	50	7.9	6.6
			100	15.6	12.4
12	OMe	Ar	50	7.3	6.1
			100	13.2	11.4
13	Cl	H	50	6.6	6.4
			100	14.4	11.7
14	H	H	50	6.4	5.3
			100	10.3	10.1
15	H	Ar	50	7.7	5.6
			100	10.6	10.8
Nystatin			10	19	13

The antifungal activities of pyrazoles (**11-15**) were studied *in vitro* at the concentration of 100 & 50 µg against two

fungal stains. The screening results indicated that all the compounds exhibited antifungal activities to the tested

fungi. It was noted that the pyrazole (**11-13**) with chloro and methoxyl groups showed a greater inhibitory activity

against both fungi compared to the remaining pyrazole derivatives (**14,15**).

Procedure:

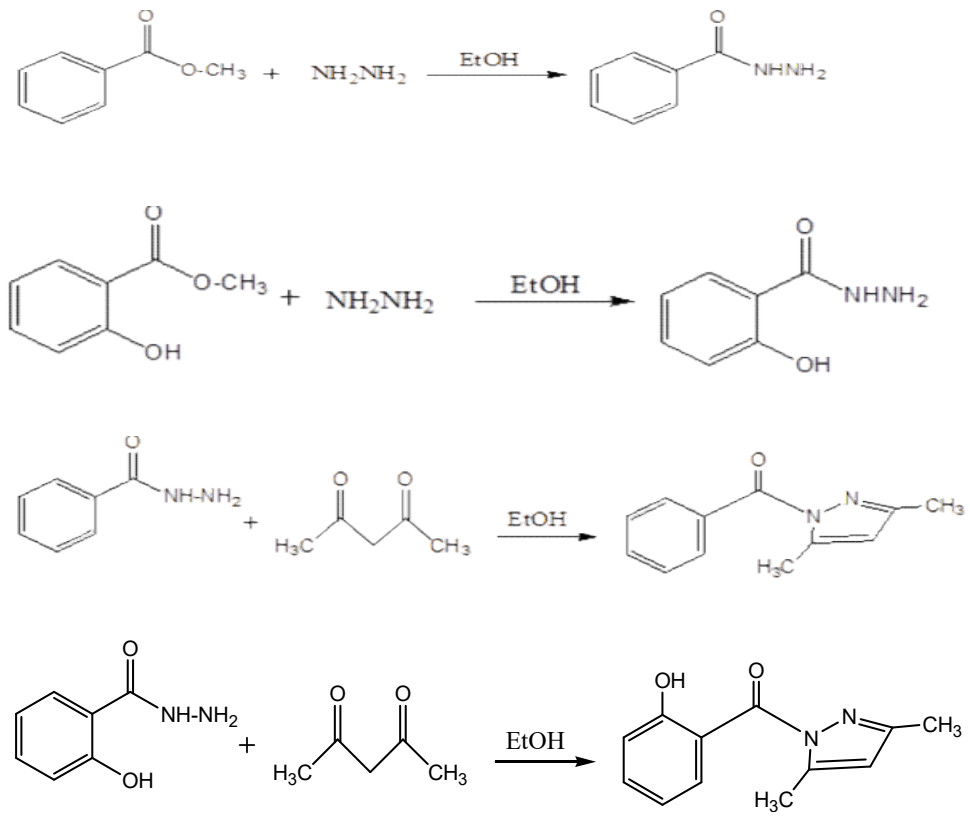


Table 3:Physical properties of pyrazole:

Compound	Molecular formula	Molecular weight (g/mole)	Crystal color and shape	m.p. (°C)
BH	$C_7H_6N_4S$	178.21	White powder	113-117
SH	$C_9H_{10}N_4S$	206.27	White powder	148-150
BP	$C_{11}H_{14}N_4S$	234.32	White powder	127-129
SP	$C_{12}H_{16}N_4S$	248.35	White powder	172-174

Results and discussion:

FT-IR Spectra of the synthesized pyrazole compounds were carried out using KBr disc method.

Table 4: Characterized bands in FT-IR spectra for prepared pyrazole compounds:

B.P.	Wave number (cm^{-1})	S.P.	Wave number (cm^{-1})
Str. Vib. C=O amide	1697*S	Str.vib.C=O amide	1662*M
str.vib.C=N	1608*M	Str.vib. C=N	1600*S
Str.vib.C=C	1558*W	Str.vib.C=C	1558*W
Str.vib. C=H (aliphatic)	1850*W	Str.vib.C=H (Al.)	3024*W
Str.vib.C=H (aromatic)	3078*W	Str.vib. C=H (Ar.)	2900*W

***S=Strong; M=Medium; W=Weak

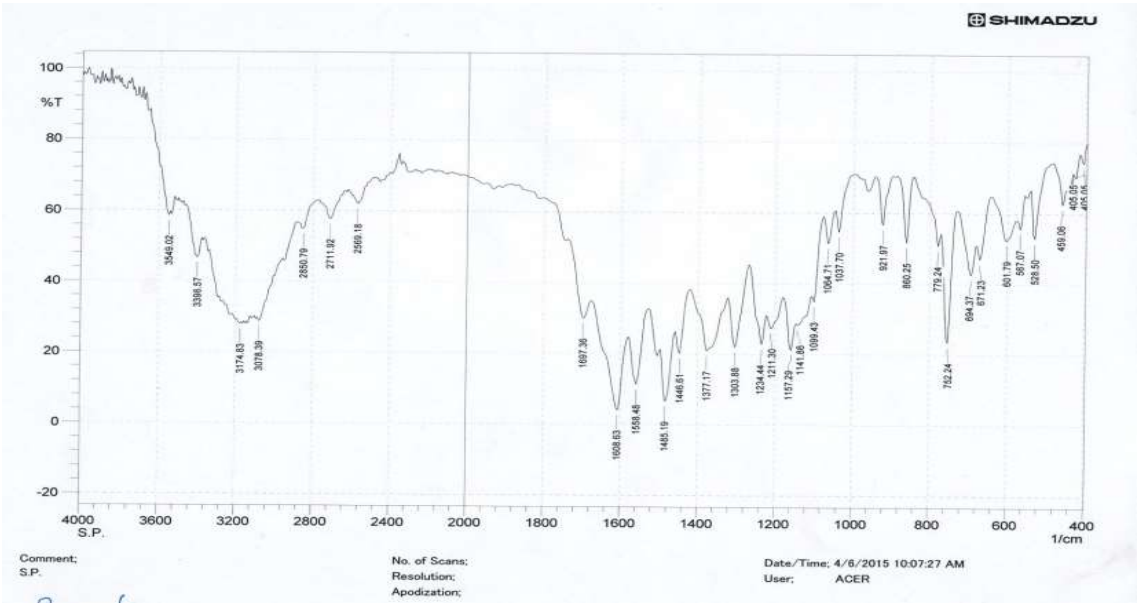


Figure 1: FT-IR Spectrum of S.P compound

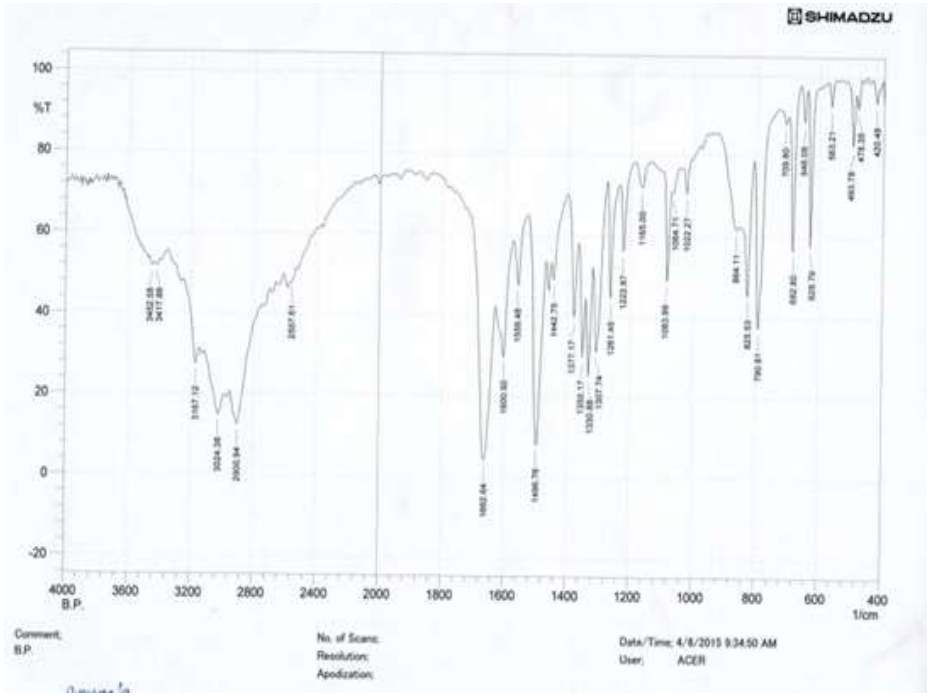


figure 2: FT-IR Spectrum of B.P compound

Preliminary antibacterial assay:

Hydrazide and pyrazole compounds were tested for their antibacterial activity against Gram negative bacteria (*E. coli*) and Gram positive bacteria (*S. aureus*) employing the filter paper disc diffusion method, the inhibition zone diameter was measured after 24 hrs. The preliminary results indicated that pyrazole compounds were active against *E. coli* and/or *S. aureus* greater than the hydrazide compounds, as shown in Table 4-2, and Figures 4-1 and 4-2.

Table 4-2 Inhibition zone of hydrazides (BH and SH) and pyrazoles (BP and SP) at 1000 µg/ml against *E. coli* and *S. aureus*

Compound	Inhibition zone (mm)	
	E. coli	*S. aureus*
BH	NI	10
SH	NI	IN
BP	10	9
SP	11	13

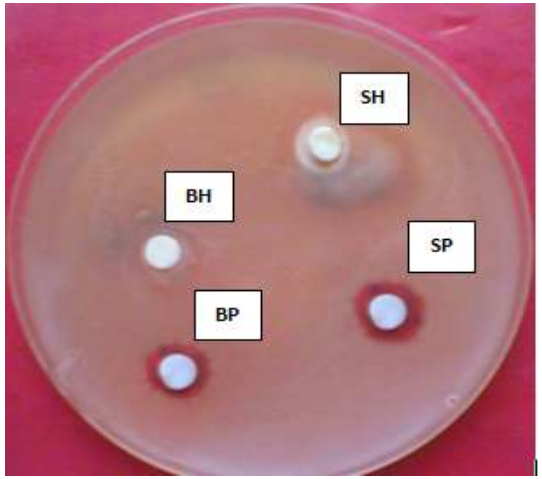


Figure 3 Antibacterial activity of hydrazides (BH and SH) and pyrazoles (BP and BP) against *E. coli*

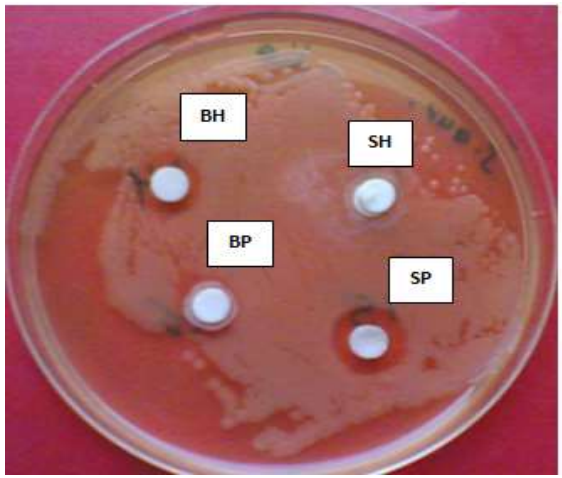


Figure 4 Antibacterial activity of hydrazides (BH and SH) and pyrazoles (BP and BP) against *S. aureus*

Conclusion:

- Pyrazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and pathological conditions, which are discussed in brief in this article. This article mainly focused on the synthetic strategies and biological activities associated with pyrazoles. Although organic chemists devised a broad range of methods for the synthesis of pyrazoles and new methods continue to appear, the design of new regioselective pyrazole forming reactions is still a compelling research topic. It is the fact that pyrazole derivatives are important compounds for biological systems, medicines, agrochemicals and many fields of industrial products. This review become a basis and is useful for researchers to device a new synthetic approach, new molecules of biological potency.

THANK YOU