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IONIC LIQUID CATALYSED ONE POT SYNTHESIS OF HIGHLY SUBSTITUTED PYRAZOLES PROMOTED BY MICROWAVE IRRADIATION

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Abstract:
A cost effective, eco-friendly procedure for one pot synthesis of highly substituted pyrazole has been developed by aromatic aldehyde, malononitrile, and phenyl hydrazine in Ionic liquid under microwave irradiation. This method provides several advantages such as simple, clean, reduced reaction time, easy workup, simple procedure and reduced environmental consequences.

Keywords: green chemistry, multicomponent reaction, pyrazole, ionic liquid-NMPYT, microwave irradiation.

Introduction:

The five membered N-linked heterocyclic compounds have received considerable attention in medicinal research. The condensation reaction suitable linear compounds are most of common and popular methods for preparing five membered heterocyclic compounds[i-vii]. Pyrazoles have long history of application in individualize agrochemical and pharmaceutical industries[viii-ix]. These compounds show promising biological activities such as antiviral[x], anti-tumor[xi], antimalarial[xii], anti-parasitic[xii-xiv], anti-pyratic[xv], anti convulsant[xvi], anti-depressant[xvii], analgesic[xviii-xix], anti-inflammatory-[xxi], antifungal[xxii], anti-microbial[xxiii-xxvii], anti-bacterial[xxviii-xxx] and antitumor[xxxi-xxxii]. The study of pyrazole derivative is significant in pesticide chemistry of their herbicidal[xxxiii] and insecticidal activities[xxxiv]. The pyrazole moiety makes the core structure of blockbuster drugs such as Celebrex (R) [xxxv] and Viagra(R) [xxxvi] that act as PDE-5 inhibitors, zoniporide[xxxvii], 1-aryl-5-aminopyrazole as NPY5 antagonist[xxxviii] and PNU-32945 as HIV-reverse transcriptase inhibitors[xxxix].

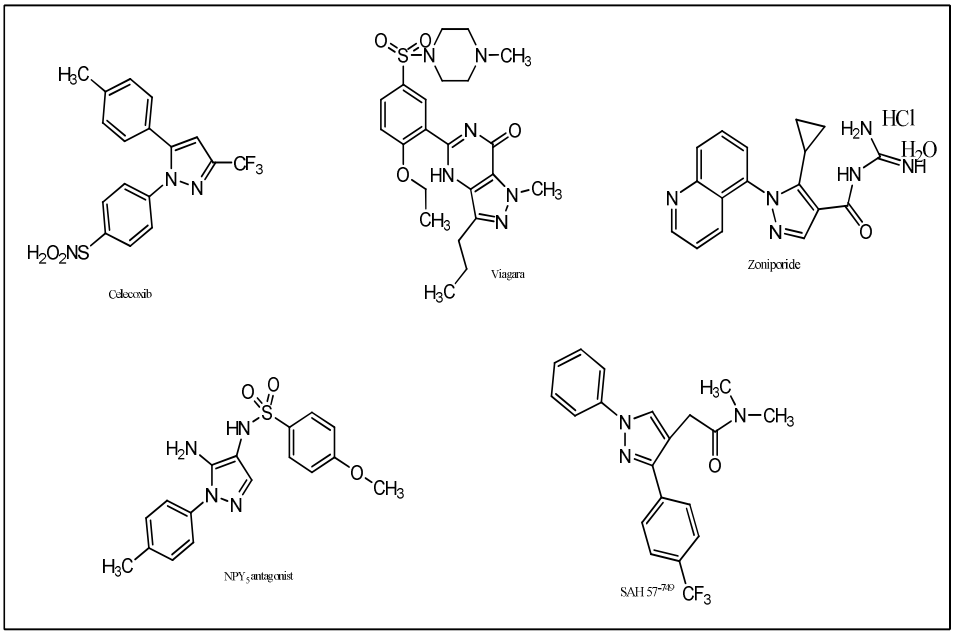


Fig. 1 Biological active compounds based on pyrazole derivatives.

The important features of pyrazoles, various synthetic methods are reported for pyrazole derivative[xl-xlv]. The preparations of highly substituted pyrazoles are the reaction between phenyl hydrazine, aromatic aldehyde, and malononitrile using ionic liquid-NMPYT under microwave irradiation **(scheme 1)**.

The problems in reported methods such as prolonged reaction time, low yield, use of hazardous solvents etc. Ionic liquid are used as green media for various organic transformation. Herein, inform that on the use of ionic liquid in cyclocondensation for obtaining highly substituted pyrazoles.

Material and method:

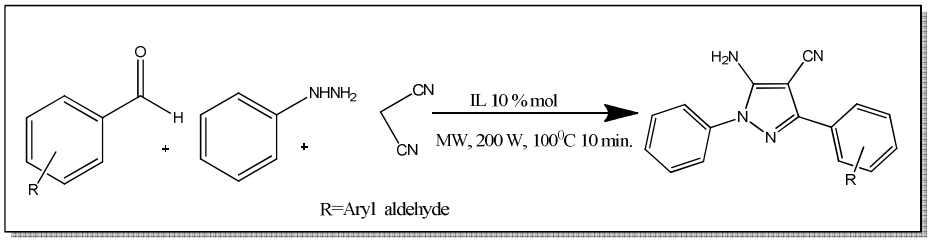
All chemicals were purchased from Merck chemical companies and they were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bucker DRX-400 spectrometer at 400 and 100 MHz respectively and IR were recorded in KBr on a Nicolet impact 410. Melting points were taken in open capillary and are uncorrected. The reaction were performed using scientific (MASS-II, Sineo) microwave radiation specially designed for organic synthesis.

General procedure for the preparation of 5-Amino-1, 3-diphenyl-1H-pyrazole-4-carbonitrile.

A mixture of aromatic aldehyde (1mmol),phenyl hydrazine (1 mmol) and 10 % Ionic liquid was placed in round bottom flask and stirred for 5 min. to it was added malononitrile (1mmol) and reaction contents were irradiated in microwave synthesis using 300 W MW power at 100^{0}C for appropriate time. After completation of the reaction (as indicated by TLC). The mixture was cooled to room temperature. Crystals of the product were formed, collected by filtration and then recrystallization from hot ethanol to obtain pure products.

Result and discussion:

Initially, the reaction was carried out under 4-methoxy Benzaldehyde, phenyl hydrazine, malononitrile and NMPYT ionic liquid[xlvi] as a model reaction. We report, an attempt has been made to develop a one pot multicomponent synthesis for highly substituted pyrazole.



Scheme 1: Synthesis of poly-substituted amino pyrazoles.

While optimizing amount of catalyst, result obtained exhibits less than 10 % of ionic liquid fails to obtained product. In our studies aromatic aldehyde, phenyl hydrazine, malononitrile and no catalyst showed no reaction at room temperature. Even after 24 hr under reflux condition, reaction was ineffective to any product **(Table-1, entry 1)**. The scope of different catalyst such as Acetic acid, Zinc chloride, Molecular iodine, Silica chloride on the product yield was investigated, but yields were very low **(Table-1, entry 2-5).** Reaction was performed under microwave radiation using NMPYT ionic liquid as a catalyst gave 90 % yield respectively **(Table-1, entry 6)**.

The extremely interesting scope of this synthetic protocol to afford highly substituted pyrazole make a less severe the use of toxic and hazardous organic solvent. We examined to study the behavior of different aromatic aldehyde in reaction with phenyl hydrazine and malononitrile under optimum conditions. All the reaction products with other details are depicted in Table-2. Interestingly, 4-Methoxy, 4-Bromo, 4-Floro, 4-Hydroxy, 4-Methyl, 2-Chloro, 4-Methoxy-3-Hydroxy, 2-Hydroxy, 4-Nitro, aromatic aldehyde with electron withdrawing and electron donating substrates in ortho, meta and para positions of the aromatic ring have also contributed positively to obtain the desired pyrazole-4-carbonitrile derivatives in good to high yields **(Table 2)**.

Physical data :

5-Amino-1-phenyl-3-p-tolyl-1H-pyrazole-4-carbonitrile (4e): Pink powder, M.P:175-176^{0}C, *v*max (KBr) 3483, 3320, 3096, 2926, 2360, 1599, 1416, 1256, 1128, 1114, 1097 cm−1. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.42 (s, 3H), 6.92 (dd, J = 3.5 Hz and J = 7.3 Hz, 1H), 7.16 (d, J = 7.76 Hz, 2H), 7.23 (d, J= 7.9 Hz, 2H), 7.30–7.34 (m, 2H), 7.60 (d, J = 7.9 Hz, 2H), 7.71 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 21.91, 104.66, 113.23, 120.45, 126.63, 129.72, 129.78, 132.96, 138.15, 138.98, 145.21, 148.83, 153.21. Anal.Calcd for $C_{17}H_{14}N_4$: C, 74.44; H, 5.15; N, 20.43%. *Found*: C, 74.89; H, 5.19; N, 20.13%.

5-Amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4i): Red powder, M.P. = 163–165°C, *v*max (KBr)3468, 3351, 3103, 2360, 1601, 1416, 1458, 1345, 1257, 11241,1108, 1096 cm−1. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.99(s, 1H) 7.19 (d, J = 7.5 Hz, 2H), 7.30–7.35 (m, 2H), 7.74– 7.80 (m, 3H), 8.06 (s, 1H), 8.25 (d, J = 7.6 Hz, 2H). Anal.Calcd for $C_{16}H_{11}N_5O_2$: C, 62.96; H, 3.64; N, 22.95%. *Found*: C, 63.06; H, 3.59; N, 23.04%.

5-Amino-3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4g): Yellow powder, M.P. = 160–162°C, *v*max (KBr) 3584, 3488, 3342, 3103, 2359, 2198, 1603, 1414, 1223, 1193, 1109, 1051cm−1. ^{1}H NMR ($CDCl_3$, 500 MHz): δ(ppm) 6.77 (t, *J* = 7.3 Hz, 1H), 6.86–6.91 (m, 2H), 6.97 (d, *J*= 7.6 Hz, 2H), 7.15–7.19 (m, 1H), 7.25 (dd, *J* = 7.5 Hz and *J*= 8.3 Hz, 2H), 7.54 (dd, *J* = 1.5 Hz and *J* = 7.7 Hz, 1H), 8.15(s, 1H), 10.39 (s, 1H), 10.53 (s, 1H).^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 112.61, 116.81, 119.84, 120.26, 121.36, 125.46, 128.18, 130.06, 130.16, 138.14, 145.63, 150.56, 152.31, 156.52. Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.56; H, 4.39; N, 20.29%. *Found*: C, 69.49; H, 4.47; N, 20.36%.

Table 1-Optimization of catalyst.

Entry	**Catalyst** [a,b]	**Reaction time (hr/min)**	**Yield**[c] **(%)**
1	None	24hr	Trace
2	AcOH	8 hr	56
3	$ZnCl_2$	5 hr	58
4	I_2	3 hr	62
5	SiO_2 Cl	2 hr	80
6	**NMPYT (ionic liquid)**	**10 min.**	**90**

[a] Amount of catalyst(10 mol%). [b]Reaction was carried at 100^{0}C. [c] isolated yield of pyrazole.

Table 2-Ionic liquid NMPYT catalyzed one pot synthesis of highly substituted pyrazoles microwave irradiation.

Entry	**Aldehyde**	**Time(min.)**	**Yield**[a] **(%)**	**Melting point (^{0}C)**
4a	4-OMe-Benzaldehyde	10 min.	90	124-125
4b	4-Br-Benzaldehyde	11 min.	92	178-179
4c	4-F-Benzaldehyde	10 min.	91	110-111
4d	4-OH-Benzaldehyde	13 min.	88	178-180
4e	4-Me-Benzaldehyde	11 min.	93	175-176
4f	4-OMe-3-OH-Benzaldehyde	10 min.	95	158-159
4g	2-OH-Benzaldehyde	10 min.	85	160-161

4h	2-Cl-Benzaldehyde	11 min.	95	126-128
4i	4-NO_2-Benzaldehyde	15 min.	80	163-165

[a] isolated yield.

Conclusion:

In summary, we have developed an expedient and clean method for the synthesis of highly substituted pyrazole. These methods advantages including shorter reaction time, simple experimentally workup procedures and non-toxic by product. This protocol represents a promising green route for synthesis of pyrazole compound.

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