



AN ENVIRONMENTALLY BENIGN ALUM CATALYZED APPROACH FOR SYNTHESIS OF POLYSUBSTITUTED AMINO PYRAZOLE

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Abstract

A cost effective, environmental friendly and productive method has been developed for the synthesis of polysubstituted 2-amino pyrazole via reaction of various substituted aldehydes, phenyl hydrazine and malononitriles in presence of 10% alum as catalyst in aqueous medium at room temperature. Present method consist of significant green concern, easy available, cheap solvent and catalyst as well as clean reaction profile, simple operational procedure and productive.

Keywords: Potassium aluminum sulfite (Alum), amino pyrazoles, water mediated, Conventional, one pot green.

Introduction

Nitrogen containing heterocyclic compounds is known for their significant medicinal utility. The extensively used method for the obtaining cyclic nitrogen containing useful intermediates or compounds is cyclisation of suitable precursor. Among all these nitrogen bearing heterocycles, pyrazole received considerable focus due to its wide spectrum of application in the field of pharmaceutical and agrochemical fields. Pyrazole derivatives exhibits biological activity as antitumor,ⁱ antibacterial,ⁱⁱ antimicrobial,ⁱⁱⁱ antifungal,^{iv} anti-inflammatory^v and analgesic^{vi}. Study reveals that pyrazole contain molecules remarkably acts as antidepressant,^{vii} antimalarial,^{viii} antitumor^{ix} as well as antiviral^x agent. 5-amino pyrazole analogues show promising medicinal utility. ([Figure 1](#)) Few synthetic strategies have been reported for pyrazole^{xi-xiii} either consist of hazardous acid, tedious workup of purification with envirohazardous organic solvents.

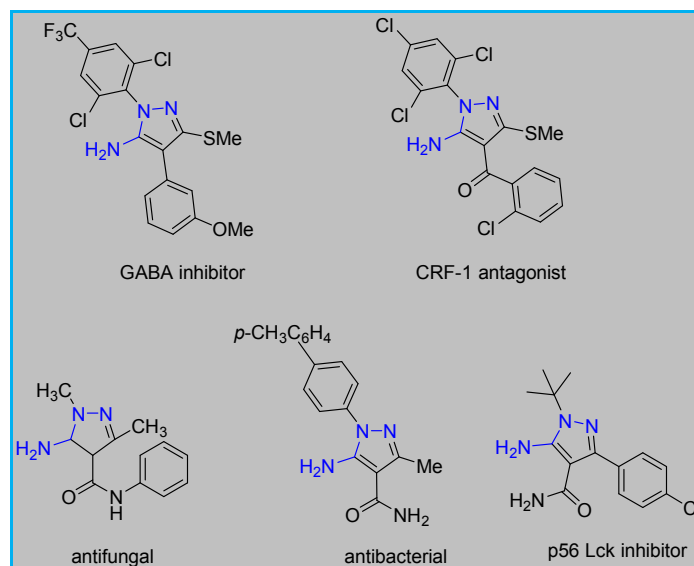


Figure 1. Biologically active 5-aminopyrazole analogues.

The most widely used synthetic methods for substituted pyrazole consist of aldehyde, malononitriles or β -ketoester and hydrazine (Figure 2)^{xiv-xvii} and reaction between 1,3-dipolar cycloaddition of diazo compounds on triple bonds.^{xviii}

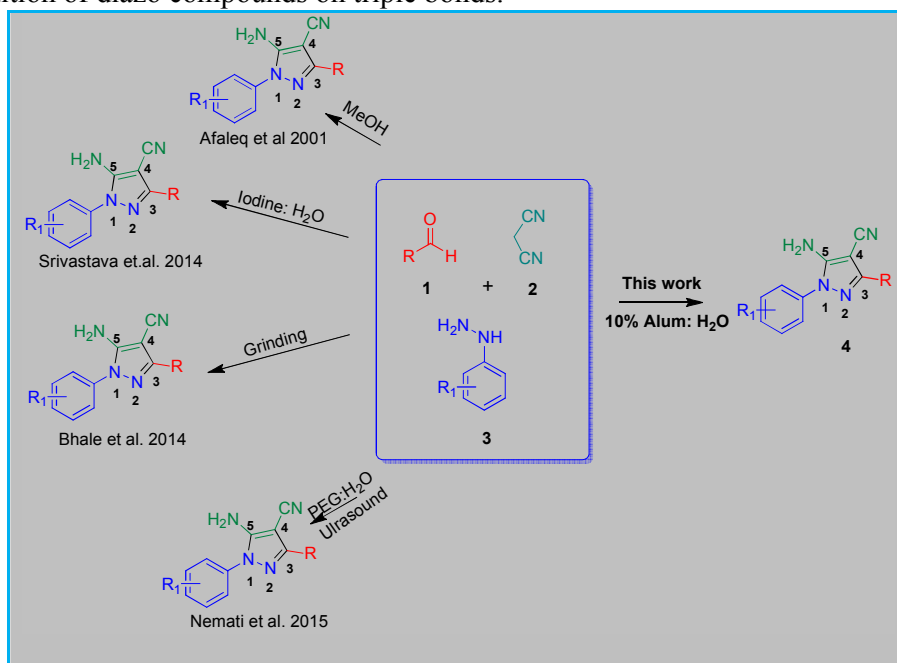


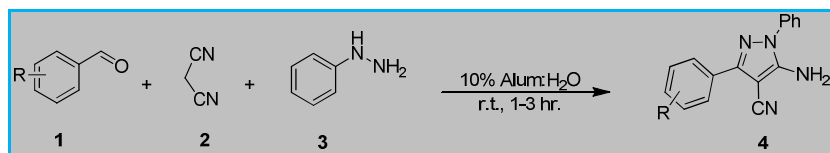
Figure 2. Reported syntheses of highly substituted pyrazole analogues from aldehyde, hydrazine and malononitriles.

Experimental

General

Aromatic aldehydes, phenyl hydrazine, malononitriles and catalyst Alum were commercially available. The major chemicals were purchased from Sigma Aldrich and Avra labs. Reaction courses were monitored by TLC on silica gel pre-coated F²⁵⁴ Merck plates. Developed plates

were examined with UV lamps. Melting points were recorded on SRS Optimelt, melting point apparatus and these are uncorrected. IR spectra were run for KBr disc on Perkin-Elmer 120-000 A apparatus (ν max in cm^{-1}), and ^1H NMR spectra were recorded on a Bruker AVII 400 spectrometer in CDCl_3 using TMS as an internal reference with chemical shift values being reported in ppm. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in CDCl_3 and TMS was used as an internal reference. Chemical shifts are reported as δ ppm units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br)



Scheme 1. Water mediated alum catalyzed one pot synthetic approach for amino pyrazole analogues.

General experimental procedure for the synthesis of compounds 4a-4j.

In a 20 mL, 10% aqueous alum solution, equimolar mixture of substituted aldehydes and malononitriles (1mmol) were added and stirred for 10 min. at room temperature. To this reaction mixture finally phenyl hydrazine (1mmol) was added in two portions for another 10 min. Reaction allowed to stirred for room temperature and monitor by TLC ((silica gel coated aluminium plates, Merk) for appropriate time. (Table 1) On completion of reaction, obtained solid filter, wash several times with water and recrystallized. Product 4i, workup changes to extraction with ethylacetate, organic layer wash several times with water, followed by evaporation of organic solvent.

Spectral analysis of selected products. (4a- 4c)

5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (4a). Whitesolid, melting point: 154–156°C. IR (KBr) ν max 3477, 3344, 3072, 2376, 1555, 1410, 1230, 1143, 1111 cm^{-1} ; ^1H NMR(400 MHz, CDCl_3) (δ ppm) 7.79 (d, 2H), 7.64 (s, 1H). 7.58 (s, 1H), 7.31 (t, 2H), 7.23 (m, 3H), 7.09–7.21 (d, 2H), 6.80 (t, 1H); ^{13}C NMR(100 MHz, CDCl_3) (δ ppm) 165.10, 155.16, 149.83, 141.47, 141.61, 131.44, 129.52, 128.21, 127.21, 121.80, 115.47, 114.47.

5-Amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4b). Cream color solid, melting point: 122–123°C; IR (KBr) ν max 3510, 3411, 3180, 2510, 2290, 1722, 1586 cm^{-1} ; ^1H NMR;(400 MHz, CDCl_3) (δ ppm) 7.80 (s, 2H) 7.73 (d, 2H), 7.42 (d, 2H), 7.21–7.36 (m, 2H), 7.20 (d, 2H), 6.90 (t, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 160.13, 148.56, 143.27, 134.35, 131.22, 130.84, 128.16, 127.54, 120.11, 116.45.

5-Amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4c). Red solid, melting point: 165–166 °C .IR (KBr) ν max. 3515, 3390, 3200, 2404, 1680, 1500, 1495, 1381, 1290, 1145, 1112, 1072 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3), (δ ppm) 8.61 (d, 2H) 8.12 (s, 1H), 7.79–7.85 (m, 3H), 7.24–7.35 (m, 2H), 7.26 (d, 2H), 7.11 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) (δ ppm) 157.13, 149.98, 146.02, 138.21, 136.30, 131.52, 131.41, 129.97, 122.78, 122.55, 123.77, 113.43, 112.76

5-Amino-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (4g). Orange color solid, melting point: 125–127°C IR (KBr) ν max 3535, 3350, 3200, 2370, 1602, 1489, 1467, 1383, 1310, 1240, 1163, 1141 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (δ ppm) 8.55 (s, 1H) 8.19 (d, 1H), 8.13 (d, 1H), 7.97 (s, 1H), 7.73 (s, 1H) 7.61 (t, 1H), 7.39 (t, 2H), 7.22 (d, 2H), 6.95 (t, 1H); ^{13}C NMR(100 MHz, CDCl_3) (δ ppm) 158.14, 150.61, 145.42, 138.41, 135.13, 132.09, 130.01, 129.66, 122.45, 122.13, 121.23, 114.14, 112.58.

Results and Discussions

In continuation of previous research work, exploring naturally occurring alum for elementary organic reactions, set and executed a series of reactions to optimized significant amount of catalyst and solvent for the cyclocondensation reaction of aromatic aldehyde, malononitriles and phenyl hydrazine. For model reaction Benzaldehyde (1mmol), Malononitriles (1mmol) and Phenyl hydrazine (1mmol) were used. While optimizing amount of catalyst, result obtained exhibits less than 10% of alum fails to obtained remarkable product in case of hydroxy containing aromatic aldehydes. No significant elevation of yield of product observed when amount of catalyst increase to 15%. Series of experiment were performed to know effect of temperature on yield of product. Reactions performed at 40°C, 50°C, 60°C and 80°C, first two reaction temperature (40°C, 50°C) reduced time of reaction but no remarkable change in yield of product observed. On further elevation of temperature (50°C, 60°C) gluey mass obtained with little product. Model reaction study also reveals that preference of sequential addition affect the profile of reaction. Benzaldehyde then immediately followed by malononitrile addition stir for few minutes and finally phenyl hydrazine is more constructive than all substrate at ones.

Table 2 Synthesis of substituted pyrazole with yield of products.

Product	R (1)	CH ₂ (CN) ₂ (2)	PhNHNH ₂ (3)	Yield ^a (%)	Time in hr.	M.P. / (Lit.) °C
4a	-H	2	3	93	2	154-156/ 155-158 [15][16]
4b	4-Cl	2	3	95	1	122-123/ 126-128 [15][16]
4c	4-NO ₂	2	3	92	1	165-166/ 162-164 [15][16]
4d	4-OCH ₃	2	3	94	1	119-120/ 116-118 [15][16]
4e	4-CH ₃	2	3	90	3	118-119/ 118-120 [15][16]
4f	Vanillin	2	3	82	3	158-160/ 159-160 [15][16]
4g	3-NO ₂	2	3	90	2	125-127/ 128-130 [15][16]
4h	3-CH ₃	2	3	93	3	117-118/ 117-118 [15][16]
4i	2-Cl	2	3	94	1	Semi-solid [15][16]
4j	2-NO ₂	2	3	89	2	158-161/ 159-160 [15][16]

^a isolated yield

Hereafter, 10% amount of Alum in water was found best *catalyst:solvent* combination at room temperature and this used as reaction condition for further derivations. Various aromatic aldehydes with electron donating (**Table 1; Entry 4b,d,e, f, h and i**) and withdrawing substituent (**Table 1; Entry 4c, g and j**) were applied with malononitriles and phenyl hydrazine. Percentage yield obtained from electron donating and withdrawing substituents are not marginal contrast (**Table 1, Entry 4c Vs 4d**), it justified by taking reaction medium in account. Reaction medium is water and polar functionality obtained yield in range, again, in support this more time required to obtained product when non-polar (**Table 1; Entry 4a, e and h**) functionalities. Excess reaction time for vanillin may due to presence of phenolic –OH group and resultant intervention. Obtained products were check TLC, melting point recorded and compared with literature. Though, all products are known, few representative products were analysis for ¹H and ¹³C spectral characterization and found adequate.

Conclusions

In summary, we reports synthesized series of highly substituted pyrazole via green catalyst and water as solvent at mild reaction condition. Easy handling experimental procedure,

readily available starting material, high productivity and especially easy purification of final products with significant eco-friendly concern are made this method unique. Exploring Alum as versatile green catalyst for elementary organic transformation reaction is ongoing laboratory work and will publish during the course of time.

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