Heterocyclic Letters
Vol. 6| No.2 |217-221| Feb-April| 2016
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

POTASSIUM ALUMINUM SULFATE: GREEN CATALYST FOR SYNTHESIS OF 1,3,5-SUBSTITUTED PYRAZOLE

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Abstract
An environmentally benign methodology for the synthesis of pyrazole derivatives has been developed. Potassium aluminum sulfate (Alum) catalyzed water mediated one pot synthesis of 1,3,5-substituted pyrazole via condensation of 1,3-dicarbonyl, substituted hydrazine. Present methodology consists of readily available substrate and genuinely environmental friendly reaction condition, simple in procedure and easy product isolation.

Keywords: Potassium aluminum sulfate (Alum), 1,3,5-substituted pyrazoles, 1,3-diketons, Hydrazine, water mediated, Conventional, Microwave.

Introduction

Nitrogen containing cyclic structures is specifically considered advantaged structure while exploring promising drugs. Pyrazole analogues occupied exclusive place in the field of medicinal chemistry and are exhibits wide range of biological activities. Anti-inflammatory,[i]anti-pyretic,[ii] anti-depression,[iii] anti-bacterial[iv] activity of pyrazole has been reported. Pyrazole also well established as anti-tumor,[v] anti-psychotic[vi] and anti-microbial[vii] properties. Utility spectrum of pyrazole analogues demonstrate as herbicides,[viii] fungicides,[ix] pesticides,[x] insecticides[xi] and dyestuffs.[xii]The synthesis of pyrazole analogue has been part of steady importance. Pyrazole analogues are very rare as naturally occurring products, due to difficulties in synthesis of nitrogen-nitrogen single bond, hence its synthesis and synthetic methodology gain its own importance.[xiii]

Literature survey reveals that synthesis of pyrazole has been reported basically by reaction of chalcone and hydrazine,[xiv]terminal alkynes and hydrazine with suitable co-substrate, [xv] reaction of 1,3-dicarbonyl functionality with hydrazine.[xvi-xviii] Easy available 1,3-dicarbonyl compounds and hydrazine condensation method has been proven most productive, single steep and easy isolation of product(s) attract considerable attraction. Above mention method demands acid catalyst and hence many methodology has been tried to optimized productivity, duration of reaction and green concern. Catalyst like Sulfuric acid, [xix] polymer supported sulfonic acid [xx] Scandium triflate,[xxi]Zeolite[xxii] has been tried.Mirjaliliet.al.[xxiii]reported Magnesium perchlorate, Silica supported phosphorus pentaoxide,[xxiv]and recently Nanosilica sulfuric acid,[xxv]Glycerol-water[xxvi]as green catalyst/solvent condition for synthesis of pyrazoles. All above reported methods contains either hazardous, non-environmental friendly

catalyst and/or solvent. Sulfuric acid, phosphorous pentaoxide has handle with extreme precautions, using organic volatile halogenated solvent increase impact of hazard. Now a days, replacing synthesis by green methodologies gain significant importance. In our laboratory, we deliberately try to introduce environmentally benign synthetic strategies for medicinally important products, precursor or intermediates.

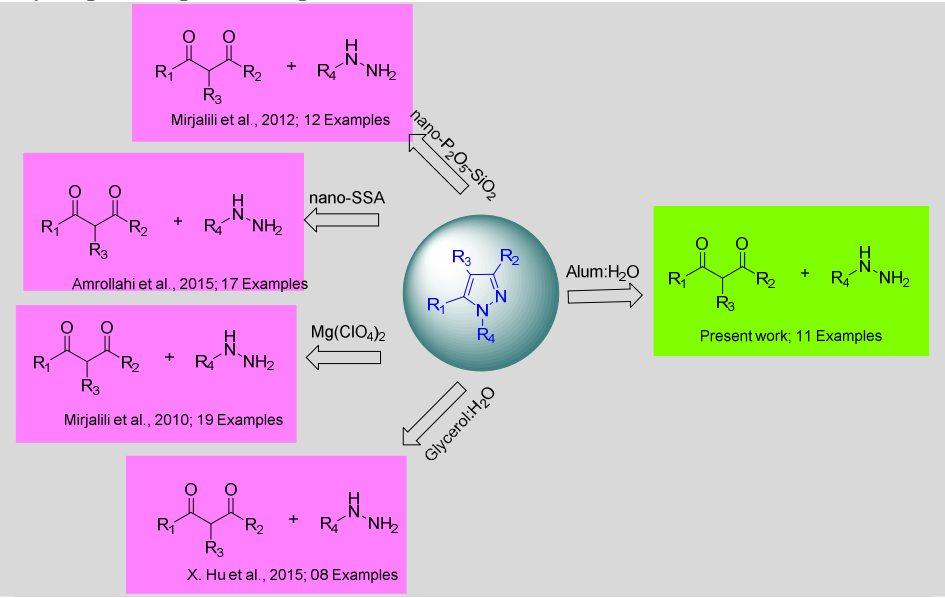
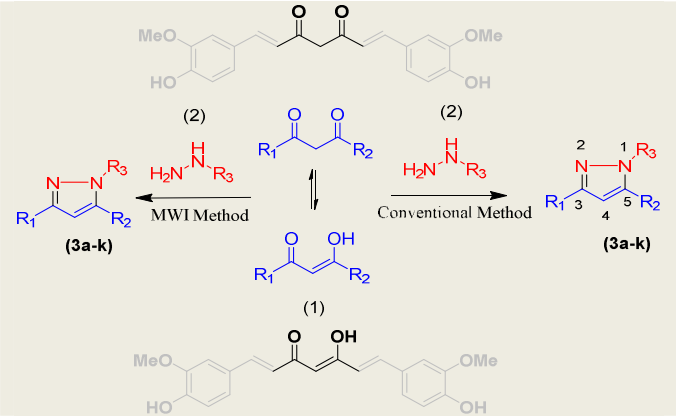


Figure 1 Previously reported methods for the synthesis of 1,3,5-substituted pyrazole by using 1,3-dicarbonyl compound and substituted hydrazine derivatives.

In our previous work[xvii] reported cyclisation of hydrazine derivatives with curcumin, naturally occurring yellow pigment contains 1,3-dicarbonyl as central part. Promising results obtained from Curcumin-pyrazole and this encourages us, to explore further possibilities with Potassium aluminum sulfate (Alum) as green catalyst with water as solvent for condensation of 1,3-dicarbonyl with hydrazine.

Results and Discussions

Synthesis of curcumin-pyrazole analogues in PEG and catalytic amount of acetic acid was our previously reported green methodology. Our continuous efforts towards development of green methodology for Curcumin-pyrazole analogues gives eventual 10% Potassium aluminum sulfate (Alum) as environmentally benign catalyst solvent combination.



Scheme 1 Synthesis of 1,3,5-substituted pyrazole derivatives from one pot condensation of 1,3-dicarbonyl with hydrazine derivatives by conventional and MWI method by using Alum as catalyst and water as solvent. Present methodology is further exploration of our previous work Curcumin-pyrazole analogues.[xvii]

1,3-dicarbonyl condensation with hydrazine demands acid catalyst combination, hence 10% aqueous Potassium aluminum sulfate (Alum) were kept as catalyst and solvent, followed by arranged a series of reactions to optimized temperature and time for conventional method, whereas watt and time for microwave irradiation method. Acetylacetone (1 eq.), 2,4-dinitrophenyl hydrazine (1.1 eq.) were taken for model reaction. Comparison of products yield, obtained by MWI method is better than conventional one. In MWI has significant abilityto transferlarge amount of energy within no time, this phenomenon overcome many hurdles and increase productivity. Hydrophobic substrate (**Table 1; Entry 3j, 3k**) shown excellent productivity with non-conventional method, whereas yield of same significantly fall down with conventional method. Polar substitution on 1,3-dicarbonyl increase yield in case of conventional method. Stoichiometry of reaction allowed for simple workup procedure. When both substrates were taken equimolar, simple water workup fail to obtained pure single spot product and essentially reaction mixture need to extracted or wash with organic solvent followed by recrystallization. During optimization process, used of excess of hydrazine increased time of reaction in conventional method, whereas multispot TLC observed in case of MWI method.

Table 1 Pyrazole analogues synthesis by condensation of 1,3-dicarbonyl and substituted hydrazine, alum as green catalyst. Table showing productive comparison of MWI and Conventional method.

Ent.	R_1	R_2	R_3	Yield[a] in %		M.P.(in °C)	Ref.(M.P.)
				MWI	Conventional		
3a	-Me	-Me	2,4-NO_2-C_6H_4	93	73	123	xxiii
3b	-Me	-Me	C_6H_5	84	70	Oil	xxiii
3c	-Me	-Me	4-Br- C_6H_4	94	80	86	xxiii
3d	-Me	-Me	4-OMe- C_6H_4	93	74	95	xxiii
3e	Ph	-Me	2,4-NO_2-C_6H_4	90	70	127	xxiii
3f	Ph	-Me	C_6H_5	78	55	53	xxiii
3g	Ph	-Me	4-Br- C_6H_4	92	76	181	xxiii
3h	Ph	-Me	4-Me- C_6H_4	78	61	80	xxiii
3i	Ph	Ph	2,4-NO_2-C_6H_4	94	88	151	xxiii
3j	Ph	Ph	C_6H_5	91	43	135	xxiii
3k	Ph	Ph	4-Br- C_6H_4	93	51	116	xxiii

Reaction :1,3-dicarbonyl (1eq.) hydrazine (1.1) and 15 mL of 10% alum; for conventional method : 8 hr. reflux; for Microwave irradiation method: 600W for 2 min. (10 sec. rest-time after 30 sec. successive irradiation)
[a]*isolated yield*

Materials and Methods

All the compounds used in synthesis were of analytical grade; the melting points of the compounds were determinedin open head capillary and are uncorrected. ^{1}H NMRspectra were recorded on a DRX-400 Bruker FT-NMR spectrophotometer in$CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are reported in ppm. The IR spectra wererecorded using Perkin Elmer spectrometer (KBr plates).The reaction was carried out in a scientificmicrowave oven (Sineo, MASS II-Microwave Synthetic Workstation). All the compounds were checked for purity by thin layerchromatography (TLC).

General Procedure

Conventional method

2,4-dintrophenyl hydrazine (436mg; 2.2mmol), acetylacetone (206µL; 2 mmol) were taken in round bottom flask equipped with water condenser containing 15 mL of 10% alum and reflux for 8 hour, progress of reaction was followed by TLC. On completion of reaction contained allowed to attain room temperature, repeatedly wash with water and recrystalised from hot aq. Alcohol.

Microwave irradiation method

2,4-dintrophenyl hydrazine (436mg; 2.2 mmol), acetylacetone (206µL; 2 mmol) were taken in round bottom flask equipped with water condenser containing 15 mL of 10% alum and placed in Scientific Microwave oven, irradiate at 600W for 2 min. (10 sec. break time placed after 30 sec. of successive irradiation), progress of reaction was followed by TLC. On completion of reaction contained allowed to attain room temperature, repeatedly wash with water and recrystalised from hot aq. Alcohol.

Spectral data of represented compound (3a)

1-(2,4-dinitrophenyl)-3,5-dimethyl-1H-pyrazole: Yellow solid, 123°C, ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.22 (s, 3H, -CH_3), 2.25 (s, 3H, -CH_3), 6.17 (s, 1H, CH), 7.74 (d, 1H, Ph-H), 8.63 (dd, 1H, Ph-H), 8.88 (s, 1H, Ph-H); IR (KBr, ν cm^{-1}): 3170, 3109, 2950, 1647, 1580, 1155, 710.

Conclusion

Present work offers easy method for the synthesis of 1,3,5-pyrazoles by using 10% of Potassium aluminum sulfate (Alum) as readily available, cheap, environmentally benign and productive catalyst. Present catalyst established high productive for conventional as well as microwave method. Clean reaction profile, simple operational methods are additional qualities of present methodology.

References

i. N. Gokhan-Kelekci, S. Yabanoglu, E. Kupeli, U. Salgin, O. Ozgen, G. Ucar, E. Yesilada, E. Kendi, A. Yesilada, A.A. Bilgin, *Bioorg. Med. Chem*., 15 (**2007**) 5775-5786.

ii. C.L. Behr, R. Fusco, C.H. Jarboe, The Chemistry of Heterocyclic Compounds,

Pyrazoles, Pyrazolines,Pyrazolidines, Indazoles and Condensed Rings, A. Weissberger, Ed. Interscience Publishers: New York, **1967**.

iii. D.M. Bailey, P.E. Hansen, A.G. Hlavac, E.R. Baizman, J.Pearl, A.F. Defelice, M.E. Feigenson, *J. Med. Chem*., 28 (**1985**) 256-260.

iv. R.N. Mahajan, F.H. Havaldar, P.S. Fernandes, *J. Indian Chem. Soc.,* 68 (**1991**) 245-246.

v. R. Lin, G. Chiu, Y. Yu, P.J. Connolly, S.Li, Y. Lu, M. Adams, A.R. Fuentes-Pesquera, S.L. Emanuel, L.M. Greenberger, *Bioorg. Med. Chem. Lett*., 17 (**2007**) 4557-4561.

vi. M. Barcelo, E. Ravina, C.F. Masaguer, E. Domínuez, F.M. Areias, J. Brea, M.I. Loza, *Bioorg. Med. Chem. Lett*., 17 (**2007**) 4873-4877.

vii. A.M. Farag, A.S. Mayhoub, S.E. Barakat, A.H. Bayomi, *Bioorg. Med. Chem*., 16 (**2008**) 4569-4578.

viii. G.G.A. Dutra, B.C. Hamper, D.A. Mischke, K. Moedritzer, M.D. Rogers, PCT Int. Appl. WO 8206, 962, Chem. Abstr.,(**1992)** 117, 69859.

ix. B. Natsume, N. Kyomura, K. Kikutake, T. Fukuch, Eur. Pat. Appl. EP. 462, 573.

x. M. Londershausen, *Pestic. Sci*., 48 (**1996**) 269-292.

xi. M. Windholz, Ed., TheMerk Index, 9th ed.; Merck and Co., Rahway: New Jersey, 1976, 8851.

xii. S.M. Fahmy, A.H. Badran, M.H. Elnagdi, *J. Chem Tech. B: Technol*. 30 (**1980**) 390-395.

xiii. Aggarwal, R., Kumar, V., Kumar, R., Singh, S.P., 2011. *Beilstein J.Org. Chem*., 7, 180.

xiv. B.A. Bhat, S.C. Puri, M.A. Qurishi, K L. Dhar, G.N.G. N. Qazi, *Synth. Commun*., 35 (**2005**) 1135-1142.

xv. M.S. M.Ahmed, K. Kobayashi, A. Mori, *Org. Lett*., 7 (**2005**) 4487-4489.

xvi. S. Fustero, R. Roman, J.F.X. Sanz-Cervera, A. Simon-Fuentes, A.C. Cunat, S. Villanova, M. Murguía, *J. Org. Chem*., 73 (**2008**) 3523-3529.

xvii. M. Shioorkar and M. Ubale, *Der PharmaChemica*, 7, 2 (**2015)** 274-277.

xviii. N. Ahsan, S. Mishra, M. K. Jain, A. Surolia, S. Gupta, *Nature:Scientific Reports* 5, Article No. (**2015**) 9862.

xix. Z. Wang, H. Qin, *Green Chem*., 6 (**2004**) 90-92.

xx. V. Polshettiwar, R. S. Varma, *Tetrahedron Lett*. 49 (**2008**) 397.

xxi. W. Xiong, J.X. Chen, M.C. Liu, J.C. Ding, H.Y. Wu, W.K. Su, *J. Braz. Chem. Soc*., 20 (**2009**) 367-374.

xxii. R. Sreekumar, R. Padmakumar, Synth.Commun., 28 (**1998**) 1661-1665.

xxiii. B.F. Mirjalili, A. Bamoniri, M.A. Amrollahi, H. Emtiazi, *Digest J. Nanomat. Biostruct*.,5 (**2010**) 897-902.

xxiv. B.F. Mirjalili, A. Bamoniri, A.A. Jafari, F. Abasaltian, *Iranian J. of Cat*., 2,2 (**2012)** 75-78.

xxv. B.F. Mirjalili, H. Emtiazi. M. A. Amrollahi, *Arabian J. of Chem*., (**2015**) 8, 793-797.

xxvi. Zhen-Li Min, Q. Zhang, X. Hong, X. Cao, X. Hu, *Asian J. of Chem*., 27, 9 (**2015**) 3205-3207.

Received on February10, 2016.