Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Research Article

Ultrasound Promoted One-pot Synthesis of Substituted Pyrazoles Using Glyoxylic Acid as a Catalyst under Solvent-free Condition.

Chandrashekhar G. Devkate*[,1], Ajay M. Patil[2], Digambar D. Gaikwad[3], Mohammad Idrees M. Siddique[4]

[1]Dept. of Chemistry, Indraraj Arts, Commerce and Science College, Sillod, Aurangabad-431112, Maharashtra, India.

[2]Dept. of Chemistry, Pratishthan Arts, Comm. and Science College, Paithan, Aurangabad-431107, Maharashtra, India.

[3]Dept. of Chemistry, Govt. College of Arts and Science, Aurangabad-431001, Maharashtra, India.

[4]Dept. of chemistry, Government Institute of Science, Nagpur-440008, Maharashtra, India.

Received 18 May 2019; received in revised form 22 February 2020; accepted 25 February 2020

***Corresponding author E-mail address:** *cgdevkate@gmail.com*

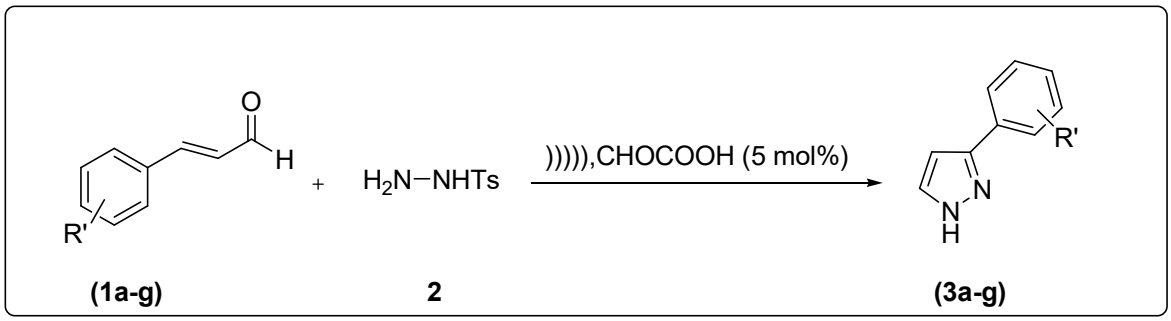
ABSTRACT
Synthesis of substituted pyrazoles by one pot condensation reaction of substituted cinnamaldehydes and tosyl hydrazine in the presence of glyoxylic acid under solvent free condition. The methodology highlights the use of ultrasonic irradiation as non conventional sources. The catalyst used is readily available and cost effective which makes the method more green and efficient.

KEYWORD
3-Substituted pyrazole, Glyoxylic acid, Ultrasound irradiation.

1. INTRODUCTION

Pyrazoles and its derivatives are usually used in medicinal chemistry as they have a large range of biological and pharmacological activities such as anti-inflammatory, analgesic, antibacterial, antidiabetic, antipyretic, antiviral, uricosuric, hypoglycemic, antineoplastic antiarthritic, and antiphlogistic properties[1–4]. Due to various important features of pyrazoles various synthetic methods are reported for the pyrazole synthesis. Condensation of hydrazonyl halides with b-dicarbonyl compounds and 1,3-dipolar cycloaddition of diazo compounds with alkynes[5–7] are found to yield pyrazoles. The most usually used synthetic protocol for obtaining polysubstituted pyrazoles is by condensation of 1,3-dicarbonyl compounds with hydrazines using acid catalysts like sulphuric acid[8], polystyrensulphonic acid[9] and hydrochloric acid[10].

Here we are interested to use glyoxylic acid as it is a strong acid with excessive large applications such as Diels Alder reaction[11], deportation of oximes[12] and for the synthesis of imidazoles[13].



Scheme 1. Synthesis of substituted pyrazoles (3a-g) using glyoxalic acid under ultrasound irradiated.

2. MATERIALS AND METHODS

2.1. General procedure for the synthesis of pyrazoles

Cinnamaldehyde (1) (1.00mmol) and tosyl hydrazine (2) (1.00 mmol) was taken in RBF to that glyoxalic acid (5 mol%) was added and then after the RBF was kept into the ultrasonic water bath, and was irradiated at 40% of the power of the ultrasonic bath at RT. By using TLC the progress of the reaction was monitor. After complete conversion the reaction mass was poured on crushed ice. The obtained solids were filtered, washed with water and dried. The crude compounds were crystallized using (1:1) DMF-Ethanol.

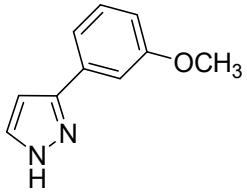
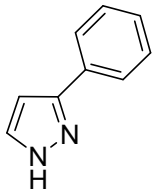
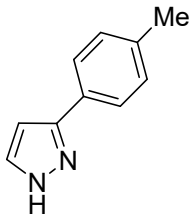
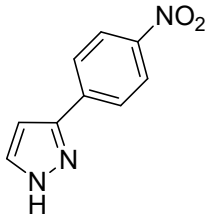
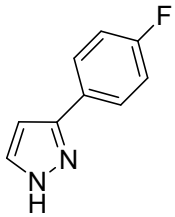
2.2. Spectral data for representative compound 3a

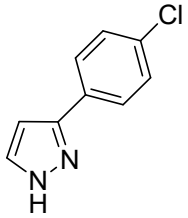
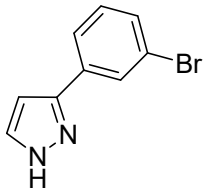
white solid, FTIR cm^{-1}: 3165 (N-H str.), 1536 (C=N str., Pyrazolyl), 1048 (C-O str.);^{1}H-NMR (400 MHz, DMSO): δ 3.77 (s, 3H, -OCH_3), 6.65 (d, 1H, Ar-H, J = 8 Hz), 7.28 (t, 1H, Ar-H, J = 8 Hz), 7.37 (d, 1H, Ar-H, J = 8 Hz), 7.44 (s, 1H, Ar-H), 7.66 (s, 2H, Pyrazolyl), and 14.02 (s, 1H, N-H) ppm;^{13}C-NMR (100 MHz, DMSO): δ 159.58, 133.87, 129.59, 117.65, 112.90, 110.50, 101.98, 54.81 ppm; MS (ESI, m/z): calcd for $C_{10}H_{10}N_{2O}$ ($M + H^{+}$) 174.0793; found: 175.1162.

3. RESULTS AND DISCUSSION

The synthesis of pyrazole using readily available starting materials such as cinnamaldehyde (1a-g) and p-toluene sulfonyl hydrazide ($TsNHNH_2$) (2). The use of glyoxylic acid as a catalyst and media for the synthesis makes the method more cost effective. Here, we have noted that the conversion takes place in less time with respect to cinnamaldehyde as the donating group increasing and as we have noticed that if there is any strong withdrawing group present than the conversion is less (Table 1, 3d). The reactions were carried out at room temperature for 30 min. The progress of the reaction was monitored by TLC. Various cinnamaldehydes (1a-g) could give target pyrazoles through the same action (3a-g). And the use of ultrasound irradiation as a non-conventional source has played a key role in the synthesis as compared to other conventional methods.

Table 1. Glyoxalic acid catalyzed synthesis of pyrazoles[a].

Entry	R'	Product	Yield	M. P. (℃)
3a	m-OMe		93	91-92
3b	-H		86	77-81
3c	p-Me		90	75-77
3d	p-NO_2		65	195-196
3e	p-F		75	102-104

3f	p-Cl		88	100-104
3g	m-Br		85	74-76

4. CONCLUSION

In conclusion, we have investigated a simple, highly efficient, and environmentally friendly method for the synthesis of substituted pyrazoles. Here, the use of glyoxalic acid works as an excellent catalyst. The use of ultrasound irradiation as a non-conventional source has played a key role in the synthesis. And the further use of the methodology for the synthesis of other useful heterocycles is going on our laboratory.

5. ACKNOWLEDGEMENT

We are thankful to the Head of place of Research, Government Science College, Gadchiroli, 442605 and Indraraj Arts, Commerce and Science College, Sillod, Aurangabad, 431112 for their support.

6. REFERENCES

1. Liu, X. H., Cui, P., Song, B. A., Bhadury, P. S., Zhu, H. L., & Wang, S. F. (2008). Synthesis, structure and antibacterial activity of novel 1-(5-substituted-3-substituted-4, 5-dihydropyrazol-1-yl) ethanone oxime ester derivatives. *Bioorganic & medicinal chemistry*, *16*(7), 4075-4082.
2. Velaparthi, S., Brunsteiner, M., Uddin, R., Wan, B., Franzblau, S. G., & Petukhov, P. A. (2008). 5-tert-Butyl-N-pyrazol-4-yl-4, 5, 6, 7-tetrahydrobenzo [d] isoxazole-3-carboxamide derivatives as novel potent inhibitors of Mycobacterium tuberculosis pantothenatesynthetase: initiating a quest for new antitubercular drugs. *Journal of medicinal chemistry*, *51*(7), 1999-2002.
3. Magedov, I. V., Manpadi, M., van Slambrouck, S., Steelant, W. F., Rozhkova, E., Przheval'skii, N. M., & Kornienko, A. (2007). Discovery and investigation of antiproliferative and apoptosis-inducing properties of new heterocyclic podophyllotoxin analogues accessible by a one-step multicomponent synthesis. *Journal of medicinal chemistry*, *50*(21), 5183-5192.

4. Ouyang, G., Cai, X. J., Chen, Z., Song, B. A., Bhadury, P. S., Yang, S., ... & Zeng, S. (2008). Synthesis and antiviral activities of pyrazole derivatives containing an oxime moiety. *Journal of agricultural and food chemistry*, *56*(21), 10160-10167.

5. Shawali, A. S., & Hassaneen, H. M. (1973). Reaction of carbanions of β-diketones and β-keto esters with hydrazidic bromides. *Tetrahedron*, *29*(1), 121-124.

6. Illa, O., Muray, E., Amsallem, D., Moglioni, A. G., Gornitzka, H., Branchadell, V., ... & Ortuño, R. M. (2002). A comparative study on the 1, 3-dipolar cycloadditions of diazomethane and bis (diisopropylamino) phosphinodiazomethane to chiral electron-deficient olefins: reactivity and diastereoselectivity. *Tetrahedron: Asymmetry*, *13*(23), 2593-2603.

7. Qi, X., & Ready, J. M. (2007). Copper-Promoted Cycloaddition of Diazocarbonyl Compounds and Acetylides. *AngewandteChemie International Edition*, *46*(18), 3242-3244.

8. Norris, T., Colon-Cruz, R., & Ripin, D. H. (2005). New hydroxy-pyrazolineintermediates, subtle regio-selectivity and relative reaction rate variations observed during acid catalyzed and neutral pyrazole cyclization. *Organic & biomolecular chemistry*, *3*(10), 1844-1849.

9. Polshettiwar, V., & Varma, R. S. (2008). Greener and rapid access to bio-active heterocycles: room temperature synthesis of pyrazoles and diazepines in aqueous medium. *Tetrahedron Letters*, *49*(2), 397-400.

10. Gosselin, F., O'Shea, P. D., Webster, R. A., Reamer, R. A., Tillyer, R. D., & Grabowski, E. J. (2006). Highly regioselective synthesis of 1-aryl-3, 4, 5-substituted pyrazoles. *Synlett*, *2006*(19), 3267-3270.

11. Augé, J., & Lubin-Germain, N. (1998). Hetero Diels-Alder Reaction with Aqueous Glyoxylic Acid: An Experiment in Organic Synthesis and 2-D NMR Analysis for Advanced Undergraduate Students. *Journal of chemical education*, *75*(10), 1285.

12. Chavan, S. P., & Soni, P. (2004). A facile deprotection of oximes using glyoxylic acid in an aqueous medium. *Tetrahedron letters*, *45*(15), 3161-3162.

13. Shelke, K., Kakade, G., Shingate, B., &Shingare, M. (2008). Microwave-induced one-pot synthesis of 2, 4, 5-triarylimidazoles using glyoxylic acid as a catalyst under solvent-free conditions. *Rasayan J. Chem*, *1*, 489-494.