



Synthesis of Pyrazole Compounds by Using Sonication Method

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ABSTRACT

A simple method for the synthesis of pyrazoles derivatives carried out by cyclization of cyanide with hydrazine hydrate by using sonication method. All the prepared compounds were characterized by ¹H, ¹³C NMR and IR Spectroscopy.

Keywords: Substituted 1H-pyrazoles, Sonication, Hydrazine hydrate, Cyclo condensation.

INTRODUCTION

Pyrazole and its derivative compounds have importance in medicinal chemistry, plays important role in agrochemicals¹, building blocks for pharmaceutical such as Zometapine,² Celebrex,³ Viagra,⁴ Cyenopyrafen,⁵ Tebufenpyrad⁶ and Fenpyroximate,⁷ are well-known compounds bearing a pyrazole unit. Majority of the pyrazole containing compounds show significant biological activities such as cholesterol-lowering,⁸ antimicrobial,⁹ anti-inflammatory,¹⁰ hypoglycemic,¹¹ antihypertensive,¹² analgesic,¹³ antidepressant,¹⁴ anticancer¹⁵, antiviral,¹⁶ antibacterial,¹⁷ antiobesity,¹⁸ appetite and suppressant,¹⁹ activities.

A literature survey reveals that several reported methods for the synthesis of Pyrazole unit generally synthesized i.e using the 3 component coupling reaction of aldehydes, 1,3-dicarbonyls, and diazo compounds, as well as tosyl hydrazones,

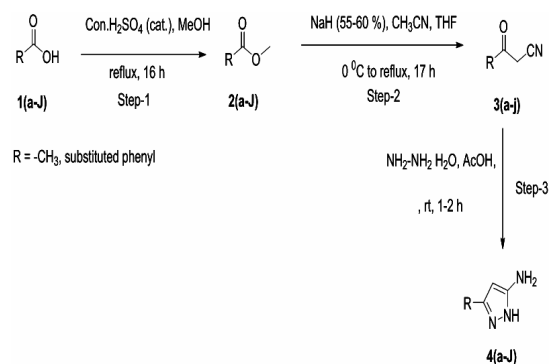
rhodium-catalyzed addition-cyclization of hydrazines with alkynes²¹ cyclic enol triflates and an elaborated set of diazoacetates²² hydrazones and β -protonation/nucleophilic addition/aromatization sequence.²³ A copper-mediated cyclization, trifluoromethylation, and detosylation.²⁴ Potassium 1,1,3,3-tetranitropropane treated readily with various (hetero)arylamines.²⁵ other methods with metals, Lewis acids, or bases were also reported.²⁶⁻³⁰ But, those techniques have their benefit whilst a number of these are the problem by the limitation of long time response, individual situations and lower yields. for this reason, the improvement of a brand new technique for the synthesis of Pyrazole derivatives might be fairly applicable.

From the last three decades, ultrasound utility has been utilized in natural product synthesis³¹ Which has an overwhelming interest because it gives chemists tremendously simple and less expensive techniques for chemical activation.³² similarly, this



method is also recognized to accelerate the rate of a chemical response, and at the same time increases the reaction yield.³³ Transition metal-free synthesis of quinolino [2', 3': 3, 4] pyrazolo [5, 1-b] quinazolin-8 (6 H)-ones via cascade dehydrogenation and intramolecular N-arylation.³⁴ Evaluation of Medicinal Effects of Isoxazole Ring Isosteres on Zonisamide for Autism Treatment by Binding to Potassium Voltage-Gated Channel Subfamily D Member 2 (Kv 4.2).³⁵ Morpholine and Thiomorpholine: A Privileged Scaffold Possessing Diverse Bioactivity Profile.³⁶ recently, there are developing pursuits in this non-conventional method because it promotes shorter response time.

laboratory result confirmed that pyrazole derivatives could be readily prepared from the beginning materials of carboxylic acid derivatives beneath ultrasound probe irradiation in neat circumstance as mentioned in this paper (Scheme 1).



Scheme 1

Table 1: Synthesis of substituted pyrazole (3a-j)

Sr. No	Starting material	Product	Reaction Time for Sonication	Yield (%)	Melting point (°C)
1			1 h 35 min	62	230
2			1 h 20 min	59	116
3			1 h 35 min	62	85
4			1 h 30 min	67	86
5			1 h 40 min	61	126
6			1 h 50 min	55	46
7			1 h 45 min	58	82
8			1 h 25 min	64	126
9			1 h 30 min	60	156
10			1 h 30 min	60	182

Methodology

General Procedure for the synthesis of pyrazole derivative in our research, we developed novel, simple, efficient, and rapid method for synthesis of pyrazole derivative by using carboxylic acid as starting material. First the carboxylic acid is converted into ester using methanol and con. sulphuric acid reflux under nitrogen atmosphere for 16 hours. In the second step acetonitrile in toluene mixed with a solution of NaH under nitrogen atmosphere and stirred for 30 min was added methyl ester and reflux reaction mixture for 17 h to give oxonitrile. In the third step the oxonitrile in acetic acid and hydrazine hydrate undergo cyclization reaction to get final products pyrazole in sonication for 1-2 hours. In this method, we used different halogen aromatic substituted carboxylic acid, nicotinic acid, and acetic acid but we observed the percentage of final products.

To study the generality of this method type of examples had been illustrated for the synthesis pyrazole and outcomes are summarized. The reaction is well matched for various substituents inclusive of CH₃, I, NO₂, CN, and F. This approach is also powerful for the heteroaromatic carboxylic acid which shapes their corresponding pyrazole derivatives in 55-67% of yields. The formation of the desired product becomes confirmed by using ¹H NMR, ¹³C NMR and IR.

EXPERIMENTAL

Melting points had been determined in an open capillary tube and are uncorrected. IR spectra have been recorded in KBr on a Perkin-Elmer spectrometer. ¹H-NMR and ¹³C spectra have been recorded on a Gemini 400 MHz tool in DMSO as solvent and TMS as an inner fashionable. The purity of products was checked by thin-layer chromatography (TLC) on silica gel.

Synthesis of ester 1(a-J)

To a stirred solution of substituted acid (1.0 eq.) in methanol (10 mL) turned into delivered con.H₂SO₄ (cat.) at 0-5°C below N₂ environment. The resultant became heated at reflux temperature for 16 hours. The reaction turned into monitored through TLC (mobile phase:- 20% ethyl acetate: hexane). Upon entire conversion reaction aggregate became distilled out, obtained crude was poured into

ice water, extracted with ethyl acetate (3 x 25 mL), blended natural layer changed into washed with sat. bicarbonate answer, dried over Na₂SO₄, distilled out organic layer underneath reduced pressure to get methyl ester intermediate (Yield :68-81%).

Synthesis of 3-oxonitril 2(a-J)

In a smooth and dry a 100 mL round bottom flask was taken acetonitrile (5.0 eq.) in toluene (10 mL), cool to 0-5°C, in that solution NaH (55%, 2.5 eq.) became introduced lot wise below N₂ atmosphere and stirred for 30 min, then an answer of substituted methyl ester intermediate in toluene (5.0 mL). Reaction combination becomes heated at reflux temperature for 17 hours. Response become monitored via TLC (30% ethyl acetate: hexane). Upon entire conversion reaction mixture was poured into ice water slowly, extracted with ethyl acetate (3 x 25 mL), layer changed into dried over Na₂SO₄, distilled out organic layer under reduced vacuum to get 3-oxonitrile intermediate (Yield:80-93 %).

Synthesis of 3-oxonitrile 3(a-J)

To a stirred of 3-oxonitrile (1.0eq.) in acetic acid (5mL), hydrazine hydrate (2.0 eq.). Reaction combination becomes sonicated for 1-2 hours. The reaction became monitored with the aid of TLC (cellular section:- 50% ethyl acetate: hexane). Upon complete conversion become poured into water, basify the use of 20% NaOH solution, extracted with ethyl acetate (3 x 30 mL), mixed natural layer became dried over Na₂SO₄, distilled out organic layer beneath reduced pressure. obtained crude turned into purified with the aid of column chromatography the usage of ethyl acetate: hexane as an eluent to get substituted three-amino pyrazole intermediate (Yield:55-67%).

The Formation of all preferred Products has been Purified through the usage of column chromatography & confirmed by ¹H & ¹³C NMR.

3-(5-fluoro-2-methyl-3-nitrophenyl)-1H-pyrazol-5-amine (4a)

FT-IR (cm⁻¹): 3350, 3245, 3100, 2950, 1477, 1292. ¹H-NMR (400 MHz; DMSO): δ: 2.33 (s, 3H CH₃), 4.32 (brs, 2H, NH₂), 6.15(s, CH), 7.68 (d, 1H, J = 2.4Hz Ar-H), 7.46 (d, 1H, J = 2.4Hz, Ar-H), 7.86 (s, NH) ¹³C-NMR 96.03, 112.53, 121.08, 126.99, 133.18, 143.08, 147.01, 151.61, 158.20, 160.68.

3-(pyridin-3-yl)-1H-pyrazol-5-amine (4b)

FT-IR (cm⁻¹): 3352, 3238, 3098, ¹H-NMR (400 MHz; DMSO): δ: 4.39 (brs, 2H, NH₂), 5.76 (s, CH), 7.81-8.81 (m-4H Ar-H), 11.54 (s, NH) ¹³C-NMR δ: 88.99, 111.21, 122.12, 142.12, 146.01, 152.21, 152.21, 158.42.

3-(5-amino-1H-pyrazol-3-yl)benzotrile (4c)

FT-IR (cm⁻¹): 3342, 3222, 3101, 2242. ¹H-NMR (400 MHz; DMSO): δ: 4.51 (brs, 2H, NH₂), 5.74 (s, CH), 7.39-7.92 (m, 4H, Ar-H), 11.85 (s, NH) ¹³C-NMR δ: 88.72, 112.30, 118.87, 128.40, 129.44, 129.62, 130.47, 135.56, 158.20, 160.68.

3-(4-fluorophenyl)-1H-pyrazol-5-amine (4d)

FT-IR (cm⁻¹): 3344, 3232, 2991, ¹H-NMR (400 MHz; DMSO): δ: 4.21 (brs, 2H, NH₂), 5.67 (s, CH), 7.56 (d, 2H, Ar-H), 6.98 (d, 2H Ar-H) 11.06 (s, NH) ¹³C-NMR δ: 87.52, 115.63, 127.04, 146.09, 152.53, 160.74, 163.17.

3-(5-bromo-2-iodophenyl)-1H-pyrazol-5-amine (4e)

FT-IR (cm⁻¹): 3342, 3233, 3104, ¹H-NMR (400 MHz; DMSO): δ: 4.31 (brs, 2H, NH₂), 5.75 (s, CH), 7.76-7.05 (m, 3H, Ar-H), 10.85 (s, NH), ¹³C-NMR δ: 91.00, 122.03, 132.07, 132.97, 140.03, 145.45, 147.88, 150.89, 168.99.

3-methyl-1H-pyrazol-5-amine (4f)

FT-IR (cm⁻¹): 3341, 3221, 3104, 2982 ¹H-NMR (400 MHz; DMSO): δ: 2.17 (s, 3H, CH₃), 5.39 (brs, 2H, NH₂), 7.26 (s, CH), 10.85 (s, NH), ¹³C-NMR δ: 18.00, 96.03, 132.07, 141.11, 148.45.

3-(3-fluorophenyl)-1H-pyrazol-5-amine (4g)

FT-IR (cm⁻¹): 3344, 3228, 3098, 2989 ¹H-NMR (400 MHz; DMSO): δ: 4.21 (brs, 2H, NH₂), 5.71 (s, CH), 6.83-7.37 (m, 4H, Ar-H), 7.78 (s, NH), ¹³C-NMR δ: 96.00, 123.12, 131.11, 133.41, 141.01, 14551, 147.52, 151.09, 161.54.

3-phenyl-1H-pyrazol-5-amine (4h)

FT-IR (cm⁻¹): 3351, 3239, 3150, 2997

¹H-NMR (400 MHz; DMSO): δ: 4.24 (brs, 2H, NH₂), 5.75 (s, CH), 7.15-7.60 (m, 5H, Ar-H), 7.78 (s, NH), ¹³C-NMR δ: 97.01, 121.16, 133.15, 134.61, 142.11, 146.25, 148.62.

3-(4-iodophenyl)-1H-pyrazol-5-amine (4i)

FT-IR (cm⁻¹): 3341, 3251, 3101, 2957 ¹H-NMR (400 MHz; DMSO): δ: 4.14 (brs, 2H, NH₂), 5.72 (s, CH), 7.17 (d, 2H, Ar-H), 7.23 (d, 2H, Ar-H), 7.91 (s, NH), ¹³C-NMR δ: 94.06, 110.89, 121.11, 129.09, 134.46, 142.12, 144.25, 147.52, 151.09, 161.54.

3-(4-bromophenyl)-1H-pyrazol-5-amine (4j)

FT-IR (cm⁻¹): 3332, 3221, 3056, 2925 ¹H-NMR (400 MHz; DMSO): δ: 4.21 (brs, 2H, NH₂), 5.72(s, CH), 7.20 (d, 2H, Ar-H), 7.35 (d, 2H, Ar-H), 8.21 (s, NH), ¹³C-NMR δ: 96.11, 111.80, 122.10, 138.49, 146.62, 151.09, 161.91.

CONCLUSION

We defined a successful approach such as an efficient and handy inexperienced synthesis, for pyrazole derivatives using a sonication technique. The approach offers several advantages increasing the yield of products, the usage of the inexpensive starting fabric, and an easy experimental workup technique that makes it a beneficial process for the synthesis of pyrazole derivatives.

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Conflict of interest

The author declare that we have no conflict of interest.

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