J. Biol. Chem. Chron. **2019**, **5***(3)*, 179-181
ISSN (Print): 2454 – 7468
ISSN (Online): 2454 - 7476
www.eresearchco/jbcc/

Ultrasound Promoted One-pot Synthesis of Substituted 3-Hydroxy-1H-Indazole Using Glyoxylic Acid as a Catalyst under Solvent-free Condition

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(Received 10 Dec, 2018; Accepted 11 Jan, 2019; Published 18 Jan, 2019)

ABSTRACT: Synthesis of substituted 3-hydroxy-1H-indazole by one pot condensation benzoate and hydrazine under solvent free condition in the presence of glyoxy;ic acid. The developed 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.

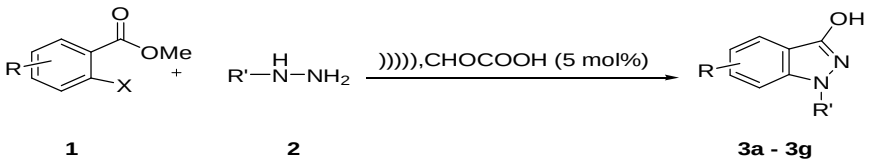
Keywords: 3-hydroxy-1H-indazole; Glyoxylic acid; Ultrasound irradiation.

INTRODUCTION: Our research work focous on indazole ring found use in biology, catalysis, and medicinal chemistry. Indazole show a range of biological activities such as antihypertensive properties, HIV protease inhibition, antitumor activity, analgesic activities and anti-arrhythmic1-6. Our interest is to synthesized 3-hydroxy-1H-indazole which is a biologically active molecules used in pharmaceuticals as antidepressants and contraceptives. Many latest methodologies have been developed for the synthesis but they are limited in scope and the reaction conditions are hard and costly7,8. Here we are interested to use glyoxalic acid as it is a strong acid with excessive large applications such as Diels Alder reaction9, deportation of oximes10 and for the synthesis of imidazoles.[11]

With reference to our previous work on ultrasound irradiated synthesis which is important technique in synthetic organic chemistry. It has been used as a significant energy source for the organic reactions. Which consist of easy experimental procedure, highly selective and clean reaction12, 13.

MATERIALS AND METHODS:

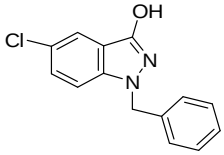
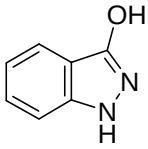
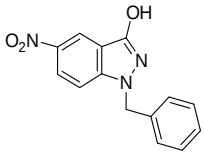
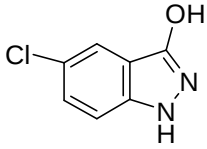
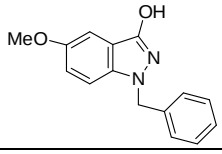
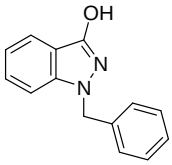
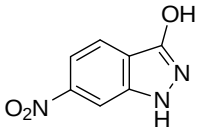
Procedure for the synthesis 3-hydroxy-1H-indazole (3a-h): A mixture of benzoate (1a-h) (1.0 mmol) and hydrazine (2) (1.2 mmol) was taken in RBF to that glyoxalic acid (5 mol%) was added and then after the RBF was kept into the ultrasonic water bath, and was irradiated at 40% of the power of the ultrasonic 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 solid was filtered, washed with water and dried. The crude compound was crystallized using DMF-Ethanol.



Where,
R = Cl, OMe, NO_2, H. R' = Ph-CH_2-, H

[Scheme: Synthesis of 3-hydroxy-1H-indazole using glyoxalic acid under ultrasound irradiation.]

Table 1: Synthesis of 3-hydroxy-1H-indazole using glyoxalic acid, under ultrasound irradiation.

Comp.	R'	Product	M.P (oC)	Yield (%)a
3a	Ph-CH2-		205 -206	80
3b	H		249 - 251	78
3c	Ph-CH2-		248 -250	78
3d	H		204-205	82
3e	Ph-CH2-		187- 188	83
3f	Ph-CH2-		167 - 168	90
3g	H		243 – 244	86

Compound 3d: Yield 93%; Brown ; mp 165-169℃. FTIR Model RZX (Perkin Elmer) cm-1: 3651 (O-H str., Alcoholic), 1552 (C=N str., Indazolyl), 1315 (C-N str. Indazolyl),1251 (C-O str., Etheral);1H-NMR (400 MHz, CDCl3): δ 5.31 (s, 2H, Benzyl), 6.95-7.63 (m, 9H, Ar-H), 10.62 (s, 1H, O-H) ppm;13C-NMR (100 MHz, CDCl3): δ 51.25, 109.12, 112.73, 118.48, 120.02, 120.02, 126.86, 126.86, 127.13, 127.22, 128.22, 137.80, 141.20, 154.53ppm;MS (ESI, m/z): calcd for C14H12N2O (M + H+) 224.095; found: 225.0839.

RESULTS AND DISCUSSION: The synthesis of 3-hydroxy-1H-indazole using readily available starting materials, such as benzoate and hydrazine. The use of glyoxalic 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 benzoate 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, 3c) . The reactions were carried out at room temperature for 30 min .The progress of the reaction was monitored by TLC. Various benzoates (1a-g) could give target 3-hydroxy-1H-indazole 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.

CONCLUSION: In conclusion, we have investigated a simple, highly efficient, and environmentally friendly method for the synthesis of substituted 3-hydroxy-1H-indazole. 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.

ACKNOWLEDGEMENTS: 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.

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