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Research Article

SILICA CHLORIDE AS AN EFFICIENT AND REUSABLE CATALYST FOR THE SYNTHESIS OF 3-HYDROXY-1H-INDAZOLE AND THEIR ANTIBACTERIAL SCREENING

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ABSTRACT

Here, we have developed novel and eco-friendly method for the synthesis of 3-hydroxy-1H-indazole. Were silica chloride (SiO_2-Cl) as heterogeneous reusable acid catalyst is used is been synthesized by reported procedure. The reaction is carried out using ultrasound irradiation under solvent free conditions. The compound **3d** was investigated in-vitro against Gram +ve and Gram –ve bacteria at different concentrations and compared with standard drug ciprofloxacin.

Keywords: Silica chloride, 3-hydroxy-1H-indazole, Ultrasound, Antibacterial.

INTRODUCTION

Indazole ring is subject of our research work the indazole derivatives are found use in biology, catalysis, and medicinal chemistry. Indazoles exhibit a variety of biological activities such as HIV protease inhibition, anti-arrhythmic and analgesic activities, antitumor activity, and antihypertensive properties[1-6]. Our interest is to synthesized 3-hydroxy-1H-indazole which is a biologically active molecules used in pharmaceuticals as antidepressants and contraceptives. Many new methodologies have been published for synthesize but they are limited in scope and the reaction conditions are hard and costly[7-9]. A mild, general method still remains a challenge. Thus to overcome the challenge the use of easily available, reusable solid acid catalyst, silica chloride there are many application of solid supported catalyst as safety in handling, rate enhancement and easy workup procedures[10 -12].

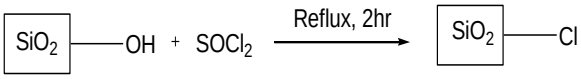
In continuation to our previous work on ultrasound irradiated synthesis which is important technique in synthetic organic chemistry. It has been used as an important energy source for the organic reactions. Simple experimental procedure, increased selectivity, very high yields, and clean reaction[13 -15].

EXPERIMENTAL SECTION

Procedure for Optimization of reaction conditions for the synthesis of 3-hydroxy-1H-indazole

The model reaction between benzoate **1d** (1.0 mmol) and 1-benzylhydrazine **2d** (1.2 mmol) (Scheme). The reaction which is condensation

reaction catalyzed by silica chloride (SiO_2-Cl) and optimization using different mol percentage for the reaction which was carried out under ultrasound irradiation. The results obtained are summarized in **Table 1**.Using (SiO_2-Cl) (15 mol %) (entry 10) with solvent free conditions at 80 - 100 ^oC for 30 min gave excellent yield as compared to other. And for our further synthesis of all other 3-hydroxy-1H-indazole derivatives we have chosen (SiO_2-Cl) (15 mol %) at solvent free under ultrasound irradiation.

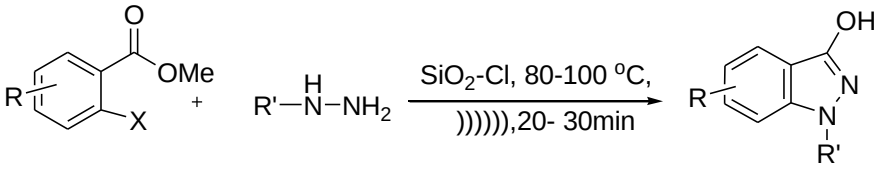


Scheme 1: Synthesis of silica chloride

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) to that (SiO_2-Cl) (15 mol %) was added and the reaction mixture was kept in the ultrasonic bath and was irradiated at 80- 100^oC for about 20-30 min. (the progress of reaction was monitored by TLC) separately as indicated in (**Table 2**). After the reaction was completed 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.

Compound **3d**: Yield 93%; Brown solid; mp 165-169℃. FTIR Model RZX (Perkin Elmer) cm^{-1}: 3650 (O-H str., Alcoholic), 1550 (C=N str., Indazolyl), 1314 (C-N str. Indazolyl),1250 (C-O str., Etheral);^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.33 (s, 2H, Benzyl), 6.95-7.63 (m, 9H, Ar-H), 10.62 (s, 1H, O-H) ppm;^{13}C-NMR (100 MHz, $CDCl_3$): 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 $C_{14}H_{12}N_2O$ (M + H^+) 224.095; found: 225.0839.



1 **2** **3a - 3h**

Where,

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

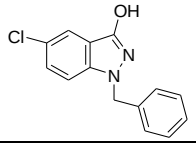
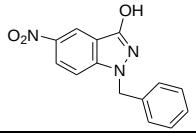
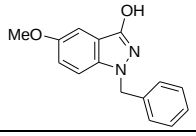
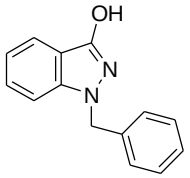
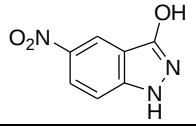
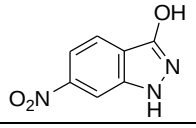
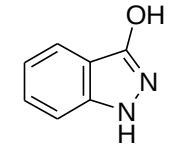
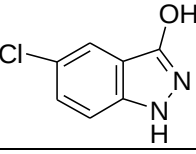
Scheme 2: Synthesis of 3-hydroxy-1H-indazole using SiO_2-Cl under ultrasound irradiation

Table 1: Optimization of reaction conditions for the synthesis of 1-aryl-3-hydroxy-1H-indazole using ultrasound irradiation

Entry	Catalyst/ mol (%)	Solvent	Time (min)	Yield[a] (%)
1	-	EtOH	90	5[b]
2	SiO_2-Cl (5)	THF	70	40
3	SiO_2-Cl (10)	THF	70	55
4	SiO_2-Cl (5)	MeCN	70	50
5	SiO_2-Cl (10)	MeCN	70	53
6	SiO_2-Cl (5)	Toluene	60	40
7	SiO_2-Cl (10)	Toluene	60	48
8	SiO_2-Cl (5)	-	40	60
9	SiO_2-Cl (10)	-	25	78
10	SiO_2-Cl (15)	-	25	94

[a]Isolated yields. [b]Not completed

Table 2: Synthesis of 3-hydroxy-1H-indazole using SiO_2-Cl under ultrasound irradiation

Comp.	Benzoate R	R'	Product	M.P (°C)	Yield (%)[a]		
3a	5-Cl	Ph-CH_2-		206 -207	90	88[b]	87[b]
3b	5-NO_2	Ph-CH_2-		249 -250	86	84	82
3c	5-OMe	Ph-CH_2-		189 - 190	90	87	85
3d	H	Ph-CH_2-		165 - 169	93	91	88
3e	5-NO_2	H		280 - 282	85	83	82
3f	4-NO_2	H		241 - 243	83	81	78
3g	H	H		248 - 252	86	84	83
3h	5-Cl	H		203-206	80	78	77

[a]Yields of isolated products.
[b]SiO_2-Cl was recovered and reused for three consecutive runs

Table 3: Recyclability and reusability of catalyst SiO_2-Cl

Number of Runs	Yield (%)[a]	Catalyst recovery (%)[b]
1	93	96
2	91	94
3	88	91
4	87	89

[a]Isolated yields
[b]SiO_2-Cl was recovered and for number of runs

ANTIBACTERIAL ACTIVITY

The procedure was repeated as give in our previous published work[14, 15]. Here compound 1-benzyl-3-hydroxy-1H-indazole **3d** was screened for in-vitro antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, Staphylococcus aureus and Bacillus subtilis and two gram negative strains, Escherichia coli and Pseudomonas aeruginosa. Ciprofloxacin was used as standard drug. The results obtained are given in **Table 4.**

RESULT AND DISCUSSION

A cyclocondensation of benzoate (**1a-h**) (1.0 mmol) and hydrazine (**2a-h**) (1.2 mmol) to give substituted 3-hydroxy-1H-indazole the reacton is catalyzed by SiO_2-Cl.The catalyst silica chloride used according to the method reported in literature for the synthesisof silica chloride the readily available material silicagel and thionyl chloride was used (**scheme 1**)[16]. The optimization of the reaction is done using different solvents and without solvent for model reaction which was carried out under ultrasound irradiation. The results were summarized in **Table 1**. Here good yields was obtained for (SiO_2-Cl) (15 mol %) (entry 10) with solvent free conditions at 80 - 100 ^oC for 30 min. And thus the reaction was optimized and the method was used for further synthesis derivatives and the results obtained are given in **Table 2**. All the reaction (**3a-h**) is repeated with recovery of catalyst for three to four times the loss of catalyst was 2-3 % with good yield which is appreciable **Table 3**.

The compound **3d** 1-benzyl-3-hydroxy-1H-indazole was screened for in-vitro antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative strains, *Escherichia coli* and *Pseudomonas aeruginosa*. Ciprofloxacin was used as standard drug and the data obtained from antibacterial study is given in **Table 4** which indicates that the test compound 1-benzyl-3-hydroxy-1H-indazole **3d** showed antibacterial activity against Gram positive bacteria, *S.aureus* and *B.subtilis* it moderate activity against *S.aureus* no activity against *B.subtilis.* In case of gram negative bacteria, 1-benzyl-3-hydroxy-1H-indazole **3d** showed moderate activity against *E.coli* and it is inactive against *P.aeruginosa* at all 4 concentrations. On the basis of data it is clear that 3-hydroxy-1H-indazole and its derivatives show moderate antibacterial activity.

Table 4: Antibacterial activity of 3d

Sr. No.	Conc. µg/mL	Zone of inhibition in mm							
		Gram +ve				Gram -ve			
		3b							
		Pathogen – Staphylococcus aureus		Pathogen – Bacillus subtilis		Pathogen – Escherichia Coli		Pathogen – Pseudomonas aeruginosa	
		Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
1	125	-	-	-	-	7	-	-	-
2	250	20	18	-	-	-	-	-	-
3	500	23	24	-	-	11	11	-	-
4	1000	29	30	-	-	13	10	-	-
Standard Ciprofloxacin									
1	125	31	31	27	27	26	26	27	27
2	250	35	36	29	29	28	28	32	32
3	500	40	41	30	31	29	31	36	34
4	1000	44	45	32	33	30	33	38	39

CONCLUSION

In conclusion, we have developed a simple and highly efficient method in were 3-hydroxy-1H-indazole and their derivatives are synthesized using silica chloride (SiO_2-Cl) as heterogeneous catalyst which is reusable and cost-effective. The reaction is performed in solvent free conditions under ultrasound irradiation. Thus the method is clean and efficient method. Antibacterial screening of **3d** compound was found to give moderate activity against selected strains. Further studies on the biological activities of the products and application of this methodology to other interesting indazole derivatives are underway in our laboratory.

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