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Silica Sulfuric Acid : An Efficient Catalyst for the Synthesis of Substituted Indazoles

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ABSTRACT

An efficient approach for the synthesis of indazoles using silica sulphuric acid (SSA) catalyst has been reported.

Keywords: Hydrazine hydrate, *o*-hydroxy aromatic aldehydes/ketones & silica sulphuric acid.

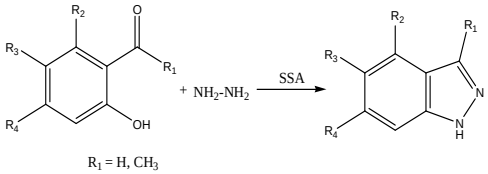
INTRODUCTION

Indazole derivatives are pharmacologically important compounds as their ring system forms a large number of drug molecules. Drug granisetron is $5HT_3$ receptor antagonist and used as an anti-inflammatory and anti-emetic in cancer chemotherapy [1]. Recently, various methods have been reported for the synthesis of substituted indazoles includes; the cyclization of 2,6-dihydroxyacetophenone hydrazones in presence of polyphosphoric acid [2], using chromium tricarbonyl complex [3], $NaHSO_3$/ DMF [4], Pd-catalyzed intramolecular amination reaction of *N*-tosylhydrazones trimethylsilylindazole [5], trimethylsilylindazole/CsF [6], 3-carboxyindazole [7], indazole-N-oxides via 1,7-electrocyclization of azomethine ylides [8], Palladium-catalyzed intramolecular amination of aryl halides 9-10]. Synthesis of indazoles has been also done by the condensation of ortho fluorobenzaldehydes and their oximes with hydrazine [11], 3-substituted indazoles and benzoisoxazoles synthesis via Pd-catalyzed cyclization reactions [12], cyclization of ortho-substituted aryl hydrazones with halogens, nitro and methoxy [13] group substituents [14] etc. Certain other method for the synthesis of substituted indazole has been also reported [15-21]. In our previous work, the indazole synthesis has been reported from o-hydroxy aryl ketones and hydrazine hydrate using Lewis acid catalysts [22].

Herein,We have been demonstrated an efficient and mild protocol for the synthesis of substituted indazoles in DMSO using catalytic amount of silica sulphuric acid in excellent yields at room temperature. The reaction proceeds effectively at room temperature and no undesirable side products were obtained.

RESULTS AND DISCUSSION

In a model condensation reaction, *o*-hydroxy aromatic aldehydes or acetophenone and hydrazine hydrate in DMSO were stirred at room temperature using catalytic amount of silica sulphuric acid **(Scheme-1)**. The progress of the reaction was monitored by TLC. After completion of the reaction, using usual workup substituted indazoles in 85% yield was afforded. To evaluate the utility of this procedure, a variety of substituted indazoles were also synthesized using the same protocol. The results and physical data are listed in **(Table-1)**.



Scheme-1

The same reactions were also studied by several peoples using various catalysts. In presence of CsF the reaction was completed in 24 hrs at room temperature [23]. In presence of TBAF at room temperature the reaction required almost same time i.e. 20 hrs [23]. While, in presence of iodine catalyst the reaction was completed within 2 hrs. only on stirring at room temperature [22]. An advantage of the catalyst silica sulphuric acid is; the reaction is completed within 2 hrs. on stirring the reaction mixture at room temperature and the separated catalyst was reused for several times with same efficiency. Hence the method is cost effective in comparison of other catalysts **(Table-2)**.

Table-2: Reaction using various catalysts

Entries	Catalyst	Temp (^{0}C)	Time	Yield %
1	CsF	rt	24hr	36[23]
2	TBAF	rt	20hr	30[23]
3	Iodine	rt	2hr	85[22]
4	**SSA**	**rt**	**2hr**	**90**

However as far as we know, an efficient synthesis of indazoles in reasonable yield has not yet been reported. The synthesis of indazoles has been demonstrated in different solvents like ethanol, acetonitrile, toluene, THF and DMSO. It was found that the reactions in DMSO affords good yield of indazoles as compare to the other solvents using catalytic amount of silica sulphuric acid **(Table-3)**.

Table-3: Synthesis of 6-amino indazole in various solvents

Entries	Solvents	Amount of SSA	Yield%
1	Ethanol	0.158 gm	40
2	Acetonitrile	0.158 gm	50
3	Toluene	0.158 gm	30
4	THF	0.158 gm	32
5	**DMSO**	**0.158 gm**	**78-90**

Reusability of the catalyst is an important factor from economical and environmental point of views and attracted much more attention in recent years. Therefore, the reusability of silica sulphuric acid was examined under optimized reaction conditions. The catalyst silica sulphuric acid is a super solid acid. It exists in solid state and easily separated from reaction mixture simply by filtration. The other advantage is, it can be reused and recycled several time with minimum loss in its efficiency **(Table-4)**. Hence it is more convenient and cost effective catalyst. The reaction need not any hazardous organic solvent indicate the method is green and ecofriendly.

Table-4: Recovery of SSA in the synthesis of Indazole

Entries	Product	% Yield of SSA		
		Recycle-1	Recycle-2	Recycle-3
1	3a	97	95	94
2	3b	95	93	90
3	3c	98	95	93
4	3d	96	94	91

Table-5: Scale up reaction condition and yields of compound 12

Entries	Reactant (gm)	Amount of SSA	Yield%
1	1 gm	1 mmol	90
2	5 gm	1 mmol	87
3	10 gm	1 mmol	82
4	25 gm	1 mmol	77

The scale up procedure has been also studied to check the amount of catalyst is sufficient for said reaction or not. It was observed that the scale up process from 1gm to 25 gm proceed

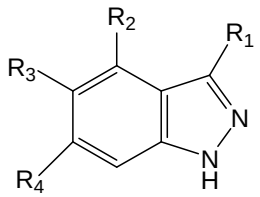
smoothly at same concentration of catalyst (1 mmol)with slight decrease in the yield of products **(Table-5)**.

In comparison to the reported methods, this protocol is rapid and offering good yields of the products. Various indazoles were also obtained in moderate to excellent yields using the same protocol.

MATERIALS AND METHODS

All the melting points are determined in open capillaries and uncorrected. TLC technique is routinely used to check the purity of synthesized indazoles on silica gel coated plates. IR spectra were recorded in KBr pellets on a Perkin-Elmer F.T.I.R.; PMR spectra were recorded on Perkin-Elmer Jeol FX 90 QC 300MHz instrument in $CDCl_3$. PMR chemical shifts are reported in δ values using tetramethyl silane (TMS) as standard.

Table-1: Substituent, melting points and yields of the synthesized compounds



Entries	R_1	R_2	R_3	R_4	m.p. ^{0}C (Lit)	% Yield
1	H	H	H	H	147[16]	80
2	H	H	H	H	147[16]	90
3	H	H	H	NH_2	205[22]	85
4	H	H	NH_2	H	175[22]	87
5	H	H	H	NO_2	180[17]	78
6	H	H	NO_2	H	208[22]	78
7	Me	OH	H	H	210[19]	89
8	Me	OMe	H	H	132[19]	90
9	Me	H	H	H	115[18]	87
10	Me	OMe	H	OMe	205[19]	90
11	Me	H	Me	H	220[22]	84
12	Me	Me	H	Me	208[22]	90
13	Me	H	Cl	H	265[22]	84
14	Me	H	H	Cl	252[22]	87

Typical procedure for the synthesis of 1H-Indazole:

A mixture of salicylaldehyde 1.22 gm (10 mmol), hydrazine hydrates 1 gm (20 mmol) and catalytic amount of silica sulphuric acid 0.158 gm (1mmol) in DMSO (5 ml) was stirred for 2 hours at room temperature. The progress of reaction was monitored on TLC. After completion of reaction, the reaction mixture was poured onto crushed ice and further stirred for 30 minutes. The reaction mixture was extracted with diethyl ether (3×10 ml). On evaporation of solvent, the crude was recrystallized in ethanol.

Similarly other indazoles were synthesized and confirmed by spectral analysis and listed in **Table No. 1.**

CONCLUSION

A simple and efficient method for the synthesis of indazoles using silica sulphuric acid (SSA) catalyst has been reported.

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Spectral Data:
All the products were characterized by IR, NMR and compared to authentic samples.

1H-indazole (1 & 2)
M. F.: $C_7H_6N_2$, Yield 80%, m.p. 147 ^{0}C, IR (cm^{-1}): 3424, 1689, 1571, ^{1}H NMR (δ): 6.95(1H, q, Ar-H) 7.03(1H, q, Ar-H) 7.35(1H, t, Ar-H) 7.37(1H, t, Ar-H) 8.25(1H, s) 8.79(1H, s, NH, D_2O, exchangeable)

3-Methyl-6-methoxy indazole (8)
M. F. : $C_9H_{10}N_2O$, Yield 90%, m.p. 132^{0}C, IR (cm^{-1}): 3427, 1623, 1596, 1525 ^{1}H NMR (δ): 2.67(3H, s, CH_3) 3.87(3H, s, OCH_3) 6.60- 7.67(3H, m, Ar-H) 8.56(1H, s, NH, D_2O, exchangeable)

3-Methyl indazole (9)
M.F. : $C_8H_8N_2$, Yield 87%, m.p. 115^{0}C, IR (cm^{-1}): 3442, 1602, 1560 ^{1}H NMR (δ): 2.61 (3H, s) 6.94 (1H, t, Ar-H) 7.02 (1H, q, Ar-H) 7.37 (1H, q, Ar-H) 7.63 (1H, t, Ar-H) 8.27 (1H, s, NH, D_2O exchangeable).

3-Methyl-4,6-dimethoxy indazole (10)
M.F.: $C_{10}H_{12}N_2O_2$, Yield 90%, m.p 205^{0}C, IR (cm^{-1}): 3382, 1636, 1602, 1531, ^{1}H NMR (δ): 2.87 (3H, s, CH_3) 4.14(3H, s, OCH_3) 4.24 (3H, s, OCH_3) 6.67-6.94(2H, m, Ar-H) 8.92 (1H, s, NH, D_2O, exchangeable).

3, 5-Dimethyl indazole (11)
M. F. : $C_9H_{10}N_2$, Yield 84%, m.p. 220^{0}C, IR (cm^{-1}): 3424,1670,1510 , ^{1}H NMR (δ): 2.61 (3H,s) 2.67 (3H, s, Ar-CH_3) 6.95 (1H, d, Ar-H) 7.20 (1H,dd, Ar-H) 7.30 (1H,d, Ar-H) 7.40 (1H,s, NH, D_2O exchangeable).

3-Methyl-5-Chloro indazole (12)
M. F. : $C_{10}H_{12}N_2$, Yield 90%, m.p. 208^{0}C, IR (cm^{-1}): 3476, 1622, 1597, 1445 ^{1}H NMR (δ): 2.64(3H, s, CH_3) 2.88(3H, s, Ar-H) 2.94(3H, s, Ar-CH_3), 7.45(2H, d, Ar-H) 7.87(1H, s, NH, D_2O, exchangeable).

3-Methyl-4-Chloro indazole (13)
M.F. : $C_8H_7N_2Cl$, Yield 84%, m.p. 265^{0}C, IR (cm^{-1}): 3428, 1602, 1560, ^{1}H NMR (δ): 2.30 (3H, s) 6.99 (1H, d, Ar-H) 7.33 (1H, d, Ar-H) 7.90δ (1H, dd, Ar-H) 7.66 (1H, s, NH, D_2O exchangeable)

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