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Silica sulfuric acid: an efficient catalyst for the synthesis of substituted indazoles

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Abstract

A simple extremely fast and efficient approach for the synthesis of substituted indazole in good to excellent yield catalyzed by using silica sulfuric acid (SSA) in DMSO solvent at room temperature. This is solid state reaction have been attracting the synthetic organic chemist as they provided enhance reaction rates, less environmental pollution, greater selectivity, cleaner products and manipulative simplicity. Various indazoles are obtained in moderate to excellent yield.

Keywords: Ortho-hydroxy aromatic aldehydes/ketones; Hydrazine hydrate; Silica sulphuric acid.

1. Introduction

Indazole derivatives are pharmacologically important compounds as their ring system forms a large number of drug molecules. These drug molecules are granisetron, $5HT_3$ receptor antagonist and also used as an anti-inflammatory and anti-emetic in cancer chemotherapy [1]. Recently, various methods have been reported for the synthesis of substituted indazoles using polyphosphoric acid [2], 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 its ortho methyloxime with hydrazine [11] , 3-substituted indazoles and benzoisoxazoles via Pd-catalyzed cyclization reactions [12], cyclisation of ortho-substituted aryl hydrazones having halogens, NO_2, OMe, and OMs [13], bi and trisustituted indazole [14, 15] and certain other method has been also reported [14-20]. In continuation of studies on indazoles synthesis using DMSO-I_2 [21], we herein reporting the silica sulfuric acid (SSA) as an efficient catalyst for the preparation of substituted indazoles.

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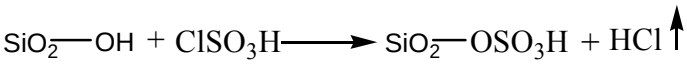


2. Experimental

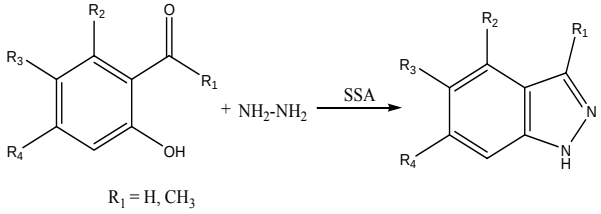
All the melting points were determined in open capillaries and uncorrected. TLC is routinely checked on silica gel coated plates. IR spectra were recorded in KBr pellets on a Perkin-Elmer F.T.I.R.; PMR spectra were recorded on Perkin-Elmer Jeol FX 90 QC 300MHz instrument in $CDCl_3$. PMR chemical shifts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

2.1. Typical procedure for the synthesis of 1H-Indazole

A mixture of salicyldehyde 1.22 g (10 mmol), hydrazine hydrates 1 g (20 mmol) and catalytic amount of silica sulphuric acid 40 mg (1 mmol) 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 (3X10 mL). After evaporation of the solvent, the desired crude product was recrystallized in ethanol.

3. Results and discussion

In a condensation reaction *ortho*-hydroxy aromatic aldehydes or acetophenone and hydrazine hydrate in DMSO were stirred at room temperature with catalytic amount of silica sulphuric acid. Progress of the reaction was monitored by TLC. After completion of the reaction, by usual workup substituted indazoles was afforded in 80% of yield. To evaluate the utility of procedure, a variety of substituted indazoles were also synthesized using the same protocol. The results and physical data are listed in Table 1.



Scheme I

The synthesis of indazoles has been demonstrated in different solvents like methanol, ethanol, acetonitrile, toluene, THF, DMF and DMSO. The reactions in DMSO affords good yield of indazoles as compare to the other solvents using catalytic amount of silica sulphuric acid.

In summary, 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. In comparison to the reported methods, this protocol is fast and offering good yields of the products.

3.1. Spectral Data

All the products were characterized by IR, NMR and compired to authentic samples. 1H-indazole (1 and 2)

M. F.: $C_7H_6N_2$, Yield 80 %, m.p. 147 °C, IR (cm^{-1}): 3424, 1689, 1571, ^1H 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).

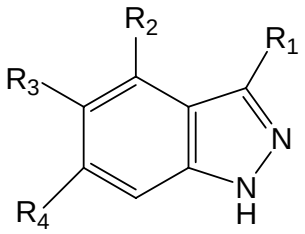


Table 1
Subsistent, yields and m.p. for the compounds.

Entry	R_1	R_2	R_3	R_4	m.p. °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 [21]	85
4	H	H	NH_2	H	175 [21]	87
5	H	H	H	NO_2	180 [17]	75
6	H	H	NO_2	H	208 [21]	78
7	Me	OH	H	H	210 [19]	92
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 [21]	84
12	Me	Me	H	Me	208 [21]	90
13	Me	H	Cl	H	265 [21]	84
14	Me	H	H	Cl	252 [21]	87

3.1.1. 3-Methyl-6-methoxy indazole (8)

M. F. : $C_9H_{10}N_2O$, Yield 90%, m.p. 132 °C, IR (cm^{-1}): 3427, 1623, 1596, 1525 ^1H 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)

3.1.2. 3-Methyl indazole (9)

M.F. : $C_8H_8N_2$, Yield 87%, m.p. 115 °C, IR (cm^{-1}): 3442, 1602, 1560 ^1H 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).

3.1.3. 3-Methyl-4,6-dimethoxy indazole (10)

M.F. : $C_{10}H_{12}N_2O_2$, Yield 90%, m.p 205 °C, IR (cm^{-1}): 3382, 1636, 1602, 1531, ^1H 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).

3.1.4. 3, 5-Dimethyl indazole (11)

M. F. :$C_9H_{10}N_2$, Yield 84%, m.p. 220 °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).

3.1.5. 3-Methyl-5-Chloro indazole (12)

M. F. : $C_{10}H_{12}N_2$, Yield 90%, m.p. 208 °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).

3.1.6. 3-Methyl-4-Chloro indazole (13)

M.F. : $C_8H_7N_2Cl$, Yield 84%, m.p. 265 °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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References

[1] J. Elguero, A. Fruchier, E.M. Tjiou, S. Trofimenko, Chem. Heterocyclic Comoud. 31 (1995) 1006-1010.
[2] Z. Zhong, T. Xu, X. Chen, Y. Qui, Z. Zhang, J. Chem. Soc Perkin Trans. I, 1 (1993) 1279-1280.
[3] M.R.G. Da-Costa, M.J.M. Curto, S.G. Davies, M.T. Duarte, C. Resende, F.C. Teixeira, J. Organometallic Chem. 604 (2000) 157-169.
[4] S.Z. Süleyman, A. Rüstem, Synthetic Comm. 32 (2002) 3399-23411.
[5] I. Kiyofumi, K. Mika, Y. Takashi, S. Ikue, H. Kou, S. Takao, Chem. Letts. 33 (2004) 1026-1027.
[6] H. Yoshiyuk, S. Yoshimichl, A. Toyohiko, Synthesis 8 (2004) 1183-1186.
[7] L.J. Barry, D.R. James, Synthetic Comm. 35 (2005) 2681-2684.
[8] N. Miklos, V. Andrea, Z. Weimin, W.G. Paul. B. Gabor, T. Laszlo, Tetrahedron 60 (2004) 9937-9944.
[9] Y.L. Artyom, S.K. Anton, Z.V. Alexander, J. Org. Chem. 70 (2005) 596-602.
[10] L. Kirill, C.H. Margaret, F.M. Dilinie, L. Robert, J. Org. Chem. 71 (2006) 8166-8172.
[11] I. Kiyofumi, K. Mika, Y. Takashi, A. Yukari, H. Kou, S. Takao, Tetrahedron 63 (2007) 2695-2711.
[12] J.S. Yadav, B.V.S. Reddy, K. Sadasive, G. Satheesh, G. Tetrahedron Lett. 43 (2002) 9695-9697.
[13] L. Bouissane, S.E. Kazzouli, J.M. Leger, C. Jarry, E.M. Rakib, M. Khouili, G. Guillaumet, Tetrahedron Lett. 61 (2005) 8218-8225.
[14] C.T. Fatima, R. Helene, F.A. Ines, M. Joao, M. Curto, D.M. Teresa, Molecules 11 (2006) 867-871.
[15] D.J. Varughese, M.S. Manhas, A.K. Bose, Tetrahedron Lett. 47 (2006) 6795-6798.
[16] C.I. Dellerba, M. Novi, G. Petrillo, C. Tsavani, Tetrahedron 50 (1994) 3529-3530.
[17] A.Y. Lebedev, A.S. Khahrtulyari, A.Z. Voskoboynikov, J. Org. Chem. 37 (2005) 257-263.
[18] P.D. Lokhande, A. Raheem, S.T. Sabale, A.R. Chabukswar, S.C. Jagdale, Tetrahedron Lett. 48 (2007) 6890-6892.
[19] M. Cheung, A. Boloor, J. A. Stafford, J. Org. Chem. 68 (2003) 4093-4095.
[20] P. Salehi, M.A. Zolfigol, F. Shirini M. Baghbanzadeh, Curr. Org Chem. 10 (2006) 2171-2189.
[21] D. Gaikwad, A. Syed, R. Pawar, Chem. Tech. 1 (2008) 442-445.