

SILICA SUPPORTED POLYPHOSPHORIC ACID CATALYZED SYNTHESIS OF SUBSTITUTED INDAZOLES

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A clean and straightforward methodology developed for the synthesis of substituted indazoles using silica supported polyphosphoric acid (PPA-SiO₂) catalyzed condensation reaction between substituted 2-hydroxybenzaldehydes or acetophenones and hydrazine hydrate or phenylhydrazine. The reaction conditions are optimized for different solvents at different temperatures. The yield of the products improved to 88 to 90 % using silica supported polyphosphoric acid as a catalyst, which is reusable, cost-effective and straightforward to synthesize.

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Introduction

Indazole and its derivatives were important pharmacological compounds as benzene attached fivemembered heterocyclic ring containing two nitrogen atom at 1,2-position forms a large number of drug moieties like HIV protease inhibition, anti-inflammatory, inhibition of protein kinase, high binding affinity for estrogen receptor,¹ 5-HT2 and HT3 receptor antagonism.² In literature precedent various methods have been reported by different researchers for the synthesis of indazoles and substituted indazoles. Main procedures involve cyclization of 2,6dihydroxyacetophenone hydrazones in the presence of polyphosphoric acid,³ using NaHSO₃/DMF,⁴ chromium tricarbonyl complex,⁵ trimethylsilylindazole/CSF,⁶ 3palladium-catalyzed carboxyindazole,⁷ intramolecular amination reaction of N-tosylhydrazones trimethylsilylindazole⁸ as well as aryl halides⁹ and copper-catalyzed synthesis of indazole.¹⁰ Indazole N-oxide are also reported through 1,7-electrocyclization of azomethine ylides.¹¹ Condensation of o-fluorobenzaldehydes and their oximes with hydrazine¹² also yield indazoles, literature survey reveals that cyclization of o-substituted aryl hydrazones with halogens, nitro and methoxy¹³ group as a substituent, 3substituted indazole and benzoisoxazoles synthesis via palladium catalyzed cyclization reactions.14

Hangirgekar reported the synthesis of indazoles from 2alkoxy-acetophenone, hydrazine hydrate and a catalytic amount of Montmorillonite K-10 in different solvents ethanol, methanol, toluene, acetonitrile, DMF, THF and DMSO.⁷

In this paper, we have reported reusable solid supported acid catalyst (PPA-SiO₂) as an efficient and mild protocol for the synthesis of indazoles. We have also optimized the

reaction temperature to get maximum yield (Table 1 and 2) in ethanol and DMSO as solvents.

Experimental

General

All chemical used were AR grade and without further purification. All the products are known and their physical parameters are confirmed by comparison with the reported literature data. The catalyst was prepared according to the literature.¹⁵ Melting points were determined in open capillaries and reported uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on at 400 MHz instruments in CDCl₃ using TMS as an internal standard.

Preparation of catalyst (PPA-SiO₂)

PPA (2.1 g) was taken in 100 ml round bottom flask and CHCl₃ (50 ml) was added. Then the reaction mixture was stirred well at room temperature and then heated 50 °C for 1 h. SiO₂ (400 mesh, 4.9 g) was added in portions to the solution. The mixture was stirred for further 1 hr. The solvent CHCl₃ was distilled off under vacuum and resulting solid was dried under vacuum at 35-40 °C for 2 h.

Synthesis of 1H-indazoles (3a,3b,3e,3f)

The mixture of salicylaldehyde (1 mmol), hydrazine hydrate (1.5 mmol) and silica supported polyphosphoric acid (20 mole %) in a solvent (5 mL) was stirred for different time intervals at different temperatures (Table 1). The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate (8:2) solvent. After completion of the reaction, the reaction mixture was cooled to room temperature and the catalyst was filtered off. The catalyst was washed with the solvent (2x2 mL) and reused for other reactions. The collected filtrate was poured onto crushed ice to obtain crude product. The product is filtered and purified by recrystallization using methanol.

Synthesis of 1-phenyl-1H-indazole (3c,3d,3g,3h)

A mixture of 2-hydroxyacetophenone (1 mmol), phenylhydrazine/2,4-dinitrophenylhydrazine (1 mmol) and PPA-SiO₂ (20 mol %) in a solvent (5 mL) was heated to 75 to 95 °C. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate (8:2) solvent. After the completion of the reaction, the reaction mixture was cooled to room temperature and the catalyst was filtered off and washed with the solvent (2x2 mL) and to use in other reaction. The filtrate was collected and poured into crushed ice (20 g), the crude product was filtered and recrystallized using methanol as solvent.

Characterization and spectral data for selected products

The physical parameters of compound **3a-3h** are determined and reported in table no. 1 and 2. The final products were characterized by ¹H NMR and ¹³C NMR.

1H-Indazole (3a)

¹H NMR (CDCl₃): δ 7.10 (1H, d, Ar-H) 7.31 (1H, d, Ar-H) 7.53 (1H, dd, Ar-H) 7.55 (1H, dd, Ar-H) 8.25 (1H, s) 13.05 (1H, s, NH, D₂O, exchangeable). ¹³CNMR (CDCl₃): δ 139.7, 133.2, 122.70, 120.0, 109.9, 78.8, 39.7.

3-Methyl-1H-indazole (3b)

¹H NMR (CDCl₃): δ 13.25 (1H, s, NH, D₂O, exchangeable), 6.91 (1H, d, Ar-H), 7.02 (1H, dd, Ar-H), 7.25 (1H, dd, Ar-H), 7.37 (1H, d, Ar-H), 2.57 (3H. s). ¹³CNMR (CDCl₃): δ δ 168.1, 160.6, 132.9, 128.9, 119.0, 117.9, 77.3, 14.8.

1-(2,4-Dinitro-phenyl)-1H-indazole (3c)

¹H NMR (CDCl₃): δ 9.26 (1H, s, Ar-H), 8.67 (1H, d, Ar-H), 7.80 (1H, d, Ar-H), 8.40 (1H, s, Ar-H), 7.84 (1H, d, Ar-H), 7.37 (1H, dd, Ar-H), 7.34 (1H, dd, Ar-H), 7.12 (1H, d, Ar-H). ¹³CNMR (CDCl₃): δ 119.8, 139.6, 148.8, 135.4, 153.5, 148.9, 134.8, 142.7, 128.4, 114.2, 121.1, 126.5.

1-(2,4-Dinitro-phenyl)-3-methyl-1H-indazole (3d)

¹H NMR (CDCl₃): δ 8.98 (1H, s, Ar-H), 8.38 (1H, d, Ar-H), 8.1 (1H, d, Ar-H), 7.89 (1H, d, Ar-H), 7.24 (1H, dd, Ar-H), 7.56 (1H, dd, Ar-H), 7.60 (1H, d, Ar-H), 2.92 (3H, s). ¹³CNMR (CDCl₃): δ 24.1, 114.8, 1462, 134.3, 143.6, 161.0, 141.9, 117.3, 150.1, 135.4, 126.4, 120.2, 117.0, 108.4.

6-Nitro-1H-indazole (3e)

¹H NMR (CDCl₃): δ 8.41 (1H, s, Ar-H) 8.31 (1H, d, Ar-H) 7.82 (1H, d, Ar-H) 8.51 (1H, d, Ar-H), 12.08 (1H, s, NH, D₂O, exchangeable). ¹³CNMR (CDCl₃): δ 128.4, 132.7, 149.4, 102.5, 165.4, 118.2, 114.2.

5-Nitro-1H-indazole (3f)

¹H NMR (CDCl₃): δ 8.21 (1H, s, Ar-H) 8.84 (1H, d, Ar-H) 7.94 (1H, d, Ar-H) 8.86 (1H, d, Ar-H), 13.18 (1H, s, NH, D₂O, exchangeable). ¹³CNMR (CDCl₃): δ 117.5, 104.0, 144.3, 128.4, 112.0, 148.0, 146.8.

1-Phenyl-1H-indazole (3g)

¹H NMR(CDCl₃): δ 8.13 (d, 1H, Ar-H), 7.75 (dd, 1H, Ar-H), 7.69-7.77 (m, 2H, Ar-H), 7.57-7.65 (m, 3H, Ar-H), 7.46 (m, 1H, Ar-H), 7.29-7.35 (m, 1H, Ar-H), 7.19 (m, 1H, Ar-H). ¹³C NMR (CDCl₃): δ 140.1, 138.6, 135.3, 129.3, 127.0, 126.5, 125.2, 122.6, 121.4, 121.2, 110.3.

3-Methyl-1-phenyl-1H-indazole (3h)

¹H NMR (CDCl₃): δ 7.94 (1H, d, Ar-H), 7.20 (1H, dd, Ar), 7.25 (1H, dd, Ar), 7.37 (1H, d, Ar), 3.09 (3H. s), 7.8-8.5 (5H, m, Ar-H). ¹³CNMR (CDCl₃): δ 18.2, 122.0, 117.2, 128.0, 135.1, 104.0, 124.1, 123.1, 114.2, 129.8, 152.8.

Result and Discussion

The condensation reaction of substituted salicylaldehyde and hydrazine hydrate using silica supported polyphosphoric acid catalyst could successfully perform according to Scheme 1. Similar type synthetic protocols were also studied using various acid catalysts such as PTSA, Montmorillonite KSF, Amberlite-15, Zeolite-HY and Montmorillonite K-10, the desired indazoles were obtained in 17, 64, 38, 57 and 85 % yields respectively.¹⁵⁻²³ The above-mentioned acid-catalyzed reactions were carried at reflux temperature for 3 h using 20 % weight of catalyst concerning the weight of all the reactant was used. Thus, silica supported polyphosphoric acid was found to be a moderate heterogeneous acid catalyst as compared with the above acid catalyst used for the synthesis of indazole derivatives.

The synthesis of indazole derivatives has been reported in two different solvents such as ethanol and DMSO. We found that the reaction in the presence of DMSO solvent at 90 to 95 °C affords good yields as compared to reflux in ethanol using the catalytic amount of silica supported polyphosphoric acid.



Scheme 1. Synthesis of substituted indazoles 3a-3h

Table 1. Phys	sical parameters	s of the substituted	indazoles at reflu	ux in ethanol solvents.
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Entry	R ₁	\mathbf{R}_2	R ₃	R ₄	Time, h	M.p. °C	Yield, %
3a	Н	Н	Н	Н	5	1476	48
3b	Н	Me	Н	Н	5	113-1156	45
3c	Ph-2,4-di-NO ₂	Н	Н	Н	8	237	31
3d	Ph-2,4-di-NO ₂	Me	Н	Н	8	194-196	38
3e	Н	Н	Н	NO_2	4	180 ⁶	40
3f	Н	Н	NO ₂	Н	5	208 ⁶	35
3g	Ph	Н	Н	Н	8	77-79 ⁷	32
3h	Ph	Me	Н	Н	8	85-87 ⁷	37

m. p. : melting point.

Table 2. Physical parameters of the substituted indazoles at 90-95 °C in DMSO solvents.

Entry	R ₁	\mathbf{R}_2	R ₃	R ₄	Time, h	M.p. °C	Yield, %	
3a	Н	Н	Н	Н	3	1476	82	
3b	Н	Me	Н	Н	3	113-115 ⁶	85	
3c	Ph-2,4-di-NO2	Н	Н	Н	4	237	72	
3d	Ph-2,4-di-NO2	Me	Н	Н	4	194-196	81	
3e	Н	Н	Н	NO_2	4	180^{6}	80	
3f	Н	Н	NO_2	Н	4	2086	68	
3g	Ph	Н	Н	Н	4	77-79 ⁷	87	
3h	Ph	Me	Н	Н	4	85-87 ⁷	86	

m. p. : melting point.

Conclusion

In summary, the efficient methodology is developed for the synthesis of indazole and its derivatives by condensation of hydrazine and an o-hydroxy aromatic carbonyl compound in the presence of a catalytic quantity of PPA-SiO₂ is reported. Reusability of the catalyst, moderated yields and simple technique used for product isolation is the crucial importance of this methodology.

The reusability of the silica supported polyphosphoric acid catalyst is an essential factor for the environmental and economic point of view. The catalyst exists in solid state and can be easily separated from the reaction mass by simple filtration. The catalyst is reusable several times with the small loss of efficacy. Hence it is cost effective and more convenient catalyst for the synthesis of indazoles. The reaction does not need hazard organic solvent since this methodology is green and eco-friendly.

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Compliance with ethical standards

The authors declare that there are no conflicts of interest in this work.

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