



SYNTHESIS OF 1H-INDAZOLES USING LEMON PEEL POWDER AS A NATURAL, GREEN AND EFFICIENT CATALYST UNDER ULTRASOUND IRRADIATION

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Keywords: 2-substituted aldehydes, 1H-indazoles, hydrazine hydrate, natural catalyst, lemon peel powder (LPP).

Bioactive 1H-indazoles were synthesized from 2-substituted aromatic aldehydes and hydrazine hydrate using DMSO and lemon peel powder as a green and efficient natural catalyst. In comparison to other reported conventional methods, this method affords good yield under ultrasonic irradiation.

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INTRODUCTION

Development of efficient synthesis methods of indazole derivatives (Figure 1) has been a long-term goal in medicinal chemistry.¹⁻⁴

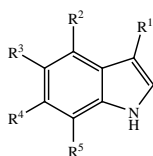


Figure 1. Structure of 1H-indazoles.

Among a large variety of nitrogen-containing heterocyclic compounds, indazoles are of great interest because they constitute an important class of natural and non-natural products.⁵ Indazole is a nitrogen containing bicyclic heterocycle that shows a wide range of biological activities including anti-microbial,⁶ anticancer,⁷ antioxidant,⁸ antiplatelet,⁹ etc.

Owing to the biological importance, scientists have developed various methods for the synthesis of indazoles by using different catalysts such as iodine,¹⁰ poly phosphoric acid,¹¹ including palladium catalyzed intramolecular amination,¹² cross coupling/cyclizations,¹³ and using montmorillonite K-10.¹⁴ Ultrasound enhances the reactivity of molecules towards many chemical reactions. Many indazoles have been synthesized by non-conventional methods^{15,16} but these are more time consuming.

Lemon peel powder (LPP) is a natural and biodegradable material which can be used as a catalyst. Citric acid is present in lemon. Albedo is the major constituent of LPP.¹⁷ The main minerals present in lemon peels includes sodium, potassium, calcium and iron.¹⁸

In continuation of our efforts for the eco-friendly approaches for the synthesis of bioactive heterocyclic compounds, herein we wish to report one pot synthesis of 1H-indazole derivatives by the reaction of an aromatic aldehyde, hydrazine hydrate and LPP as a catalyst, in DMSO, under ultrasound irradiation in a short reaction time.

EXPERIMENTAL

All the melting points were determined in open capillaries and are uncorrected. ¹H NMR spectra were recorded on a 500 MHz with Bruker ARS spectrometer. Chemical shifts were reported in δ ppm using tetramethyl silane as the internal standard in CDCl₃ solvent.

General procedure for the synthesis of substituted indazoles

A mixture of salicyldehyde (1 mmol), hydrazine hydrate (2 mmol) and LPP (10 wt %) in DMSO solvent (5 mL) was irradiated under ultra-sonication bath for appropriate time as indicated in Table 1. The progress of reaction was monitored by TLC (n-hexane: ethyl acetate, 7:3). After completion of reaction, the reaction mixture was diluted with hot ethanol and filtered. Residue, being the separated catalyst, was washed thrice (3 x 5 mL) with ethanol. The combined filtrates were concentrated to get crude product which was further purified by re-crystallization in ethanol.

Spectral data of synthesized compounds

1H-Indazoles was obtained by the reaction of the four 2-substituted salicyldehyde (Table 1, entry 1-4). The products exhibited almost identical spectroscopic data.

1H-indazole

¹H NMR (500 MHz, CDCl₃) δ = 11.10 (s, 1H, NH), 8.15 (s, 1H, CH), 7.36 (t, 1H, Ar-H), 7.34 (dd, 2H, Ar-H), 7.03 (dd, 2H, Ar-H). ESI-MS: 119(M+1).

4-Chloro-1H-indazole (5)

¹H NMR (500 MHz, CDCl₃) δ = 11.20 (s, 1H, NH), 8.18 (s, 1H, CH), 7.53 (t, 1H, Ar-H), 7.25 (t, 1H, Ar-H), 7.21 (t, 1H, Ar-H). ESI-MS: 153.1(M+1).

6-Chloro-1H-indazole (6)

¹H NMR (500 MHz, CDCl₃) δ = 12.40 (s, 1H, NH), 9.01 (s, 1H, CH), 8.07 (s, 1H, Ar-H), 7.36 (d, 1H, Ar-H), 7.34 (d, 1H, Ar-H). GCMS: 153.1 (M+1).

6-Methoxy-1H-indazole (7)

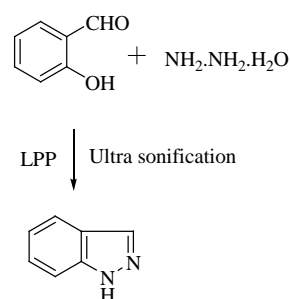
¹H NMR (500 MHz, CDCl₃) δ = 12.41 (s, 1H, -NH), 8.14 (s, 1H, -CH), 7.95 (s, 1H, Ar-H), 7.58 (d, 1H, Ar-H), 6.87-6.90 (m, 2H, Ar-H), 3.40 (s, 3H, CH₃). GCMS: 149.1(M+1).

4-(Diethylamino)-1H-indazole (8)

¹H NMR (500 MHz, CDCl₃) δ = 11.91 (s, 1H, -NH), 8.44 (s, 1H, -CH), 7.10 (d, 1H, Ar-H), 6.21-6.26 (m, 2H, Ar-H), 3.41 (q, 4H, -CH₂), 1.25 (t, 6H, -CH₃). GCMS: 190.1 (M+1).

RESULTS AND DISCUSSION

In an initial experiment, indazole was synthesized by treating a mixture of salicylaldehyde (1 mol) and hydrazine hydrate (2 mol) in DMSO (5 mL) under ultrasound irradiation in the presence of a catalytic quantity of LPP (10 % mole) for 45 min.



Scheme 1. General reaction for the synthesis of 1H-Indazole derivatives.

Table 1. Synthesis of 1H-indazole derivatives.

Entry	Aldehyde	Product	Time, min	Yield, %	Melting point, °C	
					Observed	Reported
1			30	80	146	147 ¹⁴
2			30	75	145	
3			30	78	146	
4			30	78	147	
5			30	83	154-156	155-157 ¹⁹
6			30	86	179-181	
7			30	90	192-194	
8			35	88	194-196	

After completion of the reaction (monitored by TLC), the LPP was filtered from the reaction mixture. The resulting filtrate was concentrated to get crude product which was recrystallized from ethanol to afford 1H-indazole. We optimized the effect of different solvents for the synthesis of 1H-indazole and observed that the best yield was obtained in DMSO (Table 2).

Table 2. Effect of various solvents on the synthesis of 1H-indazole.

Entry	Solvent	Yield, %
1	Water	45
2	Methanol	50
3	Ethanol	56
4	DMF	63
5	DMSO	80

Next we studied optimization of catalyst at various concentrations (Table 3). We observed that 10 wt % of catalyst was sufficient to carry out the reaction.

Table 2. Effect of catalyst on the synthesis of 1H-indazoles.

Entry	Catalyst, wt %	% of yield
1	2	36
2	4	50
3	6	65
4	8	76
5	10	80
6	12	80
7	14	83

Antifungal activity

Antifungal activity of the synthesized compounds was studied against fungal species *A. Niger* using carbendazim as the standard. Agar well diffusion method was used for the screening purpose. Observations were recorded after 72 h and the zone of inhibition was measured in mm at a concentration of 10 mg mL⁻¹ in DMSO solvent.

Table 4. Zone of inhibition in mm of synthesized 1H-indazole derivatives.

Compound	Zone of inhibition, mm
1	16
2	16
3	15
4	16
5	18
6	23
7	28
8	20
STANDARD	18

CONCLUSION

In conclusion we achieved the synthesis of 1H-indazoles using Lemon peel powder (LPP) as an efficient natural catalyst from substituted aromatic aldehyde and hydrazine hydrate in DMSO. The conversion was very efficient and

fast giving good yield of the products. All the synthesized compounds showed good to excellent antifungal activity as compare to standard carbendazim.

ACKNOWLEDGEMENT

Authors are thankful to the Principal, Deogiri College, Aurangabad, for providing necessary laboratory facilities and the Head, Department of Botany.

REFERENCES

- Gaikwad, D. D., Chapolikar, A. D., Devkate, C. G., Warad, K. D., Tayade, A. P., Pawar, R. P., Domb, A. J., Synthesis of indazole motifs and their medicinal importance: An overview. *Eur. J. Med. Chem.*, **2015**, *90*, 707-731.
- Chandrasekhar, T., Reddy, A. B., Kumar, L. V., Naik, P. J., Sree, M. K., Swamy, G. N., Synthesis and biological evaluation of some new indazole-3-carboxamide derivatives, *Scholars Res. Library*, **2012**, *4*(3), 1311-1316.
- Li, P., Wu, C., Zhao, J., Rogness, D. C., Shi, F., Synthesis of Substituted 1H-Indazoles from Arynes and Hydrazones, *J. Org. Chem.*, **2012**, *77*, 3149-3158, doi.org/10.1021/jo202598e
- Fang, Y., Wu, C., Larock, R. C., Shi, F., Synthesis of 2H-Indazoles by the [3+2] Dipolar Cycloaddition of Sydnone with arynes, *J. Org. Chem.*, **2011**, *76*(21), 8840-8851, doi:10.1021/jo201605V
- Hassankhani, A., Mosaddegh, E., Ebrahimipour, S. Y., Tungstosilic acid as an efficient catalyst for the one-pot multicomponent synthesis of triazolo[1,2-a]indazole-1,3,8-trione derivatives under solvent-free condition, *Arabian J. Chem.*, **2016**, *9*(1), 5936-5939, doi.org/10.1016/j.arabj.2011.10.003.
- Parekh, C., Modi, A., Pillai, J., Patel, B., A Novel Synthesis of Series of Indazole Derivative as Potent Antimicrobial Agents, *Int. J. Drug Res. Tech.*, **2012**, *2*(3), 279-288.
- Yakaiah, T., Lingaiah, B. P. V., Narsaiah, B., Shireesha, B., Ashok, K. B., Gururaj, S., Parthasarathy, T., Sridhar, B., Synthesis and structure-activity relationships of novel pyrimido[1,2-b]indazoles as potential anticancer agents against A-549 cell lines, *Bioorg. Med. Chem. Lett.*, **2007**, *17*(12), 3445-3453, doi.org/10.1016/j.bmcl.2007.03.087
- Polo, E., Trilleras, J., Ramos, J., Galdamez, A., Quiroga, J., Gutierrez, M., Efficient MW-assisted synthesis, spectroscopic Characterization, X-ray and antioxidant properties of indazole derivatives, *Molecules*, **2016**, *21*, 903, doi:10.3390.
- Bethanamudi, P., Bandari, S., Sankari, K., Velidandi, A., Chandramouli, G., Synthesis of Novel N¹ and N² Indazole Derivatives, *E-J. Chem.*, **2012**, *9*(4), 1676-1682.
- Gaikwad, D., Abed, S., Pawar, R., Molecular iodine as an efficient catalyst for the synthesis of indazole, *Int. J. Chem. Tech. Res.*, **2009**, *1*(3), 442-445.
- Dennler, E., Frasca, A., Synthesis of indazoles using polyphosphoric acid-1, *Tetrahedron*, **1966**, *22*(9), 3131-3141. doi.org/10.1016/S0040-4020(01)82291-2.
- Lebedev, A., Khartulyari, A., Voskoboinikov, A., Synthesis of 1-aryl-1H-indazoles via palladium-catalyzed intramolecular amination of aryl halides, *J. Org. Chem.*, **2005**, *70*(2), 596-602, doi.org/10.1021/jo048671t.

- ¹³Tang, X., Gao, H., Yang, J., Wu, W., Jiang, H., Efficient access to 1H-indazoles via copper-catalyzed cross-coupling/cyclisation of 2-bromoaryl oxime acetates and amines, *Org. Chem.*, **2014**, *1*, 1295-1298, [doi:10.1039/C4QO00244J](https://doi.org/10.1039/C4QO00244J).
- ¹⁴Hangirgekar, P., Montmorillonite K-10 catalyzed synthesis of 1-aryl-3 alkyl substituted indazoles, *J. Chem. Biol. Phys. Sci.*, **2012**, *2(4)*, 1676-1680.
- ¹⁵Meng, G., Yang, T. Liu, Y., An Improved Preparation of 4-Chloro-1H indazole, *Org. Prep. Proced. Int.*, **2011**, *43*, 354-359, dx.doi.org/10.1080/00304948.2011.594005.
- ¹⁶Lukin, K., Hsu, M., Fernando, D., Leanna, M., New practical synthesis of indazoles via condensation of o-Fluorobenzaldehydes and their O-methyloximes with hydrazine, *J. Org. Chem.*, **2006**, *71*, 8166-8172.
- ¹⁷Pathak, P., Mandavane, S., Kulkarni, B., Fruit peel Waste: characterization and its potential uses, *Curr. Sci.*, **2017**, *113(3)*, 444-454.
- ¹⁸Janati, S., Beheshti, H., Fiezy, J., Fahim, N., Chemical composition of lemon (citrus limon) and peels its Considerations as animal and food, *GIDA: The Journal of Food*, **2012**, *37(5)*, 267-271.

Received: 13.10.2019.

Accepted: 19.11.2019.