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

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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.

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.](image)

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 methods15,16 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 salicyldehalyde (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 salicylddehyde (Table 1, entry 1-4). The products exhibited almost identical spectroscopic data.
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1H-indazole

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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, CH$_3$). GCMS: 149.1 (M+1).

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

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 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, -CH$_2$), 1.25 (t, 6H, -CH$_3$). 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.](image)

Table 1. Synthesis of 1H-indazole derivatives.

| Entry | Aldehyde          | Product          | Time, min | Yield, % | Melting point, °C |
|-------|-------------------|------------------|-----------|----------|------------------|
|       |                   |                  |           |          | Observed         | Reported      |
| 1     | CHO                | N               | 30        | 80       | 146              | 147$^{14}$    |
| 2     | CHO                | N               | 30        | 75       | 145              |              |
| 3     | CHO                | N               | 30        | 78       | 146              |              |
| 4     | CHO                | N               | 30        | 78       | 147              |              |
| 5     | CHO                | N               | 30        | 83       | 154-156          | 155-157$^{19}$|
| 6     | CHO                | N               | 30        | 86       | 179-181          |              |
| 7     | CHO                | N               | 30        | 90       | 192-194          |              |
| 8     | CHO                | N               | 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.

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