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# "Microwave Assisted Synthesis of Substituted Indazole Derivatives"

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**Abstract:**
A simple and green microwave irradiation method developed for the synthesis of substituted indazoles using different catalyst like $I_2$, S.S.A., PPA-$SiO_2$ in various solvents. The condensation reaction between phenylhydrazine or hydrazine hydrate and substituted 2-hydroxy benzaldehydes or Ketones. The yield of the products improved to 90 to 93 % by using this microwave irradiation method within the 5-8 minutes.

**Keywords**: *Microwave irradiation, o-hydroxy acetophenones, phenyl hydrazine, hydrazine hydrate, and indazole.*

## INTRODUCTION

A lot of researchers are synthesizing Indazoles and its derivatives by conventional methods [1-7] due to its multiple uses. Precedent literature shows that different catalyst, solvents, techniques are used for the synthesis of Indazoles. Molecular Iodine[8], Silica Sulphuric acid[9], Palladium[10-11], Montmorillonite K-10[12], Copper[13-14] catalyst has been employed under conventional methods. Some of the Indazoles are reported as dye Properties[15]. Generally, a lot of heterocyclic compounds shows pharmacological activities among them Indazoles also shows biological activities like 5-$HT_2$ and $HT_3$ receptor antagonism[16], anti-inflammatory[17], Anticancer[18], antimicrobial[19] and so many.
Indazole are compounds like Pyrazole type ring system is attached with the benzene ring and this privileged structure of the two aromatic rings containing compound make it more biological valuable and seek the attention of chemistry researchers. We are introducing the synthesis of Indazole derivatives by using microwave irradiation method.

## EXPERIMENTAL

### General

The raw material used were AR grade and used without further purification. All the products are known and their physical parameters are confirmed by comparison with those reported literature. Melting points were determined in open capillaries and reported uncorrected. Microwave used for irradiation is of make 'Catalyst microwave synthesizer Sr. No. 130602954'. $^1$H NMR and $^{13}$C NMR spectra were recorded on at 400 MHz instruments in $CDCl_3$ using TMS as an internal standard.

### Synthesis of 1H-indazole (3a-j):

The mixture of salicylaldehyde 1.22 gm, hydrazine hydrate 1.5gm and catalyst 0.5 gm in 250 ml RBF containing a DMSO (10ml) at room temperature and stirred well. Then the reaction mass is irradiated with microwave at power 280 Watt for 5 to 8 min. The progress of reaction was monitored by TLC using n-Hexane: Ethyl acetate (8:2) solvent. After the completion, the reaction mixture was cooled to room temperature and the catalyst was filtered. Catalyst is wash with solvents (4 ml x 2) and reused for other reaction. Collect filtrate was poured onto crushed ice to obtained crude solid product. The product is filtered and purified by recrystallization using methanol. In the presence of $I_2$ catalyst poured reaction mass is treated with 10 % Sodium thiosulphate solution to remove the catalyst.

### Characterization and spectral data for selected products

The physical parameters of compound 3(a-f) are determined and reported in table no. 1. The final products were characterized by $^1$H NMR and $^{13}$C NMR.

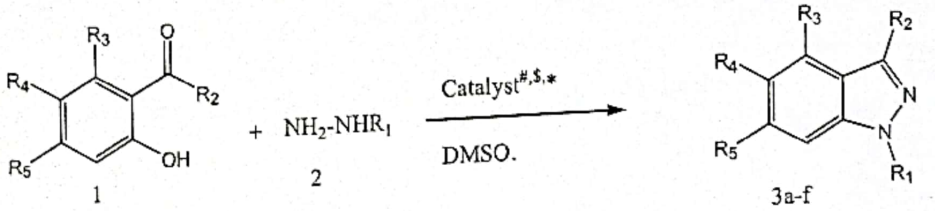
**1H-indazole (3a)::**
M.P. 147 $^0$C. Mass (ES+):- 119. $^1$H NMR (δ): 7.13 (1H, q, Ar-H) 7.38 (1H, q, Ar-H) 7.28 (1H, t, Ar-H) 7.27 (1H, t, Ar-H) 8.26 (1H, s) 13.15 (1H, s, NH, $D_2O$, exchangeable). $^{13}$CNMR (CDCl3): δ 139.7, 133.2, 122.70, 120.0, 109.9, 78.8, 39.7.

**3-methyl-1H-indazole (3b):**
M.P.113-115 $^0$C. $^1$H NMR (δ): 13.25 (1H, s, NH, $D_2O$, exchangeable), 6.96 (d, 1H, Ar), 7.08 (d, 1H, Ar), 7.29 (t, 1H, Ar), 7.30 (t, 1H, Ar), 2.51 (s, 3H). $^{13}$CNMR: δ 168.1, 160.6, 132.9, 128.9, 119.0, 117.9, 77.3, 14.8.

**1-Phenyl-1H-indazole (3e):**
M.P. 77-79 °C. $^1$H NMR: δ 8.10 (d, 1H), 7.72 (dt, 1H), 7.69-7.75 (m, 2H), 7.57-7.64 (m, 3H), 7.47 (m, 1H), 7.29-7.36 (m, 1H), 7.10 (m, 1H). $^{13}$C NMR: δ 140.1, 138.6, 135.3, 129.3, 127.0, 126.5, 125.2, 122.6, 121.4, 121.2, 110.3.

## RESULT AND DISCUSSION

The microwave irradiated condensation reaction between hydrazine hydrate and substituted salicylaldehyde is successfully reported for the synthesis of Indazole derivatives as mentioned in the scheme 1 with the different catalyst such as $I_2$, S.S.A. and Silica supported Polyphosphoric Acid in DMSO solvent. We found that the reaction in presence of all the catalyst affords good yields as compared to conventional methods used for the synthesis.
Microwave irradiation is a green approach for the synthesis of heterocyclic compounds. Microwaves are responsible for the activation of molecules to reacts and form the products with less reacting time. This microwave gives strong energy of activation in a short time period and completes the conversion in 5 to 10 min. In the convention methods of synthesis, the activation energy is provided by long heating.




1 2 3a-f

$R_1$= H, Ph.
$R_2$= H, Me.
$R_3$= H, Me.
$R_4$= H, Me.
$R_5$= H, Me.

# = $I_2$
$ = S.S.A.
* = PPA-$SiO_2$

**Scheme-1.** Synthesis of substituted indazoles (3a-f)

**Table-1.** Physical parameters of the substituted indazoles at 80 – 90 °C.

| Entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Time / min | m.p. °C |
|---|---|---|---|---|---|---|---|
| 3a | H | H | H | II | H | 05 | 147 |
| 3b | H | Me | H | H | H | 05 | 113-115 |
| 3c | H | Me | H | Me | H | 05 | 220 |
| 3d | H | Me | Me | H | Me | 05 | 208-210 |
| 3e | Ph | H | H | H | H | 08 | 77-79 |
| 3f | Ph | H | H | H | Me | 08 | 85-87 |

During the reaction it is observed that the yields of indazoles are more than 80 percent for all the catalyst used. Among the catalyst PPA-$SiO_2$ is more effective in which yields are higher by 4 to 5 percent. While S.S.A. is less effective than other catalyst used in the present studies. Still the percent yield is higher than conventional methods.

**Table-2.** Yield of Indazole derivatives in different catalyst.

| Entry | % Yields |
|---|---|

| | $I_2$ Catalyst | S.S.A. Catalyst | PPA-$SiO_2$ Catalyst |
|---|---|---|---|
| 3a | 90 | 85 | 94 |
| 3b | 92 | 80 | 90 |
| 3c | 84 | 82 | 89 |
| 3d | 86 | 78 | 87 |
| 3e | 92 | 90 | 92 |
| 3f | 88 | 83 | 94 |

$I_2$ = Molecular Iodine.
S.S.A. = Silica Sulphuric Acid.
PPA-$SiO_2$ = Silica Supported Polyphosphoric Acid.

## CONCLUSION

Here we conclude that the modern method microwave irradiation is efficient for the synthesis of indazole and its derivatives by condensation of hydrazine and o-hydroxy aromatic carbonyl compound in presence of the catalytic quantity of $I_2$, S.S.A. and PPA-$SiO_2$ in DMSO solvent.

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