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**Research Article**

# SAMARIUM (III) TRIFLATE CATALYZED SYNTHESIS OF SUBSTITUTED 1H-INDAZOLE AND THEIR ANTIBACTERIAL SCREENING

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**ABSTRACT**

Samarium (III) triflate catalyzed synthesis of substituted 1H-indazole, by the condensation of benzaldehyde and hydrazine in ethanol-water as a solvent under ultrasound irradiation. The samarium triflate is reuseable acid catalyst. The products obtained in good to moderate yields with simple work up procedure. The compound 3b was investigated in-vitro against Gram +ve and Gram –ve bacteria at different concentrations and compared with standard drug ciprofloxacin.



## INTRODUCTION

The subject of research work is indazole ring, the, which exhibit a wide range of bioactivities including serotonin 5-HT3 receptor antagonist activities, anti- HIV, anti-inflammator, anti-tumor, anti-cancer and anti-platelet [1-7]. With the growing interest in indazole derivatives. Thus there is emergence of novel methods toward indazole synthesis. The published methods of synthesis of this system are either limited in scope or poorly elaborated. A green and efficient method still remains an ongoing challenge. Therefore, an effective approach to obtaining compounds of this class is still desirable [8-11].

However, some of the reported methods for the synthesis of indazole have some drawbacks such as the use of toxic and expensive catalyst or solvent, long reaction times, low yield of the products, and difficult work-up procedures [12]. In continuation of our interest in developing green and efficient protocol for the synthesis of different heterocycles [13, 14]. Here we are interested in heterogeneous Lewis acid catalysis which has attracted considerable attention for condensation reaction. A wide range of Lewis acids has been developed but most of them are used under anhydrous conditions. As water is been useful solvent for certain Lewis acids like $Sm(OTf)_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$,$Bi(OTf)_3$ and other metal triflates which are water-tolerant and reusable Lewis acids catalyst [15,16].

With the objective of developing green and efficient protocol using of ultrasound which clean and advantageous approach in organic synthesis. The ultrasonic effect induces a high pressure and temperature inside the bubbles which is known as acoustic cavitation phenomenon which enhances mass transfer and turbulent flow in the liquid [17, 18].

### *Experimental Section*

### *General Procedure for Optimization of reaction conditions for the synthesis of 1H-indazole*

The reaction between benzaldehyde **1** and hydrazine **2c** as a model reaction (Scheme). The model reaction which is catalyzed by $Sm(OTf)_3$ and optimization using different solvents at different concentrations for model reaction which was carried out by conventional method and ultrasound method. The results were summarized in Table 1.

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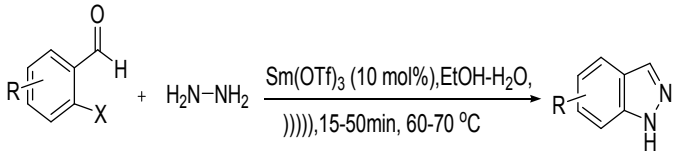
**Table 1** Optimization of reaction conditions for the synthesis of 1H-indazole

| Entry | Catalyst (mol %) | Solvent | Conventional Method[a] | | Ultrasound Method[b] | |
|---|---|---|---|---|---|---|
| | | | Time (min) | Yield[c] (%) | Time (min) | Yield[c] (%) |
| 1 | - | EtOH | 63 | 40 | 43 | 50 |
| 2 | $Sm(OTf)_3$ (5) | Toluene | 55 | 48 | 35 | 65 |
| 3 | $Sm(OTf)_3$ (10) | Toluene | 55 | 53 | 35 | 68 |
| 4 | $Sm(OTf)_3$ (5) | Dioxane | 50 | 43 | 30 | 58 |
| 5 | $Sm(OTf)_3$ (5) | MeCN | 50 | 55 | 30 | 70 |
| 6 | $Sm(OTf)_3$ (5) | EtOH | 52 | 55 | 25 | 65 |
| 7 | $Sm(OTf)_3$ (10) | EtOH | 52 | 64 | 20 | 67 |
| 8 | $Sm(OTf)_3$ (2) | EtOH-$H_2O$ (2:2) | 45 | 72 | 15 | 80 |
| 9 | $Sm(OTf)_3$ (5) | EtOH-$H_2O$ (2:2) | 45 | 78 | 15 | 85 |
| 10 | $Sm(OTf)_3$ (10) | EtOH-$H_2O$ (2:2) | 45 | 86 | 15 | 94 |

[a]Reaction condition: benzaldehyde (**1**) (1.0 mmol), hydrazine (**2**) (1.2 mmol) and $Sm(OTf)_3$ (10 mol %) in ethanol-water (2:2 mL) under conventional heating at 80- 100°C.
[b]Reaction condition: benzaldehyde (**1**) (1.0 mmol), hydrazine (**2**) (1.2 mmol) and $Sm(OTf)_3$ (10 mol %) in ethanol-water (2:2 mL)under ultrasound irradiation at 60- 70°C.
[c]Isolated yields.

Using $Sm(OTf)_3$ (10 mol %) (entry 10) in ethanol-water (2:2) at 60-70 °C gave excellent yield as compared to other solvents and concentrations. And for our further synthesis of indazoles derivatives we have chosen samarium triflate (10 %) in ethanol-water (2:2) under ultrasound irradiation.




**1** **2** **3a-3h**

Where,
R = Br, $NO_2$, Me, Cl X = Cl, F

***Scheme**:* synthesis of 1H-Indazole using $Sm(OTf)_3$ under ultrasound irradiation.

***Procedure for the synthesis indazole (3a-h)***

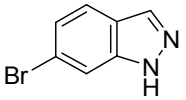
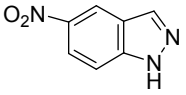
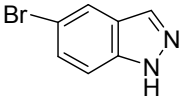
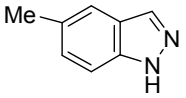
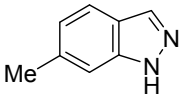
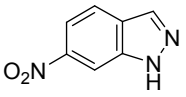
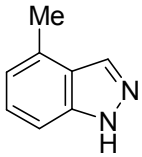
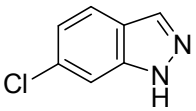
A mixture of benzaldehyde (1) (1.0 mmol) and hydrazine (2) (1.2 mmol) was dissolved in ethanol-water (2:2 mL) to that $Sm(OTf)_3$ (10 mol %) The reaction flask was kept in the ultrasonic bath and was irradiated at 60- 70°C for about 15-50 min. (the reaction was monitored by TLC) separately as indicated in (Table 2). After the reaction was completed the reaction mass was poured on crushed ice. The obtained solid was filtered, washed with water and dried. The crude compound was crystallized using DMF-Ethanol.

Compound **3b**: Yield 90%; white solid ; mp 208-211℃. FTIR Model RZX (Perkin Elmer) $cm^{-1}$: 1536 (C=N str., Indazolyl), 1239 (C-N str., C-$NO_2$), 1342, 1536 (N-O str., -$NO_2$);$^1$H-NMR (400 MHz, DMSO): δ 7.70 (d, 1H, Ar-H), 8.19 (d, 1H, Ar-H), 8.36 (s, 1H, indazolyl), 8.78 (s, 1H, Ar-H), and 13.65 (s, 1H, N-H) ppm;$^{13}$C-NMR (100 MHz, DMSO): δ 141.67, 141.46, 136.46, 121.97, 120.57, 118.47, 110.67 ppm; MS (ESI, m/z): calcd for $C_7H_5N_3O_2$ ($M - H^+$) 163.0382; found: 162.3798.

***Antibacterial Activity***

The procedure for antibacterial screening was repeted as given in our previous published research papers [13, 14, 18]. Here, compound 5-Nitro-1H-indazole 3b was screened for in-vitro antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, Staphylococcus aureus and Bacillus subtilis and two gram negative strains, Escherichia coli and Pseudomonas aeruginosa [18, 19, 20]. Ciprofloxacin was used as standard drug.

**Table 2** Synthesis of 1H-Indazole using $Sm(OTf)_3$ under ultrasound irradiation.

| Comp. | Aldehyde | Product | M.P (°C) | Yield (%)[a] | | |
|---|---|---|---|---|---|---|
| 3a | 4-Br |  | 180 -185 | 85 | 83[b] | 82[b] |
| 3b | 5-$NO_2$ |  | 210 -212 | 90 | 88 | 86 |
| 3c | 5-Br |  | 123 - 127 | 88 | 86 | 85 |
| 3d | 5-Me |  | 111 - 113 | 87 | 85 | 83 |
| 3e | 4-Me |  | 178 - 181 | 93 | 91 | 90 |
| 3f | 4-$NO_2$ |  | 180 - 182 | 88 | 86 | 85 |
| 3g | 6-Me |  | 114 - 116 | 85 | 84 | 83 |
| 3h | 6-Me |  | 140 - 181 | 87 | 86 | 85 |

[a]Yields of isolated products.
[b]$Sm(OTf)_3$was recovered and reused for three consecutive runs.

**Table 3** Recyclability and reusability of catalyst $Sm(OTf)_3$[a].

| Entry | Yield (%)[b] | Catalyst recovery (%) |
|---|---|---|
| 1 | 90 | 95 |
| 2 | 87 | 93 |
| 3 | 85 | 90 |
| 4 | 83 | 86 |

aReaction condition: benzaldehyde (1) (1.0 mmol), hydrazine (2) (1.2 mmol) and Sm(OTf)3 (10 mol %) in ethanol-water (2:2 mL)under ultrasound irradiation at 60- 70oC. bIsolated yields.

## RESULT AND DISCUSSION

The model reaction was performed to optimize the reaction conditions for the synthesis of 1H-indazole. The model reaction was carried out by the cyclocondensation of

**Table 4** Antibacterial Activity of 3b

| Sr. No. | Conc. µg/mL | Zone of inhibition in mm | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Gram +ve | | | | Gram -ve | | | |
| | | 3b | | | | | | | |
| | | Pathogen – Staphylococcus aureus | | Pathogen – Bacillus subtilis | | Pathogen – Escherichia Coli | | Pathogen – Pseudomonas aeruginosa | |
| | | Replicate 1 | Replicate 2 | Replicate 1 | Replicate 2 | Replicate 1 | Replicate 2 | Replicate 1 | Replicate 2 |
| **1** | 125 | 19 | - | - | - | 9 | 8 | - | - |
| **2** | 250 | 23 | 22 | - | - | 10 | 9 | - | - |
| **3** | 500 | 25 | 23 | - | - | 14 | 12 | - | - |
| **4** | 1000 | 28 | 26 | - | - | 16 | 15 | - | - |
| | | **Standard Ciprofloxacin** | | | | | | | |
| **1** | 125 | 31 | 31 | 27 | 27 | 26 | 26 | 27 | 27 |
| **2** | 250 | 35 | 36 | 29 | 29 | 28 | 28 | 32 | 32 |
| **3** | 500 | 40 | 41 | 30 | 31 | 29 | 31 | 36 | 34 |
| **4** | 1000 | 44 | 45 | 32 | 33 | 30 | 33 | 38 | 39 |

5-bromo-2-fluorobenzaldehyde (**1b**) (1.0 mmol) and hydrazine (**2**) (1.2 mmol) to give 5-Nitro-1H-indazoles the reacton is catalyzed by $Sm(OTf)_3$ and optimization using different solvents like ethanol, toluene, dioxane, acetonitrile, and ethanol-water at different concentrations for model reaction which was carried out by both conventional method and ultrasound method. Here we got good yield for ultrasound method as compared to conventional method. And thus the reaction was optimized at ethanol-water (2:2) of solvent and $Sm(OTf)_3$ (10 mol %). The results obtained were given in Table 1. And thus the reaction was optimized. In further synthesis of other derivatives we have used ethanol-water (2:2) of solvent and $Sm(OTf)_3$ (10 mol %) under ultrasound irradiation here we got good yields shorter time which has been summarized in Table 2. The catalyst $Sm(OTf)_3$ is been recycled and reused for three to four times each time there was loss of 2 to 4 % in catalyst recovery and in yield also which is given in Table 3.

The compound 3b 5-Nitro-1H-indazole was screened for in-vitro antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative strains, *Escherichia coli* and *Pseudomonas aeruginosa*. Ciprofloxacin was used as standard drug and the data obtained from antibacterial study is given in Table 4.

## CONCLUSION

In conclusion, we have developed a simple and highly efficient method were Samarium triflate a water tolerant and reusable acid catalyst used for synthesis of substituted 1H-indazole here ethanol-water aqueous medium as a solvent under ultrasound irradiation. Antibacterial screening of **3b** compound was found to give moderate activity against selected strains. Further studies on the biological activities of the products and application of this methodology to other interesting 1H-indazole derivatives are underway in our laboratory.

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