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## Rapid synthesis of spiro-oxindole with functionalized chromene moiety catalyzed by $H_2MoO_4$

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### ABSTRACT

The rapid synthesis of spiro-oxindole with functionalized chromene moiety by the one pot reaction between isatin, 1,3 dicarbonyl compound and active methylene reagent under neat conditions with 15 mole% of  $H_2MoO_4$  have been reported.

**Keywords:** Multi-component reaction, one-pot synthesis,  $H_2MoO_4$ , spiro-oxindole, chromene.

### INTRODUCTION

Spiro-compounds containing oxindole moiety occurred in medicinally active compounds as well as many natural products [1-5]. The spiro-oxindole with fused chromene moiety are important class of naturally occurring substances with broad spectrum of pronounced biological activities such as antitumor [6], antimicrobial [7], anti-tubercular [8], antimycobacterial [9], mutagenicity [10], antiproliferative [11], sex pheromone [12] and central nervous system activities [13]. Recently, the oxindole related spirocyclic compounds were synthesized and reported in literature like spiro-pyrrolidine-oxindoles [14-15], spiro-cyclohexanoneoxindoles [16-17], spiro-pyran-oxindoles [18-19], spirocyclopropane-oxindoles [20-21], spiro-oxazolidine-2 thioneoxindoles [22] and spirooxirane-oxindoles [23]. Multi-component reactions (MCRs) are important synthetic processes in which three or more different starting materials react together to form final product in single step and such reactions are important tools to create libraries of heterocyclic compounds. Multi-component reactions are offering significant advantages over conventional linear-type synthesis such as cost effective, comparatively fast, atom economy, simple procedures, energy savings and environmental friendly [24]. In continuation of our investigation and development towards MCRs, we have been reported rapid and efficient method for the synthesis of spiro-oxindole.

### MATERIALS AND METHODS

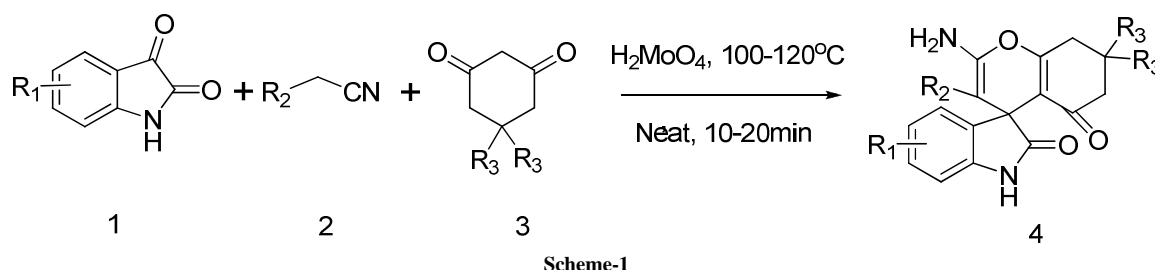
All the chemicals were purchased from Sigma-Aldrich, SD-Fine, Hi-Media and used without further purification. The melting points were determined in capillary tubes which are uncorrected, reactions were monitored by TLC and spots are visualized with help of iodine chamber. The IR spectra were recorded using KBr pellet with JASCO FT-IR-680 plus spectrometer.  $^1H$  NMR and  $^{13}C$  NMR spectra were recorded on a FT-NMR Bruker Avance ultra shield spectrometer where  $DMSO-d_6$  used as solvent and TMS as standard.

**General synthetic procedure for spiro-oxindole**

A mixture of isatin (one equivalent), malononitrile/ethylcyanoacetate (one equivalent) and 1, 3-dicarbonyl compound (one equivalent) were mixed and stirred at 100-120°C in solvent free condition with 15 mol% of H<sub>2</sub>MoO<sub>4</sub>. The progress of reaction was monitored by TLC by using 7:3 hexane and ethyl acetate as eluents. After completion of reaction, the solid was formed which was poured in ice cold water, filtered and finally recrystallized from ethanol.

**RESULTS AND DISCUSSION**

The isatin (one equivalent), malononitrile/ethylcyanoacetate (one equivalent) and 1, 3-dicarbonyl compound (one equivalent) involved in three component one-pot reaction produced respective spiro-oxindole in the presence of 15 mole% of H<sub>2</sub>MoO<sub>4</sub> under solvent free condition (Scheme-1).



To optimize the reaction conditions, we examined effects of different solvents and mole % of catalyst on a particular reaction (reaction between isatin, dimidone and malononitrile) and obtained data are given in table 2 and 3. We found that without catalyst under neat condition as well as different solvent medium provided 30-55% yield with longer reaction time. When the reaction was carried out at 100-120°C in the presence of 15 mole% of H<sub>2</sub>MoO<sub>4</sub> under solvent free condition provided good yield within 10-20 min in all the cases. The Structural features of synthesized compounds have been confirmed by the comparism of their Melting point, IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra with authentic sample reported in literature.

**Table-1: Synthesis of spiro-oxindole by using different substrates.**

| R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub>  | Time (min) | Yield (%) | Mp (°C) [Ref-25] |
|----------------|----------------|-----------------|------------|-----------|------------------|
| H              | CN             | CH <sub>3</sub> | 10         | 87        | 255-265(268)     |
| H              | COEt           | CH <sub>3</sub> | 20         | 80        | 248-252(257)     |
| H              | CN             | H               | 10         | 82        | 250-252(251)     |
| H              | COEt           | H               | 20         | 75        | 258-260(263)     |
| F              | CN             | CH <sub>3</sub> | 10         | 85        | 260-264(270)     |
| F              | COEt           | CH <sub>3</sub> | 15         | 80        | 230-235(240)     |

**Table-2: Synthesis of spiro-oxindole (reaction between isatin, dimidone and malononitrile) in the presence of 15 mol% H<sub>2</sub>MoO<sub>4</sub> at different solvent medium.**

| Entry | Solvents        | Time (min) | Yield (%) |
|-------|-----------------|------------|-----------|
| 1     | Ethanol         | 30-40      | 55        |
| 2     | Water           | 40-60      | 50        |
| 3     | Acetonitrile    | 30-40      | 64        |
| 4     | Without solvent | 10-20      | 87        |

**Table-3: Synthesis of spiro-oxindole (reaction between isatin, dimidone and malononitrile) in the presence of different mol% of H<sub>2</sub>MoO<sub>4</sub> at neat condition.**

| Entry | Catalyst (mol %) | Time (min) | Yield (%) |
|-------|------------------|------------|-----------|
| 1     | 0                | 120        | 40        |
| 2     | 5                | 45         | 60        |
| 3     | 15               | 10         | 87        |
| 4     | 25               | 10         | 88        |

## CONCLUSION

We developed simple and efficient method for synthesis of spiro-oxindole with functionalized chromene unit promoted by  $H_2MoO_4$  under solvent free condition. The operationally simple procedure, readily available catalyst, short reaction time and good yield are advantages of our method.

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