

## One-Pot Fischer Indole 화합물의 효율적인 합성

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## Highly Efficient and Facile Green Approach for One-Pot Fischer Indole Synthesis

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**요약.** HPA-phosphomolybdic acid 촉매 하에서, 아릴히드라진과 알데히드/케톤을 반응시켜서 치환기를 가지고 있는 indole 화합물을 효율적으로 합성할 수 있는 친환경적인 합성 방법을 개발하였으며, 이때 촉매는 독성이 없으며, 회수하여 재 사용할 수 있다.

**주제어:** Heteropoly acid, Fischer indole, 아릴히드라진, 알데히드/케톤

**ABSTRACT.** A simple, efficient and an environmental friendly method have been developed for the synthesis of substituted indole from aryl hydrazines and aldehydes/ ketones with HPA-phosphomolybdic acid as a heterogeneous catalyst. The catalyst is nontoxic and recyclable.

**Keywords:** Heteropoly acid, Fischer indole, Arylhydrazines, Aldehydes/ketones

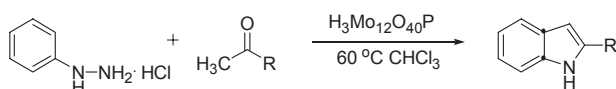
## INTRODUCTION

Indole and its derivatives are common heterocyclic compounds in nature which have attracted considerable interest in recent years due to their therapeutic and pharmacological activities.<sup>1-3</sup> Indole derivatives are used as neuroprotective agents affecting oxidative stress,<sup>4</sup> glucokinase activators,<sup>5,6</sup> neurotransmitter serotonin<sup>7</sup> (5-hydroxytryptamine 5-HT) involved in various physiological function such as appetite, sleep, body temperature and sexual behavior.<sup>8</sup> Different indole derivatives like tryptans are used as antimigrain, anti-inflammatory drugs, and dyestuffs.<sup>8,9</sup>

Indoles can be prepared by numerous methods. However, all these methods have their own limitations and a number of drawbacks such as use of toxic solvents, expensive reagents, and amount of waste solvents.<sup>10-13</sup> Amongst the various approaches for the synthesis of indole, Fischer indole synthesis has mentioned its prominent role but reagent for Fischer indole synthesis such as conc. sulphuric acid, cuprous chloride, zinc chloride, borontrifluoride, o-polyphosphoric acid,

p-toluenesulphonic acid are hazardous to environment, difficult to handle and also required in very large amount.<sup>14</sup> With the increasing interest in human health and environmental protection, more attention is being paid to "green chemistry." Therefore, it is necessary to develop an efficient, mild and practical method for the synthesis of indole.

In recent decades use of heteropoly acids (HPAs) as catalyst has become important in industries related with fine chemicals.<sup>15</sup> HPAs are more active catalyst than conventional inorganic and organic acids used for various reactions in solution.<sup>16</sup> Solid HPAs have gained importance due to easy work-up procedures, minimization of waste product generation. They are non-corrosive and environmentally benign, as they can be reused and recycled.<sup>17</sup> Thus keeping this in mind and as a part of our ongoing project to explore the catalytic activities of heteropoly acid in organic transformation,<sup>18</sup> here we have attempted the convenient and practical synthesis of substituted indole from commercially available aryl hydrazines, aldehydes/ketones and phosphomolybdic acid as heterogeneous catalyst (Scheme 1).



Scheme 1

## RESULTS AND DISCUSSION

The reaction of phenyl hydrazine hydrochloride with acetophenone was selected as model reaction to test the activity of different solid acid catalyst like zeolites-HY, Montmorillonite K10, Indion-90, Amberlite-120, Silica, Amberlyst-15, Phosphomolybdic acid at 60 °C in chloroform for 4 hrs.

The results mentioned in Table 1 demonstrate the efficient use of phosphomolybdic acid for Fischer indole synthesis. Keeping all these results in view, we generalized the protocol by treating various aldehydes and ketones with aryl hydrazine hydrochloride in presence of phosphomolybdic acid. Fischer indole synthesis of all the substrate was observed with 70–90% yield (Table 2). Electron withdrawing group on aryl hydrazine lower the rate of reaction.

In eco-friendly process, the recovery of catalyst is the key step. In this protocol we used heteropoly acid as recyclable catalyst. After the completion of reaction, the heteropoly acid

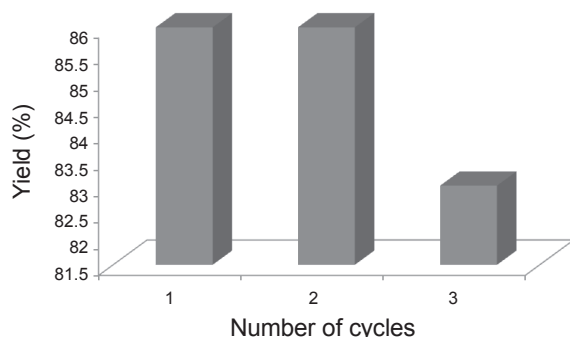


Fig. 1. Recyclability of the catalyst

Table 1. Effects of Catalysts on Fischer indole synthesis.<sup>a</sup>

Entry	Catalyst	Time (h)	Yield (%) <sup>b</sup>
1	Zeolite-HY	4	43
2	Montmorillonite K10	4	70
3	Indion-90	4	60
4	Amberlite-120	4	63
5	Silica	4	20
6	Amberlyst-15	4	68
7	Phosphomolybdic acid	4	86

<sup>a</sup>Phenyl hydrazine hydrochloride (0.01 mol), acetophenone (0.01 mol), catalyst (0.002 mol), solvent (chloroform), Temp.: 60 °C, Time: 4 hrs.

<sup>b</sup>Isolated Yield (%).

was recovered and used further for two more processes (Fig. 1).

## CONCLUSIONS

In conclusion, heteropolyacid phosphomolybdic acid has been proved useful, efficient and recyclable catalyst for Fischer indole synthesis. The catalytic activities of the heteropoly acid are much higher than those of conventional acid catalysts. It gives high yield in short reaction time.

## EXPERIMENTAL SECTION

### General

All commercial reagents are used as received without purification and all solvents were of reagent grade. The reaction was monitored by TLC using 0.25 mm E-Merck silica gel 60 F<sub>254</sub> precoated plates, which were visualized with UV light. Melting points were observed using open capillaries. The IR spectra were recorded on a Perkin-Elmer 257 spectrometer using KBr discs. <sup>1</sup>H NMR spectra were recorded on VXR-300 MHz instrument using TMS as an internal standard.

### General Experimental Procedure

Acetophenone (0.01 mol) was mixed with phosphomolybdic acid (0.002 mol) in chloroform (5 mL) solvent at room temperature, to that phenyl hydrazine (0.01 mol) was added slowly at room temperature, then the reaction mixture was heated to 60 °C for 4 hrs. Completion of reaction was monitored by TLC; catalyst was separated from reaction mixture by filtration. The product obtained was purified by column chromatography.

### Representative spectral data for product

**3-(1*H*-Indol-3-yl) propan-1-ol.** IR (Neat): 3544, 3412, 2935, 2458, 1340, 1230, 1050, 743 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 8.05 (br s, 1H), 7.59 (d, 1H, *J* = 7.8 Hz), 7.26 (d, 1H, *J* = 7.8 Hz), 7.19 (t, 1H, *J* = 7.5 Hz), 7.08 (t, 1H, *J* = 7.5 Hz), 6.8 (s, 1H), 3.65 (t, 2H, *J* = 6.4), 2.9 (t, 2H, *J* = 7.5), 2.02 (m, 2H), 3.46 (br s, 1H) ppm; MS (EI, 70 eV) *m/z* 175 (M<sup>+</sup>), 130 (100), 77 (15); Anal Calcd for C<sub>11</sub>H<sub>13</sub>NO: Calcd: C, 75.43; H, 7.43; N, 8.00; Found: C, 75.40; H, 7.45; N, 8.03.

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Table 2. Synthesis of substituted indoles.<sup>a</sup>

Entry	Aryl Hydrazine	Aldehyde/ Ketone	Product	Time (hr)	Yield <sup>b</sup> (%)
1				4	86
2				4	82
3				3.5	82
4				5	70
5				4	76
6				3.5	76
7				3.0	79
8				3.5	72
9				3.0	78
10				2.0	88
11				3.5	70
12				3.0	90

<sup>a</sup>Reaction conditions: Aryl hydrazine (0.01 mol), Aldehydes/Ketones (0.01 mol), Phosphomolybdic acid (0.002 mol), solvent: chloroform (5 mL). <sup>b</sup>Isolated Yield (%).

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