



# $H_6P_2W_{18}O_{62}$ : A Green and Reusable Catalyst for the One-pot Three-Component Synthesis of Spirooxindoles in Water

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## Abstract

Wells–Dawson tungsten heteropolyacid ( $H_6P_2W_{18}O_{62}$ ) has been applied as an effective heterogeneous catalyst for one-pot synthesis of spiro[4H-pyran-3,3'-oxindoles] via reaction of various isatins, malonitrile and 1,3-dicarbonyl compound in water. The corresponding products were obtained in high yields. The catalysts were easily recycled and reused without loss of their catalytic activity.

**Keywords:** Heteropolyacids, Spirooxindole, Multi-component reaction, Aqueous medium, 1,3-dicarbonyl compound.

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## Introduction

Multicomponent reactions (MCRs) are convergent reactions of three or more starting materials, which have emerged as an efficient method for rapidly generating complex molecules with diverse functional substituents [1]. MCRs have often been used to establish expedient and ecofriendly chemical methods for the discovery of new chemical entities required by pharmaceutical and agrochemical

industries [2].

Spirooxindoles occupy an important place in the area of heterocyclic chemistry because they are frequently found in numerous natural and synthetic products along with useful biopharmaceutical, physiopharmaceutical, and pharmaceutical activities [3-8].

In recent years, several improved protocols for the synthesis of spirooxindoles with fused chromenes have been reported by modification

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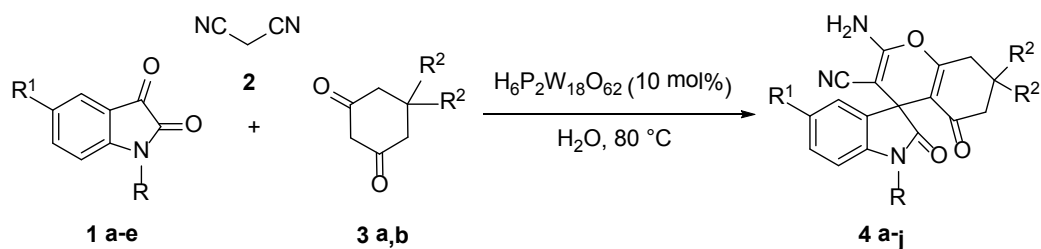
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of three-component condensation of isatin derivatives, activated methylene reagents, and 1,3-dicarbonyl compounds using various catalysts such as triethylbenzyl ammonium chloride (TEBA) [9],  $\text{InCl}_3$  [10],  $\text{NEt}_3$  [11], electrogenerated base (NaBr/ROH) [12],  $\beta$ -cyclodextrin [13],  $[\text{BMIm}]\text{BF}_4$  [14], L-proline [15], MgO [16], surfactant metal carboxylates [17], ethylenediaminediacetate [18], Carbon- $\text{SO}_3\text{H}$  [19], ZnS NPs [20]. Although all of these methods are effective, but some of them have drawbacks such as, harsh reaction conditions [9], long reaction times [9,13], technical intricacy [12], use of expensive [14], unsafe [11], and unreusable catalysts [9,11,17,18]. Therefore, the development of a new and simple synthetic method for the preparation of spirooxindole derivatives has become an interesting challenge.

In recent decades, heteropolyacids (HPAs) which are low in toxicity and being recyclable have attracted special attention [21-23]. Heteropolyacids have many advantages, thus

being economically and environmentally attractive in both academia and industry; they are useful acids and oxidation catalysts in various reactions since their catalytic features can be varied at a molecular level [24]. Furthermore, Wells-Dawson type heteropolyacids possess superacidity and a remarkable stability both in solution and in the solid state [25].

As a part of our ongoing efforts towards the development of new procedure for the synthesis of spirooxindoles through multi component reaction, we have discovered an efficient and environmentally friendly procedure for the synthesis of spiro[4H-pyran-3,3'-oxindole] derivatives. Herein, we report an efficient one-pot three-component reaction of isatin, malononitrile and 1,3-dicarbonyl compound for the synthesis of spirooxindole route to the synthesis of functionalized spirooxindole derivatives in aqueous medium employing Wells-Dawson heteropolyacid,  $[\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}]$  as an ecofriendly, reusable, inexpensive, and efficient catalyst (Scheme 1).



**Scheme 1.** Synthesis of spirooxindoles by the reaction of isatin derivatives, with malononitrile and cyclic 1,3-dicarbonyl compounds using  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$ .

## Experimental

### Methods and materials

The chemical materials used in this work were obtained from Merck and Aldrich and used without purification. <sup>1</sup>H NMR spectra was recorded on a Bruker DRX-400 AVANCE spectrometer at 400 MHz. Melting points were determined on a thermo scientific IA9200 and are uncorrected.

### General procedure for the synthesis of spirooxindoles (4)

A mixture of isatin (1mmol), malononitrile (1 mmol) and cyclic 1,3-dicarbonyl compound (1 mmol) in water (10 mL) in the presence of Wells–Dawson heteropolyacid (10 mol%) was stirred at 80 °C. After completion of the reaction, as indicated by TLC, the precipitated solid was filtered off and washed with water (2×20 mL). The pure product was obtained by recrystallization from EtOH. The catalyst could be recycled after evaporation of water from the residue. The residue was then washed with diethyl ether, dried at 130 °C for 1 h, and reused in another reaction. The recycled catalyst was used for two reactions without observation of appreciable loss in its catalytic activities. All the products were identified by comparing of melting point and <sup>1</sup>H NMR spectra with those of authentic samples reported in the literature.

### Selected spectral data

*2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-*

*tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4a).*

White powder, mp 285–287 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.00 (s, 3H), 1.03 (s, 3H), 2.14 (ABq, *J*=16 Hz, 2H), 2.50–2.61 (m, 2H), 6.79 (d, *J*=7.6 Hz, 1H), 6.89 (t, *J*=7.6 Hz, 1H), 6.98 (d, *J*=7.4 Hz, 1H), 7.14 (t, *J*=7.7 Hz, 1H), 7.23 (brs, 2H), 10.40 (s, 1H).

*2-Amino-1',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4b).*

White powder, mp 255–257 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.00 (s, 3H), 1.03 (s, 3H), 2.12 (ABq, *J*=16 Hz, 2H), 2.50–2.62 (m, 2H), 3.14 (s, 3H), 6.96–7.01 (m, 2H), 7.05 (d, *J*=7.2 Hz, 1H), 7.25 (t, *J*=7.6 Hz, 1H), 7.30 (brs, 2H).

*2-Amino-1'-benzyl-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4c).*

Off-white powder, mp 280–282 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.02 (s, 3H), 1.06 (s, 3H), 2.18 (ABq, *J*=16 Hz, 2H), 2.50–2.66 (m, 2H), 4.91 (ABq, *J*=16.2 Hz, 2H), 6.69 (d, *J*=7.6 Hz, 1H), 6.96 (t, *J*=7.2 Hz, 1H), 7.08–7.15 (m, 2H), 7.24–7.35 (m, 5H), 7.49 (d, *J*=7.2 Hz, 2H).

*2-Amino-5'-bromo-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile(4d).*

Off-white powder, mp 305–307 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.00 (s, 3H), 1.02 (s,

3H), 2.16 (ABq,  $J=16$  Hz, 2H), 2.50-2.63 (m, 2H), 6.76 (d,  $J=8$  Hz, 1H), 7.21 (d,  $J=1.8$  Hz, 1H), 7.31 (d,  $J=1.8$  Hz, 1H), 7.30 (brs, 2H), 10.57 (s, 1H).

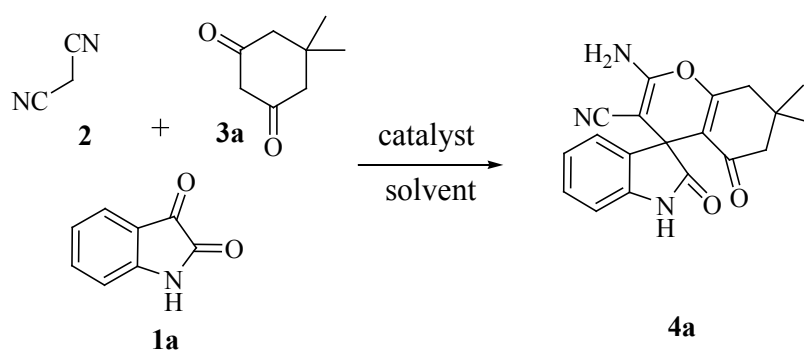
*2-Amino-7,7-dimethyl-5'-nitro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4e)*.

Off-white powder, mp 301-303°C. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  1.02 (s, 6H), 2.17 (ABq,  $J=16$  Hz, 2H), 2.50-2.69 (m, 2H), 7.03 (d,  $J=8.4$  Hz, 1H), 7.47 (brs, 2H), 7.97 (d,  $J=2.4$  Hz, 1H), 8.16 (dd,  $J=8.6, 2.2$  Hz, 1H),

## Results and discussion

We bought a mild and convenient method for the synthesis of spiro[4H-pyran-3,3'-oxindoles]. Our investigation began with the evaluation of  $H_6P_2W_{18}O_{62}$  as a catalyst in the reaction of isatin (1 mmol), malononitrile (1 mmol), and 5,5-dimethyl-1,3-cyclohexadione (1 mmol) in water at 80 °C. The use of 10 mol% of  $H_6P_2W_{18}O_{62}$  in this condition afforded a 87% yield (Table 1, entry 6) of the desired product.

**Table 1.** Optimization of reaction conditions for the synthesis of 4a.



Entry	Solvent	Temperature (°C)	Time (min)	Yield (%) <sup>b</sup>
1	THF <sup>a</sup>	80	300	45
2	EtOH	80	85	80
3	MeCN	80	300	75
4	CH <sub>2</sub> Cl <sub>2</sub>	80	300	45
5	HOAc	80	300	65
6	H <sub>2</sub> O	80	65	87
7	H <sub>2</sub> O	25	600	trace

<sup>a</sup> 10 mL solvent.

<sup>b</sup> Isolated Yields.

The influence of different solvents was also examined. The above experiment was performed in various solvents including tetrahydrofuran, acetonitrile, acetic acid, dichloromethane, water and ethanol (Table 1, entries 1-6). Of these solvents, water appears to give the best results. The effects of temperature were also examined on model reaction. Decreasing of temperature to 25 °C afforded the product **4a** in very low yield (Table 1, entry 7).

To study the scope of the reaction, a series

of substituted isatins, cyclic 1,3-dicarbonyl compounds and malononitrile were reacted using  $H_6P_2W_{18}O_{62}$  in water at 80 °C (Table 2). From the results, it is evident that all of the reactions provided the desired spirooxindole products in good to excellent yields employing isatins including different groups on aryl ring as substrates (Table 2, entries 1, 4-6 and 9-10). Substituted isatins in N-position gave desired products in high yields in reaction conditions (Table 2, entries 2-3 and 7-8).

**Table 2.** Synthesis of spirooxindole derivatives (**4**) catalyzed by  $H_6P_2W_{18}O_{62}$  in water.

Entry	R	R <sup>1</sup>	R <sup>2</sup>	Product <sup>a</sup>	Time (min)	Yield (%) <sup>b</sup>	Ref
1	H	H	CH <sub>3</sub>	<b>4a</b>	<b>65</b>	87	26
2	CH <sub>3</sub>	H	CH <sub>3</sub>	<b>4b</b>	<b>70</b>	86	26
3	Bn	H	CH <sub>3</sub>	<b>4c</b>	<b>75</b>	86	14
4	H	Br	CH <sub>3</sub>	<b>4d</b>	<b>55</b>	90	26
5	H	NO <sub>2</sub>	CH <sub>3</sub>	<b>4e</b>	<b>65</b>	87	26
6	H	H	H	<b>4f</b>	<b>55</b>	85	26
7	CH <sub>3</sub>	H	H	<b>4g</b>	<b>65</b>	85	26
8	Bn	H	H	<b>4h</b>	<b>70</b>	86	14
9	H	Br	H	<b>4i</b>	<b>55</b>	91	26
10	H	NO <sub>2</sub>	H	<b>4j</b>	<b>55</b>	90	26

<sup>a</sup> All the products were identified by comparing of melting point and <sup>1</sup>H NMR spectra with those of authentic samples reported in the literature.

<sup>b</sup> Yields refer to isolated products.

We also investigated the reusability of the catalyst. For this purpose we first carried out the reaction of isatin and malononitrile and 5,5-dimethyl-1,3-cyclohexadione in the presence of the catalyst (Table 3). After completion of the reaction, the product was filtered off and the catalyst was removed

and subjected to two successive runs of the reaction with the same substrate. No significant decrease in the yield was observed demonstrating that  $H_6P_2W_{18}O_{62}$  can be reused as a catalyst in isatins, malononitrile and 1,3-dicarbonyl compounds condensation.

**Table 3.** Recycling studies of reaction between isatin and malononitrile and 5,5-dimethyl-1,3-cyclohexadione in the presence of  $H_6P_2W_{18}O_{62}$  to give product **4a**.

Entry	Cycle	Time (min)	Yield (%) <sup>a</sup>
1	fresh	65	87
2	1	65	84
3	2	65	82

<sup>a</sup> Yields refer to isolated products.

### Conclusion

In conclusion, we demonstrated an alternative and simple procedure for the synthesis of spirooxindoles in water using Wells–Dawson heteropolyacid as an ecofriendly, reusable, inexpensive, and efficient catalyst. High yields, short reaction times, and simple workup procedure are some advantages of this protocol.

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