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$H_6P_2W_{18}O_{62}$: A green and reusable catalyst for the synthesis of 3,3-diaryloxindole derivatives in water

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Abstract An efficient and improved procedure for the synthesis of oxindoles derivatives is developed *via* the electrophilic substitution reaction of indoles with various isatins in the presence of a *Wells–Dawson* tungsten heteropolyacid in water.

Keywords Heteropolyacid; Green chemistry; Indole; Isatin; Oxindole.

Introduction

The oxindole ring is a prominent structural motif found in numerous natural products and pharmaceutically active compounds [1]. The 3,3-diaryloxindoles have been shown to possess mechanism-specific antiproliferative, antibacterial, antiprotozoal, and anti-inflammatory activities [2]. The 3,3-diaryloxindoles can be formed by the reaction of isatin and indols in acid conditions for long reaction times [3a] or promoted by $KAl(SO_4)_2$ under microwave irradiation [3b]. Other methods have also been reported employing silica sulfuric acid [4a] and ceric ammonium nitrate (*CAN*) under ultrasound irradiation [4b]. However, not only few methods have been developed for the synthesis of this class of compounds [5] but also, 3,3-di(heteroaryl)oxindoles have not been widely explored.

On the other hand great attention has been focused on the use of water as green solvent in various organic transformations. In addition to its abundance and for economical and safety reasons, water has naturally become a substitute and an alternative environmentally benign solvent in organic synthesis [6]. However, water exhibits unique reactivity and selectivity that can not be attained in conventional organic solvents [7]. Thus, the use of water instead of organic solvents has gained importance as an essential component of the development of sustainable chemistry [8].

Recently, heteropolyacids (*HPA*s) which are low in toxicity and being recyclable have attracted special attention [9–11]. 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 [12]. Furthermore, *Wells–Dawson* type heteropolyacids possess superacidity and a remarkable stability both in solution and in the solid state [13]. Many typical acid-catalyzed reactions, including synthesis of coumarins [14], preparation of organic peroxides [15], and synthesis of β-acetamido carbonyl compounds [16], are all effective in the presence of *Wells–Dawson* type heteropolyacid catalyst. To the best of our knowledge, there are no examples of the use of *Wells–Dawson* type heteropolyacids as catalyst for this type of 3,3-diaryloxindoles.

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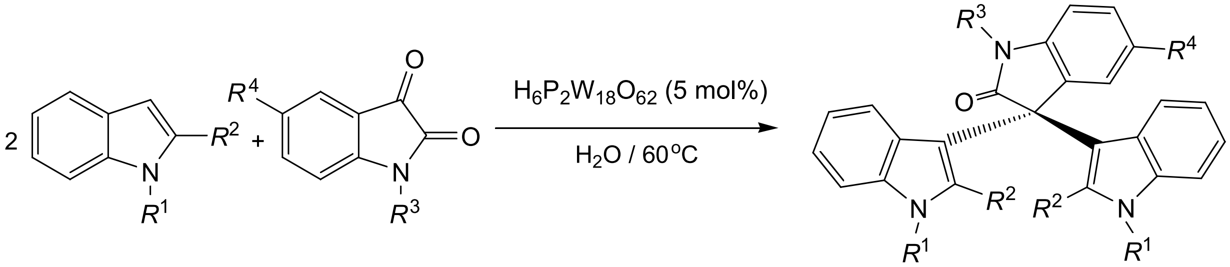
Results and discussion

In connection with our ongoing work on using water as solvent in organic synthesis [17–19], we now wish to provide an efficient route to the synthesis of 3,3-di(heteroaryl)oxindole derivatives in water using *Wells–Dawson* type tungstophosphoric heteropolyacid, $H_6P_2W_{18}O_{62}$, as a green and reusable catalyst (Scheme 1).

The reaction of indole (1 mmol) with isatin (0.5 mmol) in the presence of $H_6P_2W_{18}O_{62}$ (5 mol%) in water proceeded rapidly giving 3,3-di(indolyl)-oxindole in 95% yield for 30 min (Table 1, entry 1). The product was characterized by recording IR, ^{1}H, ^{13}C NMR spectra, and melting point. Encouraged by this result, we tried to apply this protocol to a wide range of isatin and indole derivatives (Table 1).

In all conversions, electrophilic activation occurred only at the carbonyl of the 3-position. The carbonyl at the 2-position is unreactive and this may be due to stabilization by the indole nitrogen. All products (except **11**–**13**) are known compounds and were characterized by comparison of their physical and spectroscopic data with those reported in Refs. [3a, 4]. Structures of the new compounds have also been confirmed by spectroscopic data. The ^{1}H NMR spectra of these compounds showed a singlet at $\delta = 3.71$ ppm for the two methyls (N-*Me*) of indole rings and in compound **11** the two 2-Hs of the indole rings appeared as a singlet at $\delta = 6.99$ ppm which clearly confirms their symmetrical structures. Physical properties and spectral data of new compounds **11**–**13** are reported in experimental section.

We also investigated the reusability of the catalyst. For this purpose we first carried out the reaction of isatin and indole in the presence of the catalyst. After completion of the reaction, the product was filtered off and the catalyst was removed and subjected to three 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 and indoles condensation. However, when the reaction of isatin



Scheme 1

Table 1 The reaction of isatins with indoles catalyzed by $H_6P_2W_{18}O_{62}$ in water

Product	R^1	R^2	R^3	R^4	Yield[a]/%	mp/°C	Ref. mp/°C
1	H	H	H	H	–[b], 95, 93, 92[c]	312–314	312–314 [3a]
2	H	H	H	NO_2	86	297–298	298–299 [4a]
3	H	H	H	Br	88	308–310	310–311 [4a]
4	H	H	*Ph*CH_2	H	90[d]	288–289	288–289 [4a]
5	H	H	*Me*	H	92	291–293	292–293 [3a]
6	H	*Me*	H	H	93	301–302	300–301 [4a]
7	H	*Me*	*Me*	H	91	282–284	272–273 [4a]
8	H	*Me*	*Ph*CH_2	H	91[d]	211–213	212–214 [4a]
9	*Me*	H	H	H	94	333–335	>300 [4b]
10	*Me*	H	*Me*	H	90	230–232	232–234 [4b]
11	*Me*	H	H	NO_2	87	332–333	–
12	*Me*	H	H	Br	92	324–325	–
13	*Me*	H	*Ph*CH_2	H	90[d]	223–224	–

[a] Yields of pure isolated product based on isatin; [b] Reaction carried out without catalyst; [c] The same $H_6P_2W_{18}O_{62}$ was used for each of the three runs; [d] Reaction conducted in water/acetone (4/1)

and indole was conducted in the absence of the catalyst under the same reaction conditions, no product was formed and only the starting materials were collected, so implying the role of $H_6P_2W_{18}O_{62}$ as a catalyst in this reaction (Table 1, entry 1).

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

Experimental

General procedure

A mixture of indole (1 mmol) and isatin (0.5 mmol) in 5 cm^3 water in the presence of *Wells–Dawson* heteropolyacid (5 mol%) was stirred at 60°C for 30 min. After completion of the reaction, as indicated by TLC, the precipitated solid was filtered off and washed with $2 \times 20\,cm^3$ water. The pure product was obtained by recrystallization from EtOH/H_2O. 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 three reactions without observation of appreciable loss in its catalytic activities.

3,3-Bis(1-methylindolyl)-5-nitrooxindole (**11**, $C_{26}H_{20}N_4O_3$)
IR (KBr): $\bar{\nu} = 3364, 1740\,cm^{-1}$; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 3.71$ (s, 6H, *Me*–N), 6.86 (t, $J = 7.5$ Hz, 2H), 6.99 (s, 2H), 7.09 (t, $J = 7.5$ Hz, 2H), 7.18 (d, $J = 8.6$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 8.1$ Hz, 2H), 7.96 (s, 1H), 8.23 (d, $J = 8.6$ Hz, 1H), 11.32 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 32.35$, 52.30, 109.90, 109.98, 111.85, 118.70, 120.09, 120.46, 121.27, 125.44, 125.68, 128.69, 135.09, 137.39, 142.22, 147.67, 178.63 ppm; MS: $m/z = 436$ (M^+).

3,3-Bis(1-methylindolyl)-5-bromooxindole
(**12**, $C_{26}H_{20}BrN_3O$)
IR (KBr): $\bar{\nu} = 3357, 1723\,cm^{-1}$; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 3.71$ (s, 6H, *Me*–N), 6.85 (br t, 2H), 6.92–6.96 (m, 3H), 7.09 (br t, 2H), 7.21 (d, $J = 7.5$ Hz, 2H), 7.30 (s, 1H), 7.37–7.41 (m, 3H), 10.76 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 32.82$, 53.07, 110.37, 112.18, 113.08, 113.73, 119.06, 121.15, 121.67, 126.28, 127.79, 128.98, 131.24, 137.30, 137.79, 141.06, 178.52 ppm; MS: $m/z = 470$ (M^+, ^{79}*Br*), 472 (M^+, ^{81}*Br*).

3,3-Bis(1-methylindolyl)-1-benzyloxindole (**13**, $C_{33}H_{27}N_3O$)
IR (KBr): $\bar{\nu} = 1720\,cm^{-1}$; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta =$ 3.71 (s, 6H, *Me*-N), 5.06 (s, 2H, CH_2), 6.90–6.93 (m, 5H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.18 (t, $J = 7.6$ Hz, 2H), 7.22 (t, $J = 7.7$ Hz, 1H), 7.25–7.33 (m, 7H), 7.39 (m, 2H), 7.48 (d, $J = 7.3$ Hz, 1H) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 32.74$, 44.16, 52.79, 109.17, 109.23, 113.76, 118.91, 121.50, 121.54, 122.63, 125.34, 126.41, 127.54, 127.74, 127.82, 128.65, 128.78, 134.30, 136.12, 137.75, 141.98, 177.87 ppm; MS: $m/z = 481$ (M^+).

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