



Full paper/Mémoire

An efficient ultrasound-promoted method for the synthesis of bis(indole) derivatives

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ABSTRACT

In this paper, the reaction of indole with electron-deficient alkenes in aqueous media is reported. This procedure allows the synthesis of bis(indole) derivatives in good to high yields at 90 °C under silent and ultrasound irradiation conditions. Short reaction times and high yields of desired products are the main advantages of the presented procedure. This reaction catalyzed by 12-tungstophosphoric acid is operationally simple and considers environmental aspects by avoiding toxic catalysts and solvents.

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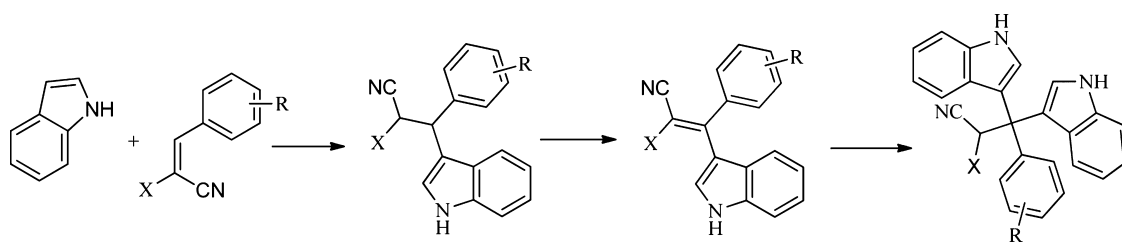
1. Introduction

Bis(indole)-based compounds have recently received much attention as important building blocks for the synthesis of various active biological compounds [1–7]. Bis(indole) derivatives have been prepared *via* condensation reactions of indole with various aldehydes or ketones in the presence of either protic or Lewis acids [8–12]. Ultrasound irradiation is a powerful technique in synthetic organic chemistry. Enhanced reaction rates, simple experimental procedures, and high yields are the notable features of the ultrasound approach as compared to established methods [13–15]. Organic synthesis in aqueous media is gaining importance in view of the fact that the use of many toxic and volatile organic solvents contributes to pollution. There have been profound

research activities in the development of organic reactions in aqueous media, offering key advantages such as rate enhancement and insolubility of final products, which facilitates their isolation by simple filtration [16]. Keggin-type heteropolyacids (HPAs) have been studied extensively for organic synthetic processes as acid or redox catalysts in homogeneous and heterogeneous media [17]. HPAs have catalyzed several organic transformations such as Diels–Alder reaction [18], oxidative dehydrogenation of alcohols and amines [19], olefin hydration [20], synthesis of dihydropyrimidinones [21], esterification reactions [22], preparation of oximes [23] and synthesis of oxazolines, imidazolines, and thiazolines [24]. In conjunction with an ongoing research program involving the synthesis of bis(indole) compounds, we report a simple method for the preparation of bis(indole) derivatives through the Michael reaction of indole with different electron-deficient alkenes. This reaction is catalyzed by 12-tungstophosphoric acid in aqueous media at 90 °C under silent and ultrasound irradiation conditions (Scheme 1).

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Scheme 1. Synthesis of bis(indole) derivatives catalyzed by 12-tungstophosphoric acid in aqueous media at 90 °C.

2. Results and discussion

In our initial study, the reaction of indole and 2-benzylidenemalonitrile was considered as a model one to optimize the conditions. The reaction was first carried out in H₂O in the absence of H₃PW₁₂O₄₀ and in reflux conditions. No reaction occurred under silent and ultrasound irradiation conditions (Table 1, entry 1). Similar reactions were then attempted in the presence of 2, 2.5, 3, and 3.5 mol-% of H₃PW₁₂O₄₀. The results in Table 1, entries 2–5, show that the use of 3 mol-% of H₃PW₁₂O₄₀ at reflux in H₂O is sufficient to push the reaction forward. Higher reaction loading of the catalyst had no significant influence on the reaction yield. To find the optimum reaction temperature, the reaction was carried out with 3 mol-% of H₃PW₁₂O₄₀ at room temperature, 60 °C, and at reflux temperature, which resulted in the isolation of the product in trace amounts and yields of 65% and 93% (Table 1, entries 7, 6, and 4), respectively. Thus, 3 mol-% of H₃PW₁₂O₄₀ and a reaction temperature at reflux were the optimal conditions. In addition, EtOH, MeCN, and MeCO₂Et were also tested as solvents. In these cases,

2-((di(H1 indol-3-yl)(phenyl)methyl)malonitrile was formed in lower yields (Table 1, entries 8–10). When H₃NSO₃ and C₁₀H₁₆O₄S were used as catalysts, 2-((di(H1 indol-3-yl)(phenyl)methyl)malonitrile was formed slightly in lower yields (Table 1, entries 13, 14).

When optimizing the model reaction, bis(indole) derivatives were synthesized in high yields under silent and ultrasound irradiation conditions. Ultrasound irradiation accelerated such reactions. The results are summarized in Table 2. It can be observed that the process tolerates both electron-donating and electron-withdrawing substituents in benzaldehydes. In all the cases, the reactions proceeded efficiently at reflux under mild conditions to afford the corresponding products in high yields. All the products were characterized by ¹H- and ¹³C-NMR, IR spectroscopy and elemental analyses.

As expected, the reaction could be extended to other electron-deficient alkenes. Under optimized conditions, 2-(pyridylmethylene)malonitriles, 3-(pyridyl)acrylates were also chosen as electron-deficient alkenes to react with indole and were found to generate the corresponding indolyl derivatives. The reaction proceeded smoothly as

Table 1
Optimization of reaction conditions on the reaction of indole and 2-benzylidenemalonitrile^a.

Entry	Temp (°C)	Solvent	Catalyst (mol %)	Yield (%) ^b
1	Reflux	H ₂ O	H ₃ PW ₁₂ O ₄₀ (0)	0
2	Reflux	H ₂ O	H ₃ PW ₁₂ O ₄₀ (2)	70
3	Reflux	H ₂ O	H ₃ PW ₁₂ O ₄₀ (2.5)	87
4	Reflux	H ₂ O	H ₃ PW ₁₂ O ₄₀ (3)	93
5	Reflux	H ₂ O	H ₃ PW ₁₂ O ₄₀ (3.5)	92
6	60	H ₂ O	H ₃ PW ₁₂ O ₄₀ (3)	65
7	Room temp	H ₂ O	H ₃ PW ₁₂ O ₄₀ (3)	Trace
8	Reflux	EtOH	H ₃ PW ₁₂ O ₄₀ (3)	30
9	Reflux	MeCO ₂ Et	H ₃ PW ₁₂ O ₄₀ (3)	20
10	Reflux	MeCN	H ₃ PW ₁₂ O ₄₀ (3)	28
11	Reflux	H ₂ O	H ₃ PMo ₁₂ O ₄₀ (5.4)	91
12	Reflux	H ₂ O	H ₄ SiW ₁₂ O ₄₀ (3.4)	92
13	Reflux	H ₂ O	C ₁₀ H ₁₆ O ₄ S (42)	70
14	Reflux	H ₂ O	H ₃ NSO ₃ (100)	75

^a Reaction conditions: indole (1 mmol), 2-benzylidenemalonitrile (0.5 mmol), and solvent (4 mL).

^b Isolated yields.

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