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Montmorillonite K10–Catalyzed Michael Addition of Indoles to Nitroolefins Under Solvent-Free Conditions

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Abstract: Montmorillonite K10 is a very inexpensive and readily available reagent and efficiently catalyzes the Michael addition of indoles to nitroolefins under solvent-free conditions. Reasonable to excellent yields of the desired products were obtained in most cases.

Keywords: Indole, Michael addition, montmorillonite K10, nitroolefin, solvent-free

Indole and many of its derivatives are present in many substances commonly found in nature, as well as in many compounds that show pharmacological and biological activities.[1–3] Thus, the development of a new, efficient, selective, and green synthetic method for the preparation of indole derivatives has attracted much attention in recent years. Because the 3-position of the indole is the ideal site for electrophilic attack, 3-substituted indoles are versatile intermediates for the synthesis of a wide variety of indole derivatives. A variety of methods have been explored for the Michael addition reaction of indoles with α,β-substituted

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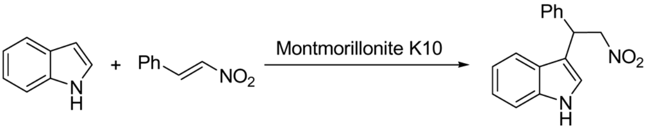
acceptors in the presence of protic or Lewis acids for the preparation of substituted indoles.[4–15]

Nowadays, the "greening" of global chemical processes has become a major issue in chemical research.[16] While designing a new methodology under investigation, chemists always keep in mind the legislation on environmental friendliness in synthetic pathways and processes to prevent waste, avoid the use of auxiliary substances (e.g., solvents, separation agents), and minimize the potential for chemical accidents (e.g., explosion, fire).[17] Among many methods, the use of solid acids such as clay and zeolites as catalysts in organic reactions (which can minimize waste emission and the formation of large quantities of environmentally hazardous toxic substances) is one of the most attractive methods to establish clean chemical processes. Montmorillonite K10, which is very cheap and commercially available, is an efficient catalyst for C–C bond formation reactions in organic synthesis.[18–21]

Herein, we report the results obtained from our study of Michael addition reaction of indoles with nitroolefins using montmorillonite K10 as a very inexpensive, easily available, and efficient catalyst under solvent-free conditions.

In our initial study, indole was first reacted with β-nitrostyrene in EtOH at rt for 2 h; the expected product was obtained smoothly in 86% yield in the presence of a catalytic amount of montmorillonite K10 (100 mg/mmol) (Table 1, entry 1). Next, the effect of solvent was investigated; when the reaction was carried out in MeOH, tetrahydrafuran

Table 1. Reaction of indole and β-nitrostyrene at various conditions[a]



Entry	Solvent	Temperature	Time (h)	Yield (%)[b]
1	EtOH	rt	2	86
2	MeOH	rt	2.5	84
3	THF	rt	3	80
4	DCM	rt	3	81
5	Toluene	rt	3	79
6	—	rt	0.5	96

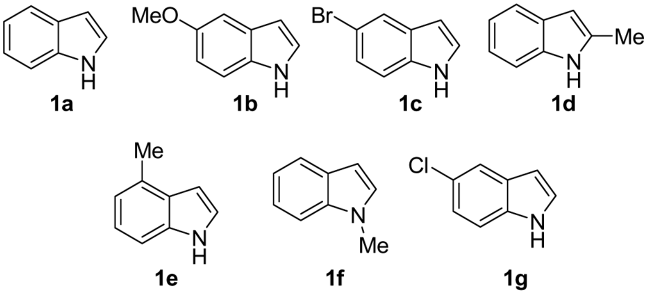
[a] Reaction conditions: indole (0.2 mmol), β-nitrostyrene (0.21 mmol), and montmorillonite K10 (20 mg).

[b] Isolated yield.

(THF), dichloromethane (DCM), and toluene, moderate to good yields could be obtained (Table 1, entries 2–5). However, the reaction could be completed in a short time and afforded the desired product in excellent yield when it was carried out under solvent-free conditions (Table 1, entry 6). The acceleration effect was probably attributed to the concentration effect.[22] To show the strong catalytic effect of montmorillonite K10, the reaction of indole and β-nitrostyrene in the absence of montmorillonite K10 was also studied. The desired Michael adduct was not observed even after a prolonged reaction time (24 h). Lesser yield was obtained by decreasing the amount of added montmorillonite K10. Furthermore, in all cases, leaving the reaction to proceed longer (>1 h) did not improve the yield of the reaction. These results showed that montmorillonite K10 was essential for the success of the Michael addition of indole to β-nitrostyrene.

Encouraged by the remarkable results obtained with indole and β-nitrostyrene, a variety of substituted indoles and nitroolefins were tested using this Michael addition method. The results clearly demonstrate that montmorillonite K10 is an excellent catalyst for this reaction under solvent-free conditions (Table 2).

By using substituted indoles (Figure 1), good to excellent yields were obtained. The substituents did not affect the reactivity of indoles significantly (Table 2, entries 2–7). The method is equally effective with nitroolefins bearing electron-withdrawing or electron-donating substituents on the aromatic ring. In all cases, no undesired side products were obtained under these reaction conditions. The only significant difference in reactivity was observed for aliphatic nitroolefins, which gave a smaller yield in comparison with aromatic nitroolefins (Table 2, entries 14, 15). Finally, montmorillonite K10 could easily be recovered by filtration and recycled for use in subsequent reactions with comparable activity; for example, the reaction of indole and β-nitrostyrene under the present reaction conditions furnished the desired product in 96, 94, and 95% yields over three cycles.

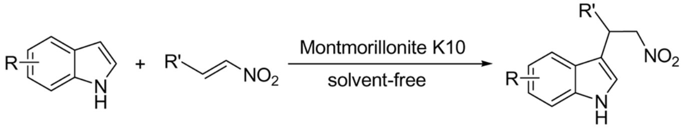


1a 1b 1c 1d

1e 1f 1g

Figure 1. Structures of indoles.

Table 2. Michael addition of indoles to nitroolefins under solvent-free conditions[a]



Entry	Indole	R′	Product	Time (h)	Yield (%)[b]
1	**1a**	Ph	**3a**	0.5	96
2	**1b**	Ph	**3b**	0.5	92
3	**1c**	Ph	**3c**	1	86
4	**1d**	Ph	**3d**	0.5	94
5	**1e**	Ph	**3e**	0.5	90
6	**1f**	Ph	**3f**	0.5	95
7	**1g**	Ph	**3g**	1	85
8	**1a**	4-$Me_2NC_6H_4$	**3h**	1	86
9	**1a**	4-$MeOC_6H_4$	**3i**	0.5	90
10	**1a**	2-Naphth	**3j**	1	83
11	**1a**	4-ClC_6H_4	**3k**	0.5	90
12	**1a**	2-Fury	**3l**	0.5	88
13	**1d**	4-$MeOC_6H_4$	**3m**	0.5	92
14	**1a**	i-Bu	**3n**	2	82
15	**1a**	$PhCH_2CH_2$	**3o**	2	80

[a] Reaction conditions: indole (0.2 mmol), nitroolefin (0.21 mmol), and montmorillonite K10 (20 mg).
[b] Isolated yield.

In conclusion, we have demonstrated a very simple, efficient, and practical method for Michael addition of indoles to nitroolefins catalyzed by montmorillonite K10. The main features of our new reaction are as follows: (1) the procedure is operationally simple and can furnish a wide variety of important 3-substituted indole derivatives in good yields; (2) the condensation reaction could be performed by exclusively using cheap, commercially available chemicals; (3) the catalyst could be recycled with comparable activity; and (4) there was no need for any other additive to promote the reaction. These results show a novel way to synthesize important 3-substituted indole derivatives.

EXPERIMENTAL

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained for solution in $CDCl_3$ with Me_4Si as internal standard on a Varian Mercury spectrometer. High-resolution mass spectra were obtained using a GCT-TOF Micromass instrument.

All experiments were operated according to the following general procedure: Indole 23.4 mg (0.2 mmol), β-nitrostyrene 31.3 mg (0.21 mmol), and montmorillonite K10 20 mg were mixed and stirred at room temperature. After the completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction mixture was filtered and washed with dichloromethane. The combined organic layers were concentrated in vacuo and purified by column chromatography on silica gel to furnish 3-(2′-nitro-1′-phenylethyl)-1H-indole (**3a**) in 96%.

3-(2′-Nitro-1′-phenylethyl)-1H-indole (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.08 (s, 1H), 7.43 (d, $J = 7.8$ Hz, 1H) 7.31–7.15 (m, 7H), 7.06 (t, $J = 7.6$ Hz, 1H), 7.00 (d, $J = 2.4$ Hz, 1H), 5.18 (t, $J = 8.1$ Hz, 1H), 5.02 (dd, $J = 7.6$, 12.4 Hz, 1H), 4.90 (dd, $J = 8.6$, 12.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 139.2, 136.5, 128.9, 127.8, 127.6, 126.1, 122.7, 121.6, 119.9, 118.9, 114.5, 111.4, 79.6, 41.6. HRMS calcd. for $C_{16}H_{14}N_2O_2$: 266.1055; found: 266.1056.

5-Methoxy-3-(2′-nitro-1′-phenylethyl)-1H-indole (3b)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.02 (s, 1H), 7.36–7.21 (m, 6H), 6.97 (d, $J = 2.4$ Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.82 (d, $J = 1.5$ Hz, 1H), 5.14 (t, $J = 8.0$ Hz, 1H), 5.03 (dd, $J = 12.3$, 7.5 Hz, 1H), 4.93 (dd, $J = 12.3$, 8.1 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.2, 139.3, 131.6, 128.8, 127.6, 127.5, 126.4, 122.3, 114.1, 112.6, 112.1, 100.9, 79.4, 55.9, 41.5. HRMS calcd. for $C_{17}H_{16}N_2O_3$: 296.1161; found: 296.1170.

3-(1′-(Furano-2-yl)-2′-nitroethyl)-1H-indole (3l)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.09 (s, 1H), 7.54–7.06 (m, 6H), 6.29–6.14 (m, 2H), 5.26–5.22 (m, 1H), 5.06–4.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.5, 142.8, 136.6, 126.1, 123.2, 123.0, 120.4, 119.2, 112.1, 111.9, 110.8, 107.8, 78.3, 36.2. HRMS calcd. for $C_{14}H_{12}N_2O_3$: 256.0848; found: 256.0856.

3-(3′-Methyl-1′-nitromethyl-butyl)-1H-indole (3n)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.07 (s, 1H), 7.63 (d, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.24–9.19 (m, 1H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.02 (d, $J = 2.3$ Hz, 1H), 4.64 (dd, $J = 7.5$, 11.8 Hz, 1H), 4.58 (dd, $J = 7.6$, 11.8 Hz, 1H), 3.91–3.84 (m, 1H), 1.95–1.86 (m, 1H), 1.52–1.46 (m, 2H), 0.90 (d, $J = 5.4$ Hz, 3H), 0.87 (d, $J = 5.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 136.5, 126.1, 122.4, 122.1, 119.8, 118.8, 114.0, 111.6, 81.0, 41.4, 34.5, 25.4, 23.4, 21.6. HRMS calcd. for $C_{14}H_{18}N_2O_2$: 246.1368; found: 246.1362.

3-(1′-Nitromethyl-3′-phenylpropyl)-1H-indole (3o)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.04 (s, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.319–7.12 (m, 5H), 7.06 (d, $J = 6.9$ Hz, 2H), 6.98 (d, $J = 2.2$ Hz, 1H), 4.69 – 4.56 (m, 2H), 3.83–3.74 (m, 1H), 2.68–2.48 (m, 2H), 2.24–2.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 141.3, 136.5, 128.5, 128.3, 126.0, 125.9, 122.4, 122.2, 119.7, 118.8, 113.3, 111.6, 80.4, 35.8, 33.9, 33.4. HRMS calcd. for $C_{18}H_{18}N_2O_2$: 294.13683; found: 294.13688.

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