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MONTMORILLONITE K10: CATALYST FOR FRIEDEL–CRAFTS ALKYLATION OF INDOLES AND PYRROLE WITH NITROALKENES UNDER SOLVENTLESS CONDITIONS

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Montmorillonite K10 was found to catalyze the Michael addition of indoles or pyrrole with nitroalkenes efficiently under solventless condition. The short reaction time, simple workup, and excellent yields were noteworthy. The green catalyst could be reused for three runs without considerable variation in yield.

Keywords: Alkylation; heterogenous catalysis; indole; montmorillonite K10; nitroalkene

INTRODUCTION

The Michael reaction has attracted much attention as one of the most important carbon–carbon (C–C) bond-formation reactions in organic synthesis. Particularly, it is a completely atom-efficient procedure.[1] Among the Michael acceptors, nitroalkenes are very attractive, because the nitro group is one of the most electron-withdrawing groups known.[2] The use of the nitroalkenes as Michael acceptors opens the way to synthetically useful C–C bond-forming reactions.[3] The nitro group can be transformed subsequently into a range of different functionalities.[2] The adducts of indole with nitroalkenes are versatile intermediates for the synthesis of many biologically active indole derivatives.[4–6] Usually, Michael addition of arenes to nitroalkenes was catalyzed by Lewis acid or organocatalysts. Several catalysts, such as $Bi(NO_3)_3$,[7] I_2,[8] SmI_3,[9] $CeCl_3 \cdot 7H_2O\text{-}NaI\text{-}SiO_2$,[10] and $H_3PW_{12}O_{40}$[11] have emerged for the Michael addition. However, to the best of our knowledge, there are few reports about the reaction catalyzed by solid catalysts in solvent-free conditions.[10,12,13] Because of the importance of indole derivatives

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and increasing environmental concerns, it is desirable to develop new, metal-free, efficient, and cost-effective catalysts for the Michael addition. Thus, we attempted to carry out the reaction on solid mineral supports without any solvent.

On the other hand, montmorillonite clays are known for their acidic properties and have generated widespread interest in synthetic organic chemistry.[14–17] In particular, they make the reaction convenient, more economical, and environmentally benign. Their importance is likely to increase with demanding environmental legislation, public pressure, and the drive toward clean technology. To our knowledge, there is no report on the Michael addition of nitroalkene to indole catalyzed by montmorillonite K10. In a continuation of our interest in the development of K10 as catalyst in organic synthesis,[18] we report herein our results on the neat reaction of nitroalkenes with indoles or pyrrole in the presence of K10.

RESULTS AND DISCUSSION

The Michael reaction of indole (1.0 mmol) and β-nitrostyrene (1.1 mmol) was performed first at room temperature in the presence of K10; it was very slow, but 3-(2′-nitro-1′-phenylethyl)-1H-indole **4a** was obtained in 87% yield after 10 h (Table 1, entry 1). When conventional heating was employed, the reaction remarkably accelerated (Scheme 1; Table 1, entry 5). It was completed within 15 min in 91% yield. Then, the addition of indole to β-nitrostyrene was chosen as the test reaction to explore the effect of catalyst loading (Scheme 1). As shown in Table 1, although more catalyst could reduce the reaction time, the yield was not improved accordingly (Table 1, entry 6). The product was obtained in comparable yield even if 0.2 g of K10 was used, albeit the reaction time was a bit longer (Table 1, entry 3). Much less catalyst could not bring favorable results in terms of reaction time and yield (Table 1, entry 2). Thus, 0.2 g of K10 was sufficient to promote the reaction of indole and β-nitrostyrene.

To gain more insight into the scope and limitations of the catalyst, different indoles were reacted with β-nitrostyrenes, and 3-substituted indole derivatives were obtained exclusively in good to excellent yields (Scheme 2; Table 2, entries 1–3 and 5–13). An exception was that the electrophilic substitution occurred at the 2-position of 3-methyl indole (Table 2, entry 4). The interesting regioselectivity demonstrates

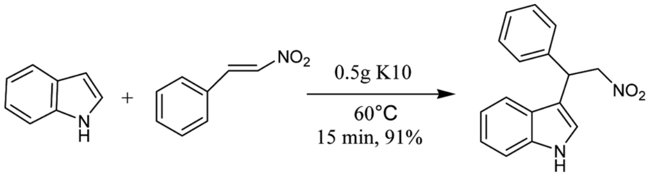
Table 1. Effect of catalyst loading of K10 on the synthesis of 3-(2′-nitro-1′-phenylethyl)-1H-indole (**4a**)[a]

Entry	Catalyst loading (g)	Time	Yield (%)[b]
1	0.5	10 h	87[c]
2	0.1	35 min	82
3	0.2	20 min	94
4	0.4	15 min	93
5	0.5	15 min	91
6	1	10 min	87

[a] Reaction conditions: indole 1.0 mmol, β-nitrostyrene 1.1 mmol, oil bath heating at 60 °C.

[b] Isolated yield.

[c] Performed at room temperature.



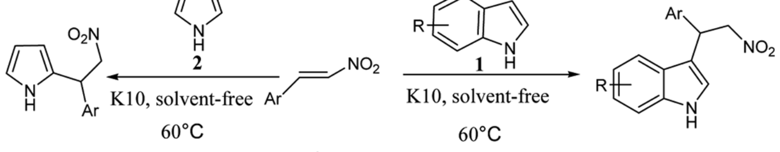
4a

Scheme 1. The Michael reaction of indole and β-nitrostyrene.

that the 3-position of the indole is the preferred site for electrophilic attack, as expected[19–21] Moreover, the electronic and steric effects were also examined. The electronic density of the heterocycle plays an important role in the reaction. For example, an indole with an electron-withdrawing group, such as 5-bromoindole, required fairly longer times than those of indoles carrying electron-donating groups, and the yield was less (Table 2, entry 2). It may be that the bromo atom reduces the overall nucleophilicity.[10,13] On the other hand, neither electron-donating nor electron-withdrawing groups in the nitroalkene moiety had significant effect on the yield and reaction time (Table 2, entries 1, 11 and entries 6, 7).

Furthermore, we found that the hindered substituent near the reaction center of indole had a negative effect on the reaction. For example, the reaction of 4-methylindole with β-nitrostyrene needed less time and resulted in greater yield than that of 4-benzyloxyindole (Table 2, entries 5 and 6). It is noteworthy that the substitution of 3-methylindole occurred at the 2-position, which was probably formed by initial attack of β-nitrostyrene at C-3, followed by a 1,2-shift in the intermediate cation.[19] This may explain why the reaction of 3-methylindole required longer time (Table 2, entry 4). In addition, the reaction of 3-methylindole with β-nitrostyrene completed smoothly at room temperature in 12 h (Table 2, entry 4), which was much less than the other catalyst in this case (2 days).[8]

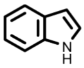
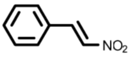
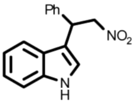
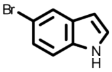
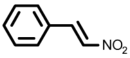
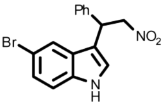
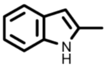
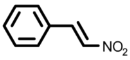
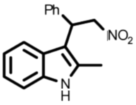
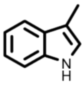
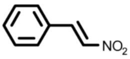
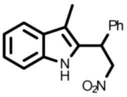
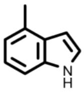
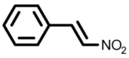
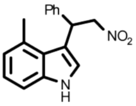
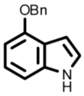
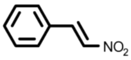
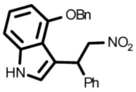
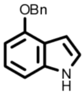
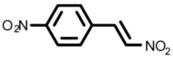
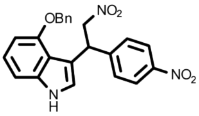
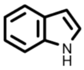
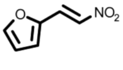
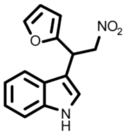
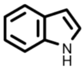
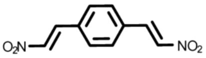
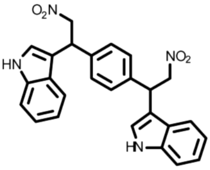
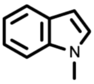
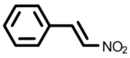
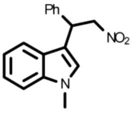
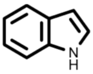
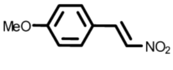
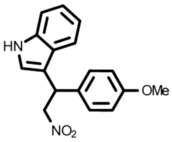
It is known that the α-position of pyrrole is the electron-rich site for Michael addition.[20,21] As shown in Table 3, pyrrole also readily reacted with several nitroalkenes under the same reaction conditions in good to excellent yields (Scheme 2; Table 3, entries 1–5), affording the corresponding 2-((1′-aryl-2′-nitro)-ethyl)pyrrole. As shown in Tables 2 and 3, 1,4-bis-(*trans*-2-nitrovinyl)-benzene derived from benzenedicarboxaldehyde could also afford the corresponding Michael adducts (Table 2, entry 9; Table 3, entry 4).



5a-5e **3** **4a-4l**

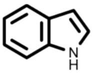
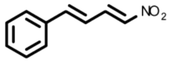
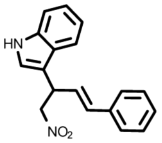
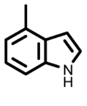
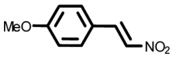
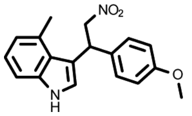
Scheme 2. The Friedel–Crafts alkylation of indoles and pyrrole with nitroalkenes.

Table 2. Michael addition of indoles to nitroalkenes catalyzed by K10 under solvent-free conditions[a]

Entry	Indole	Nitroalkene	Product	Product label	Time (min)	Yield (%)[b]
1				**4a**	20	94
2				**4b**	60	83
3				**4c**	20	94
4				**4d**	60 (12 h)[c]	86 (88)[c]
5				**4e**	20	92
6				**4f**	60	84
7				**4g**	75	81
8				**4h**	30	92
9				**4i**	30	84
10				**4j**	45	85
11				**4k**	15	96

(*Continued*)

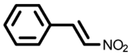
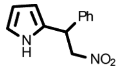
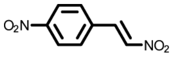
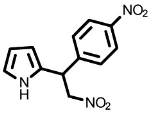
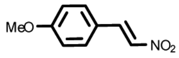
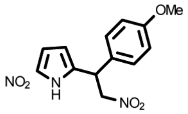
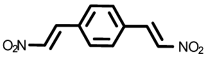
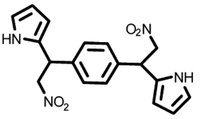
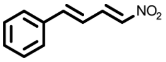
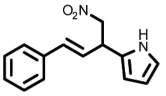
Table 2. Continued

Entry	Indole	Nitroalkene	Product	Product label	Time (min)	Yield (%)[b]
12				**4l**	60	87
13				**4m**	45	91

[a] Reaction conditions: indole 1.0 mmol, β-nitrostyrene 1.1 mmol, oil bath heating at 60 °C.
[b] Isolated yield.
[c] The reaction was carried out at room temperature.

Finally, the reusability of the catalyst was investigated. When the reaction of indole with β-nitrostyrene was completed, the catalyst montmorillonite K10 was filtered off, washed with acetone, dried in an oven at 110 °C for 3 h, and subjected to a second run with the same substrate. After three runs, the recovered catalyst was satisfactory and did not give considerable variation in yield (Table 4, entries 2–4).

Table 3. Michael addition of pyrrole to nitroalkenes catalyzed by K10 under solvent-free conditions[a]

Entry	Pyrrole	Nitroolefin	Product	Product label	Time (min)	Yield (%)[b]
1				**5a**	20	93
2				**5b**	35	89
3				**5c**	30	84
4				**5d**	30	93
5				**5e**	35	90

[a] Reaction conditions: pyrrole 1.5 mmol, β-nitrostyrene 1.0 mmol, oil bath heating at 60 °C.
[b] Isolated yield.
[c] The reaction was carried out at room temperature.

Table 4. Reusability of recovered catalyst on the reaction of indole with β-nitrostyrene[a]

Entry	Run	Reaction time (min)	Yield (%)[b]
1	1	20	94
2	2	20	92
3	3	20	92
4	4	20	89

[a] Reaction conditions: indole 1.0 mmol, β-nitrostyrene 1.1 mmol, oil bath heating at 60 °C.
[b] Isolated yield.

CONCLUSION

In summary, we have demonstrated a novel, highly efficient, and environmentally benign protocol for Friedel–Crafts alkylation of indole or pyrrole with several nitroalkenes under solventless conditions. This procedure offers the advantages such as high yields, simple workup, green and reusable catalyst, dry reaction and short reaction time, which makes it an attractive addition to the present methodology for the synthesis of these important heterocycles.

EXPERIMENTAL

Montmorillonite K10 was purchased from Alfa-Aesar company. It was used as obtained.

General Procedure for the Synthesis of Compound 4a

Indole (0.12 g, 1 mmol), β-nitrostyrene (0.17 g, 1.1 mmol), and montmorillonite K10 (0.2 g) were added to a vial. Then the vial was submerged into a hot oil bath (about 60 °C) for an appropriate time. On completion of the reaction (monitored by thin-layer chromatography, TLC), the catalyst was filtered off, and the reaction mixture was washed with acetone. The filtrate was evaporated to dryness prior to column chromatography (acetone–petroleum ether 1:8 as eluent) to give 0.25 g of pure **4a** (yield 94%). The structures of all products were confirmed by ^{1}H NMR and ^{13}C NMR.

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