Microwave-Assisted Addition of Pyrroles to Electron-Deficient Olefins: A Rapid Entry to *C*-Alkyl Pyrroles

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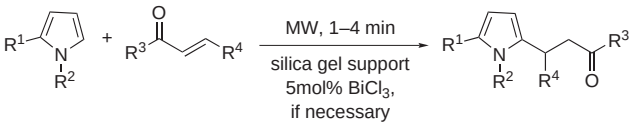
Abstract: A general procedure for the Michael addition of pyrroles with electron-deficient olefins using silica gel supported reagent under microwave irradiation, has been developed. This new method is fast, efficient, environmentally benign and solvent-free. A catalytic amount of $BiCl_3$ is employed for moderately bulk electron-deficient olefins.

Key words: microwave irradiation, bismuth trichloride, pyrroles, electron-deficient olefins, Michael reaction

The development of novel synthetic methods leading to *C*-alkyl pyrroles has attracted much attention because *C*-alkyl pyrroles are important building blocks for the synthesis of biologically active compounds and natural products that contain pyrroles skeletons.[1] There already exist several indirect routes affording *C*-alkyl pyrroles: (1) Wolff–Kishner reduction of 2-formyl or 2-acetyl pyrroles;[2] (2) the isomerization of *N*-alkyl pyrroles by thermal rearrangement at high temperature, resulting in the 2- and 3-alkyl pyrroles;[3] (3) preparation of 2- and 3-alkyl pyrroles using pyrrolyl magnesium halides.[4] However, these indirect methods share the drawbacks of multi-step synthetic reactions and they tend to polymerize under most reaction conditions. The direct C-alkylation of pyrroles by the Friedel–Crafts approach has been considered impractical because the acid catalysts employed (Brønsted and Lewis) induce polymerization and polyalkylation.[5] Until recently, it has been reported that using $InCl_3$,[6] $Cu(OTf)_2$[7] and benzyl imidazolidinone·HX salts[8] as catalysts, mono-alkylation of pyrrole with α,β-unsaturated compounds can be achieved. Though several such direct methods are available for preparation of *C*-alkyl pyrroles, it is desirable to develop new efficient methods. To our best knowledge, solvent-free C-alkylation of pyrroles under microwave irradiation has not been reported.

Nowadays, the application of microwave (MW) irradiation as an unconventional energy source for activation of reactions, in general and on inorganic solid supports in particular, has gained popularity over the usual homogeneous and heterogeneous reactions, since they can be performed rapidly to give pure products in high yields under solvent-free conditions with several eco-friendly advantages in the context of green chemistry.[9,10] As it is known that MW can promote a variety of chemical reactions because of the selective absorption of microwave energy by polar molecules,[11] we envisioned that the Michael addition of pyrroles to electron-deficient olefins might be accelerated by microwave energy because of their polar nature. In this paper, we wish to report a rapid and efficient solvent-free microwave-assisted procedure for *C*-alkyl pyrroles preparation using silica gel supported reagents. In some cases, 5% mol $BiCl_3$ was absorbed on silica gel surface to catalyze this Michael addition reaction (Scheme 1).



Scheme 1

First, we carried out the reaction of pyrrole with methyl vinyl ketone absorbed on silica gel under microwave irradiation. We were pleased to find that the reaction proceeded rapidly with high regioselectivity to afford the 2-alkyl pyrrole in 90% yield. 2,5-Dialkyl pyrrole as the side product was obtained in 6% yield (Table 1, entry 1). The reactions were clean and there was no formation of other by-products such as dimers or trimers that are normally observed under the influence of strong acids. Phenyl vinyl ketone also reacted well to give corresponding 2-alkyl pyrrole in 81% yield (entry 2). However, the more hindered chalcone was treated with pyrrole under the same condition, C-alkylation of pyrrole did not proceed and none of the corresponding 2-alkyl pyrrole was detected. While using 5% mol $BiCl_3$ absorbed on silica gel surface as Lewis acid to catalyze the reaction, C-alkylation of pyrrole with chalcone occurred leading to 2-alkyl pyrrole in 71% yield (entry 3). In contrast with free pyrrole, the reaction of 2-alkylpyrroles with α,β-unsaturated ketones afforded C-alkylation products in higher yields (entry 4, 82% vs. entry 3, 71%; entry 5, 91% vs. entry 2, 81%). 2-Benzylidenemalononitrile and diethyl 2-benzylidenemalonate failed to react with free pyrrole catalyzed by $BiCl_3$ under MW, while 2-alkylpyrrole instead of pyrrole was used as the nucleophile, this Michael reaction proceeded and corresponding *C*-alkylpyrroles products were obtained in excellent yields (entries 8, 9). The result indicated that 2-alkylpyrroles have much more reaction activity

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than pyrrole in the presence of 5% mol $BiCl_3$ under MW. Furthermore, *N*-benzylpyrrole also reacted smoothly with electron-deficient olefins with high regioselectivity and attained corresponding 2-alkylpyrroles in good yields (entries 10–13). The addition of pyrrole to β-nitrostyrene produced the corresponding 2-alkylated pyrroles in 88–90% yields (entries 14, 15). In comparison with 78% of product obtained via $InCl_3$-catalyzed reaction,[6] the solvent-free microwave-assisted procedure is more efficient for the Michael addition of pyrrole to β-nitrostyrene. Noticeably, our reactions proceeded far more rapidly (1–4 min) than the reactions involving direct alkylation of pyrroles that have been reported (1–42 h).[6–8] Our reactions showed that MW has particularly efficient promoting effect.

Table 1 Michael Addition of Pyrroles with Electron-Deficient Olefins Using Silica Gel Supported Reagents under MW[12]

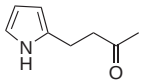
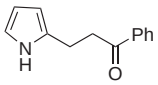
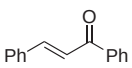
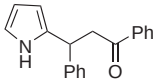
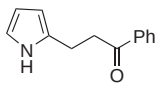
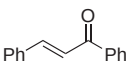
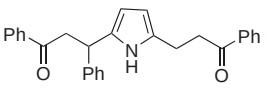
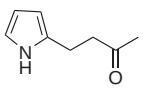
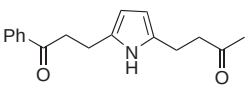
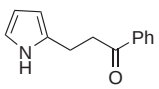
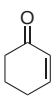
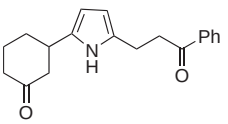
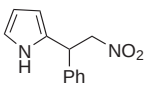
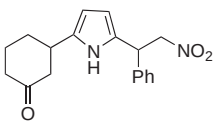
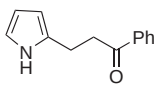
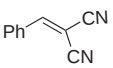
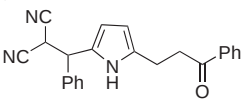
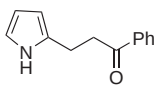
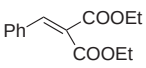
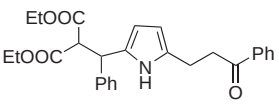
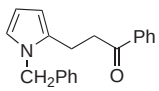
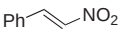
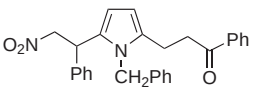
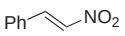
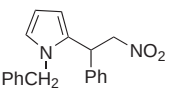
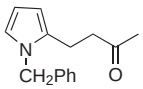
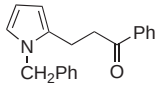
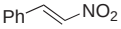
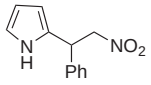
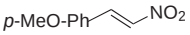
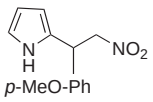
Entry	Nucleophile	Electrophile	Product	Catalyst	Time (min)	Isolated yield (%)
1			 **a**	–	1	90 (6)[a]
2			 **b**	–	1	81 (12)[a]
3			 **c**	$BiCl_3$	3	71
4			 **d**	$BiCl_3$	2	82
5			 **e**	–	2	91
6			 **f**	$BiCl_3$	2	88
7			 **g**	$BiCl_3$	2	85
8			 **h**	$BiCl_3$	4	95
9			 **i**	$BiCl_3$	3	95
10			 **j**	–	1	93
11			 **k**	–	2	80

Table 1 Michael Addition of Pyrroles with Electron-Deficient Olefins Using Silica Gel Supported Reagents under MW[12] (continued)

Entry	Nucleophile	Electrophile	Product	Catalyst	Time (min)	Isolated yield (%)
12			 **l**	–	1	85
13			 **m**	–	1	70
14			 **n**	–	1	90
15			 **o**	–	1	88

[a] Isolated yields of corresponding 2,5-dialkylpyrroles.

$BiCl_3$ has been used as a Lewis acid catalyst in many chemical transformations,[13] nevertheless, so far no examples were described that $BiCl_3$ was employed to promote the Michael reaction of pyrroles with electron-deficient olefins. Our experimental results indicated that $BiCl_3$ exhibited a high catalytic activity and did not induce polymerization and polyalkylation under microwave.

In conclusion, we have developed a new fast and efficient microwave-assisted method for the synthesis of C-alkylpyrroles using silica gel as support reagent. The procedure has the advantages of short reaction times, high regioselectivity, high yields, operational simplicity and solvent-free conditions, which makes it a useful and attractive process for the synthesis of alkylated pyrrole derivatives.

Acknowledgment

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(12) **Typical Experimental Procedure.**
Catalyst-free: To a solution of pyrrole (2 mmol) or *N*-benzyl pyrrole (2 mmol) or 2-alkylpyrroles (1 mmol) in CH_2Cl_2 (1 mL) was added electron-deficient olefin (1 mmol for pyrrole and *N*-benzyl pyrrole, 1.2 mmol for 2-alkylpyrroles) and silica gel (0.25 g). Then the mixture was mixed thoroughly and dried under reduced pressure. The contents were taken in a 5 mL conical flask and was placed in a microwave oven (cooking type, Galanz WP 700P 21-6) and irradiated for 1–4 min at 680 W. After completion of the reaction indicated by TLC, the reaction mixture was allowed to cool, diluted with CH_2Cl_2 and passed through a short silica gel column using CH_2Cl_2 as eluent. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to afford the corresponding 2-alkylpyrroles or 2,5-dialkylpyrroles.
Spectral data for selected compound.
4-(1*H*-Pyrrol-2-yl)butan-2-one (a): yield 123 mg (90%). IR (film): 3377, 1707 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 2.81 (t, *J* = 6.5 Hz, 2 H), 2.87 (t, *J* = 6.5 Hz,

2 H), 5.90 (s, 1 H), 6.10 (d, *J* = 3.0 Hz, 1 H), 6.66 (d, *J* = 3.0 Hz, 1 H), 8.54 (br, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 30.0, 44.0, 105.1, 107.7, 116.6, 131.4, 209.6. ESI-MS: *m/z* (%) = 138 (100) [M + H^+], 160 (48) [M + Na^+]. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.02; H, 8.12; N, 10.07.

Using 5% mol $BiCl_3$ as catalyst: to a solution of $BiCl_3$ (0.05 mmol) in MeCN (1 mL) was added pyrrole (2 mmol) or *N*-benzyl pyrrole (2 mmol) or 2-alkylpyrroles (1 mmol), followed by electron-deficient olefins (1 mmol for pyrrole and *N*-benzyl pyrrole, 1.2 mmol for 2-alkylpyrroles) and silica gel (0.25 g). Then the mixture was mixed thoroughly and dried under reduced pressure. For the following work up see typical experimental procedure (a).

Spectral data for selected compound.

3-[5-(3-Oxo-3-phenylpropyl)-1*H*-pyrrol-2-yl]cyclohexanone (f): yield 259 mg (88%). IR (film): 3373, 1708, 1677, 1595, 1579 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72–2.69 (m, 8 H), 3.01 (t, *J* = 6.0 Hz, 2 H), 3.04–3.11 (m, 1 H), 3.33 (t, *J* = 6.0 Hz, 2 H), 5.79 (d, *J* = 2.5 Hz, 1 H), 5.83 (d, *J* = 2.5 Hz, 1 H), 7.44–8.04 (m, 5 H), 8.52 (br, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 24.8, 31.6, 37.4, 39.4, 41.2, 47.4, 103.4, 105.2, 128.0, 128.6, 130.9, 133.4, 133.7, 136.6, 200.9, 210.9. ESI-MS: *m/z* (%) = 296 (100) [M + H^+], 318 (95) [M + Na^+]. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.14; H, 7.05; N, 4.67. Found: C, 77.26; H, 7.17; N, 4.74.

(13) (a) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373. (b) Postel, M.; Dunach, E. *Coord. Chem. Rev.* **1996**, *155*, 127.