

Short communication

Amberlyst-15: A mild, efficient and reusable heterogeneous catalyst for Michael addition of pyrroles to α,β -unsaturated ketones[☆]

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Abstract

A general procedure for the Michael addition of pyrroles with α,β -unsaturated ketones using catalytic amount of Amberlyst-15 at room temperature has been developed. This method is fast, efficient, high yielding and eco-friendly to afford the corresponding Michael adducts generally in good to excellent yields without polymerization.

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Keywords: Amberlyst-15; Pyrrole; α,β -Unsaturated ketone; Michael reaction; Heterogeneous reusable catalyst

Pyrrole and C-alkylated pyrroles are important building blocks in various biologically active molecules, such as chlorophyll, porphyrin, hemoglobin, Vitamin B₁₂, indigo and bile pigment [1]. The synthesis and reactions of pyrroles have thus attracted much attention over a century. Among pyrroles, 2-alkyl or 2-acyl pyrroles are versatile synthons for the synthesis of a wide range of pyrrole derivatives [2]. The indirect routes affording C-alkyl pyrroles involve the Wolf–Kishner reduction of 2-formyl or 2-acyl pyrroles [3], the application of pyrrolyl magnesium halides [4] and isomerization of *N*-alkyl pyrroles by thermal rearrangement at high temperature, resulting in 2- and 3-alkyl pyrroles [5]. However, these indirect methods are associated with the disadvantages of multistep reactions and of polymerization under most reaction conditions. A direct useful method for C-alkylation of pyrroles is the Friedel–Crafts type conjugate addition to α,β -unsaturated ketones. The direct synthesis of 2-alkylated pyrroles still remains a challenge for the synthetic chemists because of their sensitivity to air and acids which lead to polymerization [6]. The Lewis acids, InCl₃ [7], Bi(NO₃)₃ [8], Yb(OTf)₃ [9], CuBr₂ [10] and metal triflate [11] have recently been reported as catalysts for this reaction. A microwave-assisted method have also been used for alkylation of pyrroles [12].

As a part of our continuing effort towards the development of useful synthetic methodologies [13] with the application of Amberlyst-15, we recently observed that it can catalyze the Michael addition of pyrroles to α,β -unsaturated ketones (Scheme 1).

The reaction was initially attempted for catalytic evolution of Amberlyst-15 for conjugate addition of pyrrole with methyl vinyl ketone using equimolar ratio (entry a, Table 2). The conversion was complete within 6 min when 10% (w/w) of Amberlyst-15 was used in CH₃CN at room temperature. 2-Alkyl pyrrole, **3a** and 2,5-dialkyl pyrrole, **4a**, were obtained in a ratio of 1:3 in 91% yield (Scheme 1 and Table 2). The reaction was attempted with different solvents (Table 1) and the yield was found to be better in CH₃CN. Further increment of the amount of Amberlyst-15 did not enhance the yield of the products. No products were obtained when the reaction was conducted in absence of this catalyst. Subsequently, different other α,β -unsaturated ketones (**2b–2e**) were reacted with pyrrole at room temperature to give the corresponding 2-alkyl and 2,5-dialkyl pyrroles in various ratios and in 65–91% combined yields (Scheme 1 and Table 2).

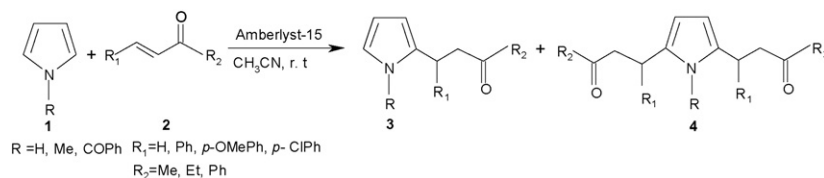
N-Methyl and *N*-benzoyl pyrroles were also applied for alkylation by the present method. *N*-Benzoyl pyrrole afforded only monoalkylated products in somewhat low yields (entry k and l, Table 2) due to low electron density on the ring carbon.

Dialkylated pyrroles were obtained exclusively by increasing the amount of the ketones. Thus, reaction of pyrroles with excess α,β -unsaturated ketones (1:3) in the presence of 10% (w/w)

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Scheme 1.

Table 1
Michael addition of pyrrole to methyl vinyl ketone with Amberlyst-15 in different solvents^a

| Entry | Solvent | Isolated yield of 3a (%) |
|-------|--------------------|---------------------------------|
| 1 | CHCl ₃ | 69 |
| 2 | EtOH | 60 |
| 3 | THF | 42 |
| 4 | DMF | 38 |
| 5 | EtOAc | 52 |
| 6 | CH ₃ CN | 91, 88, 83, 74 ^b |

^a Reaction conditions: pyrrole (1 mmol) and methyl vinyl ketone (1 mmol); solvent (5 mL); Amberlyst-15 dry (10%, w/w); r.t.; 6 min.

^b Catalyst was used over four runs.

Amberlyst-15 in CH₃CN afforded only 2,5-dialkylated pyrroles in 65–89% yield within short reaction time at room temperature (Table 3).

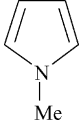
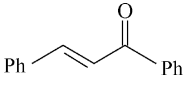
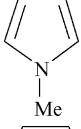
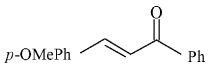
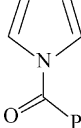
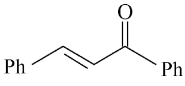
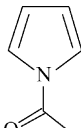
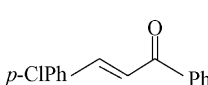
The catalyst, Amberlyst-15, is commercially available, inexpensive and non-hazardous. It works under heterogeneous conditions and can easily be handled and removed by simple filtration. The recovered catalyst was recycled consecutively three times to produce the desired products with little variation of their yields.

In summary, Amberlyst-15 has been demonstrated here as an efficient catalyst for the C-alkylation of pyrroles with α,β -unsaturated ketones. The mildness, simple experimental procedures, short reaction times, impressive yields and reusability of catalyst are the advantages of the present protocol.

Table 2
Amberlyst-15—catalyzed conjugate addition of pyrroles with α,β -unsaturated ketones (1:1) at room temperature^a

| Entry | Nucleophile | α,β -Unsaturated ketones | Time (min) | Total isolated yields (%) of 2-alkyl pyrroles (3) and 2,5-dialkyl pyrroles (4) | 3:4 |
|-------|-------------|-------------------------------------|------------|--|------------|
| a | | | 6 | 91 | 1:3 |
| b | | | 6 | 90 | 1:3 |
| c | | | 11 | 74 | 1:2 |
| d | | | 12 | 76 | 1:2 |
| e | | | 17 | 71 | 1:2 |
| f | | | 7 | 90 | 1:3 |
| g | | | 7 | 90 | 1:3 |
| h | | | 14 | 72 | 1:1 |

Table 2 (Continued)

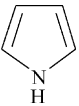
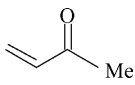
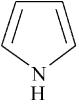
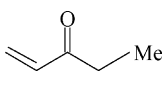
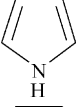
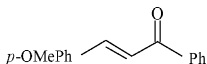
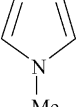
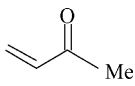
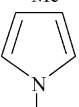
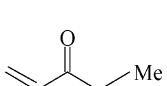
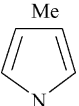
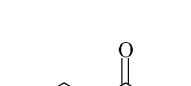
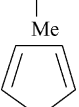

| Entry | Nucleophile | α,β -Unsaturated ketones | Time (min) | Total isolated yields (%) of 2-alkyl pyrroles (3) and 2,5-dialkyl pyrroles (4) | 3:4 | |
|-------|---|---|------------|--|-----|-----|
| i |  |  | 18 | 70 | | 1:2 |
| j |  |  | 21 | 65 | | 1:1 |
| k |  |  | 27 | 49 ^b | | – |
| l |  |  | 29 | 33 ^b | | – |

^a The structures of the products were established from their spectral (¹H NMR and MS) data.

^b Only monoalkylated product was obtained.

Table 3

Amberlyst-15—catalyzed conjugate addition of pyrroles with α,β -unsaturated ketones (1:3) at room temperature^a

| Entry | Nucleophiles | α,β -Unsaturated ketones | Time (min) | Isolated yields (%) of 2,5-dialkylated pyrroles (4) |
|-------|---|---|------------|---|
| a |  |  | 10 | 89 |
| b |  |  | 10 | 87 |
| c |  |  | 23 | 70 |
| d |  |  | 13 | 89 |
| e |  |  | 13 | 88 |
| f |  |  | 20 | 69 |
| g |  |  | 28 | 65 |

^a The structures of the products were established from their spectral (¹H NMR and MS) data.

1. Experimental

1.1. Typical experimental procedure

To a mixture of pyrrole (1 mmol) and α,β -unsaturated ketone (1 or 3 mmol) in CH_3CN (5 mL) Amberlyst-15 (10%, w/w) was added and the mixture was stirred at room temperature for the appropriate time (Tables 2 and 3). The reaction was followed by TLC. After completion of the reaction, the catalyst was separated by filtration. The solvent was evaporated from the filtrate by reduced pressure and the residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure products.

The recovered catalyst was reused for consecutive three times to form the products with a little variation of their yields.

Spectral (^1H NMR and MS) data of some representative pyrrole derivatives are given below.

1.1.1. Product 3b

^1H NMR (CDCl_3 , 200 MHz): δ 8.51 (1H, brs), 6.55 (1H, m), 5.96 (1H, m), 5.78 (1H, m), 2.82 (2H, t, $J=7.0$ Hz), 2.71 (2H, t, $J=7.0$ Hz), 2.40 (2H, q, $J=7.0$ Hz), 1.04 (3H, t, $J=7.0$ Hz); FABMS: m/z 152 [$M^\bullet + \text{H}$] $^+$.

1.1.2. Product 4b

^1H NMR (CDCl_3 , 200 MHz): δ 8.43 (1H, brs), 5.61 (2H, s), 2.78 (4H, t, $J=8.0$ Hz), 2.70 (4H, t, $J=8.0$ Hz), 2.39 (4H, q, $J=7.0$ Hz), 1.06 (6H, t, $J=7.0$ Hz); FABMS: m/z 236 [$M^\bullet + \text{H}$] $^+$.

1.1.3. Product 3g

^1H NMR (CDCl_3 , 200 MHz): δ 6.46 (1H, m), 5.94 (1H, m), 5.75 (1H, m), 3.54 (3H, s), 2.83–2.67 (4H, m), 2.48–2.39 (2H, q, $J=7.0$ Hz), 1.06 (3H, t, $J=7.0$ Hz); FABMS: m/z 166 [$M^\bullet + \text{H}$] $^+$.

1.1.4. Product 4g

^1H NMR (CDCl_3 , 200 MHz): δ 5.68 (2H, s), 3.45 (3H, s), 2.82–2.68 (8H, m), 2.45 (4H, q, $J=7.0$ Hz), 1.08 (6H, t, $J=7.0$ Hz); FABMS: m/z 238 [$M^\bullet + \text{H}$] $^+$.

Acknowledgement

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