

# Clay (Montmorillonite K10) Catalysis of the *Michael* Addition of $\alpha,\beta$ -Unsaturated Carbonyl Compounds to Indoles: The Beneficial Role of Alcohols

Jacques H. Poupaert\*, Jacques Bukuru, and Andrea Gozzo

Medicinal Chemistry, School of Pharmacy, Faculty of Medicine, UCL, B-1200 Brussels, Belgium

**Summary.** The *Michael* addition of methylvinylketone to indole can be performed under smooth conditions by running the reaction in the presence of an acidic clay catalyst (K10 Montmorillonite) and an aliphatic alcohol such as ethanol or 2-propanol. Presence of an alcohol along with a polar solvent (nitromethane) in the reaction medium considerably improves the reaction.

**Keywords.** *Michael* addition; Indole; Montmorillonite K10; Alcohol.

## Durch Montmorillonit-K10 katalysierte *Michael*-Addition von $\alpha,\beta$ -ungesättigten Carbonylverbindungen an Indole: Zur unterstützenden Wirkung von Alkoholen

**Zusammenfassung.** Die *Michael*-Addition von Methylvinylketon an Indol kann in Gegenwart eines sauren Tonkatalysators (Montmorillonit-K10) und eines aliphatischen Alkohols (Ethanol, 2-Propanol) unter schonenden Bedingungen durchgeführt werden. Die Anwesenheit eines Alkohols und eines polaren Lösungsmittels (Nitromethan) im Reaktionsgemisch verbessert die Effizienz der Reaktion beträchtlich.

## Introduction

The *Michael* addition [1] of aromatic heterocyclic compounds to  $\alpha,\beta$ -unsaturated ketones is an extremely useful reaction for medicinal chemistry applications. Among these acid-catalyzed reactions, the conjugated addition of  $\alpha,\beta$ -unsaturated ketones to the C-3 position of indoles has been found to be of considerable interest to develop melatonin analogs [2]. Along this line, in an effort to prepare a library of melatonin derivatives, we revisited different methods reported in the literature on a model reaction involving the *Michael* addition of indole and methylvinylketone (MVK). In this paper, we report a method involving the use of an acidic clay such as K10 in a polar solvent with the important feature that 2-propanol considerably promotes the reaction.

---

\* Corresponding author

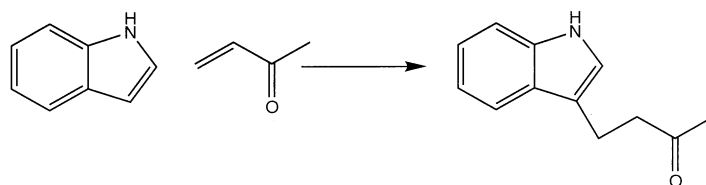


Fig. 1. *Michael* addition of methylvinylketone (MVK) to indole

The reaction of indole with *MVK* has long been known [3]. It requires long reaction times at high temperatures (typically several hours in refluxing glacial acetic acid) [4, 5]. Two major improvements have been introduced over the last decade. *Iqbal et al.* reported in 1988 that indoles react with  $\alpha,\beta$ -unsaturated carbonyl compounds in refluxing  $\text{CH}_2\text{Cl}_2$  and in the presence of Montmorillonite clay (of unspecified origin) to give *Michael* addition compounds in yields ranging from 15 to 90% depending on the nature of the carbonyl component [6]. In the case of *MVK*, the yield reported was 75%. We repeated this reaction several times with K10 Montmorillonite clay of different origins and got consistently  $\sim 45\%$  yield of analytically pure recrystallized material. We were however unable to obtain the adduct of ethyl acrylate with indole in the conditions reported by *Iqbal et al.* [6].

In another publication, *Dujardin* and *Poirier* have reported that indoles could be reacted with  $\alpha,\beta$ -unsaturated ketones under mild conditions (typically at  $-20^\circ\text{C}$  in nitroethane) in the presence of boron trifluoride etherate ( $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$ ) [7]. In the case of *MVK*, the yield which these authors reported was 86% when ethanol was added to the reaction mixture [8]. Since ethanol considerably promoted this reaction, we decided to explore the role of alcohols in the case of the use of K10 as catalyst. We also investigated the behaviour of K10 clays doped with  $\text{AlCl}_3$ ,  $\text{FeCl}_3$ , and  $\text{ZnCl}_2$ . The preparation of these catalysts has been reported previously [9, 10].

## Results and Discussion

Among the various conditions tried (cf. Table 1), the most interesting finding concerned the promotion of the reaction taking place when an alcohol was added to the reaction medium. Typically, one equivalent of each of these three components (typically 10 mmol of indole derivative,  $\alpha,\beta$ -unsaturated carbonyl compound, and aliphatic alcohol) were refluxed for 2 h in dichloromethane over a bed of commercial K10 (Aldrich). The resulting reaction mixture was filtered, evaporated *in vacuo*, and the residue was chromatographed over silicagel gel. No products resulting either from *Michael* addition in position 2 of the indole ring [7] or from *Friedel-Crafts* alkylation were detected [11] in the case of absolute ethanol and 2-propanol.

An explanation for the improvement of the reaction comes from the fact that K10 is endowed with a *Lewis* acidity as high as that of  $\text{AlCl}_3$  and can efficiently promote *e.g.* *Friedel-Crafts* reactions [9]. When K10 alone is employed, this acid catalyst can interact with the *Michael* acceptor. This point has been addressed by *Cabral et al.* [10]. Moreover, in the case studied here, we have to take into account that indole is partially protonated [12] by the clay acid sites, which is detrimental for the reaction from the kinetic point of view. Strong acid conditions are indeed

**Table 1.** *Michael* addition of *MVK* to indole

Entry	<i>t</i> /h	<i>T</i> /°C	Solvent/Catalyst	Yield/%
1	8	98	CH <sub>3</sub> COOH	52
2	8	72	CF <sub>3</sub> COOH	n.i.
3	2	rt	CH <sub>2</sub> Cl <sub>2</sub> /AlCl <sub>3</sub>	n.i.
4	2	rt	CH <sub>2</sub> Cl <sub>2</sub> /FeCl <sub>3</sub>	n.i.
5	48	rt	neat/K10	n.i.
6	2	39	CH <sub>2</sub> Cl <sub>2</sub> /K10	55
7	2	39	CH <sub>2</sub> Cl <sub>2</sub> /K10 · AlCl <sub>3</sub>	n.i.
8	2	39	CH <sub>2</sub> Cl <sub>2</sub> /K10 · FeCl <sub>3</sub>	n.i.
9	2	39	CH <sub>2</sub> Cl <sub>2</sub> /K10 · ZnCl <sub>2</sub>	n.i.
10	2	39	CH <sub>2</sub> Cl <sub>2</sub> /K10 · MeOH	69
11	2	39	CH <sub>2</sub> Cl <sub>2</sub> /K10 · EtOH	77
12	2	39	CH <sub>2</sub> Cl <sub>2</sub> /K10 · 2-PrOH	79
13	2	40	CH <sub>2</sub> Cl <sub>2</sub> /K10 · <i>t</i> -BuOH	69
14	2	40	CH <sub>3</sub> NO <sub>2</sub> /K10 · 2-PrOH	83
15	24	rt	CH <sub>2</sub> Cl <sub>2</sub> /K10 · CF <sub>3</sub> CH <sub>2</sub> OH	69

Yields (%) reported represent the recovery of pure material obtained after column chromatography; rt: room temperature; n.i.: not isolated because reaction was incomplete and/or the reaction mixture contained several components

unfavourable, since the reaction does not proceed to completion (entries 2–5 and 7–9), and secondary coloured products are often formed in large proportions.

When an alcohol is added to the reaction medium, the acidic sites of K10 will compete with the *Michael* acceptor and the added alcohol. The basicity of the alcohol added is important, since 2,2,2-trifluoroethanol did not promote the reaction (reaction not complete after 24 h at room temperature, entry 15). On the other hand, *t*-butanol gave somewhat lower yields, presumably because *Friedel-Crafts* alkylation of the indole aromatic ring took place to some extent [11].

The results presented here are reminiscent of the use of the AlCl<sub>3</sub>-DMF complex which can successfully catalyze the *Friedel-Crafts* acylation of electron rich and therefore basic aromatic heterocycles in which DMF buffers the high intrinsic acidity of AlCl<sub>3</sub> [13–17]. As already noted by *Poirier*, use of a polar solvent is also favourable since the reagent species are not charged, but charge separation develops in the transition state. Nitromethane was found suitable (boiling point) for our combinatorial chemistry applications. The improvement of the yield compared to dichloromethane was found, however, to be quite moderate (entry 14).

As a final comment, we would like to add that under the conditions described in the experimental section we were unable to obtain indole adducts from either acrylamide, acrylonitrile, or ethyl acrylate.

## Experimental

Melting points were determined using an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 457 spectrometer using KBr pellets. <sup>1</sup>H

and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AC-300 spectrometer. This layer chromatography conditions: silica gel Si60 (E. Merck, Darmstadt, Germany), ethyl acetate/acetone (60/40, v/v). High performance liquid chromatography (HPLC) was performed using a Spectra Physics solvent delivery system (P 2000) fitted with a RP-18 (10  $\mu\text{m}$ , 250 $\times$ 4.7 mm, 5 mm) column. The isocratic elution solvent was a methanol:water mixture (65:35, v/v). The solvent rate was 1.5  $\text{cm}^3/\text{min}$ . The detection wavelength was 260 nm. Under these conditions, compounds reported in Table 1 were found to be homogenous. Montmorillonite K10 was purchased from Aldrich. Different other samples of K10 were generous gifts of Dr. A. Mathy from the University of Liège (ULg), Belgium. K10 was activated at 120°C overnight before use.  $\text{CH}_2\text{Cl}_2$  and  $\text{CH}_3\text{NO}_2$  were redistilled over a bed of  $\text{P}_2\text{O}_5$ .

The yields reported in Table 1 were obtained after running the reaction on 10 mmol of indole and isolating the product by column chromatography (conditions: hexane/dichloromethane (50/50 v/v) and silica gel Si60 (particle size 0.040–0.060 mm)).

### 3-(3-Oxobutyl)-indole

To a solution of 30.0 g of indole (258 mmol) in 250  $\text{cm}^3$  of  $\text{CH}_3\text{NO}_2$ , 22  $\text{cm}^3$  of *MVK* (0.26 mol; Aldrich), 20  $\text{cm}^3$  of 2- $\text{C}_3\text{H}_7\text{OH}$  (0.26 mol, spectrophotometric grade; Acros), and 10 g of Montmorillonite K10 (Aldrich) were added. The reaction mixture was stirred at room temperature for 2 h and then heated and stirred at 40°C for another 2 h in a thermostated water bath. After cooling, the mixture was filtered, K10 was washed with 100  $\text{cm}^3$  of  $\text{CH}_2\text{Cl}_2$ , and the filtrates were evaporated *in vacuo* to give a yellow residue which was recrystallized from toluene:petroleum ether (3:1, v/v) to give 38.1 g (79%) of analytically pure material (m.p.: 94–95°C; Refs. [7, 8]; m.p.: 93–94°C). From a second crop, additional 4.0 g (8%, m.p.: 91–94°C) were recovered. The material from the first crop had IR,  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectra identical to those reported previously by Dujardin and Poirier [7].

## References

- [1] Michael A (1887) *J Prakt Chem* **35**: 349
- [2] Flaugh ME, Crowell TA, Clemens JA, Sawyer BD (1979) *J Med Chem* **22**: 63
- [3] Alder K, Schmidt C (1943) *Chem Ber* **76**: 183
- [4] Web ID, Borchardt GT (1951) *J Am Chem Soc* **73**: 752
- [5] Szmuskovicz J (1957) *J Am Chem Soc* **79**: 2819
- [6] Iqbal Z, Jackson AH, Rao KRN (1988) *Tetrahedron Lett* **29**: 2577
- [7] Dujardin G, Poirier JM (1994) *Bull Soc Chim Fr* **131**: 900
- [8] Poirier JM, Dujardin G (1987) *Heterocycles* **25**: 399
- [9] Lazlo P, Mathy A (1987) *Helv Chim Acta* **70**: 577
- [10] Cabral J, Lazlo P, Mahé L (1989) *Tetrahedron Lett* **30**: 3969
- [11] Sieskind O, Albrecht P (1993) *Tetrahedron Lett* **34**: 1197
- [12] Balon M, Carmona MC, Munoz MA, Hidalgo J (1989) *Tetrahedron* **45**: 750
- [13] Aichaioui H, Poupaert JH, Lesieur D, Hénichart JP (1991) *Tetrahedron* **47**: 6649
- [14] Aichaioui H, Poupaert JH, Lesieur D, Hénichart JP (1992) *Bull Soc Chim Belg* **101**: 1053
- [15] Yous S, Poupaert JH, Lesieur I, Depreux P, Lesieur D (1994) *J Org Chem* **59**: 1574
- [16] Poupaert JH, Kanyonyo M, Ucar H, Mouithys AM, Diouf O, Lesieur D (1996) *Bull Soc Chim Belg* **105**: 397
- [17] Ucar H, van Derpoorten K, Kanyonyo M, Isa M, Lambert D, Lesieur D, Poupaert JH (1996) *Bull Soc Chim Belg* **105**: 773

Received November 23, 1998. Accepted (revised) January 12, 1999