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Fluorapatite: efficient catalyst for the Michael addition

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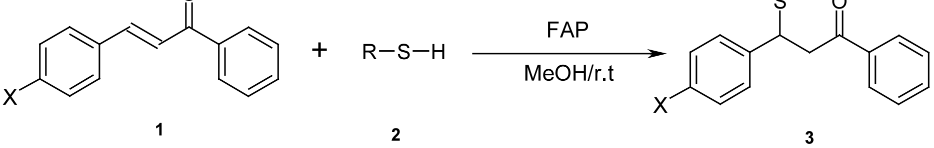
Abstract—A Michael addition assisted by fluorapatite in heterogeneous media is described. Reaction between mercaptans and chalcone derivatives was studied at room temperature in methanol as solvent. By-products of usual undesirable reactions in Michael addition such as 1,2-addition, bis-addition and polymerisation are not observed. The yields obtained are good to excellent. © 2003 Elsevier Science Ltd. All rights reserved.

Surface-mediated solid-phase reactions are of growing interest[1] because of their ease of set-up and work-up, mild reaction conditions, rate of the reaction, selectivity, high yields, lack of solvent in some cases and the low cost of the reactions as compared with their homogeneous counterparts. The development of an efficient and selective solid base catalyst for the construction of a carbon–carbon and sulfur–carbon bond continues to be a challenging exploration in organic synthesis. The versatile Michael reaction has numerous applications in synthesis of fine chemicals[2] and is classically catalysed by base[3] under homogeneous conditions. In heterogeneous phase various solid catalysts have been found useful, including natural phosphate alone and doped by potassium fluoride,[4] synthetic diphosphate $Na_2CaP_2O_7$,[5] zeolite,[6] $NiBr_2$/montmorillonite,[7] Mg–Al hydrotalcite[8] and other catalysts with more or less success.[9] In continuation of our ongoing programme to develop a heterogeneous catalysis, we describe in this paper, the use of the fluorapatite (FAP)[10] as a new solid support in Michael addition between chalcone derivatives **1** and thiols **2**, in methanolic solution at room temperature (Scheme 1).

The synthesis of FAP in powder state is carried out by reaction between diammonium phosphate, calcium nitrate and ammonium fluoride in the presence of ammonia (Scheme 2).

FAP was obtained by co-precipitation: 250 mL of a solution containing 7.92 g of diammonium hydrogen phosphate and 1 g of ammonium fluoride, maintained at pH greater than 12 by addition of ammonium hydroxide (15–20 mL), were dropped under constant stirring into 150 mL of a solution containing 23.6 g calcium nitrate ($Ca(NO_3)_2{\cdot}4H_2O$). The suspension was



Scheme 1.

Keywords: Michael addition; fluorapatite; heterogeneous catalysis; recyclable catalyst.

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refluxed for 4 h. Doubly distilled water (DDW) was used to prepare the solutions. The FAP crystallites were filtered, washed with DDW, dried overnight at 80°C and calcined in air at 700°C for 30 min before use. The final product is identified by X-ray diffraction (space group hexagonal system; $a = 9.364$ Å and $c = 6.893$ Å), infrared spectra IR and chemical analysis (Ca = 38.29%, P = 17.78% and Ca/P = 1.66). The BET specific surface area was found to be $S = 15.4$ m^2/g. The total pore volume was calculated by the BJH method at $P/P_o = 0.98$ ($V_t = 0.0576$ cm^3/g).

The use of FAP thus prepared was examined as heterogeneous catalyst in the Michael addition of three thiols **2** to enones **1** derived from acetophenone and various *p*-substituted benzaldehydes. With such combinations the 1,4-adducts were isolated, as solids, with yields ranging from 57 to 96%, depending on the electronic demand of both thiol **2** and enone **1** (Table 1).[11]

Results in Table 1 show, as expected, that the reaction time is highly dependent on the nucleophilicity of the mercaptan **2**. Moreover, the presence of electron-withdrawing groups X on the aromatic ring of the Michael acceptor **1** decreases the reaction time proportionally to the value of the Hammet constant. Meanwhile, the presence of electron-donating groups X increases the reaction time, demonstrating the participation of both the enone and the thiol in the rate controlling step of the reaction.

$$\begin{array}{c} 2NH_4F + 10Ca(NO_3)_2 + 6(NH_4)_2HPO_4 + 6NH_4OH \\ \downarrow \\ 20NH_4(NO_3) + \underset{\textbf{FAP}}{Ca_{10}(PO_4)_6F_2} + 6H_2O \end{array}$$

Scheme 2.

Table 1. Synthesis of products **3** by Michael addition using FAP

Entry	Products	X	R	Yield/% (time/min)[a]
1	**3a**	*p*-NO_2	-Ph	96 (12)
2	**3b**	*p*-NO_2	-2-NH_2Ph	93 (02)[b]
3	**3c**	*p*-NO_2	-CH_2-CO_2Et	93 (60)
4	**3d**	*p*-Cl	-Ph	94 (15)
5	**3e**	*p*-Cl	-2-NH_2Ph	95 (07)
6	**3f**	*p*-Cl	-CH_2-CO_2Et	82 (60)
7	**3g**	H	-Ph	93 (25)
8	**3h**	H	-2-NH_2Ph	91 (08)
9	**3i**	H	-CH_2-CO_2Et	72 (60)
10	**3j**	*p*-OMe	-Ph	94(105)
11	**3k**	*p*-OMe	-2-NH_2Ph	94 (10)
12	**3m**	*p*-OMe	-CH_2-CO_2Et	57 (180)

[a] Yields in pure products isolated by recrystallization with AcOEt/CH_2Cl_2 and identified by ^1H, ^{13}C NMR and IR spectroscopy.

[b] Reaction found 85% of 1,4-addition product and 15% of 1,3-addition product.

Except in one case, all the combinations lead selectively to the corresponding expected 1,4-adducts. No by-products resulting from the undesirable 1,2-addition and/or bis-addition side reactions (usually observed under classical conditions in some cases) were observed. However reaction of 2-aminothiophenol with the Michael acceptor bearing a nitro group (**1** with X = NO_2) gives an 85/15 mixture of 1,4- and 1,3-addition products (entry 2). The formation of this a priori unexpected regioisomer requires both a strong nucleophilic thiol and a strong electron-acceptor X group on the aromatic moiety of chalcone derivative.

Solid catalysts become particularly interesting when they can be regenerated. Indeed, in our case, FAP was recovered quantitatively by simple filtration and regenerated by calcination for 15 min at 700°C. The recovered catalysts was reused several times without loss of activity, even after the seventh cycle product **3g** was obtained with the same yield.

For the catalytic activity of FAP in this Michael addition we speculate that the reaction occurs at the surface rather than inside tunnels of the catalyst. The dimensions of the tunnels in our catalyst are not large enough compared to those of zeolites.[12] Thus, we estimate that probably the surface of FAP presents multicatalytic active sites. The basic sites (CaF_2 and oxygen of PO_4 group) enhance the thiol nucleophilicity and the acidic sites (Ca^{2+} and phosphorus of PO_4 group) probably increases the enone moiety polarization. Consequently, the S–C bond formation is accelerated and the final product is obtained after protonation of the resulting enolate.

In summary, a simple procedure and work-up, relatively fast reaction rates, mild reaction condition, good yields, and selectivity of the reaction make the fluorapatite an attractive and useful catalyst for the Michael addition.

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11. **General procedure**: To a flask containing an equimolar mixture (1 mmol) of thiol **2** and chalcone derivative **1** in methanol (1.5 mL), FAP (0.1 g) was added and the mixture was stirred at room temperature until completion of the reaction, as monitored by thin layer chromatography (TLC). The reaction mixture was filtered and the catalyst washed with dichloromethane. After concentration of the filtrate under reduced pressure the residue was subjected to recrystallization (AcOEt/CH_2Cl_2) leading to the Michael adduct as solid. The product structure was analysed by ^{1}H, ^{13}C NMR and IR spectrometry.
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