

Aluminum Phosphate Catalyzed Free Solvent Preparation of β -enamino Esters

Mohamed Anouar Harrad, Brahim Boualy, Larbi El Firdoussi, Mustapha Ait Ali*

Université Cadi Ayyad Faculté des Sciences Semlalia, Equipe de Chimie de Coordination et Catalyse, Département de Chimie BP 2390, 40001, Marrakech, Morocco

Abstract Aluminum phosphate (AlPO_4) efficiently catalyzed the condensation of 1,3-ketoesters with primary amines under free solvent conditions. The catalyst has been prepared and characterized by powder XRD and FT-IR studies. The AlPO_4 synthesis was performed in water at room temperature from AlCl_3 and H_3PO_4 in the presence of ammonia solution. Resultant material showed good catalytic efficiency in condensation of 1,3-ketoesters with primary amines using a domestic microwave oven with no solvent. The reaction was complete in 7 min to afford β -enamino esters in a high yield and high selectivity.

Keywords β -enamino Esters, Microwave, Solvent Free Conditions, AlPO_4

1. Introduction

β -enaminones are important intermediates in the synthesis of natural products[1] and heterocyclic compounds[2,3]. Anticonvulsive activity of several secondary enaminones has been reported[4]. A number of methods have been described for the preparation of β -enamino carbonylic compounds[5-8], such as condensation of amines with β -dicarbonylic compounds in aromatic solvents with azeotropic water removal[9] or Raney-Ni hydrogenation of isoxazoles[6]. However, these methods require high pressure and temperature[10]. The use of low boiling amines is particularly problematic. Consequently, various modified synthesis methods have been reported, in particular the addition of amide enolates[11]. Improved procedures have been reported which use protic acids such as PTSA (para-toluene sulfonic acid)[12], and Lewis acids such as $\text{BF}_3\cdot\text{OEt}_2$ [13], $\text{Mg}(\text{ClO}_4)_2$ [14], $\text{Bi}(\text{OTf})_3$ [15], $\text{Sc}(\text{OTf})_3$ [16].

As part of our work on the synthesis and reactivity of β -enaminoesters in heterogeneous media[17-19], we report here a simple and fast procedure for the synthesis of these compounds under solvent-free conditions using AlPO_4 as catalyst and a domestic microwave oven. Aluminum phosphate is of great interest in environmental, technological fields[20-27] and catalytic reactions[21-27]. It can be easily prepared by means of a sol-gel protocol[28-35]. The prepared AlPO_4 Materials have high density of Brönsted acid sites making them particularly suitable as heterogeneous catalysts for different organic synthesis reactions[34-35].

The use of microwave irradiation in the presence of catalysts or mineral-supported reagents, under solvent-free conditions[36], provides a simple chemical process with special attributes such as enhanced reaction rates, higher yields, greater selectivity and ease of manipulation[37].

2. Experimental

2.1. Instruments

NMR studies were performed on a Bruker Advance 300 spectrometer in CDCl_3 . chemical shifts are given in ppm relative to external TMS and coupling constant (J) in Hz. Infrared spectra (IR) were obtained on a Bruker-TENSOR 27 spectrometer instrument. X-ray diffraction patterns (XRD) were obtained with a Philips X'Pert MPD diffractometer using Cu K α radiation ($k = 1.54178 \text{ \AA}$). Mass spectra were recorded on a GC-MS Varian star 3400 CX. Optical rotation was measured at room temperature using an ATAGO polax-D polarimeter. Microwave irradiations were carried out in a domestic microwave oven Model AVM510/WP/WH (700 W). The products' physical and spectroscopic data were compared with those reported in the literature.

2.2. Synthesis of AlPO_4

In a 100 mL three-neck round bottom flask, $\text{AlCl}_3\cdot 6\text{H}_2\text{O}$ (7.5 mmol), and 4 mL of H_3PO_4 (37 %) are introduced dropwise with stirring at room temperature[28-35]. After 30 min, 2.3 mL of ammonia solution (24 %) was added dropwise to precipitate aluminum phosphate at a pH of 9.0. The precipitate was filtered and washed with distilled water. The resulting product was recrystallized in methanol. The white solid was filtered, washed with Methanol and dried at 120°C over night.

* Corresponding author:

aitali@uca.ma (Mustapha Ait Ali)

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2.3. Procedure of Catalytic Studies

In a typical experiment 1.7 mmol of ketoester, 1.7 mmol of amines and 0.17 mmol of AlPO_4 were used, the heterogeneous mixture was transferred to a microwave oven at 60 W for the time indicated in Table 1. At the end of the reaction, 10 mL of distilled water were added to the residue and extracted with diethyl ether (3×25 mL). The organic layer was dried over Na_2SO_4 , and the solvent was removed under vacuum. Pure β -enaminoesters was obtained by column chromatography over silica gel using hexane/ethyl acetate as eluent. All isolated pure products were fully characterized by ^1H , ^{13}C NMR and Mass spectra compared with the known compounds[17].

3. Results and Discussion

3.1. Catalyst Characterization

Structural properties of the prepared AlPO_4 were characterized using FT-IR and XRD analysis.

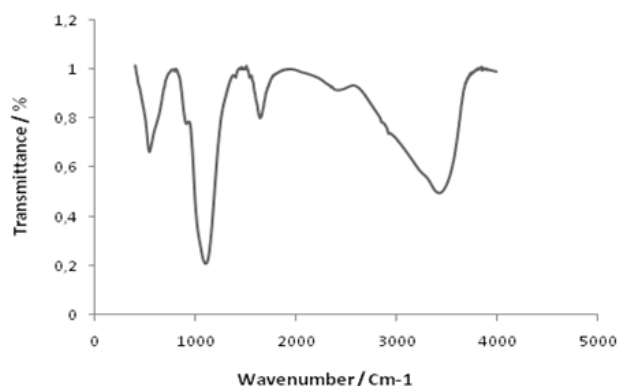


Figure 1. FT-IR spectra of prepared AlPO_4

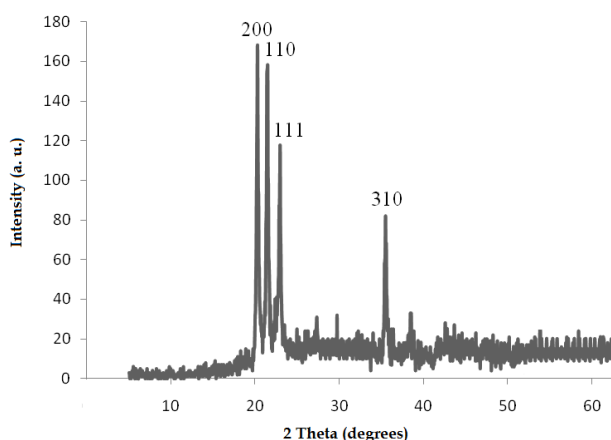


Figure 2. The XRD patterns of obtained AlPO_4

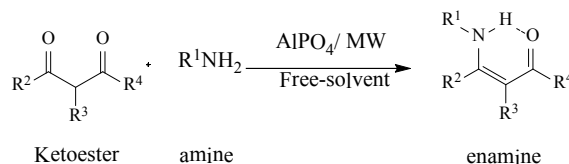
A FT-IR spectrum of prepared AlPO_4 is shown in Fig. 1. Vibrational bands are identified in relation to the crystal structure in terms of the fundamental vibrating units, namely PO_4^{3-} , H_2O [38-40]. FTIR spectra of PO_4^{3-} in AlPO_4 show the antisymmetric stretching mode (ν_3) in $1000\text{--}1200\text{ cm}^{-1}$ region and the ν_4 mode in $400\text{--}560\text{ cm}^{-1}$ region. The observed bands in $1600\text{--}1700$ and $3000\text{--}3500\text{ cm}^{-1}$ region

are attributed to the water bending and stretching vibrations, respectively[40]. These water bands confirmed that the product is in hydrate form $\text{AlPO}_4 \cdot x\text{H}_2\text{O}$.

XRD pattern of the synthesized AlPO_4 powder samples showed that all peak positions and relative peak intensities of AlPO_4 matched well with those of the standard XRD pattern. All the diffraction peaks orientated along (200), (110), (111) and (310) correspond to the well-crystalline monoclinic AlPO_4 phases (JCPDS Card No. 00-051-1674) as observed from Fig. 2.

3.2. Catalyst Activity Studies

In a typical experiment, equimolar ratio of ketoester and primary amine were mixed in the presence of a catalytic amount of AlPO_4 (10 mol%) without solvent to obtain the corresponding enaminoester in good yields (Table 1). The reaction was completed within the indicated time under microwave irradiations using a domestic microwave oven. No by-products were obtained (scheme 1).



Scheme 1. Condensation of Ketoesters with primary amines

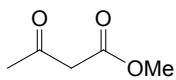
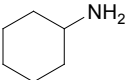
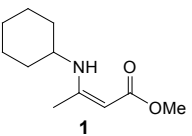
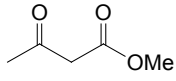

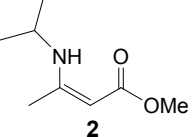
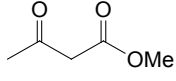
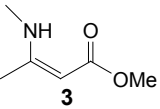
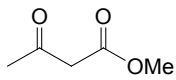
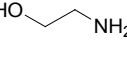
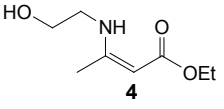
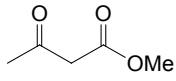
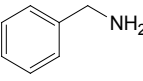
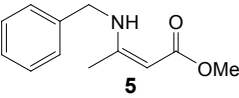
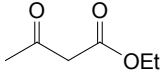
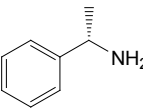
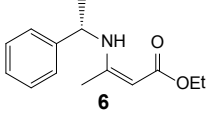
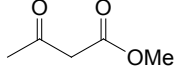
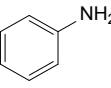
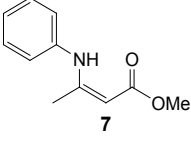
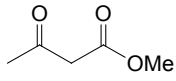
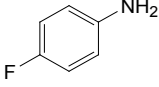
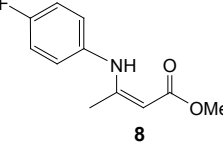
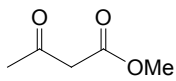
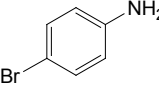
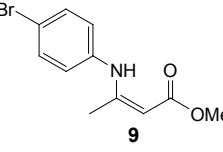
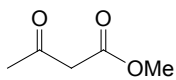
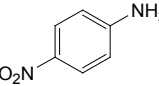
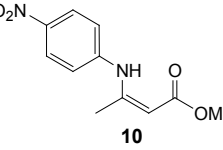
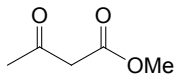
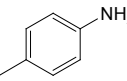
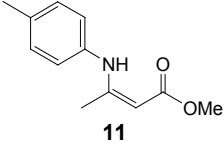
The condensation of various primary amines with ketoesters, was investigated, providing the corresponding enamino esters in good to excellent yields. Among these, aliphatic amines were more reactive and gave the corresponding β -enamino ester in excellent yields 95%–98% (Table 1, entries 1-5). This protocol efficiently condensed anilines having electron donating groups in position 4 (e.g., F, Br, Me and OMe) with ketoesters to produce the corresponding β -enamino esters in excellent yields (Table 1, entries 8–9, 11-12), whereas in the presence of electron withdrawing group (NO_2) a high decrease in the yield was observed (Table 1, entry 10). In the presence of amines possessing sterically hindering groups on the aromatic rings, the process required longer time (6 to 7 min) to obtain reasonable yield (Table 1, entries 13,15) when compared to other amines.

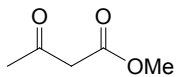
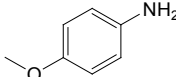
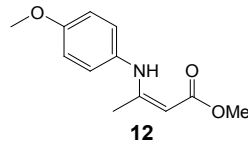
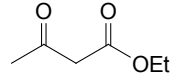
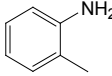
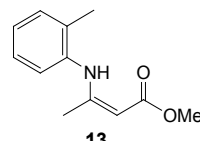
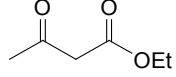
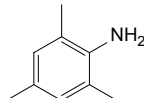
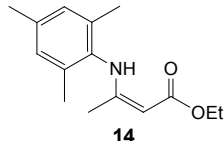
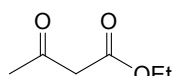
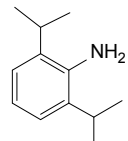
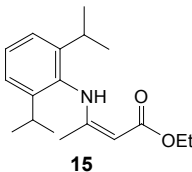
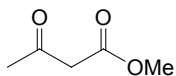
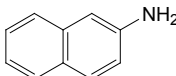
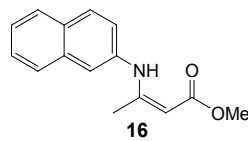
Under the same reaction conditions, the condensation of naphthylamine and ketoester affords the corresponding β -enaminoester in a moderate yield after 7 min (Entry 16).

It is noteworthy that optically active amine was converted into the corresponding β -enamino ester 6 without any racemization. The optical rotation was found to be $[\alpha]_D^{20} = -623$, $c=1.25$, in EtOH matched the literature values (entry 6)[41-42].

The reaction proceeds cleanly leading to formation of the pure product as determined by chromatography, avoiding any tedious work up. The stereoselectivity of the reaction is confirmed by ^1H NMR spectra. The signal of the $-\text{NH}-$ group appearing at a lower field ($\delta > 8.2$ ppm) indicated the formation of an intramolecular hydrogen bond, which stabilized the enamines as a (Z) configuration[17-19] (Scheme 1).

Table 1. Synthesis of β -enaminoesters using AlPO_4 assisted by MW under solvent free conditions

Entry	Ketoester	Amine	Product	Time /min	Yield %
1			 1	2	97
2			 2	2	98
3		$\text{H}_3\text{C}-\text{NH}_2$	 3	2	95
4			 4	2	97
5			 5	2	97
6			 6	2	82
7			 7	3	96
8			 8	3	79
9			 9	3	97
10			 10	7	12
11			 11	3	96

12			 12	3	94
13			 13	6	69
14			 14	7	93
15			 15	7	88
16			 16	7	63

Conditions: ketoester (1.7 mmol); amines (1.7 mmol); AlPO_4 (0.017 mmol)

4. Conclusions

Microwave irradiation in solvent-free conditions of primary amines and ketoesters using AlPO_4 as catalyst leads to the formation of β -enaminoesters compounds in good to excellent yields. The reaction employs a simple catalytic system resulting in shorter reaction time than the conventional procedure. The advantages of the novel and facile methodology are precluding volatile, clean process, economic and environmental procedure.

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