Aluminum Phosphate Catalyzed Free Solvent Preparation of β-enamino Esters

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Abstract Aluminum phosphate (AlPO4) 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 AlPO4 synthesis was performed in water at room temperature from AlCl3 and H3PO4 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, AlPO4

1. Introduction

β-enaminones are important intermediates in the synthesis of natural products[1] and heterocyclic compounds[2,3]. Anticonvulsive activity of several secondary enaminoines 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 BF3-OEt2[13], Mg(ClO4)2[14], Bi(OTf)3[15], Sc(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 AlPO4 as catalyst and a domestic microwave oven. A lum inum phosphate is of great interest in environmental, technological fields[20-27] and catalytic reactions[21-27]. The prepared AlPO4 Materials have high density of Brønsted 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 CDCl3, chemicals 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 Ka radiation (k = 1.54178 Å). 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 AVM 510/WH (700 W). The products’ physical and spectroscopic data were compared with those reported in the literature.

2.2. Synthesis of AlPO4

In a 100 mL three-neck round bottom flask, AlCl3, 6H2O (7.5 mmol), and 4 mL of H3PO4 (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.
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 AlPO₄ 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 Na₂SO₄, 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, ¹³C NMR and Mass spectra compared with the known compounds[17].

3. Results and Discussion

3.1. Catalyst Characterization

Structural properties of the prepared AlPO₄ were characterized using FT-IR and XRD analysis.

A FT-IR spectrum of prepared AlPO₄ is shown in Fig. 1. Vibrational bands are identified in relation to the crystal structure in terms of the fundamental vibrating units, namely PO₄³⁻, H₂O[38-40]. FTIR spectra of PO₄³⁻ in AlPO₄ show the antisymmetric stretching mode (ν₃) in 1000–1200 cm⁻¹ region and the ν₄ mode in 400–560 cm⁻¹ region. The observed bands in 1600–1700 and 3000–3500 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 AlPO₄·xH₂O.

XRD pattern of the synthesized AlPO₄ powder samples showed that all peak positions and relative peak intensities of AlPO₄ 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 AlPO₄ 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 AlPO₄ (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).

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 (NO₂) 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-enaminoester 6 without any racemization. The optical rotation was found to be [α]D²⁰=−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 –NH– group appearing at a lower field (δ > 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-aminoesters using APO₄ assisted by MW under solvent free conditions

| Entry | Ketoster | Amine     | Product       | Time /min | Yield % |
|-------|----------|-----------|---------------|-----------|---------|
| 1     | OMe      | NH₂       |               | 2         | 97      |
| 2     | OMe      | NH₂       |               | 2         | 98      |
| 3     | OMe      | H₃C-NH₂   |               | 2         | 95      |
| 4     | OMe      | HO-NH₂    |               | 2         | 97      |
| 5     | OMe      | NH₂       |               | 2         | 97      |
| 6     | OEt      | NH₂       |               | 2         | 82      |
| 7     | OMe      | NH₂       |               | 3         | 96      |
| 8     | OMe      | NH₂       |               | 3         | 79      |
| 9     | OMe      | NH₂       |               | 3         | 97      |
| 10    | OMe      | NH₂       |               | 7         | 12      |
| 11    | OMe      | NH₂       |               | 3         | 96      |
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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