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$AlPO_4$ as a New, Highly Efficient and Reusable Heterogeneous Catalyst for the Selective Synthesis of β-Enamino Ketones and Esters under Solvent-Free Conditions

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Abstract

The Potassium Hydrogenophosphate ($AlPO_4$) has been found to be highly efficient heterogeneous catalyst for the synthesis of β-enamino ketones and esters by the enamination of various primary amines with β-dicarbonyl compounds under solvent-free conditions. The important features of this methodology are broad substrate scope, high yield, no requirement of metal catalysts, high regio- and chemoselectivity and environmental friendliness. In addition, the catalyst could be recovered easily after the reactions and reused without evident loss of reactivity.

Keywords: β-Enaminoesters; $AlPO_4$; Catalytic enamination; β-ketoesters; Solvent-free.

Introduction

β-Enamino carbonylic compounds represent an important class of functionalized building blocks, which become increasingly important in medicinal chemistry and organic synthesis [1]. Consequently, various synthetic methods toward the preparation of β-enamino carbonylic compounds have been explored during the past years and are still desirable [2-10].

However, these methodologies suffer from some drawbacks, such as long reaction times, low yield, the use of large amounts of costly catalysts, use of volatile organic solvents, special apparatus and harsh reaction conditions, suffer from poor regioselectivity [11-15]. Therefore, the development of convenient, environmental friendliness, high yield and clean approaches is highly desirable.

Recently, heterogeneous organic reactions [16] have been recently performed with immobilized reagents on solid supports. These procedures offer several intrinsic advantages such as clean reactions, the easy separation of products, the recover and reuse of catalyst conveniently, the minimization of waste production, and eco-friendliness etc.

As a part of our great interest in developing novel synthetic routes for the formations of carbon-carbon and carbon-heteroatom bonds [17-19], we herein reported $AlPO_4$ as, efficient and reusable heterogeneous catalyst for the enamination of β-dicarbonyl compounds with amines.

Experimental

General

NMR studies were performed on a Bruker Avance 300 spectrometer in $CDCl_3$, chemicals shifts are given in ppm relative to external TMS and coupling constant (J) in Hz. Mass spectra were recorded on a GC–MS Thermofinnigan Polaris-Q mass spectrometer. All the spectroscopic data of the products were compared with those reported in the literature. Liquid chromatography was performed on silica gel (Merk 60, 220-440 mesh, eluent: hexane/ethylacetate), all the reagents and solvents used in the experiments were purchased from commercial sources as received without further purification (Aldrich, Fluka, Acros).

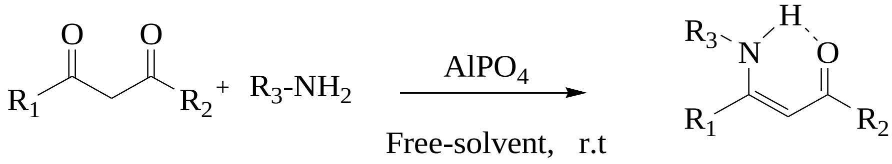
Typical reaction for synthesis of β-enaminoesters and β-enaminones

To a mixture of a dicarbonyl compound (1,7 mmol) and an amine (1,7 mmol) $AlPO_4$ (0,17 mmol) was added. The mixture was stirred at room temperature. The reaction was monitored by GC. After completion of the reaction mixture was diluted with EtOAc (5 ml) and filtered. The catalyst was recovered from the residue. The filtrate was concentrated and the gummy mass was subjected to column chromatography over silica gel using hexane–EtOAc (4:1) as eluent to obtain pure β-enaminoesters. All the spectroscopic data of the reaction products were compared with those reported in the literature.[13-19]

Results and discussion

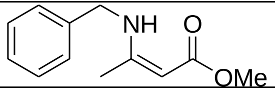
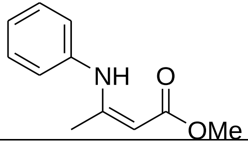
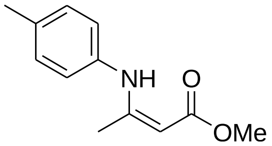
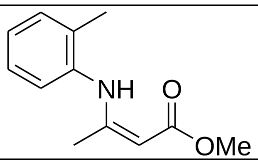
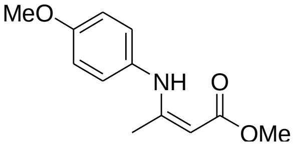
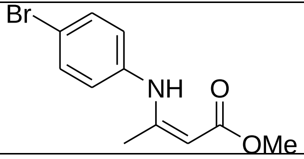
Our initial studies were focused on the optimization of the reaction conditions for the synthesis of β-enaminoesters. Methyl acetoacetate was chosen as a model substrate for the optimization process. The reaction of methyl acetoacetate with aniline in the presence of 5 mol% $AlPO_4$ at room temperature, without any solvent, afforded the target ethyl 3-(phenylamino)but-2-enoate in 90% yield (Scheme 1).

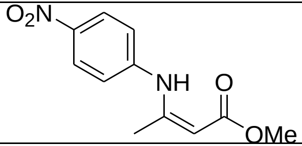
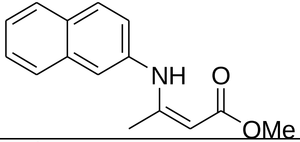
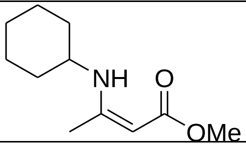
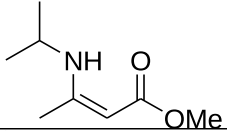
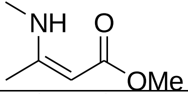
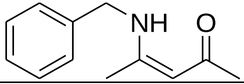
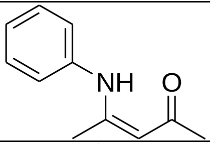
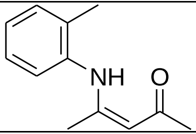
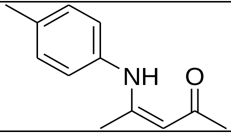
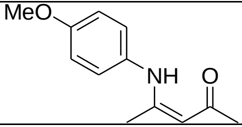
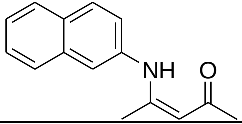
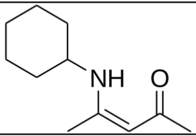
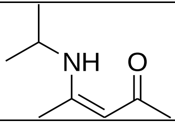
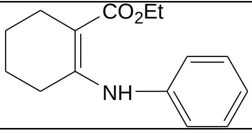
Lower catalyst loading can be used with only a marginal drop in reaction rate. With the optimized reaction condition, we next studied the reactions of a series of β-ketoesters with amines. The results presented in Table 1 indicate the generality of the method and efficacy of $AlPO_4$ as very mild catalyst. This method was successfully applied to enamination of simple linear β-ketoesters (entries 1-11, Table 1) and cyclic β-ketoesters (entries 20-23, Table 1).

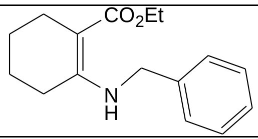
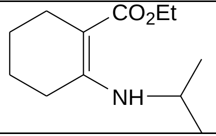
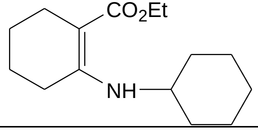


Scheme 1

Table 1. Synthesis of β-enaminoesters and β-enaminones using $AlPO_4$ as catalyst under solvent-free conditions[a].

Entry	Time(min)	Product	Conversion %[b]	Yield %[c]
1	20		100	96
2	60		95	94
3	60		92	95
4	100		90	82
5	60		87	93
6	60		100	82

7	380		35	15
8	210		60	75
9	25		100	96
10	15		100	96
11	10		90	94
12	30		100	92
13	45		98	96
14	120		90	88
15	40		100	95
16	75		100	93
17	150		73	65
18	25		98	96
19	12		100	97
20	180		88	90

21	45		100	97
22	30		100	98
23	30		100	95

[a] The structures of the products were determined from their spectroscopic (^{1}H ^{13}C NMR and MS) data.
[b] The conversion was determined by GC.
[c] Isolated yield.

The nucleophilic addition of amines to carbonyl compounds, catalyzed by $AlPO_4$, was found to be dependent on steric and electronic factors of β-ketoesters and amines.

In general, aryl amines having no substituents or electron-donating substituents on the aromatic ring were more reactive, and afforded the corresponding β-enaminoesters in better yields (entries 3, 5-6, Table 1).

An electron-withdrawing group had a strong deactivating effect, thus longer reaction time was required and the corresponding product was obtained in lower yield (entry 7, Table 1). Aniline containing strongly electron-withdrawing group, such as 4-nitroaniline afforded the corresponding β-enaminoesters in only 15% yield, which showed an obvious electronic effect. Else, a steric interference was pronounced when the group is at the ortho-position of amine, a decrease of the yield for the synthesis of corresponding β-enaminoesters was observed (entry 4, Table 1).

As shown in table 1, the condensation reaction between acetylacetonate and amines was explored in order to exrend the present method to the synthesis of β-enaminoketones. For most of the amines tested, good yields were obtained when the reaction was carried out at room temperature. However, a long reaction time was needed when an aryl-amine with an electron-withdrawing group on the benzene ring was used which is consistent with the observation for the reaction of β-keto esters.

In a similar manner, the cyclic keto ester reacted as substrate with various amines like benzylic (entry 20, Table 1), aromatic (entry 21, Table 1), and aliphatic (entry 22, 23, Table 1), to give the corresponding β-enaminoesters.

The method was found to be highly chemoselective, amine attack only at the ketone carbonyl for both diketones and β-ketoesters. The (*Z*)-selectivity in the products derived from diketones and β-ketoesters was secured by intramolecular hydrogen bonding [18-21]. In the ^{1}H NMR spectra the proton of the –NH– group appeared in the region of δ 8.5–12.5 ppm.

Table 2. Recyclability of catalyst.

Entry	Run	Yield[c] (%)
1	Fresh	96
2	First	88
3	Second	85

[c] Isolated yield, benzylamine (1,7 mmol), methyl acetoacetate (1,7 mmol).

The catalyst, $AlPO_4$ works under solvent-free heterogeneous conditions. It can easily be prepared from readily available $AlCl_3$ and H_3PO_4 [21]. An important criterion for heterogeneous catalysis is the reusability of catalyst to make the process more economical which suggests us to study the recyclability of $AlPO_4$. The series of reaction cycles were ran in order to investigate the efficiency of the catalytic system for reaction 1 in Table 1. During each cycle the catalyst was separated by simple filtration, and then used for the next reaction after washing with distilled water and ethanol. The catalyst revealed a remarkable activity and was reused up to two consecutive cycles without any significant loss in catalytic activity (Table 2).

Conclusion

In conclusion, we have developed a novel and highly efficient method for the synthesis of β-enaminones and β-enamino esters by treatment of β-dicarbonyl compounds with amines in the presence of $AlPO_4$ as a heterogeneous catalyst. The solvent-free conditions, mildness of the conversion, simple experimental procedure, clear reaction profiles, high yields and chemo- and stereoselectivities, moderate reaction times and reusability of the catalyst are the noteworthy advantages of the protocol. We feel the procedure can be utilized for large-scale eco-friendly preparation of β-enaminones and β-enaminoesters.

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References

1. Kuckländer V, in: Rappoport Z (Eds.): The Chemistry of Enamines, John Wiley & Sons, New York, Part 1 (1994) 525.
2. Mohammadizadeh M R, Hasaninejad A, Bahramzadeh M, Khanjarloo Z, *Synth. Commun*. 39 (2009) 1152.
3. Valduga C J, Squizani A, Braibante H S, Braibante M E F, *Synthesis*. (1998) 1019.
4. Gholap A R, Chakor N S, Daniel T, Lahoti R J, Srinivasan K V, *J. Mol. Catal A: Chem*. 245 (2006) 37.
5. Nagaiah K, *J. Mol. Catal. A: Chem*. 256 (2006) 234.
6. Lue P, Greenhill J V, *Adv. Heterocycl. Chem*. 67 (1996) 207.
7. Katritzky A R, Hayden A E, Kirichenko K, Pelphrey P, Ji Y, *J. Org. Chem*. 69 (2004) 5108.
8. Bartoli G, Cimarelli C, Dalpozzo R, Palmieri G, *Tetrahedron*. 51 (1995) 8613.
9. Reddy D S, Rajale T V, K.Shivakumar R, Iqbal J, *Tetrahedron Lett*. 46 (2005) 979.
10. Elaridi J, Thaqi A, Prosser A, Jackson W R, Robinson A J, *Tetrahedron: Asymmetry*. 16 (2005) 1309.
11. Khodaei M M, Khosropour R, Kookhazadeh M, *Can. J. Chem*. 83 (2005) 209.
12. Zhang Z H, Yin L, Wang Y M, *Adv. Synth. Catal*. 348 (2006) 184.
13. Biswanath D, Venkateswarlu K, Majhi A, Reddy M R, Reddy K N, Rao Y K, Ravikumar K, Sridhar B, *J .Mol. Catal A: Chem*. 246 (2006) 276.
14. Gogoi S, Bhuyan R, Barua N C*Synth. Commun*. 35 (2005) 2811.
15. Zhao Y, Zhao J, Zhou Y, Lei Z, Li L, Zhang H, *New. J. Chem*. 29 (2005) 769.
16. Blass B E, *Tetrahedron*, 58 (2002) 9301.
17. Harrad M A, Outtouch R, Ait Ali M, El Firdoussi L, Karim A, Roucoux A, *Catalysis. Commun*. 11 (2010) 442.
18. Harrad M A, Boualy B, Ait Ali M, El Firdoussi L, Corrado R, *Acta. Cryst*. E67 (2011) o1269.
19. Harrad M A, Boualy B, Oudehmane A, Avignant D, *Acta. Cryst*. E67 (2011) o1818.
20. Harrad M A, Boualy B, Ait Ali M, El Firdoussi L, *Am. J. Chem*. 2 (2012) 271.
21. Tse J S, Klug D D, *Science*. 255 (1992) 1559.