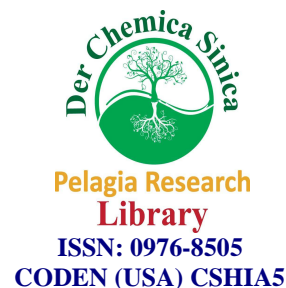




Pelagia Research Library

Der Chemica Sinica, 2011, 2 (2): 144-148



Synthesis of β -enaminoester using new phosphonium ionic liquids

Anil U. Chopade

Department of Chemistry, Dahiwadi College Dahiwadi, Tal. Man Dist. Satara(Maharashtra), INDIA

ABSTRACT

The development of an environmentally benign green methodology for the synthesis of β -enaminoester using new phosphonium ionic liquids as catalyst. Ethyl acetoacetate, ammonium acetate and catalytic amount of ionic liquid in acetonitrile was carried out at 25°C and 50°C to yield β -enaminoester.

Keywords:- Phosphonium ionic liquids; ethyl acetoacetate; β -enaminoester.

INTRODUCTION

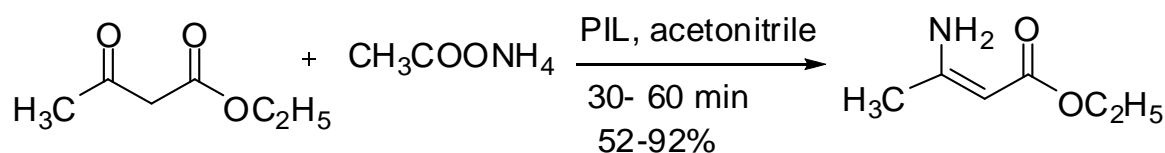
β -Enaminoester are versatile synthetic intermediates, extensively employed in organic synthesis[1]. They have attracted much attention due to the fact that they are important synthons for the synthesis of many biologically active compounds such as dopamine[2], acetylcholinesterase inhibitors [3] and anticonvulsants[4]. They are also useful intermediates for the synthesis of several aminoacids[5], aminols[6], peptides and alkaloids[7]. In particular, such compounds are important precursors for the synthesis of a wide variety of heterocycles[8]. Also they have been employed as synthons of pharmaceutical compounds having anti-epileptic[9], anti-molluscicidal and larvicidal activities[10]. The most well known and explored route to β -enaminones involves the direct condensation of β -dicarbonyl compounds with amines in refluxing aromatic hydrocarbons with azeotropic removal of water[11]. The most convenient method to synthesis of β -enaminones in the presence of NaAuCl₄[12], Bi(TFA)₃[13], ionic liquid[14], Yb(OTf)₃[15], CAN[16]. Thus it is very important to search for a convenient and efficient method for the synthesis of this type of compounds.

Due to their wide range of activity and importance, a simple and high yielding one-pot approach for the synthesis of β -enaminones is highly desirable. A simple, efficient and environment friendly, one-pot synthesis of β -enaminones by direct reaction of ammonium acetate as source of

amine with ethyl acetoacetate was undertaken using catalytic amount of some phosphonium ionic liquids.

Recently, phosphonium ionic liquids (PILs), which differ from the well known imidazolium ILs, have been introduced in organic reactions. Phosphonium ionic liquids are much more thermally stable than the corresponding ammonium salts and even have an edge on imidazolium salts. This is very important for processes which operate at temperatures greater than 100 °C. In addition to being less thermally stable, the imidazolium cation contains protons which are not entirely inert. PILs, on the other hand, have no such acidic protons and are easily recoverable by using three phase system (Hexane/Ionic liquid/Water).

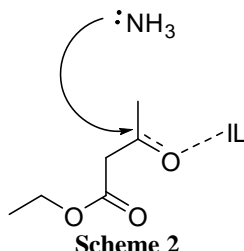
In the current strategy the reaction of ethyl acetoacetate 1.0 equivalent, 1.6 equivalent of ammonium acetate and 20% w/w of ionic liquid in acetonitrile was carried out at 25°C and 50°C to yield β -enaminoester (**Scheme 1**).



Scheme 1: Synthesis of 3-amino-but-2-enoic acid ethyl ester

RESULTS AND DISCUSSION

The reaction was studied in the presence of six different ionic liquids (**Fig 1**) as catalysts at 25°C and 50°C. Ammonium acetate was used as source of ammonia.



It was observed that the nature of the anion governs the electrophilicity of the phosphonium cation, which in turn influences the acidity of the phosphorus. This phosphorus is capable of partial bonding with acetyl oxygen generating the cationic center as shown in **scheme 2** which is easily attacked by the nucleophilic amines.

Various ionic liquids were screened in the reaction of ethyl acetoacetate and ammonium acetate at 25°C and 50°C (**Table 1**) for β -enaminoester formation reaction. The efficacy of the ILs to promote this reaction was correlated to the basicity of the anions. It was assumed that the nature of the anion would govern the electrophilicity of the phosphonium cation, which in turn has a bearing on the acidity of the PILs. It was observed that with increasing basicity of the anion, there was a progressive increase in yield (**Table 1**, entry 2, 5). The yield of desired product was

increased progressively with increasing acidity of the PILs.

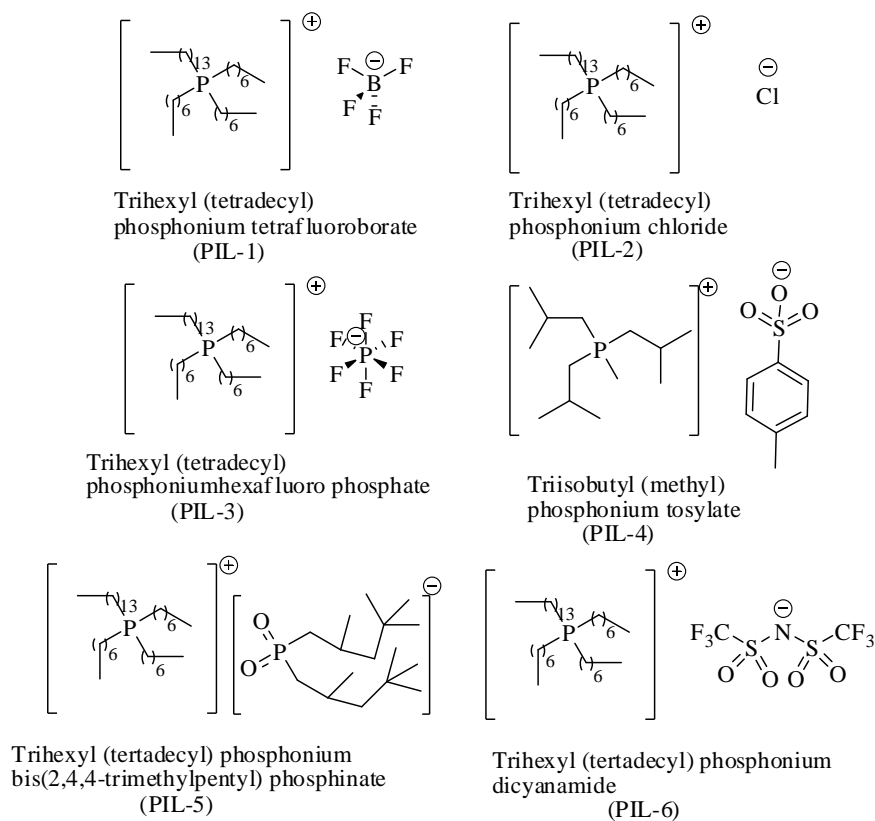


Fig. 1 Structures of various phosphonium ionic liquids

Table 1: Synthesis of β -enaminoester

Sr. No.	Ionic Liquid	Temperature (25 °C)		Temperature (50 °C)	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1	PIL-1	60	69	45	65
2	PIL-2	30	89	30	92
3	PIL-3	40	56	40	59
4	PIL-4	55	48	35	52
5	PIL-5	35	73	35	79
6	PIL-6	60	64	40	62

^aIsolated yield after column chromatography

Thus among the PILs tested in β -enaminoester formation reaction, it was found that the PIL-2 (chloride) efficiently promoted this reaction by virtue of its inherent acidity. This makes the PIL capable of bonding with the carbonyl oxygen increasing the reactivities of the parent carbonyl compounds without any added acid catalyst.

All the PILs catalyzed the reaction providing the desired products. The catalytic activities of the ionic-liquid in product formation varied slightly with different anions in the PIL catalysts. For example, in PILs from chloride anion (PIL-2) improved activity as well as higher yield (Table 1, entry 2) of the desired product was observed. In phosphinate gating higher yield comparatively borate, phosphate, tosylate, and dicyanamide in both condition. In overall, chloride gave the best outcome in terms of the yield. A rate enhancement with higher yield was observed when temperature was increased.

The recyclability and reusability of PIL were examined for the enamino reactions. It was found that PIL could be easily recycled by triphasic separation method. The PILs were recycled and reused at least four times with a slightly decreased activity. The scope and generality of this method could be validated by observing that catalytic property was well tolerated giving excellent isolated yields of the β -enaminoester. Moreover, the various ionic liquids such as chloride, borate, dicyanamide and triflate were used for the reaction resulting in the formation of β -enaminoester in excellent isolated yields.

CONCLUSION

We disclose here a simple, clean, atom-efficient, environment friendly synthesis of β -enaminoester using ionic liquids as catalysts. A simple experimental procedure, relatively fast reaction rates and excellent yields are the key advantages of our protocol. Most significantly, efficiency, cost-effectiveness and green methodology will make this procedure useful to academia as well as industry.

Acknowledgements

Dr. D.D. Sawaikar, NCL, Pune thanks for useful discussions. Dr. Al Robertson of CYTEC, Canada and Dr. A. Ramani thanks for gift of ionic liquids.

REFERENCES

- [1] The Chemistry of Enamines; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1994, Part 1.
- [2] B. W. Caprathe, J. C. Jaen, L. D. Wise, T. G. Heffner, T. A. Pudsley, L. T. Melther M. Parvez, *J. Med. Chem.* **1991**, 34, 3726.
- [3] F. Gatta, M. R. Del Giudice, M. Pomponi, M. Marta, *Heterocycles* **1992**, 34, 991.
- [4] D. E. Natalie, S. C. Donna, M. Khurana, N. S. Noha, P. S. James, J. H. Sylvia, N. Abraham, S. T. Robert, A. M. Jacqueline, *Eur. J. Med. Chem.* **2003**, 38, 49.
- [5] G. Palmieri, C. Cimorelli, *J. Org. Chem.* **1996**, 61, 5557.
- [6] (a) G. Bartoli, C. Cimorelli, E. Marcantoni, G. Palmieri, M. Peetrini, *J. Org. Chem.* **1994**, 59, 5328; (b) C. Cimorelli, S. Giuli, G. Palmieri, *Eur. J. Org. Chem.* **2006**, 1017.
- [7] (a) L. G. Beholz, P. Benovsky, D. L. Ward, N. S. Bata, J. R. Stille, *J. Org. Chem.* **1997**, 62, 1033. (b) J. D. White, D. C. Ihle, *Org. Lett.* **2006**, 8, 1081.
- [8] (a) C. Alan, A. C. Spivey, R. Srikanan, C. M. Diaper, J. David, D. Turner, *Org. Biomol. Chem.* **2003**, 1638; (b) H. M. Hassneen, T. A. Abdallah, *Molecules* **2003**, 8, 333; (c) J. P. Michael, C. B. Koning, D. Gravestock, G. D. Hosken, A. S. Howard, C. M. Jungmann, R. W. M.

- Krause, A. S. Parsons, S. C. Pelly, T. V. Stanbury, *Pure Appl. Chem.* **1999**, 71, 979.
- [9] I. O. Edafiogho, K. V. Ananthalakshmi, S. B. Kombian, *Bioorg. Med. Chem.* **2006**, 14, 5266.
- [10] M. Abass, B. B. Mostafa, *Bioorg. Med. Chem.* **2005**, 13, 6133.
- [11] D. F. Martin, G. A. Janusonis, B. B. Martin, *J. Am. Chem. Soc.* **1961**, 83, 73-75.
- [12] A. Arcadi, G. Bianchi, S. Di Giuseppe, F. Marinelli, *Green Chem.* **2003**, 64-67.
- [13] A. R. Khosropour, M. M. Khodaei, M. Kookhazadeh, *Tetrahedron Lett.* **2004**, 45, 1725-1728.
- [14] A. R. Gholap, N. S. Chakor, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *J. Mol. Cat :A.* **2006**, 245, 37-46.
- [15] F. Epifano, S. Genovese, M. Curini, *Tetrahedron Lett.* **2007**, 48, 2717-2720.
- [16] V. Sridharan, C. Avendano, J. C. Menendez, *Synlett* **2007**, 6, 0881-0884; A. S. Karpov, T. J. J. Muller, *Synthesis* **2003**, 18, 2815-2826.
- [17] **Typical procedure of 3-amino-but-2-enoic acid ethyl ester synthesis:** A mixture containing ethyl acetoacetate (300 mg, 2.30 mmol), ammonium acetate (210 mg, 2.76 mmol) and ionic liquid (60 mg, 20 % w/w) in acetonitrile was stirred at 25 and 50 °C for 30-60 min. depending upon the ionic liquid used (Table 1). The completion of reaction was followed by TLC using 10% EtOAc in petroleum ether as eluent. After completion of reaction, the product was extracted with *n*-hexane (2 × 10 ml) and the hexane layer was carefully separated leaving behind the ionic liquid and aqueous layer. The separated hexane layer was then, dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to afford the crude product. The crude product was purified by column chromatography to give 3-amino-but-2-enoic acid ethyl ester as yellow oil. The ionic liquid layer separated and reused for the next run without noticeable effect on the product yield.