Ionic Liquid Promoted Synthesis of β-Enamino Ketones at Room Temperature

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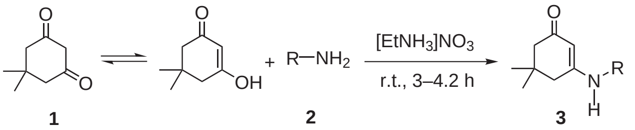
Abstract: β-Enamino ketones have been synthesised in excellent yield at room temperature in the absence of any added catalyst by the reaction of aromatic or aliphatic amines with 1,3-dicarbonyl compounds in ionic liquid. The ionic liquid is recycled and reused several times.

Key words: amination, ionic liquid, 1,3-dicarbonyl compounds, β-enaminone

β-Enaminones are useful intermediates in organic synthesis as synthons for the construction of biologically active compounds such as dopamine auto-receptor agonists,[1] acetylcholinestersase inhibitors,[2] oxytocin antagonists[3] and anticonvulsants.[4] Recently, the enamino ketone moiety has attracted much attention because of its use as an intermediate for the preparation of part of the side chain of taxol.[5]

Several methods for the preparation of β-enamino ketones have been reported. The common method used for the preparation of β-enamino ketones is the reaction between β-dicarbonylic compounds and amines in the presence of benzene by azeotropic removal of water. However, several problems are associated with the use of low boiling amines as starting materials.[6] It is necessary either to pass a rapid stream of gaseous amine through the refluxing diketone solution, or to operate a reaction in an autoclave at 130–150 °C. Moreover, the former procedure requires an excess amount of amine. For the latter the reaction cannot be easily monitored and the yields are not quantitative. Some successful modifications have been reported for these methods such as the use of ammonium or alkylammonium acetate, Lewis acids like boron trifluoride etherate, alumina (neutral) or Montmorillonite K-10 as a solid catalyst in benzene or as solid supports.[7] Other synthetic methods reported for β-enamino ketones are addition of an amine to β-halovinyl ketones, hydrogenation of isoxazoles,[8] palladium-catalyzed amination of electron-deficient olefins[9] and palladium-induced dehydrogenation of a β-amine ketone.[10] Recently, some improved methods have been also reported for the synthesis of β-enamino ketones.[11] Most of these reported methods suffer from several drawbacks like prolonged reaction period, low yields, harsh reaction conditions and expensive catalyst. Consequently, there is scope for further innovation towards milder reaction conditions, absence of catalyst, shorter reaction times and better yields. This could be achieved through the use of green ionic liquid solvents.



Scheme 1

In recent times, the use of room temperature ionic liquids (ILs) as green solvents in organic synthetic process has gained considerable importance due to its negligible vapour pressure, solvating ability and easy recyclibility.[12] Several reactions have been reported recently using ionic liquids as reaction media[13] and as rate enchancers.[14]

Herein, we wish to report an efficient method for the synthesis of β-enamino ketones **3** from 1,3-dicarbonyl compounds **1** and amine **2** in ionic liquid ethylammonium nitrate [EtNH$_3$]NO$_3$ at room temperature in the absence of any additional catalyst (Scheme 1). Excellent yields were obtained and the ionic liquid can be recycled and reused several times. The ionic liquid [EtNH$_3$]NO$_3$ was prepared as described in the literature.[15]

In a typical condensation reaction, the dimedone **1a** and aniline **2a** in ionic liquid [EtNH$_3$]NO$_3$ was stirred at room temperature. The progress of reaction was monitored by TLC. After completion of reaction, aqueous work up afforded β-enamino ketone **3a** in 88% yield. To evaluate the synthetic utility of the procedure, various amines including aromatic and aliphatic ones were chosen to be condensed with different 1,3-dicarbonyl compounds. The results are shown in Table 1.

The reaction proceeds very cleanly at room temperature and no undesirable side reactions are observed. This protocol offers advantages in terms of its simple procedure and work up, mild reaction conditions and excellent yields. The protocol neither required any additional catalyst nor azeotropic conditions and proceeded without the formation of any by-products except water. From Table 1

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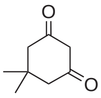
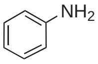
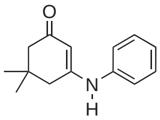
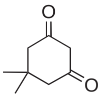
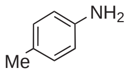
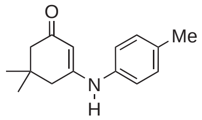
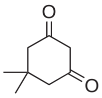
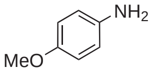
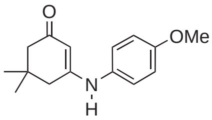
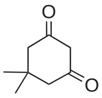
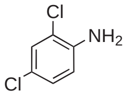
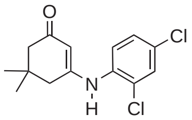
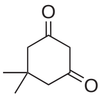
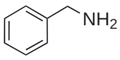
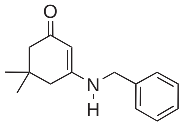
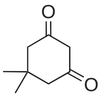
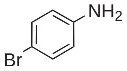
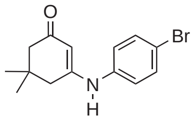
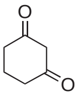
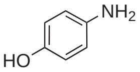
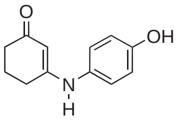
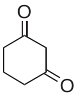
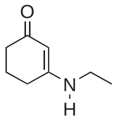
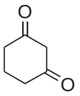
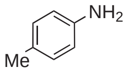
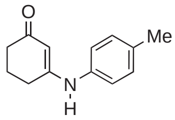
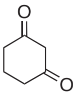
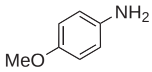
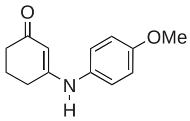
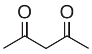
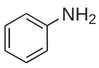
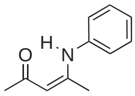
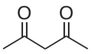
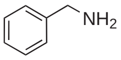
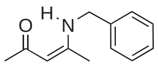
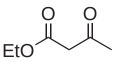
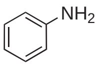
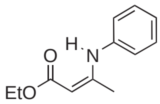
Table 1 Synthesis of β-Enamino Ketones (**3a**–**m**)[16]

Entry	1,3-Diketones **1**	Amines **2**	Products (**3a**–**m**)	Time (h)	Yield (%)[a]
a				3	88
b				3.5	90
c				3.6	87
d				4	82
e				3.8	85
f				4	84
g				4.2	82
h				3.7	80
i				3.4	85
j				3.6	87
k				3.8	83
l				4	85
m				4.1	82

[a] Isolated yield.

Table 2 Recycle Use of Ionic Liquid in β-Enamino Ketone Synthesis

Entry	1,3-Diketone	Amine	Product	Time (h)	Yield (%)		
					Recycle 1	Recycle 2	Recycle 3
1	**1a**	**2a**	**3a**	3	88	84	84
2	**1i**	**2i**	**3i**	3.4	85	82	82
3	**1j**	**2j**	**3j**	3.6	87	85	85

it is evident that both aliphatic as well as substituted aromatic amines participate well in the reaction. The protocol is also applicable for the synthesis of β-enamino ester (entry m).

Similarly, the reaction of dimedone **1a** with aniline **2a** was also carried out using 1,3-dibutyl imidazolium bromide [bbim]Br ionic liquid for comparison. The resulting β-enamino ketone **3a** forms with same yield. The ionic liquid used in β-enamino ketones synthesis was recovered and reused with identical results. Thus, the recyclibility was conformed as listed in Table 2.

In summary, we have demonstrated an efficient and mild protocol for the condensation of 1,3-dicarbonyl compounds and different amines (aliphatic and aromatic) to β-enamino ketones at room temperature in ionic liquid without adding any catalyst. The procedure is simple and can be used as an alternative to the existing producers.

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(16) **General Experimental Procedure for the Synthesis of β-Enamino Ketones:**
A mixture of 1,3-diketones **1** (2 mmol) and amine **2** (2 mmol) in ionic liquid [$EtNH_3$]NO_3 (4 mmol) was stirred at r.t. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with EtOAc and extracted with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The products obtained were purified using column chromatography on SiO_2 and identified by comparing with authentic samples by TLC, ^{1}H NMR and IR spectra.