

Enamination of β -Dicarbonyl Compounds Catalyzed by $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ at Ambient Conditions: Ionic Liquid and Solvent-Free Media

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Received 10 March 2004

Abstract: Enamination of a wide various primary amines was successfully carried out in the presence of catalytic amounts of cerium chloride heptahydrate in ionic liquid and solvent-free conditions as 'green' media under mild reaction conditions.

Keywords: ionic liquid, solvent-free, TBAB, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, chemoselectivity, primary amine, catalyst

The β -enaminone compounds are useful precursors for the synthesis of a variety of heterocycle compounds.¹ They have been used in pharmaceutical,² and as building blocks for the synthesis of aminoacids,³ peptides⁴ or alkaloids.⁵ In addition, chiral enaminones obtained from optically active compounds are useful ligands for diastereoselective synthesis.⁶ A number of methods have been reported for the preparation of β -enaminone compounds. Among them, condensation of β -dicarbonyls with amines is one of the most versatile synthetic approaches for their synthesis.⁷ Several procedures including clay K-10/ultra-sound,⁸ NaAuCl_4 ⁹ or $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ ¹⁰ were applied to improve the yields of the products. However, the application of these methods may suffer from one or more disadvantages such as the use of expensive or less easily available reagents, vigorous reaction conditions, long reaction times, unsatisfactory yields, low selectivity or the use of toxic solvents. Therefore, due to the importance of these compounds as intermediates in organic synthesis, the development of facile and 'green' synthetic methods to the β -enaminones under mild conditions is still demanded.

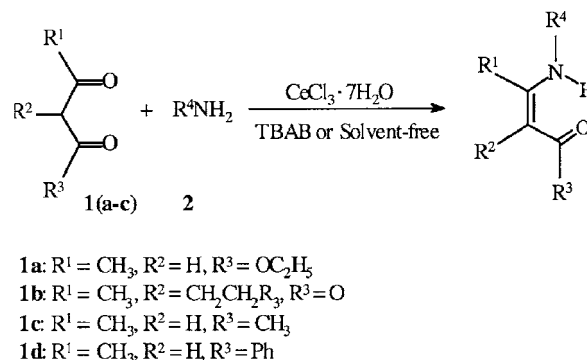
As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of fine chemicals, we interested to investigate another remarkable catalytic enamination reaction.¹¹

Cerium chloride heptahydrate has emerged as a potentially useful Lewis acid imparting high regio- and chemoselectivity in various chemical transformations. It is also a cheap, nontoxic and water-tolerant catalyst.¹²

Recently, molten tetrabutylammonium bromide (TBAB) extensively was used as a low toxic and cost ionic liquid in a number of useful synthetic transformations.¹³

Herein, we would like to report the use of cerium chloride heptahydrate in solvent-free conditions or immobilized on

molten tetrabutylammonium bromide as recyclable catalytic systems for the synthesis of Z- β -enaminones under mild reaction conditions (Scheme 1).



Scheme 1

We began our study by comparing the catalytic activity of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and other metallic derivatives or montmorillonite-K10 towards the reaction between **1d** and *p*-toluidine under two conditions (Table 1). Among all the catalysts tested, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ proved to be the most efficient since the reaction could be carried out in excellent yield (Table 1, entry 9).

Table 1 Screening of Various Catalysts for Enamination of Benzoylacetone and *p*-Toluidine

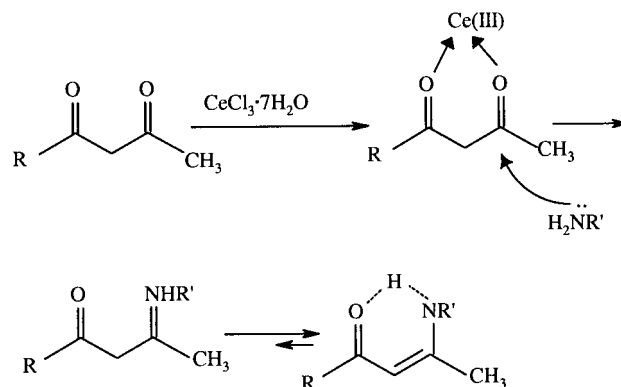
Entry	Catalyst (25 mol%)	Yield (%) ^a	
		Method A ^b	Method B ^c
1	None	10	55
2	AlCl_3	52	65
3	ZnCl_2	70	80
4	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	70	90
5	BiCl_3	85	82
6	TiCl_4	83	84
7	$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	80	80
8	Montmorillonite-K 10	74	80
9	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	88	95

^a After 260 min at r.t.

^b Method A: solvent-free conditions.¹⁴

^c Method B: ionic liquid media.¹⁵

The results presented in Table 2 indicate the scope and generality of the both methods, which are efficient not only for aliphatic as well as aromatic primary amines, but also for β -dicarbonyl compounds. The experimental procedures for these reactions are remarkably simple and require no inert atmospheres. Interestingly, when $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ was added to the molten TBAB, the mixture was not solidified at room temperature. In all cases, the reactions proceeded rapidly and smoothly at room temperature and in comparison to the other methods, the products were obtained in excellent yields and chemoselectivity to afford *Z*- β -enaminones, confirmed by ^1H NMR spectrum of the crude products ($\delta = 7.50\text{--}12.80$ ppm for NH). Probably, the reaction proceeds through the activation of carbonyl group of acetyl part by complexation with cerium(III) ion followed by nucleophilic addition of amines to the carbonyl group and subsequent the enaminone formation due to stable intramolecular hydrogen bonding (Scheme 2).

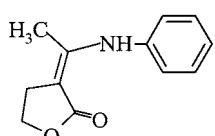
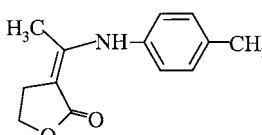
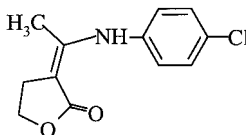
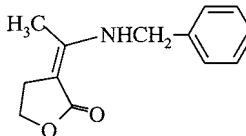
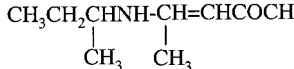
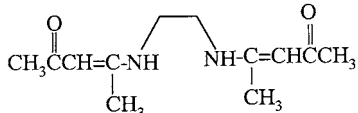
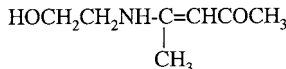
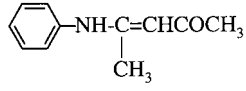
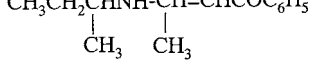
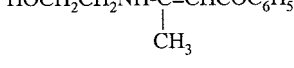
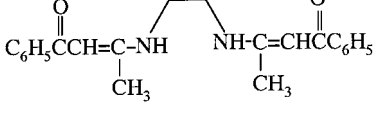
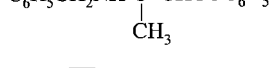
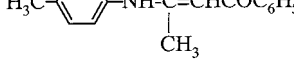


Scheme 2

Table 2 Enamination Reaction in the Presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ under Solvent-Free Conditions (Method A) or in TBAB (Method B)

Entry		R^{d}	Product ^a		Yields (%) ^b /Time (min)
1	1a	$\text{CH}_3(\text{CH}_2)_2\text{CH}_2$	$\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCO}_2\text{C}_2\text{H}_5$	A B	72/20 98/5
2	1a	$\text{H}_2\text{NCH}_2\text{CH}_2$	$\text{C}_2\text{H}_5\text{OCCH}(\text{CH}_3)=\text{CNHCH}_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCO}_2\text{C}_2\text{H}_5$	A B	76/15 96/5
3	1a	HOCH_2CH_2	$\text{HOCH}_2\text{CH}_2\text{NH-C}(\text{CH}_3)=\text{CHCO}_2\text{C}_2\text{H}_5$	A B	66/20 93/10
4	1a	$\text{C}_6\text{H}_4\text{CH}_2$	$\text{PhCH}_2\text{NH-C}(\text{CH}_3)=\text{CHCO}_2\text{C}_2\text{H}_5$	A B	87/20 99/immediately
5	1a	C_6H_5	$\text{C}_6\text{H}_5\text{NH-C}(\text{CH}_3)=\text{CHCO}_2\text{C}_2\text{H}_5$	A B	65/30 80/7
6	1a	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4$	$\text{H}_3\text{C-C}_6\text{H}_4\text{NH-C}(\text{CH}_3)=\text{CHCO}_2\text{C}_2\text{H}_5$	A B	75/20 90/5
7	1a	α -Naphthyl	$\text{CH}(\text{NHC}(\text{CH}_3)=\text{CHCO}_2\text{C}_2\text{H}_5)\text{-}\alpha\text{-Naphthyl}$	A B	50/30 80/5
8	1b	HOCH_2CH_2	$\text{H}_3\text{C-C}(\text{NHCH}_2\text{CH}_2\text{OH})=\text{CH-CO}_2\text{C}_2\text{H}_5$	A B	75/30 92/5
9	1b	$\text{CH}_3(\text{CH}_2)_2\text{CH}_2$	$\text{H}_3\text{C-C}(\text{NHCH}_2(\text{CH}_2)_2\text{CH}_3)=\text{CH-CO}_2\text{C}_2\text{H}_5$	A B	76/90 88/45

Table 2 Enamination Reaction in the Presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ under Solvent-Free Conditions (Method A) or in TBAB (Method B) (continued)

Entry		R^4	Product ^a		Yields (%) ^b /Time (min)
10	1b	C_6H_5		A B	70/45 86/10
11	1b	$p\text{-CH}_3\text{C}_6\text{H}_4$		A B	69/25 90/5
12	1b	$p\text{-ClCH}_2\text{C}_6\text{H}_4$		A B	80/20 98/5
13	1b	$\text{C}_6\text{H}_4\text{CH}_2$		A B	74/35 95/5
14	1c	$\text{CH}_3\text{CH}_2\text{CHCH}_3$		A B	82/35 96/5
15	1c	$\text{H}_2\text{NCH}_2\text{CH}_2$		A B	74/40 90/10
16	1c	HOCH_2CH_2		A B	80/50 93/10
17	1c	C_6H_5		A B	76/35 85/10
18	1d	$\text{CH}_3\text{CH}_2\text{CHCH}_3$		A B	60/50 83/5
19	1d	HOCH_2CH_2		A B	62/65 74/45
20	1d	$\text{H}_2\text{NCH}_2\text{CH}_2$		A B	58/60 82/10
21	1d	$\text{C}_6\text{H}_5\text{CH}_2$		A B	78/20 93/10
22	1d	$p\text{-CH}_3\text{C}_6\text{H}_5$		A B	80/25 95/5

^a The products were characterized by ^1H NMR, ^{13}C NMR, IR and comparison with reported data.^b Isolated yields.

In this procedure, aliphatic amines react efficiently to produce the corresponding enaminones. In the case of 1,2-ethandiamine reactions, two equivalents of β -dicarbonyls were used and the products got two enaminone groups (Table 2, entries 2, 15 and 20). It has also been observed that both weakly activated and deactivated anilines are transformed to enaminones in good to high yields. This method was successfully applied to enamination of linear β -ketoesters (Table 2, entries 1–7), cyclic β -ketoesters (Table 2, entries 8–13) and β -diketones (Table 2, entries 14–22).

It is pertinent to note that the β -enaminone formations in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ immobilized on TBAB gave consistently excellent yields in very short reaction times. However, the yields obtained by $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ under solvent-free conditions were good to high and the reaction times were longer. Also, in both conditions, regiochemistry observed from these β -dicarbonyls, limited to preferential amines attack at the acetyl position and no by-product was observed (Table 2, entries 3 and 8).

Another advantage of the method for this transformation is recyclability of the catalyst. Since $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ /TBAB or $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ under solvent-free conditions were weakly soluble in CH_2Cl_2 , thus they can be separated by washing with CH_2Cl_2 and dried at 80°C under reduced pressure and reused in three runs without any loss of activity.

In summary, the present procedure demonstrates a novel method for the enamination of aromatic and aliphatic amines with β -dicarbonyl compounds by catalytic amounts of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in TBAB as an ionic liquid or under solvent-free conditions. The notable features of this procedure are mild reaction conditions, clear reaction profiles, improved yields, enhanced rates and simplicity in operation, which make it a useful and attractive process for the synthesis of enaminones. Moreover, reusability, stability and non-toxicity of the catalyst and ionic liquid are the other noteworthy advantages of this method.

Acknowledgment

We are thankful to the Razi University Research Council for partial support of this work.

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- (14) **Typical Experimental Procedure (Method A):** To a mixture of ethyl acetoacetate (1.0 mmol) and aniline (1.0 mmol) under solvent-free conditions, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.1 mmol) was added and the reaction mixture stirred at r.t. for the appropriate time according to Table 2. After completion of the reaction as indicated by TLC, the mixture was washed with EtOAc. The crude products were separated by preparative chromatography on silica gel using *n*-heptane–EtOAc (10:1) as eluent. The pure β -enaminones were prepared in 50–87% yields.
- (15) **Typical Experimental Procedure (Method B):** To the molten of TBAB (0.5 mmol), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.1 mmol) was added and the mixture cooled to r.t., then ethyl acetoacetate (1.0 mmol) and aniline (1.0 mmol) were added to it. The reaction mixture stirred magnetically at r.t. for the appropriate time as shown in Table 2. The reaction was followed by TLC. When the reaction was completed, the mixture washed with EtOAc. The crude products were separated by preparative chromatography on silica gel using *n*-heptane/EtOAc (10:1) as eluent. The pure β -enaminones were prepared in 74–99% yields. Selected characterization

data of compounds **8**, **11**, **13** and **20** are shown below.

Compound **8**: mp 110–111 °C. IR (KBr): ν_{\max} = 3240, 2923, 1668, 1584, 1250, 1012, 955, 763 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ_{H} = 8.32 (br, 1 H, NH), 4.28 (t, J = 8.7 Hz, 2 H), 3.75 (t, J = 5.8, 2 H), 3.41 (q, J = 5.1, 2 H), 3.18 (br, 1 H, OH), 2.75 (t, J = 7.3 Hz, 2 H), 2.1 (s, 3 H, CH_3). ^{13}C NMR (50 MHz, CDCl_3): δ_{C} = 174.8, 158.4, 156.9, 85.2, 65.8, 62.1, 45.7, 26.9. Anal. Calcd for $\text{C}_8\text{H}_{13}\text{NO}_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.00; H, 7.70; N, 8.30.

Compound **11**: mp 92–94 °C IR (KBr): ν_{\max} = 3182, 3072, 2900, 1666, 1637, 1245, 1019, 955 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ_{H} = 9.9 (br, 1 H, NH), 7.25–7.00 (m, 4 H, Ar), 4.42 (t, J = 8 Hz, 2 H, OCH_2), 3.03 (t, J = 8.1 Hz, 2 H, $=\text{C}-\text{CH}_2-$), 2.45 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3). ^{13}C NMR (50 MHz, CDCl_3): δ_{C} = 174.4, 154.5, 147.8, 136.8, 135.2, 130.1, 124.9, 88.9, 65.8, 26.9, 21.3. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2$: C, 71.86; H, 6.95; N, 6.45. Found: C, 71.60; H, 7.00; N, 6.70.

Compound **13**: mp 105–107 °C; IR (KBr): ν_{\max} = 3288, 2895, 1679, 1618, 1440, 1017, 760, 740, 696 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ_{H} = 8.72 (s, 1 H, NH), 7.42–7.20 (m, 5 H, Ph), 4.46 (d, J = 3.9 Hz, 2 H, CH_2N), 4.32 (t, J = 4.7 Hz, 2 H, OCH_2), 2.85 (t, J = 4.8 Hz, 2 H, $\text{CH}_2\text{C}=\text{C}$), 1.95 (s, 3 H, CH_3). ^{13}C NMR (50 MHz, CDCl_3): δ_{C} = 174.6, 168.0, 157.4, 139.3, 129.2, 127.8, 127.0, 86.5, 65.6, 53.6, 47.1, 26.9, 16.8. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2$: C, 71.90; H, 7.00; N, 6.50. Found: C, 71.60; H, 7.00; N, 6.70.

Compound **20**: mp 177–179 °C. IR (KBr): ν_{\max} = 3360, 3120, 1525, 1512, 1080, 800, 748, 705 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ_{H} = 11.6 (s, 2 H, NH), 8.17–7.1 (m, 10 H, Ph), 5.70 (s, 2 H, $=\text{CH}-$), 3.82–3.30 (m, 4 H, $-\text{CH}_2-$), 2.10 (s, 6 H, CH_3). ^{13}C NMR (50 MHz, CDCl_3): δ_{C} = 188.7, 165.4, 140.5, 131.1, 128.7, 127.4, 93.4, 44.2, 19.7. Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$: C, 75.83; H, 6.94; N, 9.16. Found: C, 75.44; H, 6.80; N, 8.40.