

Cerium(III) Chloride Heptahydrate ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) as an Efficient Enamination Catalyst in Aqueous Media*

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Abstract—Cerium(III) chloride heptahydrate $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ catalyzes enamination of β -dicarbonyl compounds with primary amines in aqueous medium at room temperature to afford the corresponding β -enamino ketones with high chemoselectivity.

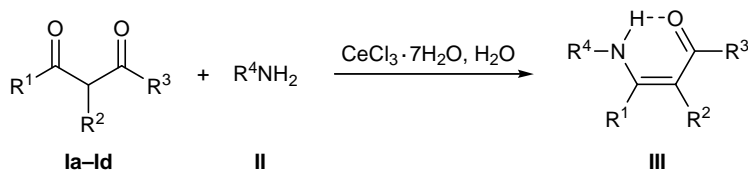
β -Enaminones are biologically active compounds and important intermediates in organic synthesis [1–3]. The traditional method for the preparation of β -enaminones involves direct condensation of β -dicarbonyl compounds with amines on heating in an aromatic solvent with simultaneous removal of the liberated water as azeotrope [4]. The other methods are based on the addition of primary amines to β -dicarbonyl compounds applied to silica gel under microwave irradiation [5], in the presence of K10 clay under ultrasonic irradiation [6], or under catalysis by NaAuCl_4 [7]. Recently, some β -enamino ketones were prepared by direct condensation of β -dicarbonyl compounds with primary amines in water as solvent [8]. However, some of these methods have a limited synthetic scope due to the use of toxic solvents, long reaction time, unsatisfactory yields of the target products, or low selectivity. Therefore, development of simple and effective procedures for the preparation of β -enaminones under mild and ecologically friendly conditions is desirable.

In modern organic synthesis, increased attention is given to reactions occurring in aqueous medium [9]. Such specific properties of water as the absence of toxicity, high heat capacity, and the possibility for easy

isolation of solid products by filtration and reuse of inorganic catalysts make water very attractive medium for organic reactions [10]. On the other hand, most catalysts and reagents decompose or undergo deactivation in water; moreover, organic compounds are generally insoluble in water. Therefore, carrying out organic reactions in aqueous medium possesses important challenges in the field of reaction design.

It was found that cerium(III) chloride heptahydrate $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ is a potentially useful Lewis acid ensuring high regio- and chemoselectivity in various chemical transformations. Its additional advantages are the absence of toxicity, cheapness, and stability in aqueous media [11]. The present communication reports on ecologically safe, mild, and efficient method for regio- and chemoselective enamination of β -dicarbonyl compounds with primary amines in water in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (Scheme 1). The results are given in table. All reactions were carried out at room temperature. Unlike other methods, the products were obtained in high yields and excellent chemoselectivity. Aliphatic amines effectively reacted to produce the corresponding enaminones. In the reactions with 1,2-ethanediamine we used 2 equiv of β -dicarbonyl compounds,

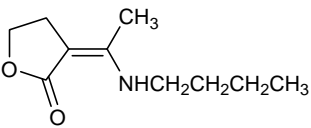
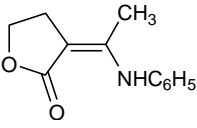
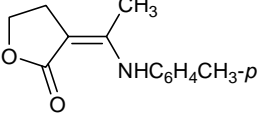
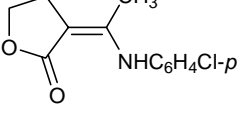
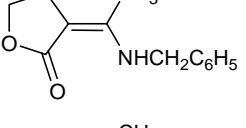
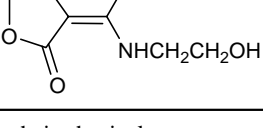
Scheme 1.



I, $\text{R}^1 = \text{R}^3 = \text{CH}_3$, $\text{R}^2 = \text{H}$ (a); $\text{R} = \text{CH}_3$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$ (b); $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{C}_2\text{H}_5\text{O}$ (c); $\text{R}^1 = \text{CH}_3$, $\text{R}^2\text{R}^3 = \text{CH}_2\text{CH}_2\text{O}$ (d).

* The text was submitted by the authors in English.

Enamination of β -dicarbonyl compounds in water in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$

Run no.	Initial comp. no.	R ⁴	Product ^a	Yield, ^b %	Reaction time, min
1	Ia	$\text{CH}_3\text{CH}_2\text{CHCH}_2$	$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{NHC}(\text{CH}_3)=\text{HCOCH}_3$	70	240
2	Ia	$\text{H}_2\text{NCH}_2\text{CH}_2$	$\text{CH}_3\text{COCH}=\text{C}(\text{CH}_3)\text{NHCH}_2\text{CH}_2\text{C}(\text{CH}_3)=\text{CHCOCH}_3$	72	120
3	Ia	HOCH_2CH_2	$\text{HOCH}_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCOCH}_3$	69	100
4	Ia	C_6H_5	$\text{C}_6\text{H}_5\text{NHC}(\text{CH}_3)=\text{CHCOCH}_3$	64	60
5	Ib	$\text{CH}_3\text{CH}_2\text{CHCH}_2$	$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{NHC}(\text{CH}_3)=\text{CHCOC}_6\text{H}_5$	75	240
6	Ib	HOCH_2CH_2	$\text{HOCH}_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCOC}_6\text{H}_5$	70	180
7	Ib	$\text{H}_2\text{NCH}_2\text{CH}_2$	$\text{C}_6\text{H}_5\text{COCH}=\text{C}(\text{CH}_3)\text{NHCH}_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCOC}_6\text{H}_5$	75	120
8	Ib	$\text{C}_6\text{H}_5\text{CH}_2$	$\text{C}_6\text{H}_5\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCOC}_6\text{H}_5$	65	50
9	Ib	$4\text{-CH}_3\text{C}_6\text{H}_4$	$4\text{-CH}_3\text{C}_6\text{H}_4\text{NHC}(\text{CH}_3)=\text{CHCOC}_6\text{H}_5$	70	180
10	Ic	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCOOC}_2\text{H}_5$	96	8
11	Ic	$\text{H}_2\text{NCH}_2\text{CH}_2$	$\text{C}_2\text{H}_5\text{OCOCH}=\text{C}(\text{CH}_3)\text{NHCH}_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCOOC}_2\text{H}_5$	95	10
12	Ic	HOCH_2CH_2	$\text{HOCH}_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCOOC}_2\text{H}_5$	93	10
13	Ic	$\text{C}_6\text{H}_5\text{CH}_2$	$\text{C}_6\text{H}_5\text{CH}_2\text{NHC}(\text{CH}_3)=\text{CHCOOC}_2\text{H}_5$	94	10
14	Ic	C_6H_5	$\text{C}_6\text{H}_5\text{NHC}(\text{CH}_3)=\text{CHCOOC}_2\text{H}_5$	73	20
15	Ic	$4\text{-CH}_3\text{C}_6\text{H}_4$	$4\text{-CH}_3\text{C}_6\text{H}_4\text{NHC}(\text{CH}_3)=\text{CHCOOC}_2\text{H}_5$	80	45
16	Id	$\text{CH}_3(\text{CH}_2)_2\text{CH}_2$		78	10
17	Id	C_6H_5		75	10
18	Id	$4\text{-CH}_3\text{C}_6\text{H}_4$		89	8
19	Id	$4\text{-ClC}_6\text{H}_4$		88	5
20	Id	$\text{C}_6\text{H}_5\text{CH}_2$		94	10
21	Id	HOCH_2CH_2		85	10

^a All products were identified by comparing their physical constants and spectral data with those of authentic samples.^b Yield of isolated product.

and the products contained two enamino fragments (see table, run nos. 2, 7, 11). Weakly activated anilines were also converted into the corresponding enaminoes in good yields (run nos. 9, 5, 18). However, anilines having strong electron-withdrawing groups (e.g., *p*-nitroaniline) failed to react under the given conditions even in 24 h.

The proposed procedure was successfully applied to enamination of β -diketones (run nos. 1–19) and linear (run nos. 10–15) and cyclic β -keto esters (run nos. 16–21). It should be noted that in all cases the attack by amine was directed exclusively at the acetyl carbonyl group; no products which could result from alternative attack were detected (run nos. 3, 6, 12).

Thus we have proposed an efficient procedure for the synthesis of β -enaminoes in aqueous medium in the presence of a catalytic amount of CeCl₃·7H₂O. It is advantageous due to high yields of the target products, high regioselectivity, mild reaction conditions, clear reactions, and ecological safety.

EXPERIMENTAL

The ¹H and ¹³C NMR spectra were recorded on a Bruker Avance spectrometer operating at 200 MHz for ¹H. The IR spectra were measured on a Shimadzu 470 spectrometer.

General procedure for enamination of β -dicarbonyl compounds. A mixture of 1 mmol of β -dicarbonyl compound, 1 mmol of amine, and 0.1 mmol of CeCl₃·7H₂O in 5 ml of water was stirred at room temperature for a time indicated in table. The progress of reactions was monitored by GLC or TLC. When the reaction was complete, the catalyst was separated by filtration, the filtrate was extracted with methylene chloride (3×10 ml), the extract was dried over magnesium sulfate, the solvent was removed, and the residue was subjected to column or preparative thin-layer chromatography on silica gel. The yields of enaminoes were 65 to 96%. Spectral parameters of some enaminoes are given below.

***N,N'*-Bis(2-benzoyl-1-methylethenyl)-1,2-ethanediamine** (run no. 7). Colorless crystals, mp 177–179°C. IR spectrum (KBr), ν , cm⁻¹: 3360, 3120, 1525, 1512, 1080, 800, 748, 705. ¹H NMR spectrum (200 MHz, CDCl₃), δ , ppm: 11.6 s (1H, NH), 8.17–7.1 m (5H, Ph), 5.7 s (1H, =CH), 3.82–3.3 m (2H, CH₂), 2.1 s (3H, CH₃). ¹³C NMR spectrum (50 MHz, CDCl₃), δ _C, ppm: 188.7, 165.4, 140.5, 131.1, 128.7, 127.4, 93.4, 44.2, 19.7. Found, %: C 75.24; H 6.8:

N 8.4. C₂₂H₂₄N₂O₂. Calculated, %: C 75.63; H 6.94; N 9.16.

3-(1-Phenylaminoethylidene)tetrahydrofuran-2-one (run no. 17). Colorless crystals, mp 90–92°C. IR spectrum (KBr), ν , cm⁻¹: 3250, 3030, 2900, 1674, 1634, 1247, 1019, 920. ¹H NMR spectrum (200 MHz, CDCl₃), δ , ppm: 10.1 br.s (1H, NH), 7.41–7 m (5H, Ph), 4.42–4.3 t (2H, OCH₂, *J* = 8.2 Hz), 3.07–2.89 t (2H, =CCH₂, *J* = 8.1 Hz), 2.1 s (3H, CH₃). ¹³C NMR spectrum (50 MHz, CDCl₃), δ _C, ppm: 174.3, 153.9, 147.8, 139.6, 129.6, 125.3, 124.6, 89.7, 65.8, 26.9. Found, %: C 70.5; H 6.5; N 7.0. C₁₂H₁₃NO₂. Calculated, %: C 70.92; H 6.45; N 6.89.

3-[1-(2-Hydroxyethylamino)ethylidene]tetrahydrofuran-2-one (run no. 21). Colorless crystals, mp 110–111°C. IR spectrum (KBr), ν , cm⁻¹: 3240, 2923, 1668, 1584, 1250, 1012, 955, 763. ¹H NMR spectrum (200 MHz, CDCl₃), δ , ppm: 8.32 br.s (1H, NH), 4.33–4.22 t (2H, CH₂, *J* = 8.7 Hz), 3.8–3.69 t (2H, CH₂, *J* = 5.8 Hz), 3.47–3.36 d.d (2H, CH₂, *J* = 5.1, 5.2 Hz), 3.18 br.s (1H, OH), 2.9–2.8 t (2H, CH₂, *J* = 7.3 Hz), 2.1 s (3H, CH₃). ¹³C NMR spectrum (50 MHz, CDCl₃), δ _C, ppm: 174.8, 158.4, 156.9, 85.2, 65.8, 62.1, 45.7, 26.9. Found, %: C 56.0; H 7.7; N 8.3. C₈H₁₃NO₃. Calculated, %: C 56.13; H 7.65; N 8.18.

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