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$CeCl_3 \cdot 7H_2O$: an efficient and reusable catalyst for the preparation of β-acetamido carbonyl compounds by multi-component reactions (MCRs)

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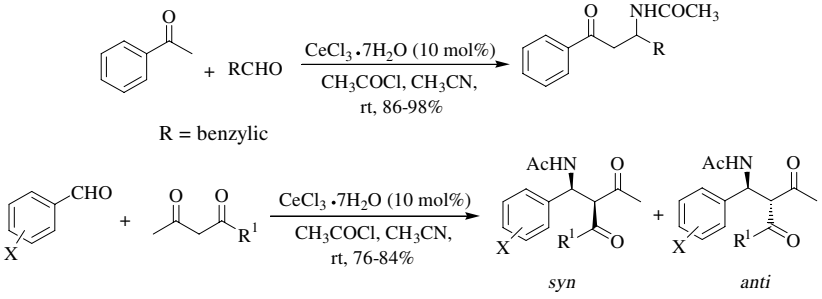
Abstract—A convenient method for the preparation of β-acetamido carbonyl compounds is described by multi-component reactions of aromatic aldehydes, enolizable ketones or β-keto esters and acetonitrile in the presence of acetyl chloride and 10 mol % $CeCl_3 \cdot 7H_2O$ at room temperature.

After the discovery of multi-component reactions (MCRs) in 1850 by Strecker,[1] the concept has stimulated substantial interest in organic chemistry because it provides useful product(s) in a single step by the creation of several new bonds in one pot. In drug discovery as well as 'Green Chemistry', MCRs are the preferred techniques due to high throughput synthesis of compounds in a cost- and time effective manner.

β-Acetamido carbonyl compounds are valuable building blocks for a number of biologically and pharmaceutically[2] important compounds, examples being for the preparation of 1,3-amino alcohols,[3] antibiotic nikkomycins or neopolyoxines.[4] Thus, the synthesis of β-acetamido carbonyl compounds has attracted much attention in organic synthesis. Conventionally, this class of compounds is prepared by the Dakin–West reaction,[5] the condensation of an α-amino acid with acetic anhydride in the presence of a base provides the α-acetamido ketones through an intermediate azalactone.[6] Iqbal et al. developed a route using aromatic aldehydes, enolizable ketones or β-keto esters and acetonitrile in the presence of acetyl chloride and a catalytic amount of a Lewis acid catalyst such as $CoCl_2$[7] or Montmorillonite K-10 clay.[8] Although these methods are valuable some drawbacks remain such as a requirement for either a long reaction time or harsh reaction conditions, or the reaction has to be carried out under an inert



Scheme 1.

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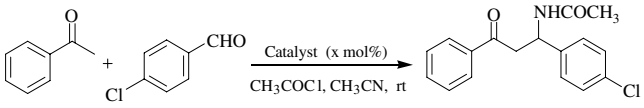
Table 1. Optimization of the $CeCl_3{\cdot}7H_2O$ catalyzed multi-component reaction



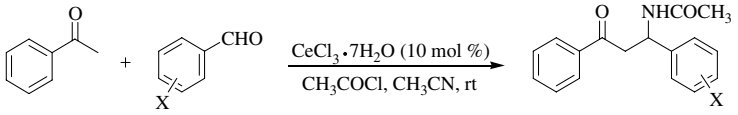
Entry	Catalyst $CeCl_3{\cdot}7H_2O$ mol %	Time (h)	Yield[a] (%)
1	0	24	15
2	5	15	87
3	10	6	98
4	10	24	0[b]

[a] Crude yields.
[b] Reaction was carried out in the absence of acetyl chloride.

atmosphere. Recently, other methods have also been reported involving $Cu(OTf)_2/Sc(OTf)_3$,[9] silica sulfuric acid,[10] BiOCl[11] and $ZrOCl_2{\cdot}8H_2O$.[12] However, most of these methods also employ either expensive catalysts or long reaction times or harsh reaction conditions. In continuation of our effort towards the development of newer and 'greener' synthetic methodologies,[13] we set out to find out a simple and improved protocol for the preparation of β-acetamido carbonyl compounds using a readily available, cheap and non-toxic catalyst.

$CeCl_3{\cdot}7H_2O$ is a relatively cheap, water, air-stable and non-toxic reagent.[14] Due to the hardness of the cerium cation, it is able to activate carbonyl functional-

Table 2. $CeCl_3{\cdot}7H_2O$ catalyzed multi-component reaction for the preparation of β-acetamido ketones



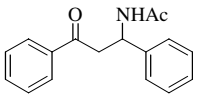
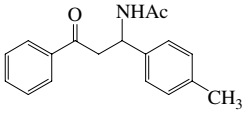
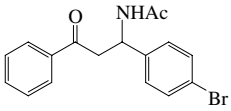
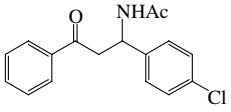
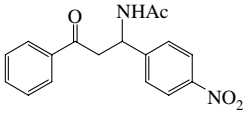
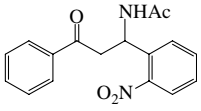
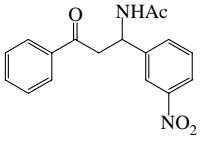
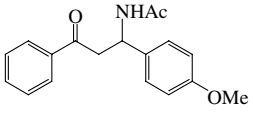
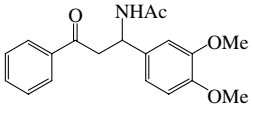
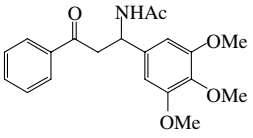
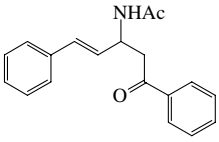
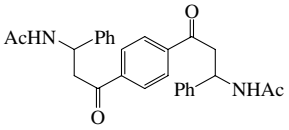
Entry	β-Acetamido ketones[a]	Time (h)	Yield[b] (%)
1		7	96
2		7	92
3		6	95
4		6	98[c]
5		12	96
6		11	86
7		10	90
8		6	89
9		6	96

Table 2 (*continued*)

Entry	β-Acetamido ketones[a]	Time (h)	Yield[b] (%)
10		5	93
11		6	94
12		8	76

[a] All the products were characterized by IR and ^{1}H NMR spectroscopy as well as by elemental analysis.
[b] Yields after work-up.
[c] The catalyst was recovered and reused in subsequent reactions three times without losing any significant activity affording 91%, 88%, and 85% yields, respectively.

ities for nucleophilic attack and has been used as a Lewis acid for several transformations.[15] Herein, we report a mild and efficient protocol for the preparation of β-acetamido carbonyl compounds by four-component reactions of an aromatic aldehyde, acetonitrile, an enolizable ketone or β-keto ester and acetyl chloride, catalyzed by $CeCl_3{\cdot}7H_2O$ at room temperature (Scheme 1).

To find the optimal conditions, a mixture of 4-chlorobenzaldehyde (2 mmol), acetophenone (2 mmol), acetyl chloride (3 mmol) and acetonitrile (5 mL) was stirred under various reaction conditions (Table 1). In the absence of the catalyst, the product β-acetamido ketone was obtained in 15% yield only after 24 h. Even with the inclusion of 5 mol % $CeCl_3{\cdot}7H_2O$, the transformation took a long time, however, using 10 mol % catalyst furnished the β-acetamido carbonyl compound in an excellent yield (Table 1).

After optimization,[16] a variety of other aromatic aldehydes having electron-donating as well as electron-withdrawing substituents were shown to undergo the reaction smoothly giving the desired products in good yields. The results are summarized in Table 2. All the products were fully characterized by spectroscopic methods and compared with the authentic spectra. Aromatic aldehydes containing a nitro substituent took longer reaction times (entries 5–7). The α,β-unsaturated aldehyde, cinnamaldehyde, also reacted under the same experimental conditions (entry 11), as did terephthalaldehyde on treatment with 2 equiv of acetophenone and the other reactants (entry 12).

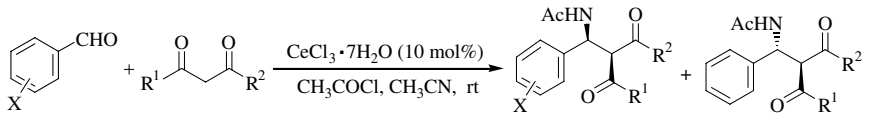
To explore the further applicability of Ce(III)-catalyzed multi-component reactions, a variety of aromatic aldehydes (Table 3, entries 1–5) were treated with methyl acetoacetate and acetyl chloride in the presence of 10 mol % of catalyst at room temperature and the corresponding β-acetamido keto esters were obtained in good yields with moderate to good diastereoselectivities. Similarly, ethyl benzoylacetate afforded the corresponding products (Table 3, entries 6–8) in excellent yields with good diastereoselectivity. Interestingly, the major products obtained using methyl acetoacetate (Table 3, entries 1–5) were the *anti* isomers, whereas ethyl benzoylacetate afforded mainly the *syn* isomers (Table 3, entries 6–8).

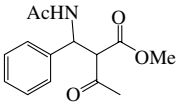
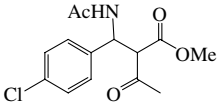
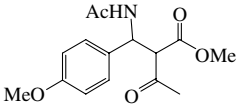
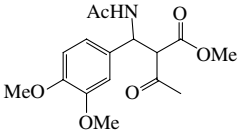
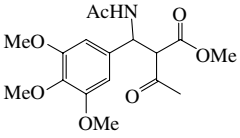
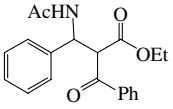
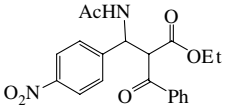
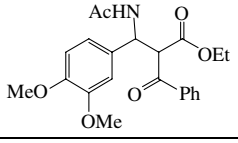
The generality and superiority of the present protocol over existing methods can be seen by comparing our results with those of some recently reported procedures, as shown in Table 4. The reaction of benzaldehyde with acetophenone for the preparation of β-acetamido-β-(phenyl)-propiophenone (Table 2, entry 1) was chosen as a model reaction and the comparison is in terms of mol % of the catalysts used, reaction time, and reaction conditions and percentage yields.

Noting that the reaction proceeds with only 15% yield even after 24 h in the absence of a catalyst, we believe that the cerium chloride activates the aldehyde group for nucleophilic attack as well as facilitating enolization. We were interested to determine whether a chalcone intermediate (by aldol condensation) is involved. Thus, a mixture of chalcone (2 mmol), acetyl chloride (3 mmol) and acetonitrile (5 mL) was stirred at room temperature for 6 h, but no β-acetamido ketone was formed.

In conclusion, we have revealed a simple, efficient and 'greener' protocol for the preparation of β-acetamido carbonyl compounds using $CeCl_3{\cdot}7H_2O$ as a reusable catalyst (Scheme 2). The salient features of this protocol include operational simplicity, high yields of the products, avoidance of column chromatography, ready availability, low toxicity, moisture compatibility and reusability of the catalyst.

Table 3. $CeCl_3{\cdot}7H_2O$ catalyzed multi-component reaction for the preparation of β-acetamido keto esters

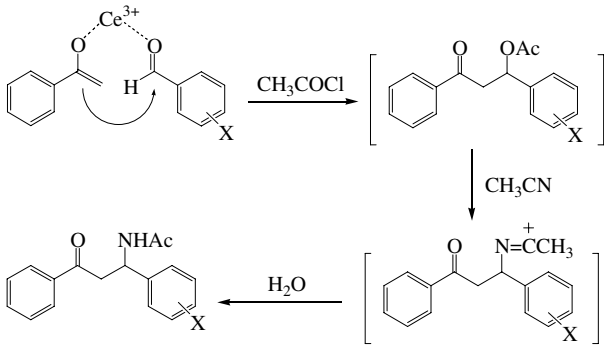


Entry	Product	Yield[a] (%)	*syn*:*anti*[b]
1		76	25:75
2		84	24:76
3		78	5:95
4		83	7:93
5		81	10:90
6		81	90:10
7		84	72:28
8		83	70:30

[a] Yields after work-up.
[b] The *syn*:*anti* ratio was determined from ^1H NMR measurements of the crude reaction mixture.

Table 4. Comparison of the results for the preparation of β-acetamido ketone (Table 2, entry 1) using multi-component reactions with other catalysts

Catalyst	mol %	Reaction time	Reaction temperature (°C)	Yield (%)
Silica sulfuric acid	78	65 min	80	91[10]
$ZrOCl_2{\cdot}8H_2O$	20	5 h	rt	90[12]
$Sc(OTf)_3$	10	30 h	rt	82[9]
BiOCl	20	7 h	rt	92[11]
$CeCl_3{\cdot}7H_2O$	10	7 h	rt	96



Scheme 2. A plausible mechanism for the $CeCl_3{\cdot}7H_2O$ catalyzed multicomponent reaction for the preparation of β-acetamido carbonyl compounds.

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16. Typical procedure: A mixture of aromatic aldehyde (2 mmol), acetophenone or β-keto ester (2 mmol), acetyl chloride (3 mmol) and $CeCl_3{\cdot}7H_2O$ (75 mg, 10 mol %) in acetonitrile (5 mL) was stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was poured into 50 mL of ice water. On solidification, it was filtered, washed with ice water and recrystallized from ethyl acetate/hexane to give the pure β-acetamido ketone. For all the substrates in Table 3, the reactions were stirred for 12 h, then 50 mL of water was added. The mixture was extracted with ethyl acetate (3×20 mL), the extracts were washed with water (3×20 mL), dried over Na_2SO_4 and the solvent was removed using a rotary evaporator. The crude mixture was recrystallized from ethyl acetate/hexane and the solid product (mixture of diastereomers) was isolated. For the recovery of the catalyst, the aqueous layer was evaporated under reduced pressure, and the residue reused in subsequent reactions without losing any significant activity. The spectral data of some representative β-acetamido carbonyl compounds are given below.
β-Acetamido-β-(3,4,5-trimethoxyphenyl)propiophenone (entry 10, Table 2): Solid; mp: 159 °C. IR (KBr): 3277, 1687, 1647, 1592, 1560, 1126, 1002 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.03 (s, 3H), 3.38 (dd, $J = 5.2$ Hz, $J = 16.4$ Hz, 1H), 3.70 (dd, $J = 5.2$, 16.8 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 6H), 5.45 (m, 1H), 6.52 (s, 2H), 6.67 (br, d, $J = 6.8$ Hz, 1H), 7.43 (t, $J = 7.2$ Hz, 2H), 7.55 (t, $J = 6.4$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.59, 43.28, 50.58, 56.18 (2C), 60.78, 103.77, 103.89, 127.97 (3C), 128.59 (3C), 133.43 (2C), 136.56, 153.11, 169.21, 198.51. Anal. Calcd for $C_{20}H_{23}O_5N$ (357.40): C, 67.21; H, 6.49; N, 3.92; found C, 67.29; H, 6.42; N 3.82. *Ethyl 2-benzoyl-3-acetamido-3-(p-nitrophenyl)propionate* (entry 7, Table 3): (mixture of diastereomers) data for the major isomer: IR (KBr): 3303, 1724, 1688, 1649, 1540, 1521, 1348, 1298, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, $J = 6.8$ Hz, 3H), 2.09 (s, 3H), 4.18 (q, $J = 6.8$ Hz, 2H), 4.98 (d, $J = 4.4$ Hz, 1H), 5.97 (dd, $J = 4.4$, 9.2 Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 3H), 7.57 (t, $J = 7.2$ Hz, 1H), 7.79 (d,$J = 7.2$ Hz, 2H), 8.10 (d, $J = 8.8$ Hz, 2H). Anal. Calcd for $C_{20}H_{20}N_2O_6$ (384.39): C, 62.50; H, 5.24; N, 7.29; found C, 62.38; H, 5.18; N, 7.36.