

# Fe(ClO<sub>4</sub>)<sub>3</sub> · 6H<sub>2</sub>O: a mild and efficient catalyst for one-pot three component synthesis of β-acetamido carbonyl compounds under solvent-free conditions

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**Abstract** A one-pot multi-component reaction for the synthesis of β-acetamido carbonyl compounds is reported. The reaction uses a variety of aldehydes, acetophenone derivatives or methyl acetoacetate, acetonitrile, and acetyl chloride in the presence of ferric perchlorate, a mild, efficient and inexpensive catalyst effective under solvent free conditions.

**Keywords** One-pot · Three-Component · 3CC, MCR, Fe(ClO<sub>4</sub>)<sub>3</sub> · 6H<sub>2</sub>O · β-Acetamido Carbonyl Compounds · Solvent-free conditions

## Introduction

One-pot multi-component reactions have recently received the attention of organic chemists because of the many advantages these reactions offer over conventional multi-step synthesis as well as their potential applications in medicinal chemistry for the generation of diverse scaffolds and combinatorial libraries for drug development [1–4].

The preparation of β-acetamido carbonyl compounds has attracted considerable attention in organic synthesis due to their importance as valuable building blocks for the synthesis of 1,3-amino alcohols and alpha-amino acids [5,6] as well as for the synthesis of various bio-active molecules such as antibiotics (i.e., nikkomycins, neopolyoxines) [7,8].

Recently, several synthetic methods have been developed for the preparation of β-acetamido ketones through the multi-component condensation of aryl aldehydes, enolizable ketones and acetyl chlorides in acetonitrile using Lewis or

Brønsted acid catalysts such as CoCl<sub>2</sub> [9,10], montmorillonite K-10 clay [11], silica sulfuric acid [12], BiCl<sub>3</sub> (generated from BiOCl) [13], ZrOCl<sub>2</sub>·8H<sub>2</sub>O [14], heteropoly acids [15], sulfuric acid absorbed on silica gel [16], Sc(OTf)<sub>3</sub> [17], silica supported H<sub>3</sub>PW<sub>12</sub>O<sub>4</sub> [18], H<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub> [19], and FeCl<sub>3</sub> [20].

Ferric perchlorate has gained widespread use as a catalyst in organic chemistry such as in the protection of alcohols and deprotection of tetrahydropyranyl ethers [21], the acetylation of alcohols and phenols [22], the aromatization of Hantzsch 1,4-dihydropyridines [23], the synthesis of 1,5-benzodiazepine derivatives [24], the acetylation of THP ethers [25], the conversion of oximes to aryl- and alkyl hydrazones [26], one-pot synthesis of α-aminonitriles using trimethyl silylcyanide [27,28], and solvent-free synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles [29].

In our continuing interest in the use of ferric perchlorate as an efficient catalyst, here we report the catalytic efficiency of Fe(ClO<sub>4</sub>)<sub>3</sub> for the synthesis of beta-acetamido ketones using aldehyde derivatives and enolizable ketones under solvent-free conditions at 80 °C (Scheme 1).

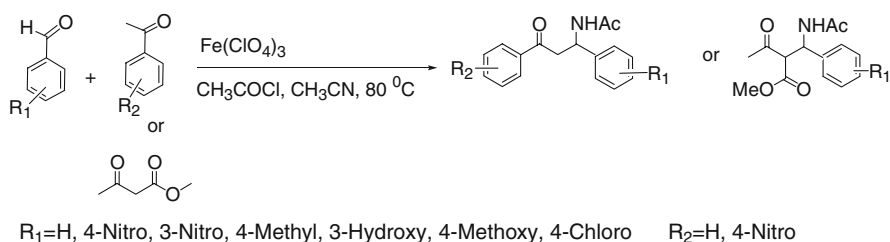
## Experimental

Synthesis of β-acetamido ketone and esters: general procedure

A mixture of 5 mmol a ketone or methyl acetoacetate, 5 mmol an aldehyde and 1.5 mL acetyl chloride in 0.5 mL acetonitrile was treated with 1 mol% of Fe(ClO<sub>4</sub>)<sub>3</sub> · 6H<sub>2</sub>O at 80 °C (Table 1). The progress of reaction was monitored by TLC [eluent: petroleum ether: ethyl acetate (4:1), silica gel was used as the support]. Upon completion of the reaction, a mixture of ice-water was added to the reaction mixture. The precipitated

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**Scheme 1** The synthesis of  $\beta$ -acetamido ketones using aldehyde derivatives and enolizable ketones in the presence of  $\text{Fe}(\text{ClO}_4)_3$



**Table 1** The comparison of Lewis acids effect on the synthesis of N-(3-oxo-1,3-diphenyl-propyl)-acetamide

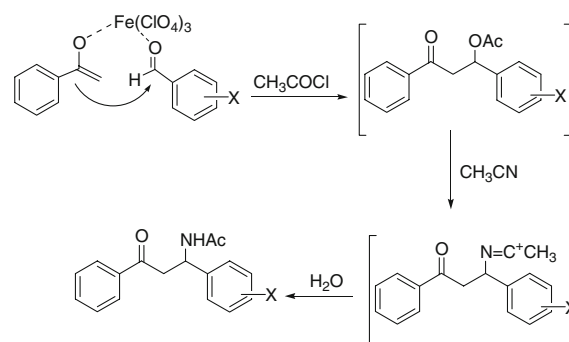
Entry	Lewis acid (mol%)	Time (h)	Isolated yield (%)	Ref.
1	$\text{Cu}(\text{OTf})_2$ (10)	30	64	12
2	$\text{Zn}(\text{OTf})_2$ (10)	30	60	12
3	$\text{LiClO}_4$ (100)	30	59	12
4	$\text{InCl}_3$ (100)	30	19	12
5	$\text{BF}_3 \cdot \text{OEt}_2$ (10)	30	48	12
6	$\text{BiCl}_3$ (100)	30	77	12
7	$\text{LaCl}_3$ (100)	30	77	12
8	$\text{CuCl}_2$ (100)	30	79	12
9 <sup>b</sup>	$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (20)	5	90	9
10 <sup>c</sup>	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (10)	8	88	15
11	$\text{Fe}(\text{ClO}_4)_3 \cdot 6\text{H}_2\text{O}$ (1)	3.5	77	This work

solid was filtered off, the residue was washed with 20 mL of diethyl ether and the crude product recrystallized from ethanol/water or n-hexane/ethyl acetate. In the cases where no solids are formed the oily products were isolated via extraction with dichloromethane.

## Results and discussion

For the preliminary study, the reaction of benzaldehyde and acetophenone, was examined without using any catalyst which gave no observable conversion. When a mixture of an enolizable ketone ( $\beta$ -ketoester or a simple aryl alkyl ketone), aldehyde and acetyl chloride were stirred at room temperature in acetonitrile for 30 h,  $\beta$ -actamido carbonyl compounds were obtained in 10–15% yields. Interestingly, when a catalytic amount of  $\text{Fe}(\text{ClO}_4)_3$  was used the reaction proceeded in 77% yield. Therefore, in a model reaction we used a mixture of 1 mmol of benzaldehyde, 1 mmol of acetophenone, 1.5 mmol of  $\text{AcCl}$ , 0.5 mL of acetonitrile and 0.05 mmol of  $\text{Fe}(\text{ClO}_4)_3$  at 80°C. Under this condition the product was obtained in good yield.

In order to evaluate the generality of this model reaction we used a variety of aldehydes with electron-donating and



**Scheme 2** The proposed mechanism for the synthesis of  $\beta$ -acetamido ketones

electron-withdrawing groups on the aromatic ring and different enolized ketones such as acetophenone and 4-nitroacetophenone or methyl acetoacetate. In all cases the expected products were obtained in good yields. The results are shown in Table 1.

The proposed mechanism for this transformation is shown in Scheme 2. Based on a reported mechanism of  $\text{Fe}(\text{ClO}_4)_3$  in the acetylation of alcohols and phenols [22] and iron(III) chloride in preparation of  $\beta$ -acetamido ketones [20], we believe that ferric perchlorate catalyzed aldol reaction followed by acetylation of the hydroxyl group of the aldol product. Subsequent ferric perchlorate catalysis of the nucleophilic displacement of the acetyl group by alkyl/aryl nitrile followed by water addition leads to the production of the desired product (Scheme 2).

## Conclusion

In conclusion, a simple and efficient procedure has been developed for the synthesis of  $\beta$ -acetamido ketones at 80°C. The salient features of this protocol include the use of a catalytic amount of the Lewis acid (Table 2), good yields, operational simplicity, short reaction times, the avoidance of column chromatography and use of non-toxic and inexpensive catalyst. We believe these advantages will make this method a useful and important addition to the present methodologies.

**Table 2** Preparation of  $\beta$ -acetamido ketones from aldehydes and enolizable ketones in the presence of acetyl chloride and acetonitrile catalyzed using  $\text{Fe}(\text{ClO}_4)_3 \cdot 6\text{H}_2\text{O}$  under solvent free condition

Entry	Aldehyde	Ketone	Time (h)	Yield (%)	m.p. ( $^{\circ}\text{C}$ )	
					Observed	Founded
1	Benzaldehyde	Acetophenone	3.5	77	105–107	102–104[6]
2	4-Nitrobenzaldehyde	Acetophenone	4.0	63	146–148	149–151[9]
3	3-Nitrobenzaldehyde	Acetophenone	4.10	67	114–117	112–115[6]
4	4-Methylbenzaldehyde	Acetophenone	3.0	72	111–114	113–115[9]
5	Benzaldehyde	4-Nitroacetophenone	3.0	72	75–77	74–76[6]
6	4-Methylbenzaldehyde	4-Nitroacetophenone	3.3	65	82–84	83–85[6]
7	4-Methoxybenzaldehyde	4-Nitroacetophenone	3.5	65	86–87	87–89[6]
8	4-Chlorobenzaldehyde	4-Nitroacetophenone	4.0	71	121–122	116–118[6]
9	Benzaldehyde	Methyl acetoacetate	4.2	70	136–138	129–131[24]
10	4-Chlorobenzaldehyde	Methyl acetoacetate	3.5	65	132–135	130–132[24]

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