One-pot preparation of β-amido ketones/esters in a three-component condensation reaction using magnesium hydrogensulfate as an effective and reusable catalyst

Hamid Reza Shaterian, Asghar Hosseinian, and Majid Ghashang

Abstract: A one-pot, three-component condensation of an aryl aldehyde, an enolizable ketone or β-keto ester, acetyl chloride, and acetonitrile or benzonitrile in the presence of magnesium hydrogensulfate as an active, recoverable, and reusable green catalyst is described for the synthesis of β-amido ketones/esters at room temperature. The key features of this methodology are simplicity, mild reaction conditions, and high to excellent yields.

Key words: multi-component reaction, magnesium hydrogensulfate, heterogeneous catalyst, β-amido ketone/ester, mild conditions.

Résumé : On décrit une condensation monotope à trois composants dont un aldéhyde aromatique, une cétone ou un β-cétoester énolisable et du chlorure d'acétyle, de l'acétonitrile ou du benzonitrile, en présence de sulfate acide de magnésium comme catalyseur vert actif, récupérable et réutilizable, pour réaliser la synthèse à la température ambiante la synthèse de β-amidocétones et de β-amidoesters. Les caractéristiques principales de cette méthodologie sont sa simplicité, des conditions réactionnelles douces et des rendements allant d'élevés à excellents.

Mots-clés : réaction à plusieurs composants, sulfate acide de magnésium, catalyseur hétérogène, β-amidocétones, β-amidoesters, conditions douces.

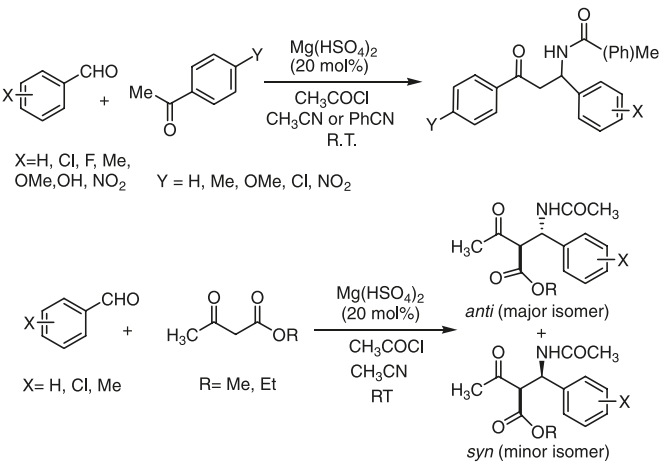
[Traduit par la Rédaction]

Introduction

Today, with the emergence of high-speed parallel synthesis, the multi-component reaction (MCR) is widely employed for the rapid assembly of arrays with high molecular diversity (1). Due to their inherent simple experimental procedures and their one-pot character, they are perfectly suited for automated synthesis. Thus, MCRs have attracted considerable interest owing to their exceptional synthetic efficiency (2–7).

β-Amido ketones are important building blocks and intermediates in synthesis For example, they are important precursors of heterocyclic compounds (8), as well as of β-amino alcohols, which are common units in both natural and synthetic biologically or pharmacologically important compounds (9). The reported one-pot syntheses of the title compounds from aldehydes, enolizable ketones, acetyl chloride, and acetonitrile or benzonitrile are based on some Lewis or Brønsted acid catalysts such as $CoCl_2$ (10, 11), Montmorillonite K-10 clay (12), silica sulfuric acid (13), $BiCl_3$ generated from BiOCl (14), $ZrOCl_2{\cdot}8H_2O$ (15), heteropoly acid (16), sulfuric acid absorbed on silica gel (17), $Sc(OTf)_3$ (18), silica supported $H_3PW_{12}O_{40}$ (19), $K_5CoW_{12}O_{40}{\cdot}3H_2O$ (20), $CeCl_3{\cdot}7H_2O$ (21), ZnO (22), iodine (23), sulfated zirconia (24), iron(III) chloride (25), and *p*-TSA (26). Herein we wish to report an efficient method for the synthesis of β-amido carbonyl compounds in high to excellent yields by employing $Mg(HSO_4)_2$ as an active environmentally friendly heterogeneous catalyst (Scheme 1). We believe that our method is simple, mild, and rapid for the synthesis of the mentioned compounds at room temperature (RT).

Scheme 1. Synthesis of β-amido carbonyl compounds using $Mg(HSO_4)_2$ as an active heterogeneous catalyst.



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This catalyst is safe, easy to handle, environmentally benign, presents fewer disposal problems, and is stable in reaction media. Magnesium hydrogensulfate has been used in some organic reactions, such as acetylation and formylation of alcohols (27), cleavage of C=N (28), and oxidation of thiols (29).

Results and discussion

First, we optimized the amount of magnesium hydrogensulfate as catalyst in the reaction among benzaldehyde, acetophenone, acetyl chloride, and acetonitrile (Table 1). The amount of magnesium hydrogensulfate was chosen to be 20 mol%.

Thus, we continued preparation of β-amido ketones in an optimum model experiment: aldehydes (1 equiv.), enolizable ketone or β-keto ester (1 equiv.), acetyl chloride (0.5 mL), and acetonitrile or benzonitrile (reactant, as well as solvent, 2 mL) in the presence of magnesium hydrogensulfate (20 mol%, Table 2).

As shown in Table 2, aromatic aldehydes and acetophenone derivatives with both electron-withdrawing and electron-donating substituents afforded to the corresponding β-amido ketones without the formation of any side products and in high to excellent yields at RT (Table 2, entries 1–22). Phenolic-OH groups under present reaction conditions were converted to acetate (-OAc) groups (Table 2, entries 19, 20).

Under the optimized reaction conditions, by using benzonitrile in place of acetonitrile, aldehydes were transformed to their corresponding β-benzamido ketones in high yields (Table 2, entries 2, 15).

We also studied the multi-component reaction of aromatic aldehydes with other enolizable ketones (methyl acetoacetate, ethyl acetoacetate, and propiophenone) and acetonitrile in the presence of acetyl chloride and $Mg(HSO_4)_2$ as catalyst. In all cases, mixtures of syn and anti diastereomers were obtained. The amount of syn and anti products was determined by ^{1}H NMR spectra, the coupling constant between H-2 and H-3 is 6–9 Hz for an anti isomer and 2–5 Hz for a syn isomer (10-12, 26). As shown in Table 3, anti diastereomers were found to be major products. The conformational preference of these anti diastereomers depend on the intramolecular H-bonding between the acidic proton and the carbonyl oxygen This phenomenon was confirmed by Ghosh et al. (15) with the X-ray crystallographic analysis data. Methyl and ethyl acetoacetate afforded the corresponding β-acetamido esters and the anti/syn diastereoselectivity further increased from 61:39 to 81:19 (Table 3).

In a typical experiment, after a period of time in which the reaction was completed, the mixture was filtered and the heterogeneous catalyst was recovered. Then, the residue solution was poured into the cooled water until a solid crude product was formed. In every experiment all of the magnesium hydrogensulfate was easily recovered from the reaction mixture. The reusability of the catalysts is one of their most important benefits and makes them useful for commercial applications. Thus, the recovery and reusability of magnesium hydrogensulfate was investigated. The separated catalyst can be reused after washing with $CHCl_3$ and drying. The reusability of the catalyst was checked by the reaction of benzaldehyde and acetophenone in the presence of acetyl chloride and acetonitrile using 20 mol% of $Mg(HSO_4)_2$ at RT. The results indicate that the catalyst can be used five times without any loss of its activity (Table 4).

Table 1. Preparation of *N*-(3-oxo-1,3-diphenylpropyl) acetamide in the presence of various amounts of $Mg(HSO_4)_2$ at room temperature.

Entry	$Mg(HSO_4)_2$ (mol%)	Time (h)	Yield (%)[a]
1	5	8	50
2	10	5	60
3	15	3	75
4	20	2.5	89
5	30	2.5	91

[a]Isolated yields.

To show the merit of the present work in comparison with reported results in the literature, we compared results of magnesium hydrogensulfate with BiOCl (14), $ZrOCl_2 \cdot 8H_2O$ (15), $CeCl_3 \cdot 7H_2O$ (21), ZnO (22), and I_2 (23) in the synthesis of β-acetamido ketone derivatives. As shown in Table 5, magnesium hydrogensulfate can act as an effective catalyst with respect to reaction times, yields, and the obtained products.

Conclusion

In summary, we have demonstrated a new and important catalytic activity of magnesium hydrogensulfate as an inexpensive, commercially available, and reusable catalyst for the synthesis of β-amido ketones/esters in high to excellent yields under mild conditions at RT. The simple experimental procedure combined with the easy work-up and high to excellent yields of products are strong features of the presented method.

Experimental

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR, ^{1}H NMR, ^{13}C NMR spectra). The NMR spectra were recorded on a Bruker Avance DEX 500 and 300 MHz instrument. The spectra were measured in $CDCl_3$ (and DMSO-d_6) relative to TMS (0.00 ppm). Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a JASCO FT-IR 460plus spectrophotometer. Mass spectra were recorded on a Agilent technologies 5973 network mass selective detector (MSD) operating at an ionization potential of 70 eV. Melting points were determined in open capillaries with a BUCHI 510. TLC was performed on silica-gel Poly-Gram SIL G/UV 254 plates.

Preparation of magnesium hydrogensulfate

A 500 mL suction flask was equipped with a constant-pressure dropping funnel. A gas outlet was connected to a vacuum system through an adsorbing solution (water) and an

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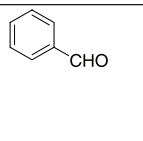
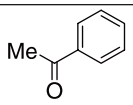
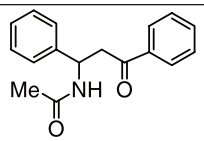
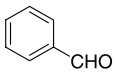
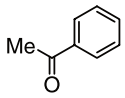
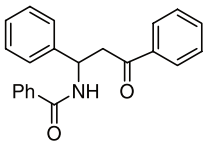
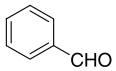
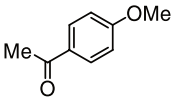
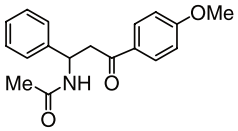
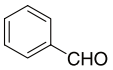
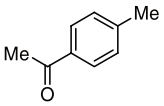
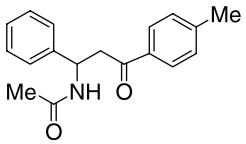
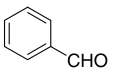
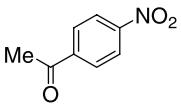
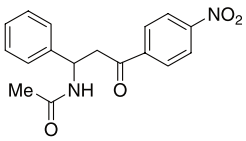
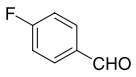
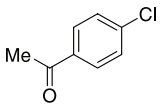
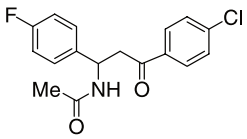
Table 2. Preparation of β-amido ketones from aldehydes and acetophenone derivatives in the presence of acetyl chloride and acetonitrile or benzonitrile catalyzed using $Mg(HSO_4)_2$ at room temperature.

Entry	Aldehyde	Ketone	Product	Time (h)	Yield (%)[a]	Mp, lit. value, ref.
1				2.5	89	102–104, 103–105, 16
2				2.5	90	153–155 153–154, 25
3				2.5	95	129–131, 130, 14
4				2.5	93	112–115, 121–123, 17
5				4	79	74–76, 74–76, 16
6				3	87	108–110, 108–110, 17

alkali trap. Anhydrous magnesium chloride (47.6 g, 0.5 mol) was charged into the flask and concentrated sulfuric acid (98.07 g, 1 mol) was added dropwise over a period of 30 min at RT. HCl gas was evolved immediately. After completing the addition of the H_2SO_4, the mixture was shaken for 30 min; meanwhile, the residual HCl was exhausted by suction. A white solid material was thus obtained (108.5 g) (28).

Typical experimental procedure for the one-pot preparation of *N*-(3-oxo-1,3-diphenylpropyl) acetamide (Table 2, entry 1)

A solution of the benzaldehyde (1 mmol), acetophenone (1 mmol), acetyl chloride (0.5 mL), and acetonitrile in the presence of magnesium hydrogensulfate (20 mol%) was stirred at RT for the appropriate time (Table 2). The progress of the reaction was followed by TLC. After completion of the reaction, the reaction mixture was filtered and the heterogeneous catalyst was recovered. Then, the residue solution was poured into 50 mL of ice water, the solid was separated and recrystallized twice using ethyl acetate/petroleum ether, which gave the desired pure *N*-(1,3-diphenyl-3-oxo-propyl) acetamide in 89% yield (Table 2, entry 1). IR (KBr, cm^{-1}): 3286, 3091, 1693, 1650, 1556, 1273, 1066, 753, 691. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.03 (s, 3H), 3.45 (dd, J = 6.0 and 16.9 Hz, 1H), 3.77 (dd, J = 5.2 and 16.9 Hz, 1H), 5.58 (dd, J = 5.6 and 13.1 Hz, 1H), 6.90 (d, J = 6.3 Hz,1H), 7.24-7.60 (m, 8H), 7.91 (d, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 23.5, 43.3, 50.0, 126.6, 127.5, 128.2, 128.7, 128.8, 133.6, 136.7, 141.6, 169.6, 199.3.

The desired pure product(s) was characterized by comparison of their physical data with those of known β-amido carbonyl compounds (10–26). The spectral data of some representative β-amido ketones/esters are given as follows.

N-(1,3-Diphenyl-3-oxo-propyl) benzamide

Table 2, entry 2. IR (KBr, cm^{-1}): 3306, 3062, 1681, 1634, 1599, 1488, 1357, 981, 754. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 3.52 (dd, J = 6.0 and 16.4 Hz, 1H), 3.87 (dd, J = 4.8 and 16.8 Hz, 1H), 5.73–5.78 (m, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H) 7.37–7.45 (m, 5H), 7.49 (t, J = 7.2 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 43.1, 50.4, 126.6, 127.2, 127.6, 128.3, 128.7, 128.8, 128.9, 131.8, 133.8, 134.4, 136.7, 141.1, 166.9, 199.3.

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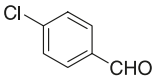
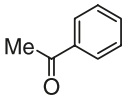
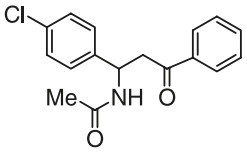
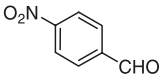
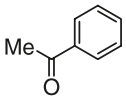
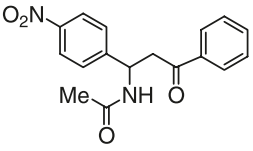
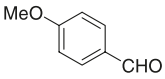
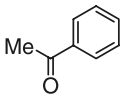
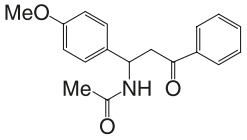
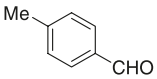
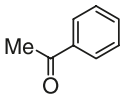
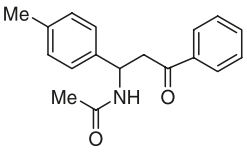
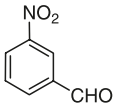
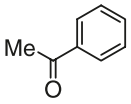
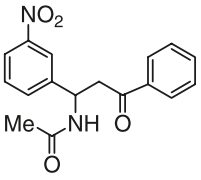
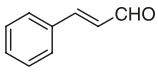
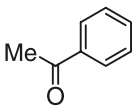
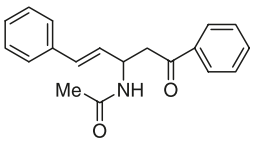
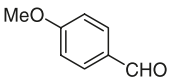
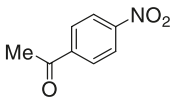
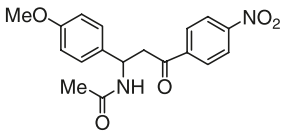
Table 2 (*continued*).

Entry	Aldehyde	Ketone	Product	Time (h)	Yield (%)[a]	Mp, lit. value, ref.
7				2	92	149–152, 149–150, 15
8				4	81	138–141, 153, 25
9				3	85	109–111, 110–112, 15
10				2.5	91	110–112, 112, 15
11				4	84	135–137, 139–140, 15
12				2	91	120–122, 120–121, 25
13				3.5	82	88–90, 87–89, 16

N-[1-Phenyl-3-oxo-3-(4-methoxyphenyl)propyl] acetamide

Table 2, entry 3. IR (KBr, cm^{-1}): 3260, 1680, 1640, 1600, 1570, 1255, 1170, 990, 700. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.00 (s, 3H), 3.34 (dd, *J* = 5.9 and 16.6 Hz, 1H), 3.67 (dd, *J* = 5.3 and 16.6 Hz, 1H), 3.84 (s, 3H), 5.50–5.57 (m, 1H), 6.86 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.18–7.34 (m, 5H), 7.88 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 23.4, 42.8, 50.0, 55.5, 113.8, 126.4, 127.3, 128.5, 129.7, 130.4, 141.1, 163.8, 169.5, 197.1.

N-[1-(2,5-Dimethoxyphenyl)-3-oxo-3-phenylpropyl] acetamide

Table 2, entry 17. IR (KBr, cm^{-1}): 3296, 3086, 1689, 1649, 1558, 1505, 1774,1296, 1226, 1047, 807, 754. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 2.00 (s, 3H), 3.46 (dd, *J* = 6.6 and 15.8 Hz, 1H), 3.56 (dd, *J* = 6.1 and 15.7 Hz, 1H), 3.73 (s, 3H), 3.85 (s, 3H), 5.69 (dd, *J* = 2.3 and 6.5 Hz, 1H), 6.73 (dd, *J* = 3.0 and 8.9 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 3.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.92 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 23.5, 43.0, 48.0, 55.7, 55.8, 111.7, 112.8, 115.0, 128.2, 128.6, 129.5, 133.2, 136.8, 150.8, 153.6, 169.0, 198.6. MS *m*/*z* (%): 327.2 (M^+, 17), 285.2 (19), 284.2 (100), 237.1 (16), 208.1 (17), 180.2 (27), 166.1 (62), 151.1 (13), 136.1 (12), 105.1 (45), 77.2 (23), 43.2 (14). $C_{19}H_{21}NO_4$ requires (%): C 69.71, H 6.47, N 4.28; found: C 69.56, H 6.39, N 4.34.

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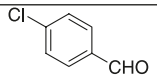
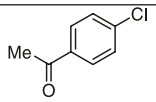
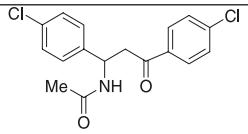
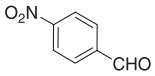
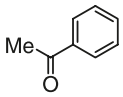
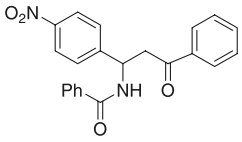
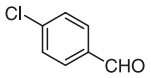
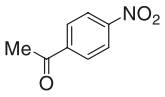
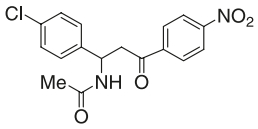
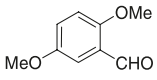
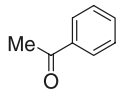
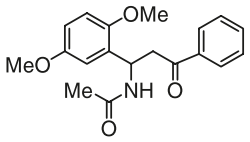
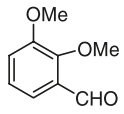
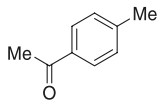
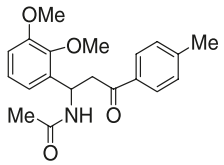
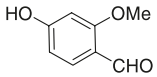
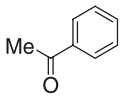
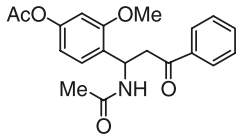
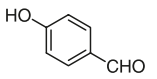
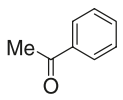
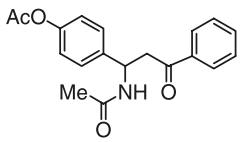
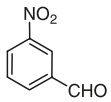
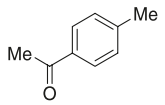
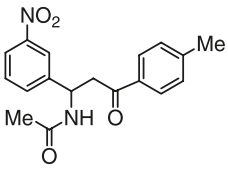
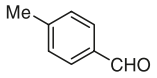
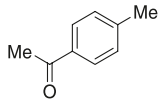
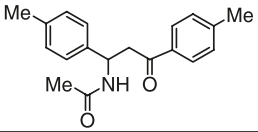
Table 2 (*concluded*).

Entry	Aldehyde	Ketone	Product	Time (h)	Yield (%)[a]	Mp, lit. value, ref.
14				2	90	141–143, 143–145,19
15				3.5	78	142–145, 142–144,25
16				3.5	86	116–118, 116–119,19
17				2	92	153–156,—
18				2	90	108–110,—
19				2.5	89	129–132,—
20				3	84	120–122,—
21				4	80	94–97,—
22				2.5	91	103–105,—

[a]Yields refer to the isolated pure products. All known products have been reported previously inthe literature and were characterized by comparison of mp, IR, and NMR spectra with authentic samples (10–26).

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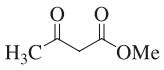
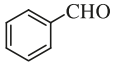
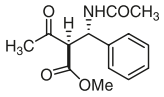
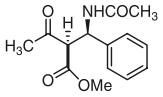
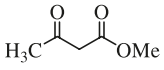
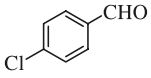
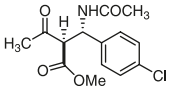
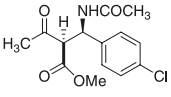
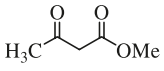
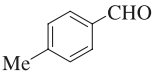
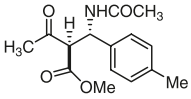
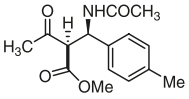
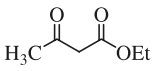
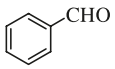
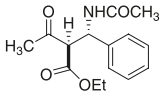
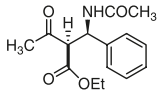
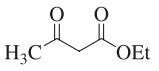
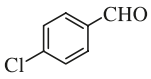
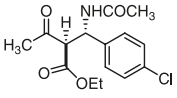
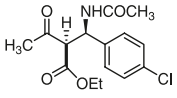
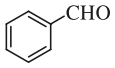
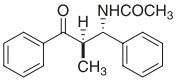
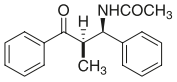
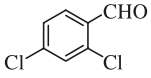
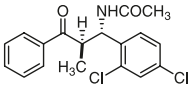
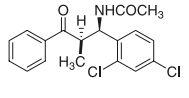
Table 3. Preparation of β-acetamido ketoesters in the presence of $Mg(HSO_4)_2$ as a catalyst at room temperature.

Entry	Enolizable ketone	Aldehyde	Time (h) ,Yield (%)[a]	Products[b] *Anti*	Products[b] *Syn*
1			2 , 84	 78 %	 22 %
2			2 , 90	 81 %	 19 %
3			2 , 87	 72 %	 28 %
4			3 , 89	 69 %	 31 %
5			3 , 91	 74 %	 26 %
6			4 , 84	 63 %	 37 %
7			4 , 85	 61 (%)	 39 (%)

[a]Yields refer to the isolated pure products.

[b]Ratio obtained from 1H NMR of the crude reaction mixture. All syn and anti diastereomers havebeen reported previously in the literature, thus we compared 1H NMR spectra with authenticsamples (10–12, 26).

Table 4. Recyclability of $Mg(HSO_4)_2$ in the synthesis of *N*-(1,3-diphenyl-3-oxo-propyl) acetamide.

Run no.	Yield (%)
1	89
2	87
3	88
4	85
5	84

N-[1-(2,3-Dimethoxyphenyl)-3-oxo-3-(4-methylphenyl)propyl] acetamide

Table 2, entry 18. IR (KBr, cm^{-1}): 3301, 3081, 2941, 1686, 1651, 1610, 1552, 1503, 1466,1372, 1284, 1225, 1047, 807, 714. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.99 (s, 3H), 2.38 (s, 3H), 3.42 (dd, *J* = 6.4 and 15.6 Hz, 1H), 3.51 (dd, *J* = 6.2 and 15.6 Hz, 1H), 3.72 (s, 3H), 3.84 (s, 3H), 5.68 (dd, *J* = 6.4 and 14.8 Hz, 1H), 6.72 (dd, *J* = 2.8 and 8.8 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.87–6.86 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 21.6, 23.4, 42.9, 47.9, 55.7, 55.8, 111.7, 112.7, 114.9, 128.3, 129.3, 129.7, 134.3, 144.0, 150.7, 153.6, 169.1, 198.2. MS *m*/*z* (%): 341.2 (M^+, 19), 299.2 (21), 298.2 (100), 251.2 (23), 208.1 (20), 180.2 (30), 166.1 (70), 151.1 (15), 136.1 (13), 119.1 (65), 105.1 (14), 91.2 (27), 77.2 (12), 43.2 (20). $C_{20}H_{23}NO_4$ requires (%): C 70.36, H 6.79, N 4.10; found: C 70.32, H 6.71, N 4.07.

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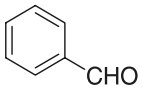
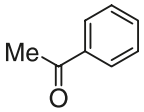
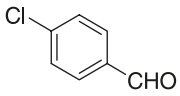
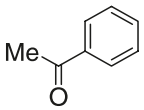
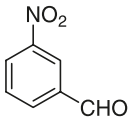
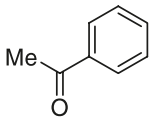
Table 5. Comparison result of magnesium hydrogensulfate with BiOCl (14), $ZrOCl_2 \cdot 8H_2O$ (15), CeCl3 $7H_2O$ (21), ZnO (22), and I_2 (23) in the synthesis of β-acetamido ketones.

Entry	Aldehyde	Enolizable Ketone	Catalyst	Molar ratio:aldehyde / enolizable ketone / catalyst (mol %)	Time (h)	Yield (%)
1			BiOCl	1/1/ (20 mol %)	7	92
			$ZrOCl_2.8H_2O$	1/1/ (20 mol %)	5	90
			$CeCl_3.7H_2O$	1/1/ (10 mol %)	7	96
			ZnO	1/1/ (50 mol %)	6	90
			I_2	1/1/ (10 mol %)	4.5	85
			$Mg(HSO_4)_2$	1/1/ (20 mol %)	2.5	89
2			BiOCl	1/1/ (20 mol %)	10	80
			$ZrOCl_2.8H_2O$	1/1/ (20 mol %)	8	91
			$CeCl_3.7H_2O$	1/1/ (10 mol %)	6	98
			ZnO	1/1/ (50 mol %)	5.5	92
			I_2	1/1/ (10 mol %)	4.5	85
			$Mg(HSO_4)_2$	1/1/ (20 mol %	2	92
3			BiOCl	1/1/ (20 mol %)	8	91
			$ZrOCl_2.8H_2O$	1/1/ (20 mol %)	6	92
			$CeCl_3.7H_2O$	1/1/ (10 mol %)	10	90
			ZnO	1/1/ (50 mol %)	5	90
			I_2	1/1/ (10 mol %)	4	85
			$Mg(HSO_4)_2$	1/1/ (20 mol %)	4	84

N-[1-(4-Acethoxy-2-methoxyphenyl)-3-oxo-3-phenylpropyl] acetamide

Table 2, entry 19. IR (KBr, cm^{-1}): 3281, 3096, 1768, 1686, 1653, 1602, 1558, 1511, 1366, 1304, 1279, 1199, 1029, 909, 741. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.98 (s, 3H), 2.28 (s, 3H), 3.42 (dd, *J* = 6.3 and 16.8 Hz, 1H), 3.69 (dd, *J* = 5.4 and 16.8 Hz, 1H), 3.78 (s, 3H), 5.53 (dd, *J* = 5.9 and 13.8 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.87–6.97 (m, 3H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 20.6, 23.3, 43.2, 49.9, 55.9, 115.5, 118.5, 122.8, 128.1, 128.7, 133.5, 136.6, 139.0, 140.0, 151.1, 169.0, 169.5, 198.4. MS *m/z* (%): 355.2 (M^+, 15), 313.2 (28), 312.2 (57), 271.2 (20), 270.2 (100), 254.2 (19), 208.2 (10), 194.2 (24), 166.2 (35), 152.2 (49), 105.2 (82), 77.2 (31), 43.2 (22). $C_{20}H_{21}NO_5$ requires (%): C 67.59, H 5.96, N 3.94; found: C 67.43, H 5.94, N 3.90.

N-[1-(4-Acethoxyphenyl)-3-oxo-3-phenylpropyl] acetamide

Table 2, Entry 20. IR (KBr, cm^{-1}): 3262, 3085, 2928, 1762, 1699, 1652, 1651, 1509, 1448, 1411, 1365, 1294, 1216, 1200, 911, 759, 691. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 2.01 (s, 3H), 2.28 (s, 3H), 3.44 (dd, *J* = 6.1 and 17.0 Hz, 1H), 3.73 (dd, *J* = 5.2 and 17.0 Hz, 1H), 5.56 (dd, *J* = 5.8 and 13.6 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 20.8, 22.6, 44.5, 48.4, 121.5, 127.7, 128.0, 128.7, 133.2, 136.5, 140.5, 149.2, 168.3, 169.2, 197.0. MS *m/z* (%): 352.2 (M^+, 8), 326.2 (2), 282.2 (100), 240.2 (41), 242.2(19), 178.2 (20), 167.1 (26), 149.1 (62), 136.2 (37), 122.2 (55), 105.2 (86), 77.2 (40), 57.2 (16), 43.2 (41). $C_{19}H_{19}NO_4$ requires (%): C 70.14, H 5.89, N 4.31; found: C 70.08, H 5.78, N 4.24.

N-[1-(3-Nitrophenyl)-3-oxo-3-(4-methylphenyl)propyl] acetamide

Table 2, entry 21. IR (KBr, cm^{-1}): 3301, 3069, 1680, 1645, 1606, 1531, 1352, 1202, 1180, 810, 741, 696. ^1H NMR (300 MHz, DMSO-d_6, ppm) δ: 1.97 (s, 3H), 2.36 (s, 3H), 3.43 (dd, *J* = 5.5 and 17.4 Hz, 1H), 3.61 (dd, *J* = 8.3 and 17.4 Hz, 1H), 5.45 (dd, *J* = 7.6 and 13.4 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.86–7.75 (m, 3H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H), 8.49 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.7, 22.6, 44.0, 48.5, 121.3, 121.8, 128.1, 129.1, 129.7, 133.7, 133.9, 143.7, 145.6, 147.8, 168.6, 196.1. MS *m/z* (%): 326.3 (M^+, 0.8), 283.2 (20), 267.2 (12), 189.2 (24), 190.2 (17), 165.2 (38), 151.2 (33), 134.2 (13),119.2 (100), 105.2 (12), 91.2

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(43), 77.2 (6), 65.2 (14), 43.2 (26). $C_{18}H_{18}N_2O_4$ requires (%): C 66.25, H 5.56, N 8.58; found: C 66.23, H 5.56, N 8.51.

_N_-[1-(4-Methylphenyl)-3-oxo-3-(4-methylphenyl)propyl] acetamide

Table 2, entry 22. IR (KBr, cm^{-1}): 3258, 3069, 1607, 1638, 1605, 1541, 1410, 1326, 1266, 1183, 998, 810, 722. ^1H NMR (300 MHz, DMSO-d_6, ppm) δ: 1.77 (s, 3H), 2.24 (s, 3H), 2.36 (s, 3H), 3.31 (dd, J = 6.1 and 15.9 Hz, 1H), 3.46 (dd, J = 8.0 and 16.7 Hz, 1H), 5.31 (dd, J = 7.7 and 14.2 Hz, 1H), 7.10 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H), 8.25 (d, J = 8.0 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ: 20.6, 21.1, 22.6, 44.5, 48.8, 126.5, 128.1, 128.7, 129.2, 134.1, 135.8, 140.0, 143.5, 168.2, 196.7. MS m/z (%): 295.2 (M^+, 12), 252.2 (100), 253.2 (21), 221.2 (13), 162.2 (10), 134.2 (49), 120.2 (70), 119.2 (91), 91.2 (44), 65.2 (14), 43.2 (14). $C_{19}H_{21}NO_2$ requires (%): C 77.26, H 7.17, N 4.74; found: C 77.20, H 7.13, N 4.70.

(_R_)-Methyl 2-((_S_)-acetamido(phenyl)methyl)-3-oxobutanoate

Table 3, entry 1 (mixture of diastereomers), data for the major isomer. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.97 (s, 3H), 2.11 (s, 3H), 3.71 (s, 3H), 4.07 (d, J = 5.5 Hz, 1H), 5.72 (dd, J = 5.5 and 9.0 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 7.22–7.30 (m, 5H).

(_R_)-Methyl 2-((_S_)-acetamido(4-chlorophenyl)methyl)-3-oxobutanoate

Table 3, entry 2 (mixture of diastereomers), data for the major isomer. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.98 (s, 3H), 2.13 (s, 3H), 3.73 (s, 3H), 4.07 (d, J = 5.5 Hz, 1H), 5.69 (dd, J = 5.5 and 9.0 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.26(d, J = 7.9 Hz, 2H).

(_R_)-Ethyl 2-((_S_)-acetamido(phenyl)methyl)-3-oxobutanoate

Table 3, entry 4 (mixture of diastereomers), data for the major isomer. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.20 (t, J = 7.1 Hz, 3H), 1.99 (s, 3H), 2.16 (s, 3H), 4.01 (d, J = 5.9 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 5.76 (dd, J = 6.2 and 8.9 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 7.24–7.33 (m, 5H).

_N_-((1_S_,2_R_)-2-Methyl-3-oxo-1,3-diphenylpropyl)acetamide

Table 3, entry 6 (mixture of diastereomers), data for the major isomer. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.32 (d, J = 7.2 Hz, 3H), 2.04 (s, 3H), 4.03–4.13 (m, 1H), 5.35 (dd, J = 4.5 and 8.9 Hz, 1H), 6.99–7.27 (m, 9H), 7.79 (d, J = 7.4 Hz, 2H).

Acknowledgments

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