Tetrahedron 65 (2009) 1026–1032

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile and diastereoselective synthesis of β-acetamido ketones and keto esters via direct Mannich-type reaction

Hui Mao, Jieping Wan, Yuanjiang Pan *

Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

ARTICLE INFO

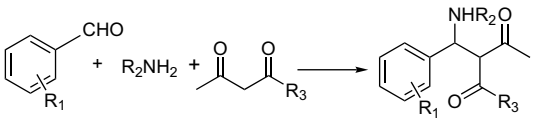
Article history:
Received 24 September 2008
Received in revised form 15 November 2008
Accepted 21 November 2008
Available online 27 November 2008

ABSTRACT

A Mannich-type three-component reaction involving aldehydes, acetamide, and enolizable ketones or β-keto esters for the preparation of β-acetamido carbonyl compounds in the presence of TMSCl is described. This newly developed protocol is operationally convenient, widely applicable, and highly diastereoselective.

1. Introduction

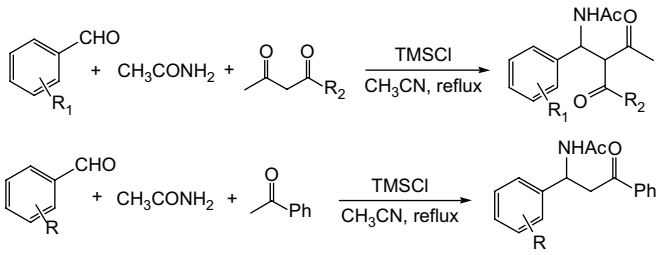
With their advantages of atom-efficient transformations, readily available materials, and various products, multicomponent reactions (MCRs) have received significant research interest from chemical and medicinal communities.[1] As one of the mostly studied MCRs, discovered in 1912, Mannich reaction is an aminoalkylation reaction of aldehyde (Scheme 1)[2] and is a very useful method for the preparation of β-amino compounds. It is also, therefore, a very important basic reaction in organic synthesis.[3]



Scheme 1.

β-Acetamido carbonyl compounds can be used as the precursor of 1,3-amino alcohols,[4] β-amino acids,[5] and γ-lactams.[6] They are the building blocks of numerous pharmaceutical and biological compounds.[7] Dakin et al. first reported the preparation of this kind of compound by Dakin–West reaction in 1928, which is exactly the condensation between an α-amino acid and acetic anhydride in the presence of a base providing the acetamido ketones.[8] Iqbal et al. meanwhile, developed the cobalt-catalyzed one-pot multicomponent coupling route involving ketones, aldehydes, acetonitrile as well as AcCl to prepare this class of compound.[5] Later on, a number of catalyst systems were reported for the synthesis of β-acetamido carbonyl compounds via the same reaction, including $ZrOCl_2 \cdot 8H_2O$,[10] PCl_3,[11] silica sulfuric acid,[12] $Cu(OTf)_2$,[13] BiOCl,[14] and $SiCl_2$-$ZnCl_2$.[15] These compounds have been disclosed as very effective catalysts. Recently, $CeCl_2 \cdot 7H_2O$[16] and $FeCl_3 \cdot 6H_2O$[17] were also successfully employed to promote this reaction.

Theoretically, since amines were able to produce β-amino ketones and keto esters through Mannich reaction, acetamide could similarly proceed to corresponding β-acetamido ketones and keto esters through this type of reaction. Surprisingly, the classical Mannich reaction is not easily applicable to amides probably due to its low reactivity character. Thus, for this study, we report an efficient Mannich-type MCR to directly prepare β-acetamido carbonyl compounds from aldehydes, acetamide, and enolizable ketones or β-keto esters in the presence of TMSCl (Scheme 2).



Scheme 2. A Mannich-type three-component reaction for the preparation of β-acetamido carbonyl compounds.

2. Results and disscussion

2.1. Optimization of Mannich-type multicomponent reaction for the synthesis of β-acetamido carbonyl compounds

Initially, the reaction of benzaldehyde, acetamide, and acetylacetone was chosen as model. We used a CH_3CN solution of

* Corresponding author. Tel.: +86 0570 8795 1264; fax: +86 0570 8795 1629.
E-mail address: cheyjpan@zju.edu.cn (Y. Pan).

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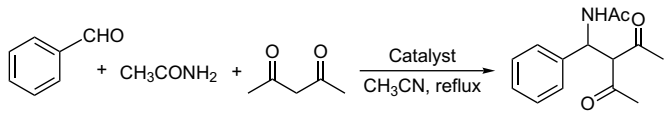
doi:10.1016/j.tet.2008.11.071

Table 1
Optimization of Mannich-type multicomponent reaction of benzaldehyde, acetamide, and acetylacetone[a]



Entry	Catalyst	Yield[b] (%)
1	HCl	0
2	$CoCl_2$	0
3	(L)-proline	0
4	TMSCl	30
5	TMSCl[c]	86
6	TMSCl[d]	85
7	No	0

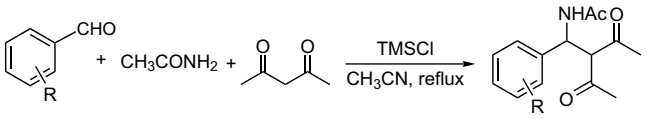
[a] Conditions: benzaldehyde (0.5 mmol), acetamide (0.6 mmol), acetylacetone (0.6 mmol), CH_3CN (3 ml), catalyst (0.1 mmol), 7 h.
[b] Isolated yield based on aromatic aldehyde.
[c] TMSCl (0.5 mmol).
[d] TMSCl (0.7 mmol).

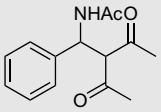
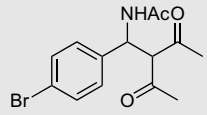
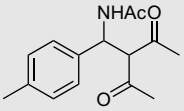
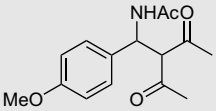
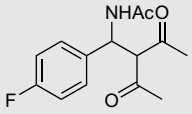
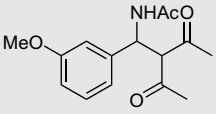
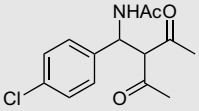
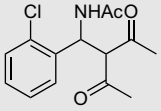
benzaldehyde (0.5 mmol), acetamide (0.6 mmol), and acetylacetone (0.6 mmol) in the presence of diluted HCl (1 mol/l, 0.1 ml) that was stirred at reflux for 7 h. Unfortunately, however, no target product was formed, and $CoCl_2$ and (L)-proline did not catalyze this reaction, either (Table 1, entries 1–3). Previously, our research group had successfully used TMSCl to promote Biginelli-type condensations,[18] isoindolinone synthesis,[19] and multicomponent synthesis of thiazines and tetrahydropyrimidones.[20] The preliminary results showed that it could also promote this reaction, but the yield was not so satisfying (Table 1, entry 4). To test the effect of the amount of TMSCl, 0.5 mmol TMSCl was added in the same condition, and the yield was increased to 86% (Table 1, entry 5). No significant impact on the yield was observed when the amount of TMSCl was added to 0.7 mmol (Table 1, entry 6). Consequently, if no catalyst was added, the results showed that there would be no corresponding product as well (Table 1, entry 7).

2.2. Mannich-type multicomponent reaction of acetamide, acetylacetone, and different aldehydes

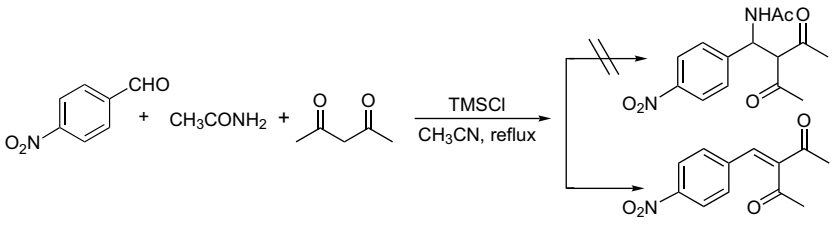
With the encouraging results, various aldehydes were employed for this reaction under the established protocol (Table 2). All reactions proceeded smoothly to give the corresponding compounds (Table 2, entries 1–8) in good yields, except for aldehyde containing a nitro group at the *para* position. It gave the Knoevenagel condensation product rather than our desired product (Scheme 3).

Table 2
Mannich-type multicomponent reaction of acetamide, acetylacetone, and different aldehydes[a]



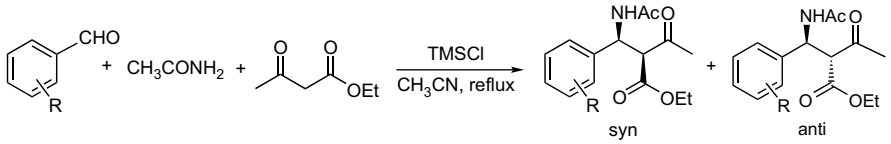
Entry	Product		Yield[b] (%)	Entry	Product		Yield[b] (%)
1		**1a**	86	5		**1e**	70
2		**1b**	78	6		**1f**	78
3		**1c**	84	7		**1g**	80
4		**1d**	75	8		**1h**	81

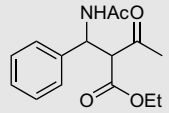
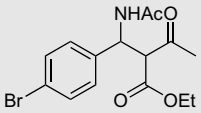
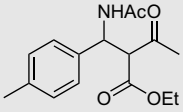
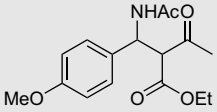
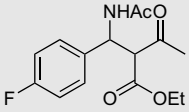
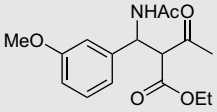
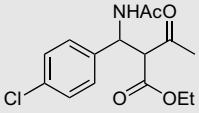
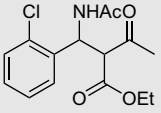
[a] Conditions: aldehyde (0.5 mmol), acetamide (0.6 mmol), acetylacetone (0.6 mmol), CH_3CN (3 ml), TMSCl (0.5 mmol), 5–10 h.
[b] Isolated yield based on aromatic aldehyde.



Scheme 3.

Table 3
Mannich-type multicomponent reaction of acetamide, ethylacetoacetate, and different aldehydes[a]



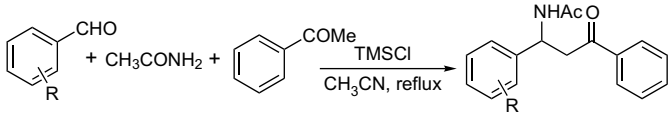
Entry	Product		Yield[b] (%)	*syn*/*anti*[c]	Entry	Product		Yield[b] (%)	*syn*/*anti*[c]
1		**2a**	84	4:96	5		**2e**	71	45:55
2		**2b**	75	15:85	6		**2f**	79	36:64
3		**2c**	82	25:75	7		**2g**	81	23:77
4		**2d**	76	6:94	8		**2h**	80	50:50

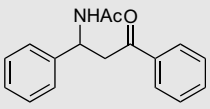
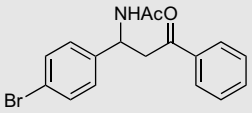
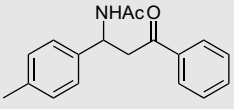
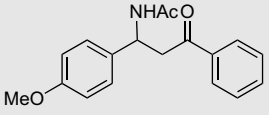
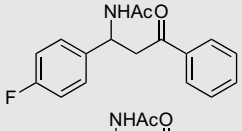
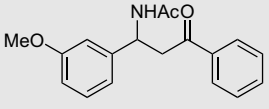
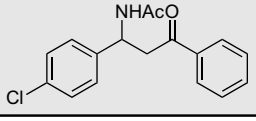
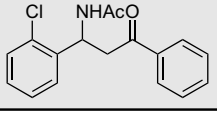
[a] Conditions: aldehyde (0.5 mmol), acetamide (0.6 mmol), ethylacetoacetate (0.6 mmol), CH_3CN (3 ml), TMSCl (0.5 mmol), 5–10 h.
[b] Isolated yield based on aromatic aldehyde.
[c] The ratio of *syn*/*anti* diastereomers was determined from the ^1H NMR spectrum of the crude mixture.

2.3. Mannich-type multicomponent reaction of acetamide, ethylacetoacetate, and different aldehydes

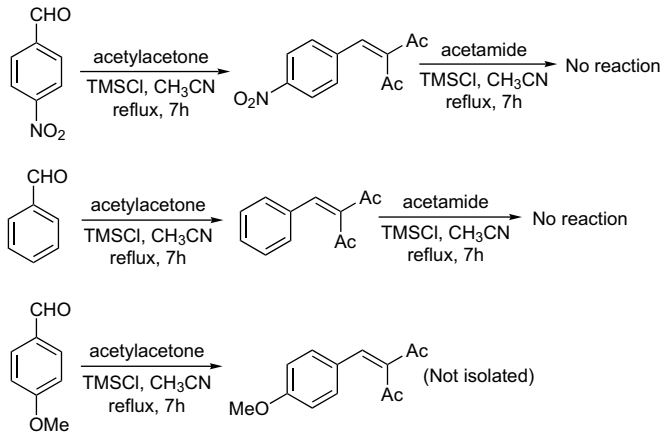
To further test the scope of the reaction, ethylacetoacetate as methylene donor was subjected to the reaction, and the corresponding β-acetamido keto esters were obtained (Table 3). Accompanied with moderate to good yield, good diasteroselectivity was found with these reactions. Specifically, the de value of the reaction with benzaldehyde was up to 92% (Table 3, entry 1). The major products obtained were the *anti* isomers (Table 3, entries

Table 4
Mannich-type multicomponent reaction of acetamide, acetophenone, and different aldehydes[a]



Entry	Product		Yield[b] (%)	Entry	Product		Yield[b] (%)
1		**3a**	80	5		**3e**	70
2		**3b**	74	6		**3f**	75
3		**3c**	73	7		**3g**	73
4		**3d**	71	8		**3h**	76

[a] Conditions: aldehyde (0.5 mmol), acetamide (0.6 mmol), acetophenone (0.6 mmol), CH_3CN (3 ml), TMSCl (0.5 mmol), 5–10 h.
[b] Isolated yield based on aromatic aldehyde.



Scheme 4.

1–7). The ratio of *syn*/*anti* diastereomers was determined from the ^{1}H NMR spectrum of the crude product compared with that reported in the literature.[21]

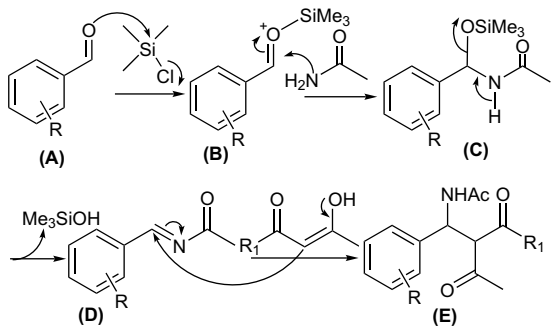
2.4. Mannich-type multicomponent reaction of acetamide, acetophenone, and different aldehydes

Finally, we focused on the reaction of acetophenone. Fortunately, the expected results were obtained. Various acetophenone were found to produce the β-acetamido ketones in good yields (Table 4).

2.5. Mechanism for Mannich-type multicomponent reaction promoted by TMSCl

From Table 1 (entry 7), the reaction including benzaldehyde, acetamide, and acetylacetone failed to give the correlative product in the absence of TMSCl, which indicated that the latter plays an important role in the reaction. To further discuss the mechanism of this Mannich-type reaction, a variety of aromatic aldehydes containing both electron withdrawing and donating group at the *para* position were treated with acetylacetone under the same experimental conditions. The results showed that this reaction can give the corresponding Knoevenagel condensation product except the aldehyde containing a electron donating group. Then, the Knoevenagel condensation product reacted with acetamide under the same conditions. However, no Mannich-type product was observed (Scheme 4).

On the basis of the results and previous related Mannich reaction mechanistic research,[22] a possible mechanism for this Mannich-type reaction was proposed in Scheme 5. Initially, TMSCl acted as a Lewis acid to activate aldehyde **A** by complexation with aldehyde oxygen.[23] Complex **B** and acetamide formed their corresponding hemiaminal **C** via standard nucleophilic addition reaction. Followed by loss of one molecular Me_3SiOH, the reactive intermediate **D** was formed. At the same time, the enolizable ketone or β-keto ester nucleophilic attacked the intermediate to afford the final product **E**.



Scheme 5. A possible mechanism for TMSCl-promoted Mannich-type reaction for the preparation of β-acetamido carbonyl compounds.

3. Conclusion

In summary, we have developed a new Mannich-type multicomponent reaction in the presence of TMSCl for the preparation of β-acetamido ketones and keto esters. This direct method provided a facile and useful supplement for those already established routes.

4. Experimental

4.1. General

The melting points were determined using XT-4 apparatus and were not corrected. The NMR spectra were recorded on a Bruker AVANCE DMX-500 spectrometry using $CDCl_3$ as solvent and TMS as the internal standard. Mass spectra were performed on a Bruker Esquire 3000 mass spectrometer equipped with ESI interface and ion trap analyzer. HRMS were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source.

4.2. General procedure for the preparation of β-acetamido carbonyl compounds

TMSCl (0.5 mmol) was added to a solution of aldehyde (0.5 mmol), acetamide (0.6 mmol), and acetylacetone or ethylacetoacetate or acetophenone (0.6 mmol) in acetonitrile (3 ml). The reaction was stirred at reflux temperature until the reaction was completed (monitored by TLC). Then the mixture was extracted with ethyl acetate (3×20 ml), washed with water (3×20 ml), dried over Na_2SO_4. After the solvent was removed, the crude mixture was recrystallized from ethyl acetate–hexane and the solid product was afforded.

*4.2.1. N-(2-Acetyl-3-oxo-1-phenyl-butyl)-acetamide (**1a**)*

White solid, yield 86%, mp 132–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16–7.25 (5H, m, Ph), 7.03 (1H, d, *J* 8.5 Hz, NH), 5.78 (1H, dd, *J* 5.0 Hz, 9.3 Hz, CH), 4.23 (1H, d, *J* 5.5 Hz, CH), 2.17 (3H, s, COMe), 2.02 (3H, s, COMe), 1.91 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.4, 202.8, 169.9, 139.5, 129.0, 128.0, 126.6, 126.5, 70.7, 52.1, 31.2, 30.1, 23.5. MS (ESI): *m*/*z* 270 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{14}H_{17}NO_3Na$: 270.1101; Found: 270.1096.

*4.2.2. N-(2-Acetyl-3-oxo-1-p-tolyl-butyl)-acetamide (**1b**)*

White solid, yield 78%, mp 150–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (2H, d, *J* 8.3 Hz, Ph), 7.08 (2H, d, *J* 8.2 Hz, Ph), 5.81 (1H, dd, *J* 6.5 Hz, 2.7 Hz, CH), 4.28 (1H, d, *J* 6.3 Hz, CH), 2.29 (3H, s, CH_3), 2.20 (3H, s, COMe), 2.10 (3H, s, COMe), 1.95 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 202.8, 169.9, 137.6, 136.6, 129.6, 126.4, 71.0, 52.0, 31.0, 30.2, 23.4, 21.2. MS (ESI): *m*/*z* 284 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{15}H_{19}NO_3Na$: 284.1257; Found: 284.1250.

*4.2.3. N-[2-Acetyl-1-(4-fluoro-phenyl)-3-oxo-butyl]-acetamide (**1c**)*

White solid, yield 84%, mp 138–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18–7.21 (2H, m, Ph), 7.13 (2H, d, *J* 9.1 Hz, NH), 6.90–6.94 (2H, m, Ph), 5.74 (1H, dd, *J* 6.5 Hz, 2.7 Hz, CH), 4.21 (1H, d, *J* 6.4 Hz, CH), 2.15 (3H, s, COMe), 2.04 (3H, s, COMe), 1.89 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.1, 202.5, 169.9, 163.3, 161.3, 135.4, 128.4, 115.9, 71.0, 51.6, 30.9, 30.2, 23.6. MS (ESI): *m*/*z* 288

([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{14}H_{16}FNO_3Na$: 288.1006; Found: 288.1000.

4.2.4. N-[2-Acetyl-1-(4-chloro-phenyl)-3-oxo-butyl]-acetamide (**1d**)

White solid, yield 75%, mp 167–169 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (2H, d, J 8.4 Hz, Ph), 7.22 (2H, d, J 8.4 Hz, Ph), 7.04 (2H, d, J 8.2 Hz, NH), 5.82 (1H, dd, J 6.5 Hz, 2.7 Hz, CH), 4.26 (1H, d, J 5.6 Hz, CH), 2.28 (3H, s, COMe), 2.10 (3H, s, COMe), 2.00 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 202.5, 170.0, 138.1, 133.9, 129.2, 128.1, 70.4, 51.5, 31.4, 30.1, 23.5. MS (ESI): m/z 304 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{14}H_{16}ClNO_3Na$: 304.0711; Found: 304.0710.

4.2.5. N-[2-Acetyl-1-(4-bromo-phenyl)-3-oxo-butyl]-acetamide (**1e**)

White solid, yield 70%, mp 188–190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (2H, d, J 8.4 Hz, Ph), 7.22 (2H, d, J 8.4 Hz, Ph), 7.04 (2H, d, J 13.8 Hz, NH), 5.73 (1H, dd, J 5.6 Hz, 3.6 Hz, CH), 4.18 (1H, d, J 5.6 Hz, CH), 2.20 (3H, s, COMe), 2.02 (3H, s, COMe), 1.92 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 202.5, 170.0, 138.6, 132.1, 128.4, 122.0, 70.4, 51.6, 31.4, 30.1, 23.5. MS (ESI): m/z 348 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{14}H_{16}BrNO_3Na$: 348.0206; Found: 348.0203.

4.2.6. N-[2-Acetyl-1-(4-methoxy-phenyl)-3-oxo-butyl]-acetamide (**1f**)

White solid, yield 78%, mp 147–149 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (2H, d, J 8.4 Hz, Ph), 7.22 (2H, d, J 8.4 Hz, Ph), 7.04 (2H, d, J 8.2 Hz, NH), 5.82 (1H, dd, J 6.5 Hz, 2.7 Hz, CH), 4.26 (1H, d, J 5.6 Hz, CH), 3.76 (3H, s, OMe), 2.28 (3H, s, COMe), 2.10 (3H, s, COMe), 2.00 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 202.5, 170.0, 138.1, 133.9, 129.2, 128.1, 70.4, 51.5, 31.4, 30.1, 23.5. MS (ESI): m/z 300 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{15}H_{19}NO_4Na$: 300.1206; Found: 300.1212.

4.2.7. N-[2-Acetyl-1-(3-methoxy-phenyl)-3-oxo-butyl]-acetamide (**1g**)

White solid, yield 80%, mp 130–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (1H, s, Ph), 7.07 (1H, d, J 8.4 Hz, NH), 6.76–6.84 (3H, m, Ph), 5.82 (1H, dd, J 6.4 Hz, 3.3 Hz, CH), 4.28 (1H, d, J 6.0 Hz, CH), 3.78 (3H, s, OMe), 2.23 (3H, s, COMe), 2.10 (3H, s, COMe), 1.97 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 202.8, 169.9, 160.0, 141.1, 130.1, 118.7, 112.9, 70.7, 55.5, 52.0, 31.2, 30.1, 23.5. MS (ESI): m/z 300 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{15}H_{19}NO_4Na$: 300.1206; Found: 300.1209.

4.2.8. N-[2-Acetyl-1-(2-chloro-phenyl)-3-oxo-butyl]-acetamide (**1h**)

White solid, yield 81%, mp 96–98 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (1H, d, J 9.2 Hz, NH), 7.26–7.47 (2H, m, Ph), 7.12–7.16 (2H, m, Ph), 6.02 (1H, dd, J 5.2 Hz, 5.1 Hz, CH), 4.41 (1H, d, J 4.2 Hz, CH), 2.29 (3H, s, COMe), 2.00 (3H, s, COMe), 1.91 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.9, 202.9, 192.8, 169.9, 136.4, 132.5, 129.8, 127.3, 66.9, 50.0, 31.9, 29.4, 23.5. MS (ESI): m/z 304 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{14}H_{16}ClNO_3Na$: 304.0711; Found: 304.0706.

4.2.9. 2-(Acetylamino-phenyl-methyl)-3-oxo-butyric acid ethyl ester (**2a**)

White solid, yield 84%, mp 106–109 °C. Data for major isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16–7.25 (5H, m, Ph), 7.01 (1H, d, J 8.0 Hz, NH), 5.68 (1H, dd, J 6.3 Hz, 3.3 Hz, CH), 4.08 (2H, q, J 3.6 Hz, CH_2), 4.03 (1H, d, J 6.8 Hz, CH), 2.09 (3H, s, COMe), 1.91 (3H, s, COMe), 1.11 (3H, t, J 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.0, 169.7, 167.4, 139.4, 128.8, 127.9, 126.7, 63.1, 62.1, 52.6, 30.8, 23.5, 14.1. MS (ESI): m/z 300 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{15}H_{19}NO_4Na$: 300.1206; Found: 300.1202.

4.2.10. 2-(Acetylamino-p-tolyl-methyl)-3-oxo-butyric acid ethyl ester (**2b**)

White solid, yield 75%, mp 98–101 °C. Data for major isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (2H, d, J 8.5 Hz, Ph), 7.01 (2H, d, J 8.5 Hz, Ph), 5.64 (1H, dd, J 6.7 Hz, 2.5 Hz, CH), 4.07 (2H, q, J 3.7 Hz, CH_2), 3.99 (1H, d, J 6.7 Hz, CH), 2.22 (3H, s, CH_3), 2.10 (3H, s, COMe), 1.88 (3H, s, COMe), 1.11 (3H, t, J 7.0 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.0, 169.9, 167.4, 137.6, 136.4, 129.5, 126.2, 63.9, 62.0, 52.3, 30.6, 23.4, 21.1, 14.1. MS (ESI): m/z 300 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{16}H_{21}NO_4Na$: 314.1363; Found: 314.1359.

4.2.11. 2-[Acetylamino-(4-fluoro-phenyl)-methyl]-3-oxo-butyric acid ethyl ester (**2c**)

White solid, yield 82%, mp 100–102 °C. Data for major isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (1H, d, J 8.9 Hz, NH), 7.33–7.38 (2H, m, Ph), 7.10–7.15 (2H, m, Ph), 5.43 (1H, dd, J 9.1 Hz, 2.4 Hz, CH), 4.04 (1H, d, J 11.2 Hz, CH), 3.87 (2H, q, J 7.1 Hz, CH_2), 2.50 (3H, s, COMe), 1.76 (3H, s, COMe), 0.92 (3H, t, J 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.0, 169.7, 168.1, 161.6, 137.7, 130.4, 116.2, 65.7, 62.2, 52.3, 30.7, 23.7, 14.7. MS (ESI): m/z 318 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{15}H_{18}FNO_4Na$: 318.1112; Found: 318.1105.

4.2.12. 2-[Acetylamino-(4-chloro-phenyl)-methyl]-3-oxo-butyric acid ethyl ester (**2d**)

White solid, yield 76%, mp 106–108 °C. Data for major isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16–7.21 (4H, m, Ph), 5.43 (1H, dd, J 6.9 Hz, 1.9 Hz, CH), 4.06 (2H, q, J 2.7 Hz, CH_2), 3.98 (1H, d, J 6.7 Hz, CH), 2.11 (3H, s, COMe), 1.89 (3H, s, COMe), 1.11 (3H, t, J 7.2 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 170.0, 167.1, 138.1, 133.7, 129.2, 127.9, 63.0, 61.8, 51.9, 30.5, 23.3, 14.1. MS (ESI): m/z 334 ([M+Na]$^+$). HRMS (ESI): ([M+ Na]$^+$): Calcd for $C_{15}H_{18}ClNO_4Na$: 334.0817; Found: 334.0811.

4.2.13. 2-[Acetylamino-(4-bromo-phenyl)-methyl]-3-oxo-butyric acid ethyl ester (**2e**)

White solid, yield 71%, mp 120–122 °C. Data for major isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14–7.25 (4H, m, Ph), 5.61 (1H, dd, J 7.1 Hz, 2.3 Hz, CH), 4.08 (2H, q, J 7.1 Hz, CH_2), 3.98 (1H, d, J 4.5 Hz, CH), 2.10 (3H, s, COMe), 1.89 (3H, s, COMe), 1.11 (3H, t, J 1.3 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 170.0, 169.0, 140.3, 132.7, 128.9, 121.3, 63.5, 61.9, 52.0, 30.6, 23.4, 14.1. MS (ESI): m/z 378 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{15}H_{18}BrNO_4Na$: 378.0311; Found: 378.0300.

4.2.14. 2-[Acetylamino-(4-methoxy-phenyl)-methyl]-3-oxo-butyric acid ethyl ester (**2f**)

White solid, yield 79%, mp 103–105 °C. Data for major isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (2H, d, J 3.4 Hz, Ph), 6.8 (2H, d, J 1.5 Hz, Ph), 5.69 (1H, dd, J 6.7 Hz, 2.3 Hz, CH), 4.12 (2H, q, J 2.9 Hz, CH_2), 4.02 (1H, d, J 6.6 Hz, CH), 3.76 (3H, s, OMe), 2.17 (3H, s, COMe), 1.95 (3H, s, COMe), 1.11 (3H, t, J 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 169.8, 167.5, 159.3, 131.6, 128.0, 114.3, 63.5, 62.0, 55.4, 52.1, 30.6, 23.5, 14.1. MS (ESI): m/z 330 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{16}H_{21}NO_5Na$: 330.1312; Found: 330.1317.

4.2.15. 2-[Acetylamino-(3-methoxy-phenyl)-methyl]-3-oxo-butyric acid ethyl ester (**2g**)

White solid, yield 81%, mp 101–103 °C. Data for major isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (1H, s, Ph), 6.84–6.98 (3H, m, Ph), 5.71 (1H, dd, J 6.4 Hz, 2.8 Hz, CH), 4.12 (2H, q, J 7.1 Hz, CH_2), 4.06 (1H, d, J 6.3 Hz, CH), 3.76 (3H, s, OMe), 2.16 (3H, s, COMe), 1.95 (3H, s, COMe), 1.11 (3H, t, J 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 169.9, 167.4, 160.0, 141.1, 129.9, 118.8, 113.1, 112.8, 63.8, 62.1, 55.4,

52.5, 30.8, 23.5, 14.1. MS (ESI): *m*/*z* 330 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{16}H_{21}NO_5Na$: 330.1312; Found: 330.1309.

4.2.16. 2-[Acetylamino-(2-chloro-phenyl)-methyl]-3-oxo-butyric acid ethyl ester (**2h**)

Colorless liquid, yield 80%. Data for major isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.42 (4H, m, Ph), 5.68 (1H, dd, *J* 5.5 Hz, 3.4 Hz, CH), 4.14 (2H, q, *J* 3.5 Hz, CH_2), 3.98 (1H, d, *J* 7.1 Hz, CH), 2.38 (3H, s, COMe), 2.01 (3H, s, COMe), 1.08 (3H, t, *J* 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 169.7, 167.3, 136.4, 132.6, 131.1, 130.0, 128.9, 127.2, 62.1, 59.6, 50.4, 31.4, 23.5, 14.0. MS (ESI): *m*/*z* 334 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{15}H_{18}ClNO_4Na$: 334.0817; Found: 334.0809.

4.2.17. N-(3-Oxo-1,3-diphenyl-propyl)-acetamide (**3a**)

White solid, yield 80%, mp 103–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* 7.4 Hz, Ph), 7.46 (1H, d, *J* 7.4 Hz, Ph), 7.35 (2H, t, *J* 7.8 Hz, Ph), 7.13–7.25 (5H, m, Ph), 6.75 (1H, d, *J* 7.5 Hz, NH), 5.48 (1H, m, CH), 3.66 (1H, dd, *J* 5.3 Hz, 11.5 Hz, CH_2), 3.35 (1H, dd, *J* 6.1 Hz, 10.7 Hz, CH_2), 1.91 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.7, 169.7, 141.1, 136.8, 133.8, 128.9, 128.3, 127.7, 126.6, 50.1, 43.5, 23.6. MS (ESI): *m*/*z* 290 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{17}H_{17}NO_2Na$: 290.1151; Found: 290.1147.

4.2.18. N-(3-Oxo-3-phenyl-1-p-tolyl-propyl)-acetamide (**3b**)

White solid, yield 74%, mp 112–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (2H, t, *J* 7.2 Hz, Ph), 7.56 (1H, t, *J* 7.4 Hz, Ph), 7.44 (2H, t, *J* 7.9 Hz, Ph), 7.22 (2H, d, *J* 8.1 Hz, Ph), 7.11 (2H, d, *J* 8.4 Hz, Ph), 6.74 (1H, d, *J* 7.4 Hz, NH), 5.51 (1H, m, CH), 3.74 (1H, dd, *J* 5.3 Hz, 11.5 Hz, CH_2), 3.44 (1H, dd, *J* 6.3 Hz, 10.5 Hz, CH_2), 2.29 (3H, s, CH_3), 2.00 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.7, 169.7, 138.1, 137.3, 136.8, 133.6, 129.5, 128.9, 128.3, 126.6, 50.0, 43.5, 23.6, 21.2. MS (ESI): *m*/*z* 290 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{18}H_{19}NO_2Na$: 304.1308; Found: 304.1303.

4.2.19. N-[1-(4-Fluoro-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (**3c**)

White solid, yield 73%, mp 109–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (2H, d, *J* 7.3 Hz, Ph), 7.58 (1H, t, *J* 7.3 Hz, Ph), 7.46 (2H, t, *J* 8.2 Hz, Ph), 7.29–7.44 (2H, m, Ph), 6.96–7.01 (2H, m, Ph), 6.74 (1H, d, *J* 7.5 Hz, NH), 5.55 (1H, m, CH), 3.74 (1H, dd, *J* 5.0 Hz, 12.0 Hz, CH_2), 3.44 (1H, dd, *J* 6.0 Hz, 10.9 Hz, CH_2), 2.05 (3H, s, CH_3), 2.00 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8, 169.7, 163.2, 161.2, 137.0, 136.8, 133.9, 129.0, 128.4, 115.8, 49.5, 43.3, 29.9, 23.7. MS (ESI): *m*/*z* 308 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{17}H_{16}FNO_2Na$: 308.1057; Found: 308.1052.

4.2.20. N-[1-(4-Chloro-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (**3d**)

White solid, yield 71%, mp 146–148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* 7.3 Hz, Ph), 7.50 (1H, t, *J* 6.5 Hz, Ph), 7.38 (2H, t, *J* 8.0 Hz, Ph), 7.18–7.20 (4H, m, Ph), 6.71 (1H, d, *J* 7.2 Hz, NH), 5.46 (1H, m, CH), 3.67 (1H, dd, *J* 5.0 Hz, 12.2 Hz, CH_2), 3.37 (1H, dd, *J* 6.4 Hz, 11.3 Hz, CH_2), 1.96 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.7, 169.7, 139.7, 136.7, 134.0, 133.4, 129.1, 129.0, 128.3, 128.1, 49.5, 43.0, 23.7. MS (ESI): *m*/*z* 324 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{17}H_{16}ClNO_2Na$: 324.0762; Found: 324.0755.

4.2.21. N-[1-(4-Bromo-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (**3e**)

White solid, yield 70%, mp 147–149 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (2H, d, *J* 7.2 Hz, Ph), 7.54 (1H, t, *J* 7.3 Hz, Ph), 7.44 (2H, t, *J* 8.0 Hz, Ph), 7.39 (2H, d, *J* 8.3 Hz, Ph), 7.20 (2H, d, *J* 8.4 Hz, Ph), 6.72 (1H, d, *J* 7.0 Hz, NH), 5.50 (1H, m, CH), 3.72 (1H, dd, *J* 5.3 Hz, 16.0 Hz, CH_2), 3.41 (1H, dd, *J* 6.2 Hz, 16.8 Hz, CH_2), 2.01 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.5, 166.7, 140.0, 136.4, 134.0, 131.8, 129.1, 129.0, 128.4, 128.3, 49.4, 43.0, 23.7. MS (ESI): *m*/*z* 368 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{17}H_{16}BrNO_2Na$: 368.0262; Found: 368.2064.

4.2.22. N-[1-(4-Methoxy-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (**3f**)

White solid, yield 75%, mp 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (2H, d, *J* 7.2 Hz, Ph), 7.55 (1H, d, *J* 7.4 Hz, Ph), 7.45 (2H, t, *J* 7.9 Hz, Ph), 7.25 (2H, t, *J* 5.1 Hz, Ph), 6.8 (2H, t, *J* 7.4 Hz, Ph), 5.51 (1H, m, CH), 3.75 (3H, s, CH_3), 3.73 (1H, dd, *J* 5.3 Hz, 11.5 Hz, CH_2), 3.42 (1H, dd, *J* 6.5 Hz, 10.3 Hz, CH_2), 1.99 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8, 169.6, 159.0, 136.8, 133.6, 133.2, 128.9, 128.3, 127.8, 114.5, 55.5, 49.8, 43.5, 23.6. MS (ESI): *m*/*z* 320 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{18}H_{19}NO_3Na$: 320.1257; Found: 320.1251.

4.2.23. N-[1-(3-Methoxy-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (**3g**)

Colorless liquid, yield 73%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (2H, d, *J* 7.3 Hz, Ph), 7.55 (1H, d, *J* 7.4 Hz, Ph), 7.45 (2H, t, *J* 7.8 Hz, Ph), 7.22 (1H, t, *J* 7.9 Hz, Ph), 6.76–6.92 (4H, m, Ph), 5.54 (1H, m, CH), 3.77 (3H, s, CH_3), 3.74 (1H, dd, *J* 5.3 Hz, 12.1 Hz, CH_2), 3.42 (1H, dd, *J* 6.1 Hz, 10.7 Hz, CH_2), 2.02 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8, 169.7, 160.0, 142.8, 136.8, 133.7, 129.9, 128.9, 118.9, 112.7, 55.5, 49.8, 43.4, 23.7. MS (ESI): *m*/*z* 320 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{18}H_{19}NO_3Na$: 320.1257; Found: 320.1252.

4.2.24. N-[1-(2-Chloro-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (**3h**)

White solid, yield 76%, mp 135–137 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (2H, d, *J* 7.3 Hz, Ph), 7.33–7.56 (5H, m, Ph), 7.16–7.22 (2H, m, Ph), 6.98 (1H, d, *J* 7.3 Hz, NH), 5.83 (1H, m, CH), 3.75 (1H, dd, *J* 6.0 Hz, 10.9 Hz, CH_2), 3.45 (1H, dd, *J* 5.5 Hz, 10.5 Hz, CH_2), 2.04 (3H, s, COMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 169.5, 138.4, 136.7, 133.9, 132.7, 130.1, 128.9, 128.6, 127.2, 48.3, 41.6, 23.6. MS (ESI): *m*/*z* 324 ([M+Na]$^+$). HRMS (ESI): ([M+Na]$^+$): Calcd for $C_{17}H_{16}ClNO_2Na$: 324.0762; Found: 324.0758.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 20775069).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.071.

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