Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 10079–10086

Synthesis of β-amino carbonyl compounds via a $Zn(OTf)_2$-catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds

Yun-Yun Yang, Wang-Ge Shou and Yan-Guang Wang*

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

Received 27 May 2006; revised 16 August 2006; accepted 21 August 2006
Available online 6 September 2006

Abstract—A $Zn(OTf)_2$-catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds was described. This one-pot three-component reaction afforded the corresponding β-amino carbonyl compounds, β-amino esters, and β-amino ketones in good to excellent yields. The reaction was also applied for the liquid-phase synthesis of β-amino carbonyl compound library using PEG as a support.

1. Introduction

β-Amino carbonyl compounds are useful building blocks for molecules with applications in pharmaceutical and material science.[1] β-Amino carbonyl moieties are found as structural units of a number of biologically active natural products.[2] The Mannich-type reactions are classical method for the synthesis of β-amino carbonyl compounds.[3] Lanthanide triflates as Lewis acids have been reported to be able to catalyze this kind of reactions.[4] High catalytic activity, low toxicity, and air tolerance make lanthanide triflates as attractive catalysts.[5] However, these catalysts suffer from some disadvantages such as requiring a large amount of Lewis acid (usually more than 10 mol %), a long reaction time, and/or atmosphere sensitive reagents. We report herein full details of a novel, rapid, and efficient three-component synthesis of β-amino esters via a $Zn(OTf)_2$-catalyzed cascade imino-formation/Mannich-type reaction of anilines with aromatic aldehydes and diethyl malonic ester,[6] and its extension to other kinds of β-amino carbonyl compounds as well as its applications in liquid-phase synthesis.

2. Results and discussion

In our initial experiments, we found that benzaldehydes **1**, anilines **2**, and diethyl malonic ester **3** in DCM were stirred in the presence of a catalytic amount (1 mol %) of $Zn(OTf)_2$ at room temperature for 4 h to give the corresponding β-amino esters **4**. As shown in Table 1, the three-component reaction of diethyl malonic ester with the electron-deficient anilines and the electron-deficient benzaldehydes afforded β-amino esters **4** in good to excellent yields (90–98%) (Table 1, entries 5–12). However, the electron-rich anilines and the electron-rich benzaldehydes gave lower (Table 1, entries 1–4) or poor yields (Table 1, entries 13 and 14).

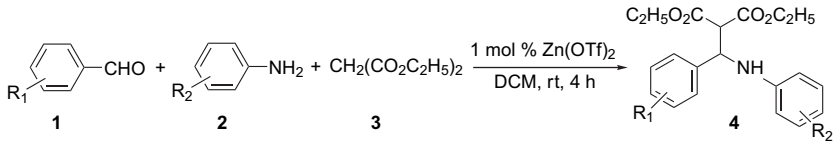
These results promoted us to examine other carbonyl compounds. We then investigated the three-component condensation of anilines with benzaldehydes and cyclohexanone using $Zn(OTf)_2$ as a catalyst, and the results are summarized in Table 2. When 1 mol % $Zn(OTf)_2$ was used, β-amino ketones **6** were obtained as a mixture of *anti* and *syn* isomers. In this case, both the electron-rich and the electron-deficient benzaldehydes gave good to excellent yields (Table 2, entries 1–10), while the electron-deficient aniline almost did not work (Table 2, entry 11). The *anti* and *syn* isomers were identified by the coupling constants (*J*) of the vicinal protons adjacent to C═O and NH in their ^{1}H NMR spectra.[7] In general, the coupling constants for *anti* isomers are greater than that for *syn* isomers.[8] The ratio of the isomers was determined by integration of the corresponding peaks in ^{1}H NMR spectra. As shown in Table 2, high *anti* selectivity was obtained in our three-component reaction.

In connection with our researches on the liquid-phase synthesis using polyethylene glycol (PEG) as a support,[9] we performed this three-component reaction on PEG support. As shown in Scheme 1, the aldehyde was attached to PEG4000 by esterification of PEG with 4-formylbenzoic acid **7** in the presence of DCC and DMAP in anhydrous DCM at room temperature.[9h] The conversion of terminal hydroxyl groups on PEG was determined by ^{1}H NMR analysis to be quantitative. The resulting PEG-bound aldehyde **8** was then treated with various anilines **2** and carbonyl compounds **5** (Table 3,

Keywords: β-Amino esters; β-Amino ketones; Cascade reaction; Mannich reactions.
* Corresponding author. Tel./fax: +86 571 87951512; e-mail: orgwyg@zju.edu.cn

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.08.063

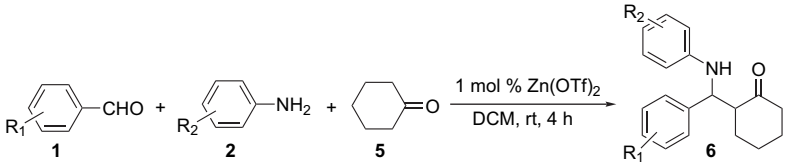
Table 1. Three-component reaction of benzaldehydes with anilines and diethyl malonic ester



Entry	R_1	R_2	Product	Yield (%)[a]
1	H	H	**4a**	50
2	2,6-Dichloro	2-CH_3	**4b**	50
3	2,6-Dichloro	4-OCH_3	**4c**	45
4	2,6-Dichloro	3-CH_3	**4d**	48
5	2-Cl	2-Cl	**4e**	88
6	2-Cl	4-Br	**4f**	92
7	3-NO_2	3-Cl	**4g**	96
8	2,6-Dichloro	4-Cl	**4h**	91
9	4-Br	4-Br	**4i**	95
10	2,6-Dichloro	3-Cl	**4j**	90
11	4-Br	4-Cl	**4k**	93
12	2,6-Dichloro	4-Br	**4l**	92
13	3,4-(OCH_2O)–	4-Cl	**4m**	5
14	3,4-(OCH_2O)–	4-OCH_3	**4n**	<1

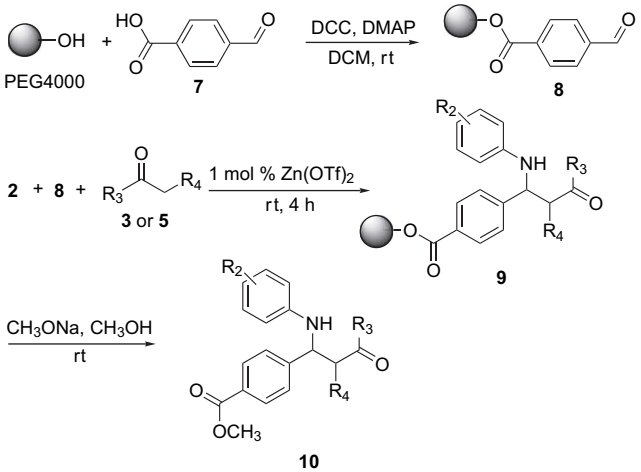
[a] Isolated yield.

Table 2. Three-component reaction of benzaldehydes with anilines and cyclohexanone



Entry	R_1	R_2	Product	Yield (%)[a]	*anti*/*syn*[b]
1	2,6-Dichloro	4-Br	**6a**	75	100:0
2	H	4-Br	**6b**	91	85:15
3	4-Cl	4-Cl	**6c**	98	97:3
4	4-Cl	4-Br	**6d**	95	100:0
5	3-NO_2	4-Cl	**6e**	96	75:25
6	4-NO_2	4-CH_3	**6f**	93	88:12
7	H	H	**6g**	93	90:10
8	H	3-Br	**6h**	85	74:26
9	4-OCH_3	4-Cl	**6i**	82	100:0
10	4-OCH_3	4-Br	**6j**	80	95:5
11	H	NO_2	**6k**	<1	—

[a] Isolated yield.
[b] Determined by ^{1}H NMR.



Scheme 1.

Table 3. The reaction of benzaldehyde with anilines and carbonyl compounds on PEG support

Entry	R_2	Carbonyl compounds	Product	Yield (%)[a]	Purity (%)[b]	*anti*/*syn*[c]
1	4-Br	**5**	**10a**	94	96	93:7
2	4-Cl	**5**	**10b**	97	99	100:0
3	3-Br	**5**	**10c**	92	93	85:15
4	3-Cl	**5**	**10d**	93	94	83:17
5	H	**5**	**10e**	91	90	71:29
6	3-CH_3	**5**	**10f**	88	89	88:12
7	4-OCH_3	**5**	**10g**	81	82	100:0
8	4-F	**5**	**10h**	99	95	89:11
9	4-NO_2	**5**	**10i**	<1	—	—
10	H	**3**	**10j**	90	89	—
11	4-Br	**3**	**10k**	98	98	—

[a] Yields refer to product cleaved from PEG.
[b] Purities were determined by HPLC analysis for the crude products.
[c] Determined by ^{1}H NMR.

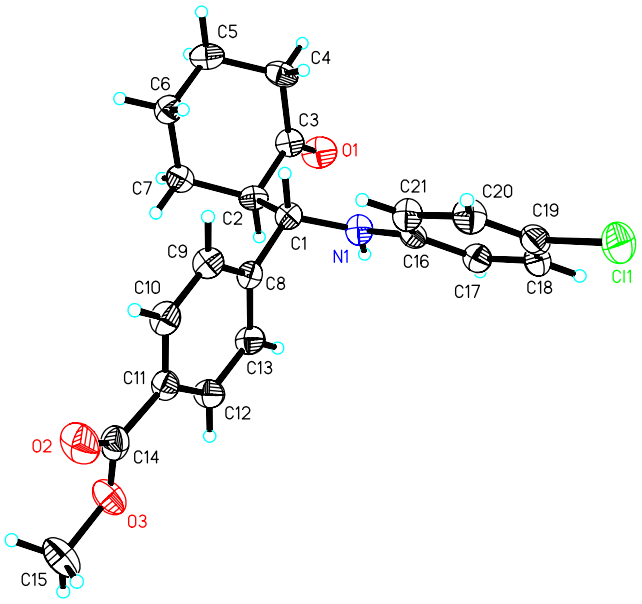


Figure 1. Crystal structure of compound **10b**.

entries 1–9) or **3** (Table 3, entries 10 and 11). Except the electron-deficient aniline (Table 3, entry 9), all reactions provided the corresponding crude products **10** in satisfactory yields (81–99%) with good purity (82–99%) as assessed by HPLC. In this case, high *anti* selectivity was also obtained. The *anti*-configuration of compound **10b** was unambiguously established by X-ray crystallographic analysis (Fig. 1).[10]

3. Conclusion

In summary, we have developed an efficient and general method for the synthesis of β-amino carbonyl compounds via $Zn(OTf)_2$-catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds. The significant features of this procedure include: (a) facile operation; (b) cheap and readily available catalyst; (c) high yields; (d) reasonably good diastereoselectivities. Furthermore, this one-pot reaction was also applied for the liquid-phase synthesis of β-amino carbonyl compound library on PEG support and would be able to find its application in combinatorial chemistry.

4. Experimental

4.1. General

IR spectra were recorded on a Perkin–Elmer 983 FT-IR spectrometer (KBr) and reported in reciprocal centimeters (cm^{-1}). Elemental analyses were recorded on a Carlo Erba 1110. ^1H and ^{13}C NMR spectra were obtained on a Bruker Advance DMX 500 instrument in $CDCl_3$ (TMS as internal standard). MS data were recorded on a Bruker Esquire 3000 plus instrument (ESI). HPLC analysis was carried out on an Agilent 1100 instrument (250×4.6 mm C18 column, gradient elution 80% MeOH and 20% H_2O, 0.8 ml/min, UV detection at λ 254 nm). Mp data were recorded on a YANACO apparatus.

4.2. General procedure for the synthesis of β-amino carbonyl compounds 4

A mixture of phenylamine (1 mmol), benzaldehyde (1 mmol), diethyl malonic ester (1 mmol), and $Zn(OTf)_2$ (3.6 mg, 0.01 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 4 h. After removal of the solvent in vacuum, the residue was purified by a flash column chromatography on silica gel with ethyl acetate–hexane (1:10) as eluent to afford pure β-amino carbonyl compound. Recrystallization from hexane–EtOAc gave crystalline product **4**.

4.2.1. Diethyl 2-(phenyl(phenylamino)methyl)malonate (4a). Colorless solid: mp 92–93 °C; IR (KBr) 3375, 1756, 1730, 1600, 1495, 1291 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.32 (m, 2H), 7.31–7.28 (m, 2H), 7.23–7.18 (m, 1H), 7.07–7.03 (m, 2H), 6.62–6.60 (m, 1H), 6.54–6.52 (m, 2H), 6.19 (t, J=10.8 Hz, 1H), 4.98 (d, J=11.0 Hz, 1H), 4.72 (d, J=10.7 Hz, 1H), 4.25 (q, J=7.2 Hz, 2H), 4.00 (q, J=7.2 Hz, 2H), 1.24 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 166.6, 147.7, 141.9, 129.3, 128.7, 127.7, 127.4, 117.9, 114.3, 62.2, 61.9, 56.3, 53.8, 14.1, 13.9 ppm; MS (ESI) m/z ($[M+1]^+$) 342. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.35; H, 6.79; N, 4.14.

4.2.2. Diethyl 2-((*o*-toluidino)(2,6-dichlorophenyl)-methyl)malonate (4b). Colorless solid: mp 85–86 °C; IR (KBr) 3398, 1721, 1598, 1531, 1352, 1269 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25–7.24 (m, 2H), 7.10–7.05 (m, 2H), 7.00–6.96 (m, 2H), 6.63 (d, J=7.3 Hz, 1H), 6.24 (t, J=11.0 Hz, 1H), 5.00 (d, J=11.1 Hz, 1H), 4.55 (d, J=10.7 Hz, 1H), 4.22–4.17 (m, 2H), 4.02–3.97 (m, 2H), 2.15 (s, 3H), 1.22 (t, J=7.2 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 166.5, 144.2, 134.6, 130.4, 129.5, 127.3, 123.0, 118.3, 112.2, 62.1, 61.8, 56.4, 53.7, 17.7, 14.2, 13.9 ppm; MS (ESI) m/z ($[M+1]^+$) 424. Anal. Calcd for $C_{21}H_{23}Cl_2NO_4$: C, 59.44; H, 5.46; N, 3.30. Found: C, 59.45, H, 5.43, N, 3.37.

4.2.3. Diethyl 2-((2,6-dichlorophenyl)(4-methoxyphenyl-amino)methyl)malonate (4c). Colorless solid: mp 102–103 °C; IR (KBr) 3394, 1745, 1596, 1499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25–7.23 (m, 2H), 7.09 (t, J=8.0 Hz, 1H), 6.79–6.78 (m, 2H), 6.72–6.70 (m, 2H), 6.11 (t, J=10.1 Hz, 1H), 4.70 (d, J=9.2 Hz, 1H), 4.50 (d, J=11.0 Hz, 1H), 4.30–4.22 (m, 2H), 4.02–3.97 (m, 2H), 3.70 (s, 3H), 1.28 (t, J=7.2 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 166.5, 153.4, 140.1, 134.5, 130.2, 129.5, 129.1, 116.8, 114.8, 62.0, 61.7, 56.3, 53.8, 14.3, 13.9 ppm; MS (ESI) m/z ($[M+1]^+$) 440. Anal. Calcd for $C_{21}H_{23}Cl_2NO_5$: C, 57.28; H, 5.26; N, 3.18. Found: C, 57.25; H, 5.26; N, 3.17.

4.2.4. Diethyl 2-((*m*-toluidino)(2,6-dichlorophenyl)-methyl)malonate (4d). Colorless solid: mp 91–92 °C; IR (KBr) 3337, 1751, 1720, 1598, 1526, 1483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.24–7.21 (m, 2H), 7.07–6.98 (m, 2H), 6.63–6.61 (m, 2H), 6.52–6.50 (m, 1H), 6.18 (t, J=11.2 Hz, 1H), 4.88 (d, J=11.4 Hz, 1H), 4.82 (d, J=11.0 Hz, 1H), 4.23–4.20 (m, 2H), 4.01–3.96 (m, 2H), 2.22 (s, 3H), 1.24 (t, J=7.1 Hz, 3H), 1.04 (t, J=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 166.4,

146.1, 139.8, 134.4, 129.5, 129.2, 120.0, 115.7, 111.9, 62.1, 61.8, 56.3, 54.2, 21.7, 14.2, 13.9 ppm; MS (ESI) *m/z* ([M+1]$^+$) 424. Anal. Calcd for $C_{21}H_{23}Cl_2NO_4$: C, 59.44; H, 5.46; N, 3.30. Found: C, 59.44; H, 5.48; N, 3.31.

4.2.5. Diethyl 2-((2-chlorophenyl)(2-chlorophenylamino)methyl)malonate (4e). Colorless solid: mp 80–81 °C; IR (KBr) 3339, 1752, 1720, 1598, 1483, 1297 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.35 (m, 2H), 7.23–7.15 (m, 3H), 7.00–6.96 (m, 1H), 6.57–6.56 (m, 1H), 6.41–6.40 (m, 1H), 6.41 (t, *J*=9.2 Hz, 1H), 4.70 (dd, *J*=4.3, 9.2 Hz, 1H), 4.22–4.09 (m, 5H), 1.20 (t, *J*=7.2 Hz, 3H), 1.17 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 167.2, 142.5, 136.1, 133.1, 130.0, 129.4, 129.3, 128.7, 127.9, 127.4, 120.0, 118.1, 112.2, 62.2, 61.8, 55.0, 54.1, 14.2, 14.1 ppm; MS (ESI) *m/z* ([M+1]$^+$) 410. Anal. Calcd for $C_{20}H_{21}Cl_2NO_4$: C, 58.55; H, 5.16; N, 3.41. Found: C, 58.52; H, 5.18; N, 3.41.

4.2.6. Diethyl 2-((4-bromophenylamino)(2-chlorophenyl)methyl)malonate (4f). Colorless solid: mp 106–107 °C; IR (KBr) 3394, 2981, 1745, 1569, 1499, 1375, 1250, 1178 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.32 (m, 2H), 7.21–7.15 (m, 4H), 6.41 (d, *J*=8.8 Hz, 2H), 5.80 (d, *J*=9.4 Hz, 1H), 5.50 (dd, *J*=4.3, 9.4 Hz, 1H), 4.24–4.02 (m, 5H), 1.20 (t, *J*=7.1 Hz, 3H), 1.11 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 167.4, 145.4, 13.16, 133.1, 132.2, 132.1, 130.1, 129.4, 128.8, 127.4, 115.3, 115.2, 109.9, 62.3, 61.8, 54.6, 54.3, 14.2, 14.1 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 478. Anal. Calcd for $C_{20}H_{21}BrClNO_4$: C, 52.82; H, 4.65; N, 3.08. Found: C, 52.78; H, 4.67; N, 2.84.

4.2.7. Diethyl 2-((3-chlorophenylamino)(3-nitrophenyl)methyl)malonate (4g). Yellow solid: mp 99–100 °C; IR (KBr) 3398, 1721, 1598, 1531, 1352, 1269 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.13–8.11 (m, 1H), 7.73 (t, *J*=7.8 Hz, 1H), 7.50 (t, *J*=8.0 Hz, 1H), 6.66–6.64 (m, 1H), 6.57–6.56 (m, 1H), 6.47–6.46 (m, 1H), 6.44 (d, *J*=6.4 Hz, 1H), 5.56 (d, *J*=9.0 Hz, 1H), 5.28 (dd, *J*=5.4, 9.0 Hz, 1H), 4.19–4.08 (m, 4H), 3.91 (d, *J*=5.4 Hz, 1H), 1.19 (t, *J*=7.1 Hz, 3H), 1.11 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 166.8, 148.8, 147.3, 142.1, 135.3, 133.3, 130.5, 130.0, 123.2, 122.1, 118.7, 113.7, 122.1, 62.5, 62.2, 57.7, 56.5, 14.1, 14.0 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 444. Anal. Calcd for $C_{20}H_{21}ClN_2O_6$: C, 57.08; H, 5.03; N, 6.66. Found: C, 57.08; H, 4.90; N, 6.58.

4.2.8. Diethyl 2-((4-chlorophenylamino)(2,6-dichlorophenyl)methyl)malonate (4h). Colorless solid: mp 83–84 °C; IR (KBr) 3385, 1731, 1598, 1513, 1443 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.24 (m, 2H), 7.10–7.05 (m, 3H), 6.74 (d, *J*=8.8 Hz, 2H), 6.13 (d, *J*=11.1 Hz, 1H), 4.93 (d, *J*=11.3 Hz, 1H), 4.71 (d, *J*=10.8 Hz, 1H), 4.24 (q, *J*=7.2 Hz, 2H), 4.01 (q, *J*=7.2 Hz, 2H), 1.24 (t, *J*=7.1 Hz, 3H), 1.04 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 166.3, 144.8, 133.9, 129.7, 129.2, 123.8, 116.0, 62.2, 61.9, 56.1, 54.5, 14.3, 13.9 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 466. Anal. Calcd for $C_{20}H_{20}Cl_3NO_4$: C, 54.01; H, 4.53; N, 3.15. Found: C, 54.02; H, 4.55; N, 3.14.

4.2.9. Diethyl 2-((4-bromophenyl)(4-bromophenylamino)methyl)malonate (4i). Colorless solid: mp 107–108 °C; IR (KBr) 3348, 1721, 1599, 1530, 1355 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J*=8.5 Hz, 2H), 7.26 (d, *J*=8.5 Hz, 2H), 7.16 (d, *J*=8.3 Hz, 2H), 6.44 (d, *J*=8.3 Hz, 2H), 5.42 (d, *J*=10.8 Hz, 1H), 5.21 (d, *J*=11.0 Hz, 1H), 4.17–4.09 (m, 4H), 3.83 (d, *J*=5.5 Hz, 1H), 1.18–1.14 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 167.1, 145.5, 138.6, 132.5, 132.2, 128.8, 122.0, 115.5, 110.1, 62.3, 62.0, 57.9, 55.8, 14.2, 14.1 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 522. Anal. Calcd for $C_{20}H_{21}Br_2NO_4$: C, 48.12; H, 4.24; N, 2.81. Found: C, 48.12; H, 4.26; N, 2.71.

4.2.10. Diethyl 2-((3-chlorophenylamino)(2,6-dichlorophenyl)methyl)malonate (4j). Colorless solid: mp 109–110 °C; IR (KBr) 3386, 1744, 1726, 1596, 1500, 1348, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27–7.26 (m, 2H), 7.12 (t, *J*=8.0 Hz, 1H), 7.04 (t, *J*=8.1 Hz, 1H), 6.81 (t, *J*=2.0 Hz, 1H), 6.69–6.65 (m, 2H), 6.15 (d, *J*=11.1 Hz, 1H), 5.00 (d, *J*=11.2 Hz, 1H), 4.48 (d, *J*=10.8 Hz, 1H), 4.23–4.21 (m, 2H), 4.01–3.98 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H), 1.05 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 166.2, 147.3, 135.1, 133.9, 130.4, 129.8, 119.0, 114.7, 112.8, 62.2, 61.9, 56.1, 54.1, 14.2, 13.9 ppm; MS (ESI) *m/z* ([M+1]$^+$) 444. Anal. Calcd for $C_{20}H_{20}Cl_3NO_4$: C, 54.01; H, 4.53; N, 3.15. Found: C, 54.00; H, 4.53; N, 3.13.

4.2.11. Diethyl 2-((4-bromophenyl)(4-chlorophenylamino)methyl)malonate (4k). Colorless solid: mp 88–89 °C; IR (KBr) 3379, 1753, 1729, 1597, 1560, 1485, 1288 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 7.04 (d, *J*=8.3 Hz, 2H), 6.49 (d, *J*=8.3 Hz, 2H), 5.40 (d, *J*=8.1 Hz, 1H), 5.12 (d, *J*=5.8 Hz, 1H), 4.12–4.07 (m, 4H), 3.83 (d, *J*=5.5 Hz, 1H), 1.18–1.14 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 167.1, 145.2, 138.7, 132.1, 129.3, 128.8, 123.0, 122.0, 115.1, 62.3, 62.0, 58.0, 56.9, 14.2, 14.1 ppm; MS (ESI) *m/z* ([M+1]$^+$) 454. Anal. Calcd for $C_{20}H_{21}BrClNO_4$: C, 52.82; H, 4.65; N, 3.08. Found: C, 52.85; H, 4.66; N, 3.04.

4.2.12. Diethyl 2-((4-bromophenylamino)(2,6-dichlorophenyl)methyl)malonate (4l). Colorless solid: mp 100–101 °C; IR (KBr) 3387, 1729, 1608, 1593, 1560, 1495 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25–7.24 (m, 2H), 7.21 (d, *J*=8.8 Hz, 2H), 7.12 (t, *J*=8.0 Hz, 1H), 6.70 (d, *J*=8.8 Hz, 2H), 6.13 (d, *J*=11.1 Hz, 1H), 4.94 (d, *J*=11.1 Hz, 1H), 4.47 (d, *J*=10.8 Hz, 1H), 4.47–4.44 (m, 2H), 4.01 (q, *J*=7.3 Hz, 2H), 1.24 (t, *J*=7.3 Hz, 3H), 1.04 (t, *J*=7.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 166.3, 145.2, 133.9, 132.1, 129.8, 116.5, 111.0, 62.2, 61.9, 56.1, 54.4, 14.3, 13.9 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 510. Anal. Calcd for $C_{20}H_{20}BrCl_2NO_4$: C, 49.10; H, 4.12; N, 2.86. Found: C, 49.11; H, 4.10; N, 2.86.

4.3. General procedure for the synthesis of β-amino carbonyl compounds 6

A mixture of aniline (1 mmol), benzaldehyde (1 mmol), cyclohexanone (1.2 mmol), and $Zn(OTf)_2$ (3.6 mg, 0.01 mmol) was stirred at room temperature for 4 h. After removal of the solvent in vacuum, the residue was purified by flash column chromatography on silica gel with ethyl acetate–hexane (1:16) as eluent to afford pure β-amino carbonyl compounds. Recrystallization from hexane–EtOAc afforded crystalline product **6**.

4.3.1. 2-((4-Bromophenylamino)(2,6-dichlorophenyl)-methyl)cyclohexanone (6a). Colorless solid: mp 128–129 °C; IR (KBr) 3362, 1704, 1596, 1519, 1489 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.22 (m, 2H), 7.17–7.15 (m, 2H), 7.10–7.07 (t, J=8.0 Hz, 1H), 6.60–6.57 (m, 2H), 5.78 (t, J=8.65 Hz, 1H), 4.68 (d, J=6.6 Hz, 1H), 3.30–3.25 (m, 1H), 2.50–2.41 (m, 2H), 1.96–1.92 (m, 2H), 1.85–1.82 (m, 1H), 1.69–1.68 (m, 1H), 1.61–1.59 (m, 1H), 1.42–1.41 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.0, 145.7, 135.1, 132.1, 130.7, 129.4, 128.9, 115.7, 110.0, 53.9, 53.7, 42.2, 31.0, 28.6, 24.4 ppm; MS (ESI) m/z ($[M+1]^+$) 426. Anal. Calcd for $C_{19}H_{18}BrCl_2NO$: C, 53.42; H, 4.25; N, 3.28. Found: C, 53.45; H, 4.26; N, 3.28.

4.3.2. 2-((4-Bromophenylamino)(phenyl)methyl)cyclohexanone (6b). Colorless solid: (*anti*/*syn*=85/15) mp 98–99 °C; IR (KBr) 3397, 1700, 1592, 1495, 1314 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 7.34–7.30 (m, 4H), 7.23–7.20 (m, 1H), 7.14–7.11 (m, 2H), 4.79 (s, 0.15H), 4.73 (s, 0.85H), 4.59 (s, 0.15H), 4.54 (d, J=6.8 Hz, 0.85H), 2.79–2.73 (m, 1H), 2.42–2.33 (m, 1H), 2.32–2.29 (m, 1H), 2.04–2.00 (m, 1H), 1.90–1.85 (m, 2H), 1.70–1.55 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 213.0, 146.7, 141.1, 132.0, 128.8, 127.7, 127.4, 115.5, 109.4, 57.7, 56.6, 42.2, 31.8, 28.2, 25.1; (minor isomer): δ 211.5, 146.5, 141.4, 131.9, 128.7, 127.6, 127.4, 115.9, 109.6, 58.4, 57.5, 42.6, 28.7, 27.1, 24.1 ppm; MS (ESI) m/z ($[M+1]^+$) 358. Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.70; H, 5.63; N, 3.94.

4.3.3. 2-((4-Chlorophenyl)(4-chlorophenylamino)-methyl)cyclohexanone (6c). Colorless solid: (*anti*/*syn*=97/3) mp 96–97 °C; IR (KBr) 3411, 1702, 1600, 1498, 1315 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 7.29–7.26 (m, 4H), 7.01 (d, J=8.8 Hz, 2H), 6.42 (d, J=8.8 Hz, 2H), 4.71 (s, 0.97H), 4.67 (s, 0.03H), 4.61 (s, 0.03H), 4.51 (d, J=5.7 Hz, 0.97H), 2.72–2.70 (m, 1H), 2.41–2.34 (m, 1H), 2.33–2.29 (m, 1H), 2.00–1.97 (m, 1H), 1.90–1.89 (m, 2H), 1.86–1.76 (m, 1H), 1.72–1.62 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.6, 145.8, 140.1, 133.2, 129.2, 128.9, 128.8, 122.6, 115.0, 58.0, 57.4, 42.4, 31.9, 28.1, 24.4; (minor isomer): δ 211.4, 145.8, 139.7, 133.2, 129.1, 128.9, 128.8, 122.6, 115.4, 57.3, 56.4, 42.6, 28.9, 27.1, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 348. Anal. Calcd for $C_{19}H_{19}Cl_2NO$: C, 65.53; H, 5.50; N, 4.02. Found: C, 65.59; H, 5.49; N, 4.01.

4.3.4. 2-((4-Bromophenylamino)(4-chlorophenyl)-methyl)cyclohexanone (6d). Colorless solid: mp 134–135 °C; IR (KBr) 3402, 1702, 1594, 1491, 1316 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.25 (m, 4H), 7.14 (d, J=8.8 Hz, 2H), 6.38 (d, J=8.8 Hz, 2H), 4.80 (s, 1H), 4.51 (d, J=4.8 Hz, 1H), 2.73–2.70 (m, 1H), 2.40–2.31 (m, 2H), 1.99–1.96 (m, 1H), 1.90–1.89 (m, 2H), 1.77–1.70 (m, 1H), 1.69–1.60 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.6, 146.3, 140.1, 133.2, 132.1, 128.9, 128.8, 115.5, 109.7, 57.9, 57.4, 42.4, 32.0, 28.1, 24.4 ppm; MS (ESI) m/z ($[M+1]^+$) 392. Anal. Calcd for $C_{19}H_{19}BrClNO$: C, 58.11; H, 4.88; N, 3.57. Found: C, 58.16; H, 4.88; N, 3.58.

4.3.5. 2-((4-Chlorophenylamino)(3-nitrophenyl)methyl)-cyclohexanone (6e). Yellow solid: (*anti*/*syn*=75/25) mp 125–126 °C; IR (KBr) 3344, 1705, 1599, 1529, 1492, 1352 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 8.22 (d, J=9.3 Hz, 1H), 8.09 (m, 1H), 7.75 (t, J=6.0 Hz, 1H), 7.49–7.45 (m, 1H), 7.03 (d, J=8.7 Hz, 2H), 6.45 (d, J=8.7 Hz, 2H), 4.97 (d, J=7.6 Hz, 0.25H), 4.80 (d, J=6.4 Hz, 0.75H), 4.68 (d, J=6.6 Hz, 0.75H), 4.63 (d, J=7.0 Hz, 0.25H), 2.88–2.84 (m, 1H), 2.45–2.30 (m, 2H), 2.10–2.00 (m, 2H), 1.94–1.93 (m, 1H), 1.80–1.73 (m, 1H), 1.65–1.56 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.1, 148.6, 145.5, 144.2, 134.3, 129.7, 129.3, 122.9, 122.7, 122.6, 114.9, 58.2, 57.2, 42.6, 32.5, 28.1, 24.8; (minor isomer): δ 210.9, 148.6, 145.4, 143.8, 133.7, 129.6, 129.3, 123.2, 122.6, 122.4, 115.4, 57.4, 56.3, 42.8, 29.3, 27.2, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 359. Anal. Calcd for $C_{19}H_{19}ClN_2O_3$: C, 63.60; H, 5.34; N, 7.81. Found: C, 63.59; H, 5.34; N, 7.83.

4.3.6. 2-((4-Toluidino)(4-nitrophenyl)methyl)cyclohexanone (6f). Yellow solid: (*anti*/*syn*=88/12) mp 137–138 °C; IR (KBr) 3364, 1697, 1518, 1346 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 8.14 (d, J=8.7 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 6.89 (d, J=8.1 Hz, 2H), 6.42 (d, J=8.1 Hz, 2H), 4.82 (s, 0.12H), 4.74 (s, 0.88H), 4.68 (s, 0.88H), 4.46 (m, 0.12H), 2.84–2.81 (m, 1H), 2.41–2.29 (m, 2H), 2.17 (s, 3H), 2.04–1.98 (m, 2H), 1.93–1.92 (m, 1H), 1.77–1.62 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.0, 150.3, 144.5, 130.0, 128.5, 127.6, 123.9, 113.9, 58.2, 57.3, 42.6, 32.1, 27.9, 24.7, 20.5; (minor isomer): δ 210.9, 149.9, 147.2, 129.9, 128.8, 127.8, 123.8, 114.5, 58.1, 56.5, 42.7, 29.2, 27.3, 25.2, 20.5 ppm; MS (ESI) m/z ($[M+1]^+$) 359. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.99; H, 6.55; N, 8.26.

4.3.7. 2-(Phenyl(phenylamino)methyl)cyclohexanone (6g). Colorless solid: (*anti*/*syn*=90/10) mp 115–116 °C; IR (KBr) 3330, 1702, 1602, 1497 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 7.36–7.33 (m, 2H), 7.30–7.27 (m, 2H), 7.23–7.18 (m, 1H), 7.07–7.03 (m, 2H), 6.62–6.60 (m, 1H), 6.54–6.52 (m, 2H), 4.80 (s, 0.10H), 4.71 (s, 0.90H), 4.62 (d, J=7.0 Hz, 0.90H), 4.51 (s, 0.10H), 2.76–2.72 (m, 1H), 2.43–2.29 (m, 2H), 1.90–1.81 (m, 4H), 1.72–1.61 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 213.1, 147.4, 141.9, 129.3, 128.7, 127.5, 127.4, 117.7, 113.8, 58.2, 57.7, 42.0, 31.5, 28.1, 23.8; (minor isomer): δ 211.5, 147.7, 141.8, 129.2, 128.6, 127.7, 127.2, 117.9, 114.3, 57.4, 56.8, 42.6, 28.9, 27.2, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 280. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.68; H, 7.49; N, 5.02.

4.3.8. 2-((3-Bromophenylamino)(phenyl)methyl)cyclohexanone (6h). Colorless solid: (*anti*/*syn*=74/26) mp 114–115 °C; IR (KBr) 3379, 1700, 1598, 1476 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 7.35–7.29 (m, 4H), 7.25–7.21 (m, 1H), 6.89–6.87 (m, 1H), 6.73–6.67 (m, 2H), 6.44–6.42 (m, 1H), 4.80 (s, 0.74H), 4.76–4.74 (m, 0.26H), 4.65 (m, 0.26H), 4.54 (s, 0.74H), 2.78–2.75 (m, 1H), 2.42–2.29 (m, 2H), 2.04–2.02 (m, 1H), 1.90–1.86 (m, 2H), 1.71–1.57 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.9, 148.8, 141.3, 130.6, 128.8, 127.7, 127.3, 123.1, 120.5, 116.9, 112.4, 58.2, 57.5, 42.6, 31.8, 28.2, 24.1; (minor isomer): δ 211.4, 148.9, 141.0, 130.5, 128.7, 127.6, 127.4, 123.2, 120.6, 116.4, 112.7, 56.5, 57.3, 42.2, 28.8, 27.1, 25.0 ppm; MS (ESI) m/z ($[M+1]^+$) 358.

Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.70; H, 5.63; N, 3.94.

4.3.9. 2-((4-Chlorophenylamino)(4-methoxyphenyl)-methyl)cyclohexanone (6i). Colorless solid: mp 122–123 °C; IR (KBr) 3332, 1703, 1603, 1512, 1493, 1247 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J=8.7 Hz, 2H), 7.00 (d, J=8.9 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 6.44 (d, J=8.9 Hz, 2H), 4.69 (s, 1H), 4.50 (d, J=7.0 Hz, 1H), 3.76 (s, 3H), 2.69–2.68 (m, 1H), 2.42–2.38 (m, 1H), 2.43–2.32 (m, 1H), 1.93–1.81 (m, 4H), 1.68–1.63 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.2, 158.9, 146.1, 133.3, 129.1, 128.5, 122.3, 115.0, 114.2, 57.9, 57.7, 55.4, 42.1, 31.6, 28.1, 23.9 ppm; MS (ESI) m/z ($[M+Na]^+$) 366. Anal. Calcd for $C_{20}H_{22}ClNO_2$: C, 69.86; H, 6.45; N, 4.07. Found: C, 69.94; H, 6.41; N, 4.06.

4.3.10. 2-((4-Bromophenylamino)(4-methoxyphenyl)-methyl)cyclohexanone (6j). Colorless solid: (*anti*/*syn*=95/5) mp 131–132 °C; IR (KBr) 3331, 1702, 1597, 1511, 1489, 1246 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J=8.6 Hz, 2H), 7.13 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.6 Hz, 2H), 6.40 (d, J=8.8 Hz, 2H), 4.71 (s, 0.95H), 4.64 (s, 0.05H), 4.50 (d, J=6.8 Hz, 0.95H), 4.49 (s, 0.05H), 3.76 (s, 3H), 2.71–2.68 (m, 1H), 2.42–2.38 (m, 1H), 2.34–2.32 (m, 1H), 1.94–1.80 (m, 4H), 1.68–1.63 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 213.2, 158.9, 146.5, 133.3, 131.9, 128.5, 115.5, 114.2, 109.4, 57.8, 57.7, 55.4, 42.1, 31.6, 28.1, 23.9; (minor isomer): δ 213.2, 158.9, 146.5, 133.3, 131.9, 128.8, 115.9, 114.0, 109.4, 57.8, 57.2, 56.6, 42.6, 29.0, 27.1, 25.0 ppm; MS (ESI) m/z ($[M+Na]^+$) 410. Anal. Calcd for $C_{20}H_{22}BrNO$: C, 61.86; H, 5.71; N, 3.61. Found: C, 61.84; H, 5.72; N, 3.65.

4.4. General procedure for the synthesis of β-amino carbonyl compounds 10

To the solution of PEG-bounded aldehyde **8** (2.0 g, 0.50 mmol) in DCM (10 ml) were added aniline (4 mmol), carbonyl compound (8 mmol), and $Zn(OTf)_2$ (3.6 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 4 h. Then Et_2O (40 ml) was added dropwise. The resulting polymer **9** as a precipitate was collected by filtration and then dissolved in methanol (5 ml). To the solution was added 0.1 N MeONa in methanol (5 ml). The mixture was stirred at room temperature for 5 h and then diluted with Et_2O (50 ml). After removing the precipitate by filtration, the filtrate was washed with saturated aqueous NaCl solution and dried over Na_2SO_4. Removal of the solvent afforded the crude product **10**. Further purification of the crude product for structural analysis was performed by silica gel column chromatography (hexane–EtOAc, 10:1, v/v) and recrystallization from hexane–EtOAc.

4.4.1. Methyl 4-((4-bromophenylamino)(2-oxocyclohexyl)methyl)benzoate (10a). Colorless solid: (*anti*/*syn*=93/7) mp 145–146 °C; IR (KBr) 3371, 1724, 1703, 1590, 1496, 1284 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J=8.3 Hz, 2H), 7.43 (d, J=8.8 Hz, 2H), 7.14 (d, J=8.3 Hz, 2H), 6.39 (d, J=8.8 Hz, 2H), 4.87 (d, J=5.1 Hz, 0.93H), 4.78 (m, 0.07H), 4.62 (s, 0.07H), 4.59 (m, 0.93H), 3.88 (s, 3H), 2.80–2.78 (m, 1H), 2.41–2.38 (m, 1H), 2.34–2.32 (m, 1H), 1.91–1.90 (m, 3H), 1.71–1.66 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.4, 167.0, 147.0, 146.3, 132.1, 130.1, 129.5, 127.5, 115.4, 109.7, 58.4, 57.3, 52.3, 42.5, 32.1, 28.1, 24.4; (minor isomer): δ 212.4, 167.0, 147.0, 146.3, 132.0, 130.0, 129.5, 127.8, 115.9, 109.7, 57.6, 55.4, 52.3, 42.6, 28.8, 27.2, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 416. Anal. Calcd for $C_{21}H_{22}BrNO_3$: C, 60.59; H, 5.33; N, 3.36. Found: C, 60.61; H, 5.27; N, 3.43.

4.4.2. Methyl 4-((4-chlorophenylamino)(2-oxocyclohexyl)methyl)benzoate (10b). Colorless solid: mp 133–134 °C; IR (KBr) 3348, 3312, 1713, 1712, 1701, 1491, 1278 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J=8.3 Hz, 2H), 7.43 (d, J=8.3 Hz, 2H), 7.01–7.00 (m, 2H), 6.43–6.40 (m, 2H), 4.85 (d, J=5.6 Hz, 1H), 4.60 (t, J=5.9 Hz, 1H), 3.88 (s, 3H), 2.80–2.78 (m, 1H), 2.40–2.32 (m, 2H), 2.00–1.98 (m, 1H), 1.91–1.89 (m, 2H), 1.76–1.66 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.4, 167.0, 147.0, 145.8, 130.1, 129.5, 129.2, 127.5, 122.6, 114.9, 58.5, 57.3, 52.3, 42.5, 32.1, 28.1, 24.4 ppm; MS (ESI) m/z ($[M+1]^+$) 372. Anal. Calcd for $C_{21}H_{22}ClNO_3$: C, 67.83; H, 5.96; N, 3.77. Found: C, 67.84; H, 5.95; N, 3.86.

4.4.3. Methyl 4-((3-bromophenylamino)(2-oxocyclohexyl)methyl)benzoate (10c). Colorless solid: (*anti*/*syn*=85/15) mp 134–135 °C; IR (KBr) 3403, 1721, 1698, 1597, 1508, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00–7.97 (m, 2H), 7.44–7.41 (m, 2H), 6.92–6.88 (m, 1H), 6.75–6.73 (m, 1H), 6.67–6.65 (m, 1H), 6.42–6.40 (m, 1H), 4.95 (d, J=7.4 Hz, 0.85H), 4.79 (m, 0.15H), 4.68 (m, 0.15H), 4.60 (t, J=6.6 Hz, 0.85H), 3.90 (s, 0.45H), 3.89 (s, 2.55H), 2.81–2.79 (m, 1H), 2.41–2.32 (m, 2H), 2.01–1.99 (m, 1H), 1.94–1.89 (m, 2H), 1.76–1.66 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.4, 167.0, 148.6, 146.9, 130.7, 130.1, 129.5, 127.5, 123.3, 120.8, 116.4, 112.3, 58.2, 57.3, 52.3, 42.5, 32.2, 28.1, 24.5; (minor isomer): δ 211.0, 167.0, 148.6, 146.6, 130.6, 130.0, 129.5, 127.8, 123.2, 121.0, 117.0, 112.7, 57.4, 56.3, 52.3, 42.6, 28.9, 27.1, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 416. Anal. Calcd for $C_{21}H_{22}BrNO_3$: C, 60.59; H, 5.33; N, 3.36. Found: C, 60.53; H, 5.32; N, 3.41.

4.4.4. Methyl 4-((3-chlorophenylamino)(2-oxocyclohexyl)methyl)benzoate (10d). Colorless solid: (*anti*/*syn*=83/17) mp 137–138 °C; IR (KBr) 3403, 1721, 1700, 1600, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J=8.3 Hz, 2H), 7.44 (d, J=8.3 Hz, 2H), 6.97 (t, J=8.0 Hz, 1H), 6.60–6.59 (m, 1H), 6.50–6.48 (m, 1H), 6.38–6.37 (m, 1H), 4.96 (d, J=7.4 Hz, 0.83H), 4.80–4.79 (m, 0.13H), 4.70 (d, J=6.6 Hz, 0.17H), 4.61 (t, J=7.4 Hz, 0.83H), 3.90 (s, 0.51H), 3.89 (s, 2.49H), 2.81–2.79 (m, 1H), 2.41–2.32 (m, 2H), 2.02–1.99 (m, 1H), 1.93–1.89 (m, 2H), 1.77–1.69 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.4, 167.0, 148.5, 146.9, 135.1, 130.3, 130.1, 129.5, 127.8, 117.9, 113.5, 112.0, 58.2, 57.3, 52.3, 42.5, 32.2, 28.1, 24.4; (minor isomer): δ 211.0, 167.0, 148.5, 146.6, 135.0, 130.3, 130.0, 129.5, 127.5, 118.1, 114.0, 112.4, 57.4, 56.3, 52.3, 42.6, 28.9, 21.1, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 372. Anal. Calcd for $C_{21}H_{22}ClNO_3$: C, 60.83; H, 5.96; N, 3.77. Found: C, 60.83; H, 5.94; N, 3.80.

4.4.5. Methyl 4-((2-oxocyclohexyl)(phenylamino)-methyl)benzoate (10e). Colorless solid: (*anti*/*syn*=71/29)

mp 104–105 °C; IR (KBr) 3410, 1719, 1698, 1602, 1277 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97–7.95 (m, 2H), 7.45–7.43 (m, 2H), 7.07–7.04 (m, 2H), 6.66–6.62 (m, 1H), 6.52–6.50 (m, 2H), 4.83 (s, 0.29H), 4.78 (s, 0.71H), 4.67 (d, J=6.2 Hz, 0.71H), 4.54 (s, 0.29H), 3.87 (s, 3H), 2.81–2.77 (m, 1H), 2.43–2.29 (m, 2H), 2.04–2.03 (m, 1H), 1.96–1.89 (m, 2H), 1.72–1.58 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.4, 167.1, 147.5, 147.2, 130.0, 129.3, 129.2, 127.6, 118.0, 113.8, 58.1, 57.4, 52.2, 42.3, 31.8, 28.0, 24.3; (minor isomer): δ 211.1, 167.1, 147.4, 147.3, 129.9, 129.3, 129.2, 127.9, 118.2, 114.3, 57.5, 56.6, 52.2, 42.6, 28.9, 27.2, 25.1 ppm; MS (ESI) m/z ([M+1]$^+$) 338. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.75; H, 6.84; N, 4.22.

4.4.6. Methyl 4-((*m*-toluidino)(2-oxocyclohexyl)methyl)-benzoate (10f). Colorless solid: (*anti*/*syn*=88/12) mp 97–98 °C; IR (KBr) 3411, 1720, 1700, 1605, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00–7.98 (m, 2H), 7.49–7.46 (m, 2H), 6.98 (d, J=7.8 Hz, 1H), 6.50–6.48 (m, 1H), 6.39 (s, 1H), 6.33–6.31 (m, 1H), 4.86 (br s, 1H), 4.85 (d, J=4.3 Hz, 0.12H), 4.68 (d, J=6.3 Hz, 0.88H), 3.90 (s, 3H), 2.83–2.80 (m, 1H), 2.45–2.40 (m, 1H), 2.36–2.34 (m, 1H), 2.20 (s, 3H), 1.99–1.90 (m, 3H), 1.79–1.68 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.5, 167.1, 147.5, 147.0, 139.1, 130.0, 129.2, 127.6, 119.1, 114.8, 110.8, 58.2, 57.3, 52.3, 42.3, 31.8, 28.1, 24.2; (minor isomer): δ 211.1, 167.2, 147.5, 147.3, 139.0, 129.9, 129.1, 127.8, 119.2, 115.2, 111.2, 57.4, 56.6, 52.3, 42.6, 28.9, 27.2, 25.1 ppm; MS (ESI) m/z ([M+1]$^+$) 352. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.20; H, 7.14; N, 4.02.

4.4.7. Methyl 4-((4-methoxyphenylamino)(2-oxocyclo-hexyl)methyl)benzoate (10g). Gray solid: mp 121–122 °C; IR (KBr) 3417, 1718, 1690, 1514, 1276 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J=8.1 Hz, 2H), 7.45 (d, J=8.1 Hz, 2H), 6.67 (d, J=8.8 Hz, 1H), 6.47 (d, J=8.8 Hz, 2H), 4.60 (d, J=6.6 Hz, 1H), 4.50 (s, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 2.76–2.74 (m, 1H), 2.44–2.40 (m, 1H), 2.34–2.32 (m, 1H), 1.97–1.95 (m, 1H), 1.90–1.86 (m, 3H), 1.68–1.65 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.4, 167.0, 152.4, 147.6, 141.2, 129.9, 129.2, 127.6, 115.3, 114.8, 59.0, 57.3, 55.7, 52.1, 42.1, 31.6, 27.9, 24.1 ppm; MS (ESI) m/z ([M+1]$^+$) 368. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.81; H, 6.86; N, 3.99.

4.4.8. Methyl 4-((4-fluorophenylamino)(2-oxocyclo-hexyl)methyl)benzoate (10h). Colorless solid: (*anti*/*syn*=92/8) mp 130–131 °C; IR (KBr) 3411, 1719, 1701, 1511, 1276 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00–7.98 (m, 2H), 7.46–7.43 (m, 2H), 6.78–6.74 (m, 2H), 6.44–6.42 (m, 2H), 4.80 (s, 0.8H), 4.68 (s, 0.92H), 4.58 (d, J=6.4 Hz, 1H), 3.88 (s, 3H), 2.77–2.75 (m, 1H), 2.43–2.39 (m, 1H), 2.36–2.33 (m, 1H), 2.20–1.97 (m, 1H), 1.89–1.87 (m, 2H), 1.78–1.66 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.5, 167.0, 157.0 (d, J_{C-F}=234.5 Hz), 147.3, 143.6, 130.1, 129.4, 127.6, 115.9 (d, J_{C-F}=21.9 Hz), 114.9 (d, J_{C-F}=7.6 Hz), 59.0, 57.4, 52.3, 42.4, 31.9, 28.1, 24.4; (minor isomer): δ 211.2, 167.0, 157.0 (d, J_{C-F}=234.5 Hz), 147.3, 143.6, 130.0, 129.3, 127.8, 115.8 (d, J_{C-F}=22.1 Hz), 115.4 (d, J_{C-F}=7.5 Hz), 58.2, 56.6, 52.3, 42.6, 28.7 27.2, 25.1 ppm; MS (ESI) m/z ([M+1]$^+$) 356. Anal. Calcd for $C_{21}H_{22}FNO_3$: C, 70.97; H, 6.24; N, 3.94. Found: C, 70.96; H, 6.23; N, 3.98.

4.4.9. Diethyl 2-((4-(methoxycarbonyl)phenyl)(phenyl-amino)methyl)malonate (10j). Colorless solid: mp 105–106 °C; IR (KBr) 3398, 1751, 1720, 1700, 1605, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97–7.95 (m, 2H), 7.45–7.43 (m, 2H), 7.07–7.04 (m, 2H), 6.67–6.63 (m, 1H), 6.52–6.50 (m, 2H), 6.10 (t, J=11.0 Hz, 1H), 4.96 (d, J=11.1 Hz, 1H), 4.55 (d, J=10.7 Hz, 1H), 4.22–4.17 (m, 2H), 4.02–3.97 (m, 2H), 3.87 (s, 3H), 1.22 (t, J=7.2 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 167.1, 166.5, 147.5, 147.2, 130.0, 129.3, 129.2, 127.6, 123.0, 118.0, 113.8, 62.1, 61.8, 56.4, 53.7, 52.3, 14.2, 13.9 ppm; MS (ESI) m/z ([M+1]$^+$) 400. Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.16; H, 6.29; N, 3.50.

4.4.10. Diethyl 2-((4-bromophenylamino)(4-(methoxy-carbonyl)phenyl)methyl)malonate (10k). Colorless solid: mp 140–141 °C; IR (KBr) 3398, 1729, 1703, 1596, 1496, 1284 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J=8.4 Hz, 2H), 7.43 (d, J=8.7 Hz, 2H), 7.14 (d, J=8.4 Hz, 2H), 6.39 (d, J=8.7 Hz, 2H), 6.21 (t, J=11.2 Hz, 1H), 5.01 (d, J=11.3 Hz, 1H), 4.67 (d, J=10.8 Hz, 1H), 4.24 (q, J=7.2 Hz, 2H), 4.01 (q, J=7.2 Hz, 2H), 3.88 (s, 3H), 1.24 (t, J=7.2 Hz, 3H), 1.06 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 167.5, 167.0, 166.5, 147.5, 147.0, 132.1, 130.1, 129.5, 127.5, 115.0, 110.0, 62.1, 61.8, 56.4, 53.7, 52.3, 14.2, 13.9 ppm; MS (ESI) m/z ([M+1]$^+$) 478. Anal. Calcd for $C_{22}H_{24}BrNO_6$: C, 55.24; H, 5.06; N, 2.93. Found C, 55.25; H, 5.06; N, 2.92.

Acknowledgements

The authors thank the Specialized Research Fund for Doctoral Program of Higher Education (No. 20050335101), the Natural Science Foundation of Zhejiang Province (R404109) as well as the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, PR China.

References and notes

1. (a) *Enantioselective Synthesis of β-Amino acids*; Juaristi, E., Ed.; Wiley-VCH: New York, NY, 1997; (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232; (c) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973–980; (d) Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070.
2. (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44; (b) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97–99; (c) Kleinmann, E. F. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: New York, NY, 1991; Vol. 2, Chapter 4.1; (d) Davis, F. A.; Szewczyk, J. M. *Tetrahedron Lett.* **1998**, *39*, 5951–5954.
3. (a) Schunk, S.; Enders, D. *Org. Lett.* **2001**, *3*, 3177–3180; (b) Fujita, T.; Nagasawa, H.; Uto, Y.; Hashimoto, T.; Asakawa,

Y.; Hori, H. *Org. Lett.* **2004**, *6*, 827–830; (c) Ishimaru, K.; Kojima, T. *Tetrahedron Lett.* **2003**, *44*, 5441–5444; (d) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem.* **2003**, *68*, 8061–8064; (e) Evans, G. B.; Furneaux, R. H.; Tyler, P. C.; Schramm, V. L. *Org. Lett.* **2003**, *5*, 3639–3640; (f) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron Lett.* **2003**, *44*, 9189–9192; (g) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895–904; (h) Wenzel, A. G.; Jacobern, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; (i) Müller, R.; Röttele, H.; Henke, H.; Waldmann, H. *Chem.—Eur. J.* **2000**, *6*, 2032–2043.

4. (a) Periasamy, M.; Suresh, S.; Ganesan, S. S. *Tetrahedron Lett.* **2005**, *46*, 5521–5524; (b) Jacobsen, M. F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792–4796; (c) Komoto, I.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 680–688; (d) Chung, W. J.; Omote, M.; Welch, J. T. *J. Org. Chem.* **2005**, *70*, 7784–7787; (e) Pandey, G.; Singh, R. P.; Garg, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 2137–2140; (f) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1999**, 545–546; (g) Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1995**, 233–234; (h) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143–145; (i) Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 3395–3397.
5. Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292–9295.
6. For a preliminary communication of a part of this work see: Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Tetrahedron Lett.* **2006**, *47*, 1845–1847.
7. (a) Loh, T. P.; Liung, S. B. K. W.; Tan, K. L.; Wei, L. L. *Tetrahedron* **2000**, *56*, 3227–3237 and references cited therein; (b) Gennari, C.; Venturini, I.; Gislon, F.; Schimperma, G. *Tetrahedron Lett.* **1987**, *28*, 227–230; (c) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331–4334.
8. Ranu, B. C.; Samanta, S.; Guchhait, S. K. *Tetrahedron* **2002**, *58*, 983–988.
9. (a) Shang, Y. J.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 2247–2249; (b) Xia, M.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 7703–7705; (c) Shang, Y. J.; Shou, W. G.; Wang, Y. G. *Synlett* **2003**, 1064–1066; (d) Wang, Y. G.; Zhang, J.; Lin, X. F.; Ding, H. F. *Synlett* **2003**, 1467–1468; (e) Wang, Y. G.; Lin, X. F.; Cui, S. L. *Synlett* **2004**, 1175–1178; (f) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 530–536; (g) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866–2869; (h) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 3535–3540.
10. CCDC-615741 (**10b**) contains the supplementary crystallographic data for this paper. These can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html (or CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).