A Straightforward Approach towards α-Amino-β-keto Esters via Acylation of Chelated Amino Acid Ester Enolates

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Abstract: Chelated enolates were found to be good nucleophiles for reactions with acyl halides affording α-amino-β-keto esters. In most cases, the reactions are over after a few minutes and preparatively useful yields are obtained, independent of the protecting groups and halides used. Besides acyl halides, also the corresponding imidazolides can be used with similar success. With chloroformates as acylating agents different protected amino malonates become accessible.

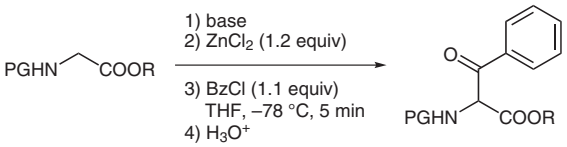
Key words: acylation, acyl halides, amino acids, amino malonates, chelated enolates, ketones

β-Keto-α-amino acids are not only important precursors for the synthesis of β-hydroxy-α-amino acids,[1] but are also interesting building blocks for pharmaceuticals[2] and natural products, such as the miuraenamides.[3] Therefore, straightforward concepts towards their synthesis are highly desired. Classical approaches are based on the diazotation of the corresponding β-keto esters[4] or on the ring opening of oxazoles.[5] Acylations of hippuric acid derivatives[6] and iminoglycinates[7] were also reported, but here the yields were moderate and varied significantly. An interesting approach was reported by Hamada et al. starting from acylimides of glycinates.[8] Deprotonation with strong bases such as LDA (lithium diisoproylamide) resulted in an intramolecular N → C acyl shift and the formation of the required protected β-keto amino acid. Tanabe et al. described an interesting cross-Claisen condensation approach of titanium enolates and acyl imidazolides, formed in situ from the corresponding acyl halides.[9] In principle, this approach is also suitable for α-amino-β-keto esters. The acyl halides could not be used directly, because of decomposition under the reaction conditions. But acyl halides can directly be used in acylations of α-amino malonic acid monoesters, providing the β-keto esters after decarboxylation.[10]

Our group is involved in amino acid synthesis since several years, investigating reactions of chelated amino acid ester enolates. These enolates show a higher thermal stability compared to nonchelated enolates and excellent stereoselectivities in a wide range of reactions, such as Claisen rearrangements,[11] Michael additions,[12] or transition-metal-catalyzed allylic alkylations.[13] Therefore, we were interested to find out if these enolates might also be suitable for the synthesis of β-keto-α-amino acid esters via nucleophilic attack on acyl halides or derivatives thereof.

Our investigations began with the N-tosylated *tert*-butyl glycinate and benzoyl chloride as electrophile (Table 1). The tosylated amino acid was chosen because of good results obtained previously in aldol additions.[14] With three equivalents of LDA as a base, the desired β-keto-α-amino acid ester was obtained in acceptable yield (Table 1, entry 1). Increasing the amount of base to 3.8 equivalents resulted in an increase of the yield (entry 2), but also a higher ratio of side products. A significant amount of N-benzoylated product also was obtained, which could not be separated easily. By lowering the amount of base to 2.5 equivalents (entry 3) the formation of the side products could be suppressed, but the yield dropped significantly. Therefore, we investigated also LHMDS (lithium hexamethyldisilazide) and LTMP (lithium tetramethylpiperidide) as sterically demanding alternative bases (entries 4

Table 1 Benzoylation of Chelated Glycine Enolates



Entry	PG	R	Base	Equiv	Product	Yield (%)
1	Ts	*t*-Bu	LDA	3.0	**1**	54
2	Ts	*t*-Bu	LDA	3.8	**1**	61
3	Ts	*t*-Bu	LDA	2.5	**1**	31
4	Ts	*t*-Bu	LHMDS	3.8	**1**	59
5	Ts	*t*-Bu	LTMP	3.8	**1**	59
6	Ts	Me	LDA	3.8	**2**	53
7	Ts	Bn	LDA	3.8	**3**	50
8	TFA	Bn	LDA	3.8	**4**	48
9	TFA	Bn	LHMDS	3.0	**4**	60
10	TFA	Bn	LTMP	3.0	**4**	62
11	TFA	*t*-Bu	LHMDS	3.0	**5**	67
12	Boc	Me	LDA	3.0	**6**	79
13	Boc	*t*-Bu	LDA	3.0	**7**	83

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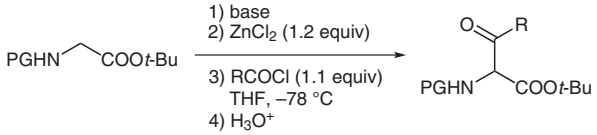
and 5). The yields obtained were comparable to those of the LDA reaction, but the side product formation could be suppressed nearly completely, which made the workup more convenient, because only the starting material had to be removed.

Next the influence of the protecting groups on the outcome of the reaction was investigated. When the ester functionality (entries 6 and 7) was changed the yield dropped slightly, but obviously there is no great influence from this protecting group. Therefore, we focused next on the N-protecting group. Based on the good results obtained in Michael additions[12] and allylic alkylations,[13] the trifluoroacetyl protecting group (TFA) was investigated. With the corresponding benzyl ester, a comparable yield was obtained if LDA was used as a base (entry 8). In our previous investigations of TFA enolates it was observed that under certain conditions this protecting group can be cleaved by the LDA used in excess, and that this problem can be solved by applying sterically more demanding bases such as LHMDS and LTMP. And indeed, by using these bases, the yield could be increased to around 60% (entries 9 and 10). A further improvement brought the switch from the benzyl ester to the *tert*-butyl ester (entry 11), our standard nucleophile used in allylic alkylations,[13] which also gave the best results here. As representatives of the carbamate protecting groups, two Boc-protected esters have been investigated as well, and they gave the best yields so far (entries 12 and 13). Obviously, there are no restrictions concerning the protecting groups that can be used.

We also proved the generality of the acyl halide component in the reaction of the N-tosylated *tert*-butyl glycinate (Table 2). With 4-phenylbenzoyl chloride, a slightly lower yield was obtained (Table 2, entry 1). But in contrast to aromatic acyl halides, their aliphatic relatives are more critical candidates, because under the basic reaction conditions ketene formation might be an optional pathway, resulting in the formation of various side products. For example, the yield obtained with hexanoyl chloride was only in the range of 50% (entry 2), probably because of ketene formation. To eliminate this side reaction, pivaloyl chloride was used as the electrophile. And indeed, with this sterically demanding acyl halide (without α-H) the yield increased significantly (entry 3). Especially with the TFA derivative an excellent yield was obtained (entry 4). Therefore, the reaction was investigated with several aliphatic acyl halides with this nucleophile. Linear as well as branched acyl chlorides provided the acylation products in yields of 61–87% (entries 5–8).

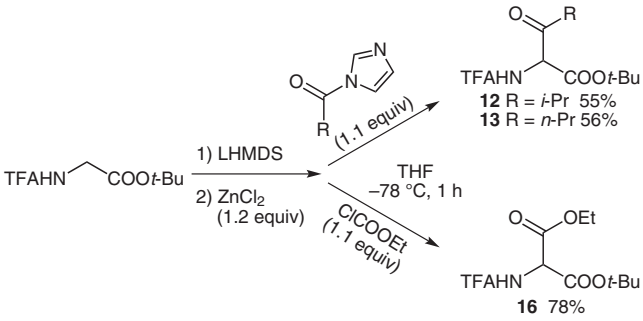
As an alternative to acyl chlorides the corresponding acylimidazolides were also investigated (Scheme 1). These activated acyl derivatives can easily be generated in situ from the corresponding carboxylic acid and carbonyldiimidazole.[15] The yields obtained were slightly lower compared to the acyl chlorides, but still in a preparatively useful range. Therefore, the imidazolides might be an interesting alternative in case the required acyl chlorides are unstable or difficult to prepare.

Table 2 Acylation of Chelated Glycine Enolates



Entry	PG	R	Base	Product	Yield (%)
1	Ts	4-PhC_6H_4	LDA	**8**	54
2	Ts	*n*-C_5H_{11}	LDA	**9**	47
3	Ts	*t*-Bu	LDA	**10**	68
4	TFA	*t*-Bu	LHMDS	**11**	93
5	TFA	*i*-Pr	LHMDS	**12**	61
6	TFA	*n*-Pr	LHMDS	**13**	62
7	TFA	Ad[a]	LHMDS	**14**	67
8	TFA	*c*-C_6H_{11}	LHMDS	**15**	87

[a] Ad: 1-Adamantyl.



Scheme 1 Acylations using acyl imidazolides and chloroformates

To increase the generality of this approach chloroformates were also subjected to our standard reaction conditions. Although no β-keto esters are formed in this case, this approach gives direct access to differentially protected α-amino malonates **16**, which are also interesting building blocks.

It should be mentioned, that the β-keto-α-amino acid esters should be subjected to further modifications of the β-keto group, before cleavage of the protecting group, because the N- and/or O-deprotected amino acids are not stable. Cleavage of the ester functionality provides the corresponding β-keto-α-amino acid, which undergoes fast decarboxylation towards the corresponding α-amino ketone, and cleavage of the N-protecting group results in the formation of several side products (e.g., dimerization of the free amino ketone).

In conclusion, we have shown that the direct acylation of chelated enolates is a straightforward approach towards β-keto-α-amino acid derivatives. Generally, preparatively useful yields are obtained, nearly independent on the pro-

tecting groups and the acyl halides used. Obviously, the highly reactive chelated enolates can compete successfully with undesired side reactions such as amide and ketene formation. Applications of this approach in natural product syntheses are currently under investigation.

All reactions were carried out in oven-dried glassware (100 °C) under N_2. All solvents were dried before use; THF was distilled from $LiAlH_4$. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of EtOAc and hexanes were generally used as eluents. Analysis by TLC was carried out on commercially precoated Polygram SIL-G/UV 254 plates (Macherey-Nagel, Düren). Visualization was accomplished with UV light, $KMnO_4$ solution, or I_2. ^1H and ^{13}C NMR spectroscopic analyses were performed on a Bruker Avance II 400 (400 MHz) spectrometer. Chemical shifts are reported on the δ (ppm) scale and the coupling constant are given in Hz. High-resolution mass spectra were recorded on a Finnigan MAT 95S mass spectrometer at the Institute of Organic Chemistry, and on a Thermo LTQ-Orbitrap Hybrid-FT mass spectrometer at the Institute of Pharmazeutical Biotechnology at Saarland University. Elemental analyses were carried out at the Department of Chemistry at Saarland University.

Acylation of Chelated Glycine Enolates; General Procedure

In a Schlenk tube, hexamethyldisilazane, diisopropylamine, or tetramethylpiperidine (3.3 mmol, 3.3 equiv) was dissolved in anhyd THF (5.0 mL). After cooling the solution to –78 °C, a 1.6 M solution of *n*-BuLi (1.88 mL, 3.00 mmol, 3.0 equiv) was added slowly. The solution was stirred for 10 min before the cooling bath was removed and the solution was stirred further for 10 min. In a second Schlenk tube, $ZnCl_2$ (164 mg, 1.2 mmol, 1.2 equiv) was dried with a heat gun under vacuum. After cooling to r.t., protected glycine (1.0 mmol, 1 equiv) and THF (5.0 mL) were added and the solution was cooled to –78 °C before the above prepared base solution was added slowly. The resulting solution was stirred for 30 min at –78 °C. The corresponding acyl halide or imidazolide (1.1 equiv) was added at –78 °C, and the reaction mixture was allowed to stir for 5 min before it was hydrolyzed with aq 1 M $KHSO_4$ (10 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (silica gel, hexanes–EtOAc).

***tert*-Butyl 2-(Tosylamino)-3-oxo-3-phenylpropanoate (1)**

According to the general procedure, Ts-Gly-O*t*-Bu (229 mg, 0.80 mmol) and LDA (326 mg, 3.04 mmol) were reacted with benzoyl chloride (126 μL, 154 mg, 1.10 mmol) to give **1**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as colorless needles; yield: 190 mg (0.488 mmol, 61%); mp 136–137 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.3 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.46 (dd, *J* = 7.3, 7.3 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 5.86 (d, *J* = 9.0 Hz, 1 H), 5.45 (d, *J* = 9.0, 1 H), 2.36 (s, 3 H), 1.18 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5, 165.9, 143.7, 134.7, 134.0, 130.7, 129.7, 128.9, 128.3, 127.3, 82.9, 61.5, 27.8, 21.5.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{24}NO_5S$ $[M + H]^+$: 390.1375; found: 390.1373.

Anal. Calcd for $C_{20}H_{23}NO_5S$ (389.47): C, 61.68; H, 5.95; N, 3.60. Found: C, 61.57; H, 5.94; N, 3.56.

Methyl 2-(Tosylamino)-3-oxo-3-phenylpropanoate (2)

According to the general procedure, Ts-Gly-OMe (234 mg, 0.96 mmol) and LDA (391 mg, 3.65 mmol) were reacted with benzoyl chloride (115 μL, 141 mg, 1.00 mmol) to give **2**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 176 mg (0.51 mmol, 53%); mp 102–103 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.5 Hz, 2 H), 7.70 (d, *J* = 8.2 Hz, 2 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 7.46 (dd, *J* = 8.3, 7.6 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 5.92 (d, *J* = 8.8 Hz, 1 H), 5.58 (d, *J* = 8.8 Hz, 1 H), 3.51 (s, 3 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 166.5, 149.0, 134.6, 130.2, 129.7, 129.3, 128.9, 128.5, 127.3, 60.6, 53.2, 21.4.

HRMS (CI): *m*/*z* calcd for $C_{17}H_{18}NO_5S$ $[M + H]^+$: 348.0906; found: 348.0905.

Anal. Calcd for $C_{17}H_{17}NO_5S$ (347.39): C, 58.78; H, 4.93; N, 4.03. Found: C, 58.72; H, 5.10; N, 3.88.

Benzyl 2-(Tosylamino)-3-oxo-3-phenylpropanoate (3)

According to the general procedure, Ts-Gly-OBn (263 mg, 0.82 mmol) and LDA (335 mg, 3.12 mmol) were reacted with benzoyl chloride (105 μL, 128 mg, 0.91 mmol) to give **3**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 174 mg (0.41 mmol, 50%); mp 80–82 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (dd, *J* = 8.4, 1.3 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.59 (tt, *J* = 7.5, 1.3 Hz, 1 H), 7.41 (dd, *J* = 8.4, 7.5 Hz, 1 H), 7.45–7.22 (m, 3 H), 7.18 (d, *J* = 8.2 Hz, 2 H), 7.17 (m, 2 H), 5.95 (d, *J* = 8.8 Hz, 1 H), 5.61 (d, *J* = 8.8 Hz, 1 H), 4.93 (d, *J* = 12.4 Hz, 1 H), 4.89 (d, *J* = 12.0 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 166.0, 143.6, 136.5, 134.6, 134.3, 133.6, 129.9, 129.7, 129.0, 128.5, 128.1, 127.4, 127.3, 68.1, 60.9, 21.6.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{22}NO_5S$ $[M + H]^+$: 424.1213; found: 424.1192.

Benzyl 2-(Trifluoroacetamido)-3-oxo-3-phenylpropanoate (4)

According to the general procedure, TFA-Gly-OBn (261 mg, 1.00 mmol) and LHMDS (518 mg, 3.10 mmol) were reacted with benzoyl chloride (130 μL, 155 mg, 1.10 mmol) to give **4**, after flash chromatography (silica gel, hexanes–EtOAc, 15:1), as a colorless solid; yield: 220 mg (0.60 mmol, 60%); mp 60–61 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.5 Hz, 2 H), 7.73 (br s, 1 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.48 (m, 2 H), 7.30–7.22 (m, 3 H), 7.07 (d, *J* = 6.2 Hz, 2 H), 6.15 (d, *J* = 7.1 Hz, 1 H), 5.15 (d, *J* = 11.9 Hz, 1 H), 5.09 (d, *J* = 11.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.0, 164.5, 135.0, 134.1, 133.3, 129.8, 128.9, 128.7, 128.6, 128.1, 68.7, 58.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}F_3NO_4$ $[M + H]^+$: 366.0953; found: 366.0998.

***tert*-Butyl 2-(Trifluoroacetamido)-3-oxo-3-phenylpropanoate (5)**

According to the general procedure, TFA-Gly-O*t*-Bu (682 mg, 3.00 mmol) and LHMDS (1.56 g, 9.30 mmol) were reacted with benzoyl chloride (345 μL, 421 mg, 3.00 mmol) to give **5**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 671 mg (2.02 mmol, 67%); mp 84–85 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 7.5 Hz, 2 H), 7.66 (m, 2 H), 7.52 (dd, *J* = 7.5, 7.5 Hz, 2 H), 6.01 (d, *J* = 7.0 Hz, 1 H), 1.30 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 163.4, 156.7 (q, *J* = 38.3 Hz), 134.8, 133.8, 129.7, 128.7, 115.6 (q, *J* = 287 Hz), 85.0, 59.1, 27.6.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}F_3NO_4$ $[M + H]^+$: 332.1104; found: 332.1109.

Methyl 2-(*tert*-Butoxycarbonylamino)-3-oxo-3-phenylpropanoate (6)

According to the general procedure, Boc-Gly-OMe (189 mg, 1.00 mmol) and LDA (332 mg, 3.10 mmol) were reacted with benzoyl chloride (127 μL, 155 mg, 1.10 mmol) to give **6**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 232 mg (0.79 mmol, 79%); mp 88–89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 7.2 Hz, 2 H), 7.61 (t, *J* = 7.2 Hz, 1 H), 7.49 (m, 2 H), 5.95 (d, *J* = 8.0 Hz, 1 H), 5.87 (d, *J* = 8.0 Hz, 1 H), 3.70 (s, 3 H), 1.44 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 167.3, 157.2, 134.3, 133.3, 129.5, 128.8, 84.6, 63.2, 53.1, 28.2.

HRMS (CI): *m*/*z* calcd for $C_{15}H_{20}NO_5$ [M + H]$^+$: 294.1336; found: 294.1310.

Anal. Calcd for $C_{15}H_{19}NO_5$ (293.32): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.37; H, 6.44; N, 4.55.

***tert*-Butyl 2-(*tert*-Butoxycarbonylamino)-3-oxo-3-phenylpropanoate (7)**

According to the general procedure, Boc-Gly-O*t*-Bu (300 mg, 1.30 mmol) and LDA (431 mg, 4.00 mmol) were reacted with benzoyl chloride (165 μL, 200 mg, 1.43 mmol) to give **7**, after flash chromatography (silica gel, hexanes–EtOAc, 15:1), as a colorless solid; yield: 362 mg (1.08 mmol, 83%); mp 68–69 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.5 Hz, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.47 (dd, *J* = 7.5 Hz, 2 H), 5.87–5.80 (m, 2 H), 1.43 (s, 9 H), 1.29 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7, 165.8, 155.0, 134.7, 133.9, 129.5, 128.5, 83.5, 80.4, 60.2, 28.3, 27.7.

HRMS (CI): *m*/*z* calcd for $C_{18}H_{26}NO_5$ [M + H]$^+$: 336.1805; found: 336.1797; *m*/*z* calcd for $C_{18}H_{27}NO_5$ [M + 2 H]$^+$: 337.1883; found: 337.1889.

***tert*-Butyl 2-(Tosylamino)-3-oxo-3-(4-phenyl)phenylpropanoate (8)**

According to the general procedure, Ts-Gly-O*t*-Bu (229 mg, 0.80 mmol) and LDA (326 mg, 3.04 mmol) were reacted with 4-phenylbenzoyl chloride (217 mg, 1.00 mmol) to give **8**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as colorless needles; yield: 200 mg (0.43 mmol, 54%); mp 135–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.5 Hz, 2 H), 7.73 (d, *J* = 8.5 Hz, 2 H), 7.67 (d, *J* = 8.5 Hz, 2 H), 7.61 (m, 2 H), 7.47 (m, 2 H), 7.40 (m, 1 H), 7.23 (m, 2 H), 5.88 (d, *J* = 9.0 Hz, 1 H), 5.48 (d, *J* = 9.0 Hz, 1 H), 2.36 (s, 3 H), 1.21 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.3, 165.0, 147.0, 143.8, 139.4, 136.7, 132.4, 130.0, 129.7, 129.0, 128.6, 127.4, 127.3, 127.2, 84.0, 61.5, 27.5, 21.5.

HRMS (CI): *m*/*z* calcd for $C_{26}H_{28}NO_5S$ [M + H]$^+$: 466.1688; found: 466.1682.

Anal. Calcd for $C_{24}H_{27}NO_5S$ (465.56): C, 67.08; H, 5.85; N, 3.01. Found: C, 66.88; H, 5.48; N, 2.72.

***tert*-Butyl 2-(Tosylamino)-3-oxooctanoate (9)**

According to the general procedure, Ts-Gly-O*t*-Bu (285 mg, 1.00 mmol) and LDA (332 mg, 3.10 mmol) were reacted with hexanoyl chloride (152 μL, 144 mg, 1.08 mmol) to give **9**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 180 mg (0.47 mmol, 47%); mp 75–76 °C.

Besides the expected product **9**, the enol form was also observed in the NMR spectra.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 5.64 (d, *J* = 7.9 Hz, 1 H), 4.50 (d, *J* = 7.9 Hz, 1 H), 2.60 (dt, *J* = 17.6, 7.4 Hz, 1 H), 2.50 (dt, *J* = 17.6, 7.2 Hz, 1 H), 2.37 (s, 3 H), 1.51 (m, 2 H), 1.31 (s, 9 H), 1.28–1.16 (m, 4 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 164.8, 143.9, 136.5, 129.7, 127.3, 84.1, 65.0, 39.9, 31.7, 27.7, 22.9, 22.5, 21.2, 14.0.

Enol Form (selected signals)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.7 (br s, 1 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 5.40 (s, 1 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 129.5, 127.8, 115.4, 82.6, 13.8.

HRMS (CI): *m*/*z* calcd for $C_{19}H_{30}NO_5S$ [M + H]$^+$: 384.1845; found: 384.1887.

***tert*-Butyl 2-(Tosylamino)-4,4-dimethyl-3-oxopentanoate (10)**

According to the general procedure, Ts-Gly-O*t*-Bu (229 mg, 0.80 mmol) and LDA (326 mg, 3.04 mmol) were reacted with pivaloyl chloride (132 μL, 129 mg, 1.07 mmol) to give **10**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 180 mg (0.47 mmol, 47%); mp 120–121 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 5.59 (d, *J* = 10.0 Hz, 1 H), 4.94 (d, *J* = 10.0 Hz, 1 H), 2.37 (s, 3 H), 1.25 (s, 9 H), 1.14 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.3, 165.2, 143.9, 136.7, 129.6, 127.4, 83.7, 58.9, 46.6, 27.6, 26.2, 21.5.

Anal. Calcd for $C_{18}H_{27}NO_5S$ (369.48): C, 58.51; H, 7.37; N, 3.79. Found: C, 58.73; H, 7.15; N, 3.56.

***tert*-Butyl 2-(Trifluoroacetamido)-4,4-dimethyl-3-oxopentanoate (11)**

According to the general procedure, TFA-Gly-O*t*-Bu (227 mg, 1.00 mmol) and LHMDS (518 mg, 3.10 mmol) were reacted with pivaloyl chloride (135 μL, 132 mg, 1.10 mmol) to give **11**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 290 mg (0.93 mmol, 93%); mp 48–49 °C.

Besides the expected product **11**, the enol forms were also observed in the NMR spectra.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (br s, 1 H), 5.57 (d, *J* = 7.9 Hz, 1 H), 1.45 (s, 9 H), 1.25 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.7, 164.2, 156.3 (q, *J* = 38.9 Hz), 115.5 (q, *J* = 287 Hz), 83.4, 56.5, 44.9, 27.8, 26.4.

Enol Forms (selected signals)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (br s, 2 H), 1.47 (s, 9 H), 1.27 (s, 9 H), 1.24 (m, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 174.0, 161.5, 157.9, 118.0, 84.9, 39.5, 37.0, 28.2, 27.7, 27.1, 26.5.

HRMS (CI): *m*/*z* calcd for $C_{13}H_{21}F_3NO_4$ [M + H]$^+$: 312.1423; found: 312.1414.

***tert*-Butyl 2-(Trifluoroacetamido)-4-methyl-3-oxopentanoate (12)**

According to the general procedure, TFA-Gly-O*t*-Bu (227 mg, 1.00 mmol) and LHMDS (518 mg, 3.10 mmol) were reacted with isobutyryl chloride (117 mg, 1.10 mmol) to give **12**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a yellow liquid; yield: 182 mg (0.61 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (br s, 1 H), 5.25 (d, *J* = 6.5 Hz, 1 H), 3.13 (qq, *J* = 6.9, 6.8 Hz, 1 H), 1.48 (s, 9 H), 1.23 (d, *J* = 7.1 Hz, 3 H), 1.14 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5, 163.3, 156.5 (q, *J* = 38.6 Hz), 115.5 (q, *J* = 38.6 Hz), 85.1, 61.3, 38.9, 27.8, 18.8, 17.4.

HRMS (CI): *m*/*z* calcd for $C_{12}H_{19}F_3NO_4$ [M + H]$^+$: 298.1260; found: 198.1282.

Anal. Calcd for $C_{12}H_{18}F_3NO_4$ (297.27): C, 48.48; H, 6.10; N, 4.71. Found: C, 47.98; H, 5.93; N, 4.73.

***tert*-Butyl 2-(Trifluoroacetamido)-3-oxohexanoate (13)**

According to the general procedure, TFA-Gly-O*t*-Bu (227 mg, 1.00 mmol) and LHMDS (518 mg, 3.10 mmol) were reacted with butyryl chloride (117 mg, 1.10 mmol) to give **13**, after flash chromatography (silica gel, hexanes–EtOAc 10:1), as a pale yellow liquid; yield: 185 mg (0.61 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (br s, 1 H), 5.08 (d, *J* = 6.3 Hz, 1 H), 2.79 (t, *J* = 7.3 Hz, 1 H), 2.67 (t, *J* = 7.0 Hz, 1 H), 1.68 (tq, *J* = 7.3, 7.3 Hz, 2 H), 1.49 (s, 9 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2, 163.1, 156.5, 115.4, 84.9, 62.9, 42.5, 27.6, 16.7, 13.3.

HRMS (CI): *m*/*z* calcd for $C_8H_{10}F_3NO_4$ [M – *t*-Bu + H]$^+$: 241.0556; found: 241.0518.

Anal. Calcd for $C_{12}H_{18}F_3NO_4$ (297.27): C, 48.48; H, 6.10; N, 4.71. Found: C, 48.53; H, 5.95; N, 4.79.

***tert*-Butyl 2-(Trifluoroacetamido)-3-adamantyl-3-oxopropanoate (14)**

According to the general procedure, TFA-Gly-O*t*-Bu (227 mg, 1.00 mmol) and LHMDS (518 mg, 3.10 mmol) were reacted with adamantyl chloride (219 mg, 1.10 mmol) to give **14**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 248 mg (0.68 mmol, 67%); mp 104–105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (br s, 1 H), 5.56 (d, *J* = 7.9 Hz, 1 H), 2.07–2.08 (m, 3 H), 1.87–1.97 (m, 6 H), 1.68–1.77 (m, 6 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.3, 164.5, 156.2 (q, *J* = 38.6 Hz), 115.2 (q, *J* = 286 Hz), 85.1, 56.1, 47.4, 38.1, 36.4, 27.9.

Anal. Calcd for $C_{19}H_{26}F_3NO_4$ (389.41): C, 58.60; H, 6.73; N, 3.60. Found: C, 58.22; H, 6.62; N, 3.59.

***tert*-Butyl 2-(Trifluoroacetamido)-3-cyclohexyl-3-oxopropanoate (15)**

According to the general procedure, TFA-Gly-O*t*-Bu (227 mg, 1.00 mmol) and LHMDS (518 mg, 3.10 mmol) were reacted with cyclohexanecarbonyl chloride (161 mg, 1.10 mmol) to give **15**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a colorless solid; yield: 248 mg (0.68 mmol, 67%); mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (br s, 1 H), 5.22 (d, *J* = 6.5 Hz, 1 H), 2.87 (m, 1 H), 1.49 (s, 9 H), 1.58–2.06 (m, 6 H), 1.28–1.34 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.3, 164.1, 157.6 (q, *J* = 38.6 Hz), 112.6 (q, *J* = 284 Hz), 85.8, 62.4, 49.5, 30.1, 28.5, 26.3, 25.9.

HRMS (CI): *m*/*z* calcd for $C_{11}H_{13}F_3NO_3$ [M – *t*-BuO]$^+$: 264.0842; found: 264.0804.

Anal. Calcd for $C_{15}H_{22}F_3NO_4$ (337.33): C, 53.41; H, 6.57; N, 4.15. Found: C, 53.33; H, 6.41; N, 4.15.

1-*tert*-Butyl 3-Ethyl 2-(Trifluoroacetamido)malonate (16)

According to the general procedure, TFA-Gly-O*t*-Bu (227 mg, 1.00 mmol) and LHMDS (518 mg, 3.10 mmol) were reacted with ethyl chloroformate (187 mg, 1.10 mmol) to give **16**, after flash chromatography (silica gel, hexanes–EtOAc, 10:1), as a pale yellow oil; yield: 222 mg (0.78 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (br s, 1 H), 5.01 (d, *J* = 6.8 Hz, 1 H), 4.35 (dq, *J* = 7.2, 7.2 Hz, 1 H), 4.26 (dq, *J* = 7.2, 7.2 Hz, 1 H), 1.49 (s, 9 H), 1.32 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 163.0, 156.0 (q, *J* = 38.4 Hz), 114.9 (q, *J* = 38.9 Hz), 62.5, 56.4, 27.2, 13.5.

HRMS (CI): *m*/*z* calcd for $C_7H_7F_3NO_4$ [M – *t*-BuO]$^+$: 226.0322; found: 226.0288.

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