Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 2629–2634

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

FACILE SYNTHESIS OF N-PROTECTED γ AND δ-AMINO-β-KETO-ESTERS

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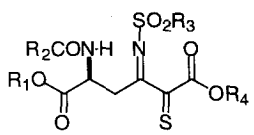
Received 14 July 1999; accepted 5 August 1999

Abstract: The C-acylation of Meldrum's acid by protected amino acids, using isopropenyl chloroformate (IPCF) as the condensing agent, is described. The process is used to synthesize γ and δ-amino-β-keto-esters.

Introduction The development of new methodologies for the synthesis of γ-amino-β-keto acids or their analogs, which are precursors of γ-amino-β-hydroxy acids[1] that are found in many natural products,[2] continues as an active area of investigation.[3] In connection with our study[4] of the directed synthesis of N-glycopeptides via double heteroatom cycloaddition reactions of glycals with thiono-oximinoesters **1**, we required an efficient preparation for the infrequently reported 4-oxo-norvaline **2** (i.e.δ-amino-β-keto) from readily available materials. For precedents, we examined the literature for preparation of the more common γ-amino-β-keto series. Thus far, the reported methods for the synthesis of γ-amino-δ-keto esters include activation of the carboxyl group of an α-amino acid as its imidazolide followed by C-C bond formation with lithioacetate(Eq.1);[5] and, similarly, reaction of urethane N-protected-N-carboxyanhydride (UNCAS) with the lithium enolate of ethyl acetate (Eq.2).[6]



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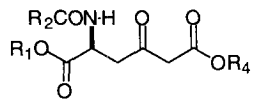

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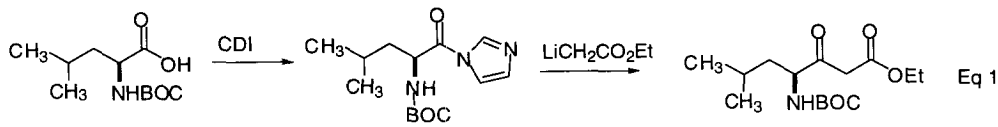

3 **4** **5** Eq 1

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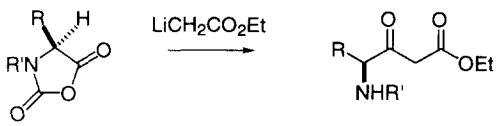
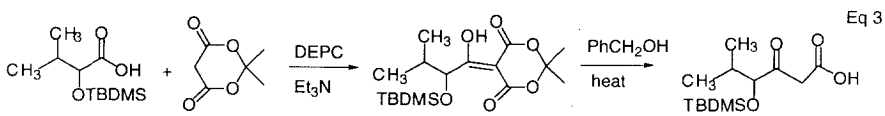


6 7 Eq 2

In addition, an N-protected δ-amino-β-keto-ester, for example, N-(carbobenzyloxy)-4-oxo-5-(ethoxyacetyl)-DL-norvaline, has been prepared via insertion of ethyl diazoacetate into the formyl group of β-aspartyl semialdehyde.[7] The published methods appeared to be unsuitable for our purpose, especially for the preparation of δ-amino-β-keto-ester **2** since products were obtained in modest yield [5] or the starting materials were not readily available[6]. In this paper, we wish to report an efficient method for the synthesis of δ-amino-β-keto-esters that is applicable to the γ-amino-β-keto ester series as well.

Results and Discussion

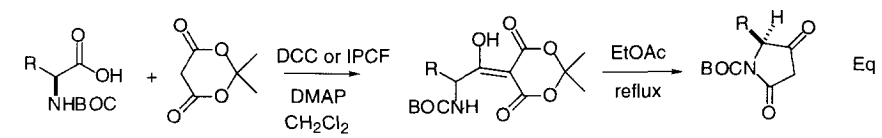
The acylation of Meldrum's acid has been well established as a synthesis of β-keto-esters,[8] but apparently has never found use in the synthesis of amino-keto-esters. But, a closely-related and relevant example for us is the condensation of α-hydroxy-carboxylic acid **8** with Meldrum's acid **9** by use of diethyl phosphorocyanidate (DEPC), followed by refluxing with benzyl alcohol in benzene, afforded the β-keto-ester **11** (Eq 3).[9]



Eq 3

8 9 10 11

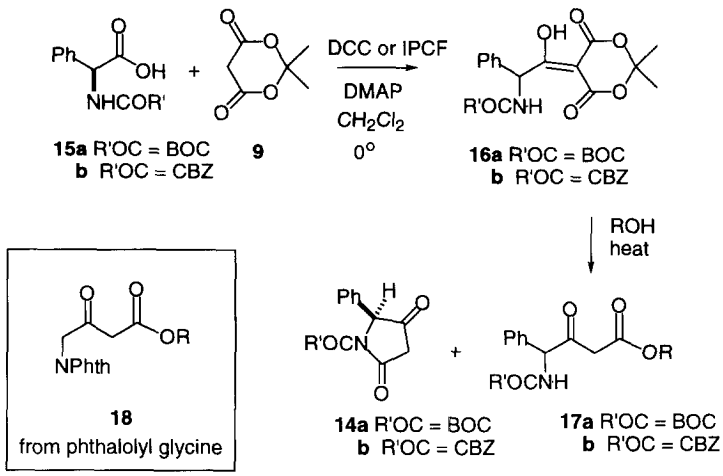
Our plan was to exploit the similar condensation of N-protected amino acids with Meldrum's acid as the means of two carbon extension. Accordingly, condensation of N-protected α-amino acids **12** with Meldrum's acid in the presence of isopropenyl chloroformate (IPCF) or DCC as activating agents, followed by refluxing in acetonitrile or ethyl acetate, afforded only tetramic acid **14** (Eq.4), the unwanted product of subsequent cyclization of the desired chain-extended amino acid.[10]



Eq 4

12 9 13 14

Scheme 1



15a R'OC = BOC
b R'OC = CBZ

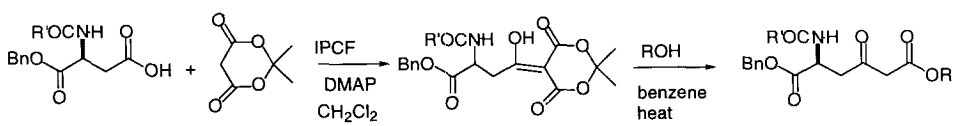
9

16a R'OC = BOC
b R'OC = CBZ

entry	Amino acid	R'OC	R	**17:14**	Yield %
1	Phe-OH	BOC	Et	1:2	90
2	Phe-OH	BOC	i-Pr	2:5	78
3	Phe-OH	BOC	t-Bu	1:3	83
4	Phe-OH	CBz	Et	1:2	81
5	Gly-OH	Phth	Et	only **18**	78

In a modification of the above procedure, the intermediate **13** was treated with 2 equiv. of alcohol in refluxing benzene. Along with the γ-amino-δ-keto esters **17**,[11] we also obtained the easily separated cyclic product (N-protect tetramic acid derivative) **14** (Scheme 1). In the case of N-phthaloylglycine where the nitrogen was fully protected, no tetramic acid is formed (entry 5, table in scheme).[12] The example of the phthalimido protecting group shows that our method could easily be applied across the entire γ-amino-β-keto ester series.

The synthesis of the desired δ-amino-β-keto-esters **21** through the use of N-protected aspartic acid **19** as the starting material was the natural extension of the above methodology. Thus, condensation of commercially available N-protected aspartic acids **19** with Meldrum's acid **9** by use of isopropenyl chloroformate (IPCF) as activating agent in the presence of DMAP, afforded the intermediate **20**. Without further purification, the intermediate **20** was then refluxed with various alcohols in benzene to give δ-amino-β-keto-esters **21** in excellent yield (Table 1). In this case, there were no cyclic products detected, presumably because the 6-membered ring is formed less easily than the 5-membered examples.



19a R'OC = BOC
b R'OC = CBZ

9

20a R'OC = BOC
b R'OC = CBZ

21a R'OC = BOC
b R'OC = CBZ

Table 1. Preparation of δ-amino-β-keto-esters from N-protected aspartic acids

entry	R'OC	R	Yield(%) of **21**
1	BOC	Bn	86
2	BOC	Et	92
3	BOC	i-Pr	90
4	BOC	t-Bu	72
5	CBZ	Bn	77

In conclusion, we have shown that δ-amino-β-keto-esters can be easily obtained from commercially available β-amino acids. The reaction sequence proceeds smoothly and rapidly, is compatible with CBZ, BOC, and phthalimido N-protecting groups and affords a variety of N-protected derivatives of δ-amino-β-keto-ester in good yields.

Experimental Section with representative examples

All reactions were carried out under a dry argon or nitrogen atmosphere at ambient temperature unless otherwise stated. Low temperature reactions were recorded as bath temperatures. Chromatography was carried out on silica gel 60, 230-400 mesh, using flash chromatography techniques. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica 60 F_{254} plates. Petroleum ether, dichloromethane, and ethyl acetate used as eluants were ACS reagent grade solvent. Dichloromethane was purified by distillation from P_2O_5. NMR spectra were measured with a GE QE 300 MHz instrument. Chemical shifts are reported in δ units, coupling constants in Hz. TMS (δ = 0.0) was used as internal reference for spectra measured in $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer.

General procedure for preparation of amino-keto-ester

To a solution of N-protected amino acid (1 mmol), DMAP (0.28 g, 1.1 mmol), and Meldrum's acid (0.15 g, 1 mmol) in dichloromethane (5 mL), was added IPCF (0.13 mL, 1.1 mmol) in dichloromethane (1 mL) during 20 min at –5 ^{0}C. The resulting mixture was stirred for a further 1.5 h at this temperature. The mixture was then quenched by adding 10% aqueous potassium hydrogen sulfate. The organic phase was washed with water and brine, and dried over Na_2SO_4. Removal of the solvent gave a white solid. The white solid was treated with alcohol (2 mmol) in refluxing benzene (10 ml) for 4 h. The solvent was removed. Purification of the residue by chromatography over a silica gel gave product.

(5S)-5-benzyl-4-hydroxy-1-t-butoxycarbonylpyrrol-2(5H)-one: ^{1}HNMR ($CDCl_3$) 7.3 -7.0 (m,5H), 4.65 (m, 1H), 3.4 -3.2 (m, 2H), 2.9 -2.2 (m, 2H), 1.6 (s, 9H).

Ethyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-tert-butyl ester: This compound was prepared according to the above general procedure from N-α-t-BOC-phenylalanine (265 mg, 1 mmol) by using ethanol to workup the Meldrum's acid adduct. Yield: 90%; m.p.: 60-62 ^{0}C. (Lit.[6a] 61 - 62 ^{0}C); FTIR: 3376, 2979, 2934, 1715, 1504, 1456, 1393, 1368, 1163. ^{1}HNMR ($CDCl_3$), δ 7.24 (m, 5H), 5.0 (d, J = 8.2, 1H), 4.58 (m, 1H), 4.19 (q, J = 7.1, 2H), 3.42 (m, 2H), 3.16 (m, 2H), 1.41 (s, 9H), 1.18 (t, J = 7.1, 3H). ^{13}CNMR ($CDCl_3$), δ 201.8, 166.8, 136.1, 129.2, 128.7, 128.4, 127.0, 61.4, 60.4, 46.9, 37.0, 29.7, 28.2, 14.0.

Tert-butyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-tert-butyl ester: This compound was prepared according to the above general procedure from N-α-t-BOC-phenylalanine (265 mg, 1 mmol) by using tert-butyl alcohol to workup the Meldrum's acid adduct. Yield: 78%; ^{1}HNMR ($CDCl_3$), δ 7.31-7.16 (m, 5H), 5.03 (d, J = 8.3, 1H), 4.53 (m, 1H), 3.42 (q, J = 7.1, 2H), 3.21-2.93 (m, 2H), 1.45 (s, 9H), 1.32 (s,

9H).). ^{13}CNMR ($CDCl_3$), δ 201.5, 165.7, 155.6, 136.1, 135.7, 129.2, 128.6, 128.4, 128.1, 127.9, 127.0, 82., 66.9, 60.7, 48.1, 37.0, 28.2, 27.8.

Ethyl-4-(carboxyamino)-5-phenyl-3-oxopentanoate 4-benzyl ester: This compound was prepared according to the above general procedure from N-α-t-CBZ-phenylalanine (299 mg, 1 mmol) by using ethyl alcohol to workup the Meldrum's acid adduct. Yield: 81%; m.p.: 57-59 ^{0}C (lit.[6a] 57-61 ^{0}C); FTIR: 3339, 2980, 1718, 1519, 1251. ^{1}HNMR ($CDCl_3$), δ 7.39-7.10 (m, 10H), 5.40 (d, J = 7.2, 1H), 5.03 (s, 2H), 4.63 (q, J = 6.5), 4.18 (q, J = 7.1, 2H), 3.41 (m, 2H), 3.20-2.91 (m, 2H), 1.20 (t, J=7.1, 3H). ^{13}CNMR ($CDCl_3$), δ 200.9, 166.2, 155.3, 135.6, 135.3, 128.7, 128.3, 128.0, 127.9, 127.8, 127.7, 127.5, 126.7, 66.6, 61.0, 60.3, 46.5, 36.5, 13.5.

Ethyl-4-(phthalimido)-3-oxoheptanoate: This compound was prepared according to the above general procedure from N-phthaloylglycine (205 mg, 1 mmol) by using ethyl alcohol to workup the Meldrum's acid adduct. Yield: 78%; ^{1}HNMR ($CDCl_3$), δ 7.8 (m, 4H), 4.63 (s, 2H), 4.21 (q, J = 7.1, 2H), 3.60 (s, 2H), 1.23 (t, J = 7.1, 3H).

N-(tert-butoxycarbonyl)-4-oxo-5-(benzyloxyacetyl)-norvaline: This compound was prepared according to the above general procedure from N-α-t-BOC-aspartic acid α-benzyl ester (0.323 g, 1 mmol) by using benzyl alcohol to workup the Meldrum's acid adduct. Yield: 86%; m.p.: 54 – 55 ^{0}C; ^{1}HNMR ($CDCl_3$), δ 7.34-7.25 (m, 10H), 5.51 (d, J = 8.1, 1H), 5.15 (m, 4H), 4.55 (m, 1H), 3.45 (s, 2H), 3.44-3.09 (m, 2H), 1.41 (s, 9H). ^{13}CNMR ($CDCl_3$), δ 200.1, 170.3, 165.8, 154.9, 134.7, 134.6, 128.0, 127.8, 127.6, 79.5, 66.9, 66.7, 49.0, 48.5, 44.2, 27.7.

N-(tert-Butoxycarbonyl)-4-oxo-5-(ethoxyacetyl)-norvaline: This compound was prepared according to the above general procedure from N-α-t-BOC-aspartic acid α-benzyl ester (0.323 g, 1 mmol) by using ethyl alcohol to workup the Meldrum's acid adduct. Yield: 92%; m.p. 53 - 56 ^{0}C (lit.[6a] 54 - 57 ^{0}C); FTIR: 3374, 2979, 1738, 1713, 1501, 1367, 1164. ^{1}HNMR ($CDCl_3$), δ 7.32 (m, 5H), 5.43 (d, J = 8.9, 1H), 5.18 (s, 2H), 4.60 (m, 1H), 4.2 (q, J = 7.2, 2H), 3.41 (s, 2H), 3.20 (m, 2H), 1.42 (s, 9H), 1.23 (t, J = 7.2, 3H). ^{13}CNMR ($CDCl_3$), δ 201.2, 171.3, 166.8, 155.8, 135.6, 128.9, 128.7, 128.5, 80.5, 67.8, 61.2, 49.9, 49.5, 45.1, 28.6, 14.4.

N-(tert-Butoxycarbonyl)-4-oxo-5-(tert-butoxyacetyl)-norvaline: This compound was prepared according to the above general procedure from N-α-t-BOC-aspartic acid α-benzyl ester (0.323 g, 1 mmol) by using tert-butyl alcohol to workup the Meldrum's acid adduct. Yield: 87%; FTIR: 3376, 2979, 1715, 1503, 1368, 1163; ^{1}H-NMR ($CDCl_3$), δ 7.36 (m, 5H), 5.46 (d, J = 8.7, 1H), 5.16 (s, 2H), 4.56 (m, 1H), 3.24 (s, 2H), 3.24 (m, 2H), 1.42 (s, 9H), 1.41 (s, 9H); ^{13}CNMR ($CDCl_3$), δ 200.7, 170.5, 165.2, 155.0, 134.9, 128.1, 127.9, 127.7, 81.9, 79.6, 66.9, 50.0, 49.0, 44.2, 27.8, 27.5.

Acknowledgement: This research was supported by NIH grants GM 51216 and RR 03037 and PSC-CUNY funds.

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