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

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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. © 1999 Elsevier Science Ltd. All rights reserved.

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 acids¹ that are found in many natural products,² continues as an active area of investigation.³ In connection with our study⁴ 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-oxonorvaline 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





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 available⁶. 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



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



Scheme 1



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.



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

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

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 Nprotecting groups and affords a variety of Nprotected 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 P₂O₅. 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 CDCl₃. 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 °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 Na₂SO₄. 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: ¹HNMR (CDCl₃) 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 ⁰C. (Lit.^{6a} 61 - 62 ⁰C); FTIR: 3376, 2979, 2934, 1715, 1504, 1456, 1393, 1368, 1163. ¹HNMR (CDCl₃), 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). ¹³CNMR (CDCl₃), 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%; ¹HNMR (CDCl₃), 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).). ¹³CNMR (CDCl₃), 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. ¹HNMR (CDCl₃), 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). ¹³CNMR (CDCl₃), 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%; ¹HNMR (CDCl₃), 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 ⁰C; ¹HNMR (CDCl₃), 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). ¹³CNMR (CDCl₃), 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. ¹HNMR (CDCl₃), 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). ¹³CNMR (CDCl₃), 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; ¹H-NMR (CDCl₃), 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); ¹³CNMR (CDCl₃), 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.

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