Synthesis of 4-Maleimidobutyric Acid and Related Maleimides

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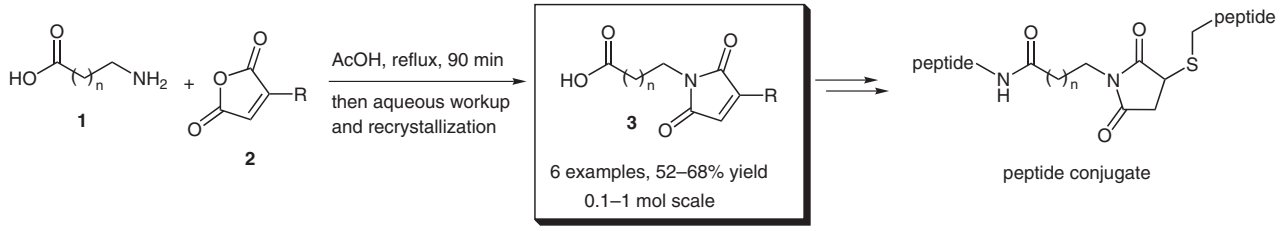
Abstract: Maleimidoalkanoic acids and their activated derivatives, such as their *N*-hydroxysuccinimide esters, are important, though expensive, linkers for the conjugation of biomolecules. During our synthesis of UCS1025A, we have developed a chromatography-free preparation of 4-maleimidobutyric acid on a one-mole scale.

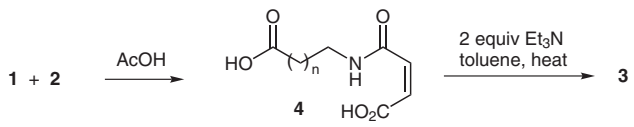
Key words: imides, condensations, maleic anhydride, aminobutanoic acid, cross-linking reagents



Scheme 1

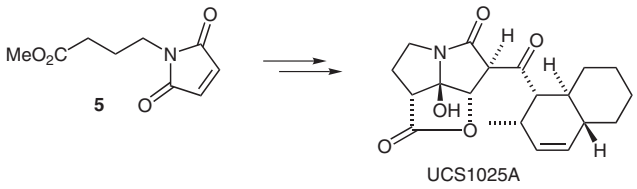
Introduction

In the mid-1970s Rich et al. introduced peptides with an *N*-maleoylamino terminus as an alkylating trap for sulfanyl groups.[1] Since that time many groups have exploited the orthogonal reactivity of maleimidoalkanoic acids **3** for the cross-linking of peptides and other biomolecules.[2] Rich's initial synthesis involved a two-step procedure; formation and isolation of the amide **4** was followed by separate cyclization (Scheme 2). Accordingly, heating of **4** with two equivalents of triethylamine in an aromatic solvent afforded the desired products.



Scheme 2 Rich's synthesis of maleimidoalkanoic acids

More recently, Danishefsky[3] and Hoye[4] identified methyl 4-maleimidobutyrate (**5**) as a starting material for the pyrrolizidine fragment of the telomerase inhibitor UCS1025A (Scheme 3).[5] Our group has developed a scalable enantioselective synthesis of the pyrrolizidine scaffold using the direct cyclization of maleimidobutyric acid **3b** (Scheme 1).[6]



Scheme 3 Methyl 4-maleimidobutyrate (**5**) in the total synthesis of UCS1025A

Scope and Limitations

In this context, we now wish to report the large-scale synthesis of maleimidoalkanoic acids **3**. Before we describe our refinements, we would like to briefly discuss the original procedures on which they are based. Although the Rich protocol[1] is still in use, it is known that this reaction can be carried out as a one-step procedure by heating of the starting materials in acetic acid. Thus column chromatography affords sufficiently pure maleimidoalkanoic acids in 41–53% yield.[7] On a larger scale, chromatographic separation of >50% side products did not seem an attractive venture to us. Therefore, we decided to first minimize the formation of side products, and then try to increase the purity of the desired product by extraction and finally recrystallization of the crude product. Toward this end, the reaction between **1** and **2** in acetic acid was monitored periodically by NMR spectroscopy. After 90 minutes at reflux, increased addition of acetic acid to the Michael

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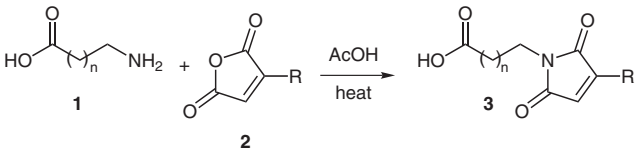
acceptor was observed. We therefore stopped the reaction at this point and evaporated the solvent in vacuo. Polar impurities were easily removed by partitioning between ethyl acetate and water. After some experimentation, we found that the crude product could be recrystallized from fairly concentrated ethyl acetate solutions to give the crystalline products in acceptable to good yields (Table 1). This material is sufficiently pure for most reactions. However, if higher purity (>99%) is required, the maleimidoalkanoic acids can be purified by Kugelrohr distillation. The maleimidoalkanoic acids proved surprisingly robust toward heat as little decomposition was detected even after extended heating.

Table 1 Synthesis of Maleimidoalkanoic Acids **3a–f**



Entry	Product	n	R	Yield[a] (%)
1	**3a**	1	H	57
2	**3b**	2	H	52
3	**3c**	3	H	60
4	**3d**	4	H	57
5	**3e**	2	Me	68
6	**3f**	4	Me	66

[a] Yield of isolated products.

Gratifyingly, **3a** afforded crystals suitable for X-ray crystallography and its structure is shown in Figure 1.[8]

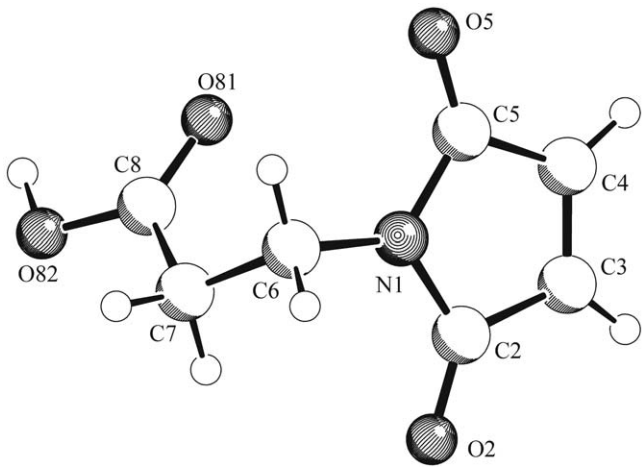


Figure 1 Crystal structure of 3-maleimidopropionic acid (**3a**)

In summary, we have developed a reliable protocol for the preparation of maleimidoalkanoic acids, which is amenable to large-scale synthesis due to its operational simplicity and the absence of chromatographic separations.

Melting points were determined with a Büchi 510 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 and a Varian Unity 500 instrument. ^{1}H NMR are reported relative to residual $CHCl_3$ (for $CDCl_3$) δ = 7.26 or TMS. ^{13}C NMR are reported for $CDCl_3$ relative to the central line of the triplet at δ = 77.0. IR spectra were recorded neat on a Perkin-Elmer PE 1759 FT instrument. LR-MS were recorded on a Varian MAT 212 S instrument using EI ionization (EI, 70 eV). Elemental analyses were performed by the Microanalytical Laboratory of the Institute of Organic Chemistry.

3-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanoic Acid (3a); Typical Procedure

A suspension of maleic anhydride (9.95 g, 102 mmol) and β-alanine (9.18 g, 103 mmol) in AcOH (75 mL) was heated to reflux (bath temperature: 170 °C) for 90 min. The soln was cooled to r.t. and the solvent was evaporated in vacuo. Residual AcOH was removed by azeotroping with toluene (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The crude residue was recrystallized (EtOAc, 50 mL, 7 °C) to give **3a** (9.83 g, 57%) as colorless prisms (mp 108–109 °C). Alternatively, the purity can be upgraded by Kugelrohr distillation (170 °C, 0.1 mbar); R_f = 0.52 (EtOAc).

IR (KBr): 3454, 1706, 1413, 834, 772 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.72 (s, 2 H), 3.83 (t, *J* = 7.2 Hz, 2 H), 2.70 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.4, 170.3 (2 ×), 134.2 (2 ×), 33.2, 32.5.

MS (EI): *m*/*z* (%) = 169 (M^+, 4), 151 (34), 123 (100), 110 (81), 82 (40), 70 (18), 54 (29).

Anal. Calcd for $C_7H_7NO_4$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.76; H, 4.26; N, 8.30.

4-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoic Acid (3b)

A 2-L-round bottom flask equipped with a heating mantle and a reflux condenser was charged with maleic anhydride (100 g, 1.02 mol) and 4-aminobutanoic acid (106 g, 1.03 mol). AcOH (750 mL) was added and the mixture was heated to reflux for 90 min. The soln was cooled to r.t. and the solvent was evaporated in vacuo. Residual AcOH was removed by azeotroping with toluene. The residue was dissolved in H_2O (1 L) and extracted with EtOAc (3 × 1 L). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The crude residue was recrystallized (EtOAc). The mother liquor was concentrated and the crystallization was repeated (3 ×) to give **3b** (97 g, 52%) as a colorless solid; mp 93–94 °C; R_f = 0.55 (EtOAc).

IR (KBr): 1702, 1453, 1413, 1225, 910, 834, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.71 (s, 2 H), 3.60 (t, *J* = 6.9 Hz, 2 H), 2.37 (t, *J* = 7.4 Hz, 2 H), 1.96–1.89 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.3, 170.8 (2 ×), 134.1 (2 ×), 36.9, 31.1, 23.5.

MS (EI): *m*/*z* (%) = 183 (M^+, 13), 165 (52), 137 (28), 124 (30), 123 (18), 110 (100), 99 (27), 82 (38), 54 (19).

Anal. Calcd for $C_8H_9NO_4$: C, 52.49; H, 4.96; N, 7.65. Found: C, 52.32; H, 5.02; N, 7.53.

5-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)pentanoic Acid (3c)

Colorless solid; mp 84–85 °C; R_f = 0.55 (EtOAc).

IR (KBr): 1704, 1457, 1408, 1320, 1220, 831, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.69 (s, 2 H), 3.53 (t, *J* = 6.8 Hz, 2 H), 2.37 (t, *J* = 7.1 Hz, 2 H), 1.69–1.55 (m, 4 H).

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^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1, 170.8 (2 ×), 134.0 (2 ×), 37.3, 33.3, 27.8, 21.7.

MS (EI): *m*/*z* (%) = 197 (M^+, 10), 179 (36), 151 (29), 116 (15), 110 (100), 98 (17), 82 (37), 54 (18).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.58; H, 5.81; N, 7.01.

6-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoic Acid (3d)
Colorless solid; mp 78 °C; R_f = 0.60 (EtOAc).

IR (KBr): 1700, 1446, 1409, 944, 837, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (s, 2 H), 3.51 (t, *J* = 7.2 Hz, 2 H), 2.34 (t, *J* = 7.4 Hz, 2 H), 1.71–1.55 (m, 4 H), 1.38–1.28 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 170.7 (2 ×), 134.0 (2 ×), 37.6, 33.8, 28.2, 26.2, 24.1.

MS (EI): *m*/*z* (%) = 211 (M^+, 10), 193 (34), 175 (16), 111 (23), 110 (100), 98 (21), 82 (26), 54 (14).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.91; H, 6.20; N, 6.60.

4-(3-Methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoic Acid (3e)
Recrystallization (pentane–EtOAc, 3:1, 4 °C, 12 h then 25 °C, 48 h) gave a colorless solid; mp 61–64 °C; R_f = 0.54 (EtOAc).

IR (KBr): 1709, 1446, 1288, 1215, 926, 871, 750, 713 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.32 (q, *J* = 1.8 Hz, 1 H), 3.55 (t, *J* = 6.7 Hz, 2 H), 2.35 (t, *J* = 7.3 Hz, 2 H), 2.06 (d, *J* = 2.1 Hz, 3 H), 1.90 (quint, *J* = 7.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6, 171.8, 170.9, 145.7, 127.2, 36.9, 31.1, 23.6, 10.9.

MS (EI): *m*/*z* (%) = 197 (M^+, 30), 179 (53), 151 (25), 138 (59), 137 (33), 124 (100).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.74; H, 5.61; N, 7.01.

6-(3-Methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoic Acid (3f)
Recrystallization (pentane–EtOAc, 3:1, –18 °C) gave a colorless solid; mp 60 °C; R_f = 0.65 (EtOAc).

IR (KBr): 1710, 1440, 1407, 917, 872 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (s, 1 H), 3.47 (t, *J* = 7.1 Hz, 2 H), 2.33 (t, *J* = 7.4 Hz, 2 H), 2.06 (s, 3 H), 1.68–1.49 (m, 4 H), 1.36–1.27 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4, 171.8, 170.9, 145.4, 127.2, 37.7, 33.8, 28.3, 26.2, 24.2, 11.1.

MS (EI): *m*/*z* (%) = 225 (M^+, 21), 207 (38), 123 (100), 111 (29), 96 (15), 68 (10), 56 (10).

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.72; H, 6.54; N, 6.18.

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(8) CCDC 651593 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44(1223)336033, E-mail: deposit@ccdc.cam.ac.uk.

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