# Preparation of Fused Bis(α-methylene-γ-lactams)

Najat El Alami, Chantal Belaud, Jean Villieras

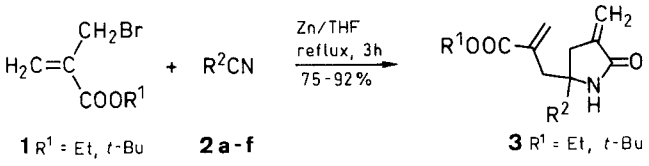
Laboratoire de Synthèse Organique, URA CNRS n°475, Faculté des Sciences et des Techniques, 2, Rue de la Houssinière, F-44072 Nantes Cedex 03, France

*Received 18 May 1993*

Lactamization of amidoacids **4**, prepared from the corresponding *tert*-butylesters, give fused bis(α-methylene-γ-lactams) **5** in high yields.

During the last few years, we have been interested in developing synthetic routes to α-methylene-γ-lactams[1-5] because some of these products exhibit a cytotoxic behaviour towards P388 leukaemia while their toxicity is ten times lower compared to the parent lactones.

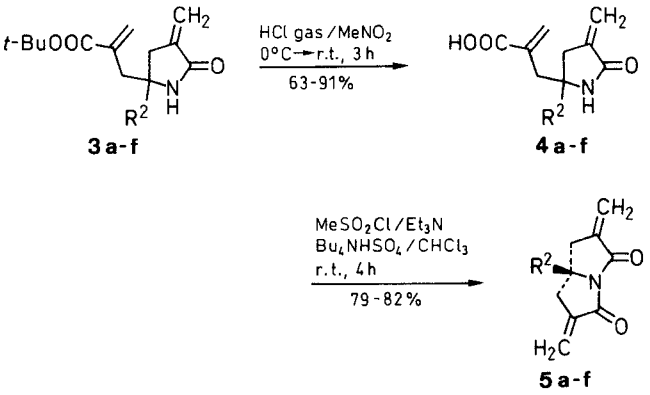
We have previously described the reaction of the organozinc reagent derived from 2-(bromomethyl)acrylates **1** with nitriles **2**[6] which affords new compounds **3** resulting from two successive additions of the organozinc intermediate reagent to the nitrile function, followed by a cyclization. This class of α-methylene-γ-lactams seems to exhibit interesting properties against P388 leukaemia and lung tumour cells[7] probably owing to the presence of two electrophilic methylene moieties on the same molecule (Scheme 1).




**Scheme 1**

We describe here the synthesis of fused bis(α-methylene-γ-lactams) **5** from **3** which could exhibit important cytotoxic properties.

Compounds **3** (R = *t*-Bu) have been prepared in a one-step reaction of the organozinc reagent **1**, derived from *tert*-butyl 2-(bromomethyl)acrylate, with the corresponding nitriles **2**. The *tert*-butyl esters **3** are hydrolysed in the presence of dry hydrochloric acid in nitromethane. Lactamization of amidoacids **4** is then performed in the presence of methanesulfonyl chloride (1.5 equivalents), triethylamine (3 equivalents) and tetrabutylammonium hydrogen sulfate (0.05 equivalent) and gives yields of the corresponding fused bis(α-methylene-γ-lactams) **5** (Scheme 2).




| 3-5 | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| R² | Me | *i*-Pr | MeOCH₂ | $Me_2C{=}C(CO_2Et)$ | Ph | 3,4,5-$(MeO)_3C_6H_2$ |

**Scheme 2**

This set of reactions affords good yields of pure crystallized fused bis(α-methylene-γ-lactams) **5** which have been previously used for the synthesis of β-lactams from β-amino esters.[8]

The cytotoxic behaviour of compounds **5** towards P 388 leukaemia is now being studied.

**Table 1.** Compounds **3a–f** Prepared

| Product | Yield (%)[a,b] | mp (°C) | IR (KBr) ν (cm⁻¹) | $^1$H NMR ($CDCl_3$/TMS) δ, J (Hz) | $^{13}$C NMR ($CDCl_3$/TMS) δ |
|---|---|---|---|---|---|
| **3a** | 89 | 70 | 3200, 1710, 1690, 1620 | 1.27 (s, 3H), 1.48 (s, 9H), 2.53 (s, 3H), 2.48, 2.83 (2d, $J$ = 17, 2H), 5.29 (m, 1H), 5.57 (m, 1H), 5.94 (t, $J$ = 2.5, 1H), 6.19 (d, $J$ = 1.6, 1H), 6.87 (s, 1H) | 27.9, 28.4, 39.5, 42.8, 56.0, 81.1, 113.9, 128.7, 137.5, 140.0, 166.7, 169.3 |
| **3b** | 85 | 106 | 3220, 1690, 1660, 1620 | 0.92, 1.0 (2d, $J$ = 4.2, 6H), 1.49 (s, 9H), 1.77 (m, 1H), 2.56 (s, 2H), 2.64 (m, 2H), 5.22 (m, 1H), 5.58 (m, 1H), 5.84 (t, $J$ = 3.4, 1H), 6.20 (d, $J$ = 2.5, 1H), 7.52 (s, 1H) | 17.1, 17.2, 27.9, 33.7, 37.3, 37.6, 61.7, 80.8, 114.8, 129.5, 137.2, 140.8, 167.1, 170.1 |
| **3c** | 75 | 100 | 3190, 1700, 1660, 1620 | 1.49 (s, 9H), 2.47, 2.53 (2d, $J$ = 2.8, 2H), 2.23, 2.75 (2d, $J$ = 13.4, 2H), 3.24 (d, $J$ = 1.7, 2H), 3.32 (s, 3H), 5.28 (m, 1H), 5.87 (m, 1H), 5.94 (t, $J$ = 2.6, 1H), 6.19 (d, $J$ = 1.6, 1H), 6.49 (s, 1H) | 28.0, 34.7, 38.5, 58.6, 59.2, 79.0, 81.1, 116.3, 128.8, 137.2, 139.4, 166.9, 169.5 |
| **3d** | 20 | 105 | 3220, 1720, 1690, 1660, 1625 | 1.32 (t, $J$ = 6.8, 3H), 1.49 (s, 9H), 1.79 (s, 3H), 2.88 (s, 2H), 2.9, 3.3 (2d, $J$ = 18, 2H), 4.22 (q, $J$ = 6.8, 2H), 5.22 (m, 1H), 5.60 (m, 1H), 5.87 (m, 1H), 6.24 (m, 1H), 6.51 (s, 1H) | 14.2, 21.7, 23.7, 28.0, 39.6, 42.0, 60.0, 60.9, 81.0, 115.7, 130.5, 136.0, 136.3, 139.2, 166.7, 169.2, 169.5 |
| **3e** | 90 | 121 | 3180, 1680, 1650, 1620 | 1.57 (s, 9H), 2.94 (s, 2H), 2.94, 3.25 (2d, $J$ = 17, 2H), 5.27 (m, 1H), 5.5 (m, 1H), 5.94 (m, 1H), 6.14 (t, $J$ = 1.3, 1H), 7.29 (s, 5H), 7.68 (s, 1H) | 27.9, 40.9, 44.0, 62.1, 80.9, 115.9, 125.1, 127.0, 129.9, 136.8, 139.7, 145.2, 166.6, 170.5 |
| **3f** | 92 | 134 | 3200, 1700, 1675, 1615 | 1.47 (s, 9H), 2.70 (s, 2H), 2.9, 3.25 (2d, $J$ = 18, 2H), 3.81 (s, 3H), 3.84 (s, 6H), 5.32 (m, 1H), 5.52 (m, 1H), 5.96 (t, $J$ = 4.2, 1H), 6.15 (d, $J$ = 2, 1H), 6.52 (s, 1H), 7.51 (s, 1H) | 27.9, 40.7, 44.2, 56.2, 60.7, 62.4, 80.9, 102.7, 115.9, 129.7, 136.9, 139.9, 141.3, 153.2, 166.6, 170.6 |

[a] Yield of **3** based on **1**.

[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.15, N ±0.30.

**Table 2.** Compounds **4a–f** Prepared

| Product | Yield (%)[a,b] | mp (°C) | IR (KBr) $\nu$ ($cm^{-1}$) | $^1H$ NMR (DMSO-$d_6$/TMS) $\delta$, $J$ (Hz) | $^{13}C$ NMR (DMSO-$d_6$/TMS) $\delta$ |
|---|---|---|---|---|---|
| **4a** | 83 | 164 | 3280, 1710, 1650, 1600 | 1.19 (s, 3H), 2.33, 2.79 (2d, $J$ = 16.8, 2H), 2.44 (s, 2H), 5.21 (m, 1H), 5.65 (m, 2H), 6.18 (m, 1H), 8.12 (s, 1H) | 28.3, 38.2, 41.6, 56.6, 113.9, 129.0, 136.6, 141.6, 167.9, 168.5 |
| **4b** | 88 | 165 | 3280, 1720, 1650, 1610 | 0.86 (d, $J$ = 3.4, 3H), 0.95 (d, $J$ = 3.4, 3H), 1.7 (m, 1H), 2.3, 2.66 (2d, $J$ = 15.2, 2H), 2.52 (s, 2H), 5.23 (m, 1H), 5.55 (m, 1H), 5.7 (m, 1H), 6.15 (m, 1H), 8.09 (s, 1H) | 16.9, 32.7, 36.7, 36.9, 60.9, 113.0, 129.5, 136.4, 141.9, 168.5, 168.7 |
| **4c** | 77 | 152 | 3300, 1700, 1650, 1620 | 2.3, 2.6 (2d, $J$ = 17.1, 2H), 2.61 (s, 2H), 3.13 (s, 2H), 3.25 (s, 3H), 5.23 (m, 1H), 5.71 (m, 1H), 5.76 (m, 1H), 6.28 (m, 1H), 8.19 (s, 1H) | 33.3, 37.1, 58.4, 58.6, 78.2, 113.0, 129.2, 135.9, 141.2, 168.5 |
| **4d** | 63 | 198 | 3290, 1720, 1695, 1645, 1620 | 1.22 (t, $J$ = 8.2, 3H), 1.65 (s, 3H), 1.85 (s, 3H), 2.56, 2.86 (dd, $J$ = 12.5, 2H), 2.72, 3.13 (dd, $J$ = 14.6, 2H), 4.1 (q, $J$ = 8.2, 2H), 5.18 (m, 1H), 5.6 (m, 1H), 5.89 (m, 1H), 6.22 (m, 1H), 7.9 (s, 1H) | 13.9, 20.8, 23.9, 38.2, 39.5, 59.7, 60.1, 113.9, 130.8, 132.8, 137.1, 140.4, 168.5, 168.8 |
| **4e** | 91 | 193 | 3280, 1690, 1650, 1600 | 2.78, 3.24 (2dd, $J$ = 13.5, 2H), 3.05 (s, 2H), 5.27 (m, 1H), 5.61 (m, 1H), 5.89 (m, 1H), 6.30 (m, 1H), 7.25 (m, 6H) | 39.5, 42.5, 61.4, 114.1, 125.1, 126.7, 128.2, 129.9, 135.8, 140.6, 146.5, 168.4, 168.7 |
| **4f** | 82 | 218 | 3290, 1685, 1645, 1600 | 2.64, 2.98 (dd, $J$ = 10, 2H), 2.94, 3.32 (dd, $J$ = 1, 2H), 3.69 (s, 3H), 3.83 (s, 6H), 5.26 (m, 1H), 5.62 (m, 1H), 5.72 (m, 1H), 6.19 (m, 1H), 6.73 (s, 2H), 8.85 (s, 1H) | 41.6, 45.4, 58.1, 62.0, 63.8, 105.4, 116.3, 131.5, 138.7, 142.9, 144.2, 154.9, 170.9 |

[a] Yield of **4** based on **3**.

[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.15, N ±0.30.

**Table 3.** Compounds **5a–f** Prepared

| Product | Yield (%)[a,b] | mp (°C) | IR (KBr) $\nu$ ($cm^{-1}$) | $^1H$ NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) | $^{13}C$ NMR ($CDCl_3$/TMS) $\delta$ |
|---|---|---|---|---|---|
| **5a** | 79 | 144 | 1765, 1750, 1680, 1650 | 1.35 (s, 3H), 2.81 (m, 4H), 5.61 (t, $J$ = 2.2, 2H), 6.25 (t, $J$ = 2.5, 2H) | 28.1, 41.6, 60.1, 122.0, 141.0, 163.0 |
| **5b** | 82 | 142 | 1780, 1750, 1680, 1650 | 0.81 (d, $J$ = 8.5, 6H), 1.77 (m, 1H), 2.64 (dt, $J$ = 17, 3.4, 2H), 3.09 (d, $J$ = 17, 2H), 5.54 (dd, $J$ = 1.3, 2.6, 2H), 6.15 (dd, $J$ = 1.3, 2.6, 2H) | 17.1, 37.3, 37.8, 65.7, 121.0, 141.0, 164.8 |
| **5c** | 78 | 144 | 1775, 1750, 1690, 1650 | 2.67 (dt, $J$ = 17, 3.2, 2H), 3.05 (d, $J$ = 17, 2H), 3.25 (s, 2H), 3.33 (s, 3H), 5.57 (dd, $J$ = 1.4, 2.8, 2H), 6.21 (dd, $J$ = 1.4, 2.8, 2H) | 37.3, 59.6, 63.4, 77.3, 121.6, 140.7, 164..4 |
| **5d** | 75 | 155 | 1780, 1750, 1720, 1690, 1650 | 1.22 (t, $J$ = 7.6, 3H), 1.66 (s, 3H), 1.8 (s, 3H), 3.21–3.6 (m, 4H), 4.1 (q, $J$ = 7.6, 2H), 5.55 (t, $J$ = 2.5, 2H), 6.18 (t, $J$ = 2.7, 2H) | 13.8, 21.2, 22.8, 43.8, 61.3, 63.3, 121.5, 134.7, 136.6, 140.1, 164.5, 168.6 |
| **5e** | 81 | 211 | 1770, 1750, 1690, 1650 | 3.25 (m, 4H), 5.45 (t, $J$ = 2.2, 2H), 6.13 (t, $J$ = 2.5, 2H), 7.29 (s, 5H) | 44.1, 65.8, 122.2, 124.9, 127.9, 128.9, 140.0, 144.6, 164.5 |
| **5f** | 82 | 178 | 1770, 1750, 1690, 1650 | 3.3 (m, 4H), 3.81 (s, 3H), 3.9 (s, 6H), 5.63 (t, $J$ = 2.2, 2H), 6.23 (t, $J$ = 2.5, 2H), 6.56 (s, 2H) | 44.2, 56.3, 60.7, 65.9, 102.4, 122.3, 137.7, 140.0, 153.6, 164.6 |

[a] Yield of **5** based on **4**.

[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.15, N ±0.30.

All solvents were dried by standard methods. All experiments were carried out with exclusion of moisture. The melting points are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on JEOL FX 90Q $^1H$ (90 MHz) $^{13}C$ (22.5 MHz). IR spectra were recorded on Perkin-Elmer 1420.

**5-Substituted 5-(3-*tert*-Butoxycarbonyl-2-methylenepropyl)-3-methylene-2-pyrrolidones (3); General Procedure:**

To a suspension of granulated Zn 30 mesh (2.48 g, 38 mmol) in a THF solution (15 mL) of nitrile **2** (14 mmol) under $N_2$, a solution of *tert*-butyl-2-(bromomethyl)acrylate (6.63 g, 30 mmol) in dry THF (10 mL) was added dropwise at r.t. The mixture was then stirred under reflux for 2 h, poured into sat. aq $NH_4Cl$ (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and finally evaporated under reduced pressure. The crude yellow oil was purified by chromatography on silica gel with hexane/EtOAc (30/70) as eluent to afford the corresponding α-methylene-γ-lactam *tert*-butyl ester **3**.

**5-Substituted 5-(3-Carboxy-2-methylenepropyl)-3-methylene-2-pyrrolidones (4); General Procedure:**

A stream of dry HCl was bubbled through a solution of lactam ester **3** (8 mmol) in cool (0° C) anhydr. $MeNO_2$ (40 mL) until saturation. The mixture was then stirred for 3 h at r.t, and the solvent removed under reduced pressure. The crude acid **4** was purified by recrystallization from MeOH.

**8-Substituted Hexahydro-2,6-dimethylene-1*H*-pyrrolizine-3,5-diones 5 [Fused Bis(α-methylene-γ-lactams)]; General Procedure:**

A mixture of acid **4** (3.89 mmol), $Bu_4NHSO_4$ (66 mg, 0.2 mmol), $CH_3SO_2Cl$ (0.5 mL, 5.83 mmol), $Et_3N$ (1.5 mL, 11.67 mmol) and freshly purified $CHCl_3$ (50 mL) was stirred at r.t. for 4 h (TLC control). The reaction flask was then evacuated under reduced pressure. The brown residue was chromatographed on a silica gel column using hexane/EtOAc as eluent.

(1) Belaud, C.; Roussakis, C.; Letourneux, Y.; El Alami, N.; Villieras, J. *Synth. Commun.* **1985**, *15*, 1223.
(2) El Alami, N.; Belaud, C.; Villieras, J. *Tetrahedron Lett.* **1987**, *28*, 59.
(3) El Alami, N.; Belaud, C.; Villieras, J. *J. Organomet. Chem.* **1988**, *348*, 1.
(4) El Alami, N.; Belaud, C.; Villieras, J. *J. Organomet. Chem.* **1988**, *353*, 157.
(5) El Alami, N.; Belaud, C.; Villieras, J. *Synth. Commun.* **1988**, *18*, 2073.
(6) El Alami, N.; Belaud, C.; Villieras, J. *J. Organometal. Chem.* **1987**, *319*, 303.
(7) Roussakis, C.; Verbist, J.F., unpublished results.
(8) Watanabe, Y.; Mukayama, T. *Chem. Lett.* **1981**, 443.