Indium-Promoted Preparation of α-Methylene-γ-butyrolactams from 2-(Bromomethyl)acrylic Acid and Aldimines†

Prabir K. Choudhury, Francisco Foubelo, and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

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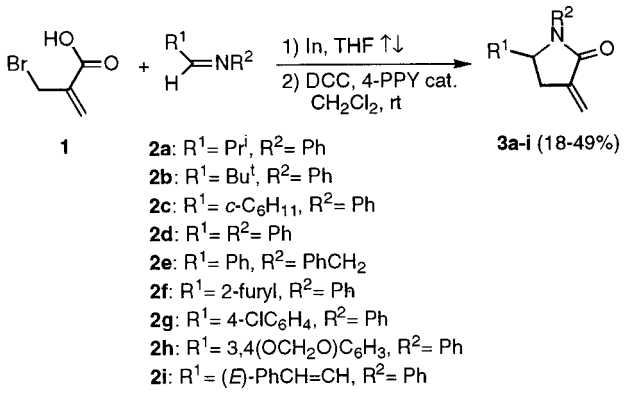
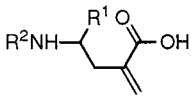
α-Methylene-γ-butyrolactams[1] are interesting compounds from a biological point of view because they exhibit less cytotoxic activity than the corresponding α-methylene-γ-butyrolactones,[2] making them suitable for cancer treatment; in fact, this class of compounds constitutes potential anticancer agents.[3] Compared to α-methylene-γ-buryrolactones, the preparation of the corresponding nitrogenated derivatives is the subject of few reports in the literature. Among them, metal-promoted syntheses (Zn,[4−9] Pd,[10,11] B,[12] Rh[13]) as well as anionic,[14,15] radical,[16] or other[17] methodologies have been used to prepare α-methylene-γ-butyrolactams: one disadvantage of many of these procedures is that together with the expected compound the corresponding endocyclic unsaturated lactam is obtained, resulting from an undesired isomerization. Despite the observed disadvantages and because of our continuing interest in indium-promoted reactions,[18] we report here the use of this metal[19] for the preparation of α-methylene-γ-butyrolactams by addition of 2-(bromomethyl)acrylic acid to aldimines.[20]

Scheme 1



Equimolar amounts of indium powder, 2-(bromomethyl)-acrylic acid, and the corresponding aldimine **2** were refluxed in THF for 2−18 h (see Table 1) and then quenched with saturated NH_4Cl. After extraction and evaporation, the crude residue was treated with dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-pyrrolidinopyridine (4-PPY) in dichloromethane at room temperature for 20−45 min (see Table 1) to give the corresponding α-methylene-γ-butyrolactams **3a**−**i** (Scheme 1 and Table 1).

Treatment with DCC after the first step is necessary in order to avoid the formation of a mixture of the expected lactam **3** and the γ-amino acid **4**. In only one case, even with poor yield, no formation of the amino acid was observed, so the second step was not necessary (Table 1, entry 5). In this case, an aldimine (**2e**) derived from an aliphatic amine was used as the imino component, and in the other cases, aniline was always the amine component. Other related systems, such as aldimines derived from butylamine, cyclohexylamine, and *tert*-butylamine, and benzaldehyde work with very poor yields (<10%). Finally, ketimines were not reactive enough to carry out the reaction shown in Scheme 1.



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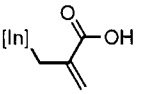

5: [In] = $In_{2/3}Br$

From a mechanistic point of view, an allylindium sesquihalide of type **5** has been previously proposed[18] in other similar processes. The addition of this species to the aldimine followed by cyclization would give the obtained lactams **3**.

† This Paper is dedicated to Professor E. J. Corey on occasion of his 70th birthday.

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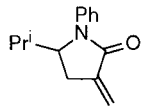
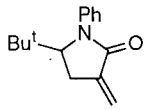
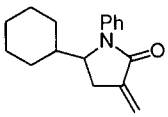
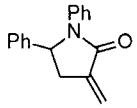
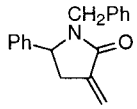
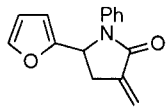
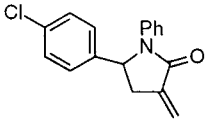
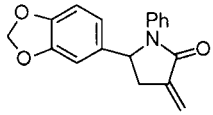
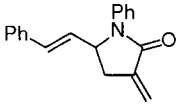
Table 1. Preparation of α-Methylene-γ-butyrolactams 3

		reaction time		product 3[a]		
entry	aldimine	step 1	step 2	structure	(no.)	yield (%)[b]
1	**2a**	18 h	30 min		(**3a**)	37
2	**2b**	18 h	30 min		(**3b**)	40
3	**2c**	18 h	30 min		(**3c**)	44
4	**2d**	16 h	30 min		(**3d**)	35
5	**2e**	18 h	- [c]		(**3e**)	18
6	**2f**	2 h	45 min		(**3f**)	49
7	**2g**	16 h	30 min		(**3g**)	32
8	**2h**	16 h	30 min		(**3h**)	35
9	**2i**	4 h	20 min		(**3i**)	36

[a] All compounds **3** were >95% pure (GLC and/or 300 MHz ^{1}H NMR). [b] Isolated overall yield of pure (>95% from 300 MHz ^{1}H NMR) compounds after column chromatography (silica gel, hexane/ethyl acetate) and recrystallization based on the starting imine **2**. [c] DCC treatment was not necessary.

As a conclusion, we report here a new route to preparation of α-methylene-γ-butyrolactams starting from easily available materials and promoted by indium metal. Even considering that the overall yields (of recrystallized compounds) are only moderate, we think that this methodology can be useful for the preparation of this type of interesting molecules.

Experimental Section

General Methods. The general experimental information is similar to that recently described.[21] Starting aldimines **2a**−**c**[22] as well as **2d**−**h**[23] were prepared according to the literature procedures.

Preparation of Compounds 3 from 2-(Bromomethyl)-acrylic Acid and Imines. General Procedure. A mixture of indium powder (0.126 g, 1.1 g mol) and 2-(bromomethyl)acrylic acid (0.165 g, 1.0 mmol) in THF (3 mL) was heated at 66 °C for 15 min under nitrogen, and then an aldimine (0.1 mmol) THF solution (3 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 2−18 h (reaction time was confirmed from TLC observations and is given in Table 1). After that, it was quenched with a saturated NH_4Cl aqueous solution (0.5 mL), filtered through a $MgSO_4$ pad, and washed with ethyl acetate. The filtrate was evaporated (15 mmHg), and a mixture of the resulting residue, DCC (0.222 g, 1.1 mmol), and a catalytic amount of 4-PPY (0.015 g) in dichloromethane (5 mL) was stirred at room temperature for 30−45 min (the reaction was monitored by TLC; see Table 1).[24] The resulting mixture was hydrolyzed with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated (15 mmHg). The residue was then purified by column chromatography (silica gel; hexane/ethyl acetate) and recrystallized to yield pure product

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3a−**i**. Yields, R_f, and mp data are included in Table 1; analytical and spectroscopic data as well as literature references follow.

5-Isopropyl-3-methylene-1-phenyl-2-pyrrolidinone (3a):[25] R_f 0.55 (silica gel; hexane/ethyl acetate 2/1); mp 140−144 °C (pentane/dichloromethane); IR (KBr) 2960, 2922, 1677, 1653, 803 cm^{-1}; ^{1}H NMR δ 0.67 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 7.3 Hz, 3H), 1.98−2.09 (m, 1H), 2.57−2.70 (m, 1H), 2.83 (ddt, J = 17.7, 8.5, 3.1 Hz, 1H), 4.27 (dt, J = 8.7, 3.6 Hz, 1H), 5.41 (t, J = 2.4 Hz, 1H), 6.10 (t, J = 2.4 Hz, 1H) 7.17−7.52 (m, 5H); ^{13}C NMR δ 13.6, 18.3, 24.6, 28.3, 60.6, 116.3, 123.7, 125.8, 128.9, 137.7, 140.1, 167.2; MS m/z 215 (M$^+$, 5), 53 (100); HRMS calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1313. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.50. Found: C, 76.46; H, 7.98; N, 6.20.

5-*tert*-Butyl-3-methylene-1-phenyl-2-pyrrolidinone (3b):[25] R_f 0.44 (silica gel; hexane/ethyl acetate 2/1); mp 153−155 °C (pentane/dichloromethane); IR (KBr) 3068, 2961, 1679, 1659, 807 cm^{-1}; ^{1}H NMR δ 0.76 (s, 9H), 2.77 (dq, J = 17.4, 2.1 Hz, 1H), 2.93 (ddt, J = 17.1, 8.5, 3.1 Hz, 1H), 4.14 (dd, J = 8.7, 2.1 Hz, 1H), 5.38 (t, J = 2.3 Hz, 1H), 6.06 (t, J = 2.4 Hz, 1H), 7.15−7.46 (m, 5H); ^{13}C NMR δ 26.5, 28.2, 37.0, 65.6, 115.7, 124.9, 126.0, 128.7, 140.1, 140.2, 167.7; MS m/z 229 (M$^+$, 12), 53 (100); HRMS calcd for $C_{15}H_{19}NO$ 229.1466, found 229.1464. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.10. Found: C, 77.30; H, 8.32; N, 5.71.

5-Cyclohexyl-3-methylene-1-phenyl-2-pyrrolidinone (3c): R_f 0.49 (silica gel; hexane/ethyl acetate 2/1); mp 137−140 °C (pentane/dichloromethane); IR (KBr) 3055, 2926, 2853, 1680, 1657, 930 cm^{-1}; ^{1}H NMR δ 0.78−1.78 (m, 11H), 2.65−2.76 (m, 1H), 2.86 (ddt, J = 17.4, 8.5, 2.7 Hz, 1H), 4.23 (quintet, J = 3.3 Hz, 1H), 5.39 (t, J = 2.2 Hz, 1H), 6.08 (t, J = 3.1 Hz, 1H), 7.15−7.54 (m, 5H); ^{13}C NMR δ 24.3, 25.5, 26.15, 26.2, 26.4, 29.0, 39.0, 60.5, 116.1, 123.7, 125.8, 128.9, 137.8, 140.2, 167.2; MS m/z 255 (M$^+$, 3), 53 (100). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.48. Found: C, 80.08; H, 8.36; N, 5.20.

3-Methylene-1,5-diphenyl-2-pyrrolidinone (3d):[4] R_f 0.58 (silica gel; hexane/ethyl acetate 2/1); mp 147.5−148 °C (pentane/dichloromethane); IR (KBr) 2932, 2858, 1682, 1658, 944 cm^{-1}; ^{1}H NMR δ 2.67−2.76 (m, 1H), 3.37 (ddt, J = 16.8, 8.8, 2.7 Hz, 1H), 5.25 (dd, J = 8.5, 3.4 Hz, 1H), 5.45 (t, J = 2.1 Hz, 1H), 6.22 (t, J = 2.4 Hz, 1H), 7.04−7.09 (m, 1H), 7.18−7.35 (m, 7H), 7.48−7.61 (m, 2H); ^{13}C NMR δ 35.4, 60.5, 117.5, 122.1, 125.1, 125.7, 127.8, 128.7, 129.0, 138.3, 138.9, 141.3, 167.6; MS m/z 249 (M$^+$, 26), 77 (100).

1-Benzyl-3-methylene-5-phenyl-2-pyrrolidinone (3e): R_f 0.45 (silica gel, hexane/ethyl acetate 2/1); IR (KBr) 2389, 1693, 1662, 1080 cm^{-1}; ^{1}H NMR δ 2.47−2.62 (m, 1H), 3.05 (ddt, J = 17.4, 8.5, 2.4 Hz, 1H), 3.45 (d, J = 14.6 Hz, 1H), 4.32 (dd, J = 8.5, 3.7 Hz, 1H), 5.10 (d, J = 14.6 Hz, 1H), 5.31 (t, J = 2.5 Hz, 1H), 6.06 (t, J = 2.7 Hz, 1H), 6.99−7.09 (m, 4H), 7.16−7.34 (m, 6H); ^{13}C NMR δ 34.6, 44.7, 58.0, 116.2, 126.7, 127.5, 128.2, 128.5, 128.6, 129.0, 136.1, 138.8, 140.7, 168.1; MS m/z 263 (M$^+$, 43%), 91 (100); HRMS calcd for $C_{18}H_{17}NO$ 263.1310, found 263.1346.

5-(2-Furyl)-3-methylene-1-phenyl-2-pyrrolidinone (3f): R_f 0.45 (silica gel, hexane/ethyl acetate 2/1); mp 178−179 °C (pentane/dichloromethane); IR (KBr) 3154, 3066, 1677, 1655, 1595, 1596, 740 cm^{-1}; ^{1}H NMR δ 2.91−3.04 (m, 1H), 3.18−3.31 (m, 1H), 5.27 (dd J = 8.5, 3.7 Hz, 1H), 5.48 (br s, 1H), 6.10 (d, J = 2.4 Hz, 1H), 6.17−6.25 (m, 2H), 7.10−7.47 (m, 6H); ^{13}C NMR δ 31.8, 54.6, 107.8, 110.3, 117.4, 122.8, 125.7, 128.7, 137.9, 138.6, 142.4, 152.7, 166.9; MS m/z 239 (M$^+$, 23), 40 (100). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.47; N, 5.85. Found: C, 75.96; H, 5.51; N, 5.88.

5-(4-Chlorophenyl)-3-methylene-1-phenyl-2-pyrrolidinone (3g): R_f 0.47 (silica gel; hexane/ethyl acetate 2/1); mp 129−133 °C (pentane/dichloromethane); IR (KBr) 3061, 2922, 2852, 1685, 1658, 1260 cm^{-1}; ^{1}H NMR δ 2.67 (dq, J = 16.8, 2.4 Hz, 1H), 3.37 (ddt, J = 16.5, 8.5, 3.1 Hz, 1H), 5.24 (dd, J = 8.8, 3.0 Hz, 1H), 5.46 (t, J = 2.5 Hz, 1H), 6.22 (t, J = 3.1 Hz, 1H), 7.04−7.17 (m, 3H), 7.20−7.33 (m, 4H), 7.42−7.52 (m, 2H); ^{13}C NMR δ 35.2, 59.9, 117.8, 122.1, 125.3, 127.2, 128.7, 129.2, 133.6, 137.9, 138.5, 140.1, 167.4; MS m/z 283 (M$^+$, 15), 40 (100). Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.95; H, 4.97; N, 4.93. Found: C, 71.63; H, 4.85; N, 4.67.

5-(1,3-Benzodioxol-5-yl)-3-methylene-1-phenyl-2-pyrrolidinone (3h): R_f 0.43 (silica gel; hexane/ethyl acetate 2/1); mp 194−195 °C (pentane/dichloromethane); IR (KBr) 3055, 2909, 1684, 1655, 1482, 1035 cm^{-1}; ^{1}H NMR δ 2.58−2.77 (m, 1H), 2.32 (ddt, J = 16.5, 8.5, 3.1 Hz, 1H), 5.16 (dd, J = 8.5, 3.1 Hz, 1H), 5.44 (t, J = 2.4 Hz, 1H), 5.89 (d, J = 1.2 Hz, 2H), 6.20 (t, J = 3.1 Hz, 1H), 6.60−6.74 (m, 3H), 7.01−7.14 (m, 1H), 7.19−7.35 (m, 2H), 7.42−7.58 (m, 2H); ^{13}C NMR δ 35.4, 60.3, 101.1, 105.8, 108.4, 117.5, 119.4, 122.2, 125.1, 128.6, 135.5, 138.1, 138.9, 167.4; MS m/z 293 (M$^+$, 21), 77 (100). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.77. Found: C, 73.18; H, 5.14; N, 4.70.

(*Z*)-3-Methylene-1-phenyl-5-(2-phenyl-1-ethenyl)-2-pyrrolidinone (3i):[25] R_f 0.50 (silica gel; hexane/ethyl acetate 2/1); mp 162−165 °C (pentane/dichloromethane); IR (KBr) 3055, 2922, 1680, 1656, 1595, 969 cm^{-1}; ^{1}H NMR δ 2.64−2.78 (m, 1H), 3.22 (ddt, J = 17.1, 8.5, 2.4 Hz, 1H), 4.85 (sextet, J = 3.7 Hz, 1H), 5.46 (t, J = 2.4 Hz, 1H), 6.07 (dd, J = 15.8, 7.9 Hz, 1H), 6.18 (t, J = 3.0 Hz, 1H), 6.51 (d, J = 15.9 Hz, 1H), 7.07−7.65 (m, 10H); ^{13}C NMR δ 32.8, 59.1, 117.3, 122.7, 125.4, 126.5, 128.0, 128.6, 128.8, 129.0, 132.5, 135.8, 138.1, 138.9, 167.1; MS m/z 275 (M$^+$, 20), 77 (100); HRMS calcd for $C_{19}H_{17}NO$ 275.1310, found 275.1311. Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.08. Found: C, 81.13; H, 6.20; N, 5.02.

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Supporting Information Available: Copies of ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of new compounds lacking microanalyses (**3e**) or with no precise microanalyses (**3a**,**b**,**i**).

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(25) For compounds **3a**,**b**,**i**, it was not possible to obtain more accurate % C figures after several attempts.