Intramolecular Cyclization of Acyl Radicals onto the Azido Group: a New Radical Approach to Cyclized Lactams

Luisa Benati,^{*} Rino Leardini, Matteo Minozzi, Daniele Nanni, Piero Spagnolo,^{*} Samantha Strazzari,
and Giuseppe Zanardi

Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Viale Risorgimento 4,
I-40136 Bologna (Italy), e-mail: spagnolo@ms.fci.unibo.it

SUPPORTING INFORMATION

General Procedures. All melting points (Kofler melting point apparatus) are uncorrected. ¹H and ¹³C NMR spectra were normally carried out in CDCl₃ solutions, using tetramethylsilane as the internal standard. Mass spectra were determined by the electron impact method (70 eV). IR spectra were recorded in CHCl₃ solutions. Column chromatography was performed on ICN silica gel (63-200 Å) by gradual elution with light petroleum (bp 40-70 °C)/diethyl ether and/or ethyl acetate/diethyl ether mixtures and final elution with ethyl acetate/diethyl ether/methanol mixtures.

Materials. Thioesters **1a,b**, **2a-c** were prepared from the corresponding azido acyl chlorides **11a,b**, **15a-c** and thiol **3** according to the procedure of Crich;¹ chlorides **11a**² and **15a**³ were prepared according to the literature, whereas chlorides **11b** and **15b,c** were synthesized according to the following retrosynthetic scheme:

Methyl 2-(2-azidoethyl)benzoate (13b). Bromoester **14b**⁴ (2.95 g, 12.15 mmol) was dissolved in DMSO (10 mL) and treated at r.t. with sodium azide (1.60 g, 24.30 mmol) under magnetic stirring. After 6 h the mixture was poured into water (150 mL) and extracted with ether (3 × 60 mL). The organic phase was washed with brine and dried over MgSO₄. The solvent was evaporated to give the title compound (2.35 g, 94%), oil; IR ν_{max} 1716 (CO), 2101 (N₃) cm⁻¹; ¹H NMR (200 MHz) δ 3.21-3.31 (2 H, m), 3.49-3.59 (2 H, m), 3.90 (3 H, s), 7.27-7.36 (2 H, m), 7.47 (1 H, td, $J_t = 7.4$ Hz, $J_d = 1.5$ Hz), 7.96 (1 H, dd, $J_t = 8.0$ Hz, $J_2 = 1.5$ Hz); ¹³C NMR (50 MHz) δ 34.83, 52.67, 52.96, 127.57, 130.05 (C), 131.75, 132.46, 132.94, 140.54 (C), 168.15 (CO).

2-(2-Azidoethyl)benzoic acid (12b). A mixture of **13b** (2.35 g, 11.50 mmol) in 2 M NaOH (11.5 mL) and methanol (11.5 mL) was stirred at r.t. for 15 h. Water (50 mL) was then added and the mixture was extracted with ether (50 mL). The aqueous phase was acidified (HCl conc.) and then extracted with ether; the organic phase was washed with brine and dried over MgSO₄. The solvent was removed to give acid **12b** (1.94 g, 89%) as a white solid, mp = 49-50 °C; IR ν_{max} 1691 (CO), 2101 (N₃) cm⁻¹; ¹H NMR (200 MHz) δ 3.29-3.40 (2 H, m), 3.52-3.63 (2 H, m), 7.31-7.43 (2 H, m), 7.54 (1 H, td, $J_t = 7.4$ Hz, $J_d = 1.5$ Hz), 8.14 (1 H, dd, $J_t = 7.9$ Hz, $J_2 = 1.5$ Hz), 11.50 (1 H, br s); ¹³C NMR (50 MHz) δ 35.09, 52.97, 127.83, 128.77 (C), 132.83, 132.90, 134.08, 141.65 (C), 173.69 (CO).

2-(2-Azidoethyl)benzoyl chloride (11b). Acid **12b** (1.00 g, 5.23 mmol) was dissolved in SOCl₂ (2 mL) and refluxed for 1 h. The excess of thionyl chloride was removed in vacuo to give the title azide (1.03 g, 94%), oil; IR ν_{max} 1735 (CO), 1773 (CO), 2100 (N₃) cm⁻¹; ¹H NMR (200 MHz) δ 3.18 (2 H, t, $J = 6.9$ Hz), 3.51 (2 H, t, $J = 6.9$ Hz), 7.33-7.49 (2 H, m), 7.59 (1 H, td, $J_t = 7.5$ Hz, $J_d = 1.5$ Hz), 8.26 (1 H, dd, $J_t = 7.9$ Hz, $J_2 = 1.5$ Hz); ¹³C NMR (50 MHz) δ 34.82, 52.31, 128.24, 132.78, 133.26 (C), 134.93, 135.08, 141.28 (C), 168.74 (CO).

Methyl 4-phenylbutanoate (19b). Commercially available 4-phenylbutanoic acid (5.00 g, 30.50 mmol) was dissolved in methanol (50 mL) with a catalytic amount of conc. HCl (0.5 mL) and kept overnight at r.t. under magnetic stirring. Water (50 mL) and ether (50 mL) were added and the organic phase was separated, washed with aq. sat. NaHCO₃, and dried over MgSO₄. The solvent was evaporated to give the title ester (5.20 g, 96%). Spectral data in agreement with those reported in the literature.⁵

Methyl 4-azido-4-phenylbutanoate (17b). Ester **19b** (2.00 g, 11.24 mmol) was dissolved in CCl₄ (40 mL) and treated with NBS (2.20 g, 12.34 mmol) and dibenzoyl peroxide (traces). The mixture was refluxed for 1 h and then cooled and filtered; the solvent was evaporated to give the crude bromide **18b**, which was used for the next step without further purification. The crude **18b** was dissolved in methanol (8 mL) and treated at r.t. under magnetic stirring with sodium azide (1.22 g, 18.68 mmol) for 18 h. The

mixture was then poured into water (50 mL) and extracted with ether (3 × 50 mL). The organic phase was washed with brine and dried over MgSO₄. The solvent was evaporated and the residue chromatographed (light petroleum/diethyl ether 98:2 v/v) to give the title compound (2.20 g, 89% with respect to **19b**), oil; IR $\nu_{\max}$ 1733 (CO), 2099 (N₃) cm⁻¹; ¹H NMR (300 MHz) δ 2.00-2.18 (2 H, m), 2.38 (2 H, t, J = 7.4 Hz), 3.66 (3 H, s), 4.53 (1 H, dd, J_1 = 7.8 Hz, J_2 = 6.4 Hz), 7.28-7.41 (5 H, m); ¹³C NMR (75 MHz) δ 31.12, 31.93, 52.30, 65.87, 127.48, 129.06, 129.50, 139.54 (C), 173.74 (CO).

4-Azido-4-phenylbutanoic acid (16b). According to the procedure previously described for **12b**, acid **16b** was obtained (98%) as a white solid, mp = 63-64 °C; IR $\nu_{\max}$ 1712 (CO), 2097 (N₃), 3450 (br, OH) cm⁻¹; ¹H NMR (200 MHz) δ 1.92-2.23 (2 H, m), 2.44 (2 H, t, J = 7.3 Hz), 4.56 (1 H, br t, J = 7.1 Hz), 7.27-7.46 (5 H, m); ¹³C NMR (50 MHz) δ 31.18, 31.67, 65.74, 127.52, 129.23, 129.62, 139.41 (C), 179.90 (CO).

4-Azido-4-phenylbutanoyl chloride (15b). According to the procedure previously described for **11b**, chloride **15b** was obtained (99%) as an oil; IR $\nu_{\max}$ 1791 (CO), 2100 (N₃) cm⁻¹; ¹H NMR (200 MHz) δ 2.00-2.22 (2 H, m), 2.98 (2 H, t, J = 7.3 Hz), 4.54 (1 H, br t, J = 7.1 Hz), 7.24-7.48 (5 H, m); ¹³C NMR (50 MHz) δ 32.16, 44.25, 65.07, 127.42, 129.48, 129.78, 138.81 (C), 173.97 (CO).

Methyl 5-phenylpentanoate (19c). Commercially available 5-phenylpentanoic acid (5.00 g, 28.00 mmol) was dissolved in methanol (50 mL) with a catalytic amount of conc. HCl (0.5 mL) and kept overnight at r.t. under magnetic stirring. Water (50 mL) and ether (50 mL) were added and the organic phase was separated, washed with aq. sat. NaHCO₃, and dried over MgSO₄. The solvent was evaporated to give the title ester (5.00 g, 93%). Spectral data in agreement with those reported in the literature.⁶

Methyl 5-azido-5-phenylpentanoate (17c). Ester **19c**⁶ (3.25 g, 16.90 mmol) was dissolved in CCl₄ (60 mL) and treated with NBS (3.30 g, 18.50 mmol) and dibenzoyl peroxide (traces). The mixture was refluxed for 1 h and then cooled and filtered; the solvent was evaporated to give the crude bromide **18c**, which was used for the next step without further purification. The crude **18c** was dissolved in methanol (12 mL) and treated at r.t. under magnetic stirring with sodium azide (1.62 g, 25.00 mmol) for 18 h. The mixture was then poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic phase was washed with brine and dried over MgSO₄. The solvent was evaporated and the residue chromatographed (light petroleum/diethyl ether 98:2 v/v) to give the title compound (3.35 g, 85% with respect to **19c**), oil; IR $\nu_{\max}$ 1731 (CO), 2100 (N₃) cm⁻¹; ¹H NMR (200 MHz) δ 1.45-1.95 (4 H, m), 2.30 (2 H, t, J = 7.2 Hz), 3.60 (3 H, s), 4.43 (1 H, dd, J_1 = 7.6 Hz, J_2 = 6.0 Hz), 7.21-7.41 (5 H, m); ¹³C NMR (50 MHz) δ 21.96, 33.69, 35.76, 51.75, 66.27, 127.19, 128.61, 129.12, 139.76 (C), 173.69 (CO).

5-Azido-5-phenylpentanoic acid (16c). According to the procedure previously described for **12b**, acid **16c** was obtained (95%) as an oil; IR $\nu_{\max}$ 1711 (CO), 2100 (N₃), 3500 (br, OH) cm⁻¹; ¹H NMR (200 MHz) δ 1.42-1.97 (4 H, m), 2.37 (2 H, t, J = 7.2 Hz), 4.43 (1 H, dd, J_1 = 7.6 Hz, J_2 = 6.0 Hz), 7.23-7.43 (5 H, m), 11.00 (1 H, br s); ¹³C NMR (50 MHz) δ 22.03, 34.14, 36.03, 66.65, 127.52, 129.04, 129.52, 139.93 (C), 180.33 (CO).

5-Azido-5-phenylpentanoyl chloride (15c). According to the procedure previously described for **11b**, chloride **15c** was obtained (95%) as an oil; IR $\nu_{\max}$ 1795 (CO), 2097 (N₃) cm⁻¹; ¹H NMR (300 MHz) δ 1.55-1.92 (4 H, m), 2.87-2.94 (2 H, m), 4.44 (1 H, dd, J_1 = 7.6 Hz, J_2 = 6.0 Hz), 7.25-7.45 (5 H, m); ¹³C NMR (75 MHz) δ 22.50, 35.46, 47.14, 66.41, 127.45, 129.18, 129.60, 139.58 (C), 174.05 (CO).

S-(2-iodophenethyl) 2-(azidomethyl)benzenecarbothioate (1a). Chromatographed with light petroleum/diethyl ether 97:3 v/v, yield 93%, oil; IR $\nu_{\max}$ 1661 (CO), 2100 (N₃) cm⁻¹; ¹H NMR (300 MHz) δ 3.10 (2 H, dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz), 3.30 (2 H, dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz), 4.63 (2 H, s), 6.91 (1 H, ddd, J_1 = 8.0 Hz, J_2 = 6.8 Hz, J_3 = 2.7 Hz), 7.26-7.41 (3 H, m), 7.45-7.56 (2 H, m), 7.83 (1 H, dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 7.90 (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz); ¹³C NMR (75 MHz) δ 30.29, 41.00, 53.05, 101.14 (C), 128.85, 129.08, 129.12, 129.77, 130.41, 130.77, 133.05, 134.99 (C), 137.21 (C), 140.24, 143.05 (C), 194.06 (CO).

S-(2-iodophenethyl) 2-(2-azidoethyl)benzenecarbothioate (1b). Chromatographed with light petroleum/diethyl ether 98:2 v/v, yield 75%, oil; IR $\nu_{\max}$ 1660 (CO), 2094 (N₃) cm⁻¹; ¹H NMR (300 MHz) δ 3.04-3.13 (4 H, m), 3.26-3.33 (2 H, m), 3.48-3.54 (2 H, m), 6.93 (1 H, ddd, J_1 = 8.0 Hz, J_2 = 6.4 Hz, J_3 = 2.6 Hz), 7.27-7.36 (4 H, m), 7.45 (1 H, td, J_t = 7.5 Hz, J_d = 1.5 Hz), 7.80-7.85 (2 H, m); ¹³C NMR (75 MHz) δ 30.36, 34.10, 41.07, 53.06, 101.18 (C), 127.68, 129.10, 129.13, 129.70, 130.77, 132.30, 132.63, 137.30 (C), 138.26 (C), 140.26, 143.11 (C), 194.59 (CO).

S-(2-iodophenethyl) 4-azidobutanethioate (2a). Chromatographed with light petroleum/diethyl ether 97:3 v/v, yield 60%, oil; IR $\nu_{\max}$ 1683 (CO), 2100 (N₃) cm⁻¹; ¹H NMR (300 MHz) δ 1.88-1.98 (2 H, m), 2.66 (2 H, t, J = 7.2 Hz), 2.96-3.02 (2 H, m), 3.10-3.16 (2 H, m), 3.33 (2 H, t, J = 6.8 Hz), 6.91 (1 H, ddd, J_1 = 7.9 Hz, J_2 = 6.7 Hz, J_3 = 2.5 Hz), 7.23-7.31 (2 H, m), 7.81 (1 H, dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz); ¹³C NMR (75 MHz) δ 25.38, 29.54, 41.09, 41.39, 51.05, 101.05 (C), 129.05, 129.09, 130.64, 140.23, 143.03 (C), 198.70 (CO).

S-(2-iodophenethyl) 4-azido-4-phenylbutanethioate (2b). Chromatographed with light petroleum/diethyl ether 98:2 v/v, yield 65%, oil; IR $\nu_{\max}$ 1682 (CO), 2097 (N₃) cm⁻¹; ¹H NMR (300 MHz) δ 2.02-2.21 (2 H, m), 2.73 (2 H, t, J = 7.3 Hz), 2.94-3.03 (2 H, m), 3.09-3.18 (2 H, m), 4.49 (1 H,

br t, $J = 7.2$ Hz), 6.91 (1 H, ddd, $J_1 = 8.0$ Hz, $J_2 = 6.5$ Hz, $J_3 = 2.5$ Hz), 7.18-7.42 (7 H, m), 7.81 (1 H, br d, $J = 8.0$ Hz); ^{13}C NMR (75 MHz) δ 29.57, 32.42, 41.06, 41.12, 65.75, 101.10 (C), 127.53, 129.08, 129.12, 129.20, 129.60, 130.67, 139.45 (C), 140.25, 143.06 (C), 198.75 (CO).

S-(2-iodophenethyl) 5-azido-5-phenylpentanethioate (2c). Chromatographed with light petroleum/diethyl ether 95:5 v/v, yield 72%, oil; IR ν_{max} 1682 (CO), 2100 (N_3) cm^{-1} ; ^1H NMR (300 MHz) δ 1.55-1.95 (4 H, m), 2.57 (2 H, t, $J = 6.8$ Hz), 2.92-3.03 (2 H, m), 3.08-3.17 (2 H, m), 4.42 (1 H, dd, $J_1 = 7.6$ Hz, $J_2 = 6.0$ Hz), 6.90 (1 H, ddd, $J_1 = 7.8$ Hz, $J_2 = 6.3$ Hz, $J_3 = 2.8$ Hz), 7.18-7.42 (7 H, m), 7.80 (1 H, dd, $J_1 = 7.8$ Hz, $J_2 = 1.0$ Hz); ^{13}C NMR (75 MHz) δ 22.94, 29.50, 35.96, 41.14, 44.04, 66.64, 101.06 (C), 127.51, 129.04, 129.52, 130.64, 139.93 (C), 140.22, 143.10 (C), 199.20 (CO) (2 aromatic CH overlapped).

General Procedure for the Reactions of Thioesters 1a,b, 2a-c with Tributyltin Hydride or Tris(trimethylsilyl)silane [(TMS) $_3$ SiH]. To a refluxing solution of thioester (2 mmol) and AIBN (0.2 mmol) in degassed benzene (80 mL) tributyltin hydride [or (TMS) $_3$ SiH] (2.2 mmol) was added under a nitrogen atmosphere and the resulting mixture was refluxed for 2-3 h. After cooling, the solvent was removed in vacuo and the residue chromatographed on silica gel. Eluting with light petroleum, all the reactions afforded dihydrobenzothiophene **4** (80-85%).¹ The reactions of thioesters **2a,b** always gave small amounts (< 5%) of the uncyclized reduction product (**2a,b**, I = H). The following reactions were carried out according to this general procedure.

Reaction of 1a with Bu $_3$ SnH or (TMS) $_3$ SiH. Chromatography with diethyl ether/ethyl acetate/methanol 45:45:10 v/v/v gave 1-isoindolinone (**7a**) (87% and 81% from Bu $_3$ SnH and (TMS) $_3$ SiH, respectively), mp = 150-152 °C (lit.⁷ mp = 149-151 °C).

Reaction of 1b with Bu $_3$ SnH or (TMS) $_3$ SiH. Chromatography with diethyl ether/ethyl acetate 50:50 v/v gave 3,4-dihydro-1(2H)-isoquinolinone (**7b**) (87% and 75% from Bu $_3$ SnH and (TMS) $_3$ SiH, respectively), oil, crystallizing on cooling at -20 °C, mp = 55-56 °C (lit.⁸ an oil).

Reaction of 2a with Bu $_3$ SnH. Chromatography with diethyl ether/ethyl acetate/methanol 45:45:10 v/v/v afforded 2-pyrrolidinone (**9a**) (35%), oil, identified by comparison with an authentic, commercial sample.

Reaction of 2b with Bu $_3$ SnH. Chromatography with light petroleum afforded 1-phenylpropyl azide **10a** (16%), oil; IR ν_{max} 2093 (N_3) cm^{-1} ; ^1H NMR (300 MHz) δ 0.93 (3 H, t, $J = 7.3$ Hz), 1.70-1.94 (2 H, m), 4.43 (1 H, br t, $J = 7.1$ Hz), 7.25-7.41 (5 H, m). Chromatography with diethyl ether/ethyl acetate/methanol 45:45:10 v/v/v gave 5-phenyl-2-pyrrolidinone (**9b**) (35%), mp = 108-109 °C (lit.⁹ mp 103-103.5 °C).

Reaction of 2c with Bu₃SnH. Chromatography with light petroleum afforded a mixture of **4** and 1-phenylbutyl azide **10b** (15%), oil; IR $\nu_{\max}$ 2098 (N₃) cm⁻¹; ¹H NMR (300 MHz) δ 0.92 (3 H, t, J = 7.3 Hz), 1.25-1.45 (2 H, m), 1.65-1.88 (2 H, m), 4.40 (1 H, br t, J = 7.3 Hz), 7.27-7.40 (5 H, m). Eluting with light petroleum/diethyl ether 90:10 v/v, a small, complicated mixture was collected containing presumable 5-azido-5-phenylpentanal [IR $\nu_{\max}$ 1724 (CO), 2099 (N₃) cm⁻¹; ¹H NMR (300 MHz) δ 9.73 (1 H, t, J = 1.4 Hz, CHO)]. Chromatography with diethyl ether/ethyl acetate/methanol 45:45:10 v/v/v gave 6-phenyl-2-piperidone (**9c**) (31%), mp = 138-139 °C (lit.¹⁰ mp 137 °C).

Reaction of 1a with Allyltributylstannane or Allyltriphenylstannane. A solution of **1a** (2 mmol), allyltributyl- (or allyltriphenyl) stannane (8 mmol), and AIBN (0.2 mmol) in degassed benzene (15 mL) was refluxed under a nitrogen atmosphere for 2 h. Extra AIBN (0.2 mmol) was added three times every 2 h until complete disappearance of the starting material (8 h overall reaction time). Chromatography with light petroleum afforded **4**. Further elution with light petroleum/diethyl ether 60:40 v/v gave 2-allyl-1-isoindolinone (**8**) (40% and 60% from allyltributylstannane and allyltriphenylstannane, respectively), oil; ¹H NMR (300 MHz) δ 4.23 (2 H, br d, J = 6.0 Hz), 4.36 (2 H, s), 5.19-5.29 (2 H, m), 5.79-5.92 (1 H, m), 7.40-7.57 (3 H, m), 7.85 (1 H, dd, J_1 = 6.8 Hz, J_2 = 1.5 Hz); ¹³C NMR (75 MHz) 45.52, 50.09, 118.41, 123.28, 124.19, 128.49, 131.82, 133.21 (C), 133.52, 141.77 (C), 168.79 (CO); MS m/z (rel. inten.) 173 (M⁺, 100), 146 (22), 132 (8). Anal. Calcd. for C₁₁H₁₁NO: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.26; H, 6.47; N, 8.10. Final elution with diethyl ether/ethyl acetate/methanol 45:45:10 v/v/v gave 1-isoindolinone (**7a**) (45% and 25% from allyltributylstannane and allyltriphenylstannane, respectively).

References

1. Crich, D; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566.
2. Wada, T.; Ohkubo, A.; Mochizuki, A.; Sekine, M. *Tetrahedron Lett.* **2001**, *42*, 1069.
3. Khoukhi, N.; Vaultier, M.; Carrié, R. *Tetrahedron* **1987**, *43*, 1811.
4. Baer, H. H.; Naik, S. R. *J. Org. Chem.* **1970**, *35*, 3161.
5. Satoh, T.; Unno, H.; Mizu, Y.; Hayashi, Y. *Tetrahedron* **1997**, *53*, 7843.
6. Toda, S.; Miyamoto, M.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600.
7. Broadus, K. M.; Kass, S. R. *J. Org. Chem.* **2000**, *65*, 6566.
8. Brunet, J. J.; Sidot, C.; Caubere, P. *J. Org. Chem.* **1983**, *48*, 1166.
9. Maldaner, A. O.; Pilli, A. R. *Tetrahedron* **1999**, *55*, 13321.
10. Ondrus, T. A.; Knaus, E. E.; Giam, C. S. *Can. J. Chem.* **1979**, *57*, 2342.