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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lsyc20</u>

SYNTHESIS OF ENANTIOPURE PYRROLO[3,4-CPYRAZOLE DERIVATIVES VIA INTRAMOLECULAR CYCLOADDITION OF HOMO-CHIRAL NITRILIMINES

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To cite this article: Gianluigi Broggini, Giorgio Molteni, Tullio Pilati & Gaetano Zecchi (2001) SYNTHESIS OF ENANTIOPURE PYRROLO[3,4-cPYRAZOLE DERIVATIVES VIA INTRAMOLECULAR CYCLOADDITION OF HOMO-CHIRAL NITRILIMINES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:24, 3799-3806, DOI: <u>10.1081/SCC-100108230</u>

To link to this article: <u>http://dx.doi.org/10.1081/SCC-100108230</u>

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SYNTHETIC COMMUNICATIONS, 31(24), 3799-3806 (2001)

SYNTHESIS OF ENANTIOPURE PYRROLO[3,4-c]PYRAZOLE DERIVATIVES VIA INTRAMOLECULAR CYCLOADDITION OF HOMO-CHIRAL NITRILIMINES

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ABSTRACT

Intramolecular cycloaddition of homochiral nitrilimines **8** was exploited to obtain enantiopure pyrrolo[3,4-*c*]pyrazole derivatives **9** and **10** with high overall yields.

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Due to their versatility, intramolecular nitrilimine cycloadditions constitute a powerful approach to a wide range of heterocyclic systems.^{1–5} The construction of the pyrrolo[3,4-*c*]pyrazole skeleton belongs to the first success of this synthetic methodology.⁶ In the context of our recent framework of research focused to intramolecular cycloadditions of homochiral nitrilimines⁷ we describe here a version of the above methodology leading to enantiopure 3,3a,4,5-tetrahydro-6-oxo-pyrrolo[3,4-*c*]pyrazole derivatives.

Aiming at this target, we devised the inexpensive (S)-1-phenylethylamine and L-alanine benzylester as the starting chiral unities. The latter were reacted with allyl bromide to give the corresponding amines **1** and **2** as the fundamental chiral building blocks (see scheme).



Scheme.

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ENANTIOPURE PYRROLO[3,4-c]PYRAZOLE DERIVATIVES

Our synthetic approach involved, as further stages, the sequence $1 \rightarrow 3 \rightarrow 5$ or $2 \rightarrow 4 \rightarrow 6$. Subsequent treatment of the α -chloro acetoacetamides 5 and 6 with the appropriate arenediazonium chloride gave the hydrazonoyl chlorides 7, whose marked lability precluded full characterization.⁸ The desired nitrilimine intermediates 8 were then generated *in situ* by reacting crude 7 in dioxane solution with silver carbonate. Cycloaddition products, isolation yields, reaction times and eluents are collected in the table.

Structures 9 and 10 are supported by elemental analyses and IR and NMR spectra, and the absolute (S) configuration to the pyrazolinic C-3a of minor cycloadducts 10 are substantiated by the X-ray diffractometric analysis of 10a.

Finally, the control of the absolute stereochemistry was modest with both chiral inductors (see table). The large distance between the starting stereocentre and the new one is perhaps responsible for the observed

Table. Conversion of 5 and 6 into Cycloadducts 9 and 10					
		Products and	d Yields (%) ^a	Product Ratio	
Entry	Time (h)	9	10	9:10	Eluent ^b
a	140	44	38	54:46	AcOEt-LP 1:1
b	76	34	27	56:44	AcOEt-n-hexane 1:1
c	140	28	21	57:43	AcOEt-LP 3:1
d	71	43	32	57:43	CH ₂ Cl ₂ - <i>n</i> -hexane 3:1

Table. Conversion of 5 and 6 into Cycloadducts 9 and 10

^aIsolation yield of pure product; ^bLP = light petroleum, b.p. 40–60°C.



Figure. ORTEP projection of **10a** with the crystallographic numbering scheme. Ellipsoids are at 50% probability level. H atoms not to scale.



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disappointing outcome. However, the conversions $5 \rightarrow 9+10$ and $6 \rightarrow 9+10$ seem synthetically valuable in view of the high overall yields as well of the easy separation of diastereoisomeric cycloadducts 9 and 10 in enantiopure state.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus and are not corrected. IR spectra were recorded with a Perkin-Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ¹H-NMR spectra (300 MHz) were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in CDCl₃ solutions). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. Optical rotations, $[\alpha]_{D}^{25}$, were recorded on a Perkin-Elmer Model 241 polarimeter at the sodium D line.

Compound 2 was prepared according to literature methods.⁹

Preparation of benzyl *N*-(1-prop-2-enyl)-L-alaninate (1). A solution of L-alanine benzylester (5.00 g, 27.9 mmol) in dry toluene (35 mL) was added with KI (0.46 g, 2.8 mmol). Allyl bromide (1.58 g, 13.0 mmol) in dry toluene (5 mL) was slowly added and the mixture was warmed to 65°C for 4 h under stirring. Toluene (25 mL) was added, the white precipitate was filtered off, and the solvent was evaporated under reduced pressure affording 1 (2.31 g, 81% yield) as undistillable yellow oil; $[\alpha]_D^{25} = -26.3$ (CH₂Cl₂, c = 0.16); IR (neat): 3330, 1735 (cm⁻¹); ¹H-NMR δ : 1.30 (3H, d, *J* 7.0), 1.85 (1H, br s), 3.12 (1H, dd, *J* 13.7, 6.1), 3.25 (1H, dd, *J* 13.7, 6.1), 3.41 (1H, q, *J* 7.0), 5.02–5.18 (2H, m), 5.14 (2H, s), 5.83 (1H, ddd, *J* 16.5, 12.9, 6.1), 7.25–7.40 (5H, m); MS: m/z 219 (M⁺).

General procedure for the preparation of benzyl N-(1-prop-2-enyl)-N-(1,4-dioxobutyl)-L-alaninate (3) and (S)-N-(1-phenyleth-1-yl)-N-(1-prop-2-enyl)-3-oxobutanamide (4). A solution of 1 or 2 (18.0 mmol) in dry Et₂O (30 mL) was cooled to 0°C, and then added with diketene (1.66 g, 19.8 mmol). The mixture was stirred at 0°C for 2 h, then for 5 h at room temperature. Evaporation of the solvent gave 3 or 4 as undistillable oils not analytically pure.

3 (5.24 g, 96%) as pale yellow oil; $[\alpha]_D^{25} = -30.5$ (CH₂Cl₂, c = 0.26); IR (neat): 1740, 1655 (cm⁻¹); ¹H-NMR δ : 1.44 (3H, d, *J* 7.2), 2.20 (3H, s), 3.46 (2H, s), 3.80 (1H, ddd, *J* 18.0, 6.0, 3.2), 3.97 (1H, ddd, *J* 18.0, 6.0, 3.6), 4.74 (1H, q, *J* 7.2), 5.05–5.27 (2H, m), 5.13 (2H, s), 5.70–5.87 (1H, m), 7.25–7.40 (5H, m); MS: *m/z* 303 (M⁺).

4 (4.19 g, 95%) as pale yellow oil; $[\alpha]_D^{25} = -136$ (CH₂Cl₂, c = 0.28); IR (neat): 1730, 1640 (cm⁻¹); ¹H-NMR δ : 1.50 (3H, d, *J* 7.2), 2.26 (3H, s), 3.49

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(1H, dd, *J* 17.3, 3.9), 3.56 (2H, s), 3.62 (1H, dd, *J* 17.3, 3.6), 4.97–5.62 (3H, m), 6.06 (1H, q, *J* 7.2), 7.20–7.40 (5H, m); MS: *m*/*z* 245 (M⁺).

General procedure for the preparation of benzyl *N*-(1-prop-2-enyl)-*N*-(1,4-dioxo-3-chlorobutyl)-L-alaninate (5) and (*S*)-*N*-(1-prop-2-enyl)-3-oxo-2-chlorobutanamide (6). A solution of 3 or 4 (10.0 mmol) in dry CHCl₃ (20 mL) was cooled to 0° C and then sulfuryl chloride (1.34 g, 10.0 mmol) in dry CDCl₃ (3 mL) was added dropwise. The mixture was stirred at 0° C for 1 h and then the solvent was evaporated under reduced pressure affording 5 or 6 as undistillable oils not analytically pure.

5 (3.27 g, 97%) as yellow oil; IR (neat): 1740, 1655 (cm⁻¹); ¹H-NMR δ : 1.48 (3H, d, *J*7.1), 2.30 (3H, s), 3.86–4.20 (2H, m), 4.60 (1H, q, *J*7.1), 4.84 (1H, s), 5.13 (2H, s), 5.22–5.74 (3H, m), 7.30–7.40 (5H, m); MS: *m*/*z* 337 (M⁺).

6 (2.68 g, 96%) as yellow oil; IR (neat): 1730, 1650 (cm⁻¹); ¹H-NMR δ : 1.54 (3H, d, *J* 7.2), 2.41 (3H, s), 3.64 (1H, dd, *J* 17.2, 3.6), 3.83 (1H, dd, *J* 17.2, 3.4), 4.90 (1H, s), 5.10–5.75 (3H, m), 5.98 (1H, q, *J* 7.2), 7.23–7.40 (5H, m); MS: m/z 279 (M⁺).

General procedure for the conversion of 5,6 into 9,10. A solution of 5 or 6 (4.0 mmol) in MeOH (6.0 mL) was cooled to 0° C, and a cold aqueous solution of 4-chlorobenzenediazonium chloride or 4-nitrobenzenediazonium chloride (4.0 mmol) was added dropwise under vigorous stirring by keeping the temperature between 0 and 5°C. During the addition, the pH was adjusted to 5 by adding sodium acetate. The mixture was stirred at $0^{\circ}C$ for 2h, then at room temperature for 5h, and extracted with Et₂O (50 mL). The organic layer was washed firstly with 5% NaHCO₃ (15 mL), then with water (50 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give an oily residue that was dissolved in dry dioxane (180 mL). Silver carbonate (1.98 g, 7.2 mmol) was added and the mixture was stirred in the dark at room temperature for the time indicated in the table. After evaporation of the solvent, the crude was chromatographed on a silica gel column with the eluents indicated in the table affording pyrrolo[3,4-c] pyrazole cycloadduts 9 and 10. Major diastereoisomers 9 was eluted first, followed by minor diastereoisomers 10.

9a (0.70 g, 44%) m.p. 150°C (from diisopropyl ether); $[\alpha]_D^{25} = -200.0$ (CH₂Cl₂, c = 0.14); IR (nujol): 1740, 1690 (cm⁻¹); ¹H-NMR δ : 1.45 (3H, d, *J*7.4), 3.28 (1H, dd, *J*9.1, 6.9), 3.41 (1H, dd, *J*14.0, 9.7), 3.62–3.78 (1H, m), 3.92 (1H, dd, *J* 9.0, 8.8), 4.37 (1H, dd, *J* 10.3, 10.1), 5.10 (1H, q, *J* 7.4), 5.14 (1H, d, *J* 12.2), 5.20 (1H, d, *J* 12.2), 7.00–7.40 (9H, m); MS *m*/*z* 397 (M⁺) (44%). Anal Cald for C₂₁H₂₀ClN₃O₃: C, 63.40; H, 5.07; N, 10.56. Found: C, 63.46; H, 5.11; N, 10.60.

10a (0.61 g, 38%) m.p. 183°C (from diisopropyl ether); $[\alpha]_D^{25} = +342.0$ (CH₂Cl₂, c = 0.11); IR (nujol), 1735, 1695 (cm⁻¹); δ_H : 1.50 (3H, d, J 7.4), 3.27 (1H, dd, J 9.1, 6.9), 3.30 (1H, dd, J 14.0, 9.7), 3.53–3.70

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(1H, m), 3.78 (1H, dd, J 9.0, 8.8), 4.33 (1H, dd, J 10.3, 10.0), 5.06 (1H, d, J 12.2), 5.10 (1H, q, J 7.4), 5.17 (1H, d, J 12.2), 7.00–7.30 (9H, m); MS m/z397 (M⁺) (32%). Anal Calcd for $C_{21}H_{20}CIN_3O_3$: C, 63.40; H, 5.07; N, 10.56. Found: C, 63.44; H, 5.05; N, 10.50.

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9b (0.46 g, 34%) m.p. 159°C (from diisopropyl ether); $[\alpha]_{D}^{25} =$ -268.9 (CH₂Cl₂, c = 0.22); IR (nujol): 1685 (cm⁻¹); ¹H-NMR δ : 1.55 (3H, d, J 7.0), 3.22 (1H, dd, J 9.3, 6.5), 3.35-3.63 (3H, m), 4.33 (1H, dd, J 9.5, 9.3), 5.67 (1H, q, J 7.0), 7.00–7.40 (9H, m); MS m/z 339 (M⁺) (26%). Anal Calcd for C₁₉H₁₈ClN₃O: C, 67.15; H, 5.34; N, 12.37. Found: C, 67.21; H, 5.30; N, 12.44.

10b (0.27 g, 27%) m.p. 209°C (from diisopropyl ether); $[\alpha]_D^{25} =$ +118.3 (CH₂Cl₂, c = 1.6); IR (nujol): 1690 (cm⁻¹); ¹H-NMR δ : 1.66 (3H, d, J 7.0), 2.80 (1H, dd, J 9.2, 6.3), 3.30 (1H, dd, J 13.7, 9.7), 3.58-3.77 (3H, m), 4.30 (1H, dd, J 10.1, 9.8), 5.70 (1H, q, J 7.0), 7.05–7.45 (9H, m); MS m/z 339 (M⁺) (26%). Anal Calcd for $C_{19}H_{18}ClN_{3}O$: C, 67.15; H, 5.34; N, 12.37. Found: C, 67.17; H, 5.28; N, 12.40.

9c (0.46 g, 28%) m.p. 168°C (from hexane-benzene); $[\alpha]_{D}^{25} =$ -30.8 (CH₂Cl₂, c = 0.21); IR (nujol): 1740, 1690 (cm⁻¹); ¹H-NMR δ : 1.47 (3H, d, J 7.4), 3.35 (1H, dd, J 9.5, 6.7), 3.59 (1H, dd, J 13.2, 9.5), 3.74-3.88 (1H, m), 3.97 (1H, dd, J 8.9, 8.7), 4.47 (1H, dd, J 10.4, 10.1), 5.10 (1H, q, J 7.4), 5.15 (1H, d, J 12.2), 5.22 (1H, d, J 12.2), 7.10–8.20 (9H, m); MS m/z 408 (M⁺) (44%). Anal Calcd for C₂₁H₂₀N₄O₅: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.81; H, 5.01; N, 13.80.

10c (0.35 g, 21%) m.p. 130° C (from hexane-benzene); $[\alpha]_{D}^{25} =$ +225.0 (CH₂Cl₂, c = 0.18); IR (nujol); 1740, 1690 (cm⁻¹); ¹H-NMR δ: 1.51 (3H, d, J 7.5), 3.37 (1H, dd, J 8.9, 6.6), 3.49 (1H, dd, J 13.0, 9.9), 3.60-3.80 (1H, m), 3.84 (1H, dd, J 8.7, 8.6), 4.43 (1H, dd, J 10.4, 10.0), 5.08 (1H, d, J 12.1), 5.11 (1H, q, J 7.5), 5.19 (1H, d, J 12.1), 7.10-8.30 (9H, m); MS m/z 408 (M⁺) (40%). Anal Calcd for C₂₁H₂₀N₄O₅: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.71; H, 5.01; N, 13.77.

9d (0.60 g, 43%) m.p. 202°C (from diisopropyl ether); $[\alpha]_D^{25} =$ -307.0 (CH₂Cl₂, c = 0.20); IR (nujol): 1690 (cm⁻¹); ¹H-NMR δ : 1.57 (3H, d, J 7.0), 3.27 (1H, dd, J 9.6, 6.4), 3.43-3.70 (3H, m), 4.40 (1H, dd, J 7.7, 7.5), 5.66 (1H, q, J 7.0), 7.10–8.20 (9H, m); MS m/z 350 (M⁺) (16%). Anal Calcd for C₁₉H₁₈N₄O₃: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.18; H, 5.13; N, 16.06.

10d (0.45 g, 32%) m.p. 267°C (from diisopropyl ether); $[\alpha]_D^{25} =$ +82.4 (CH₂Cl₂, c = 0.20); IR (nujol): 1685 (cm⁻¹); ¹H-NMR δ : 1.68 (3H, d, J 7.0), 2.87 (1H, dd, J 8.5, 5.6), 3.49 (1H, dd, J 12.8, 10.1), 3.69-3.84 (2H, m), 4.43 (1H, dd, J 10.5, 10.1), 5.74 (1H, q, J 7.0), 7.10-8.20 (9H, m); MS m/z 350 (M⁺) (28%). Anal Calcd for C₁₉H₁₈N₄O₃: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.21; H, 5.19; N, 16.09.

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X-ray structure determination of 10a. Crystal data were collected with graphite monochromated Mo-K α radiation $\lambda = 0.71073$ Å. The structure was solved by *SIR*92,¹⁰ and refined on *F*2 by full-matrix least-squares using *SHELX*97;¹¹ heavy atoms anisotropic; H atoms isotropic; H of metyl and benzyl groups calculated. Absolute configuration was based on the reactants knowledge and confirmed by refinement [Flack parameter -0.01(7)]. **Data of 10a.** C₂₁H₂₀ClN₃O₃, M_r=397.85, monoclinic, space group *P*2₁, *a*=12.6252(11), *b*=5.6152(7), *c*=14.4206(15) Å, β =98.644(7), γ =82.907(6)°, *V*=1010.71(19) Å, ³*T*=291(1) K, *Z*=2, *d*_{calc}=1.307 g cm⁻¹, μ (Mo-K α) = 0.215 mm⁻¹; $\omega/2\theta$ scans, $4 < 2\theta < 60^\circ$; 4646 unique reflections collected used for all calculations. Final *R*=0.0594 and *wR*=0.1014, g.o.f. 1.019, $-0.12 < \Delta \rho < 0.18$ eÅ⁻³. Detailed crystallographic data were deposited (as CCDC 147230) with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

ACKNOWLEDGMENTS

We are grateful to CNR and MURST for financial support.

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Received in the UK November 7, 2000



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