Tetrahedron Letters,Vol.28,No.49,pp 6175-6178,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ASYMMETRIC SYNTHESIS XI[1] : A SHORT SYNTHESIS OF THE CHIRAL PYRROLIDINE SYNTHON, 2-CYANO-5-OXAZOLOPYRROLIDINE

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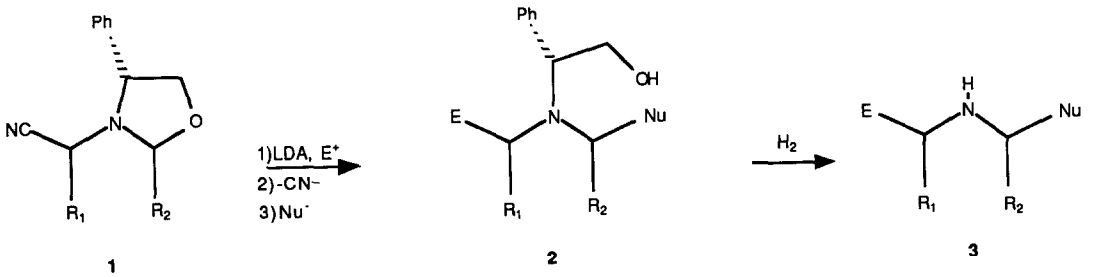
Abstract

The Robinson-Schopf condensation of dimethoxytetrahydrofuran with R(-)phenylglycinol in the presence of KCN followed by reflux in ethanol leads to the formation of 2-cyano-5-oxazolopyrrolidine 1b in 52% overall yield.

Within the context of asymmetric synthesis of nitrogen-containing natural products (aminoacids, aminoalcohols, alkaloids, etc.) we have reported a general strategy based upon electrophilic-nucleophilic α,α' substitution of the nitrogen atom of synthons 1a[2], 1b[1] or 1c[3] (scheme 1) derived from R(-) phenylglycinol.



1 2 3

a $R_1 = R_2 = H$

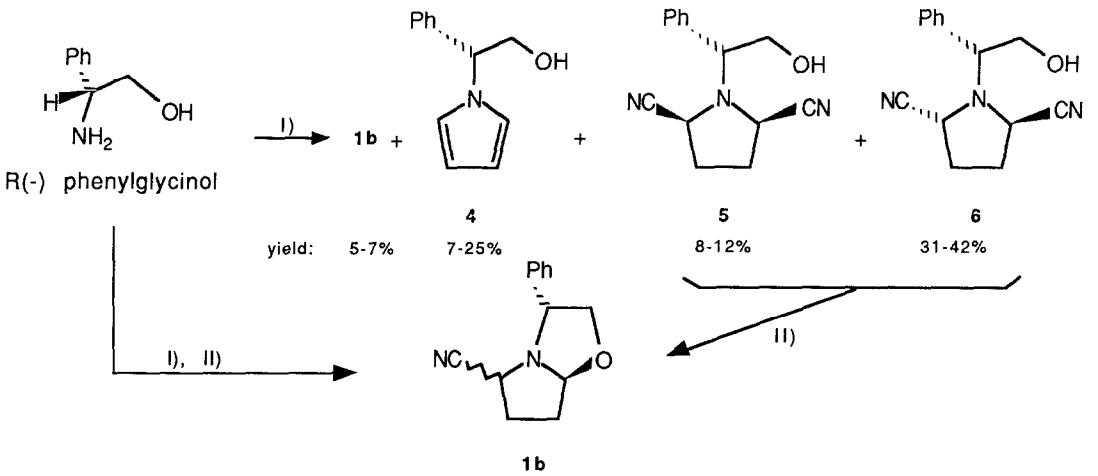
b $R_1, R_2 = CH_2 - CH_2$

c $R_1, R_2 = CH_2 - CH_2 - CH_2$

Scheme 1

The condensation of R(-) phenylglycinol with formaldehyde in the presence of KCN led in a one pot reaction to the formation of 1a[2]. The Robinson-Schopf condensation of glutaraldehyde with the same aminoalcohol emerged as a particularly attractive route to the piperidine synthon 1c[3]. At the time however, the pyrrolidine synthon 1b could be obtained in only 5% yield using succinaldehyde in an analogous reaction. For this reason, we devised a viable route for the preparation of 1b based on a different strategy[1]. Nevertheless, this scheme was somewhat disavantageous in that it involves three steps and considerable care was required during its execution.

Synthon 1b constitutes the basis of a general method for the synthesis of enantiomerically pure pyrrolidine[4] and pyrrolizidine alkaloids[5] and may also be used as starting material for the preparation of chiral auxiliaries useful in asymmetric synthesis[6]. We considered this to be a sufficient motivation to develop a means of obtaining 1b in a more straightforward fashion.



Reagents: I) dimethoxytetrahydrofuran, KCN, citric acid (H_2O, r.t., 24-48 h) ; II) EtOH (reflux , 96 h)

Scheme 2

A reexamination of our previous experiments leads us now to propose in this letter a simpler and more efficient synthesis of 1b.

The condensation of succinaldehyde (or its synthetic equivalent dimethoxytetrahydrofuran) with R(-) phenylglycinol in the presence of KCN at pH 3 during 24-48h at room temperature gave a mixture of four compounds 1b, 4, 5 and 6 in variable yields (scheme 2). In particular, the amount of pyrrole 4[7] was greatly increased when KCN was introduced into the reaction mixture 1 or 2h after the other reagents. The ratio of the

dicyano derivatives[8] 5[7] and 6[7] was constant (5/6 : 1/3.5) in the equilibrating reaction conditions.

It appeared that it was not possible to increase the yield of 1b under these standard conditions[9]. The formation of approximately 50% of dicyano derivatives suggested that they might be useful as intermediates for 1b. Indeed, it has been shown that such compounds epimerise when heated in ethanol[8,10], which implies the intermediacy of an iminium ion. Thus, we considered that it might be possible to form an oxazolidine ring by intramolecular cyclization of the primary alcohol function. When compounds 5 and/or 6 were heated in refluxing ethanol for 24h, an epimeric mixture of synthon 1b[11] was produced in 55% yield (7:3 ratio). It was thus possible to prepare the synthon 1b in 52% overall yield using the Robinson-Schopf type condensation of phenylglycinol and dimethoxytetrahydrofuran at pH $\sim$ 3 during 48h followed by refluxing the crude reaction extract in EtOH for 96h.[12].

The difference in the condensations of phenylglycinol with glutaraldehyde and with succinaldehyde probably arises from the difficult ring closure of the strained oxazolidine ring in the latter case, leading to the preferential formation of the dicyano compounds. Some dicyano-piperidine derivatives have been detected during the synthesis of 1c ; these compound were easily cyclized into 1c at room temperature[13].

References and Notes

1 For part X see : P.Q. HUANG, S. ARSENIYADIS and H.-P. HUSSON, Tetrahedron Lett., 1987, 28, 547.

2 J.L. MARCO, J. ROYER and H.-P. HUSSON, Tetrahedron Lett., 1985, 26, 3567.

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4 S. ARSENIYADIS, P.Q. HUANG and H.-P. HUSSON, to be published.

5 The ant venom alkaloid [3S, 5R, 8S]-3-heptyl-5-methylpyrrolizidine has been synthesized : S. ARSENIYADIS, P.Q. HUANG and H.-P. HUSSON, unpublished results.

6 R.H. SCHLESSINGER and E.J. IWANOWICZ, Tetrahedron Lett., 1987, 28, 2083.

7 4 : oil ; MS m/z (C.I.) : 188 (MH^+). ^1H NMR ($CDCl_3$, 80 MHz) δ (ppm) : 1.91 (m, 4H), 4.12 (d, J = 6.5 Hz, 2H, CH_2OH), 5.2 (t, J = 6.5 Hz, 1H, CHPh), 6.16 (t, J = 1 Hz, 2H, pyrrole ring), 6.71 (t, J = 1Hz, 2H, pyrrole ring), 7.18 (m, 5H, ar.). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 59.7 (CHN and CH_2OH), 103.4, 115.1 (pyrrole), 121.7, 122.8, 123.6, 133.9 (phenyl).

5 : white crystals mp 118°C (hexane-AcOEt 1:1) ; IR ($CHCl_3$) : 2270 cm^{-1} (CN) ; MS m/z (relative intensity) : 241 ($M^{+\cdot}$, 1), 210(100), 184(18), 157(15), 158(17), 131(18), 130(13), 104(69) ; ^1H NMR ($CDCl_3$, 80 MHz) δ (ppm) : 2.3 (m, 4H), 3.8-4.1 (m, 5H), 7.35 (m, 5H) ; ^{13}C NMR ($CDCl_3$, 50 MHz) δ : 29.5 (2 ring CH_2), 51.7 (2 C-CN), 66.1 (CH_2OH), 67.9 (N-C-Ph), 119.3 (2 CN), 128.0, 128.6, 129.1, 138.4 (ar.)

6 : white crystals mp 89°C (hexane-AcOEt 1:1) ; IR ($CHCl_3$) : 2260, 2280 (CN) ; MS m/z (relative intensity) : 241 ($M^{+\cdot}$, 0.5), 210(80), 131(78), 130(42), 116(21), 104(100) ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) : 2.2-2.6 (m, 4H), 3.82 (t, J = 5.5 Hz, 1H) 3.97 (m, 2H), 4.22 (dd, J = 6 Hz, J' = 4 Hz, 1H), 4.58 (dd, J = 4 Hz, J' = 6 Hz, 1H), 7.43 (m, 5H) ; ^{13}C NMR ($CDCl_3$, 50 MHz) δ : 27.5, 29.1 (2 ring CH_2), 50.3, 50.9 (2 C-CN), 64.8 (CHPh), 65.6 (CH_2OH), 117.2, 117.7 (2 CN), 128.1, 128.4, 128.8, 137.5 (ar.). The absolute stereochemistry at the two aminonitriles centers is at present arbitrarily assigned as depicted in scheme 2.

8 A series of 1-substituted 2,5-dicyanopyrrolidines has been recently prepared by K. TAKAHASHI, H. SAITOH, K. OGURA and H. IIDA, Heterocycles, 1986, 24, 2905.

9 We have obtained very similar results starting from succinaldehyde, from dimethoxytetrahydrofuran in citric acid solution or from the succinaldehyde sodium bisulfite addition compound.

10 M. BONIN, A. CHIARONI, C. RICHE, J.-C. BELOEIL, D.S. GRIERSON and H.-P. HUSSON, J. Org. Chem., 1987, 52, 382.

11 Compound 1b consisted of two epimeric nitriles identical in all respects to those previously obtained[1].

12 A typical procedure was as follows : A mixture of (-)phenylglycinol (1.37 g ; 10^{-2} mole), dimethoxytetrahydrofuran (1.5mL ; 1.16 10^{-2} mole), potassium cyanide (0.65g ; 10^{-2} mole), citric acid (4 g) and water (100mL) was stirred at room temperature for 48h. The mixture was then made alkaline (Na_2CO_3) and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated. The crude reaction mixture was then dissolved in EtOH (100mL) and refluxed for 96h. After distillation of the solvent, the residual oil was subjected to flash chromatography (silica ; 8:2 hexane-AcOEt) to give 1b (1.13g ; 52% two epimers, partially separated, rf 0.4 and 0.33), and 4 (332mg ; 18%, rf 0.27) ; further elution with more polar eluent (pure AcOEt) furnished a mixture of 5 and 6 together with more polar products (645mg ; < 27%).

13 M. BONIN, J. ROYER, D.S. GRIERSON and H.-P. HUSSON, unpublished results.

(Received in France 15 September 1987)