Pergamon

Tetrahedron Letters 40 (1999) 3731–3734

TETRAHEDRON LETTERS

Asymmetric Synthesis of Polyfunctionalized Piperidines: Substitution at the C-4 Position.

Florence Billon-Souquet[a], Thierry Martens[a] and Jacques Royer[b*]

[a] Laboratoire de Chimie Analytique et d'Electrochimie, UMR 8638, Université René Descartes, Faculté de Pharmacie, 4, Avenue de l'Observatoire, 75782 Paris Cedex 06, France.

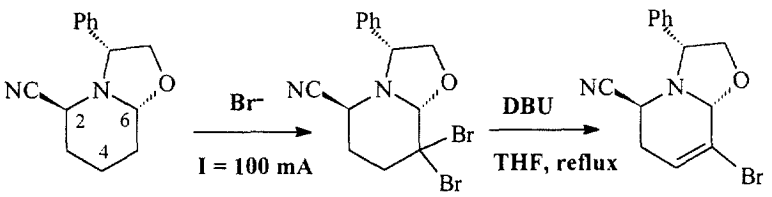
[b] Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France.

Received 22 February 1999; accepted 23 March 1999

Abstract: The electrochemical bis-bromination of the chiral building block **1** followed by a dehydrobromination step allowed the preparation of a bromopiperideine **3**. The stereoselective addition of nucleophiles onto this key intermediate permitted the synthesis of various 4-substituted piperidine derivatives.

The 2-cyano-6-oxazolopiperidine **1** is a chiral non-racemic building block designed[1] and used[2,3] for the asymmetric synthesis of piperidine alkaloids. We recently described the electrochemical oxidation of **1** giving halogenation at C-5[4,5]. Notably, we reported that the regioselective anodic bis-bromination of **1** afforded in 82% yield the 5,5'-dibrominated product **2**[5]. In order to demonstrate the synthetic potential of electrochemical reactions in the preparation of piperidine derivatives from **1**, we undertook the investigation of the chemical reactivity of **2**, a compound which can be prepared on a 1.5-2.5g scale when the electrolysis is performed galvanostically.

Compound **2** was easily dehydrobrominated (DBU, THF)[6] to afford the bromopiperideine **3**[7] (64%) which appeared to us to be a possible precursor of variously substituted piperidine derivatives (Scheme 1). Indeed, we have now in hand a potential α,β-unsaturated iminium ion (5,6-dihydropyridinium) which allows introduction of substituents at the C-4 and C-5 positions, in addition to the possible substitutions at the C-2 and C-6 positions already available from compound **1**.



1 **2 (82%)** **3 (64%)**

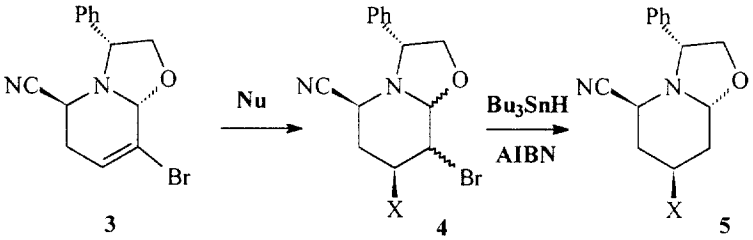
Scheme 1

The chemistry of 2-cyano-Δ^3-piperidine compounds as latent 5,6-dihydropyridinium salt has been particularly documented[8]. Furthermore, addition of organocuprates to α,β-unsaturated oxazolidines was reported to give regiospecific 1,4-addition with good diastereoselectivity[9].

* fax: (33) 01 69 07 72 47; e-mail: royer@icsn.cnrs-gif.fr

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00625-5

In this paper, we wish to disclose our investigations related to the addition of various nucleophiles to compound **3** (Scheme 2). Oxygen, nitrogen and carbon nucleophiles (**Nu**) were studied and the results are listed in the Table. Addition at the C-4 position was observed in each case giving rise to compound **4** in good yields. Debromination of **4** was easily achieved using Bu_3SnH[10] affording **5**.



Scheme 2

With oxygen nucleophiles (entries a and b, Table) the reaction was conducted at 50°C in H_2O (and acetone) or MeOH in the presence of acetic acid (10 equiv.). Compounds **4a** and **4b** were obtained in very good yields and as a single diastereomer. The configuration of these compounds, easily deduced from ^1H NMR spectra, is depicted in the Table.

When a primary amine was used as a nucleophile, aprotic conditions were necessary. Among the numerous Lewis acids studied, only $TiCl_4$ proved to be efficient. Indeed, the presence of a large excess of amine (4.5 equiv.) previously treated in CH_2Cl_2 at -20°C with $TiCl_4$ (3.0 equiv.) (suggesting the formation of a $TiCl_{4-n}(BnNH)_n$ type of species) was necessary. In this case **4c** was isolated in 45% yield as a mixture of two epimers at C-5 (and / or C-6) in a 4:1 ratio as proved by ^1H NMR and transformation to a single compound **5c**.

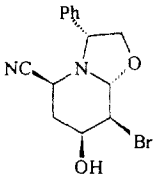
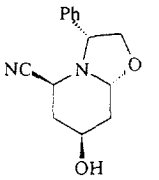
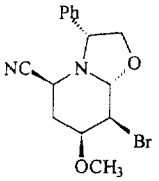
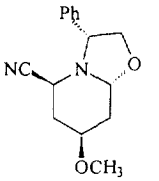
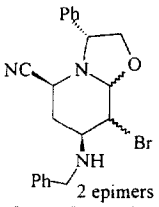
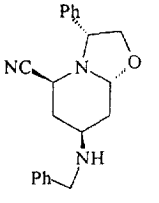
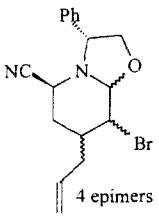
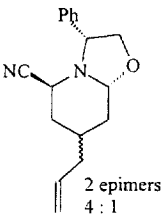
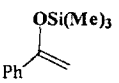
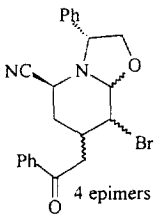
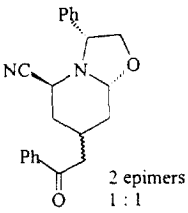
Addition of carbon-π nucleophiles was conducted in CH_2Cl_2 at -20°C and in the presence of 1 equiv. of $BF_3.OEt_2$[11,12]. Compounds **4d** and **4e** were obtained in good yields but as a complex mixture of four products. Transformation of **4** into **5** reduced this to a mixture of only 2 separable epimers at C-4 in a ratio of 4:1 (**5d**) and 1:1 (**5e**), respectively.

It should be noticed that compounds **4a**, **4b** and **5a-e**[13] exhibit the same configuration at C-2 and C-6 as starting material **1** even though these two centers can be epimerized. The excellent diastereoselectivity observed for oxygen nucleophiles in forming **4a** and **4b** as unique components could be explained by a reaction under thermodynamic control. This is consistent with the observed configuration as well as the good to poor stereocontrol obtained with the carbon-π nucleophiles.

In conclusion electrochemical halogenation of 2-cyano-6-oxazolopiperidine **1** has opened new synthetic perspectives in the way of bromopiperideine **3** which can be stereoselectively substituted at C-4 particularly with oxygen nucleophiles.

Acknowledgements: The authors wish to thank Professors M.-B. Fleury and H.-P. Husson for their interest in this work and valuable discussions

Table: Addition of nucleophiles to the bromopiperideine **3**.

Entry	Nu	Conditions	4	Yield (%)	5[d]	$[\alpha]_D$ (CH_2Cl_2)	Yield (%)
a	H_2O	Acetic Acid[a] 50 °C (water/ acetone)		85		-236 (c, 1.0)	85
b	MeOH	Acetic Acid[a] 50 °C (MeOH)		82		-223 (c, 1.1)	90
c		$TiCl_4$[b] -20 °C (CH_2Cl_2)		45		-149 (c, 1.2)	77
d		$BF_3.OEt_2$[c] -20 °C (CH_2Cl_2)		62		/	60
e		$BF_3O.Et_2$[c] -20 °C (CH_2Cl_2)		66		/	60

[a] **3** (1 mmol) was dissolved in a mixture of water:acetone 50:50 v/v (3 mL) containing acetic acid (0.6 mL, 10 mmol) and stirred at 50 °C for 2 h. [b] benzylamine ($BnNH_2$) (0.16 mL; 1.5 mmol) was added to a solution (2 mL) of $TiCl_4$ (1 mmol) in CH_2Cl_2. The suspension obtained was stirred at -20 °C. After 1 h, a solution (1 mL) of **3** (92 mg, 0.33 mmol) in CH_2Cl_2 was added. The resulting mixture was stirred at -20 °C for 1 h. [c] $BF_3.OEt_2$ (0.06 mL, 0.33 mmol) was added to a solution (1 mL) of **3** (92 mg, 0.33 mmol) in CH_2Cl_2 containing allyltrimethylsilane (0.1 mL, 0.6 mmol) or α-(trimethylsiloxy)styrene (0.2 mL, 1 mmol). The resulting solution was stirred at -20°C for 3 h. [d] Typical procedure for debromination of compound **4** is as follows: to a solution (10mL) of **4** (0.35 mmol) in toluene were added tributyltin hydride (1 mL, 3.7 mmol) and AIBN (30 mg, 0.2 mmol). The resulting solution was stirred at 60°C for 3 h.

References and notes:

1. Guerrier, L.; Royer, J.; Grierson, D.S.; Husson, H.-P., *J. Am. Chem. Soc.*, **1983**, *105*, 7754-7755.
2. Royer, J.; Husson, H.-P., *Janssen Chimica Acta*, **1993**, *11*, 3-8;
3. Royer, J.; Husson, H.-P., in « Advances in the Use of Synthons in Organic Chemistry » vol 2, Dondoni, A. Ed. Jai Press, London, **1995**, 1-68.
4. Martens, T.; Souquet, F.; Royer, J., *Tetrahedron Lett.*, **1994**, *35*, 6879-6882.
5. Billon-Souquet, F.; Martens,T.; Royer, J., *Tetrahedron.*, **1996**, *52*, 15127-15136.
6. Torii, S.; Inokuchi, T.; Akahasi, F.; Kubota, M., *Synthesis*, **1987**, *28*, 242-245.
7. 2-cyano-6-oxazolopiperidine **1** (1.0g; 4.4 mmol) was dissolved in dry acetonitrile (400 mL) containing lithium perchlorate (2.0g; 20 mmol) as supporting electrolyte and tetraethylammonium bromide (3.6g, 17.1 mmol). The resulting solution was oxidized (i_{ox} = 100 mA), at a platinum electrode (grid, 6 cm diameter), under nitrogen, at 5°C using a two compartments cell. When 5 F/ mol of electricity was passed the solvent was distilled off and the residue was diluted in CH_2Cl_2 (50 mL) and washed with water (2x20 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude product obtained was then purified by flash chromatography (toluene:acetone 95:5) to give the 5,5'-dibromo derivative **2** (1.4g, 3.6 mmol, 82%). To a stirred solution of **2** (1.4g, 3.6 mmol) in THF (10 mL) was added DBU (1.1 g, 7.2 mmol). The mixture was refluxed for 24h. After cooling, the suspension obtained was filtered and the solvent was evaporated under reduced pressure. The residue obtained was then purified by flash chromatography (ether:cyclohexane; 4:6) to give the bromopiperideine **3** (708mg; 2.31 mmol 64% yield from **2**) as a colorless oil. MS m/z 305, 307 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.37 (m, 1H); 2.71 (m, 1H); 3.90 (m, 2H); 4.08 (t, 1H, J = 8.0 Hz); 4.37 (t, 1H, J = 7.8 Hz); 4.79 (bs. 1H); 6.10 (m, 1H); 7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 32.1; 43.1; 63.6; 73.3; 87.4; 115; 117; 126.1; 127.8-130.4; 136.0.
8. Grierson, D.S.; Harris, M.; Husson, H.-P., *J. Am. Chem. Soc.*, **1980**, *102*, 1064-1082.
9. Mangeney, P; Alexakis, A.; Normant, J.-F, *Tetrahedron Lett.*, **1983**, *24*, 373-376. Berlan, J.; Besace, Y., *Tetrahedron.*, **1986**, *42*, 4767-4776.
10. Kasai, M.; Kono, M.; Ikeda, S.; Yoda, N., *J.Org.Chem.*, **1992**, *57*, 7296-7299.
11. Shono, T.; Matsumara, Y.; Tsubata, K., *J. Am. Chem. Soc.*, **1981**, *103*, 1172-1176.
12. Shono, T.; Fujita, T.; Matsumara, Y., *Chemistry Letters*, **1991**, 81-84.
13. **5a:** white crystals: mp 130°C; $[\alpha]_D^{20}$ -276 (CH_2Cl_2, c 1.0); MS m/z 245 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.70 (m, 1H); 1.95 (m, 1H); 2.10 (dd, 1H, J = 14.0, 2.0 Hz); 2.35 (ddd, 1H, J = 14.0, 2.0, 2.0 Hz); 2.70 (bs, 1H, OH, D_2O exchanged); 3.80 (m, 2H); 4.0 (dd, 1H, J = 8.0, 8.0 Hz); 4.30 (dd, 1H, J = 8.0, 8.0 Hz); 4.40 (dd, 1H, J = 3.0, 2.0 Hz); 4.60 (dd, 1H, J = 10.0, 3.0 Hz); 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 34.3; 37.1; 43.6; 63.4; 64.9; 72.8; 85.9; 117; 127.7-129.0; 137.0.
5b: white crystals: mp 160°C; $[\alpha]_D^{20}$ -223 (CH_2Cl_2, c 1.1); MS m/z 259 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.65 (ddd, 1H, J = 14.0, 10.0, 3.0 Hz); 1.85 (ddd, 1H, J = 14.0, 6.0, 3.0 Hz); 2.30 (dd, 1H, J = 14.0, 2.0 Hz); 2.45 (ddd, 1H, J = 14.0, 2.0, 2.0 Hz); 3.40 (s, 3H); 3.80 (m, 3H); 4.0 (dd, 1H, J = 8.0, 8.0 Hz); 4.30 (dd, 1H, J = 8.0, 8.0 Hz); 4.50 (dd, 1H, J = 10.0, 3.0 Hz); 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 30.2; 34.5; 43.6; 56.1; 63.4; 72.8; 73.6; 86.0; 116.5; 127.8-128.8; 137.0.
5c: white hygroscopic crystals: $[\alpha]_D^{20}$ -149 (CH_2Cl_2, c 1.2); MS m/z 334 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.75 (ddd, 1H, J = 14.0, 10.0, 4.0 Hz); 1.95 (ddd, 1H, J = 14.0, 6.0, 3.0 Hz); 2.15 (dd, 1H, J = 14.0, 2.0 Hz); 2.25 (ddd, 1H, J = 14.0, 2.0, 2.0 Hz); 3.35 (dd, 1H, J = 2.0, 2.0 Hz); 3.80 (m, 3H); 3.95 (d, 1H, J = 13.0 Hz); 4.05 (dd, 1H, J = 8.0, 8.0 Hz); 4.25 (dd, 1H, J = 8.0, 8.0 Hz); 4.65 (dd, 1H, J = 10.0, 3.0 Hz); 7.3 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 30.8; 35.2; 43.8; 50.5; 51.3; 63.4; 72.8; 86.0; 117; 127.7-129.0; 136.3; 139.9.
5d: major isomer colorless oil MS m/z 269 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.75 (m, 1H) 2.0 (m, 2H); 2.15 (m, 2H); 2.45 (m, 2H); 3.8 (m, 2H); 4.0 (t, 1H, J = 8.0 Hz); 4.25 (dd, 1H, J = 8.0, 7.0 Hz); 4.35 (dd, 1H, J = 10.0, 3.0 Hz); 5.1 (m, 2H); 5.75 (m, 1H); 7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):30.1; 31.5; 33.5; 37.0; 44.5; 63.6; 72.6; 86.3 117.4; 119; 127.7-135.0; 136.9.
5e: less polar isomer colorless oil MS m/z 347 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.1 (m, 4H); 3.05 (m, 1H); 3.45 (m, 2H); 3.80 (m, 2H); 4.0 (dd, 1H, J = 8.0, 9.0 Hz); 4.3 (dd, 1H, J = 8.0, 9.0 Hz); 4.40 (dd, 1H, J = 10.0, 3.0 Hz); 7.4 (m, 7H); 7.6 (m, 1H); 7.95 (d, 1H, J = 7.0 Hz); 8.05 (d, 1H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 26.6 ; 31.6; 34.1; 41.0; 44.8; 63.7; 72.8; 86.5; 117.6; 124.3-133.6; 136.7; 147.5; 198.1.