Anodic Cyanation of (*S*)-(–)-1-(1-Phenylethyl)piperidine: an Expeditious Synthesis of (*S*)-(+)-Coniine

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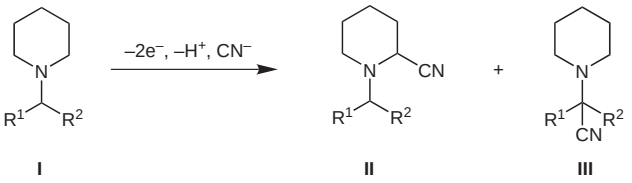
Abstract: A short and efficient asymmetric synthesis of enantiopure (*S*)-(+)-coniine is reported. Anodic cyanation of (–)-1-[(1*S*)-1-phenylethyl]piperidine, derived from [(1*S*)-1-phenylethyl]amine, results in regioselective formation of the corresponding α-aminonitrile, which was alkylated with propyl iodide to give a bifunctional derivative. The latter underwent a stereoselective reductive decyanation (80% de), the product of which was hydrogenolyzed to afforded (*S*)-(+)-coniine (99% ee) with an overall 35% yield from (–)-1-[(1*S*)-1-phenylethyl]piperidine.

Key words: alkaloids, anodic cyanation, alkylation, metallation, stereoselective synthesis

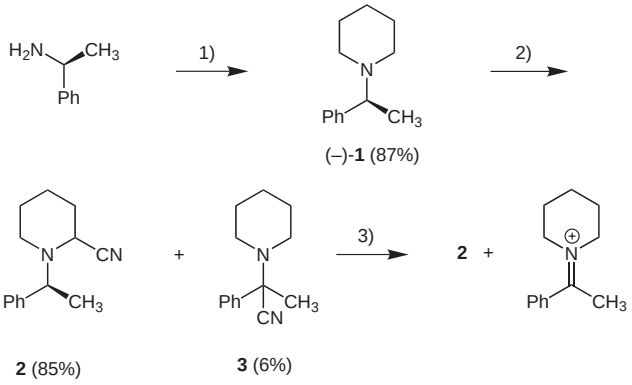
Chiral piperidines constitute the framework of numerous natural products and synthetic substances with important biological activities.[1] Accordingly, the discovery of new synthetic schemes[2] aimed at the elaboration of a new chiral center adjacent to the nitrogen atom is an area of active research. In the last decade, several methods based on the utilization of chiral catalysts[3] have led to the asymmetric synthesis of alkaloids with ee greater than 99%. Despite these successful approaches, synthetic strategies involving the use of auxiliaries derived from the chiral pool play a prominent role. Their success is mainly due to established synthetic methods including diastereoselective addition of organolithium and Grignard reagents to the C=N bond of preformed building blocks,[4] or stereoselective alkylation of chiral dipole-stabilized anions.[5] In this context, α-aminonitriles occupy an interesting position.[6] These synthetic intermediates can serve both as an imine or iminium ion precursor, or on contact with a base can generate a nitrile-stabilized carbanion which can be alkylated with an electrophile. Photochemical[7] or electrochemical[8] oxidation of tertiary amines of the type of **I** is performed under mild conditions and the expected aminonitriles **II** and **III** are obtained in high yields. As shown in Scheme 1 the general absence of regioselectivity in many electrochemical methods[9] has limited its synthetic utility, but sometimes a single ring-cyanated product **II** ($R^1 = C_6H_5$, $R^2 = H$)[10] is detected. A 'retro-Strecker' decomposition of quaternary aminonitriles (**III**) should be taken into account to explain abnormal regioselectivities. These considerations prompted us to investigate the anodic cyanation of (–)-1-[(1*S*)-1-phenylethyl]piperidine (**1**, Scheme 2, $R^1 = C_6H_5$, $R^2 = CH_3$). The objectives were twofold. Firstly, to widen the scope of our electrochemical approach to the regioselective synthesis of aminonitriles **II**; secondly, to evaluate if the electrochemical approach could be efficient for the synthesis of enantiomerically pure 2-alkyl piperidines.



Scheme 1 General oxidation pathway for the anodic cyanation of tertiary amines.

The requisite amine **1** (>99.0% ee) was prepared according to Eguchi's procedure[11] by heating (–)-[(1*S*)-1-phenylethyl]amine with 1,5-dibromopentane in DMSO in the presence of solid K_2CO_3 for 2 hours. (–)-1-[(1*S*)-1-phenylethyl]piperidine (**1**) was obtained in 87% yield after vacuum distillation {$[\alpha]_D^{22}$, –26.55, (*c* 1.45, $CHCl_3$)}.

Prior to macroscale electrolyses, an electrochemical investigation was undertaken. Cyclic voltammetry (CV) was performed at a glassy carbon electrode, peak potentials were expressed in V/SCE; **1** was dissolved (20 mmol/L) in a solution of $LiClO_4$ (15 g/L) in the presence of 6 equivalents of NaCN. A first irreversible oxidation peak



Scheme 2 Synthesis of α-aminonitrile **2** from (–)-[(1*S*)-1-phenylethyl]amine. *Reagents and conditions*: 1) 1,5-dibromopentane (1.2 equiv), DMSO, K_2CO_3 (3 equiv) 100 °C, 2 h; 2) $–2e^-$, $–H^+$, NaCN (6 equiv), MeOH/$LiClO_4$ (15 g/L), MeONa (6 equiv); 3) 50 °C, 45 min.

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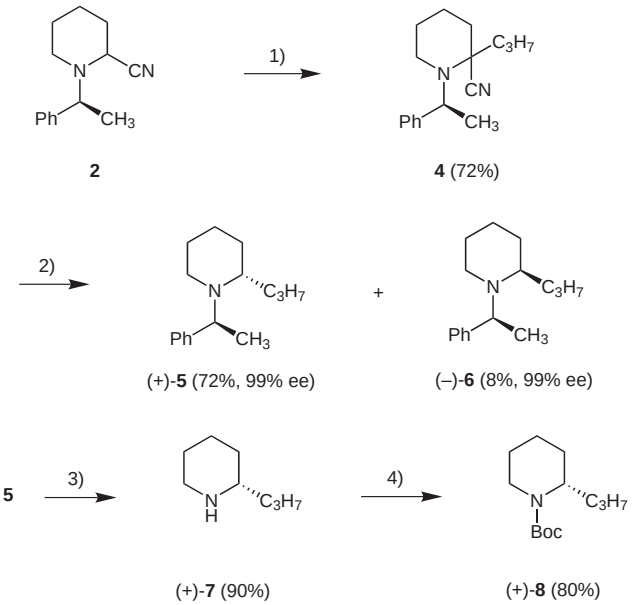
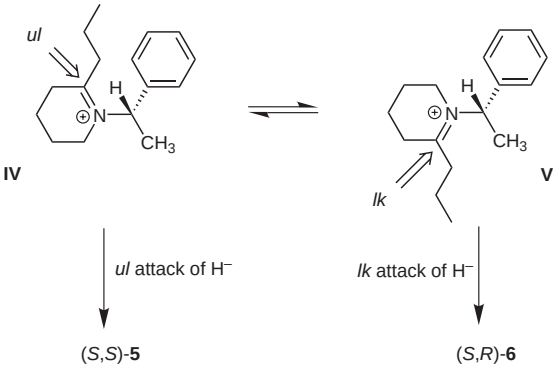
was recorded at *E*pa1 = +1.0 V/SCE, while a second ill-defined wave was found at *E*pa2 = +1.45 V/SCE. These observations suggest that a selective transformation could be performed at the first oxidation peak. Electrolyses were conducted at controlled potential (E = +1.0 V/SCE) in a non-divided cell at a vitreous carbon electrode (diameter = 100 mm, Carbone Lorraine®) as anode and a carbon rod as cathode. For the synthesis of α-aminonitrile **2** a set of conditions was investigated. First trials were made in the presence of 6 equivalents of NaCN and in the absence of added base. The electrolysis was monitored by CV and by gas chromatography. GC analysis of the crude reaction mixture indicated the formation of α-aminonitrile **2** together with its regioisomer **3**, in a (93:7) ratio. In connection with the amount of electricity that was consumed during the electrolysis (up to 4 F/mol) it was assumed that a redox reaction between the nitrogen-centered radical cation and cyanide anions took place.[12] To overcome this drawback, 6 equivalents of sodium methylate (formed in situ by the addition of Na) were added in the electrolysis medium. Under these more basic conditions the intermediate radical cation was readily deprotonated and the electrolysis consumed 2.1 F/mol of amine and the current efficiency was 85%. In this way, α-aminonitriles **2** and **3** were obtained in a satisfactorily 91% yield after filtration over a silica column. α-Aminonitrile **3** eluted first, followed by the ring-cyanated adduct **2**, which was obtained as a mixture of diastereomers (1:1). The ^{13}C NMR spectrum of **2** contains a set of four independent resonance lines between δ = 46.07 and 52.12 ppm which were attributed to the N–CH and N–CH_2 carbon atoms. After several experiments, optimized reaction conditions were founded. Heating (55 °C, 45 min) the electrolysis medium, in which an equal amount of water has been added, led to the unexpected disappearance of the unwanted α-aminonitrile **3**. As shown in Scheme 2, it seemed likely that **3** is more prone to the 'retro-Strecker' decomposition than its endocyclic conterpart.[13] In this way, compound **2** was obtained cleanly and reproducibly on a 15 g scale in a 85% yield. To further illustrate the advantages of our synthetic approach, we turned to coniine[14] (the toxic hemlock alkaloid) whose simple structure is an attractive target to test asymmetric methodologies.[15] Alkylation of the anion of **2** [LDA (1.1 equiv); THF, –80 °C, then 0 °C] with propyl iodide provided the substitution product **4** (72% yield, 9:1 mixture of diastereomers). Reductive decyanation was made in the presence of an excess of $NaBH_4$ (4 equiv) in EtOH at 0 °C, to produce amines (+)-**5** and (–)-**6** which were obtained in a 72% and 8% yield, respectively (Scheme 3). Interestingly, these two diastereomers could be easily separated over a silica column using a mixture of diethyl ether and petroleum ether (9:1) as eluent. Major 2*S*-diastereomer {$[\alpha]_D^{22}$ +10.4, (*c* 2.83, $CHCl_3$); lit.[16] $[\alpha]_D^{26}$ +14.0, (*c* 0.86, $CHCl_3$)} eluted first, followed by the more polar 2*R*-diastereomer {$[\alpha]_D^{22}$ –60.8, (*c* 1.08, $CHCl_3$). Optical purity of (+)-**5** was checked by GC on a CP-Chirasil-Dex CB column and showed to be greater than 99%. The formation of (+)-**5** can be understood when considering the prior formation of the iminium intermediate **IV** (Scheme 4) in which steric interactions between the propyl chain and the chiral appendage are minimized. The subsequent hydride delivery from the least hindered *ul* face produced the major 2*S*-diastereomer.



Scheme 3 Synthesis of (*S*)-(+)-Boc-coniine (**8**) from α-aminonitrile **2**. *Reagents and conditions*: 1) LDA, (1.15 equiv), THF, –80 °C to 0 °C, C_3H_7I, –80 °C to 0 °C; 2) $NaBH_4$, (4.0 equiv), EtOH, 0 °C; 3) H_2, Pd/C (10%), MeOH, 48 h; 4) $(Boc)_2O$ (1.1 equiv), $[(CH_3)_2CH]_2NC_2H_5$, (3 equiv), MeCN, 80 °C, 2 h.

Interestingly, this result (80% de) is in keeping with that reported by Shipman et al.[16] In their approach, 1-[(1*S*)-1-phenylethyl]-2-methylaziridine was utilized as substrate to introduce chirality for the synthesis of (*S*)-(+)-coniine. In the final reductive step, the same chiral iminium system **IV** was postulated to explain the high level of diastereocontrol (97% de) for the formation of (+)-**5**.



Scheme 4 Mechanistical rationales for the diastereoselectivity.

Hydrogenolysis of the chiral appendage afforded optically pure (*S*)-(+)-coniine (**7**) in 90% yield after chromatographic purification over a silica column (Et_2O saturated with gaseous NH_3). The optical rotation of the hydrochloric salt of our synthetic coniine was dextrorotatory and

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was consistent with those reported in the literature {(*S*)-(+)-coniine·HCl, $[\alpha]_D^{22}$ +7.5, (*c* 1.46, EtOH); lit.[16] $[\alpha]_D^{20}$ +8.1, (*c* 1.0, EtOH)}. In a similar fashion, the *N*-Boc-protected (*S*)-(+)-coniine (**8**) {$[\alpha]_D^{22}$ +30.0, (*c* 1.34, $CHCl_3$); lit.[3a] $[\alpha]_D^{26}$ +29.8, (*c* 1.45, $CHCl_3$)} matched in all aspects with the spectral data reported in the literature.

In conclusion, an efficient process (5 steps, 35% overall yield) to (*S*)-(+)-coniine starting from commercially available [(1*S*)-1-phenylethyl]amine is described. A clean and scalable electrochemical process was effective for the preparation of a chiral non-racemic aminonitrile derivative in high yield. The latter has been used in a classical alkylation–reduction process, to synthesize optically pure unnatural (*S*)-(+)-coniine. Further developments of this methodology will be reported on due course.

Typical Procedures

1-[(1*S*)-1-phenylethyl]piperidine-2-carbonitrile (2)

Compound (+)-**1** (3.0 g, 15.9 mmol) was dissolved in MeOH (150 mL) in the presence of $LiClO_4$ (1.5 g) and 4.66 g (6 equiv) of NaCN. Then, 2.19 g (6 equiv) of Na (cut into small cubes) were dissolved in the electrolysis medium. When all the Na had reacted, the resulting solution was transferred in a non-divided cell equipped with a vitreous carbon electrode (diameter 100 mm, Carbone Lorraine®) as anode and a carbon rod as cathode. The working potential was adjusted to +1.0 V/SCE. After the consumption of 3200 C, the electrolysis was stopped and 150 mL of H_2O (**Caution**: $LiClO_4$ may lead to severe explosions when evaporated to dryness) were added to the solution, which was evaporated under reduced pressure at +50 °C. The resulting aqueous phase was extracted with Et_2O (2×100 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by silica gel chromatography (PE–Et_2O, 9:1) to give aminonitrile **2** (2.72 g, 85% yield, yellow oil) as a mixture (1:1) of diastereomers: R_f = 0.35 (PE–Et_2O, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (d, ^3J = 6.65 Hz, 3 H), 1.36 (^3J = 6.50 Hz, 3 H), 1.40–2.00 (m, 12 H), 2.14 (td, $^2J = {}^3J$ = 12.00 Hz, ^3J = 2.80 Hz, 1 H), 2.33 (td, $^2J = {}^3J$ = 11.60 Hz, ^3J = 2.7 Hz, 1 H), 2.60 (dm, ^2J = 11.50 Hz, 1 H), 3.19 (dm, ^2J = 12.3 Hz, 1 H), 3.46 (q, ^3J = 6.60 Hz, 1 H), 3.51 (q, ^3J = 6.60 Hz, 1 H), 3.56–3.59 (m, 1 H), 4.21–4.24 (m, 1 H), 7.21–7.35 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.47, 20.66, 21.01, 21.47, 25.06, 25.27, 28.79, 29.11, 45.58, 48.10, 49.55, 51.62, 62.98, 63.11, 116.87, 117.04, 127.05, 127.10, 127.17, 127.49, 128.49, 128.74, 143.82, 144.70. HRMS (EI): *m/z* calcd for $C_{14}H_{18}N_2$ [M^+]: 214.1470; found: 214.14802. GC: t_R = 3.04 min (200 °C).

1-[(1*S*)-1-phenylethyl]-2-propylpiperidine-2-carbonitrile (4)

To a THF solution (20 mL) containing 2.25 mL (1.62 g, 1.5 equiv) of diisopropylamine at –80 °C were added (by syringe) 6.10 mL (12.20 mmol) of *n*-BuLi (2 M). The solution was stirred at that temperature for 30 min and was warmed up to 0 °C for 30 min. The resulting LDA solution was transferred (by syringe) to a THF solution (20 mL) cooled at –80 °C containing the aminonitrile **2** (2.30 g, 10.70 mmol). The solution was allowed to warm up to –15 °C for 90 min to afford a yellow anion solution. The solution was cooled at –80 °C and *n*-iodopropane (1.25 mL, 12.80 mmol) was added. The reaction mixture was stirred at that temperature for 90 min and at 0 °C overnight. THF was evaporated in vacuo and the residue was purified by silica gel chromatography (PE–Et_2O, 8:2) to give aminonitrile **4** (1.95 g, 72% yield, yellow oil) as a mixture (9:1) of diastereomers. R_f = 0.8 (PE–Et_2O, 8:2).[17] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.3 Hz, 3 H), 1.20–2.05 (m, 13 H), 2.50–2.52 (m, 2 H), 4.47 (q, ^3J = 6.8 Hz, 1 H), 7.25–7.46 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.16, 14.37, 16.78, 22.29, 25.46, 36.26, 40.23, 42.74, 53.46, 59.76, 122.06, 126.50, 127.05, 128.11, 144.27. HRMS (EI): *m/z* calcd for $C_{17}H_{24}N_2$ [M^+]: 256.1939; found: 229.18305 [M – HCN^+]. GC: t_R = 4.33 min (200 °C). Anal. Calcd for $C_{17}H_{24}N_2$: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.74; H, 9.39; N, 10.94.

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(17) Aminonitrile **3** readily decomposed on TLC plate, R_f value is given for guidance.

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