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Synthesis of Tetrahydroisoquinoline Alkaloids via Anodic Cyanation as the Key Step

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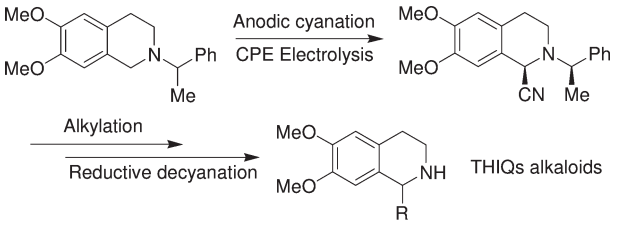

We report a new route to tetrahydroisoquinoline (THIQ) alkaloids involving the alkylation of α-aminonitrile **2** as a key step. The latter compound was prepared by anodic cyanation of the corresponding tertiary amine **1**. Reductive decyanation of α-aminonitriles **6a−c** proceeded diastereoselectively (up to 95% de) to deliver the C1-substituted alkaloids precursors **9a−c**. The syntheses of (±)-carnegine, (±)-norlaudanosine, and (±)-*O*,*O*-dimethylcoclaurine have been achieved.

Nitrogen oxidation that proceeds through a single electron transfer (SET) mechanism is an ubiquitous process that is found in the biosynthetic pathway of alkaloids. In organic synthesis, SET reactions can be effected by one-electron oxidants,[1] photochemically,[2] or electrochemically.[3−8] In the first step, one electron is removed from the substrate to yield a radical cation that is deprotonated,[4−7] desilylated,[9] or decarboxylated[8] to yield an α-amino radical, which is readily oxidized to produce an immonium ion which is trapped in situ by a variety of nucleophiles (Nu) to form stable α-alkoxylated (Nu = OR) or α-acyloxylated (Nu = OCOR) products. In this context, the photochemical[10] or electrochemical[11] direct synthesis of α-aminonitrile systems has occupied an interesting, although often understated position in organic chemistry. In that case, stronger nucleophiles such as cyanide anions intervene in the SET process to intercept the unstable iminium cation to yield the stable α-aminonitrile compound. Despite its synthetic utility this process has received little attention due to a general lack of regioselectivity. Indeed, oxidation of nonsymmetrical amines can give rise to two different iminium species (Scheme 3) and hence two regioisomers.[11e]

In a series of papers, we have shown that problems associated with the nonselective deprotonation at both the *N*-CH positions can be avoided by the right selection of amine *N*-substituent.[11c,d] As a part of our program in the elaboration of new α-aminonitrile systems, we became interested in the anodic cyanation of tetrahydroisoquinoline **1** (Scheme 1). If successful, this strategy would provide a new pathway for the synthesis of C1-substituted tetrahydroisoquinolines (THIQs).[12] However, several questions about the electrochemical behavior of **1** needed to be addressed. First, the anodic oxidation reaction could lead to the formation of a radical cation that could arise from the nitrogen atom or from the electron-rich catechol moiety.[13] In other words, can the electrode act as a selective oxidant so that a single product

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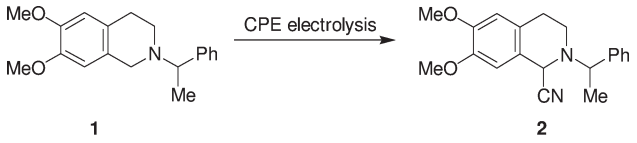
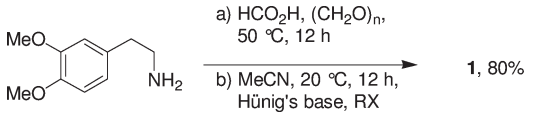
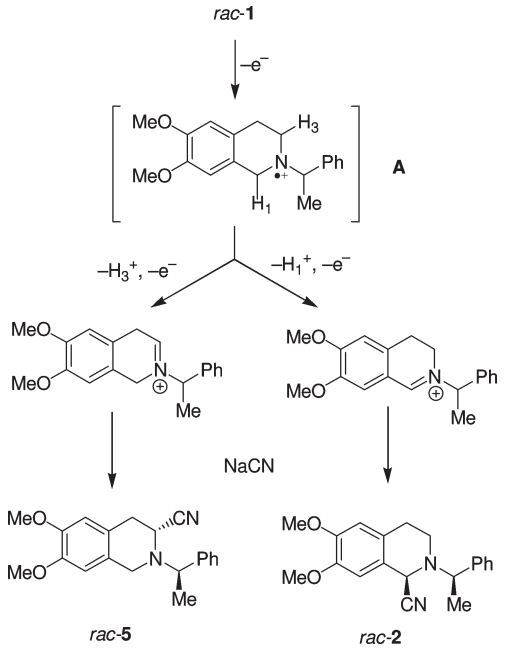
SCHEME 1. Electrochemical Synthesis of α-Aminonitrile 2



SCHEME 2. Synthesis of THIQ 1



SCHEME 3. Electrochemical Pathway for the Formation of α-Aminonitriles 2 and 5



could be formed during the anodic process? Second, the regiochemical preferences for the deprotonation step (i.e. at C1, C1′, or C3) under our electrolysis conditions are unknown. We were also curious to investigate the influence of the asymmetric carbon on the stereochemical outcome of the subsequent chemical manipulations.[14] With these questions in mind, we report here the electrochemical synthesis of α-aminonitrile **2**, and its use in the synthesis of C1-substituted THIQs. In this study, all compounds are racemic, and all the stereogenic centers are represented in a relative configuration.

As outlined in Scheme 2, our synthesis began with the Pictet−Spengler cyclization of homoveratrylamine according to the protocol described by Fukuyama.[15] The intermediary tetrahydro-6,7-dimethoxyisoquinoline was then condensed with 1.1 equiv of (1-bromo)ethylbenzene to form **1** in an overall 80% yield.

Analytical Study and Anodic Cyanation. Then, an analytical study was carried out at a vitreous carbon electrode at a sweep rate of 50 mV s^{-1}. Peak potentials expressed in V vs SCE are collected in Table 1. THIQ **1** (20 mmol L^{-1}) was dissolved in a 0.1 M $LiClO_4$ in MeOH electrolyte solution. In the absence of NaCN, compound **1** displayed two successive irreversible peaks at *E*pA = +0.90 V and *E*pB = +1.30 V (entry 1, Table 1). After the addition of 4 equiv of NaCN per mol of substrate, two successive distinct irreversible peaks were recorded at *E*pA = +0.95 V and *E*pB = +1.30 V (entry 2, Table 1).

TABLE 1. Peak Potentials from Cyclic Voltammograms of Compounds 1, 3, and 4

entry	compd	*E*pA	*E*pB
1	**1**	+0.90[a]	+1.30[a]
2	**1**	+0.95[b]	+1.30[b]
3	**3**	+0.95[a]	
4	**4**	+1.45[a]	

[a]In the absence of NaCN. [b]In the presence of 4 equiv of NaCN.

TABLE 2. Anodic Cyanation of THIQ 1

entry	compd (mmol/L)	NaCN (equiv)	products[a,b]	AcOH (equiv)	yield (%)[b]
1	4	6.0	**2**		75
2	30	6.0	**2** (9); **5** (1)		50
3	22	2	**2**		75
4	22	2.5	**2**	0.5	85

[a]The regioisomer ratios are in parentheses and were determined by integration of the ^{1}H NMR signals in the crude precipitate. [b]Yield represents a mass balance of the isolated regioisomers. In all cases the electrolyses went to completion.

Previous studies in our laboratory have shown that the first oxidation peak was attributable to the oxidation of the amine into the corresponding iminium cation, while the second oxidation peak could be attributed to the oxidation of the catechol moiety. As a confirmation, the first oxidation peak was present in the voltammograms of 2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (**3**) (*E*pA = +0.95 V, entry 3, Table 1) and the second one was recorded for veratrole (**4**) (*E*pB = +1.45 V, entry 4, Table 1).[13e] Then, the anodic cyanation of **1** was first effected on a 4 mmol L^{-1} scale (entry 1, Table 2) in an undivided cell with a vitreous carbon anode (see the schematic diagram in the SI), at a controlled potential of +0.95 V vs SCE. Amine **1** was dissolved in a 0.1 M $LiClO_4$ in MeOH electrolyte solution in the presence of 4 equiv per mol of NaCN. After the consumption of 2.1 F/mol of substrate, the completion of the reaction was attested by the disappearance of the first oxidation peak and workup afforded the ring cyanated product **2** (75%) after crystallization in hot ethanol. Single crystals were also obtained in this way, and the X-ray diffraction study revealed the presence of a single diastereoisomer, the configuration of which was found to be *R**,*R**. Surprisingly, when the ^{1}H NMR spectrum of these crystals was recorded in $CDCl_3$ we noticed the presence of two diastereoisomers in a 42/58 ratio. This observation pointed out that **2** exists in a single configuration in the solid state and it was also felt that epimerization of C1 may take place rapidly in $CDCl_3$. Indeed, when the ^{1}H NMR spectrum of **2** was recorded in [D_6]benzene, within 5 min, we observed the presence of a single adduct as shown by the presence of one singlet resonance signal at δ 4.73. We can observe that a slow epimerization also occurred in [D_6]benzene. After standing for 48 h at 25 °C in this solvent, the sample was analyzed and found to be a mixture (45/55) of two diastereoisomers as shown by the presence of an additional singlet resonance signal at δ 5.12. The subsequent electrolyses were carried out at higher NaCN and

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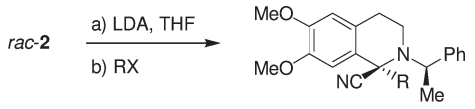
TABLE 3. Synthesis of α-Aminonitriles 6a−c



rac-**6a-c**

entry	RX, equiv	product, % yield[a]	% de[b]
1	MeI, 2.0	**6a**, 40	80
2	MeI, 6.0	**6a**, 67	80
3	4-MeO-Ph-CH_2Br (**7**), 1.5	**6b**, 77	80
4	3,4-$(MeO)_2$-Ph-CH_2Br (**8**), 1.5	**6c**, 75	80

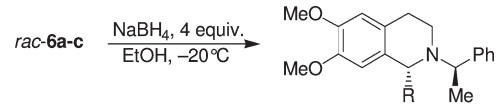
[a]Yields are of isolated products after crystallization in ethanol. [b]Determined by ^{1}H NMR spectroscopy.

amine concentration values (up to 30 mmol/L, entry 2, Table 2) and failed to reproduce the first results. Yields were generally lower and ring cyanated products **2** and **5** were obtained as a mixture (9/1) of regioisomers which could not be separated by column chromatography. Fortunately, after several chemical manipulations (for a detailed procedure, see the SI) α-aminonitrile **5** could be obtained as colorless plates. An X-ray diffraction experiment revealed an *R**,*R** relative configuration of both the stereogenic centers.

The product distribution **2**/**5** provided a direct indication of the site of deprotonation of the intermediary radical cation **A** (Scheme 3). Albeit obtained in low yields, the presence of the unwanted regioisomer **5** in the crude reaction mixture suggests that a competitive kinetic deprotonation occurred at C3 in the presence of a high concentration of NaCN or in the presence of an electrogenerated base produced at the cathode. With this in mind, the reaction conditions were altered in order to increase the **2**/**5** ratio. This was first accomplished by decreasing the concentration of NaCN. Indeed, when the reaction was allowed to proceed in a 20 mmol L^{-1} scale in the presence of 2.0 equiv of NaCN, the adduct **2** was obtained as a sole product in 75% yield (entry 3, Table 2). Finally, the addition of 0.5 equiv of AcOH (entry 4, Table 2) led to the formation of **2** in an improved 85% yield. Under these reaction conditions, it seemed likely that the HCN/CN^- buffer system should balance the excess of base that was produced at the cathode. In addition, one cannot exclude the formation of an intermediary unstable N−O geminated compound that results from the reversible condensation between MeOH and the iminium cation.[18]

Alkylation. The condensation of the lithiated α-aminonitrile **2** with requisite alkyl halides is the key step in our synthetic approach (Table 3). The lithiation procedure was carried out at a temperature of −80 °C by the slow addition of a solution of 1.3 equiv of LDA (prepared from *n*-BuLi 2.5 M and diisopropylamine) on a stirred suspension of α-aminonitrile **2** in anhydrous and oxygen free THF. Then, the clear red anion solution was allowed to warm to −20 °C over a 2 h period, and the electrophiles were added at a temperature of −80 °C. After workup, the α-aminonitriles **6a−c** were obtained in yields ranging from 67% and 77%. When 2 equiv of iodomethane was introduced onto the intermediary α-amino carbanion (entry 1, Table 3), the yield was poor (30−40%). However, addition of a large excess (6 equiv) of iodomethane (entry 2, Table 3) gave the C1-methyl product **6a** as a yellow powder in an improved 67% yield.[19]

TABLE 4. Reductive Decyanation of α-Aminonitriles 6a−c



rac-**9a-c**

entry	product	% yield[a]	% de[b]
1	**9a**, R = Me	76	98
2	**9b**, 4-MeO-Ph-CH_2	85	80
3	**9c**, 3,4-$(MeO)_2$-Ph-CH_2	88	80

[a]Yields are of isolated products after column chromatography. [b]Determined by ^{1}H NMR spectroscopy.

Interestingly, single crystals could be obtained from a slow crystallization in ethanol and the X-ray diffraction study revealed a *R**,*R** configuration of the two stereogenic centers. Having successfully installed a methyl group at the C1 carbon atom we turned our efforts to the synthesis of α-aminonitriles **6b**,**c**, which are potential precursors of *O*,*O*-dimethylcoclaurine and norlaudanosine, respectively. This involved the condensation of the benzyl bromides **7** and **8** which were readily prepared by reacting the corresponding alcohols with PBr_3 according to a modified version of the Van Vranken's procedure.[16] Treatment of the anion solution of **2** with a THF solution of bromide **7** afforded the bifunctional α-aminonitrile **6b** as a yellow powder in a 77% yield. Likewise, the alkylation of **2** with bromide **8** afforded the adduct **6c** as a yellow powder in a 75% yield. Single crystals of adducts **6b** and **6c** were obtained from a slow crystallization in ethanol, and the X-ray diffraction studies revealed that these adducts displayed a *R**,*R** relative configuration.

Reductive Decyanation. The reductive decyanation of α-aminonitrile systems is a common procedure that consists of the neat replacement of the cyano group by a hydrogen atom. According to the reducing agent, the reaction proceeds through a ionic or a radical pathway.[17] In the first mode of reactivity, the α-aminonitrile yields an iminium cation that is reduced in situ by a variety of hydride donors such as $NaBH_4$,[20] BH_3,[21] $AgBF_4$/$Zn(BH_4)_2$,[22] $NaBH_3CN$,[23] or $NaBH(OAc)_3$.[24] In the second mode, the α-aminonitrile is reduced by a two-electron-transfer mechanism involving Li/NH_3,[25] Na/NH_3,[26] or LiDBB[27] as reducing agents. Therefore, the reduction of α-aminonitriles **6a−c** was carried out at −20 °C in ethanol in the presence of 4 equiv of $NaBH_4$; results are collected in Table 4. THIQ **9a** was

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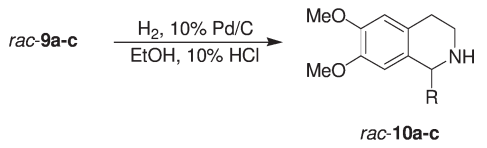
TABLE 5. Hydrogenolysis of THIQs 9a−c



entry	product	% yield[a]
1	**10a**, R = Me	95
2	**10b**, 4-MeO-Ph-CH_2	80
3	**10c**, 3,4-$(MeO)_2$-Ph-CH_2	90

[a]Yields are of isolated products after column chromatography.

obtained as a single diastereoisomer as evidenced by the presence of a set of 18 independent resonance lines in the ^{13}C NMR spectrum. Likewise, the ^1H NMR spectrum exhibits two distinct doublet systems at δ 1.31 and 1.38 ppm. However, the relative configuration of the stereogenic centers could not be determined from the ^1H NMR spectrum. Similarly, compound **9b** was obtained as a solid in an improved 85% yield but in a lower diastereoselectivity (80% de). Fortunately, single crystals were obtained from a slow crystallization of **9b** in ethanol and the subsequent X-ray diffraction study revealed that compound **9b** displayed a *R**,*R** relative configuration.

Hydrogenolysis. In the last step, a selective catalytic hydrogenolysis of benzylic amines **9a−c** was cleanly achieved in the presence of 10% Pd/C in a mixture of ethanol and hydrochloric acid under 3 atm of H_2. After workup, THIQs **10a−c** were obtained in yields ranging from 80% to 95% (Table 5).

A reliable route to THIQ alkaloids (±)-carnegine (32%), (±)-norlaudanosine (40%), and (±)-*O*,*O*-dimethylcoclaurine (35%) has been developed from homoveratrylamine. In this process, the α-C1H bond of the THIQ nucleus has been activated regioselectively by a SET process to produce a stable α-aminonitrile system that serves to construct the new C1−Cα bonds.

Experimental Section

2: THIQ **1** (2.0 g, 6.72 mmol) was dissolved in a 0.1 M $LiClO_4$ in MeOH electrolyte solution (0.3 L), in the presence of 0.82 g (16.73 mmol) of NaCN and 0.19 mL (0.19 g, 3.32 mmol) of glacial acetic acid. The working potential was adjusted to +1.0 V/SCE and after the consumption of 1360 C (2.1 F/mol), the electrolysis was stopped. Then, water (150 mL) was added (Caution: $LiClO_4$ may lead to severe explosions when the material is evaporated to dryness; the cyanide anions were destroyed by the addition of an excess of $KMnO_4$; due to the possible release of HCN, the electrolyses should be carried out under a well-ventilated hood) and methanol was evaporated under reduced pressure at +50 °C. The resulting aqueous phase was extracted with dichloromethane (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting white solid was triturated with diethyl ether and was recrystallized from 50 mL of hot ethanol to give 1.87 g (86%) of **2** as crystalline white powder. Colorless plates, mp 172−174 °C (ethanol); R_f (diethyl ether/petroleum ether, 70:30) 0.3. ^1H NMR (C_6D_6, 500 MHz) δ 1.37 (d, J = 6.5 Hz, 3 H), 2.46 (dd, J = 16.5, 3.5 Hz, 1 H), 2.79 (td, J = 11.8, 3.8 Hz, 1 H), 2.96 (ddd, J = 16.5, 11.8, 6.3 Hz, 1 H), 3.15 (s, 3 H), 3.21 (ddm, J = 11.8, 6.3 Hz, 1 H), 3.46 (s, 3 H), 3.97 (q, J = 6.5 Hz, 1 H), 4.73 (s, 1 H), 6.12 (s, 1 H), 6.42 (s, 3 H), 7.20 (tt, J = 6.8, 1.5 Hz, 1 H), 7.29, (tm, J = 6.8 Hz, 2 H), 7.55 (dm, J = 6.8 Hz, 2 H) ppm. ^{13}C NMR (C_6D_6, 125 MHz) δ 21.7, 28.6, 42.8, 54.1, 55.2, 55.3, 62.1, 110.1, 112.0, 117.1, 122.1, 126.3, 129.1, 143.9, 148.7, 149.91 ppm. HRMS ($C_{20}H_{22}N_2O_2$ [M^+]) calcd 322.1681, found 322.1679. $C_{20}H_{22}N_2O_2$: calcd C 74.51, H 6.88, N 8.69; found C 74.29, H 6.82, N 8.74.

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Supporting Information Available: General procedures for the synthesis of compounds; ^1H NMR and ^{13}C NMR spectra of **1**, **2**, **5**, **6a−c**, **7**, **8**, **9a−c**, and **10a−c**; crystallographic data of **2**, **5**, **6a−c**, and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.