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Dedicated to the memory of Professor Margareta Avram on the remembrance of her 100th anniversary

RuO_4-MEDIATED OXIDATION OF TERTIARY AMINES. STEREOELECTRONIC EFFECTS

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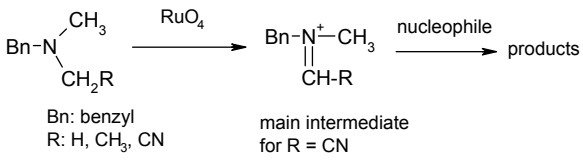
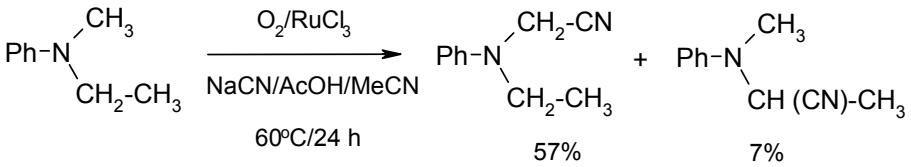
Tertiary amines like $PhCH_2$-NMe-CH_2R (R = H, Me, CN) underwent RuO_4-mediated oxidation by attack at all three *N*-α-positions. The various reaction products were classified in three groups, according to the functionalized site: methylic, benzylic or methylenic (CH_2R). The respective sums of yields were calculated, as well as the relative regioselectivities *Me/Bn* and *CH_2/Bn*. The least attacked was the benzylic position and the most preferred was the methylenic CH_2CN one. The implied stereoelectronic effects were discussed.



INTRODUCTION

Ruthenium-based catalysts (including ruthenium tetroxide) were often used to oxidize various organic compounds, from aromatics to alcohols or amines.[1–6] Electrophilic RuO_4 prefers to attack sp^3 C-H bonds in α to a heteroatom, like those in amines of general structure RCH_2-NR^1R^2. Primary amines (R^1=R^2=H) underwent oxidation to nitriles or amides,[1,4] but secondary amines (R^1=H) were transformed in imines (RCH=NR^2).[7,8] Tertiary amines were oxidized to iminium ions (RCH=$N^+R^1R^2$), which were further trapped by nucleophiles.[9–14] In this last case, amides (RCO-NR^1R^2) resulted with water as a nucleophile, but α-aminonitriles [RCH(CN)-NR^1R^2] were formed if a cyanide ion is present.

When R^1 and/or R^2 substituents in the amine RCH_2-NR^1R^2 have hydrogens in α to N, oxidative competition between all these methylene groups can occur. This was proven by us with tertiary cyclic[10] or acyclic amines.[11] At the same time, *N*-ethyl-*N*-methylaniline underwent ruthenium-catalyzed oxidation, in the presence of cyanide, mainly by attack at the methyl group[13] (Scheme 1). This regioselectivity was assigned to a steric inhibition by the methyl group of the ethyl substituent.



Scheme 1

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In continuation of our studies on the regioselectivity in the RuO_4-mediated oxidation of tertiary amines,[10–12,14] we decided to study the behaviour of three *N*-alkyl-*N*-methylbenzylamines (**1a-c**, Scheme 2). These substrates have three types of *N*-CH_2 groups prone to be oxidized: methylic, benzylic, and the so-called methylenic (CH_2R). According to the nature of R, the compounds **1b-c** can be viewed as deriving from **1a** (R=H) by changing R either by an electron-donating group (CH_3 in **1b**) or by an electron-withdrawing substituent (CN in **1c**). The influence of R on the oxidation's regioselectivity is presented and discussed in this paper.

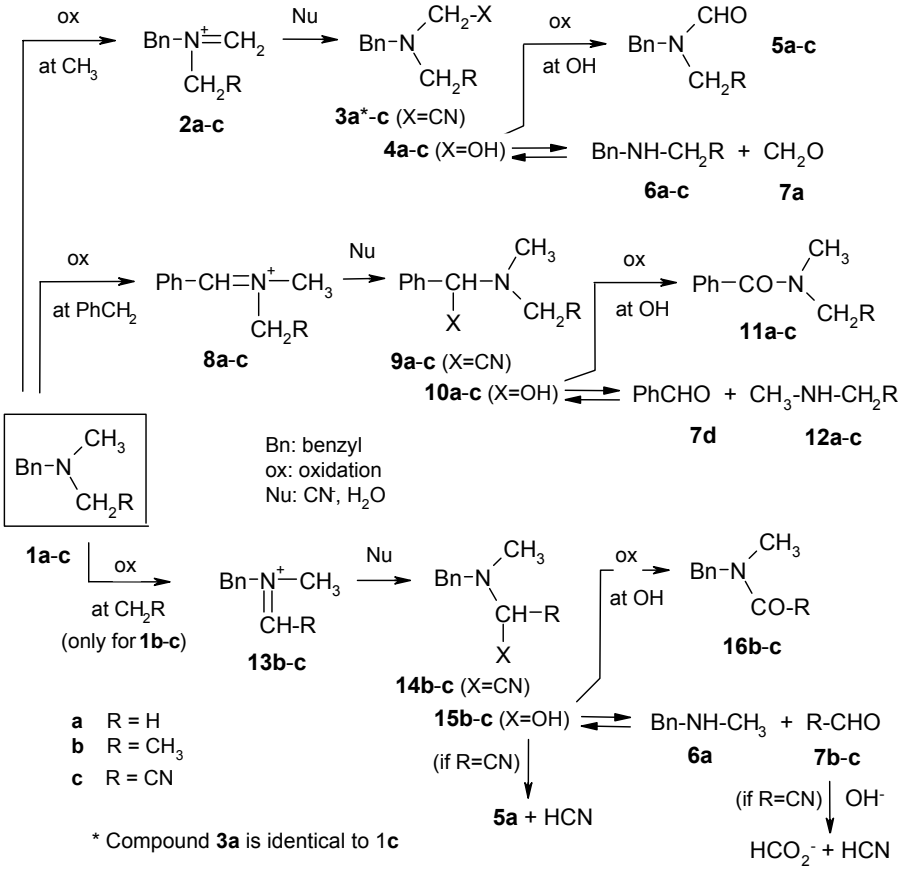
RESULTS AND DISCUSSION

Although the oxidation of **1a** was already studied by us,[11] we repeated it in the new reaction conditions adopted for **1b-c**. Formation of the primary oxidation products is presented in Scheme 2. Since the regioselectivity cannot be calculated for the oxidations without cyanide,[11] we only considered the reactions made in the presence of cyanide. All the results are summarized in Table 1. As in our preceding papers,[7,8,10–12,14] the amount of benzaldehyde (**7d**) in Table 1 includes that of benzoic acid. This is allowed because **7d** is the unique source of benzoic acid.

The last column of Table 1 contains the regioselectivities of the oxidation reactions. Since the benzylic position of **1a–c** was the least attacked, the regioselectivities for methylic and methylenic (CH_2R in Scheme 2) sites were calculated relatively to it. In the corresponding formulas (see below), the amount of a particular compound, taken from Table 1, is written as the compound number in square brackets. When followed by "t" or "react" subscript, the respective amount refers to the "total" or "reacted" amount of the considered compound.

Oxidation of N,N-dimethylbenzylamine (1a)

Oxidative attack at the methyl group of **1a** gives the iminium ion **2a**. Trapping of **2a** by the two nucleophiles present in excess, cyanide ion and water molecule, forms the α-aminonitrile **3a** and the hemiaminal **4a**, respectively. Intermediate **4a** is oxidized further to the formamide **5a**. Alternatively, since **4a** is the adduct of an amine with formaldehyde, it can be split back into a stoichiometric mixture of **6a** and **7a**.



Scheme 2

Table 1

RuO_4-mediated oxidation of **1a-c**

Nr.	Substrate (conv., %)[a]	Reaction products[b] (molar yields, %)[c]	Regioselectivity *RS*[d]
0	1	2	3
1.	**1a** (75)	**3a** (80), **5a** (1), **6a** (3), **7d** (1), **9a** (13.5)	*Me*/*Bn* = 1.9 CH_2/*Bn* = 1.9
2.	**1b** (64)	**3a** (1), **3b** (38.1), **5a** (0.5), **5b** (2.8), **6a** (5.5), **6b** (6.1), **7d** (2.6), **9b** (14.3), **11b** (0.5), **14b** (22.1), **16b** (0.2), **18a** (0.5), **18b** (0.4)	*Me*/*Bn* = 1.7 CH_2/*Bn* = 1.6
3.	**1c** (9)	**3c** (21.5), **5a** (16), **5c** (4.6), **6a** (6), **6c** (5.6), **7d** (4.9), **9c** (6.5), **11c** (0.4), **14c** (21), **16c** (5.5), **18a** (0.3), **20a** (0.8), **20c** (0.9)	*Me*/*Bn* = 1.6 CH_2/*Bn* = 3.6

[a] Conversion is calculated against the reacted substrate. [b] Formulae are given in Schemes 2 (**1**-**16**) and 3 (**17**-**20**). Compound **3a** is identical to **1c**. [c] Yields are calculated as moles against the reacted substrate, considered as 100 moles. [d] Regioselectivities (*RS*) were calculated with equations 1-13.

At the same time, the oxidant can attack also the benzylic position of **1a**. The iminium ion **8a** thus formed can suffer nucleophilic attack by CN^- and H_2O, as described before, to form α-aminonitrile **9a** and the hemiaminal **10a**, respectively. Analogously with **4a**, **10a** may be oxidized to benzamide **11a**, but also split back into an equimolar mixture of benzaldehyde (**7d**) and amine **12a**.

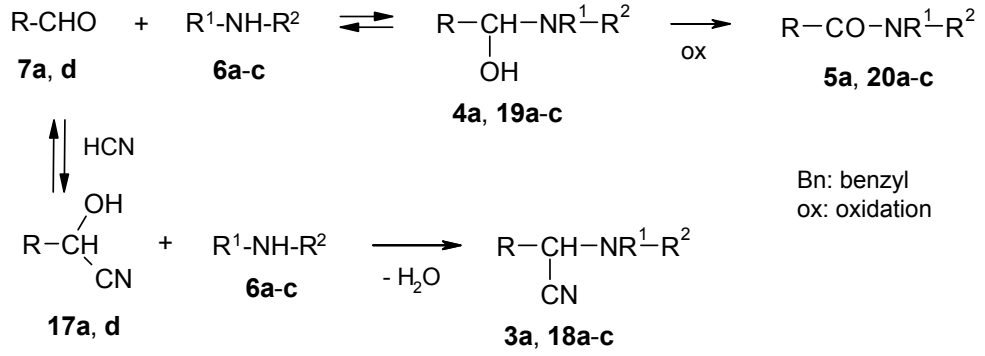
In this way the formation of all reaction products derived from **1a** (Table 1, entry 1) found an explanation. It is possible now to calculate the oxidation regioselectivities.

The preference for oxidative attack at the methyl (*Me*) or benzyl (*Bn*) position can be calculated by the equations 1 or 2, respectively, where each sum was corrected by the number of identical hydrogen atoms, available to oxidative attack. Since **1a** has two identical methyl groups (R=H), the regioselectivities *Me/Bn* and CH_2/*Bn* are identical too (equation 3).

(eq. 1) $Me = CH_2 = \{[\mathbf{3a}]+[\mathbf{5a}]+[\mathbf{6a}]\}/6 = 14.0\%$
(eq. 2) $Bn = \{[\mathbf{7d}]+[\mathbf{9a}]\}/2 = 7.25\%$
(eq. 3) $RS_{\mathbf{1a}}$ (*Me/Bn*) = $RS_{\mathbf{1a}}$ (CH_2/*Bn*) = (eq. 1) /(eq. 2) = 1.9

Oxidation of N-ethyl-N-methylbenzylamine (1b)

Oxidation of **1b** can follow three different routes. Methyl (*Me*) and benzyl (*Bn*) routes are similar to the corresponding routes described before for **1a**. Thus, the *Me* route gave α-aminonitrile **3b**, formamide **5b**, and amine **6b** (+**7a**). The *Bn* route was the source of **9b**, **11b**, and **7d** (+**12b**). The third route (CH_2) refers the oxidative attack at the methylenic group of the ethyl substituent. In this case, the iminium ion **13b** was the source of both α-aminonitrile **14b** and hemiaminal **15b**. As aforementioned for **4a** or **9a**, acetamide **16b** and amine **6a** (+**7b**) resulted from intermediate **15b**.



	R	R^1	R^2
(reaction 1) **17a**/**7a** + **6a** ---> **3a** / **4a**, **5a**	H	Bn	Me
(reaction 2) **17d**/**7d** + **6a** ---> **18a** / **19a**, **20a**	Ph	Bn	Me
(reaction 3) **17d**/**7d** + **6b** ---> **18b** / **19b**, **20b**	Ph	Bn	Et
(reaction 4) **17d**/**7d** + **6c** ---> **18c** / **19c**, **20c**	Ph	Bn	CH_2CN

Scheme 3

All these routes generate secondary amines (**6a**, **6b**, **12b**), as well as aldehydes (**7a**, **7b**, **7d**). Since the pH of the oxidation medium is about 9, close to the pK_a of HCN (9.15), the added cyanide exists as an equimolar mixture of cyanide and hydrogen cyanide. In the presence of CN^-/HCN mixture, the aldehydes could be in equilibrium with the corresponding cyanohydrins (**17**). As depicted in Scheme 3, compounds **17** can react with the secondary amines **6** to give the respective α-aminonitriles **18**. At the same time, aldehydes **7** and amines **6** can also react yielding the corresponding amides **20**. New products might come from the reaction of each secondary amine with the two aldehyde/cyanohydrin pairs: **6b** with **7b**/**17b** and/or **7d**/**17d**, **12b** with **7a**/**17a** and/or **7b**/**17b**, and **6a** with **7a**/**17a** and/or **7d**/**17d**. From these six combinations only three were observed, namely those giving **3a**+**5a** (reaction 1, Scheme 3), **18a** (reaction 2, Scheme 3) and **18b** (reaction 3, Scheme 3). Obviously, the amount of **18b** contributes to the methyl route and those of **3a**, **5a** and **18a** to the methylenic route. At the same time, [**18a**] plus [**18b**] must be added to the benzyl route contributors. Using the amounts of Table 1 (entry 2), the regioselectivities *Me*/*Bn* and CH_2/*Bn* can be calculated on the basis of equations 4-8:

(eq. 4) $Me = \{[\mathbf{3b}]+[\mathbf{5b}]+[\mathbf{6b}]_t\}/3 = 15.8\%$, where $[\mathbf{6b}]_t = [\mathbf{6b}]+[\mathbf{6b}]_{react} = 6.5$ and $[\mathbf{6b}]_{react} = [\mathbf{18b}] = 0.4$

(eq. 5) $Bn = \{[\mathbf{7d}]_t+[\mathbf{9b}]+[\mathbf{11b}]\}/2 = 9.15\%$, where $[\mathbf{7d}]_t = [\mathbf{7d}]+\ ]+[\mathbf{7d}]_{react} = 3.5$ and $[\mathbf{7d}]_{react} = [\mathbf{18a}]+[\mathbf{18b}] = 0.9$.

(eq. 6) $CH_2 = \{[\mathbf{6a}]_t+[\mathbf{14b}]+[\mathbf{16b}]\}/2 = 14.9\%$, where $[\mathbf{6a}]_t = [\mathbf{6a}]+[\mathbf{6a}]_{react} = 7.5$ and $[\mathbf{6a}]_{react} = [\mathbf{3a}]+[\mathbf{5a}]+[\mathbf{18a}] = 2.0$.

(eq. 7) $RS_{\mathbf{1b}}$ (*Me*/*Bn*) = (eq. 4)/(eq. 5) = 1.7

(eq. 8) $RS_{\mathbf{1b}}$ (CH_2/*Bn*) = (eq. 6)/(eq. 5) = 1.6

It is interesting to note that, in our reaction conditions, only 26% of total **7d** $\{[\mathbf{7d}]_{react}/[\mathbf{7d}]_t\}$, 27% of total **6a** $\{[\mathbf{6a}]_{react}/[\mathbf{6a}]_t\}$ and 23% of total **7a** $\{[\mathbf{7a}]_{react}/[\mathbf{7a}]_t$, where $[\mathbf{7a}]_{react}=[\mathbf{3a}]+[\mathbf{5a}]=1.5$ and $[\mathbf{7a}]_t \equiv [\mathbf{6b}]_t\}$ are involved in the reactions of Scheme 3. At the same time, when attacking the iminium ions **2b**, **8b** and **13b**, the cyanide/water nucleophilic ratio is 4.1 {[**3b**]/[**4b**], where $[\mathbf{4b}]=[\mathbf{5b}]+[\mathbf{6b}]_t=9.3\}$, 3.6 {[**9b**]/[**10b**]} and 2.9 {[**14b**]/[**15b**], where $[\mathbf{15b}]=[\mathbf{16b}]+[\mathbf{6a}]_t=7.7\}$, respectively. This occurs because cyanide is a better nucleophile than water, despite the great difference in their relative concentrations.

We note also that the net preference for the methyl attack (Me/Et=57/7=8.1) shown by *N*-ethyl-*N*-methylaniline (Scheme 1) was not followed by **1b**. In the last case, the methyl and ethyl route interested 47.4% {[**3b**]+[**4b**]} and 29.8% {[**14b**]+[**15b**]} of the reacted substrate. Therefore, the statistically uncorrected ratio Me/CH_2(Me) is 1.6 for **1b**. Clearly, the phenyl group is no more directly bound to nitrogen and cannot influence the regioselectivity of **1b**.

Oxidation of 2-(benzylmethylamino)acetonitrile (1c)

Similarly to **1b**, three routes were followed during the oxidation of amine **1c**: methylic, benzylic and methylenic. Attack at the methyl group gave α-aminonitrile **3c**, formamide **5c**, and the secondary amine **6c** (+**7a**). Analogously to **1a** and **1b**, the benzylic attack of **1c** was the source of **9c**, **11c**, and **7d** (+**12c**).

The first step of the oxidative attack at CH_2CN in **1c** gave α-aminonitrile **14c** and **15c**. Contrarily to **15a-b**, the intermediate **15c** has both the cyano and the hydroxy groups on the same carbon atom. Consequently, besides the expected oxidation to carbamoyl cyanide **16c** and splitting into a **6a**+**7c** mixture, elimination of the cyano group as HCN/CN^- from **15c** might occur as well, thus explaining the formation of formamide **5a**. As detailed below, this might be not the only route giving **5a**.

Analogously to the case of **1b**, the described transformations of **1c** generated three secondary amines (**6a**, **6c**, **12c**) and three aldehydes (**7a**, **7c**, **7d**). Actually, only two aldehydes are of interest, since formyl cyanide (**7c**) is too sensitive to hydrolysis, as indicated in Scheme 2. The half-life of **7c** would be about 0.1 seconds in our reaction conditions (pH~9).[15] This means that the transformation of **15c** into **6a**+**7c** is an irreversible reaction, identically to the generation of **5a** from the same **15c**.

Considering the oxidation products derived from **1c** (Table 1, entry 3), it results that, from all possible combinations between the remaining two aldehydes (and their cyanohydrins **17**) and the three secondary amines, only three combinations were active: **7d**/**17d** with **6c** (reaction 4, Scheme 3), **7d**/**17d** with **6a** (reaction 2, Scheme 3) and **7a**/**17a** with **6a** (reaction 1, Scheme 3). The first two combinations are the sources of **20c** and of both **18a** and **20a**, respectively. The third possible reaction (**7a**/**17a** with **6a**) will be discussed at the end of this chapter.

Summing up all these considerations on the oxidation of **1c**, one can write the following equations 9-13 in order to calculate the regioselectivities:

(eq. 9) *Me* = {[**3c**]+[**5c**]+[**6c**]$_t$}/3 = 10.9%, where [**6c**]$_t$ = [**6c**]+[**6c**]$_{react}$ = 6.5 and [**6c**]$_{react}$ = [**20c**] = 0.9
(eq. 10) *Bn* = {[**7d**]$_t$+[**9c**]+[**11c**]}/2 = 6.9%,
where [**7d**]$_t$ = [**7d**]+]+[**7d**]$_{react}$ = 6.9 and [**7d**]$_{react}$ = [**18a**]+[**20a**]+[**20c**] = 2.0.
(eq. 11) CH_2 = {[**5a**]+[**6a**]$_t$+[**14c**]+[**16c**]}/2 = 24.8%,
where [**6a**]$_t$ = [**6a**]+[**6a**]$_{react}$ = 7.1 and [**6a**]$_{react}$ = [**18a**]]+[**20a**] = 1.1.
(eq. 12) $RS_{\mathbf{1c}}$ (*Me/Bn*) = (eq. 9/(eq. 10) = 1.6
(eq. 13) $RS_{\mathbf{1c}}$ (CH_2/*Bn*) = (eq. 11)/(eq. 10) = 3.6

As pointed out before, three ways are possible to generate the formamide **5a** during the oxidation of **1c**: (i) directly from **15c**, as discussed before and depicted in Scheme 2, (ii) through the reaction of **7a** (±**17a**) with **6a** (reaction 1 of Scheme 3), and (iii) from **16c**, by hydrolysis. Actually, the last route (iii) can be safely cancelled out, because control experiments indicated that **16c** is stable in our two-layers oxidation conditions; formation of **5a** (accompanied by **1c** and other compounds) occurs really in more drastic conditions (pH>10, temperature over 60°C). [16]

The aforementioned route (ii) would generate **3a** (identical to **1c**) and/or **5a**. The extent of (ii) is governed by the amount of limiting compound (**7a** or **6a**) in reaction 1 of Scheme 3. Simple calculus reveals **7a** as the limiting compound. More specifically, according to Scheme 2, formaldehyde derives from **4c** and its total amount equals 6.5% {[**7a**]$_t$≡[**6c**]$_t$}, similar but smaler than [**6a**]$_t$ (7.1% in equation 11). Even assuming the complete consumption of **7a** (6.5%) with **6a**, the value of 6.5 is too small to explain the formation of all **5a** (16% in Table 1, entry 3). However, a part of **5a** might be really formed from some **7a**. As already mentioned for **1b**, only about one quarter (more exactly 23%) of **7a** reacted with **6a** and there are no reasons to think it is otherwise in the case of **1c**. This assumption is strengthened also by the similar values of the ratio [**7d**]$_{react}$/[**7d**]$_t$ calculated with equations 5 and 10: 26% and 29%, respectively. Therefore, one can suppose that [**7a**]$_{react}$ could be only 1.6% (about one quarter of 6.5). It results that about one tenth (1.6/16) of the experimentally found **5a** could originate from reaction 1 of Scheme 3. Accordingly, the routes (i) and (ii), advanced before for the formation of **5a**, could be both in action, but the route (i) is more favored.

The dual origin of **5a** will affect a little the terms of the former equation 11, but not its total value:
(eq. 11') CH_2 = {[**5a**]-1.6+[**6a**]$_t$+[**14c**]+[**16c**]}/2 = 24.8%,
where [**6a**]$_t$ = [**6a**]+[**6a**]$_{react}$ = 8.7 and [**6a**]$_{react}$ = [**18a**]]+[**20a**]+1.6 = 2.7.

Accordingly, the regioselectivities $RS_{\mathbf{1c}}$ (*Me/Bn*) and $RS_{\mathbf{1c}}$ (CH_2/*Bn*) calculated with equations 12 and 13 remain correct.

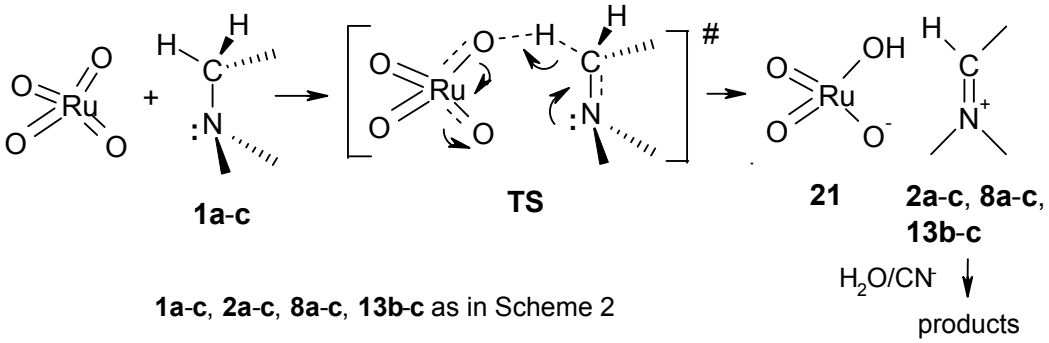
The cyanide/water nucleophilic ratio for the attack at the iminium ions **2c**, **8c** and **13c**, is 1.9 {[**3c**]/[**4c**], where [**4c**]=[**5c**]+[**6c**]$_t$=11.1}, 0.9 {[**9c**]/[**10c**], where [**10c**]=[**11c**]+[**7d**]$_t$=7.3} and 0.7 {[**14c**]/[**15c**], where [**15c**]=[**5a**]+[**16c**]+[**6a**]$_t$= 28.6}, respectively. It is for the first time that the cyanide/water ratio has a subunit value in the case of RuO_4-mediated oxidation of tertiary amines.[9-14] At the same time, these values are 2-4 times smaller than those calculated for the analogous ratios derived from **1b**. When comparing the values of [**14b**]/[**15b**] (2.9) and [**14c**]/[**15c**] (0.7), one might be tempted to invoke the respective reversible/irreversible nature of the transformations of **15b**/**15c**. However, although this dichotomy could have a role, it cannot explain the remaining ratios. Unfortunately, a reasonable explanation for all these differences cannot be presented yet.

Stereoelectronic effects

It is known that the oxidation of amines by RuO_4 occurs in two steps (Scheme 4).[9,13,14] The first step consists in the formation of an ion pair of ruthenate anion (**21**) and iminium ion (**2a–c**, **8a–c** or **13b–c**). In the corresponding transition state (**TS**), the electronic lone pair on nitrogen is used to create a new C=N$^+$ double bond, concomitantly to hydrogen abstraction (*HAB*) and generation of a Ru^{VI} species. In the second step, the nucleophilic capture of iminium ions gives the observed oxidation products listed in Table 1.

As pointed out in the introduction of this paper, the amines **1a-c** (Scheme 2) differ only by the nature of R. Substituent R cannot influence the π-donating capability of nitrogen, nor the accommodation of the new C=N$^+$ double bond, except for the formation of **13b-c** iminium ions. Therefore, it is conceivable that the steric and electronic demands of R will influence mainly the CH_2/*Bn* regioselectivity and only in a minor extent the *Me*/*Bn* regioselectivity. This was confirmed by the *RS* values listed in Table 1, as discussed below.

The *Me*/*Bn* regioselectivities varied between 1.9 (for **1a**) and 1.6 (for **1c**). Since the estimated error on *RS*'s is ±0.2, it results that variation of R from H to Me or CN has little influence on the indicated *RS*'s, as just presumed. The same difference was shown by the CH_2/*Bn* regioselectivities of **1a** (1.9) and **1b** (1.6). Even if a steric effect might be present for **1b**, especially to generate **13b**, it seems to be quite small.



Scheme 4

Changing R into CN as in **1c** determines a significant preference for the methylenic CH_2CN route. The *CH*$_2$/*Bn* regioselectivity rose to 3.6 for **1c**, a value by far greater than those aforementioned for **1a** and **1b**. This might be assigned rather to an electronic effect than to a steric one, since the geometry around the methylenic carbon is only slightly modified by the linear cyano substituent. At first sight, one can deduce that a methylenic CH_2R is the preferred attacked position if R is an electron-withdrawing group. This is quite surprising because the hydrogen abstraction (*HAB*) should be facilitated by R with opposite tendency, namely electron-donating. In our opinion, the reason might lie in the energetic gain brought by the extension of the π-system over four atoms (N^+=C-C≡N) in the intermediate iminium ion. This is possible only for cyano as substituent in **13c**. This cyano directing effect was present also in oxidation of amines by other oxidants.[17]

EXPERIMENTAL PART

Materials

Except for **1a**, **7d**, benzoic acid and $RuO_2.xH_2O$, which are from commercial sources, all other compounds are known from the literature and were synthesized according to the indicated references: **1b**,[18] **1c (3a)**,[7] **3b**,[7] **3c**,[19] **5a–b**,[7] **5c**,[8] **6a–c**,[7] **9a**,[11] **9b**,[20] **9c**,[21] **11b**,[22] **11c**,[23] **14b**,[24] **14c**,[25] **16b**,[26] **16c**,[27] **18a–b**,[7] **20a**,[7] **20c**.[28] They were characterized by NMR and MS techniques, as described below.

NMR and MS spectra

NMR and MS characteristics of **1c (3a)**,[7] **3b**,[7] **5a–b**,[7] **5c**,[8] **6a–c**,[7] **7d**,[7] benzoic acid,[7] **16c**,[27] **18a-b**,[7] and **20a**[7] were previously reported by us. The corresponding data of the remaining compounds are given below. Only the MS characteristics are presented for **1a** and **9a**; the corresponding NMR data were already reported.[11]

NMR spectra were acquired in $CDCl_3$ solutions, on a Varian ICON 300 apparatus operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). The corresponding chemical shifts (δ scale) were referenced to internal TMS (δ_H = 0 ppm) or $CDCl_3$ (δ_C = 77.16 ppm). Coupling constants *J* were given in Hz. Aromatic hydrogens and carbons in *ortho*, *meta* and *para* position are abbreviated as *o*, *m* and *p*, respectively; *i* stands for *ipso* aromatic carbons. Benzylic hydrogens or carbons are symbolized by Bn.

Two *E*/*Z* isomers are present in the NMR spectra of **11b** and **16b**; the chemical shifts of the major isomer are underlined. The *E*/*Z* isomerism in **11c** and **20c** determined weak and/or broad NMR signals due to the proximity of the coalescence temperature.

Mass spectra were obtained with a GC 6890 Agilent Technologies gas chromatograph coupled with a MS 5975B mass spectrometer, using 70 eV as ionization energy. The m/z peak value is followed by its relative intensity, in parenthesis; the mass peak is indicated.

***N,N*-Dimethylbenzylamine (1a)**. MS: 135 (M^+, 55), 134 (42), 92 (11), 91 (63), 65 (17), 58 (100).

***N*-Ethyl-*N*-methylbenzylamine (1b)**. δ_H: 1.10 (t, *J*=7.15, 3H, CH_2-C*H*$_3$), 2.19 (s, 3H, N-CH_3), 2.45 (q, *J*=7.15, 2H, C*H*$_2$-CH_3), 3.48 (s, 2H, Bn), 7.20-7.37 (m, 5H, Ph); δ_C: 12.6 (CH_2-*C*H$_3$), 41.8 (N-CH_3), 51.3 (*C*H$_2$-CH_3), 62.1 (Bn), 127.0 (*p*), 128.3 (*m*), 129.2 (*o*), 139.3 (*i*). MS: 149 (M^+, 14), 134 (48), 92 (9), 91 (100), 72 (13), 65 (11).

***N*-Benzyl-*N*,*N*-bis(cyanomethyl)amine (3c)**. δ_H: 3.58 (s, 4H, CH_2-CN), 3.78 (s, 2H, Bn), 7.33-7.39 (m, 5H, Ph); δ_C: 41.7 (*C*H$_2$-CN), 58.1 (Bn), 114.3 (CN), 128.7 (*p*), 129.10+129.14 (*m*+*o*), 134.9 (*i*). MS: 185 (M^+, 9), 92 (21), 91 (100), 65 (10). MS: 185 (M^+, 9), 92 (21), 91 (100), 65 (10).

***N*,*N*-Dimethylbenzamide (9a)**. MS: 160 (M^+, 55), 159 (21), 134 (17), 117 (23), 116 (85), 89 (23), 83 (100), 63 (9), 44 (17).

α-(*N*-Ethyl-*N*-methylamino)-benzeneacetonitrile (9b). δ_H: 1.10 (t, *J*=6.8, 3H, CH_2-C*H*$_3$), 2.21 (s, 3H, N-CH_3), 2.54 (qd, *J*=6.8 and 0.9, 2H, C*H*$_2$-CH_3), 4.91 (s, 1H, CH), 7.25-7.45 (m, 5H, Ph); δ_C: 12.3 (CH_2-CH_3), 37.7 (N-CH_3), 48.8 (*C*H$_2$-CH_3), 61.3 (CH), 115.4 (CN), 127.7 (*o*), 128.9 (*p*), 129.0 (*m*), 134.0 (*i*). MS: 174 (M^+, 9), 159 (37), 117 (11), 116 (100), 89 (11).

α-[(Cyanomethyl)methylamino]-benzeneacetonitrile (9c). δ_H: 2.51 (s, 3H, CH_3), 3.44 (s, 2H, CH_2), 4.88 (s, 1H, CH), 7.25-7.45 (m, 5H, Ph); δ_C: 39.4 (CH_3), 42.0 (CH_2), 60.4 (CH), 114.77+114.80 (CH_2-*C*N+CH-*C*N), 128.0 (*o*), 128.9 (*p*), 129.0 (*m*), 132.0 (*i*). MS: 185 (M^+, 13), 117 (23), 116 (100), 89 (17).

***N*-Ethyl-*N*-methylbenzamide (11b)**. δ_H: 1.12+1.24 (t+t, *J*=6.4, 3H, CH_2-C*H*$_3$), 2.92+3.06 (s+s, 3H, N-CH_3), 3.27+3.59

(q+q, *J*=6.4, 2H, C*H*$_2$-CH$_3$), 7.39 (s, 5H, Ph); δ_C: 12.2+13.7 (CH$_2$-*C*H$_3$), 32.3+36.8 (N-CH$_3$), 42.2+46.0 (*C*H$_2$-CH$_3$), 126.5+126.9 (*o*), 128.4 (*m*), 129.3 (*p*), 136.9 (*i*), 171.1+171.8 (CO). MS: 163 (M$^+$, 21), 162 (65), 105 (100), 77 (44), 51 (10).

***N*-(Cyanomethyl)-*N*-methylbenzamide (11c)**. δ_H: 3.13 (s, 3H, CH$_3$), 4.30-4.60 (br s, 2H, CH$_2$), 7.46 (s, 5H, Ph); δ_C: 35.5 (weak, CH$_2$), 37.6 (weak, CH$_3$), 115.3 (CN), 127.3 (br, *o*), 128.7 (br, *m*), 130.7 (*p*), 133.9 (*i*), 171.6 (CO). MS: 174 (M$^+$, 27), 105 (100), 77 (51), 51 (14).

2-(Benzylmethylamino)propionitrile (14b). δ_H: 1.43 (d, *J*=7.2, 3H, CH-C*H*$_3$), 2.30 (s, 3H, N-CH$_3$), 3.45+3.75 [d+d (ABq), J_{AB}=13.2, 1+1H, Bn], 3.69 (q, *J*=7.2, 1H, C*H*-CH$_3$), 7.20-7.42 (m, 5H, Ph); δ_C: 17.7 (CH-*C*H$_3$), 37.78 (N-CH$_3$), 50.6 (*C*H-CH$_3$), 59.7 (Bn), 117.5 (CN), 127.6 (*p*), 128.6 (*m*), 128.9 (*o*), 137.5 (*i*). MS: 174 (M$^+$, 14), 159 (15), 97 (14), 92 (12), 91 (100), 65 (12).

2-(Benzylmethylamino)propiodinitrile (14c). δ_H: 2.56 (s, 3H, CH$_3$), 3.69 (s, 2H, Bn), 4.64 (s, 1H, CH), 7.27-7.40 (m, 5H, Ph); δ_C: 39.7 (CH$_3$), 59.1 (Bn), 46.3 (CH), 110.1 (CN), 128.8 (*p*), 129.07+129.11 (*m*+*o*), 135.0 (*i*). MS: 185 (M$^+$, 12), 184 (35), 92 (16), 91 (100), 65 (12).

***N*-Ethyl-*N*-benzylacetamide (16b)**. δ_H: 2.148+2.150 (sh+s, 3H, CO-CH$_3$), 2.91+2.94 (s+s, 3H, N-CH$_3$), 4.52+4.59 (s+s, 2H, Bn), 7.17+7.24 (d+d, *J*=7.2, 2H, *o*), 7.25-7.39 (m, 3H, *p* and *m*); δ_C: 21.5+21.9 (CO-*C*H$_3$), 33.8+35.6 (N-CH$_3$), 50.7+54.3 (Bn), 126.4+128.1 (*o*), 127.4+127.7 (*p*), 128.6+129.0 (*m*), 136.6+137.5 (*i*), 170.7+171.0 (CO). MS: 164 (12), 163 (M$^+$, 100), 162 (13), 120 (53), 106 (77), 91 (59), 65 (17).

***N*-Benzyl-*N*-(cyanomethyl)benzamide (20c)** [The sign prime (') refers to the atoms of benzylic ring]. δ_H: 4.27±0.2 (br, 2H, CH$_2$CN), 4.73±0.2 (br, 2H, Bn), 7.13-7.50 (m, 8H, *m*+*p*+*o'*+*m'*+*p'*), 7.54 (d, *J*=7.2, 2H, *o*); δ_C: 32.8±0.1 (weak br, CH$_2$), 53.0±0.1 (weak br, Bn), 115.3 (CN), 127.2 (*o*), 128.5 (*p'*), 128.7 (*o'*), 129.0 (*m'*), 129.4 (*m*), 131.0 (*p*), 134.0 (*i'*), 134.7 (*i*), 172.0 (CO). MS: 250 (M$^+$, 9), 210 (46), 105 (100), 91 (14), 77 (39), 51 (9).

Oxidation of 1a–c.[7,8,14,27] To a NaCN solution [196 mg (4 mmol) in water (10 mL)] was added $RuO_2.xH_2O$ (10-15 mg), amine **1** (1 mmol in 10 mL of $CHCl_3$), and the co-oxidant ($NaIO_4$) aqueous solution (0.4 M; 10 mL, 4 mmol), in this order. The heterogeneous reaction mixture was magnetically stirred at room temperature for 3h and then worked-up as extensively described in our previous papers.[7,8,14,27] Identification of the various reaction products was made by comparison of the NMR and MS spectra before and after the addition of small samples of the pure compounds into the analyzed samples. The amounts quoted in Table 1 were calculated from the NMR and MS data obtained in the presence of 1.4-dimethoxybenzene, added as an internal standard.[27]

CONCLUSIONS

Tertiary aliphatic amines like PhCH$_2$-NMe-CH$_2$R (R=H, Me, CN) underwent RuO_4-mediated oxidation by attack at all three *N*-α-methylenic positions (methyl, benzyl and CH$_2$R) to give mainly α-aminonitriles, in the presence of NaCN. Considering the products obtained by each route, it was possible to calculate the relative regioselectivities *Me/Bn* and *CH$_2$/Bn*. Changing R from H to Me or CN had little influence (if any) on the *Me/Bn* regioselectivities, but for CN the *CH$_2$/Bn* regioselectivity had the highest value. This cyano directing effect was assigned to the gain in energy due to the extension of the π-system over four atoms (N$^+$=C-C≡N) in the transiently resulted iminium ion [Bn-N$^+$(Me)=C-CN].

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