RuO$_4$-mediated oxidation of secondary amines. Part 1. Are hydroxylamines the main intermediates?

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Abstract: The RuO$_4$-catalyzed oxidation of secondary amines Bn–NH–CH$_2$R (**1a** and **b**; R=H, Me) gave mainly amides, but minute amounts of nitrones PhCH=N(O)–CH$_2$R (**9a** and **b**) and traces of Bn–N(OH)–CH$_2$R (R=H, **4a**) were also detected. In the presence of cyanide, up to 22 reaction products were identified, but mainly α-aminonitriles. Comparison of the oxidation products of **1a** and **b** with those of **4a** and **b** and **9a** and **b**, and Bn–N(O)=CHR (**10a** and **b**) showed that **4a** and **b** cannot be the main reaction intermediates formed from **1a** and **b**.
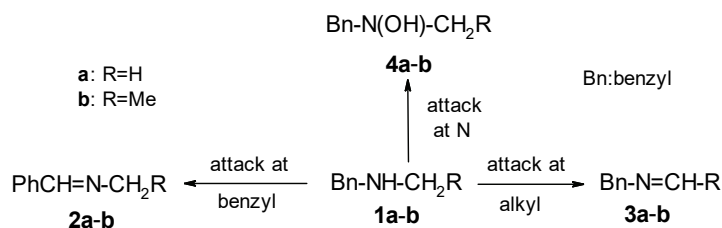
INTRODUCTION

Ruthenium-based catalysts, ruthenium tetraoxide (RuO$_4$) included, have been extensively used to oxidize a wide variety of organic compounds, such as aliphatic and aromatic hydrocarbons, alkenes, alkynes, alcohols, ethers, amines, or amides.[1–11] The versatility, specificity, the high yields obtained in many cases, and the environmentally friendly reaction conditions have strongly recommended ruthenium-containing catalysts be successfully utilized in fine and green chemistry.[1–10] In the case of tertiary amines of the RCH$_2$–NR^{1}R^2 type, earlier papers[12–16] indicated that RuO$_4$ attacks the N–CH$_2$ positions to afford amides (RCO–NR^{1}R^2) and for about 30 years, this reaction was viewed as a highly regioselective oxidation.

However, the RuO$_4$-mediated oxidation of tertiary amines containing different types of N–CH$_2$ groups, such as *N*-benzylazacycloalkanes,[17,18] *N,N*-dialkylbenzylamines[19] or *N*-benzyl-2-azanorbornane derivatives,[20,21] caused doubts on the previously claimed high regioselectivity. In the case of *N,N*-dialkylbenzylamines, the oxidation compounds were derived from both reactive N–CH$_2$ sites

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(*i.e.*, benzylic and alkylic). In addition, some N-oxides were also formed, indicating the existence of a third, minor oxidative route. In the presence of the cyanide ion, only the first two routes were followed. Formation of two kinds of *N-α*-cyano derivatives suggested the transient existence of iminium cations as intermediates. The statistically corrected alkyl/benzyl regioselectivity of the oxidation reaction was relatively poor (4.1 for *N,N*-dimethyl- and 2.1 for *N,N*-diethyl-benzylamine).[19]

In continuation of previous work on the RuO_4-mediated oxidation of tertiary amines,[17–19] it was considered useful to extend the study on secondary amines, more precisely on *N*-methyl- (**1a**) and *N*-ethylbenzylamine (**1b**). By analogy with the behavior of tertiary amines presented before, the secondary amines **1a** and **b** could suffer oxidative attack at three positions: 1) benzylic, 2) alkylic, and/or 3) at the nitrogen atom (Scheme 1). Depending on the followed path, the first oxidation step should give *N*-alkyl imines **2a** and **b**, *N*-benzyl imines **3a** and **b**, and/or hydroxylamines **4a** and **b**, respectively. In this paper, it was analyzed whether **4a** and **b** could be the main reaction intermediates.

$$Bn\text{-}N(OH)\text{-}CH_2R$$

a: R=H
b: R=Me

4a-b

Bn:benzyl

attack
at N

$$PhCH=N\text{-}CH_2R \xleftarrow[\text{benzyl}]{\text{attack at}} Bn\text{-}NH\text{-}CH_2R \xrightarrow[\text{alkyl}]{\text{attack at}} Bn\text{-}N=CH\text{-}R$$

2a-b   **1a-b**   **3a-b**

Scheme 1. Oxidative routes for **1a** and **b**.

EXPERIMENTAL

Instrumentation

The FT-IR spectra were registered on a Bruker Vertex 70 instrument, equipped with a diamond crystal ATR. The NMR spectra were recorded with a Varian Unity INOVA 400 spectrometer, operating at 400 MHz (^1H) and 100 MHz (^{13}C). The mass spectra were obtained using a GC 6890 Agilent Technologies gas chromatograph coupled with a MS 5975 B quadrupole mass spectrometer, using the standard 70 eV ionization energy.
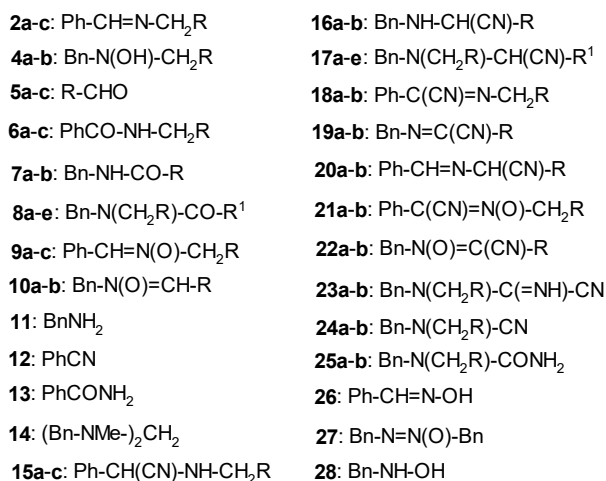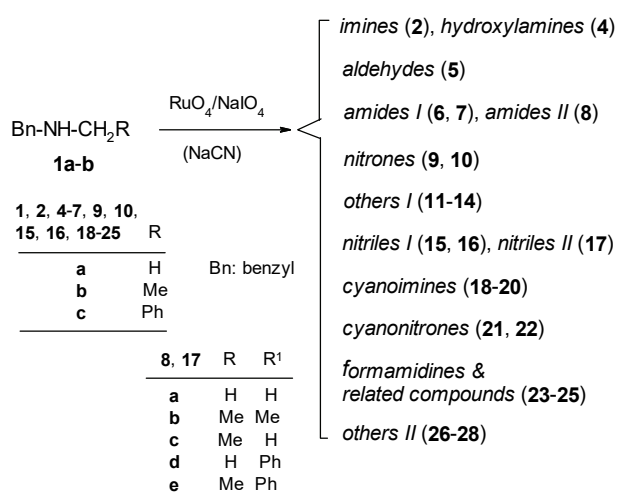
NMR (^1H and ^{13}C) and MS data for **1**, **2** and **4**–**28** are given in Supplementary material to this paper.

Materials

The formulae of all substrates and reaction products **1**, **2** and **4**–**28** are given in Scheme 2. Compounds **1a**, **2c**, hydrated RuO_2 (all from Aldrich), **1b**, **5c**, **6c**, **7a**, **11**–**13**, **26**, benzoic acid, $NaIO_4$ (all from Merck) and the organic solvents (from Chemical Co., Iaşi, Romania) were used as purchased, except for $CHCl_3$ and CH_2Cl_2, which were stored over anhydrous Na_2CO_3 and filtered prior to use. Derivatives **2a** and **b**, **6a** and **b**, **7b**, **8a–e**, **9a** and **b**, **14**, **15a** and **b**, **16a** and **b**, **17a–e**, **18a** and **b**, **19a** and **b**, **20a** and **b**, **21a** and **b**, **22a** and **b**, **23a** and **b**, **24a** and **b** and **25a** and **b** were prepared and characterized previously.[19,22] Compounds **4a** and

b,[23] **9c**,[24,25] **10a**,[26] **10b**,[27] **15c**,[28] **27**[29] and **28**[30] are all known from the literature and were prepared according to the indicated procedures. The purity of all non-commercial chemicals was checked by FT-IR, NMR and GC–MS.

NMR and MS spectroscopies were extensively used to identify the oxidation products. Even though the NMR characteristics of most of compounds depicted in Scheme 2 have been already reported[19,22] or are widely known (*i.e.*, **5c** and **11**–**13**), it was judged useful to present the corresponding NMR (and MS) spectral data of all these compounds (**1**, **2** and **4**–**28**) as Supplementary material.

imines (**2**), hydroxylamines (**4**)

aldehydes (**5**)

Bn-NH-CH$_2$R $\xrightarrow[\text{(NaCN)}]{\text{RuO}_4/\text{NaIO}_4}$ amides I (**6**, **7**), amides II (**8**)

1a-b

nitrones (**9**, **10**)

others I (**11-14**)

1, 2, 4-7, 9, 10, 15, 16, 18-25	R
a	H
b	Me
c	Ph

Bn: benzyl

nitriles I (**15**, **16**), nitriles II (**17**)

cyanoimines (**18-20**)

cyanonitrones (**21**, **22**)

8, 17	R	R^1
a	H	H
b	Me	Me
c	Me	H
d	H	Ph
e	Me	Ph

formamidines & related compounds (**23-25**)

others II (**26-28**)

2a-c: Ph-CH=N-CH$_2$R

4a-b: Bn-N(OH)-CH$_2$R

5a-c: R-CHO

6a-c: PhCO-NH-CH$_2$R

7a-b: Bn-NH-CO-R

8a-e: Bn-N(CH$_2$R)-CO-R^1

9a-c: Ph-CH=N(O)-CH$_2$R

10a-b: Bn-N(O)=CH-R

11: BnNH$_2$

12: PhCN

13: PhCONH$_2$

14: (Bn-NMe-)$_2$CH$_2$

15a-c: Ph-CH(CN)-NH-CH$_2$R

16a-b: Bn-NH-CH(CN)-R

17a-e: Bn-N(CH$_2$R)-CH(CN)-R^1

18a-b: Ph-C(CN)=N-CH$_2$R

19a-b: Bn-N=C(CN)-R

20a-b: Ph-CH=N-CH(CN)-R

21a-b: Ph-C(CN)=N(O)-CH$_2$R

22a-b: Bn-N(O)=C(CN)-R

23a-b: Bn-N(CH$_2$R)-C(=NH)-CN

24a-b: Bn-N(CH$_2$R)-CN

25a-b: Bn-N(CH$_2$R)-CONH$_2$

26: Ph-CH=N-OH

27: Bn-N=N(O)-Bn

28: Bn-NH-OH

Scheme 2. Oxidation products of **1a** and **b**.

Oxidation by RuO$_4$/NaIO$_4$ (± NaCN). General procedure

To a heterogeneous mixture of CHCl$_3$ (5 mL) and aqueous solution of NaIO$_4$ (0.4 M; 10 mL, 4 mmol) was added solid RuO$_2$·xH$_2$O (10–15 mg), followed by the substrate (1 mmol),

previously dissolved in CHCl$_3$ (5 mL) (reaction conditions A). In the case of the cyano-trapping experiments (reaction conditions B), to the NaCN solution [196 mg (4 mmol) in water (10 mL)] was added RuO$_2$, the substrate (1 mmol in 10 mL of CHCl$_3$), and the co-oxidant NaIO$_4$ solution (10 mL, as before), in this order. Several other organic solvents (CH$_2$Cl$_2$, Me$_2$CO$_3$ and AcOEt) were tried with no significant differences. In all cases the heterogeneous reaction mixture was magnetically stirred at room temperature for 3–5 h and then worked up as described in a previous paper.[22] Identification of the various reaction products was made by comparison of the NMR and GC–MS spectra before and after the addition of pure compounds into the analyzed samples. 1,4-Dimethoxybenzene (DMB) was employed as an internal standard for quantitative analyses.[22] Work-up losses were determined on synthetic mixtures and then used to correct the experimentally found amounts. These corrected amounts were used to calculate the yields given in Table I (see below).

Oxidation of 1a and b by H$_2$O$_2$/Na$_2$WO$_4$

Hydrogen peroxide (30 %; 1 mL, 9.8 mmol) was added dropwise into a magnetically stirred methanolic solution (10 mL) of **1a** (0.53 mL, 4 mmol) and Na$_2$WO$_4$·2H$_2$O (132 mg, 0.4 mmol), maintaining the temperature within 25–30°C with a water bath. The mixture was stirred at room temperature for another 4–5 h and then filtered. The clear filtrate was evaporated to dryness, the residue taken up in CHCl$_3$, the solution filtered again, and the organic solvent eliminated *in vacuo*. The obtained liquid residue was analyzed by NMR, as such and with a known amount of DMB. Besides benzaldehyde and other compounds, **9a** and **10a** resulted in about 32 and 17 % yield, respectively. Treatment of this oxidation residue with LiAlH$_4$/ether[23] transformed both nitrones into hydroxylamine **4a**. Analogously, **9b** (≈31 %) and **10b** (≈25 %) were formed from **1b**; reduction of the nitrones gave **4b**.

RESULTS AND DISCUSSION

The oxidations were performed in the absence/presence of cyanide (A- and B-conditions, respectively) and the corresponding results are shown in Table I. The yield of benzaldehyde **5c** in Table I actually refers to the yield of **5c**+benzoic acid. This is allowed because benzoic acid is always derived from **5c**, merely by air oxidation during the reaction mixture work-up. To gain in simplicity, the desired entries (let them be *x* and *y*) of Table I will be cited as TI-*x,y* throughout this paper.

Oxidation of amines 1a–b. Reaction products

The various components of the oxidation mixtures obtained from **1a–b** in the absence of cyanide (TI-1,2) can be divided into imines (**2a–c**), hydroxylamines (only **4a** was detected), aldehydes (only **5c** was detected as such), amides (**6–8**), nitrones (**9**), benzonitrile (**12**), and benzamide (**13**). In the case of **1a**, diamine **14** was also present.

Some reaction products contain more carbon atoms than in the starting amines. Whatever the following oxidation route, they cannot be primary reaction products. Thus, amides **8a–e** (amides II in Scheme 2) should be formed in two steps, as depicted in Scheme 3: *i*) the condensation of the appropriate amine **1** with aldehyde **5** affords the intermediate **29**, which *ii*) is oxidized further at the

OH level.[31,32] Besides oxidation to **8a**, the hemiaminal **29a** could also react with **1a** to give the diamine **14**. It should be noted that **8a** and **8d** resulted from **1a** (TI--1), but **8b**, **8c**, and **8e** from **1b** (TI-2). According to Scheme 3, this implies the formation of aldehydes **5a** and **5c** during the oxidation of **1a** and of **5a**, **5b**, and **5c** during the analogous reaction of **1b**.

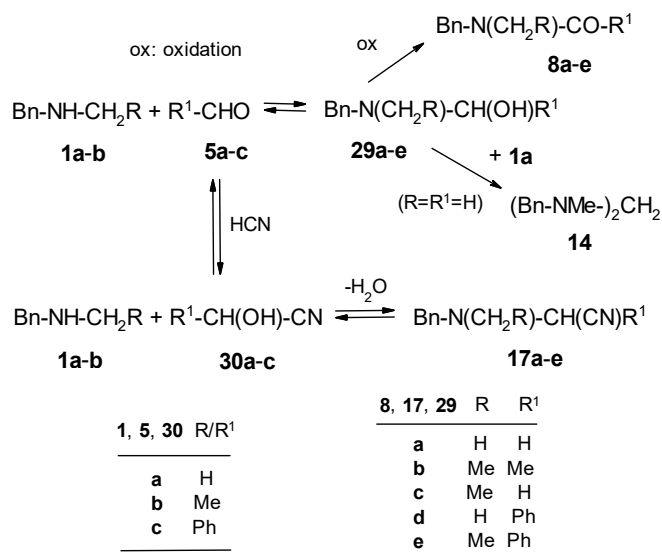TABLE I. Oxidation of selected compounds

Entry No.	Compd. (conversion, %)[a]	Reaction products[b] (yield, %)[c]
0	1	2
		A) Oxidations in the absence of cyanide[d]
1	**1a** (55)	**2a** (2.2), **2c** (8.6), **4a** (0.2), **5c** (8.0), **6a** (2.2), **6c** (1.8), **7a** (3.8), **8a** (30.0), **8d** (7.4), **9a** (2.4), **12** (2.0), **13** (0.6), **14** (1.3)
2	**1b** (81)	**2b** (2.1), **2c** (4.1), **5c** (34.3), **6b** (3.9), **6c** (3.1), **7a** (1.7), **7b** (4.1), **8b** (3.5), **8c** (15.2), **8e** (3.8), **9b** (0.3), **12** (7.4), **13** (0.5)
3	**4a** (100)	**5c** (55.0), **6a** (1.9), **7a** (1.8), **12** (7.7), **13** (4.1), **26** (2.3), **27** (1.4)
4	**4b** (100)	**5c** (40.8), **6b** (3.6), **7b** (4.0), **12** (8.6), **13** (10.9), **26** (4.7), **27** (2.8)
5	**9a** (100)	**5c** (75.6), **6a** (0.8), **12** (0.4), **13** (0.8)
6	**9b** (100)	**5c** (78.1), **6b** (0.6), **12** (9.6), **13** (0.3)
7	**10a** (100)	**5c** (48.7), **7a** (4.6), **9c** (0.6), **12** (7.1), **13** (5.8), **26** (5.7), **27** (3.0)
8	**10b** (100)	**5c** (50.1), **7b** (4.0), **9c** (0.5), **12** (7.0), **13** (6.0), **26** (3.1), **27** (1.8)
9	**28** (100)	**5c** (10.7), **9c** (4.0), **12** (4.3), **13** (0.5), **26** (34.7), **27** (8.7)
		B) Oxidations in the presence of cyanide[d]
10	**1a** (13)[e]	**2c** (1.2), **5c** (0.9), **6a** (0.4), **7a** (0.7), **8a** (1.8), **8d** (8.9), **11** (2.5), **12** (0.9), **15a** (6.3), **16a** (2.2), **17a** (18.2), **17d** (15.3), **18a** (0.6), **20a** (0.3), **21a** (0.4), **22a** (0.8), **23a** (2.9), **24a** (1.0), **25a** (4.5)
11	**1b** (37)[e]	**2b** (5.2), **2c** (1.8), **5c** (0.5), **6b** (0.5), **7b** (0.6), **8b** (1.0), **8c** (0.6), **8e** (2.7), **9b** (7.8), **12** (1.5), **15b** (15.6), **16b** (10.9), **17b** (9.9), **17c** (1.0), **17e** (8.1), **18b** (0.8), **20b** (0.5), **21b** (0.5), **22b** (0.9), **23b** (4.2), **24b** (0.9), **25b** (8.0)
12	**4a** (100)	**5c** (2.5), **6a** (0.7), **7a** (2.7), **9a** (28.8), **9c** (1.2), **12** (4.0), **13** (6.0), **18a** (7.3), **21a** (7.6), **22a** (2.0), **26** (0.3)
13	**4b** (100)	**5c** (1.8), **6b** (0.3), **9b** (39.4), **10b** (25.8), **12** (8.8), **13** (3.6), **18b** (1.1), **21b** (3.0), **22b** (5.8)
14	**9a** (20)	**5c** (34.7), **6a** (1.2), **12** (6.9), **18a** (22.0), **21a** (9.7)
15	**9b** (22)	**5c** (37.5), **6b** (1.5), **12** (6.0), **18b** (20.2), **21b** (8.1)
16	**10a** (100)	**5c** (14.0), **7a** (2.5), **9c** (5.0), **12** (8.7), **13** (2.9), **22a** (11.9), **26** (2.9), **27** (3.6)
17	**10b** (93)	**5c** (12.3), **7b** (1.5), **9c** (5.1), **12** (8.3), **13** (5.9), **22b** (12.1), **26** (4.3), **27** (2.0)

[a]Conversion calculated against the reacted substrate; [b]formulae in Scheme 2; [c]yields (mole ratios of product/ /reacted substrate) were calculated from the NMR and MS spectra, regardless of the stoichiometry; [d]reaction conditions (for 1 mmol of substrate): A – RuO$_2$·xH$_2$O(10–15 mg), NaIO$_4$ (4 mmol), CHCl$_3$/water = = 10/10 (mL/mL), room temperature, 3–5 h; B – as in A, but NaCN (4 mmol) in water (10 mL) was also added; [e]literature data[22]

Secondary reaction products could also be the derivatives **2c** and **6c**, their existence implying the transient formation of benzylamine **11**. Thus, benzamide **6c** might be formed by a sequence similar to that depicted in Scheme 3 (*i.e.*, **11**+**5c** → Bn–N*H*–CH(OH)–Ph → **6c**). Moreover, unlike **29**, the generated hemiaminal has an N–H proton (in *italics*) thus allowing the concurrent dehydration to imine **2c**. As presented in a forthcoming paper,[33] compounds **5c** (some of it), **12** and **13**, were also derived from benzylamine. It is worth mentioning that the origin of **6a** and **b** and **7a** and **b** (amides I in Scheme 2) will be clarified elsewhere.[33]

ox: oxidation

$$\text{Bn-N(CH}_2\text{R)-CO-R}^1$$
8a-e

$$\text{Bn-NH-CH}_2\text{R} + \text{R}^1\text{-CHO} \rightleftharpoons \text{Bn-N(CH}_2\text{R)-CH(OH)R}^1$$

1a-b **5a-c** **29a-e** + **1a**

(R=R¹=H) $(\text{Bn-NMe-})_2\text{CH}_2$
14

HCN

−H₂O

$$\text{Bn-NH-CH}_2\text{R} + \text{R}^1\text{-CH(OH)-CN} \rightleftharpoons \text{Bn-N(CH}_2\text{R)-CH(CN)R}^1$$

1a-b **30a-c** **17a-e**

1, 5, 30	R/R¹
a	H
b	Me
c	Ph

8, 17, 29	R	R¹
a	H	H
b	Me	Me
c	Me	H
d	H	Ph
e	Me	Ph

Scheme 3. Formation of **8**, **14** and **17**.

These considerations are also supported by the results obtained in the presence of cyanide (TI-10,11). In this case, along with some compounds encountered in the corresponding cyanide-free reactions, most of the starting amine was consumed in the formation of new, cyano-containing products: nitriles **15**–**17**, cyanoimines **18** and **20**, cyanonitrones **21** and **22**, as well as derivatives **23**–**25**. Identification of benzylamine **11** in the oxidation mixture derived from **1a** (TI-10) confirmed the preceding deductions on its formation. As already reported,[22] formamidines **23** and their hydrolysates **24** and **25** are side products, which do not involve oxidation of **1a** and **b**. Therefore, they are not important for the present discussion.

In general, all nitriles (**15**–**17**) could be formally derived by substituting the C=O function in the analogous amides **6**–**8** with the CH–CN group. As depicted in Scheme 3, nitriles **17a**–**e** might result from **1a** and **b** and cyanohydrins **30a**–**c**,

formed in turn from **5a–c**. It is well known that cyanohydrins result easily by adding an aldehyde (or aliphatic ketone) to a cyanide-containing medium.

Compounds **18** and **20–22** are not primary oxidation products of **1a** and **b**. As presented below, some of them might derive from the oxidation of **4a** and **b**, *via* **9a** and **b** and **10a** and **b**. The existence of nitrones **9a** and **b** (TI-1,2,11) implies the transient formation of **4a** and **b** in all oxidations of **1a** and **b**, respectively. In fact, it is well known that nitrones are usually prepared by oxidation of hydroxylamines under various conditions.[34–36] It is also known that secondary amines can give nitrones directly, especially under tungsten catalysis,[37] but low--valent ruthenium compounds can also be used under certain conditions (for instance, with catalytic tetra-*n*-propylammonium perruthenate).[38] The possible oxidation of imines to nitrones (such as **2a–c** → **9a–c**) can be excluded in the present case, because it requires peracids.[39]
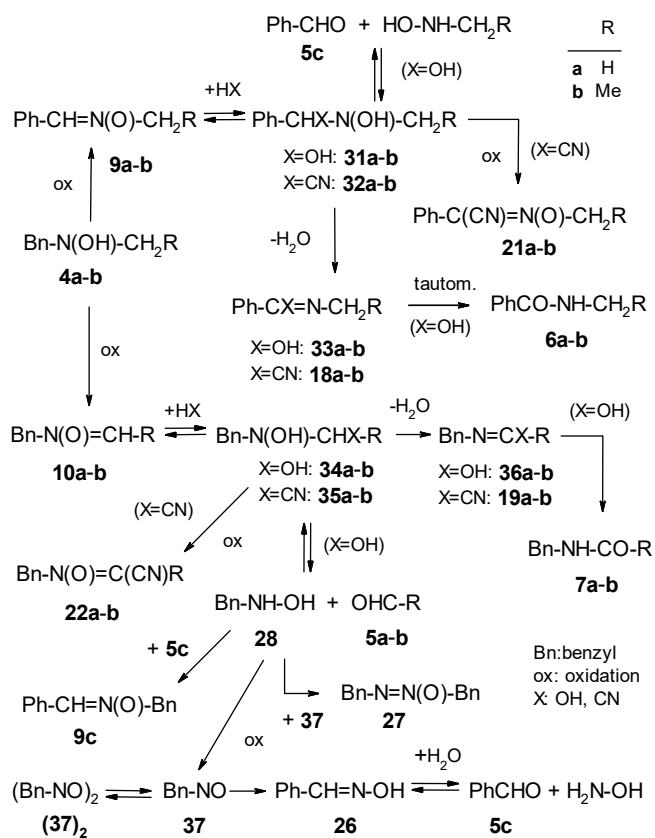
The oxidation of **1a** and **b** was performed with the H_2O_2/Na_2WO_4 system and the expected mixtures of nitrones **9a**+**10a** and **9b**+**10b**, respectively, were obtained. The cumulated yields of about 50 % (see Experimental) were in contrast to the very modest values obtained under RuO_4-catalysis (TI-1,2,10,11). This raises doubts about the implication of nitrones (and by extension of hydroxylamines) as the main intermediates during the RuO_4-oxidation of **1a** and **b**. A detailed comparison of oxidation products would clarify this supposition.

Oxidation of hydroxylamines 4a and b and related nitrones

Under cyanide-free conditions (TI-3,4), **4a** and **b** gave mainly benzaldehyde (**5c**) and small amounts of **6a**+**7a**/**6b**+**7b**, **12** and **13**. In both cases, two new compounds appeared, which were identified as benzaldoxime (**26**) and 1,2-bis(phenylmethyl)diazene 1-oxide (**27**).

In the presence of cyanide (T1-12), the oxidation of **4a** gave mainly nitrone **9a**, but cyano-containing derivatives **18a**, **21a**, and **22a** were also formed. More informative was the behavior of **4b** (T1-13). Analogously with **4a**, compounds **9b**, **18b**, **21b**, and **22b** were present, but accompanied by another nitrone, **10b**. The two nitrones, **9b** and **10b**, accounted for 65 % of the reacted **4b**. The formation of the nitrones **9b** and **10b** suggested that **4b** was attacked at both N-α-positions, namely benzylic and alkylic, respectively (Scheme 4). This is probably the first reaction step in all RuO_4-mediated oxidations of **4a** and **b**, but, usually, only the most stable nitrones (under the considered conditions) are observed.

The behavior of all four nitrones was verified and it was found that the N-alkylic ones (**9a** and **b**) were completely transformed under conditions A (conversion of 100 % in TI-5,6), but only partially under conditions B (≈21 % in TI-14,15). At the same time, the N-benzyl nitrones **10a** and **b** were completely transformed under both A (TI-7,8) and B conditions (TI-16,17), meaning that they are less stable than their N-alkyl analogs **9a** and **b**.

Ph-CHO + HO-NH-CH$_2$R   R
         5c   ――――
                        (X=OH)   **a** H
   +HX   **b** Me

Ph-CH=N(O)-CH$_2$R ⇌ Ph-CHX-N(OH)-CH$_2$R ―――
                                              (X=CN)
                      X=OH: **31a-b**   ox
    ↑ **9a-b**   X=CN: **32a-b**
 ox   Ph-C(CN)=N(O)-CH$_2$R
                                           21a-b
Bn-N(OH)-CH$_2$R   -H$_2$O ↓
    4a-b
                                    tautom.
                   Ph-CX=N-CH$_2$R ――――― PhCO-NH-CH$_2$R
    ox   (X=OH)
                     X=OH: **33a-b**   **6a-b**
                     X=CN: **18a-b**
        +HX   -H$_2$O   (X=OH)
Bn-N(O)=CH-R ⇌ Bn-N(OH)-CHX-R ―→ Bn-N=CX-R ―――
  10a-b   X=OH: **34a-b**   X=OH: **36a-b**
                X=CN: **35a-b**   X=CN: **19a-b**
   (X=CN)   ↓
          ╱   ↕ (X=OH)   Bn-NH-CO-R
      ox   **7a-b**
Bn-N(O)=C(CN)R
   22a-b   Bn-NH-OH + OHC-R
                                          Bn:benzyl
      + 5c ╱   **28**   **5a-b**   ox: oxidation
          ╱   X: OH, CN
Ph-CH=N(O)-Bn   └―→ Bn-N=N(O)-Bn
    9c   + 37   **27**
            ╱ ox
                         +H$_2$O
(Bn-NO)$_2$ ⇌ Bn-NO ―→ Ph-CH=N-OH ⇌ PhCHO + H$_2$N-OH
  (37)$_2$ **37**   **26**   **5c**

Scheme 4. Oxidation of **4a** and **b**, **9a** anb **b**, **10a** and **b** and **28**.

The behavior of **9a** and **b** and **10a** and **b** is more consistent with hydrolysis than with oxidation, at least in the first step. For instance, **9a** and **b** gave large (≈77 %) or medium (≈33 %) amounts of benzaldehyde (**5c**) under conditions A and B, respectively. The imagined formations of the corresponding intermediates **31a** and **b** and **32a** and **b** are presented in Scheme 4. Under A-conditions, **31a** and **b** can be either broken to a mixture of **5c** + an aliphatic hydroxylamine, or dehydrated to **33a** and **b**, the enolic form of the most stable benzamides **6a** and **b**. Under B-conditions, the intermediates **32a** and **b** can suffer either oxidation to cyanonitrones **21a** and **b**, or dehydration to the corresponding cyanoimines **18a** and **b**. Actually, it is well known that, under non-oxidative conditions, imines **18a** and **b** can easily be obtained from **9a** and **b** and sodium cyanide in aqueous ethanol.[40]

A similar reaction scheme was imagined also for **10a** and **b** (Scheme 4). Nucleophilic addition of HX affords **34a** and **b** (X=OH) or **35a** and **b** (X=CN). Analogously to **31a** and **b**, the intermediates **34a** and **b** can give **28**+**5a** and **b**

and/or amides **7a** and **b** (*via* **36a** and **b**). Similarly to **32a** and **b**, the intermediates **35a** and **b** could be the sources of cyanonitrones **22a** and **b** and/or cyanoimines **19a** and **b**. However, no explanation can offered for the absence of **19a** and **b**. Turning back to the reactions of **10a** and **b** (TI-7,8), it was noted that about 50 % of the substrate was consumed towards benzaldehyde **5c**. Why **5c** and not benzyl-hydroxylamine **28**, the logical output of hydrolyzed **10a** and **b**, as expected from Scheme 4?

To understand these transformations, the oxidation of **28** was studied separately. In the reaction mixture (TI-9), **5c**, nitrone **9c**, benzaldoxime **26**, and the azoxy compound **27** were found; a similar composition was obtained under B-conditions (absent in Table I). Remember that all these compounds were also present in the oxidation mixtures of **10a** and **b**. The reaction was interpreted as depicted in Scheme 4, where **28** is oxidized first to the nitroso derivative **37**, which is in equilibrium with its dimer **(37)$_2$**. The key intermediate **37** could give **26** (by tautomerization), but also **27** by condensation with unreacted **28**. Benzaldehyde **5c**, generated from **26** by hydrolysis, could be the source of nitrone **9c**, after condensation with **28**. The dimer **(37)$_2$** was not synthesized, but a rapid NMR scan of the analyzed sample showed the presence of a transient compound with NMR characteristics (a CH$_2$–singlet at 5.37 ppm (63.1 ppm) long-range coupled with peaks at 129.4 (*ortho*-arom. CH) and 134.1 ppm (*ipso*-arom. C), similar to those given in the literature for 1,2-bis(phenylmethyl)diazene 1,2-di-oxide (**(37)$_2$**).[41,42] Moreover, in the absence of **28** and directly in the NMR tube, it gave **26** quantitatively, in a few hours. This is not surprising, since transformations such **37** → **26** are well known for about 125 years; the reaction is catalyzed by acids or bases.[43,44]

The presence of **9c**, **26** and **27** in an oxidation mixture might be considered as a fingerprint for the previous existence of nitrones **10a** and **b**. The fact that some of them are absent in the reaction mixtures of **4a** and **b** (TI-3,4,12) is probably due to their relative amounts, presumably too small to be detected. The same reason could be invoked for entry 13, when all three compounds were missing, probably because too little **10b** underwent hydrolysis. It is now clear that the behavior of **4** is the sum of that of corresponding nitrones **9** and **10**.

Comparison of results

Now it is possible to compare the reaction products formed from **1a** and **b** with those derived from **4a** and **b**. In these comparisons, compounds **8a–e** (amides II in Scheme 2), **14** and **17a–e** (nitriles II) were not considered, as they could not result from **4a** and **b**, because their formation requires the presence of amines **1a** and **b**. However, if **4a** and **b** are the main reaction intermediates, their oxidative outputs should explain the formation of benzylamine **11**, as well as of aldehydes **5a**+**5c** and **5a**+**5b**+**5c**, respectively.

Comparison of the reaction products derived from **1a** (TI-1,10) with those resulting from **4a** (TI-3,12) and/or **9a**+**10a** (TI-5,14 + TI-7,16) shows that **2a**, **2c**, **6c**, **11**, **15a**, **16a** and **20a** were derived from **1a** only. On the contrary, **9c**, **26** and **27** resulted from **4a** only. Similar observations could be made comparing the outputs of **1b** (TI-2,11) with those of **4b** (TI-4,13) and **9b**+**10b** (TI-6,15 + TI-8,17): **2b**, **2c**, **5a**, **6c**, **15b**, **16b** and **20b** came from **1b** only, but the unique source of **9c**, **26** and **27** was **4b** (or **9b**+**10b**). This means that, under conditions A, the oxidation of **4a** and **b** cannot explain the formation of imines **2a** and **b** and benzylamine (source of **2c** and **6c**). In the case of **4b**, it must add also the lack of any species implying formaldehyde (**5a**), used by **1b** to generate **8c**, as in Scheme 3. Moreover, under conditions B, the oxidation of **4a** and **b** does not imply the formation of nitriles **15a** and **b** and **16a** and **b** (the HCN-trapped forms of **2a** and **b** and **3a** and **b**, respectively).[33] At the same time, although **18**+**21**+**22** are generated from hydroxylamines **4** as well as from amines **1**, the cyanoimines **20** are formed only from **1**. This causes doubts regarding the route followed to generate all cyanoderivatives **18** and **20**–**22**. Actually, it will be shown[33] that during the oxidation of **1a** and **b**, the real source of **18**+**20**+**21**+**22** is just the oxidation of **15a** and **b** and **16a** and **b**. At the same time, no **9c**, **26**, nor **27** seemed to be ever formed from **1a** and **b**.

All these considerations do not favor **4a** and **b** as the main intermediates during the RuO$_4$-mediated oxidation of **1a** and **b**. However, this route does exist, but its minor role consists only in the formation of small amounts of nitrones **9a** and **b** and **10a** and **b**.

CONCLUSIONS

Hydroxylamines Bn–N(OH)–CH$_2$R (**4a** and **b**; R=H and Me) and nitrones PhCH=N(O)–CH$_2$R (**9a** and **b**) are present in minute amounts in the RuO$_4$-mediated oxidation mixtures derived from the secondary amines Bn–NH–CH$_2$R (**1a** and **b**). Careful comparative analysis of the complex reaction mixtures showed that **4a** and **b**, **9a** and **b**, as well as nitrones Bn–N(O)=CH–R (**10a** and **b**) cannot be the main oxidation intermediates of **1a** and **b**.

SUPPLEMENTARY MATERIAL

NMR (^{1}H and ^{13}C) and MS data for **1**, **2** and **4**–**28** are available electronically from http://www.sbd.org.rs/JSCS/ or from the corresponding author on request..

И З В О Д

ОКСИДАЦИЈА СЕКУНДАРНИХ АМИНА УЗ ПОСРЕДОВАЊЕ RuO$_4$. ДЕО 1. ДА ЛИ СУ ХИДРОКСИЛАМИНИ ГЛАВНИ ИНТЕРМЕДИЈЕРИ?

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Оксидација секундарних амина Bn–NH–CH$_2$R (**1a** и **b**; R=H, Me) RuO$_4$ катализатором даје као главне производе амиде, али и незнатне количине нитрона PhCH=N(O)–CH$_2$R (**9a** и **b**) и Bn–N(OH)–CH$_2$R (R=H, **4a**) у траговима. У присуству цијанида идентификована су 22 производа, углавном α-аминонитрили. Поређењем производа оксидације **1a** и **b** са производима оксидације **4a** и **b**, **9a** и **b** и Bn–N(O)=CHR (**10a** и **b**) закључено је да производи **4a** и **b** не могу бити главни реакциони интермедијери који се формирају из полазних једињења **1a** и **b**.

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