ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2016, *61*(4-5), 319-325

Dedicated to Professor Alexandru T. Balaban on the occasion of his 85th anniversary

1-CYANOFORMAMIDINES. FORMATION DURING THE RuO_4-MEDIATED OXIDATION OF SECONDARY AMINES

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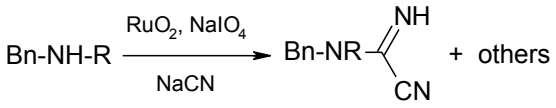
Received July 23, 2015

When performed in the presence of cyanide and at pH smaller than 5, the RuO_4-mediated oxidation of secondary amines Bn-NH-R (**1a-b**; R=Me, Et) gave mainly 1-cyanoformamidines Bn-NR-C(=NH)-CN (**2a-b**) and their hydrolysis products Bn-NR-COCN (**3a-b**), Bn-NR-CN (**4a-b**), Bn-NR-$CONH_2$ (**5a-b**). Carboxamides **5a-b** can result also directly from **1a-b**.



INTRODUCTION

Amidines are interesting compounds in many fields of chemistry and technology. They have been used extensively as pharmacological agents,[1] pesticides,[2] linkers in solid-phase reactions,[3] or as electrophiles,[4] but also in organic synthesis to build heterocycles,[5] as protective groups for primary amino function (*i.e.* in nucleosides),[6] and even in asymmetric preparations.[7]

The synthesis of amidines starts in principle from amines and compounds having C=N or C≡N bonds like those in amides or nitriles.[8] Actually, the reactions proceed well with some more active derivatives, such as metallated amines, imidoyl halides or imido esters. Quite unexpectedly, our experiments on the RuO_4-mediated oxidation of secondary amines[9] like *N*-methyl- (**1a**) and *N*-ethylbenzylamine (**1b**) revealed the formation of 1-cyanoformamidines **2a-b** (Scheme 1). Trial experiments showed also that the compounds **3-5** derived from **2**. We report in this paper the experimental proofs on the structures **2-5** and their affiliations. The quantitative results are presented in Table 1. To gain in simplicity, the entries of Table 1 (let be x and y) will be cited as T1-x,y, throughout this paper.

RESULTS AND DISCUSSION

In the same conditions as those for the tertiary aliphatic amines, studied by us before,[10] the RuO_4-mediated oxidation of secondary amines **1a-b** in the presence of NaCN gave a plethora of reaction products (T1-1,2), which, for practical purposes, were divided in two categories: **2-5** and **6-25**. As indicated in Scheme 1, the compounds **6-25** have various structures: imines (**6**), α-diamines (**7**), amides (**8-12**), α-aminonitriles (**13-17**), cyanoimines (**18-19**), cyanonitrones (**20-21**), nitrones (**22**), etc. All of them derive from the

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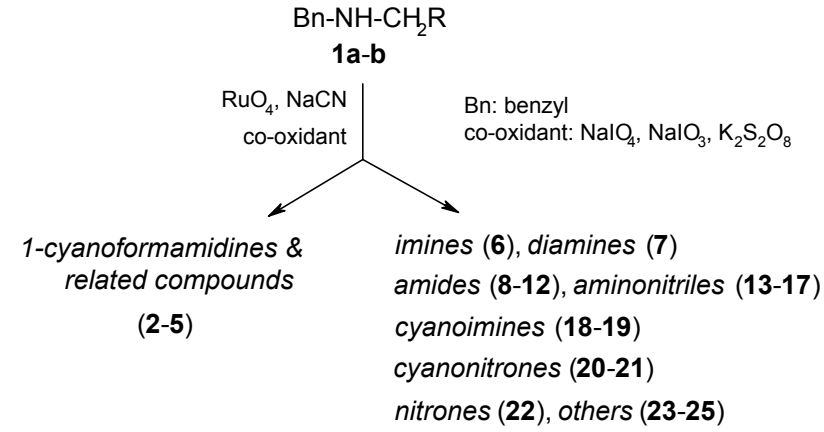
oxidation of **1a-b**, by a mechanism which will be presented elsewhere.[9] Just as an example, imine **6b** is the result of the oxidative attack at the benzylic site of **1b**; nucleophilic addition of water or HCN at the C=N bond of **6b** gave benzamide **8b** or aminonitrile **13b**, respectively. Analogously, the oxidative attack at the *N*-α-alkylic site of **1b** produces the imine Bn-N=CH-CH_3, which is trapped by water or HCN to give acetamide **10b** or α-aminonitrile **15b**, respectively.

At variance with **6-25**, derivatives **2-5** are not oxidation products of **1a-b**. They originate from another oxidation step, that of cyanide. For instance, 1-cyanoformamidines **2a-b** resulted as the addition adducts between **1a-b** and dicyan, where dicyan came from the oxidation of cyanide by the co-oxidant (Scheme 2, route *a*). Actually, this type of reaction is widely used to obtain 1-cyanoformamidines[8b, 11] and we followed it to synthesize **2a-b** for the first time (see Experimental).



R: H (**a**), Me (**b**), Ph (**c**)

2a-b Bn-N(CH_2R)-C(=NH)-CN
3a-b Bn-N(CH_2R)-CO-CN
4a-b Bn-N(CH_2R)-CN
5a-b Bn-N(CH_2R)-CO-NH_2
6a-c Ph-CH=N-CH_2R
7a,c (Bn-NMe-)$_2$CH-R
8a-b PhCO-NH-CH_2R
9a-b PhCO-N(CH_2R)-Bn
10a-b Bn-NH-CO-R
11a-b Bn-N(CH_2R)-CO-R
12 Bn-NEt-CHO
13a-b Ph-CH(CN)-NH-CH_2R
14a-b Ph-CH(CN)-N(CH_2R)-Bn
15a-b Bn-NH-CH(CN)-R
16a-b Bn-N(CH_2R)-CH(CN)-R
17 Bn-NEt-CH_2-CN
18a-b Ph-C(CN)=N-CH_2R
19a-b Ph-CH=N-CH(CN)-R
20a-b Ph-C(CN)=N(O)-CH_2R
21a-b Bn-N(O)=C(CN)-R
22a-b Ph-CH=N(O)-CH_2R
23 PhCHO
24 PhCN
25 PhCONH$_2$

Scheme 1

Table 1

Oxidation of **1a-b** in the presence of cyanide

Entry nr.	Substrate (conv., %)[a]	Method[b]	Reaction products (yield, %)[c]	
			Compds. **2-5**	Compds. **6-25**
0	1	2	3	4
1.	**1a** (13)	*A*	**2a** (2.9), **4a** (1.0), **5a** (4.5)	**6c** (1.2), **8a** (0.4), **9a** (8.9), **10a** (0.7), **11a** (1.8), **13a** (6.3), **14a** (15.3), **15a** (2.2), **16a** (18.2), **18a** (0.6), **19a** (0.3), **20a** (0.4), **21a** (0.8), **23** (0.9), **24** (0.9)

Table 1 (continued)

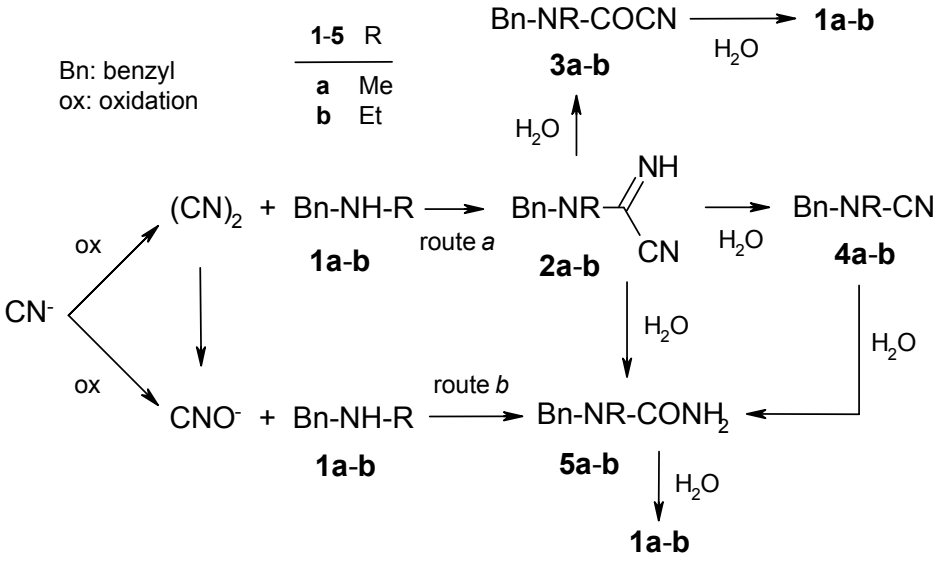
2.	**1b** (37)	*A*	**2b** (4.2), **4b** (0.9), **5b** (8.0)	**6b** (5.2), **6c** (1.8), **8b** (0.5), **9b** (2.7), **10b** (0.6), **11b** (0.6), **12** (1.0), **13b** (15.6), **14b** (8.1), **15b** (10.9), **16b** (1.0), **17** (9.9), **18b** (0.8), **19b** (0.5), **20b** (0.5), **21b** (0.9), **22b** (7.8), **23** (0.5), **24** (1.5)
3.	**1a** (74)	A_1	**2a** (36.6), **3a** (0.2), **4a** (0.4), **5a** (30.8)	**9a** (2.8), **11a** (1.7), **14a** (5.3), **16a** (2.7), **24** (0.6)
4.	**1b** (72)	A_1	**2b** (50.3), **3b** (0.2), **4b** (0.5), **5b** (17.2)	**9b** (2.6), **11b** (2.2), **12** (8.3), **14b** (3.4), **17** (2.9), **24** (0.5)
5.	**1b** (89)	A_2	**5b** (84.1)	**6b** (0.7), **6c** (1.0), **9b** (0.3), **11b** (0.6), **12** (0.3), **22b** (0.5), **23** (2.7)
6.	**1a** (10)	A_3	**2a** (1.0), **4a** (0.5), **5a** (6.4)	**6c** (1.2), **8a** (0.9), **9a** (7.4), **11a** (2.7), **13a** (6.2), **14a** (15.7), **15a** (14.8), **16a** (16.0), **24** (0.4), **25** (0.6)
7.	**1a** (25)	A_4		**6c** (1.7), **7a** (3.0), **7c** (3.3), **8a** (2.9), **9a** (16.0), **11a** (2.7), **13a** (23.0), **14a** (5.4), **15a** (4.8), **16a** (2.4), **24** (1.9)
8.	**1b** (14)	A_4		**6c** (4.4), **9b** (17.9), **11b** (2.3), **12** (4.6), **13b** (17.0), **14b** (1.1), **15b** (6.1), **16b** (5.0), **17** (0.6), **23** (1.7), **24** (1.7)
9.	**1b** (10)	A_5	**2b** (19.7), **3b** (0.2), **4b** (3.9), **5b** (1.8)	**6c** (2.2), **8b** (1.2), **9b** (5.6), **11b** (1.8), **12** (2.2), **14b** (6.9), **17** (0.6), **24** (0.3)

[a] Conversion calculated against the reacted substrate. [b] Reaction conditions (for 1 mmol of substrate): *A* - RuO_2 (10-15 mg), co-oxidant $NaIO_4$ (4 mmol), NaCN (4 mmol), $CHCl_3$/water = 10/20 (mL/mL), room temperature, 3h; A_1 - as in *A*, but AcOH (1 mL) was added too; A_2 - as in *A*, but KOCN (2 mmol) was used instead of NaCN; A_3 - as in *A*, but $K_2S_2O_8$ (3 mmol) was used as a co-oxidant; A_4 - as in *A*, but $NaIO_4$ was replaced by $NaIO_3$; A_5 - as in A_4, but AcOH (1 mL) was added too. [c] Yields (molar ratios of product/reacted substrate) are calculated from NMR and MS spectra (see also Experimental), regardless of the stoichiometry.

Formamidines **2a-b** are not very stable, but full spectral characterization was possible (see Experimental). Thus, the ^{1}H-NMR spectrum of **2a** shows two rather broad singlets for methyl and benzyl protons at 2.98 and 4.65 ppm, respectively. Interestingly, the corresponding carbon signals are missing, but very broad signals (centered at about 34 and 55 ppm, respectively) could be seen in more concentrated solutions. However, the *C*(=NH) signal (142.6 ppm) was coupled with methyl and benzyl protons in the long range heteronuclear correlation experiment (HMBC), in accord with the proposed molecular structure. Its high field-shifted value is due to the electronic effect exerted by the C≡N substituent. Unlike **2a**, the amidic analog **3a** presented two sets of signals for its protons and carbons (*i.e.* two species are present) and well resolved ^{1}H-^{13}C correlations (either for directly bound atoms or for long range connections). The same is true for the pair **2b**/**3b**.

The mentioned NMR features of **2** can be due to the restricted rotation about the (Bn)N-C(=NH) single bond,[12] similarly to the well-known rotation about the (Bn)N-C(=O) amidic bond[13] in **3**. The reason of this *E*/*Z* isomerism lies in the partial double bond character of these bonds. On going from one amidic isomer to another, the corresponding energetic hill ($\Delta G^{\#}$) to be passed is high enough (usually 20 kcal/mol) for the NMR-time scale and separate signals are generally observed for each isomer, which is actually the case of **3**. On the contrary, the just described NMR characteristics of **2a** correspond to a mediate spectrum, taken around the coalescence temperature. In other words, the $\Delta G^{\#}$ value in **2** should be smaller than that in **3**. Indeed, it is known that rotational barriers for simple amidines fall mostly in the range of 12-15 kcal/mol.[12] Full characterization of the restricted rotation in **2a-b** and **3a-b** is out of the scope of this paper.

The instability of **2a-b** is due especially to hydrolysis. The rate of reaction is greater in alkaline media,[9] in accord with the literature data on the hydrolysis of amidines. It is known that the hydrolysis rate is subjected to general acid-base catalysis[14] and that base-catalyzed reactions are usually more rapid than those in acidic media.[14,15] The last hydrolysis product is the corresponding parent amine **1**, but various amounts of the intermediates **3-5** can be seen in the earlier stages. Compounds **3-5** are hydrolysable compounds too, but at different rates. For instance, on one hand, carbamoyl cyanides **3** are much more reactive (**3**→**1**) than **2** and, on the other hand, cyanamides **4** are at least three times more easily hydrolysable than carboxamides **5** (**4**→**5**→**1**). These considerations might explain the relative amounts of **2-5** found by us in T1-1,2. The fact that some **1** resulted always during the hydrolysis of **2** has two important consequences: (i) the "real" conversions of **1a-b** should be higher than those written in column 1 of Table 1 and (ii) the inverse situation holds for the yields in columns 3 and 4. Unfortunately, these corrected values cannot be known. All transformations of **1-5** are summarized in Scheme 2.



Scheme 2

The sums **2**+**3**+**4**+**5** cover only about 10% of the reacted amine in our standard[9,10] *A*-conditions (T1-1,2), for which pH ~ 9. On changing the pH at about 4.5, the same sums become about 68% (T1-3,4). This is due to two factors acting in the same direction in acid *vs.* alkaline media: (i) the equilibria (1) and (2) are shifted more to the right and (ii) as mentioned before, since **2** is more stable, less **1** is generated by hydrolysis and, consequently, the quoted yields and conversions are more close to the "true" values.

(1) $CN^- + H^+ \rightleftharpoons HCN$

(2) $HCN \overset{\text{oxidant}}{\rightleftharpoons} (CN)_2$

At the same time, the highest contributions in the indicated sums belong to **2** and **5** whatever the pH, but their ratio depends on it. Thus, **2a**/**5a** is 0.6 in T1-1, but 1.2 in T1-3. Analogously, **2b**/**5b** passes from 0.5 (T1-2) to 2.9 (T1-4). Again, this pH-dependence might reflect the greater stability of **2** in acidic media. However, in our opinion, in basic media, the formation of cyanate [either by direct oxidation of CN^-, or by hydrolysis: $(CN)_2 + H_2O \rightarrow HCN + HCNO$] is relatively favored and extra **5** could result by the direct reaction **1** + CNO. This last possibility is exemplified in T1-5, where, by using OCN^- instead of CN^-, about 84% of the reacted **1b** was found as **5b**, without traces of **2b**, **3b**, and/or **4b**. The analogous reaction with **1a** is missing from Table 1, to avoid unnecessary duplication of results. This alternative path to obtain more **5** is also shown in Scheme 2 (route *b*).

At the beginning of this work, we suspected that cyanamides **4** came from the reaction **1** + ICN → **4** + HI, where ICN is the reduced form of IO_4^- in the presence of cyanide. However, the additional experiments of T1-6,7,8 cancelled out this supposition. More specifically, when using $K_2S_2O_8$ as a co-oxidant (T1-6) instead of $NaIO_4$ (T1-1), the cyanamide **4a** is still formed, despite the fact that ICN cannot be present. Clearly, the oxidation HCN → $(CN)_2$ was involved in both cases and dicyan is the source of all four derivatives **2a**-**5a**. It emerges also that the reduced form of the co-oxidant IO_4^- was IO_3^- and not I^+ (as in ICN). We verified this by titration:[16] at the end of reaction, the initial amount of IO_4^- was found to be a mixture of about 80% IO_3^- and 20% of unreacted IO_4^-.

What happens when $NaIO_3$ replaces $NaIO_4$ as a co-oxidant? As indicated in T1-7,8, all compounds **2**-**5** were missing. This means that, unlike periodate, iodate cannot oxidize HCN into $(CN)_2$ at basic pH. This is not surprising since the iodate, a less powerful oxidant than periodate, requires acid conditions to operate.[16] In fact, all **2**-**5** reappeared by setting the pH value to about 4.5 (T1-9 *vs*. T1-8).

EXPERIMENTAL

General. Melting points were taken on a Boetius hot plate and are uncorrected. Elemental analyses were performed with EAS32 Station Costech 2002. FT-IR spectra were registered on a Bruker Vertex 70 apparatus. NMR spectra were recorded with a Varian Unity INOVA 400 spectrometer, operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). Mass spectra were

obtained by electron impact (70 eV), with a GC-MS 6890 Agilent apparatus. The gas-chromatograph module consisted of an Agilent 19091s-433 capillary column (0.25 mm × 30 m) fitted with 5% phenyl methyl siloxane, operating under constant flow of helium as carrier gas and a temperature range from 40 to 300°C with a 10°C/min heating rate.

Materials. Compounds **1a**, **6c**, hydrated RuO_2, $K_2S_2O_8$ (all from Aldrich), **1b**, **10a**, **23-25**, $NaIO_3$, and $NaIO_4$ (all from Merck) were used as purchased. Derivatives **6a-b**, **7a**, **8a-b**, **10b**, **11a-b**, **12**, **16a-b**, and **17** were from our previous work.[10b] Compounds **7c**,[17] **9a**,[18] **9b**,[19] **13a**,[20] **13b**,[21] **14a-b**,[22] **15a**,[23] **15b**,[24] **18a-b**,[25] **19a**,[26] **19b**,[27] **20a-b**,[28] **21a-b**,[23] **22a**,[29] and **22b**[30] are all known and were prepared according to the indicated procedures. The NMR characteristics of **2-5**, the most interesting compounds from the point of view of this paper, are presented in Table 2, where the chemical shifts are expressed in ppm against internal $(CH_3)_4Si$ ($\delta_H = 0$) or $CDCl_3$ ($\delta_C = 77.16$). Compound **7c** appeared only in the conditions of T1-7[9,10b] and for this reason its NMR features were also included in Table 2.

N-Benzyl-N-methyl-carbonocyanidimidic amide (**2a**). Dicyan gas, generated from copper sulphate (10 g, 0.04 mol) and potassium cyanide (7.8 g, 0.12 mol),[31] was passed at 6°C and under argon through a solution of **1a** (1 g, 8.2 mmol) in anhydrous benzene (15 mL). The solution was washed with saturated Na_2CO_3 aqueous solution, anhydrized over Na_2SO_4 and then the solvent was removed. The obtained viscous liquid (1.2 g; yield 84%) is **2a** sufficiently pure (~95%, by NMR). The compound is moderately stable at room temperature and it can be kept unchanged for a few days only. Decomposition occurs also on attempted distillation. The analytical sample was obtained by a rapid passage through a short column of basic alumina (Merck) eluted with a 7/3 (v/v) benzene/ethyl acetate mixture. Slow chromatographic process caused partial or total transformation of **2a**. *Elemental analysis* (%): found 69.03 (C), 6.19 (H), 24.51 (N); calculated 69.34 (C), 6.40 (H), 24.26 (N) for $C_{10}H_{11}N_3$. *FT-IR spectrum* (neat, cm^{-1}): 3328 (ν_{NH}), 2226 (weak, $\nu_{C\equiv N}$), 1672 ($\nu_{C=N}$), 1448. *MS spectrum* (m/z, %): 173 (M^+, 28), 172 (27), 158 (28), 120 (40), 106 (12), 92 (9), 91 (100), 77 (10), 65 (24).

N-Benzyl-N-ethyl-carbonocyanidimidic amide (**2b**) was obtained as an oil (yield 80%), from **1b** and dicyan, as described for **2a**. *Elemental analysis* (%): found 70.27 (C), 6.75 (H), 22.68 (N); calculated 70.56 (C), 7.00 (H), 22.44 (N) for $C_{11}H_{13}N_3$. *FT-IR spectrum* (neat; ν_{max}, cm^{-1}): 3328, 2230, 1598. *MS spectrum* (m/z, %): 187 (27, M^+), 186 (23), 158 (60), 134 (18), 106 (12), 91 (100), 79 (16), 77 (11), 65 (22).

Benzylmethylcarbonocyanidic amide (**3a**). Carbamic chloride Bn-NMe-COCl (**26**) was prepared from **1a** and triphosgene (Aldrich) in anhydrous benzene and in the presence of Et_3N as HCl scavenger.[32] The major impurity in the crude product was (Bn-NMe-)$_2$CO. Distillation gave pure **26** with b.p. of 118-120°C/1 mmHg (lit.[32] b.p. 98-99°/ 0.15 mm Hg). A solution of **26** (2.94 g, 16 mmol) in anhydrous dichloromethane (10 mL) was added dropwise to a stirred solution of tetraethylammonium cyanide (Aldrich; 2.5 g, 16 mmol) in anhydrous dichloromethane (15 mL) and the whole mixture was stirred for one hour. The solvent was evaporated, the residue taken in ether and the red solid discharged by filtration. Ether evaporation leaves 2.5 g of liquid **3a** (90% yield). The analytical sample was obtained by column chromatography on silica gel with benzene as eluent. The NMR characteristics shown in Table 2 matched well those given in the literature.[33]

Benzylethylcarbonocyanidic amide (**3b**) was obtained as an oil (yield 88%), from *N*-benzyl-*N*-ethylcarbamoyl chloride[32] and tetraethylammonium cyanide, just as described for **3a**. The purification was achieved by column chromatography on silica gel eluted with a 2/1 hexane/ethyl acetate mixture. *Elemental analysis* (%): found 70.31 (C), 6.69 (H), 14.58 (N); calculated 70.19 (C), 6.43 (H), 14.88 (N) for $C_{11}H_{12}N_2O$. *FT-IR spectrum* (neat; ν_{max}, cm^{-1}): 2230, 1685, 1498. *MS spectrum* (m/z, %): 189 (10), 188 (78, M^+), 187 (14), 159 (58), 107 (18), 92 (16), 91 (100), 79 (30), 77 (11), 65 (23).

Benzylmethylcyanamide (**4a**). A solution of **1a** (6.05 g, 0.05 mol) in CCl_4 (150 mL) was combined with an aqueous solution (140 mL) of NaCN (2.7 g, 0.055 mol). To this heterogeneous mixture and under vigorous stirring a solution of iodine (12.7 g, 0.05 mol) in CCl_4 (300 mL) was added dropwise at a rate ensuring the complete decolorization of the reaction mixture. The mixture was stirred for one hour, the lower layer separated, washed with aqueous 5% Na_2CO_3 solution, and anhydrized over Na_2SO_4. Solvent evaporation and distillation of the residue gave **28a** as a colorless liquid (6.2 g, yield 85%) with b.p. 120°C/8 mmHg (lit.[34] b.p. 139-142°C/12 mmHg). *MS spectrum* (m/z, %): 146 (M^+, 16), 92 (8), 91 (100), 65 (11.5).

Table 2

NMR characteristics of **2-5** and **7c**

Compd.	Chemical shifts ($CDCl_3$, δ, ppm) and assignments[a]
2a	δ_H: 2.98 (s, 3H, CH_3), 4.65 (s, 2H, Bn), 7.22-7.26 (br d, *J*~7.8, 2H, *o*), 7.28-7.42 (m, 3H, *m*+*p*), 7.56-7.76 (br s, 1H, NH);[b] δ_C: 32-36 (v. br, CH_3), 53-57 (v. br, Bn), 111.4 (C≡N), 127.7 (~br, *o*), 128.2 (*p*), 129.0 (*m*), *135.9*, 142.6 (C=N).
2b	δ_H: 1.13 (t, ^3J=7.0, 3H, CH_3), 3.43 (q, ^3J=7.0, 2H, CH_2), 4.63 (s, 2H, Bn), 7.24 (d, *J*=8, 2H, *o*), 7.26-7.50 (m, 4H, *m*+*p*), 7.52-7.72 (br s, 1H, NH);[b] δ_C: 12.0-12.6 (br, CH_3), 41.5-42.5 (v. br, CH_2), 49.5-50.5 (v. br, Bn), 111.5 (CN), 127.6-126.8 (br, *o*), 127.95 (*p*), 128.9 (*m*), *136.35*, 142.1 (C=N).
3a[c]	δ_H: 2.91+3.16 (s+s, 1.5+1.5H, CH_3), 4.59+4.76 (s+s, 1+1H, Bn), 7.22-7.46 (m, 5H, *o*+*m*+*p*); δ_C: 32.3+35.5 (CH_3), 50.5+54.7 (Bn), 110.6+110.8 (CN), 127.7+128.5 (*o*), 128.6+128.9 (*p*), 129.1+129.3 (*m*), *133.9*+*134.3*, 144.9+145.3 (CO).
3b[c]	δ_H: 1.10+1.26 (t+t, ^3J=7.1, 1.35+1.65H, CH_3), 3.38+3.56 (q+q, ^3J=7.1, 0.9+1.1H, CH_2), 4.61+4.76 (s+s, 1.1+0.9H, Bn), 7.23-7.29 (m, 2H, *o*), 7.32-7.43 (m, 3H, *m*+*p*); δ_C: 11.9+14.1 (CH_3), 40.1+43.2 (CH_2), 47.7+52.3 (Bn), 110.8+111.0 (CN), 127.7+128.45 (*o*), 128.48+128.85 (*p*), 129.1+129.3 (*m*), *134.3*+*134.85*, 144.7+145.2 (CO).
4a	δ_H: 2.78 (s, 3H, CH_3), 4.16 (s, 2H, Bn), 7.30-7.45 (m, 5H, *o*+*m*+*p*); δ_C: 37.9 (CH_3), 57.3 (Bn), 119.0 (CN), 128.5 (*o*), 128.7 (*p*), 129.0 (*m*), *134.45*.

Table 2 (continued)

4b	δ_H: 1.24 (t, ^3J=7.2, 3H, CH_3), 2.92 (q, ^3J=7.2, 2H, CH_2), 4.17 (s, 2H, Bn), 7.30-7.40 (m, 5H, *o*+*m*+*p*); δ_C: 12.5 (CH_3), 44.9 (CH_2), 55.4 (Bn), 117.6 (CN), 128.2 (*o*), 128.3 (*p*), 128.7 (*m*), *134.7*.
5a	δ_H: 2.91 (s, 3H, CH_3), 4.49 (s, 2H, Bn), 4.52-4.64 (br s, 2H, NH_2),[b] 7.20-7.30 (m, 3H, *o*+*p*), 7.34 (t, ^3J=7.2, 2H, *m*); δ_C: 34.9 (CH_3), 52.5 (Bn), 127.3 (*o*), 127.6 (*p*), 128.9 (*m*), *137.6*, 159.2 (CO).
5b	δ_H: 1.16 (t, ^3J=7.16, 3H, CH_3), 3.33 (q, ^3J=7.1, 2H, CH_2), 4.48 (s, 2H, Bn), 7.20-7.37 (m, 5H, *o*+*m*+*p*); δ_C: 13.3 (CH_3), 42.4 (CH_2), 50.3 (Bn), 127.1 (*o*), 127.6 (*p*), 128.9 (*m*), *137.8*, 158.9 (CO).
7c[d]	δ_H: 2.11 (s, 6H, CH_3), 3.60+3.68 [d+d (ABq), J_{AB}=13.7, 2+2H, Bn], 3.95 (s, 1H, N-CH-N), 7.18-7.46 (m, 15H, *o*+*m*+*p*+*o'*+*m'*+*p'*); δ_C: 37.8 (CH_3), 57.2 (Bn), 87.7 (N-CH-N), 126.7+128.3+128.8+*140.3* (*p*+*m*+*o*+*i*, resp.), 127.6+127.8+129.0+*135.6* (*p'*+*m'*+*o'*+*i'*, resp.).

[a] Benzyl and aromatic (*ortho*, *meta*, *para*) protons or carbons are abbreviated as Bn, *o*, *m*, and *p*, respectively. Aromatic *ipso* carbons are given in *italics*. [b] Vanishes with D_2O. [c] Two *E*/*Z* isomers are present. The values belonging to the major one are underlined; if of equal population, the "major" isomer was chosen arbitrarily. [d] Sign prime (') for *Ph*-CH atoms.

Benzylethylcyanamide (**4b**) was obtained from **1b** (0.05 mol), as described for **4a**. Colorless liquid (7.2 g, yield 90%) with b.p. 140°C/8 mmHg (lit.[34] b.p. 160°C/12 mmHg). *MS spectrum* (m/z, %): 160 (M^+, 16), 92 (8), 91 (100), 65 (9).

N-Benzyl-N-methylcarboxamide (**5a**). Nitrourea[35] (0.7 g, 6.7 mmol) was added portionwise to a solution of **1a** (0.86 mL, 6.7 mmol) in acetonitrile (20 mL). The mixture was heated at reflux for one hour and then cooled at 0°C. The precipitated white solid was recovered by filtration and it was dried in an oven at 100°C. Yield 0.76 g (70%) of white solid with m.p. 133-135°C. *Elemental analysis* (%): found 65.71 (C), 7.19 (H), 17.33 (N); calculated 65.83 (C), 7.37 (H), 17.06 (N) for $C_9H_{12}N_2O$. *FT-IR spectrum* (solid, cm^{-1}): 3387, 3188, 1655, 1592, 1492. *MS spectrum* (m/z, %): 165 (12), 164 (M^+, 98), 121 (15), 120 (71), 119 (24), 118 (35), 106 (64), 92 (13), 91 (100), 79 (17), 77 (17), 65 (25), 51 (12), 44 (41), 42 (28).

N-Benzyl-N-ethylcarboxamide (**5b**) was prepared in 55% yield from **1b** and nitrourea, as described for **5a**. M.p. 71-72°C (from acetonitrile). *Elemental analysis* (%): found 67.25 (C), 7.68 (H), 15.99 (N); calculated 67.39 (C), 7.92 (H), 15.72 (N) for $C_{10}H_{14}N_2O$. *FT-IR spectrum* (solid, cm^{-1}): 3456, 3398, 3213, 1630, 1598, 1497. *MS spectrum* (m/z, %): 178 (M^+, 25), 120 (18), 106 (40), 92 (11), 91 (100), 79 (11), 77 (10), 65 (14), 44 (11).

Oxidation of **1a**-**b**. To a solution of NaCN [196 mg (4 mmol) in 10 mL of water] was added $RuO_2.xH_2O$ (10-15 mg), followed by amine (1 mmol in 10 mL of $CHCl_3$) and the co-oxidant (4 mmol of $NaIO_4$ or $NaIO_3$, and 3 mmol of $K_2S_2O_8$; each in 10 mL of water), in this order, and the reaction mixture was vigorously stirred at room temperature for 3 hours. The mixture was filtered from a black solid and the two layers of the filtrate separated (*Note*). The aqueous layer was extracted with $CHCl_3$, the new organic layer combined with the older one, anhydrized (Na_2SO_4), and the solvent removed to give the residue I. The last aqueous layer was acidified with HCl, the $CHCl_3$-extraction repeated in order to obtain the residue II. Known quantities (usually 0.2 mmol) of *p*-dimethoxybenzene (DMB; internal standard) were added in residues I and II, the new mixtures taken up in $CDCl_3$ and the NMR and GC-MS spectra recorded. For most reaction products, the yields were calculated against DMB from the NMR data. In the case of compounds in small amounts or difficultly discernible by NMR (like **24** or **25**), the yields obtained from the MS spectra against DMB were corrected using known mixtures of DMB and pure compounds. As usually,[10] the yield of benzaldehyde (**23**) in Table 1 includes that of benzoic acid.

Identification of the various reaction products was performed on preliminary experiments, by adding small amounts of pure compounds into the analyzed $CDCl_3$ solutions and comparing the new NMR and GC spectra with the older ones. Meanwhile, the aforementioned residues were chromatographed on columns filled with silica gel or neutral alumina and eluted with hexane (or benzene)/ethyl acetate (or CH_2Cl_2) mixtures. The substrates **1a**-**b**, practically the main constituents of the samples, remained at the start point and could be recovered with methanol as eluent. The NMR and GC analyses of the various fractions evidenced the existence of all major compounds listed in Scheme 1 and clarified the formation of some products (like **9a**-**b**, **24**, **25**), hardly observable in more complex mixtures. At the same time, pure samples of **14a**-**b** were obtained this way. As mentioned in the main text, column chromatography cannot be used to separate from the reaction mixtures sensitive compounds such as **2a**-**b**.

Note. Sometimes, acetic acid (1 mL) was added before adding the co-oxidant (T1-3,4,9). In this case, the reaction mixture was first basified (aq. Na_2CO_3), before the filtration step.

CONCLUSIONS

Oxidation of aliphatic secondary amines BnNHR (**1a**-**b**; R=Me, Et) by the RuO_4/co-oxidant/NaCN system is in competition with the addition reaction between **1a**-**b** and dicyan, where dicyan comes from the oxidation of NaCN itself. The addition gives 1-cyanoformamidines BnNR-C(=NH)-CN (**2a**-**b**), which, at their turn, hydrolyze partially towards BnNR-CO-CN, BnNR-CN, and BnNR-$CONH_2$. The co-oxidant nature and the reaction pH govern the competition. Powerful co-oxidants like $NaIO_4$ or $K_2S_2O_8$ and pH < 5 favor the addition reaction. No addition occurs at all with a softer co-oxidant like $NaIO_3$ and at pH ~ 9. A reaction scheme is developed and discussed.

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