RuO$_4$-Mediated oxidation of N-benzylated tertiary amines. Four- and three-membered azacycloalkanes as substrates

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Abstract

Similarly to N-benzylpiperidine and -pyrrolidine, N-benzylazetidine underwent RuO$_4$-catalyzed oxidation by attack at both types of N-methylene C-H bonds: endocyclic and exocyclic (benzylic). If the reaction is performed in the presence of cyanide, α-aminonitriles were obtained instead of amides. The regioselectivity (endocyclic/exocyclic) decreased constantly with the decrease of the azacycle size, from about 2 (for N-benzylpiperidine) to about 0.6 (for N-benzylazetidine). The highest regioselectivity was found for N-benzylaziridine, for which only products of benzylic functionalization resulted. Iminium ions, complexed to ruthenium species, were proposed as reactive intermediates during the oxidation of N-benzylated azacycloalkanes.

Keywords: Oxidation, azacycloalkanes, ruthenium tetroxide, iminium ions, α-aminonitriles
Introduction

The powerful oxidant ruthenium tetroxide (RuO$_4$) is widely used to functionalize C-H bonds in various organic compounds, such as hydrocarbons, halides, ethers, alcohols, amines, or amides. Rarely, the oxidative attack takes place at a heteroatom, like in the transformation of sulfide into sulfone. Since RuO$_4$ has electrophilic character, the more electron-rich C-H bonds are attacked first. This explains why the C-H bonds in $\alpha$-position to a heteroatom are oxidized preferentially in alcohols, ethers or amines. In most cases these reactions result in products that are biologically active intermediates useful in the synthesis of amino acids, fragrances and drugs.

Regarding the oxidation of amines, primary or secondary ones (R$_2$CH-NH-R) are transformed by RuO$_4$ into imines (R$_2$C=N-R), by a formal 1,2-dehydrogenation process. In addition, a less common 1,1-dehydrogenation reaction transforms tertiary amines (R-CH$_2$-NR$_2$) to amides (R-CO-NR$_2$), with iminium ions as intermediates.

Our previous research on oxidation of tertiary amines focused on the oxidative behaviour of medium-size azacycloalkanes, namely 1-benzylpiperidine (1a) and 1-benzylpyrrolidine (1b). In this paper the studies are completed with the oxidation of small-ring analogues, 1-benzylazetidine (1c) and -aziridine (1d) (Scheme 1).

Results and Discussion

A general overview of the oxidation reactions of 1-benzylazacycloalkanes is presented in Scheme 1. Influence of the ring size on the reactivity and regioselectivity, in the RuO$_4$-mediated oxidation, revealed interesting aspects of the reaction mechanism.

![Scheme 1. Oxidative routes for 1a-d.](image-url)
Previously studied substrates 1a-b are tertiary amines with two types of N-CH$_2$ groups: endocyclic and exocyclic (benzylic). Both types of methylene C-H bonds are attacked to yield the corresponding iminium ions as intermediates (Scheme 1): endocyclic (2a-b) and exocyclic (3a-b). At the same time, small amounts of N-oxides (4a-b) were present in the reaction mixtures, indicating that an N-oxidative attack (Scheme 1) was possible only to a minor extent.

**Scheme 2. Oxidation products of 1a-d.**
The cations gave the final oxidation products after capture by nucleophiles, namely water under normal conditions (Scheme 2; part A). Along this pathway, the expected lactams 5a-b resulted from 2a-b, respectively, in essentially two steps. These steps are similar to those shown explicitly for the transformation of 3a-b into 6a-b: (i) formation of hemiaminals 7a-b and (ii) oxidation of these alcohols to yield benzamides 6a-b, respectively. Alternatively, the hemiaminals can split into benzaldehyde (BzH) and the corresponding unsubstituted azacycloalkanes 8a-b. Since iminium ions 2a-b carry β-N protons, stabilization to enamines 9a-b through deprotonation can occur. Further oxidation of the C=C double bond in 9a-b was the source of dioxygenated derivatives 10a-b and 11a-b.

When the oxidation was performed in the presence of NaCN, the initial iminium ions were trapped as the corresponding cyano derivatives 12a-b and 13a-b (Scheme 2, part B).

In this work, identically to the case of 1a-b,8 the oxidation of 1c-d was performed in two ways: in the absence of cyanide (conditions A) or in its presence (conditions B). The respective results are presented in Table 1, together with those previously obtained for 1a-b. For simplicity, the desired entry (x) of Table 1 will be cited as T-x. Since free benzoic acid is always derived from benzaldehyde (BzH),8-10,15,16 the amount quoted in Table 1 for BzH actually refers to the sum BzH+benzoic acid.

Values of endocyclic/exocyclic ratio (Selectivity) are shown in the last column of Table 1. Values smaller than 1 indicate that the exocyclic attack is favored. Analogously, the endocyclic attack will be favored when the Selectivity is greater than 1. A value of 1 for Selectivity means no regioselectivity. Selectivity was calculated with equations (1)-(3), where the amount of a particular compound is symbolized by its number in brackets:

\[
\text{endocyclic} = (5) + (10) + (11) + (12) \text{ [plus unk for T-2]} \\
\text{exocyclic} = (\text{BzH}) + (6) + (13) \\
\text{Selectivity} = \frac{\text{endocyclic}}{2 \times \text{exocyclic}}
\]

Since there are two identical endocyclic CH₂ groups, but only one exocyclic (benzylic), a statistical correction (the factor 2) is needed in equation (3).
<table>
<thead>
<tr>
<th>Entry no.</th>
<th>Substrate (recovd., %)</th>
<th>Reaction products (molar, %)</th>
<th>Selectivity</th>
</tr>
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<tr>
<td>0</td>
<td>1</td>
<td>A) Oxidations without NaCN</td>
<td>2.1</td>
</tr>
<tr>
<td>1</td>
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<td>4a (4), 5a (33.5), 10a (1), 11a (42), BzH (16), 6a (2)</td>
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<tr>
<td>2</td>
<td>1b (0)</td>
<td>4b (6.5), 5b (40.5), 10b (1.5), 11b (13.5), unk (5.5), BzH (27), 6b (4)</td>
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<tr>
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<td>1d (10)</td>
<td>BzH (51.3), 6d (3.2), 15 (2.7), 16 (0.5), 17 (1.3)</td>
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</tr>
<tr>
<td>5</td>
<td>1a (52)</td>
<td>4a (1.9), 5a (0.2), 11a (0.2), 12a (38.2), BzH (0.2), 13a (7.9)</td>
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</tr>
<tr>
<td>6</td>
<td>1b (6)</td>
<td>4b (4.7), 5b (&lt;0.5), 11b (&lt;0.5), 12b (60.6), BzH (1.9), 6b (0.5), 13b (24)</td>
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</tr>
<tr>
<td>7</td>
<td>1c (82)</td>
<td>4c (0.1), 12c (6.5), BzH (0.3), 13c (5.4)</td>
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<tr>
<td>8</td>
<td>1d (92)</td>
<td>BzH (0.2), 15 (1.7), 23 (0.4)</td>
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</table>

\[a\] Molar amounts calculated against the initially added substrate, taken as 100; see also Experimental. \[b\] Formulae in Schemes 1-3. \[c\] Regioselectivity (endocyclic/exocyclic) was calculated with eqs. (1)-(3). \[d\] Reaction conditions (for 1 mmol of substrate): A - RuO$_2$.xH$_2$O (10-15 mg), co-oxidant NaIO$_4$ (4 mmol), CCl$_4$ (for 1a-b) or CHCl$_3$ (for 1c-d) (10 mL), water (10 mL), room temperature, 3-5 h; B - as in A, but NaCN (4 mmol) in water (10 mL) was also added. \[e\] Data from ref. 8. \[f\] Including 1% of 1-benzyl-2,6-piperidinedione. \[g\] Including 1% of 1-benzyl-2,5-pyrrolidinedione. \[h\] Unknown benzylic compound. \[i\] Including variable amounts of oxazoline 14 (see text).

**Oxidation of azetidine 1c**

In the absence of cyanide (conditions A), azetidine 1c gave mainly benzaldehyde and benzamide 6c (T-3). Azetidinone 5c was formed too, albeit in a very small amount (T-3). No doubly oxygenated compounds such as 10c$^{17}$ or 11c$^{18}$ were present, in contrast to the results obtained for piperidine 1a (T-1) or pyrrolidine 1b (T-2).

In the presence of cyanide (conditions B), comparable amounts of cyano derivatives 12c and 13c resulted from 1c (T-7), indicating that both iminium ions 2c and 3c (Scheme 1) were generated. The presence of the N-oxide 4c, although in a relatively small amount, indicated that the third oxidative route (by N-attack, Scheme 1) was also active. Therefore, the oxidation of azetidine 1c follows the same scheme as that previously discussed for 1a-b.

Judging from the substrate recovery (7% in T-3, 82% in T-7), it appears that the oxidation occurred with more difficulty under conditions B. This appears to be true also for 1a and 1d (see below), but not for 1b. Some of this effect could be due to the involvement of cyanide in another reaction, namely the oxidation towards cyanogen.$^{19}$ This reaction subtracts both cyanide and periodate (co-oxidant) from the desired amine oxidation.
Interesting aspects come from the values of Selectivity. On one hand, the decrease of the size of the acyclic (1a → 1b → 1c) led to decreasing Selectivity values. Thus, the endocyclic route is relatively preferred by piperidine 1a (Selectivity ~ 2 in T-1 and T-5), no selectivity is shown by pyrrolidine 1b (Selectivity ~ 1 in T-2 and T-6), and the exocyclic route becomes favored in the case of azetidine 1c (Selectivity ~ 0 in T-3, but 0.6 in T-7). Practically, the absence of one CH₂ unit in the heterocycle resulted in a two-fold reduction of Selectivity, at least under conditions B.

On the other hand, for the same substrate, Selectivity has higher values under conditions B than under conditions A. In the case of 1a-b, there is only a tendency, but in the case of azetidine 1c the difference is quite clear: still being less favored than the exocyclic route, the endocyclic route seems to recover some order of magnitude on passing from conditions A (Selectivity = 0.002) to conditions B (Selectivity = 0.6). No explanation can be given for this yet. For instance, at first sight, one could invoke a possible change in the active oxidant, in connection with the known relationship between pH and the most stable oxidant structure: Ru⁸⁺O₄ under conditions A (pH ~ 5), but possibly the less aggressive agent [Ru⁷⁺O₄]⁺ under conditions B (pH ~ 9). This could explain the aforementioned variation of substrate recovery, but not that of Selectivity. In fact, a softer oxidant (like perrhenate) should be more selective than a stronger one (like ruthenium tetroxide), which is just opposite to the experimental evidence.

2-Cyanoazetidines like 12c are versatile intermediates for a wide variety of catalysts,²¹ biological amines,²² or nitrogen heterocycles.²³ Even if it is out of the scope of this paper, the RuO₄-oxidation of 1c under cyanide-trapping conditions (T-7) might be viewed, after further optimization, as a new way to synthesize 2-cyanoazetidines and may be added to the already known methods.²⁴,²⁵

Oxidation of aziridine 1d

Aziridine 1d behaved differently (Scheme 3) than 1a-c. Under conditions A (T-4), BzH was by far the main reaction product, but some benzamide 6d was detected too. Sometimes, 6d was accompanied by variable amounts of its isomer, the oxazoline 14, thermally formed during work-up.²⁶ The reaction mixture contained also the piperazine 15 (a “dimer” of 1d), piperazinedione 16 and the acyclic diformamide 17 (Scheme 3). It is worth mentioning that BzH, 16 and 17 are, all three, main products of the RuO₄-oxidation of 15.¹⁰ At the same time, it is known that 15 undergoes oxidation more easily than 1d.²⁷ Taking into account also that the value of 2.6 for the ratio (17)/(16) is almost the same as that found in the RuO₄-oxidation of 15,¹⁰ it appears logical that 6d+14 came from 3d and 16+17 from 15. At the same time, since both routes produce benzaldehyde, the value of 51.3% in T-4 is the sum of two contributions: from 3d (BzH from 3d) and from 15 (BzH from 15). No aziridinone 5d was detected, but, at first sight, this does not exclude its transient formation and subsequent fast oxidation towards formamide 18 and CO₂ (Scheme 3). This is suggested by the known²⁹ behaviour of aziridine 19 (lower part of Scheme 3), for which the intermediacy of the non isolable aziridinone 20 was proven: both 19 and 20 (synthesized independently) gave the same products, 21 and CO₂. In our case, formamide 18 was not detected in the oxidation mixture of 1d (T-4). Therefore, the existence of 5d, even transiently, can be ruled out, as indicated in Scheme 3.

Several previous works,²⁷,³⁰,³¹ performed with 1d and oxidants acting according to known mechanisms (bona fide oxidants) certified that dimer 15 can result from 1d either by oxidation or heterolytically (HETERO). In the latter case, the aziridinium ion 22, generated transiently from 1d, undergoes an S₅/₂-type ring opening by reaction with 1d itself,³²,³³ followed by ring closure to 15.
Control experiments were performed with \textbf{1d} under conditions similar to those of T-4, but without oxidants. Working in the two-layer system of CHCl$_3$/buffered water (pH 5), 1 mmole of \textbf{1d} gave 50 μmoles of 15, corresponding to a relative amount of 5%. This value is quite close to that found in T-4 [(15)+(16)+(17)+(BzH$_{\text{from 15}}$) = 4.5+(BzH$_{\text{from 15}}$)]. Therefore, the dotted arrow marked by “ox?” connecting \textbf{1d} and 15 in Scheme 3 can be safely cancelled out.

Thus, the exclusive oxidation products of \textbf{1d} in T-4 are BzH$_{\text{from 3d}}$ and \textbf{6d}. Since only the benzylic position of \textbf{1d} has been attacked, the corresponding value of \textit{Selectivity} is zero.

Under cyanide-trapping conditions (T-8), aziridine \textbf{1d} did not give the nitriles 12c and 13c (Scheme 2). Instead, piperazine 15 and the open chain nitrile 23 (Scheme 3) have been detected in the reaction mixture.
Control experiments with 1d at pH 9 and without oxidants showed the formation of 15 and 23 in 1.5% and 0.3% molar amounts, respectively, values close to those found in T-8. Therefore, piperazine 15 and nitrile 23 resulted both by a HETERO mechanism, as discussed before for T-4. Summing up, it appears that RuO₄ was practically not active towards 1d in the presence of cyanide, in contrast to the aforementioned cases of 1a-c.

Therefore, the behaviour of aziridine 1d is a consequence of the competition between the RuO₄-mediated oxidation and the heterolytic steps, just as in other oxidative media.²⁷,³⁰,³¹ In the case of RuO₄-oxidation, only the exocyclic (benzylic) route was active under conditions A, as in the case of azetidine 1c. However, unlike 1c, the oxidation of 1d is largely or totally suppressed under conditions B and the reaction follows only the HETERO route.

Mechanistic considerations

Two very similar mechanisms have been proposed so far¹,⁷,¹¹,¹² for the oxidation by RuO₄ of tertiary amines like 1a-d. Based on these we propose the multi-step mechanism of Scheme 4.⁸-¹⁰ The first step consists in the formation of the ion pair consisting of ruthenate (Ru⁶⁺) anion 24 and iminium ion 25. In the corresponding transition state (TS), the electronic lone pair on nitrogen is used to create a new C=N double bond (Electron Transfer process), concomitantly to hydrogen abstraction (HAB) and generation of a Ru⁶⁺ species. The existence of both ET and HAB processes in the rate-determining step was already proven.⁴,⁷ Prior to ET+HAB, the substrate could give also a complex with a low-valent ruthenium species⁷ (not displayed in Scheme 4).

Cation 25 is then trapped by nucleophiles, in our case water or cyanide, to form the corresponding derivative 26. The reaction stops at this stage if Y=CN, but in the case of a hemiaminal (26, Y=OH), the reaction continues with two new oxidation steps, giving the final product, amide 27. The hemiaminal is a transient, non-isolable intermediate: it undergoes oxidation presumably faster than the initial amine, because the involved C-H bond is now in α-position to two electron-rich heteroatoms (O and N). The catalytic cycle is completed by oxidizing back all Ru⁶⁺ species to Ru⁸⁺, at the expense of the co-oxidant (for instance NaIO₄).

The substrate reactivity and the corresponding endocyclic/exocyclic Selectivity should be governed by the activation energies required on passing from the reactants to the respective transition states TS. The governing factors could be of (i) electronic (ET+HAB) and (ii) steric nature, as presented below.

A high electron-donating ability of the nitrogen atom is known to reduce the energy of the adjacent C-H bond. Since the donating ability decreases with the increase of the s-character of the nitrogen lone pair,³² it emerges that, within the homologous series 1a-d, the highest C-H bond energy will belong to aziridine 1d. However, the energies of both endocyclic and exocyclic α-C-H bonds are influenced in the same way and, consequently, the regioselectivity of a particular substrate might remain unchanged.

At the same time, on going from 1a to 1d, that is towards azacycles with increasing geometrical constraints,³⁴ the accommodation of the new C=N bond in TS should be easier in the exocyclic position relative to that in the more energetically demanding endocyclic position. An approximation of this effect might be revealed by the differences in heats of formation (ΔΔHₓ) calculated for endocyclic-25 and exocyclic-25. We remember that the system 24+25 could be a good approximation for TS, if TS is structurally more similar to the products than to the reactants. By a proper choice of ruthenium catalyst and reaction conditions, this hypothesis was already experimentally proven.⁷ Working with the PM6 method (free MNDO-version), the computed ΔΔHₓ’s were: -1.4 (2a-3a), +1.5 (2b-3b), +13.4 (2c-3c), and +24.5 kcal/mol (2d-3d). These differences parallel closely the experimental endocyclic/exocyclic selectivities (Table 1, column 3).
Scheme 4. Mechanism of the RuO$_4$-oxidation of tertiary amines

For the steric factor (ii), RuO$_4$ is supposed to approach less easily the endocyclic position of the amine than the exocyclic one. This derives from the more rigid azacycle structure compared to the freely rotating benzylic group around the PhCH$_2$-N bond. The energetic difference between the endocyclic and exocyclic attack seems to increase in the order 1a<1b<1c<1d. Since the endocyclic and the exocyclic transition states are both more polar than the reactants, solvation could influence the relative stability. More sophisticated theoretical calculations are needed for better accuracy.

Summing up, all these considerations suggest that Selectivity (endocyclic/exocyclic) should decrease going from 1a to 1d, in accord with the experimental findings.

Conclusions

1-Benzylazetidine (1c) showed the same RuO$_4$-oxidation pattern as that followed by the analogous 1-benzylpiperidine (1a) and 1-benzylpyrrolidine (1b) derivatives: both endocyclic and exocyclic (benzylic) C-H bonds in α to the nitrogen atom are attacked. If the reaction is conducted in the presence of cyanide, α-aminonitriles were obtained instead of amides. The statistically corrected endocyclic/exocyclic regioselectivity diminishes constantly with the decrease of the azacycle size, from 2.4 for 1a to 0.6 for 1c. The oxidation of 1-benzylaziridine (1d) occurred only in the absence of cyanide and took place exclusively at the benzylic position. The proposed reaction mechanism was discussed and used to explain the variation of selectivity. The key step is the formation of an ion pair: an iminium ion and a ruthenate anion.

Experimental Section

General. NMR spectra were acquired mainly on a Varian ICON 300 apparatus, operating at 300 MHz (1H) and 75 MHz (13C). In particular cases, a Bruker Avance DRX 400 spectrometer, operating at 400 MHz (1H) and 100 MHz (13C), was employed. Mass spectra were obtained with a GC 6890 Agilent Technologies gas-
Oxidations by RuO$_4$/NaIO$_4$ (with or without NaCN)

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 of 1c or 1d), previously dissolved in CHCl$_3$ (5 mL) (reaction conditions A). In the case of the cyanide-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. The heterogeneous reaction mixture was magnetically stirred at room temperature for 3-5 h and then worked-up as described in a previous paper.$^{19}$

Identification of the various reaction products was made by comparison of the NMR and GC-MS data obtained in the presence of 1.4-dimethoxybenzene, added as internal standard.$^{19}$

2-(1-Azetidinyl)-2-phenylacetonitrile (13c). Aqueous NaHSO$_3$ solution (39%, 0.4 mL, 2 mmol) was added under stirring to benzaldehyde (0.2 mL, 2 mmol). To the formed white solid a suspension of azetidine hydrochloride (1.4 g, 11 mmol) in cold, aqueous NaOH solution (80 mg, 2 mmol; 1.5 mL of water) was added and the stirring was maintained for another hour. The mixture was extracted with CHCl$_3$ (187 mg, 2 mmol), the substrate (1 mmol in 10 mL of CHCl$_3$), and the co-oxidant NaIO$_4$ solution (10 mL, as before), in this order. The heterogeneous reaction mixture was magnetically stirred at room temperature for one hour. A solution of NaCN (98 mg, 2 mmol; 1 mL of water) was added and the stirring was maintained for another hour. The mixture was extracted with CHCl$_3$, the organic extract was dried over Na$_2$SO$_4$, and the solvent was evaporated. The residue was chromatographed on a silica gel column eluted first with benzene (30 mL). The fraction eluted with PhH/EtOAc (9/1, v/v) afforded 110 mg of oily 13c.

Yield: 32%. Anal. calcd. for C$_{11}$H$_{12}$N$_2$: C, 76.72; H, 7.01; N, 16.27%. Found: C, 76.42; H, 6.87; N, 16.45%.$^{1}$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 2.13 (2H, quintet, $^{3}$J 7.1 Hz, N-CH$_2$-CH$_2$), 3.31+3.39 (2+2H, symmetrical q+i , $^{3}$J 7.0 Hz, CH$_2$-N-CH$_2$), 4.69 (1H, s, CH), 7.30-7.55 (5H, m, arom.).$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 17.3 (N-CH$_2$-CH$_2$), 51.9 (CH$_2$-N-CH$_2$), 61.3 (CH), 116.2 (CN), 127.6 (o), 128.9 (m), 129.0 (p), 133.1 (i). EI-MS [70 eV, m/z (relative abundance, %)]: 172 (M$^+$, 43.5), 171 (78), 117 (15), 116 (100), 95 (7), 91 (7), 90 (6), 89 (20).

Spectral data of selected compounds

The $^1$H and $^{13}$C NMR chemical shifts of the following compounds are referenced to internal (CH$_3$)$_4$Si ($\delta$$_H$ = 0) and CDCl$_3$ ($\delta$$_C$ = 77.16 ppm).$^{42}$ Aromatic ortho, meta, and para hydrogens or carbons are labeled o, m, and p, respectively; ipso carbons are abbreviated as i. All NMR data were in accordance with those cited in literature, but with complete assignments. In addition, the corresponding MS data are presented, except for 4c (unstable), 16 and 17 (experimental limitations).

1-Benzylazetidine (1c).$^{35,36}$ $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 2.07 (2H, quintet, $^{3}$J 7.1 Hz, N-CH$_2$-CH$_2$), 3.20 (4H, t, $^{3}$J 7.1 Hz, CH$_2$-N-CH$_2$), 3.55 (2H, s, Ph-CH$_2$), 7.20-7.32 (5H, m, arom.).$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 17.6 (N-CH$_2$-CH$_2$), 55.1 (CH$_2$-N-CH$_2$), 63.9 (Ph-CH$_2$), 126.8 (p), 128.2 (o), 128.4 (m), 138.4 (i). EI-MS [70 eV, m/z (relative abundance, %)]: 147 (M$^+$; 22), 146 (47), 92 (9.5), 91 (100), 70 (5.5), 65 (11).
1-Benzylaziridine (1d). 1H-NMR (300 MHz, CDCl3) δ (ppm) 1.23-1.29 + 1.78-1.83 (2+2H, m+m, CH2-CH2), 3.37 (2H, s, Ph-CH2), 7.20-7.40 (5H, m, arom.). 13C-NMR (75 MHz, CDCl3) δ (ppm) 27.6 (CH2-CH2), 65.3 (Ph-CH2), 127.1 (p), 128.0 (o), 128.4 (m), 139.3 (i). El-MS [70 eV, m/z (relative abundance, %)]: 133 (M+, 13), 132 (45), 105 (6.0), 104 (8), 92 (8), 91 (100), 89 (7), 77 (10), 65 (22), 63 (7), 51 (10), 42 (57).

1-Benzylazetidin-1-oxide (4c). 1H-NMR (400 MHz, CDCl3) δ (ppm) 1.90-1.94 + 2.33-2.40 (1+1H, m+m, N+CH2CH2), 4.25-4.29 (4H, m, CH2-CH2N-CH2), 4.41 (2H, s, Ph-CH2), 7.33-7.44 (3H, m, m+p), 7.54 (2H, d, J 6.4 Hz, o). 13C-NMR (100 MHz, CDCl3) δ (ppm) 12.1 (N+CH2CH2), 68.9 (CH2-CH2N-CH2), 70.2 (Ph-CH2), 128.4 (p), 129.3 (m), 130.1 (i), 131.9 (o).

1-Benzyl-2-azetidinone (5c). 1H-NMR (300 MHz, CDCl3) δ (ppm) 2.94 (2H, t, J 4.0 Hz, N-CH2-CH2), 3.12 (2H, t, J 4.0 Hz, N-CH2-CH2), 4.36 (2H, s, Ph-CH2), 7.25-7.35 (5H, m, arom.). 13C-NMR (75 MHz, CDCl3) δ (ppm) 36.6 (N-CH2-CH2), 38.3 (N-CH2-CH2), 46.0 (Ph-CH2), 127.5 (p), 128.0 (o), 128.5 (m), 135.5 (i), 167.5 (CO). El-MS [70 eV, m/z (relative abundance, %)]: 161 (M+, 41.5), 133 (28.5), 132 (11), 105 (55), 104 (15), 92 (8.5), 91 (100), 77 (24).

1-Benzoylazetidine (6c). (the underlined signals show the C-H correspondence). 1H-NMR (300 MHz, CDCl3) δ (ppm) 2.32 (2H, quintet, J 7.4 Hz, N-CH2-CH2), 4.22 + 4.28 (2+2H, t+t, J 7.4 Hz, CH2-N=CH2), 7.32-7.48 (3H, m, m+p), 7.62 (2H, dd, J 7.4 Hz, J 1.5, o). 13C-NMR (75 MHz, CDCl3) δ (ppm) 15.9 (N-CH2-CH2), 48.7 + 53.2 (CH2-N=CH2), 127.6 (o), 128.1 (m), 130.7 (p), 133.1 (i), 170.1 (CO). El-MS [70 eV, m/z (relative abundance, %)]: 161 (M+, 25), 160 (7), 106 (8.5), 105 (100), 77 (43.5).

1-Benzoylaziridine (6d). 1H-NMR (300 MHz, CDCl3) δ (ppm) 2.39 (4H, s, CH2-CH2), 7.55-7.65 (3H, m, m+p), 8.07 (2H, d, J 7.6 Hz, 2H, o). 13C-NMR (75 MHz, CDCl3) δ (ppm) 26.1 (CH2-CH2), 128.0 (o), 129.3 (m), 132.9 (p), 134.2 (i), 179.3 (CO). El-MS [70 eV, m/z (relative abundance, %)]: 147 (M+, 7), 105 (100), 77 (72), 51 (19).

1-Benzoylazetidine-2-carbonitrile (12c). 1H-NMR (300 MHz, CDCl3) δ (ppm) 2.35-2.45 (2H, m, N-CH2-CH2), 3.12+3.35 (1+1H, q+q, J 7.2 Hz, N-CH2-CH2), 3.64+3.72 [1+1H, d+d (ABq), JAB 13.2 Hz, Ph-CH2], 3.90 (1H, t, J 7.2 Hz, CH-CN), 7.15-7.18 (5H, m, arom.). 13C-NMR (75 MHz, CDCl3) δ (ppm) 22.9 (N-CH2-CH2), 51.7 (CH-CN), 52.4 (N-CH2-CH2), 60.8 (Ph-CH2), 118.8 (CN), 127.5 (o), 128.6 (p), 128.8 (m), 136.1 (i). El-MS [70 eV, m/z (relative abundance, %)]: 172 (M+, 22), 171 (20), 120 (9), 95 (8), 92 (15), 91 (100), 81 (6), 65 (13).

2-Phenoxazoline (14). 1H-NMR (300 MHz, CDCl3) δ (ppm) 4.05 (2H, t, J 9.2 Hz, N-CH2), 4.41 (2H, t, J 9.2 Hz, O-CH2), 7.35-7.50 (3H, m, m+p), 7.94 (2H, d, J 7.8 Hz, o) 13C-NMR (75 MHz, CDCl3) δ (ppm) 54.9 (N-CH2), 67.5 (O-CH2), 127.7 (i), 128.1+128.2 (o+m), 131.2 (p), 164.4 (C=N). El-MS [70 eV, m/z (relative abundance, %)]: 148 (10), 147 (M+, 85), 118 (15), 117 (100), 105 (12), 91 (13), 77 (25), 51 (13).

1,4-Dibenzylpiperazine (15). 1H-NMR (300 MHz, CDCl3) δ (ppm) 2.48 (8H, s, CH2-CH2), 3.51 (4H, s, 4H, Ph-CH2), 7.21-7.30 (10H, m, arom.). 13C-NMR (75 MHz CDCl3) δ (ppm) 53.1 (CH2-CH2), 63.1 (Ph-CH2), 127.0 (p), 128.2 (o), 129.2 (m), 138.2 (i). El-MS [70 eV, m/z (relative abundance, %)]: 266 (M+, 25), 175 (42), 146 (11), 132 (12), 120 (28), 119 (7.5), 92 (8), 91 (100), 65 (9).

1,4-Dibenzy-2,3-piperazinedione (16). 1H-NMR (300 MHz, CDCl3) δ (ppm) 3.34 (4H, s, CH2-CH2), 4.67 (4H, s, Ph-CH2), 7.20-7.30 (10H, m, arom.). 13C-NMR (75 MHz, CDCl3) δ (ppm) 43.6 (CH2-CH2), 50.7 (Ph-CH2), 128.2 (p), 128.6 (o), 129.0 (m), 135.6 (i), 157.6 (CO).

Bis-(N-Benzylformamido)ethylene (17). Mixture of 3 isomers: A (48%; asymmetric E,Z), B (45%; symmetric E,E), and C (7%; symmetric Z,Z). No specific assignments could be made for the aromatic m+p protons and carbons (see below under isomers A+B+C). The following integrals are intended for the considered isomer. Isomer A: [the N atoms are labelled as (E)-N1 and (Z)-N2]. 1H-NMR (400 MHz, CDCl3) δ (ppm) 3.19 (2H, t, J 6.4 Hz, N2-CH2), 3.29 (2H, t, J 6.4 Hz, N1-CH2), 4.31 (2H, s, Ph-CH2-N1), 4.48 (2H, s, Ph-CH2-N2), 7.15 (2H, d, J 6.4 Hz, o of Ph-CH2-N1), 7.20 (2H, d, J 6.4 Hz, o of Ph-CH2-N2), 8.01 (1H, s, N2-CHO), 8.30 (1H, s, N1-CHO). 13C-NMR
(100 MHz, CDCl₃) δ (ppm) 40.9 (N¹-CH₂), 43.6 (N²-CH₂), 45.3 (Ph-CH₂-N²), 52.2 (Ph-CH₂-N¹), 127.6 (o of Ph-CH₂-N¹), 128.3 (o of Ph-CH₂-N²), 135.4 (i of Ph-CH₂-N²), 136.1 (i of Ph-CH₂-N¹), 162.7 (N²-CHO), 163.0 (N¹-CHO).

Isomer B: ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 3.38 (4H, s, CH₂-CH₂), 4.46 (4H, s, Ph-CH₂), 7.21 (4H, d, J 6.8 Hz, o), 8.26 (2H, s, CHO). ³¹C-NMR (100 MHz, CDCl₃) δ (ppm) 37.7 (CH₂-CH₂), 50.8 (Ph-CH₂), 127.6 (o), 128.8 (m), 135.7 (i), 163.3 (CHO).

Isomer C: ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 3.17 (4H, s, CH₂-CH₂), 4.49 (4H, s, Ph-CH₂), 7.21 (4H, d, J 6.8 Hz, o), 7.91 (2H, s, CHO). ³¹C-NMR (100 MHz, CDCl₃) δ (ppm) 45.3 (CH₂-CH₂), 46.0 (Ph-CH₂), 128.4 (o), 135.9 (i), 162.6 (sh, CHO). Isomers A+B+C: ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.25-7.40 (10H, m, m+p). ³¹C-NMR (100 MHz, CDCl₃) δ (ppm) 127.7+128.0+128.2+128.9+129.0 (m+p).

3-(Benzylationamo)propanenitrile (18).⁴⁴ ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 2.45 (2H, t, J 6.5 Hz, CH₂-CN), 2.87 (2H, t, J 6.5 Hz, N-CH₂-CH₂), 3.80 (2H, s, Ph-CH₂), 7.20-7.40 (5H, m, arom.). ³¹C-NMR (75 MHz, CDCl₃) δ (ppm) 18.7 (CH₂-CN), 44.3 (N-CH₂-CH₂), 53.1 (Ph-CH₂), 118.7 (CN), 127.1 (p), 128.0 (m), 128.4 (o), 139.5 (i). EI-MS [70 eV, m/z (relative abundance, %)]: 160 (M⁺, 5), 120 (40), 92 (10), 91 (100); 65(15).

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