Reactivity of a Cyclic α-Bromoiminium Bromide towards Nucleophiles [1]

Donato Donati, Stefania Fusi, Maria Adelaide Macripò and Fabio Ponticelli*

Istituto di Chimica Organica dell'Università,
Siena, Italy

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Piperidine-pyrrolidine ring contraction of 1-piperideinium bromide (**1**) was observed by reaction with aqueous bases, sodium methoxide, phenylhydrazine, (*S*)-1-phenylethylamine and sodium borohydride, whereas diazomethane addition mainly gave pyrrolo[3,4-*b*]pyridine derivative **8**. Some stereochemical features of these reactions have been investigated. **1** gave back bromine under suitable conditions.

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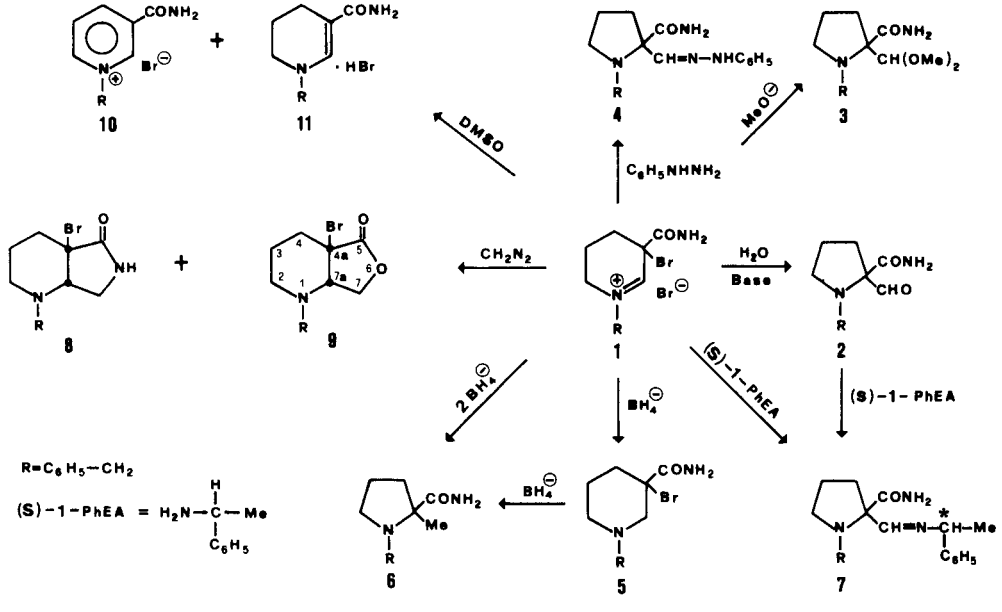
In connection with our interest on the chemistry and photoreactivity of reduced nicotinamides [2], we prepared the iminium bromide **1**, *via* the facile bromine addition on 1-benzyl-1,4,5,6-tetrahydronicotinamide. Structure of compound **1** followed from ir and nmr data (Experimental), both showing the presence of $HC=N^+$ moiety. Unlike some previously reported α-bromoiminium bromides [3], **1** was isolated as pure solid material having good stability at room temperature under anhydrous conditions.

As expected [3], treatment of this compound with bases afforded ring contraction products. Thus, reaction of **1** with aqueous pyridine or hydrogen carbonate quantitatively yielded 1-benzyl-2-formylpyrrolidin-2-carboxamide (**2**). Likewise, sodium methoxide or phenylhydrazine gave the corresponding acetal **3** and phenylhydrazone **4**, respectively. Spectroscopic data of compounds **2-4** are in agreement with the assigned structures.

The mechanism of nucleophilic attack on the adduct **1** was evidenced in the reaction with sodium borohydride. In fact, using a 1:1 molar ratio, we isolated the 1-benzyl-3-bromopiperidine-3-carboxamide (**5**), showing that the first attack occurred on C_2. The structure of compound **5** followed from nmr spectra: the ^1H spectrum (200 MHz) showed two AB systems, centered at $\delta = 2.93$ and $\delta = 3.54$, attributable to benzylic and C_2 diastereotopic protons; the ^{13}C spectrum of **5**, beside peaks at $\delta = 23.6(C_5)$, $\delta = 37.4(C_4)$ and $\delta = 52.7(C_6)$, showed a signal at $\delta = 62.3$ and an overlapping broad signal at $\delta = 62.5$. The last two peaks were attributed to C_3, C_2 and CH_2-C_6H_5 [4]. The chemical shift of C_2, excluding the presence of a CH_2Br moiety, confirmed the piperidine structure **5**. Compound **5**, on treatment with sodium borohydride, afforded the ring contracted product **6**, which was also obtained by the reaction of **1** with two equivalents of the reducing agent.



Further insight into the mechanism of this ring contraction was obtained performing the reaction of **1** in (*S*)-1-phenylethylamine as solvent and obtaining the two diastereoisomeric Schiff bases **7** in the ratio 7:3, as determined by ^{1}H-nmr spectrum of the crude reaction mixture, after removal the amine in excess. On the other hand, 1:1 diastereoisomers ratio was obtained using equimolecolar amounts of **1** and (*S*)-1-phenylethylamine in chloroform and triethylamine. These findings indicates that in our case, the chiral solvent plays a role in determining the configuration of C_2 in **7**. Since the reported mechanism *via* an intermediate aziridinium ion [5], involving a stereospecific intramolecular attack, cannot justify these results, we think that the ring contraction can also proceed through a carbocation as intermediate: the chiral solvent induces the attack of N_1 on a preferential side of the carbocation.

When the bromine adduct **1** was treated with an excess of diazomethane, a good yield of pyrrolo[3,4-*b*]pyridine derivative **8** and a small amount of the furo[3,4-*b*]pyridine derivative **9** were recovered. Their structures were determined by ir and nmr spectroscopy (experimental). In this case, after the attack of diazomethane on C_2, the lactame ring was formed instead of the piperidine-pyrrolidine ring contraction. The *cis* fusion of the two rings resulted mainly from the coupling constants between the C_7 methylenic protons and the C_{7a} proton. Their values (*i.e.* 3.2 and 0.0 Hz for **8**; 2.8 and 0.0 Hz for **9**) require a dihedral angle of ~90°. Modelistic considerations showed that such condition is satisfied only by the structures **8** and **9** bearing equatorial bromine. The good yield of **8** indicates the *trans* selectivity in respect to 3-bromine, of the diazomethane addition to **1**. Similar selectivity was previously found when a CN^- attack on 3-benzyl-3-cyano or 3-benzyl-3-carboxamido-1-methylpiperideinium bromide was carried out [6]. The formation of compound **9** may be understood taking into account the non-anhydrous conditions of the reaction.

Another interesting property of **1** is the ability to give back bromine. In fact, a dimethylsulfoxide solution of **1**, left at room temperature for about 24 hours, gave 1-benzylnicotinamidium bromide (**10**) and tetrahydronicotinamide (**11**). In addition, warming a chloroform suspension of **1** in presence of 1-pentene, **11** (as free base) and 1,2-dibromopentane were quantitatively formed.

An attempt to perform the addition of a carboanion, like sodium diethylmalonate, to **1** was unsuccessful: compound **11** (free base) and tetraethyl 1,1,2,2-ethanetetracarboxylate were recovered. This result may be understood if we consider the easy release of bromine by **1** and the well known [7] oxidative coupling of carboanions.

The good yiels obtained and the easy preparation of the starting material indicate a valuable synthetic interest of the described reactions.

EXPERIMENTAL

Melting points were measured on an hot stage apparatus and are uncorrected. Silica gel 60 (Merck, 230-400 mesh) or neutral alumina (Fluka, 100-125 mesh) were used for column chromatography. Tlc was performed using Riedell De Haen silica gel precoated sheets (0.2 mm). The ^{1}H-nmr spectra were recorded on a Perkin Elmer R 600 (60 MHz) or Varian XL-200 (200 MHz) spectrometer; chemical shifts are reported in ppm downfield from internal tetramethylsilane. The ^{13}C-nmr spectra were recorded on Varian XL-200 spectrometer; assignments were confirmed by off resonance and selective heterodecoupling experiments. The ir spectra were recorded on a Perkin Elmer 782 spectrometer for potassium bromide disks.

1-Benzyl-3-bromo-3-carbamoyl-1-piperideinium Bromide (**1**).

A solution of bromine (0.64 g, 4 mmoles) in chloroform (20 ml) was added dropwise with stirring to 1-benzyl-1,4,5,6-tetrahydronicotinamide [8] (0.87 g, 4 mmoles) in chloroform (100 ml). After 1 hour the solid was filtered off, washed with carbon tetrachloride and dried *in vacuo* to yield 1.46 g (97%) of **1**, mp 118-120°; ir: 3270, 3140 (NH_2), 1700 (CO), 1675 (C=N$^+$) cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): 60 MHz, 2.61 (m, 4H, H_4 and H_5), 4.09 (m, 2H, H_6), 5.21 (s, 2H, $CH_2C_6H_5$), 7.50 (s, 5H, C_6H_5), 8.90 (s, 1H, H_2); ^{13}C-nmr (deuteriotrifluoroacetic acid): 18.4 (C_5), 30.3 (C_4), 51.2 (C_3), 51.6 (C_6), 67.5 ($CH_2C_6H_5$), 128.4, 129.8, 130.4, 131.5 (C_6H_5), 168.1 (C_2), 171.4 (CO).

Anal. Calcd. for $C_{13}H_{16}Br_2N_2O$: C, 41.52; H, 4.29; N, 7.45. Found: C, 41.36; H, 4.10; N, 7.20.

1-Benzyl-2-formylpyrrolidine-2-carboxamide (**2**).

Compound **1** (2.5 g, 6.65 mmoles) was treated with 2*N* sodium hydrogen carbonate (50 ml). After two hours the aldehyde **2** was collected by filtration; yield 1.25 g (81%), mp 106-108° (sublimation at 80° and 0.05 mm Hg); ir: 3410, 3260, 3190 (NH_2), 1725 (*HCO*), 1660 (*CONH*$_2$) cm^{-1}; ^{1}H-nmr (deuteriochloroform): 200 MHz, 1.86-1.99 (m, 2H, H_4), 2.06-2.19 and 2.27-2.42 (m, 2H, H_3), 2.76-2.88 and 3.06-3.16 (m, 2H, H_5), 3.88 (AB, J_{AB} = 13.4 Hz, 2H, $CH_2C_6H_5$), 6.37 and 7.37 (exch br 2H, NH_2), 7.22-7.36 (m, 5H, C_6H_5), 9.97 (s, 1H, CHO); ^{13}C-nmr (deuteriochloroform): 23.2 (C_4), 34.9 (C_3), 52.4 (C_5), 54.4 ($CH_2C_6H_5$), 75.6 (C_2), 127.8, 128.1, 128.4, 138.6 (C_6H_5), 175.3 ($CONH_2$), 201.9 (CHO).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.42; H, 6.81; N, 12.07.

1-Benzyl-2-(dimethoxymethyl)pyrrolidine-2-carboxamide (**3**).

Compound **1** was added in portions, with stirring, to a solution of sodium (92 mg, 4 mg-atoms) in methanol (10 ml). Solvent was evaporated and chloroform was added to remove the insoluble inorganic material. Evaporation of the solvent gave a residue mainly constituted (tlc and nmr) by the acetal **3**, which was purified on chromatographic column (silica) eluted with ether, yield 0.2 g (36%), mp 117-119° (sublimation at 80° and 0.05 mm Hg); ir: 3400, 3220, 3140 (NH_2), 1685 (CO) cm^{-1}; ^{1}H-nmr (deuteriochloroform): 200 MHz, 1.65-1.81 (m, 2H, H_4), 2.11-2.19 (m, 2H, H_3), 2.82-2.88 (m, 2H, H_5), 3.57, 3.59 (2s, 6H, 2 OCH_3), 4.13 (AB, J_{AB} = 14.2 Hz, 2H, $CH_2C_6H_5$), 4.76 (s, 1H, CH), 5.97, 7.45 (exch br, 2H, NH_2), 7.15-7.38 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.54; H, 7.84; N, 10.10.

1-Benzyl-2-phenylethylhydrazonomethylpyrrolidine-2-carboxamide (**4**).

Compound **1** (0.5 g, 1.33 mmoles) was added in portions, with stirring to phenylhydrazine (6 ml). After 12 hours water and methanol (few mls) were added and the solid filtered, washed with water and crystallized from benzene; yield 0.4 g (93%); mp 158-160°; ir: 3400, 3270, 3180 (NH_2), 1665 (CO) cm^{-1}; ^{1}H-nmr (deuteriochloroform): 200 MHz, 1.75-2.22 and 2.56-2.67 (m, 4H, H_3 and H_4), 2.65-2.78 and 3.03-3.12 (m, 2H, H_5), 3.76 (AB, J_{AB} = 13.3 Hz, 2H, $CH_2C_6H_5$), 5.80 and 7.55 (exch br, 2H, NH_2), 6.75-7.33 (m, 10H, 2 C_6H_5), 7.48 (s, 1H, CH=N), 7.68 (exch br 1H, NH).

Anal. Calcd. for $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38. Found: C, 70.48; H, 6.85; N, 17.73.

1-Benzyl-2-(1-phenylethylimino)methylpyrrolidine-2-carboxamide (**7**).

(*S*)-1-Phenylethylamine (1 ml) was added to **1** (0.376 g, 1 mmole). After two hours the excess of amine was evaporated *in vacuo* and the residue chromatographed on column (alumina) with ether/methanol 4:1 to give the imine **7** (mixture of diastereoisomers), yield 0.15 g (45%), mp 109-112° (sublimed at 80° and 0.04 mm Hg); ir: 3410, 3270, 3190 (NH_2), 1650 (CO) cm^{-1}; ^1H-nmr (deuteriochloroform): 200 MHz, 1.49 [9] and 1.54 (2 d, J = 6.6 Hz, 3H, CH_3), 1.90-2.01 (m, 2H, H_4), 2.10-2.27 and 2.30-2.52 (m, 2H, H_3), 2.74-3.16 (m, 2H, H_5), 3.68 [9] and 3.79 (2 AB systems, J_{AB} = 13.7 and 13.3 Hz, 2H, $CH_2C_6H_5$), 4.42 [9] and 4.44 (2 q, J = 6.6 Hz, 1H, $CHCH_3$), 6.65 and 8.20 (exch br, 2H, NH_2), 7.20-7.41 (m, 10H, 2 C_6H_5), 8.04 [9] and 8.06 (s, 1H, CH=N).

Anal. Calcd. for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 74.92; H, 7.53; N, 12.50.

The same mixture of diastereoisomers in the 1:1 molar ratio was obtained from the aldehyde **2** (3 mmoles) and (*S*)-1-phenylethylamine (3 mmoles), by refluxing in ethanol for 14 hours (yield 80%).

Reaction of **1** (1 mmole) in chloroform (5 ml), triethylamine (3 mmoles) and (*S*)-1-phenylethylamine (1 mmole) gave the diastereoisomeric mixture **7** in the ratio 1:1 as determined by ^1H-nmr of the crude material.

Reaction of **1** with Sodium Borohydride.

Compound **1** (0.376 g, 1 mmole) was added in portions under stirring and cooling (ice-water bath) to a solution of sodium borohydride (0.083 g, 2 mmoles) in anhydrous dimethylformamide (6 ml). After 1 hour, water was added and the solution extracted with dichloromethane. The organic layer was washed with water and evaporated to give 1-benzyl-2- methylpyrrolidine-2-carboxamide (**6**), yield 0.15 g (69%), mp 128-130° (from benzene); ir: 3420, 3260, 3180, (NH_2), 1650 (CO) cm^{-1}; ^1H-nmr (deuteriochloroform): 200 MHz, 1.32 (s, 3H, CH_3), 1.69-1.89 and 2.13-2.18 (m, 4H, H_3 and H_4), 2.31-2.44 and 2.93-3.03 (m, 2H, H_5), 3.60 (AB, J_{AB} = 13.0 Hz, 2H, $CH_2C_6H_5$), 6.09 and 7.50 (exch br 2H, NH_2), 7.24-7.33 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.74; H, 8.38; N, 12.86.

This reaction was also carried out employing 1:1 molar ratio between **1** and sodium bohydride. On evaporation of dichloromethane solution, 1-benzyl-3-bromopiperidine-3-carboxamide (**5**) was obtained as waxy solid. **5** decomposed on column chromatography and on attempted recrystallization; ir: 3320, 3190, (NH_2), 1665 (CO) cm^{-1}; ^1H-nmr (deuteriochloroform): 200 MHz, 1.64-1.80, 1.82-2.00, 2.22-2.38, 2.43-2.58 and 2.65-2.80 (m, 6H, H_4, H_5 and H_6), 2.93 (AB, J_{AB} = 12.0 Hz, 2H, H_2), 3.54 (AB, J_{AB} = 13.1 Hz, 2H, $CH_2C_6H_5$), 7.25-7.33 (m, 5H, C_6H_5).

When **5** was treated with an equimolecolar amount of sodium borohydride in dimethylformamide, the pyrrolidine **6** was obtained in quantitative yield.

Reaction of **1** with Diazomethane.

A suspension of **1** (1.8 g, 4.8 mmoles) in ether (30 ml) was treated with ethereal solution of diazomethane (1 g, 24 mmoles) and the mixture stirred overnight. The reaction mixture was filtered and the solution evaporated *in vacuo* and chromatographed on column (silica) with ether to give (in order of mobility): 1-benzyl-4a-bromooctahydrofuro[3,4-*b*]pyridin-5-one (**9**), yield 0.03 g (2%); mp 71-73° (sublimed at 55° and 0.05 mm Hg); ir: 1780 (CO) cm^{-1}; ^1H-nmr (deuteriochloroform): 200 MHz, 1.48-1.63 (m, 2H, H_3), 2.02-2.21 (m, 2H, H_4), 2.65-2.85 (m, 2H, H_2), 3.36 (d, $J_{7a,7'}$ = 2.8 Hz, 1H, H_{7a}), 3.65 (AB, J_{AB} = 14.5 Hz, 2H, $CH_2C_6H_5$), 4.39 (d, $J_{7,7'}$ = 9.8 Hz, 1H, H_7), 4.57 (dd, $J_{7,7'}$ = 9.8, $J_{7a,7'}$ = 2.8 Hz, 1H, $H_{7'}$), 7.22-7.37 (m, 5H, C_6H_5); ^{13}C-nmr (deuteriochloroform): 24.4 (C_3), 33.6 (C_4), 50.2 (C_2), 56.1 (C_{4a}), 59.5 ($CH_2C_6H_5$), 67.7 (C_{7a}), 69.7 (C_7), 127.5, 128.3, 128.6, 137.5 (C_6H_5), 173.4 (C_5).

Anal. Calcd. for $C_{14}H_{16}BrNO_2$: C, 54.21; H, 5.20; N, 4.52. Found: C, 54.56; H, 5.35; N, 4.70.

1-Benzyl-4a-bromooctahydropyrrolo[3,4-*b*]pyridin-5-one (**8**).

Compound **8** eluted after **9** above. Compound **8** was obtained in a yield of 0.9 g (61%), mp 83-85° (from hexane); ir: 3260, 3320 (NH), 1690, 1670 (CO) cm^{-1}; ^1H-nmr (deuteriochloroform) 200 MHz, 1.48-1.72 (m, 2H, H_3), 2.09-2.24 (m, 2H, H_4), 2.74-2.87 (m, 2H, H_2), 3.31 (d, $J_{7a,7'}$ = 3.2 Hz, 1H, H_{7a}), 3.61 (AB, J_{AB} = 14.2 Hz, 2H, $CH_2C_6H_5$), 4.30 (d, $J_{7,7'}$ = 9.5 Hz, 1H, H_7), 4.51 (dd, $J_{7,7'}$ = 9.5 Hz, $J_{7a,7'}$ = 3.2 Hz, 1H, $H_{7'}$), 7.24-7.35 (m, 5H, C_6H_5); ^{13}C-nmr (deuteriochloroform): 24.2 (C_3), 35.0 (C_4), 50.6 (C_2), 59.5 ($CH_2C_6H_5$), 60.1 (C_{4a}), 69.2 (C_{7a}), 70.4 (C_7), 127.3, 128.3, 128.4, 137.6 (C_6H_5), 170.11 (C_5).

Anal. Calcd. for $C_{14}H_{17}BrN_2O$: C, 54.38; H, 5.54; N, 9.06. Found: C, 54.54; H, 5.58; N, 9.22.

Reaction of **1** with 1-Pentene.

A mixture of **1** (0.376 g, 1 mmole), chloroform (6 ml) and 1-pentene (0.22 ml, 2 mmoles) was heated at 70° in a sealed tube for 5 hours. The solvent was removed and the residue repeatedly extracted with light petroleum (40-60° bp). The insoluble material was 1-benzyl-1,4,5,6-tetrahydronicotinamide (as hydrobromide) (**11**); evaporation of the solvent gave an oily residue identified as 1,2-dibromopentane by comparison with an authentic sample.

Reaction of **1** with Sodium Diethylmalonate.

Compound **1** (0.50 g, 1.33 mmoles) was added to a solution of sodium diethylmalonate prepared from diethylmalonate (0.404 ml, 2.66 mmoles), ethanol (5 ml) and sodium (0.061 g, 2.66 mg-atoms). Sodium bromide was filtered off and the solvent evaporated. Tlc and nmr analyses showed the presence of 1-benzyl-1,4,5,6-tetrahydronicotinamide and tetraethyl 1,1,2,2-ethanetetracarboxylate as the only components of the reaction mixture.

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