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Reduction of 5-(bromomethyl)-1-pyrrolinium bromides to 2-(bromomethyl)pyrrolidines and their transformation into piperidin-3-ones through an unprecedented ring expansion-oxidation protocol

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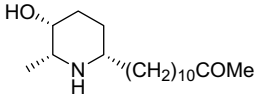
ABSTRACT

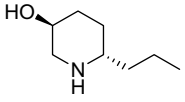
3,3-Dialkyl-5-(bromomethyl)-1-pyrrolinium bromides, prepared via bromocyclization of *N*-(2,2-dialkyl-4-pentenylidene)amines by means of bromine in dichloromethane, were reduced to 4,4-dialkyl-2-(bromomethyl)pyrrolidines for the first time using borane dimethyl sulfide in dichloromethane. Furthermore, the latter 2-(bromomethyl)pyrrolidines were transformed into the corresponding piperidin-3-ones through an unprecedented ring expansion-oxidation protocol in dimethylsulfoxide in the presence of potassium carbonate. Reduction of 5,5-dialkylpiperidin-3-ones by means of sodium borohydride in methanol afforded 5,5-dialkyl-3-hydroxypiperidines in good yields.

From a synthetic point of view, electrophile-induced cyclizations constitute a powerful methodology for the preparation of a large variety of functionalized azaheterocyclic compounds.[1] In this respect, *N*-(2,2-dialkyl-4-pentenylidene)amines have been proven to be excellent substrates for electrophile-induced cyclization reactions affording a variety of aziridines, pyrrolidines and piperidines via intermediate cyclic iminium salts.[2] Previously, the reduction of this type of 5-(bromomethyl)-1-pyrrolinium salts has been performed using classical reducing agents such as sodium borohydride in methanol and lithium aluminium hydride in THF or diethyl ether, resulting in the isolation of piperidines as the major reaction components instead of pyrrolidines.[2h,i] The observed ring enlargement has been explained considering an intramolecular substitution of bromide by nitrogen in the initially formed 2-(bromomethyl)pyrrolidines, giving rise to intermediate bicyclic aziridinium salts which suffer from ring opening at the more hindered aziridine carbon atom. To date, the only approach towards 2-(bromomethyl)pyrrolidines starting from 5-(bromomethyl)-1-pyrrolinium salts involves a two-step procedure in which these pyrrolinium bromides are first ring expanded into 3-methoxypiperidines upon treatment with sodium methoxide in methanol and subsequent reduction,[3] followed by ring contraction of the latter 3-methoxypiperidines by means of boron(III) bromide.[2h]

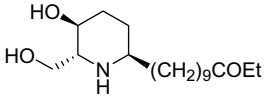
Biologically spoken, the 3-hydroxypiperidine motif is of interest due to its presence in a large number of natural products with a range of bioactivities.[4] Among others, cassine, deoxocassine, pseudoconhydrine, spectalin, prosophylline, prosopinine, febrifugine and prosafrinine are important representatives of this particular class of piperidine alkaloids.[4]



(-)-Cassine



(+)-Pseudoconhydrine



(+)-Prosopinine

In the literature, a variety of synthetic approaches towards 3-hydroxypiperidines are known, including nucleophilic cyclizations of pentylamines bearing a suitable leaving group at the 5-position,[5] radical cyclization reactions,[6] intramolecular Michael reactions,[7] Diels–Alder reactions,[8] and reductions of 3-hydroxypyridines[9] or piperidin-3-ones.[10] Furthermore, a convenient entry into 3-hydroxypiperidines has been described based on the

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ring expansion of 2-(hydroxymethyl)pyrrolidines via intermediate bicyclic aziridinium salts upon initial activation of the hydroxyl group.[11a,b]

In the present Letter, the straightforward one-step reduction of 3,3-dialkyl-5-(bromomethyl)-1-pyrrolinium bromides, obtained via bromocyclization of *N*-(2,2-dialkyl-4-pentenylidene)amines, towards the corresponding 2-(bromomethyl)pyrrolidines is described for the first time using borane dimethyl sulfide in dichloromethane. Furthermore, the latter 2-(bromomethyl)pyrrolidines were transformed into piperidin-3-ones in dimethylsulfoxide through an unprecedented ring expansion-oxidation protocol. Subsequent reduction of these piperidin-3-ones with sodium borohydride led to 3-hydroxypiperidines.

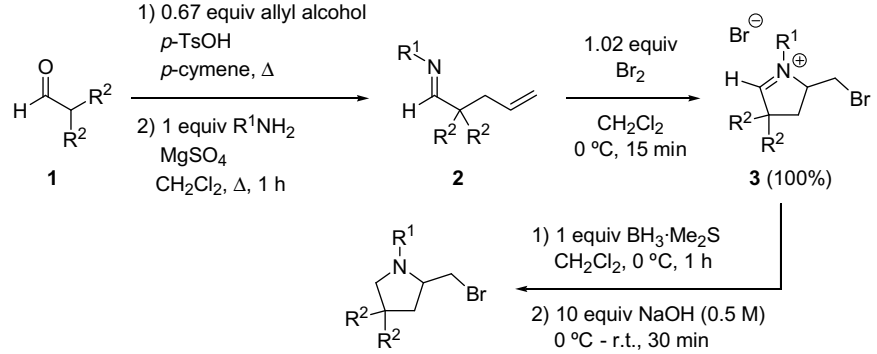
In the literature, two different methodologies are known for the preparation of *N*-(2,2-dialkyl-4-pentenylidene)amines **2**, both starting from isobutyraldehyde **1** (R^2 = Me) and from cyclohexanecarbaldehyde **1** (R^2–R^2 = $(CH_2)_5$). The first method entails a four-step approach involving imination with *tert*-butylamine, α-alkylation using lithium diisopropylamide (LDA) and allyl bromide, hydrolysis of the imine by aqueous oxalic acid and imination of the aldehyde utilizing a primary amine R^1NH_2.[12] As the direct allylation of the starting aldehydes with allyl bromide and LDA is not a selective process and leads to intractable reaction mixtures, a detour via *N-tert*-butyl imines is required and offers a suitable and flexible way for the synthesis of the desired imines **2**. Alternatively, imines **2** can be accessed more easily through direct α -allylation of the required aldehydes **1** via a Claisen rearrangement using allyl alcohol in the presence of *p*-toluenesulfonic acid in *p*-cymene,[13] followed by an imination step (Scheme 1). Treatment of the thus obtained γ,δ-unsaturated imines **2** with 1.02 equiv of bromine in dichloromethane at 0 °C for 15 min afforded 5-bromomethyl-1-pyrrolinium bromides **3** quantitatively (Scheme 1), which were used immediately and as such for further elaboration due to their instability.

Subsequently, the reduction of cyclic iminium salts **3** towards the corresponding 2-(bromomethyl)pyrrolidines **4** was envisaged. As mentioned before, the reduction of 5-(bromomethyl)-1-pyrrolinium salts by means of classical reducing agents such as $NaBH_4$ or $LiAlH_4$ results in ring expansion to piperidines.[2h,i] In order to prepare the desired 2-(bromomethyl)pyrrolidines **4**, 1-pyrrolinium bromides **3** were treated with 1 equiv of borane dimethyl sulfide in dichloromethane at 0 °C for 1 h, followed by the addition of 10 equiv of an aqueous solution of sodium hydroxide (0.5 M) to convert the in situ formed stable amine-borane complex to the free amine (Scheme 1).[14] The use of borane dimethyl sulfide as a mild reducing agent has been reported before for the reduction of α-chloroimines towards the corresponding secondary β-chloroamines, as the use of complex metal hydrides only leads to aziridines instead.[15] Probably, the less alkaline properties of borane as compared to ionic reducing agents such as $LiAlH_4$ or $NaBH_4$ can account for these observations. Up to now, borane dimethyl sulfide has not been used for the reduction of cyclic iminium salts towards the corresponding tertiary amines.

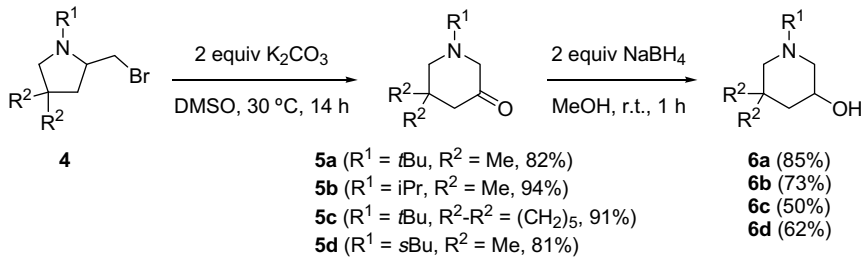
In the next stage, the reactivity of 2-(bromomethyl)pyrrolidines **4** with regard to the oxidant dimethylsulfoxide (DMSO) was investigated as a potential entry into pyrrolidine-2-carbaldehydes, which are known to be attractive synthons for further elaboration.[16] The oxidation of organic halides to the corresponding carbonyl compounds comprises a well-known transformation in organic synthesis. Several methods have been developed to carry out this conversion such as the Hass–Bender reaction,[17] the Kröhnke reaction[18] and the Kornblum reaction,[19] although all these procedures are limited in scope and require high reaction temperatures. In order to circumvent these limitations, improved variants of the Kornblum oxidation of alkyl halides to aldehydes and ketones by means DMSO have been described.[20] In analogy, 2-(bromomethyl)pyrrolidines **4** were stirred in DMSO at 30 °C for 14 h in the presence of 2 equiv of potassium carbonate, resulting in full consumption of the starting material. However, spectroscopic analysis of the obtained reaction products revealed their molecular structure to be piperidin-3-ones **5** instead of pyrrolidine-2-carbaldehydes (Scheme 2, crude yields). The addition of potassium carbonate appeared to be essential, as piperidin-3-ones **5** were isolated in very low yields (10%) if no K_2CO_3 was used.

Whereas many reports on the synthesis and application of piperidin-3-ones bearing an electron-withdrawing group at nitrogen (usually acyl) are available in the literature,[21] often associated with the preparation of biologically relevant target compounds, less information can be found regarding the synthesis of *N*-alkylpiperidin-3-ones. The latter piperidones are usually prepared via oxidation of 3-hydroxypiperidines[22] or acid hydrolysis of the vinylether moiety in 5-methoxy-1,2,3,4-tetrahydropyridines,[3,23] although also the cyclization of 4-(alkoxycarbonylmethylamino)butanoates has been described.[24]

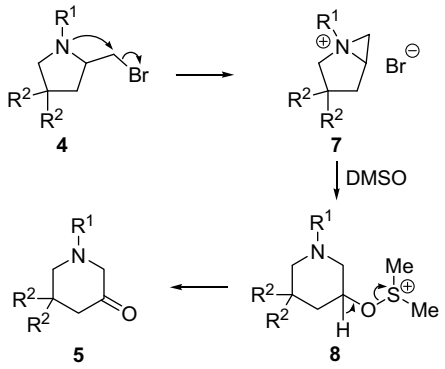
From a mechanistic point of view, the following rationale can be suggested. Apparently, 2-(bromomethyl)pyrrolidines **4** are first transformed into intermediate bicyclic aziridinium salts **7** (in equilibrium with the corresponding 3-bromopiperidines), which are converted into piperidines **8** upon ring opening with dimethylsulfoxide, either via direct nucleophilic ring opening at the substituted aziridine carbon atom or via initial spontaneous ring opening and



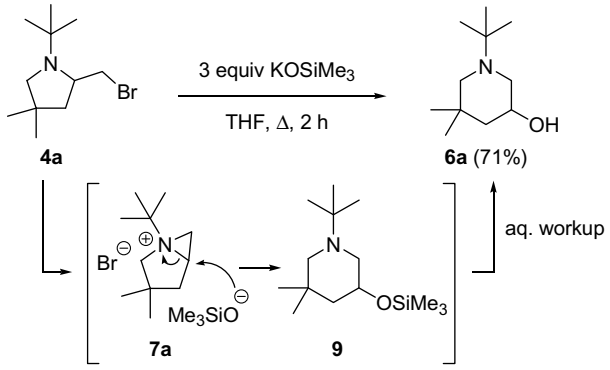
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

subsequent substitution of the thus formed carbenium ion. Abstraction of the acidic proton at the oxygenated carbon atom by potassium carbonate results in the liberation of dimethylsulfide and piperidin-3-ones **5** (Scheme 3).

It should be mentioned that in some cases a substantial amount (upto 50%) of 3-hydroxypiperidines **6** was obtained along with piperidin-3-ones **5** after heating of pyrrolidines **4** (e.g., **4c** and **d**) in DMSO, which might be the result of an incomplete oxidation reaction or direct hydrolysis of the strained intermediates **7**, probably due to water present in DMSO. As the isolation of 3-piperidones **5** in analytically pure form by means of column chromatography was unsuccessful, their immediate reduction was performed by means of 2 equiv of sodium borohydride in methanol, affording the corresponding 3-hydroxypiperidines **6a–d** in good yields after 1 h at room temperature (Scheme 2).[25] Indeed, 3-piperidones are fairly labile substances which are better handled as their hydrohalides.[26]

In order to confirm the molecular structure of 3-hydroxypiperidines **6**, the direct conversion of 2-(bromomethyl)pyrrolidines **4** into 3-hydroxypiperidines **6** was investigated. In the literature, only one report is available regarding the direct hydrolysis of 2-(halomethyl)pyrrolidines, in which 2-(iodomethyl)pyrrolidines were converted into mixtures of the corresponding 2-(hydroxymethyl)pyrrolidines (75%) and 3-hydroxypiperidines (25%) in a water/acetone solvent system.[27] In the present work, 2-(bromomethyl)-1-*tert*-butylpyrrolidine **4a** as a selected example was treated with 3 equiv of potassium trimethylsilanolate in THF, affording the anticipated 1-*tert*-butyl-3-hydroxypiperidine **6a** after reflux for 2 h (Scheme 4). This approach provides an improved alternative for the above-mentioned literature protocol. The direct conversion of pyrrolidine **4a** to piperidine **6a** proceeds through the formation of a transient bicyclic intermediate **7a**, which is ring opened by the trimethylsilanyloxy anion (either directly or via an intermediate carbenium ion) towards the corresponding 3-(trimethylsilanyloxy)piperidine **9**. Hydrolysis of the silanyloxy group during aqueous workup afforded 3-hydroxypiperidine **6a** (Scheme 4). The spectral data of piperidine **6a** obtained via both pathways were judged to be identical.

In summary, the electrophile-induced cyclization of *N*-(2,2-dialkyl-4-pentenylidene)amines by means of bromine in dichloromethane furnished 3,3-dialkyl-5-(bromomethyl)-1-pyrrolinium bromides, which were reduced into 4,4-dialkyl-2-(bromomethyl)pyrrolidines for the first time using borane dimethyl sulfide in dichloromethane. The latter 2-(bromomethyl)pyrrolidines were transformed into the corresponding piperidin-3-ones through an unprecedented ring expansion-oxidation protocol by heating in dimethylsulfoxide in the presence of potassium carbonate. Finally, reduction of 5,5-dialkylpiperidin-3-ones using sodium borohydride in methanol afforded 3-hydroxypiperidines in good yields.

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25. *1-tert-Butyl-3-hydroxy-5,5-dimethylpiperidine* **6a**. Isolated by means of preparative gas chromatography in order to obtain an analytically pure sample. Mp 66 °C. ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.96 (6H, s); 1.05 (9H, s); 1.20–3.30 (7H, m); 3.60–4.10 (1H, m). ^{13}C NMR (20 MHz, $CDCl_3$): δ 26.4, 27.0, 29.5, 31.5, 46.7, 53.4, 54.5, 58.5, 66.7. IR (NaCl): ν_{OH} = 3330 cm^{-1}. MS (70 eV): m/z (%): 185 (M^+, 7); 170 (100); 94 (11); 70 (14); 58 (14); 57 (33); 56 (11); 55 (13). Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.47; H, 12.66; N, 7.41.
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