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Rearrangement of 5-(Bromomethyl)-1-pyrrolinium Salts into Functionalized Piperidines

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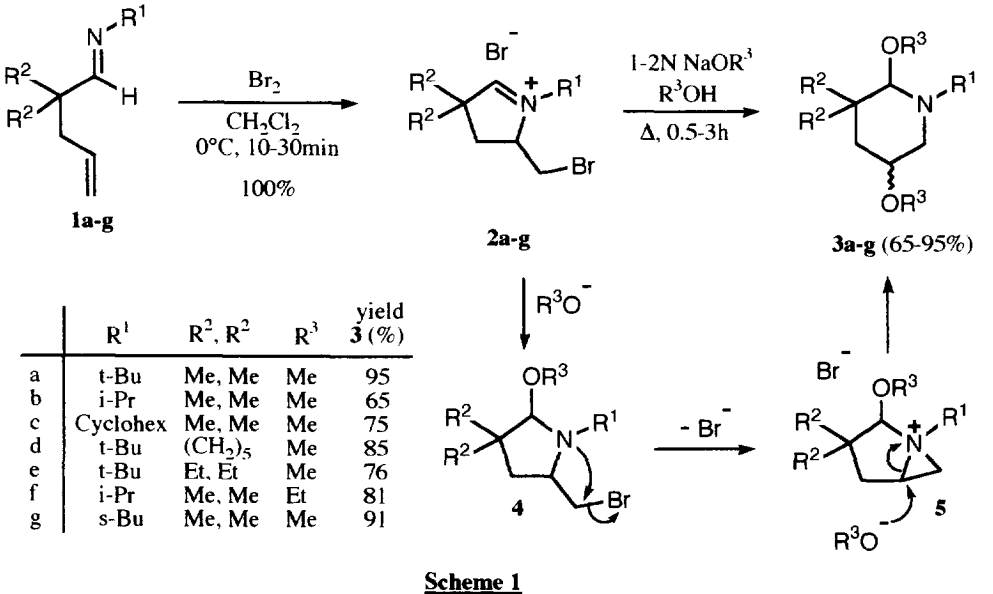
Abstract : 5-(Bromomethyl)-1-pyrrolinium bromides undergo rearrangement with alkoxides in the corresponding alcohol to afford 2,5-dialkoxypiperidines, which are easily converted into 3-alkoxypiperidines. 2,5-Dialkoxypiperidines undergo a peculiar thermal rearrangement to afford 5-alkoxy-1,2,3,4-tetrahydropyridines. Copyright © 1996 Elsevier Science Ltd

Piperidines are very important compounds because of their presence in numerous alkaloids, pharmaceuticals, agrochemicals and synthetic intermediates.[1] A large variety of syntheses of piperidines have been developed in the literature, but these syntheses are not always applicable for oxygenated piperidines, which occur in natural products.[1] The 3-oxygenated piperidine nucleus[2,3] is found in several alkaloids, e.g. spectaline,[4] canavaline,[4] leptophyllins,[4] pseudoconhydrine,[5] deoxocassine,[6] and Bao Gong Teng A.[7]

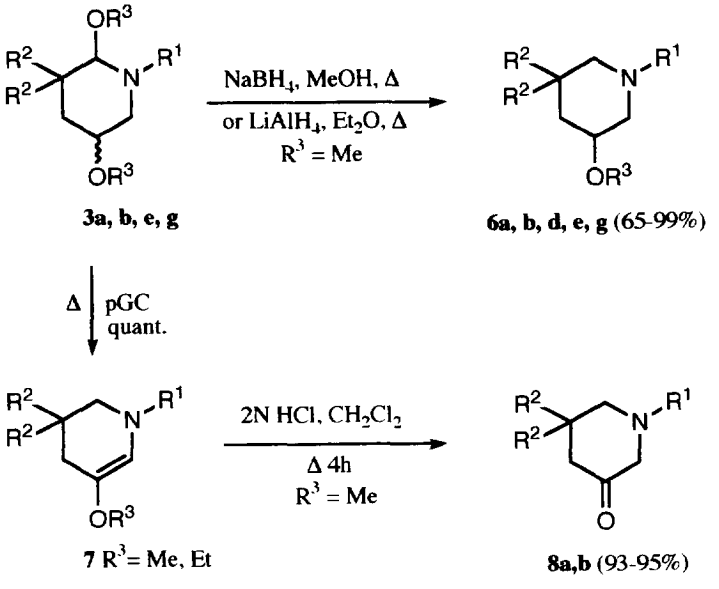


	R^1	R^2, R^2	R^3	yield **3** (%)
a	t-Bu	Me, Me	Me	95
b	i-Pr	Me, Me	Me	65
c	Cyclohex	Me, Me	Me	75
d	t-Bu	$(CH_2)_5$	Me	85
e	t-Bu	Et, Et	Me	76
f	i-Pr	Me, Me	Et	81
g	s-Bu	Me, Me	Me	91

Scheme 1

The recently described ring transformation of functionalized pyrrolidines to 3-hydroxypiperidines[8] urged us to report our results on the skeletal rearrangement of 5-(bromomethyl)-1-pyrrolinium salts to new oxygenated piperidines.

5-(Bromomethyl)-1-pyrrolinium bromides **2** are easily accessible by electrophile-induced cyclization of γ,δ-unsaturated aldimines **1** with bromine.[9] The cyclic iminium salts **2** have been shown to rearrange with nucleophilic hydrides to piperidines devoid of any functionality.[9] It is demonstrated now that the skeletal rearrangement of 1-pyrrolidinium salts with alkoxides gives ready access to novel 2,5-dialkoxylated piperidines **3** which have received a negligible interest so far in the literature due to the unavailability of straightforward synthetic routes. A clean rearrangement of 1-pyrrolinium salts **2a-g** with 3 to 4 equivalents of 2N sodium methoxide in methanol under reflux (0.5-3 h) or 1N sodium ethoxide in ethanol (1 h) gave rise to 2,5-dialkoxypiperidines **3a-g** in good yield (Scheme 1). Compounds **3** occurred predominantly as one geometrical isomer, presumably the trans-isomer (>95%). Due to the α-amino ether moiety, 2,5-dialkoxypiperidines **3** are sensitive to acid (e.g. decomposition during flash chromatography). They were obtained sufficiently pure (~95%) for further elaboration, while some derivatives can be distilled under vacuum, e.g. 1-t-butyl-2,5-dimethoxy-3,3-dimethylpiperidine **3a** (bp. 110-111°C/11 mmHg) or 1-isopropyl-2,5-diethoxy-3,3-dimethylpiperidine **3f** (bp. 80°C/0.07 mmHg). In this way, 2-azaspiro[5.5]-undecanes, e.g. **6d**, with potential insect repellent properties,[10] became easily accessible. The structural elucidation of 2,5-dialkoxypiperidines **3** proved to be difficult due to complex NMR spectral data. Extensive NMR investigations (double irradiation, 2D-COSY, HETCOR, ...) secured the structural attribution but no conclusive information on the stereo



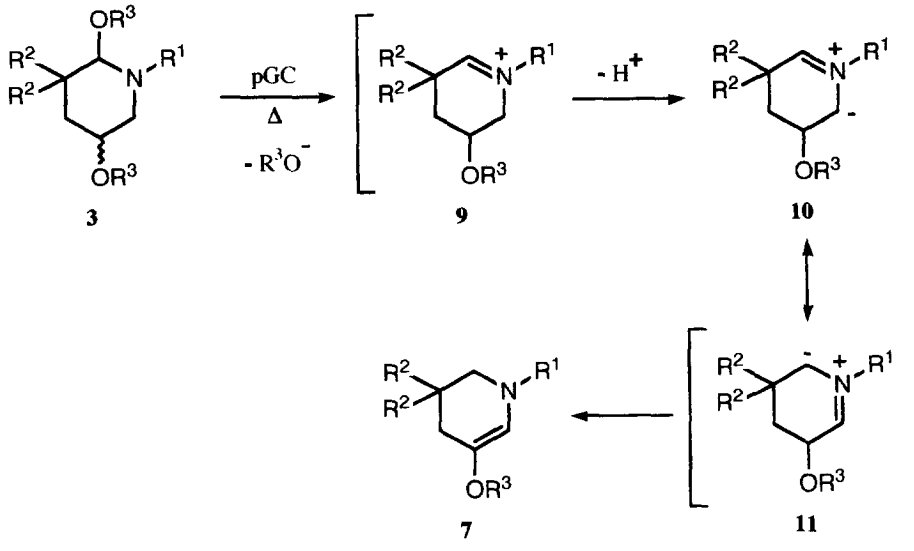
Scheme 2

chemistry was obtained from NOE and DIFNOE experiments. The possibility that it concerned 5,6-dimethoxypiperidines, formed via zwitterionic intermediates, i.e. azomethine ylids, was ruled out by the absence of deuterium incorporation in the final piperidines upon reaction of iminium salt **2a** with sodium methoxide in d_1-methanol.

The formation of 2,5-dialkoxypiperidines **3** is explained by addition of the alkoxide across the iminium bond of **2** to give 5-(bromomethyl)-2-alkoxypyrrolidines **4** which suffer intramolecular nucleophilic substitution to form transient bicyclic aziridinium ions **5**. Such intermediates **5** have been postulated previously in reactions of pyrrolidines or piperidines carrying the β-haloamine moiety.[11-16] Aziridinium ions **5** are finally opened by alkoxide in a regioselective way to produce 2,5-dialkoxypiperidines **3**. It is known that oxygen nucleophiles show a higher tendency for ring opening of bicyclic aziridinium ions of type **5** at the more substituted carbon atom, giving rise to piperidine derivatives.[14,17] The conversion of aziridinium ions **5** into 2,5-alkoxypiperidines **3** might be due to a substantial contribution of the unbridged carbenium ion in the reaction mechanism.

Because of the importance of 3-oxygenated piperidines (*vide supra*), an easy and straightforward synthesis of 3-methoxypiperidines **6** was developed by reductive removal of the 2-methoxy substituent in 2,5-dimethoxypiperidines **3** with sodium borohydride in methanol (reflux 1.5 h) or lithium aluminium hydride in diethyl ether (reflux 16 h) (Scheme 2). This constitutes a synthesis of 3-methoxypiperidines **6** from α-allylaldimines **1** in three steps without the necessity to isolate the intermediates **2** and **3**.

2,5-Dialkoxypiperidines **3** showed a peculiar transformation during preparative gas chromatographic analysis, resulting in methanol or ethanol and 1,2,3,4-tetrahydropyridines **7** as the sole products. That indeed a cyclic enamine **7** was formed was proven by acidic hydrolysis of β-methoxyenamines **7** to 1,5,5-trialkyl-3-piperidinones **8** in 93-95% yield. The loss of methanol or ethanol from piperidines **3** and the creation of insaturation at the 5,6-position is not so obvious. A possible interpretation of the mechanism involves expulsion of alkoxide at the 2-position to give **9**, followed by generation of a zwitterionic azomethine ylid **10**, the mesomeric form of which (**11**) being able to form the cyclic enamine **7** (Scheme 3).



Scheme 3

In conclusion, a short and efficient synthesis of 2,5-dioxygenated and 3-oxygenated piperidines from aldehydes, the precursors of α-allylaldimines **1**, is described. These 3-functionalized piperidines are suitably functionalized for further elaboration.

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