Synthesis of (±)-Allosedamine by Iodide Treatment of Isoxazolidinium Salts

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A simple stereospecific route to the (±)-allosedamine alkaloid has been accomplished by ring opening of the isoxazolidinium salt **2** with lithium iodide.

Among the ring-opening reaction processes of substituted isoxazolidinium salts[1-5], the lithium iodide treatment has recently shown to be a simple and efficient procedure for the formation of 1,3-amino alcohols having various chiral centers[6].

Prior to such experiments, examples of this type of chemical modification have been restricted to more complex approaches[1,2,4]. The use of LiI allows for the extension of the N–O bond cleavage in isoxazolidinium precursors to a broad range of N,O-heterocyclic derivatives obtained with high stereoselectivity by 1,3-dipolar cycloaddition of nitrones to alkenes[7,8]. On this basis, a modified route to the (±)-allosedamine system is described here which offers the benefits of simplicity and availability of reagent materials[6] and which is potentially applicable to other members of this group of natural products.

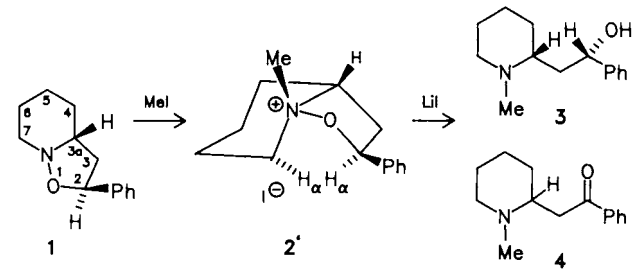
Isoxazolidine **1** can be easily obtained as the major component (98%) of the reaction mixture, together with its diastereoisomer, by 1,3-dipolar cycloaddition of 2,3,4,5-tetrahydropiridine 1-oxide to styrene. The stereoselectivity of this process, compared to that observed for the 1,3-dipolar cycloaddition of the same nitrone to unconjugated olefins[2], appears to be very high, leading nearly exclusively to the 5-substituted isoxazolidine **1** whose configuration results from an *exo* rather than an *endo* addition[3].

The corresponding isoxazolidinium salt **2** (Scheme) has been isolated in quantitative yield from methyl iodide treatment of **1**[6] and was characterized by fast-atom bombardment mass spectrometry (m/z = 218 [M^+]). The ^{1}H-NMR spectrum of **2** showed 3a-H and 2-H as multiplets centered at δ = 4.00 and 6.05, respectively. The methyl group absorbed as a singlet at δ = 3.84, while 3-H_2 gave rise to an ABXY system with A and B resonances centered at δ = 2.82 and 3.23, respectively. Interestingly, the signals of the methylene protons at C-7, adjacent to the nitrogen atom, appeared as a multiplet at δ = 4.16, well separated from the other methylene signals. The assignments have been confirmed by selective decoupling experiments and by NOE difference spectroscopy (NOEDS) measurements[9].

In particular, irradiation of the resonance of 2-H resulted in a positive enhancement of the signals for the CH_2 protons adjacent to the nitrogen atom and of the upfield resonance of 3-H_2. Likewise, when 3a-H was irradiated, the signal for the methyl group was enhanced, together with the downfield resonance of 3-H_2 (3β-H). These results are indicative of a *syn* relationship between 2-H and the 7α proton. With respect to the 5-membered ring, in particular, these data suggest a preferential conformation in solution which brings 2-H and the α proton at C-7 close enough to induce enhancements in their respective signals, as supported by the magnitude of the observed NOE (8%)[10].

The isoxazolidinium salt **2** was then treated with lithium iodide in dioxane solution for 8 h to give (±)-allosedamine (**3**) and the amino ketone **4**. The isolated products have the structures assigned on the basis of their spectral properties[2,3].

Scheme



A similar synthetic approach to the (±)-allosedamine system was reported which employed the $LiAlH_4$ treatment of the isoxazolidinium salt **2** to give a mixture of (±)-allosedamine (78%) and (±)-sedamine (22%)[2]. The results obtained are amenable to two competing ring-opening reaction pathways: the simple N–O bond rupture, which leads exclusively to the formation of allosedamine (**3**), and a slower reaction leading to ketone **4** by abstraction of the hydrogen atom at C-2 in **2**, with elimination of the positively charged nitrogen[3]. The subsequent nonstereoselective reduction by $LiAlH_4$ gives a 1:1 mixture of sedamine and allosedamine.

As reported[6,10], both structural and stereochemical features of the substrate deeply affect the reaction pathway of the isoxazolidinium salts. The ring-opening elimination towards ketone **4**, observed here during the LiI treatment of the isoxazolidinium salt **2** and previously postulated for the $LiAlH_4$ process[3], is effectively competing with the amino alcohol formation. In fact, although the NOE analysis just discussed suggests the preferential conformation **2'**, on the basis of the consideration that the pseudorotation of the pentatomic ring is only a few kcal·mol^{-1}, the transperiplanar arrangement of the C–H and O–N bonds around the C–O bond is quite readily accessible; this favors stereoselectively the formation of the keto derivative **4**[6,10]. The elimination process can of course be drastically suppressed by changing the configuration at C-2 of the isoxazolidinium salt[6,10].

In contrast to the $LiAlH_4$ procedure, the use of LiI for the ring-opening reaction of isoxazolidinium salt **2** to allosedamine (**3**) offers the advantage of overcoming most of the separation problems present in the $LiAlH_4$ procedure. The synthetic scheme proposed here leads, in fact, to two reaction products (**3** and **4**) which show distinct physicochemical properties and are easily recognizable and separable by conventional column chromatography.

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Formation of allosedamine (**3**) occurs through a redox reaction with formation of iodine, experimentally ascertained, from the iodide oxidation, probably by a single-electron transfer mechanism. An inversion of the yields for **3** and **4** has been observed when the reaction was performed at lower temperatures (35% and 65%, respectively, at 65°C). This behavior is interpreted by different temperature dependence of the two competing routes, starting from **2**: an increase of the reaction temperature improves the electron-transfer process, and the radical pathway, leading to the formation of (±)-allosedamine, becomes the preferred one.

Finally, with reference to other available synthetic routes to (±)-allosedamine[2,3] (**3**), the ring-opening reaction achieved by the use of LiI proves to be an effective and valuable procedure, since the very mild experimental conditions required allow for the extension of the same process to other cycloadducts, also in the presence of different functional groups which often are not compatible with $LiAlH_4$ or catalytic reduction processes.

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Experimental

IR spectra: Perkin-Elmer 377. – ^{1}H-NMR spectra: Bruker WM 300, $CDCl_3$ solutions with tetramethylsilane as internal standard. NOE measurements were performed at 300 MHz by the FT difference method on carefully degassed $CDCl_3$ solutions[9]. A 90° observation pulse and a recovery time of 10 T_1 were used. – Mass spectra: VG ZAB 2F, 60 eV with an ion source temperature of 150°C.

2-Phenyl-3,3a,4,5,6,7-hexahydro-2H-isoxazolo[2,3-a]pyridine (**1**) was prepared in 98% yield by flash-chromatographic treatment of the isomeric mixture obtained from the 1,3-dipolar cycloaddition of 2,3,4,5-tetrahydropyridine 1-oxide with styrene[2].

Isoxazolidinium Salt **2** was prepared according to the previously reported method[6] in nearly quantitative yield; light yellow solid, mp 143–145°C (ether). – IR (neat): $\tilde{\nu}$ = 3000 cm^{-1}, 2800, 1490, 1450, 1370, 1270, 970, 930, 760. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.04 (m, 6H, 4-, 5-, and 6-H_2), 2.96 and 3.23 (m, 2H, 3-H_2), 3.84 (s, 3H, CH_3), 4.16 (m, 2H, NCH_2), 5.03 (m, 1H, 3a-H), 6.05 (dd, 1H, 2-H), 7.3–7.5 (m, 5H, aromatic H).

Preparation of (±)-Allosedamine (**3**) *and N-Methyl-2-phenacylpiperidine* (**4**): To a solution of the isoxazolidinium salt **2** (0.50 g, 1.4 mmol) in anhydrous dioxane (35 ml), lithium iodide (0.38 g, 2.8 mmol) was slowly added, and the mixture was heated at reflux under stirring for 8 h. A 10% sodium sulfite solution (10 ml) was then added, and the solution was extracted with chloroform (3 × 15 ml). Concentration of the combined organic extracts afforded an oily product which was subjected to flash chromatography methanol/chloroform (8:92)] to give 0.19 g (61%) of **3** as the first eluted product. IR, NMR, and mass spectra were completely superimposable with those reported in the literature[11].

Further eluted fractions gave 0.12 g (39%) of **4** as an oil. – IR (neat): $\tilde{\nu}$ = 2930 cm^{-1}, 2840, 2760, 1670, 1140, 1200, 1000, 760, 700. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.25–1.90 (m, 6H, piperidine 3-, 4-, and 5-H_2), 2.31 (s, 3H, NCH_2), 2.78–3.04 (m, 3H, piperidine CH and 6-H_2), 3.30–3.52 (m, 2H, 7-H_2), 7.50–8.10 (m, 5H, aromatic H). – MS (70 eV): *m/z* (%) = 217 (4) [M^+], 105 (8), 99 (5), 98 (100). 77 (10).

CAS Registry Numbers

1: 70546-85-9 / **2**: 70561-78-3 / **3**: 70561-76-1 / **4**: 121961-27-1 / styrene: 100-42-5 / 2,3,4,5-tetrahydropyridine 1-oxide: 34418-91-2

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