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Synthesis of Oxazolinyl Aziridines

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Abstract: Aziridinyllithiums **4a** and **4b**, which are stable at low temperature, can be generated by deprotonation of **3a** and **3b**. Oxazolinyl aziridines **5a–j** and **6a–b** have been prepared by the reaction of oxazolinyl aziridinyllithiums **4a** and **4b** with electrophiles. Aziridines **6c** and **6d** were, instead, synthesized by a Darzens-like reaction from 2-(1-chloroethyl)-2-oxazoline **1b**.

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Aziridines, of considerable interest in the field of natural products [1,2], are versatile synthetic intermediates. Many preparative methods for aziridines involve two component reactions [1], such as the aza-Darzens reaction [3], the intermediacy of carbenes [4] and ylides [5], and the 1,2-dihalide route [6]. Aziridinyl anions, which were not widely known and studied until a few years ago [7], have rarely been used as key intermediates for the synthesis of more complex aziridines, possibly due to the difficulty of their generation and trapping with electrophiles. Stabilized aziridinyl anions can be generated by deprotonation [3a,8–13], the nonstabilized ones by desulfinylation [3b,14], desilylation [15], destannylation [16] and even by deprotonation *via* preliminary Lewis acid activation [17].

Oxazolinylaziridines seem to be useful intermediates in synthetic organic chemistry as the oxazolinyl and the aziridinyl groups are amenable to numerous synthetic transformations. In the present paper we report a simple and convenient route to oxazolinylaziridines based on the deprotonation-alkylation of simpler oxazolinyl aziridines.

Treatment of 2-chloromethyl-4,4-dimethyl-2-oxazoline **1a** [18a–c] (Scheme 1) with LDA in THF at –78 °C followed by the immediate addition of the Schiff base **2a** afforded aziridine **3a**. Lithiation of **3a** (*n*-BuLi, THF, –78 °C) resulted in the formation of the aziridinyllithium **4a** that was stable at –78 °C and could be converted back to its precursor **3a** upon quenching with aq. NH_4Cl. Moreover, the reaction of **4a** with D_2O gave deuterated aziridine **5a** almost quantitatively. The stability and the usefulness of aziridinyllithium **4a** could also be proved by its trapping with a number of electrophiles to give functionalized aziridines **5b-e**. Aziridine **5b**

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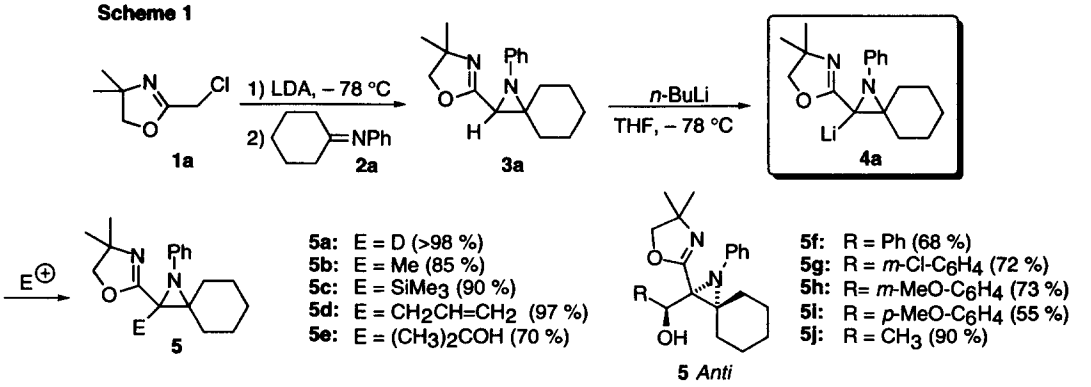
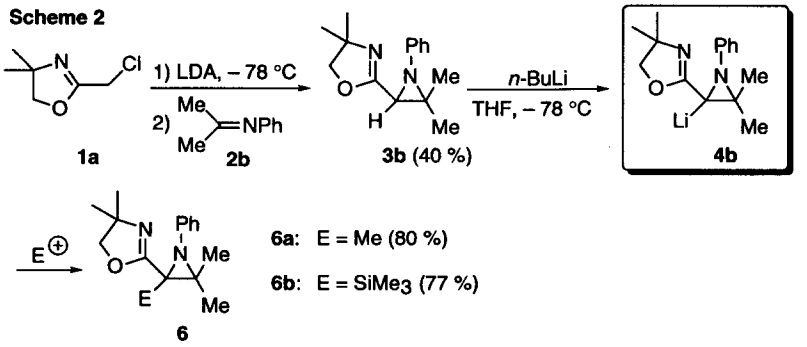
could be also prepared from lithiated 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline **1b** [19] and imine **2a** (55 % yield).

Scheme 1



In a similar way, lithiation of **1a** (LDA, –78 °C, THF) followed by quenching with imine **2b** produced aziridine **3b**. Treatment of **3b** with *n*-BuLi (1 eq., THF, –78 °C) generated aziridinyllithium **4b** that reacted cleanly with MeI and Me_3SiCl to give **6a** [20] and **6b**, respectively (Scheme 2).

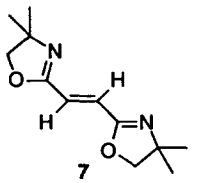
Scheme 2



The reaction of **4a** with aldehydes turned out to be completely *anti* diastereoselective. Indeed, the reaction of **4a** with benzaldehyde led to the hydroxyalkyl aziridine **5f**, which was assigned the *anti* configuration [21] on the basis of the AB system found for the two geminal protons of the oxazoline ring combined with a large chemical shift difference ($\Delta\nu$ = 0.51 ppm) for the two oxazoline methyl groups by analogy with what had been found in the case of oxazolinyl hydroxyalkyl oxiranes [22]. Equally *anti* diastereoselective were the reactions of **4a** with other aromatic aldehydes giving hydroxyalkyl aziridines **5g-i**. It is, however, noteworthy that the deprotonation-alkylation of oxazolinyl oxiranes had been found to be nonstereoselective [22]. Much less *anti* diastereoselective was the reaction of **4a** with acetaldehyde (*anti/syn* ratio = 2/1). The diastereomers **5j** could, however, be easily separated by column chromatography and assigned configurations on the basis of the chemical shifts of the

methyne protons on the hydroxy-bearing carbon atoms. Such a methyne proton in the *syn* isomer resides at lower field with respect to the *anti* isomer, as reported for similar hydroxyalkyl aziridines [23].

It was not possible to couple lithiated **1a** with imines derived from aromatic aldehydes or ketones as homocoupling with its precursor **1a** giving the *trans*-dioxazolinyl ethene **7**, after elimination, largely prevailed [18a].



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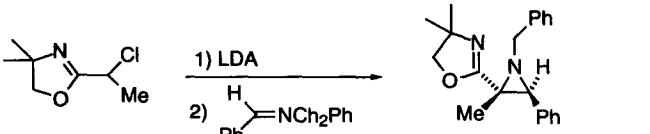
Aziridine **6c** (Scheme 3), however, could be prepared in a highly diastereoselective manner (*E*/*Z*=94 / 6) [24a] *via* the Darzens reaction of **1b** with imine **2c**.

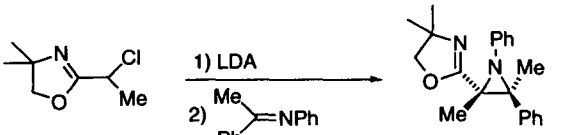
Scheme 3



1b **2c** **6c** (53 %; *E* / *Z*: 94 / 6)

In a similar way aziridine **6d** could be prepared (Scheme 4). Indeed, lithiated **1b** is stable for at least 1 h at low temperature and reacts with imine **2d** to furnish the tetrasubstituted aziridine *trans*-**6d** stereoselectively [24b, 25].

Scheme 4



1b **2d** **6d** (70 %)

In conclusion, we have reported here a simple synthesis of functionalized aziridines based on lithiation-alkylation of simple easily available aziridines. As mentioned above, the utility of oxazolinyl aziridines resides in the fact that both the oxazolinyl (a well known masked carbonyl function) and aziridinyl groups can be synthetically elaborated. More work is in progress in our lab to this end.

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[20] Compound **6a** could be prepared also by a Darzens-like reaction from **1b** and imine **2b** (60 % yield).

[21] The *syn* or *anti* configuration is referred to the relative position of the aziridine ring and the OH function (both projecting at the same or opposite side, respectively) when the main chain is written in an extended (zig-zag) conformation. **5f**: Solid, m.p. 145–147 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.54 (s, 3 H), 1.05 (s, 3 H), 1.23–1.40 (m, 1 H), 1.66–1.78 (m, 3 H), 1.78–1.92 (m, 3 H), 2.10–2.18 (m, 1 H), 2.26–2.36 (m, 1 H), 2.42–2.52 (m, 1 H), 3.41 (d, *J* = 8.0 Hz, 1 H), 3.64 (d, *J* = 8.0 Hz, 1 H), 4.81 (d, *J* = 8.0 Hz, 1 H), 5.44 (d, *J* = 8.0 Hz, 1 H), 6.70 (t, *J* = 7.2 Hz, 1 H), 6.89 (d, *J* = 8.3 Hz, 2 H), 7.16–7.36 (m, 5 H), 7.48 (d, *J* = 7.7 Hz, 2 H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.67, 23.74, 25.00, 27.46, 28.04, 31.26, 33.82, 61.76, 66.35, 76.95, 96.47, 113.73, 116.66, 126.68, 127.91, 129.09, 136.21, 143.26, 163.37.– GC-MS (70 eV); *m/z* (rel. int.): 390 (M^+, 339), 361 (28), 347 (1000), 275 (72), 194 (120), 104 (260), 91 (84), 77 (96), 55 (57). $C_{25}H_{30}N_2O_2$ (390.52): calcd. C 76.89, H 7.74, N 7.17; found C 76.48, H 7.39, N 7.07.

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[24] [24a] The *E* configuration of aziridine **6c** was established on the basis of the vanishing $^3J_{CH}$ ~ 0 Hz between the aziridine ring hydrogen and the CH_3 on the adjacent ring carbon as discussed in: Kingsbury CA, Durham DL, Hutton R. J. Org. Chem. 1978;43:4696–4700. [24b] The *E* configuration of aziridine **6d** was assigned by comparing its methyl carbons ^{1}H chemical shifts with those of **3b** and **6a**. The chemical shift of Me α to the oxazoline ring system of **6a** (δ = 1.32) was shifted upfield by 0.36 ppm in the case of **6d**. It has been reported a similar 0.3 ppm high field displacement for a Me group in the case of a *cis* relationship with a Ph group. On the other hand, a Me group could induce only a 0.1 ppm upfield shift on a *cis* one. Alvernhe G, Laurent A. Bull. Soc. Chim. France 1970; 8–9: 3003–3010. **6d**: Oil. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (s, 3 H), 0.96 (s, 3 H), 1.53 (s, 3 H), 1.55 (s, 3 H), 3.44 (d, *J* = 8.0 Hz, 1 H), 3.60 (d, *J* = 8.0 Hz, 1 H), 6.86–7.01 (m, 3 H), 7.21–7.33 (m, 5 H), 7.48–7.53 (m, 2 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.04, 16.56, 27.59, 27.71, 46.28, 51.15, 66.64, 78.76, 120.05, 121.08, 126.67, 127.03, 127.56, 128.58, 141.82, 145.20, 164.37. – GC-MS (70 eV); *m/z* (rel. int.): 320 (M^+, 445), 305 (22), 289 (1000), 247 (187), 232 (207), 144 (78), 77 (113).

[25] All new compounds showed consistent IR, MS, ^{1}H NMR, ^{13}C NMR spectra and satisfactory microanalytical data.