A CONVENIENT PREPARATION OF CHIRAL AND ACHIRAL 2-SUBSTITUTED N-ALKYLAZIRIDINES

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Résumé: Au cours de ce travail, nous avons développé une méthode générale de synthèse des N-alkylaziridines 2-substituées chirales et achirales par condensation d’une série d’aamines sur des α-bromoesters suivie de la réduction par LiAlH₄. Les α-aminoalcools ainsi obtenus ont été mis à réagir dans les conditions de la réaction de Mitsunobu pour générer les aziridines fonctionnalisées attendues.

Abstract: In this paper, we describe a new and general method of preparation of chiral and achiral 2-substituted N-alkylaziridines is described. Good to high yields were obtained.

Aziridines are valuable synthetic reagents and intermediates [1, 2]. In particular they benefit from a high reactivity due to the ring strain. One of the most important methods for the preparation of 2-substituted N-alkylaziridines starts from N-protected (N-tosyl, N-acyl and N-carbamoyl) natural α-aminoacids [3-5]. This method is most frequently used and applies the Mitsunobu reaction [6]. The disadvantages of this procedure, however, are the limited number of available aminoacids, the difficulty to remove the tosyl group and possibilities of formation of 5-membered oxazolonium intermediate rather than the required aziridines, from N-acyl and N-carbamoyl derivatives. However, only a limited number of methods for N-alkylaziridination exist [7-11]. Therefore, there is need for development of new methods for synthesis of 2-substituted N-alkylaziridines.

In this paper, we describe a simple and expedient route for the synthesis of N-alkylaziridines 5 from treatment of readily available starting materials, primary amines 1 with α-bromoesters 2 followed by reduction of aminoesters 3 with LiAlH₄. Ring closure of aminoalcohols 4 under Mitsunobu conditions resulted in the formation of 2-substituted aziridines 5 in fair to excellent yields. Alternatively, optically pure N-(S) and N-(R)-(α-methylbenzyl)aziridines 5f and 5g were prepared from (S) and (R)-phenylethylamines 1f and 1g respectively. For example, the α-aminoester 3f was reduced with LiAlH₄ to afford a diastereoisomeric mixture of aminoalcohols [12] 4f. The isomers were separated quite easily by column chromatography on silica gel. Treatment of each diastereoisomer with diethylazodicarboxylate and triphenylphosphine gave optically pure N-(S)-(α-methylbenzyl)aziridine-(2R or 2S)-methyl 5f (Scheme 1). The cyclocondensation reaction was then carried out in a variety of solvents and it was observed that THF gave reasonable yields of the desired 2-substituted N-alkylaziridines 5 (Table I).

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Scheme 1

Table I: Preparation of aziridines

<table>
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<tr>
<th>Entry</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
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<th>Yields (%)</th>
<th>d.e (%)</th>
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<td>THF</td>
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<td>85</td>
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<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
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<td>ethyl</td>
<td>THF</td>
<td>83</td>
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<tr>
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In summary, we have developed a general method for preparation of chiral and achiral 2-substituted N-alkylaziridines using primary amines and α-bromoesters. We are currently investigating the use of enantiomerically pure α-bromoesters 2 for preparation of optically pure 2-alkyl N-alkylaziridines.

**Experimental section:**

The NMR spectra were determined on a Bruker instrument (AM 300 WB, 300 MHz) using CDCl₃ with TMS as internal standard. IR spectra were recorded on a Perkin Elmer 1310 spectrophotometer. MS spectra were obtained in the electronic impact mode on Hewlett Packard 5792 apparatus coupled to a gas chromatograph (HP-5890A, equipped with a capillary column, stationary phase: 5% diphenyl, 95% dimethylpolysiloxane) or in the chemical ionization mode on a Nermag R10-10C quadrupole apparatus. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F₂₅₄; column chromatography was performed using Merck silica gel 60 (0.063-0.200 mm).

**Cyclisation of aminoalcohols 4 to Aziridines 5:**

To a solution of aminoalcohol 4 (10 mmol) and triphenylphosphine (3.34 g, 15 mmol) in ether or tetrahydrofuran (30 mL, choice of solvent depends on substrate solubility) stirred under nitrogen in an ice bath, is slowly added diethylazodicarboxylate (95%, 2.5 ml, 15 mmol) via a syringe. The bath is removed, and the mixture is stirred at room temperature for 16 h to 20 h. A crystalline precipitate (triphenylphosphine oxide/diethyl hydrazinedicarboxylate complex) is filtered off and washed with hexane/ether (1/1, 50 ml). The filtrate is evaporated on a rotary evaporator. The crude reaction mixture was purified by column chromatography (80% hexane-20% ethylacetate).

5a: \(^{1}H\) NMR: 0.93-0.91 (d, 6H; J= 4Hz); 1.27-1.22 (t, 3H; J= 5Hz ); 1.87-1.59 (m, 1H); 3.79-3.89 (q, 1H); 4.21-3.91 (m, 2H). \(^{13}C\) NMR: 52.56; 50.48; 48.45; 32.23; 20.48; 16.23; 13.76; Anal. Calcd for C₇H₁₅N: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.18; H, 13.32; N, 12.34; SM (IE): C₇H₁₅N; PM = 113; (M⁺ = 113; 20%); m/z = 98 (C₆H₁₂N; 20%); m/z = 70 (C₄H₈N; 100%); m/z = 43 (C₂H₅; 30%).

5b: \(^{1}H\) NMR: 0.93-0.91 (d, 6H; J= 4Hz); 1.27-1.22 (t, 3H; J= 5Hz ); 1.83 –1.59 (m, 1H) ; 3.71-3.85 (q, 1H); 4.11-3.81 (m, 2H). \(^{13}C\) NMR: 52.56; 50.48; 48.45; 32; 20.48; 16.23; 14.58; 13.76. Anal. Calcd for C₈H₁₇N: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.47; H, 13.42; N, 10.94; SM (IE): C₈H₁₇N; PM = 127; (M⁺ = 127; 20%); m/z = 98 (C₆H₁₂N; 20%); m/z = 70 (C₄H₈N; 100%); m/z = 43 (C₂H₅; 30%).

5c: \(^{1}H\) NMR: 7.25 (m, 1H); 6.21-6.08 (m, 2H); 3.42-3.3 (m, 2H); 3.65-3.61 (q, 1H); 1.32 (s, 2H); 1.12-1.10 (d, 3H; J= 4Hz). \(^{13}C\) NMR : 109.90; 109.82; 106.77; 106.59; 49.33; 34.51; 33.9 ; 17.45. Anal. Calcd for C₈H₁₁NO: C, 70.04; H, 8.08; N, 10.21; O, 11.66. Found: C, 70.00; H, 8.02; N, 10.17; O, 11.61; SM (IE): C₈H₁₁NO; PM = 137; (M⁺ = 137; 1%); m/z = 81 (C₅H₅O; 100%); m/z = 56 (C₃H₆N ; 100%).

5d: \(^{1}H\) NMR: 7.25 (m, 1H); 6.21-6.08 (m, 2H); 3.42-3.31 (m, 2H); 3.65-3.61 (q, 1H); 1.32 (s, 2H); 1.12-1.10 (d, 3H; J= 4Hz). \(^{13}C\) NMR : 109.57; 109.09; 106.87; 106.40; 49.27; 34.54; 33.82; 17.32; 13.89. Anal. Calcd for C₉H₁₃NO: C, 71.49; H, 8.67; N, 9.26; O, 10.58. Found: C, 71.45; H, 8.63; N, 9.22; O, 10.54; SM (IE): C₉H₁₃NO; PM = 151; (MH⁺ = 152; 30%).

5e: \(^{1}H\) NMR: 0.87-0.90 (t, 3H; J= 3Hz); 1.01-1.13 (d, 3H; J= 4Hz); 1.28-1.38 (m, 2H); 1.45-1.60 (m, 2H) ; 2.41-2.59 (m, 2H); 3.,57-3.68 (q, 1H); 3.88-3.98 (m, 2H). \(^{13}C\) NMR: 52.56 ; 50, 48; 48.45 ;32,23 ; 20,48 ; 16,23 ; 13,76.

5f: \([\alpha]D^{25}_{2} = +58.6 (c = 1, CH₂Cl₂); \(^{1}H\) NMR: 7.78-7.65 (m, 5H); 4.01–3.81 (m, 2H); 3.72-3.62 (q, 1H); 2.56-2.46 (m, 1H); 1.42-1.39 (d, 3H; J= 6Hz); 1.05-1.03 (d, 3H; J= 4Hz). \(^{13}C\) NMR: 145.12; 129.89; 129.05; 126.89; 58.43; 49.48; 46.12; 17.89; 17.48. Anal. Calcd for C₁₁H₁₅N: C, 81.94; H,
9.38; N, 8.69. Found: C, 81.89; H, 9.35; N, 8.66; SM: C$_{11}$H$_{16}$N; PM = 161; obs (M$^+$ = 1%); m/z = 105 (C$_{5}$H$_{10}$; 40%); m/z = 56 (C$_{3}$H$_{6}$N; 100%); m/z = 77 (C$_{5}$H$_{6}$; 25%).

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References
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