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'amines sur des α-bromoesters suivie de la réduction par $LiAlH_4$. 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 benefict 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 $LiAlH_4$. 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 $LiAlH_4$ 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-(2*R* or 2*S*)-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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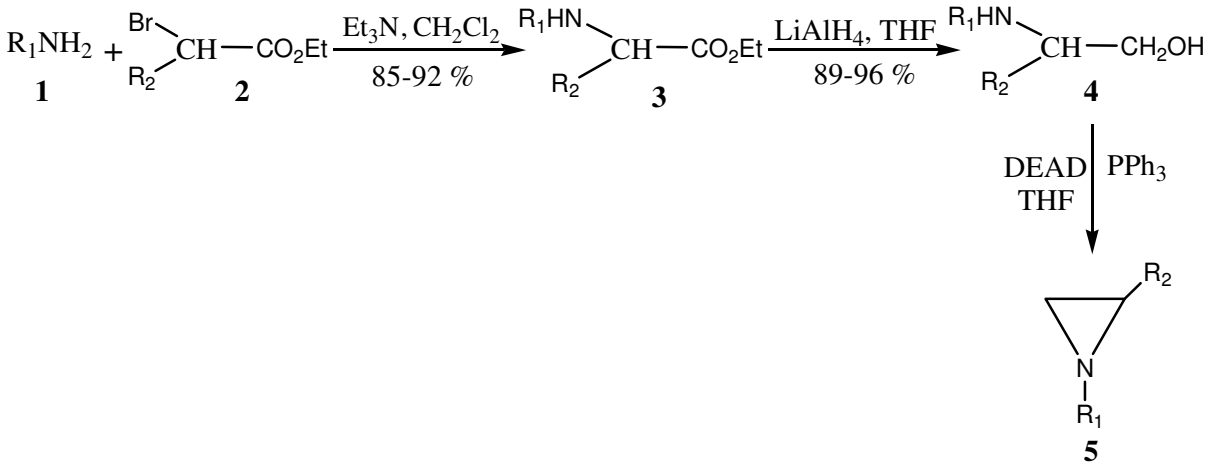

Scheme 1

Table I: Preparation of aziridines

Entry	R_1	R_2	Solvent	Yields (%)	d.e (%)
5a	Isobutyl	methyl	THF	75	-
5a	Isobutyl	methyl	CH_2Cl_2	54	-
5b	Isobutyl	ethyl	THF	78	-
5b	Isobutyl	ethyl	$CHCl_3$	61	-
5c	Furfuryl	methyl	THF	85	-
5c	Furfuryl	methyl	C_6H_6	72	-
5d	Furfuryl	ethyl	THF	83	-
5d	Furfuryl	ethyl	$CHCl_3$	69	-
5e	Butyl	methyl	THF	78	-
5e	Butyl	methyl	$CHCl_3$	59	-
5f	(S)-1-phenyl ethyl	methyl	THF	81	65
5f	(S)-1-phenyl ethyl	methyl	CH_2Cl_2	60	65
5g	(R)-1-phenyl ethyl	methyl	THF	77	69
5g	(R)-1-phenyl ethyl	methyl	CH_2Cl_2	55	69

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 $CDCl_3$ 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 Heweltt 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 quadripole apparatus. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254}; column chromatography was performed using Merck silica gel 60 (0.063-0.200 mm).

Cyclisation of aminoalcohols 4 to Aziridines 5: General Procedure:

To a solution of aminoalcohol **4** (10 mmol) and triphenylphosphine (3.34 g, 15mmol) 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 $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.18; H, 13.32; N, 12.34; SM (IE): $C_7H_{15}N$; PM = 113; (M^+ = 113; 20%); m/z = 98 ($C_6H_{12}N$; 20%); m/z = 70 (C_4H_8N; 100%); m/z = 43 (C_3H_7; 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;23; 20.48; 16.23; 14.58; 13.76. Anal. Calcd for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.47; H, 13.42; N, 10.94; SM (IE): $C_8H_{17}N$; PM = 127; (M^+ = 127; 20%); m/z = 98 ($C_6H_{12}N$; 20%); m/z = 70 (C_4H_8N; 100%); m/z = 43 (C_3H_7; 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 $C_8H_{11}NO$: 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): $C_8H_{11}NO$; PM = 137; (M^+ = 137; 1%); m/z = 81 (C_5H_5O; 100%); m/z = 56 (C_3H_6N ; 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 $C_9H_{13}NO$: 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 (IC): $C_9H_{13}NO$; 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: $[\alpha]_D^{25}$ = +58.6 (c = 1, CH_2Cl_2); ^{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 $C_{11}H_{15}N$: 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_8H_{10}; 40%); m/z = 56 (C_3H_6N; 100%); m/z = 77 (C_6H_6; 25%).

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