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A novel procedure for the synthesis of aziridines: application of Simmons–Smith reagents to aziridination

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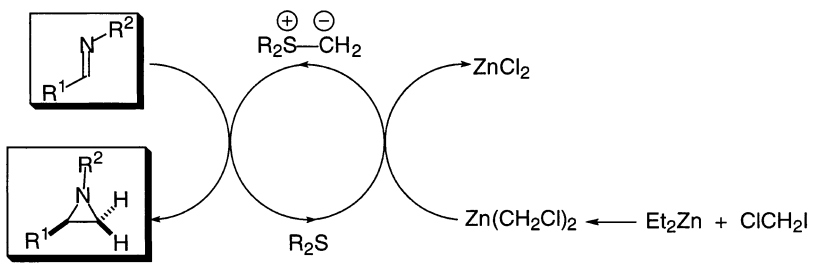
Abstract—The reaction of Simmons–Smith carbenoids with imines in the presence of sulfides provides *N*-(*p*-toluenesulfonyl)- and *N*-[(1,1,1-trimethylsilyl)ethyl]sulfonyl-substituted aziridines in high yield.

1. Introduction

Aziridines are versatile synthetic intermediates that can undergo regio- and stereoselective ring-opening reactions with both heteroatomic and carbon nucleophiles.[1] Non-racemic, terminal aziridines are an important class of these saturated heterocycles and have been prepared from α-amino acids,[2] epoxides,[3] carbohydrates,[4] or by transformations of C=C[5] and C=N bonds.[6] We have described a novel method for the synthesis of terminal epoxides from aldehydes[7] using sulphur ylides generated in situ by the reaction of Simmons–Smith carbenoids[8] with tetrahydrothiophene (THT). This process operated under neutral conditions and gave high yields, even with base sensitive substrates. The success of this work prompted us to consider extending the methodology to the synthesis of terminal aziridines from imines (Scheme 1).

We were particularly encouraged by a report which indicated that the reaction of dimethylsulphonium methylide with *N*-aryl substituted imines proceeded in high yield.[6a] Disappointingly, the combination of $Et_2Zn/ClCH_2I$/THT with *N*-benzylidenaniline (entry 1), using the protocol that was successful for epoxidation, only gave traces of aziridine. Changing the substituent on nitrogen to a more electron-withdrawing group (tosyl) was ultimately successful and, after optimising the conditions, good yields were obtained with a range of aromatic and aliphatic imines[9] (Table 1). Both electron-withdrawing and electron-donating aromatic substituents (R^1) were tolerated, but substrates at the extremes required some modification of the reaction conditions (Table 1, entries 2–6). For example, under standard conditions, *N*-(*p*-tolylsulphonyl)-2-(*p*-nitrophenyl)aziridine (entry 3) was obtained in 51% yield together with a by-product (11%) resulting from direct



Scheme 1. Application of organozinc reagents to aziridination.

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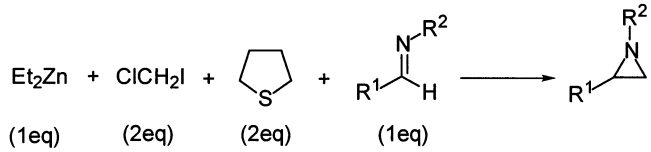
Table 1. Organozinc-mediated aziridination reactions of imines



Entry	R^1	R^2	Isolated yield (%)
1	C_6H_5	C_6H_5	<3
2	C_6H_5	Tosyl	68
3	p-NO_2-C_6H_4	Tosyl	66[a]
4	p-Cl-C_6H_4	Tosyl	71
5	p-AcO-C_6H_4	Tosyl	68
6	p-MeO-C_6H_4	Tosyl	33[b,c]
7	C_6H_{11}	Tosyl	72
8	n-C_4H_9	Tosyl	53
9	t-C_4H_9	Tosyl	77
10	C_6H_5	SES	72
11	C_6H_5	o-MeO-C_6H_4	79[d] (94)[10]
12	C_6H_5	p-MeO-C_6H_4	<3

[a] 2.5 equiv. $ClCH_2I$.
[b] The reaction mixture was quenched after 3.5 h.
[c] The major by-product was the N-(p-toluenesulphonyl)amino alcohol (19%).
[d] Yield determined by ^1H NMR.

addition of an ethyl group to the C=N bond. However, when the bis(chloromethyl)zinc reagent was generated independently, by reaction of Et_2Zn and 2.5 equiv. $ClCH_2I$ (instead of 2 equiv.), an improved yield was obtained. By employing this protocol the competing ethyl addition was minimised. The presence of strongly electron-donating substituents (e.g. p-MeO, entry 6) also caused problems due to the sensitivity of the aziridine toward ring opening, either during reaction or on work-up. The extent of ring opening could be reduced using a less powerful donating group (e.g. p-AcO, entry 5). Aliphatic enolisable imines were also tolerated. The imine derived from cyclohexanecarboxaldehyde (entry 7) was aziridinated in good yield, although the competing reduction giving N-1-cyclohexylmethyl-1-p-toluenesulphonamide (15%) was also observed. In a control experiment the imine was reacted with 1 equivalent of diethyl zinc in CH_2Cl_2 and the reduction product, N-1-cyclohexylmethyl-1-p-toluenesulphonamide, was obtained in 77% yield. Clearly, N-tosyl imines with a relatively Lewis basic nitrogen have a greater propensity for reduction relative to direct addition in reactions with Et_2Zn (compare entry 3). N-(Pentylidene)toluene-p-sulphonamide was also aziridinated in 53% yield (entry 8).

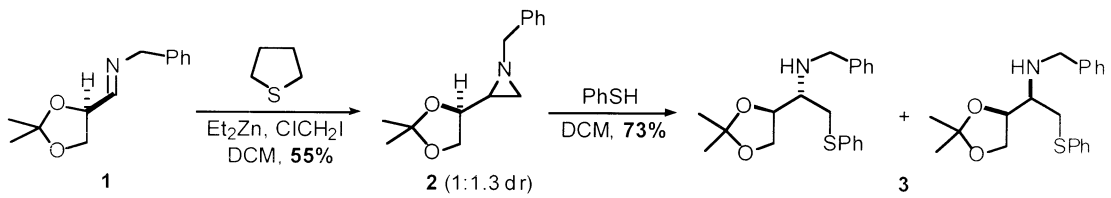
The aziridination reaction is tolerant of steric congestion at the α-position: 2-t-butyl-1-(p-tolylsulphonyl)aziridine was obtained in high yield (entry 9) together with N-(2,2-dimethylpropyl)-4-methyl-benzenesulphonamide (11%).

The N-tosyl group can be a difficult group to remove from aziridines and so we prepared and tested the N-[(trimethylsilyl)ethyl]sulphonyl (SES) imine derived from benzaldehyde and found that it was equally effective (entry 10). The SES protecting group can be easily removed from amines[11] and aziridines[12] with fluoride.

In a further study, initial results have shown that the requirement for strongly electron-withdrawing groups on nitrogen is negated when the imine substrate is capable of bidentate co-ordination. For example, N-benzylidine-o-anisidine[13] was readily aziridinated (entry 11). We postulate that as a result of chelation, the imine is activated towards attack by the sulphur ylide. The p-substituted analogue (entry 12), which is incapable of bidentate co-ordination, was unreactive under identical reaction conditions.

We have extended the process to more functionalised imines and describe our work on the imine of glyceraldehyde acetonide **1**. Although we were unable to prepare the N-Ts analogue of **1**, we found that the simple N-benzyl imine was effective and the aziridine was obtained in 55% yield and 1:1.3 dr. Presumably the additional electron-withdrawing oxygens contribute to the greater reactivity of the N-benzyl imine. The low diastereoselectivity suggests that chelation controlled addition was probably not occurring. No racemisation occurred during aziridination as comparisons with racemic samples were made and the products analysed by chiral HPLC.[14] The aziridine can be ring opened regioselectively with thiophenol[15] to give amino sulphides **3**, which are important subunits in the synthesis of nelfinavir, a potent HIV-protease inhibitor[16] (Scheme 2).

In conclusion, the application of Simmons–Smith carbenoids to aziridination has provided a novel route for the preparation of a range of terminal aziridines. Mild reaction conditions afford N-(p-toluenesulphonyl)- and N-[(trimethylsilyl)ethyl]sulphonyl-substituted aziridines in high chemical yield. Studies towards the asymmetric synthesis of these substrates are ongoing in our laboratories.



Scheme 2. Application to synthesis of fragment of nelfinavir.

2. General procedure

N-(p-Tolylsulphonyl)-2-(p-chlorophenyl)aziridine (Table 1, entry 4): Diethyl zinc (1.1 M in toluene, 1.0 mL) was added to a stirred solution of *N*-(*p*-chlorobenzylidene)toluene-*p*-sulphonamide (0.29 g, 1.0 mmol), chloroiodomethane (0.15 mL, 2.0 mmol) and tetrahydrothiophene (0.18 mL, 2.0 mmol) in CH_2Cl_2 (5 mL) at room temperature under a positive pressure of argon. After 16 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and the reaction products extracted into CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with triethanolamine (2N, 2×10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (CH_2Cl_2) gave *N*-(*p*-tolylsulphonyl)-2-(*p*-chlorophenyl)aziridine as a white crystalline solid (0.22 g, 71%), mp 117–118°C (hexane/EtOAc) [lit.[17] 115–116°C]; δ_H (250 MHz, $CDCl_3$) 2.33 (1H, d, *J* 4.6 Hz, C*H*H′N), 2.43 (3H, s, $PhCH_3$), 2.97 (1H, d, *J* 7.0 Hz, CH*H*′N), 3.72 (1H, dd, *J* 7.0 and 4.6 Hz, ArCH), 7.14 (2H, br d, *J* 8.5 Hz, ArH), 7.25 (2H, br d, *J* 8.5 Hz, ArH), 7.33 (2H, br d, *J* 8.2 Hz, ArH), 7.85 (2H, d, *J* 8.2 Hz, ArH).

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10. 1-[2-(Methyloxy)phenyl]-2-phenylaziridine: Chloroiodomethane (0.15 mL, 2.0 mmol) was added to a solution of diethyl zinc (1.1 M in toluene, 2.0 mL) in CH_2Cl_2 (9 mL) at 0°C under argon. The solution was stirred for 10 min before adding tetrahydrothiophene (0.27 mL, 3.0 mmol), followed by a solution of *N*-benzylidine-*o*-anisidine (0.21 g, 1.0 mmol) in CH_2Cl_2 (1 mL). The mixture was then allowed to warm to ambient temperature. After 16 h the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the products were extracted into CH_2Cl_2 (3×15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by Kugelrohr distillation (150°C/0.02 mmHg) gave title compound as a yellow oil (0.23 g, 100%, 94% pure; inseparable from recovered imine), ν_{max} (NaCl disc, liquid film)/cm^{-1} 2834 (C–OCH_3), 1269 (C–O), 1028 (C–O); δ_H (250 MHz, $CDCl_3$) 2.42 (1H, dd, *J* 6.4 and 0.9 Hz, C*H*H′N), 2.50 (1H, dd, *J* 3.7 and 0.9 Hz, CH*H*′N), 3.07 (1H, dd, *J* 6.4 and 3.7 Hz, PhCH), 3.81 (3H, s, OCH_3), 6.83–7.02 (4H, m, ArH), 7.25–7.45 (5H, m, ArH); δ_C (63 MHz, $CDCl_3$) 37.9, 42.0, 55.5, 111.2, 120.5, 120.7, 123.0, 126.4, 127.1, 128.3, 139.6, 143.1, 152.4; *m*/*z* (CI) 226 (MH^+, 78%), 225 (85), 224 (100), 211 (13), 134 (88) (found: MH^+, 226.1233. $C_{15}H_{16}NO$ requires MH^+, 226.1232).
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