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Aziridination of 3-methyl-4-nitro-5-styrylisoxazoles

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ABSTRACT

Herein we describe the preparation of a novel class of isoxazolyl aziridines. The products were obtained exclusively as cis diastereoisomers.

The aziridine nucleus is present in several natural products exhibiting biological activity such as antitumour and antibiotic.[1] A number of synthetic aziridines have also been shown to exhibit useful biological properties (Fig. 1).[2] For example, 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acid **1** is a potent, irreversible inhibitor of the bacterial enzyme diaminopimelic acid epimerase,[2a] whilst 2-(2-carboxyethyl)aziridine-2-carboxylic acid **2** is an irreversible inhibitor of glutamate racemase.[2b] Since these are the nitrogen analogues of epoxides, they also display similar electrophilic reactivity: aziridines undergo various nucleophilic ring-opening reactions and serve as synthetic intermediates for nitrogen-containing compounds.[3] For instance, aziridines have been used for the synthesis of amino acids and alkaloids,[1] substituted amines, diamines, amino alcohols and α- or β-amino acids.[4]

As part of our ongoing studies on the generation of chemical diversity using polyfunctional scaffold **4**,[5–13] we became interested in the preparation of a family of aziridines **3** (Scheme 1). In analogy to compounds **4**, aziridines **3** still possess two electrophilic centres that could be reacted selectively. Indeed, α,β-aziridines undergo regio- and stereoselective ring opening when reacted with suitable nucleophiles.[14]

From this standpoint, compounds **3** constitute a stereospecific version of scaffolds **4** that we hope to employ to generate diversity in a stereoselective fashion. Additional features adding versatility to scaffold **3** are (i) the reactivity of the 4-nitroisoxazole core that can be converted to a carboxylate[8–11] or to a polyaminoalcohol;[13]

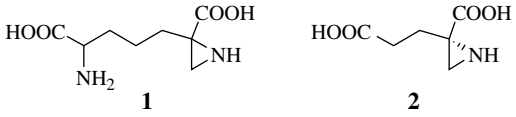

Figure 1. Examples of synthetic bioactive aziridines.

(ii) the modular nature of compounds **4** which can be prepared from commercially available isoxazole **5** and an aromatic or heteroaromatic aldehyde. Considering the reactivity of aziridines[14] and 4-nitroisoxazoles,[5–13] we envisaged the potential of compounds **3** for the generation of libraries of small organic compounds. For example, aziridine ring opening followed by hydrolysis of the 4-nitroisoxazole to a carboxylic acid could furnish amino acids **8–9** (Scheme 2). Alternatively, reduction of the 4-nitroisoxazole[13] core could lead to aziridine-containing polyaminoalcohols **7** (Scheme 2).

We started our investigation by reacting styrylisoxazole **4a** and bromamine-T **10** in the presence of ruthenium chloride.[15] This reaction furnished isoxazolyl aziridine **11** in 20% yield as an 8:2 mixture of diastereoisomers (Scheme 3), the remainder being unconverted **4a**.

Several attempts were made to improve the yield of compound **11**, including increasing the amount of oxidant (1–5 equiv), changing the metal catalyst ($RuCl_3$ or $FeCl_3$), employing a ligand (Salen or aminoalcohols), changing the amount of catalyst (0.1–1 equiv), changing the solvent (DCM, acetonitrile, THF), the temperature and reaction time. Unfortunately, no significant increase in the yield of **11** was observed. The reaction of **4a** with sulfonyl azide in the presence of various amounts of $RuCl_3$ gave only unreacted **4a**.

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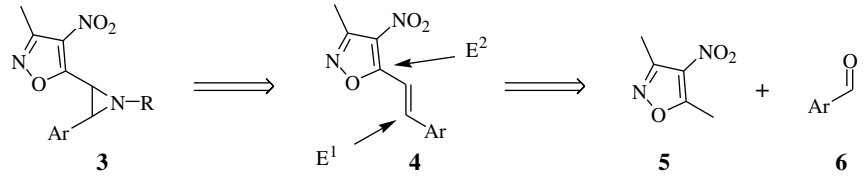
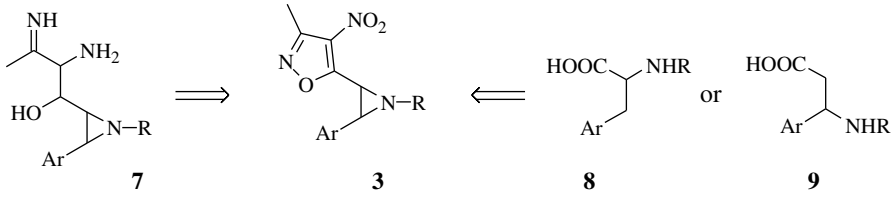
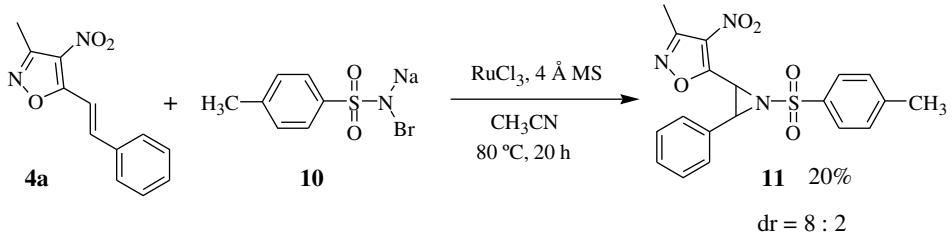


Scheme 1. Retrosynthetic analysis of target **3**.



Scheme 2. Planned synthetic transformations of isoxazolyl aziridine **3**.

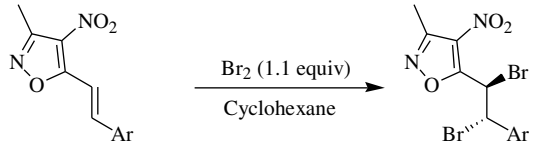


Scheme 3. Reaction of styrylisoxazole **4a** and bromamine-T **10**.

The unexpected lack of reactivity of compound **4a** can be explained considering the electronic deficiency of the exocyclic alkene.

It was, therefore, decided to pursue the preparation of **3** using an alternative strategy involving alkene bromination and subsequent conversion to an aziridine. The preparation of compounds such as **12** (Table 1) has been previously reported,[16] which gave us renewed confidence in the synthesis of compounds **3**. We have repeated this work and confirmed that variously substituted isoxazoles **4a–k** underwent efficient reaction with bromine to give the expected *anti*-dibromo derivatives **12a–k** in excellent yields (Table 1). With compounds **12a–k** in hand, we next studied their reactivity towards benzylamine. The reaction of **12a** with benzylamine in CH_3CN afforded a diastereoisomeric mixture of the expected aziridines. The use of bases such as Na_2CO_3 or pyridine augmented the amounts of aziridine, however, the selectivity was not improved. Following a report describing the effect of Cs_2CO_3 in a related aziridination,[17] we undertook a screening of the reaction conditions to identify an optimum experimental setup (Table 2).

Table 1
Synthesis of isoxazolyl dibromides **12a–k**



4a-k **12a-k**

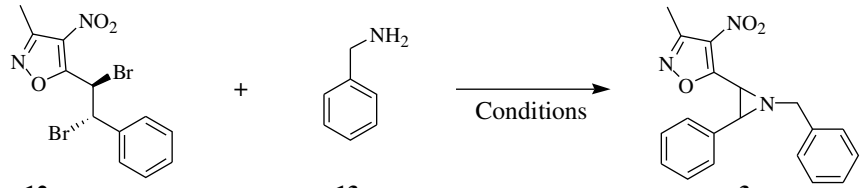
Entry	Ar	Product	Yield[a] (%)
1	C_6H_5	**12a**[b]	98
2	*p*-Cl–C_6H_4	**12b**[b]	96
3	*p*-F–C_6H_4	**12c**	99
4	*p*-Br–C_6H_4	**12d**[b]	94
5	*m*-Cl–C_6H_4	**12e**[b]	95
6	2-Pyridyl	**12f**	99
7	*p*-Me–C_6H_4	**12g**[b]	93
8	*p*-MeO–C_6H_4	**12h**	91
9	2-Naphthyl	**12i**	77
10	2-Quinolinyl	**12j**	94
11	2-Thienyl	**12k**	96

[a] Isolated yield after work up.
[b] Compounds described in Ref. 16.

Reaction of dibromide **12a** with 1.2 equiv of Cs_2CO_3 led to formation of the desired aziridine **3a** as a 2:1 mixture of stereoisomers. However, a 3.5 equiv excess of Cs_2CO_3 gave **3a** as single diastereoisomer and in improved yield (Table 2, entry 3). Larger excesses of Cs_2CO_3 (5 equiv) did not lead to further improvement of the reaction yield (Table 2, entry 6), similar to using an excess of benzylamine (Table 2, entry 7). DCM, toluene and CH_3CN were examined with the latter giving better results. As a result, the optimized procedure involved the use of 1 equiv of benzylamine, 3.5 equiv of Cs_2CO_3 and dry CH_3CN as the solvent (Table 2, entry 3). Aryl-substituted dibromo isoxazoles **12a–k** were then reacted with benzylamine **13** in the presence of Cs_2CO_3 (Table 3).

Compounds **12a–f** reacted promptly giving the desired aziridines **3a–f** in moderate isolated yields (Table 3). Compounds **12g–k**, bearing an electron-donating group, did not react, and starting materials were recovered even after prolonged reaction times. These results can be explained considering that the presence of an electron-withdrawing group on the benzylic bromide enhanced the reaction rates towards nucleophiles. Compounds **3a–f** were obtained as a single diastereomer. The cis stereochemistry of compounds **3a–f** was assigned by (a) determination of the coupling constant between H_a and H_b; and (b) NOE experiments. In particular, in compounds **3a–f**, J_{a-b} appeared to be ≈6.4 Hz which is typical of a *cis* aziridine ring.[18] Additionally, a significant enhancement was observed for proton H_b, when H_a was irradiated in aziridines **3a** and **3b**.

Table 2
Screening of the reaction conditions

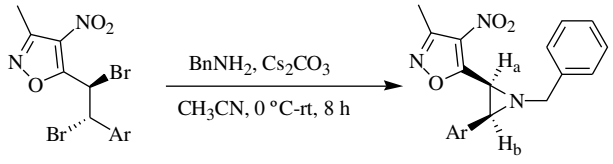


12a **13** **3a**

Entry	**13** (equiv)	Cs_2CO_3 (equiv)	Solvent	Temp (°C)	Yield[a] (%)	Cis:trans[b]
1	1	1.2	CH_3CN	20	30	2:1
2	1	3.5	DCM	20	0	—
3	1	3.5	CH_3CN	20	50	1:0
4	1	3.5	CH_3CN	60	35	2:1
5	1	3.5	Toluene	20	15	2:1
6	1	5	CH_3CN	20	31	1:0
7	3	3.5	CH_3CN	20	49	1:0

[a] Isolated yield after flash chromatography.
[b] Determined by relative integrations in the crude ^1H NMR spectra.

Table 3
Synthesis of isoxazolyl aziridines **3a–f**



12a-k **3a-f**

Entry	Ar	Product	Yield[a] (%)
1	C_6H_5	**3a**	50
2	*p*-Cl–C_6H_4	**3b**	50
3	*p*-F–C_6H_4	**3c**	45
4	*p*-Br–C_6H_4	**3d**	46
5	*m*-Cl–C_6H_4	**3e**	38
6	2-Pyridyl	**3f**	41

[a] Isolated yield after chromatography.

The stereochemical outcome of this reaction can be explained by considering that bis-additions of the amine to the *anti*-dibromo derivative occur, in an S_N2-manner. In conclusion, we have studied the preparation of a novel class of isoxazolyl aziridines **3a–f**. This study identified an optimized set of conditions and allowed aziridines **3** to be obtained in moderate yields and as cis stereoisomers, exclusively. Studies aimed at using aziridines **3a–f** for the preparation of unnatural amino acids are in progress.

1. Preparation of 3-methyl-4-nitro-5-[3-phenyl-1-(toluene-4-sulfonyl)-aziridin-2-yl]-isoxazole 11

To a solution of 3-methyl-4-nitro-5-styrylisoxazole **4a** (1 mmol, 230 mg) in anhydrous CH_3CN (20 mL) under N_2 were added 4 Å molecular sieves (2 g), bromamine-T **10** (2 mmol, 544 mg) and $RuCl_3$ (0.2 mmol, 41 mg), and the resulting mixture was stirred for 20 h at 80 °C. The resulting crude product was purified by column chromatography to give the desired product **11** in 20% yield as an 8:2 mixture of diastereoisomers. Yellow oil (20%); R_f: 0.3 (petroleum ether/EtOAc v/v 15:1); ^1H NMR major isomer δ: (400 MHz, $CDCl_3$): 7.98 (2H, d, J = 8 Hz), 7.41 (2H, d, J = 8 Hz), 7.23–7.28 (m, 5H), 4.72 (1H, d, J = 6.8), 4.40 (1H, d, J = 6.8 Hz), 2.48 (s, 3H), 2.42 (s, 3H); ^{13}C NMR major isomer δ: (100 MHz, $CDCl_3$): 164.7, 154.8, 144.7, 132.6, 131.1, 129.2, 129.1, 128.0, 127.6, 127.2, 126.0, 46.2, 39.6, 20.8, 10.2.

2. General procedure for the preparation of aziridines 3a–f

To a solution of dibromide **12** (1 mmol) in dry CH_3CN (6 mL) at 0 °C was added benzylamine (1 mmol, 107 mg) followed immediately by Cs_2CO_3 (3.5 mmol, 1.14 g). The solution was slowly warmed to room temperature and stirred for 8 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with DCM (2 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and the solvent removed under vacuum. The crude product was purified by silica-gel column chromatography with an appropriate mixture of petroleum ether and EtOAc to afford the *cis*-aziridine **3a–f**.

2.1. *cis*-5-(1-Benzyl-3-phenyl-aziridin-2-yl)-3-methyl-4-nitroisoxazole 3a

Yellow oil (50%); R_f: 0.2 (petroleum ether/EtOAc v/v 15:1); ^1H NMR δ: (400 MHz, $CDCl_3$): 7.47 (2H, d, J = 7.2), 7.37–7.19 (8H, m), 3.99 (1H, d, J = 14), 3.92 (1H, d, J = 14.0), 3.68 (1H, d, J = 6.4), 3.49 (1H, d, J = 6.4), 2.39 (3H, s); ^{13}C NMR δ: (100 MHz, $CDCl_3$): 170.3, 155.4, 137.4, 134.2, 128.7, 128.4, 128.1, 128.0, 127.9, 127.4, 63.9, 50.5, 42.8, 11.5; IR: ν_{max} (KBr)/cm^{-1}: 3056, 2932, 2851, 1599, 1402, 1379, 832; HRMS: calcd for $C_{19}H_{17}N_3O_3$ ($[M]^+$): 335.1270, found: 335.1265.

2.2. *cis*-5-[1-Benzyl-3-(4-chlorophenyl)-aziridin-2-yl]-3-methyl-4-nitroisoxazole 3b

Yellow oil (50%); R_f: 0.2 (petroleum ether/EtOAc v/v 15:1); ^1H NMR δ: (400 MHz, $CDCl_3$): 7.46 (2H, d, J = 7.2), 7.37–7.34 (2H, m), 7.31–7.27 (3H, m), 7.20–7.18 (2H, m), 3.97 (1H, d, J = 14.0), 3.93 (1H, d, J = 14.0), 3.69 (1H, d, J = 6.4), 3.44 (1H, d, J = 6.4), 2.42 (3H, s); ^{13}C NMR δ: (100 MHz, $CDCl_3$): 169.9, 155.5, 137.2, 133.9, 132.8, 128.8, 128.7, 128.6, 128.1, 127.8, 63.8, 49.6, 42.9, 11.5; IR: ν_{max} (KBr)/cm^{-1}: 3055, 2920, 2851, 1593, 1454, 1379, 1086, 822; HRMS: calcd for $C_{19}H_{16}ClN_3O_3$ ($[M]^+$): 369.0880, found: 369.0884.

2.3. *cis*-5-[1-Benzyl-3-(4-fluorophenyl)-aziridin-2-yl]-3-methyl-4-nitroisoxazole 3c

Yellow oil (45%); R_f: 0.1 (petroleum ether/EtOAc v/v 20:1); ^1H NMR δ: (400 MHz, $CDCl_3$): 7.46 (2H, d, J = 7.6), 7.38–7.29 (5H, m), 6.93–6.89 (2H, m), 3.97 (1H, d, J = 13.6), 3.92 (1H, d, J = 13.6), 3.67 (1H, d, J = 6.4), 3.46 (1H, d, J = 6.4), 2.41 (3H, s); ^{13}C NMR δ:

(100 MHz, $CDCl_3$): 170.1, 155.5, 137.3, 129.1, 129.0, 128.8, 128.1, 127.8, 63.9, 49.7, 42.8, 11.5; IR: ν_{max} (KBr)/cm^{-1}: 3060, 2920, 2851, 1603, 1508, 1379, 1225, 827, 693; HRMS: calcd for $C_{19}H_{16}FN_3O_3$ ($[M]^+$): 353.1176, found: 353.1170.

2.4. *cis*-5-[1-Benzyl-3-(4-bromophenyl)-aziridin-2-yl]-3-methyl-4-nitroisoxazole 3d

Yellow oil (46%); R_f: 0.2 (petroleum ether/EtOAc v/v 15:1); ^1H NMR δ: (400 MHz, $CDCl_3$): 7.46 (2H, d, J = 7.2), 7.37–7.34 (4H, m), 7.31–7.29 (1H, m), 7.22 (2H, d, J = 8.4), 3.95 (2H, t, J = 14.4), 3.69 (1H, d, J = 6.4), 3.43 (1H, d, J = 6.4), 2.42 (3H, s); ^{13}C NMR δ: (100 MHz, $CDCl_3$): 169.8, 155.5, 137.2, 133.3, 131.5, 129.1, 128.7, 128.0, 127.8, 122.1, 63.8, 49.7, 42.8, 11.5; IR: ν_{max} (KBr)/cm^{-1}: 3060, 2916, 2851, 1528, 1459, 1374, 1011, 827, 693; HRMS: calcd for $C_{19}H_{16}BrN_3O_3$ ($[M]^+$): 413.0375, found: 413.0376.

2.5. *cis*-5-[1-Benzyl-3-(3-chlorophenyl)-aziridin-2-yl]-3-methyl-4-nitroisoxazole 3e

Yellow oil (38%); R_f: 0.1 (petroleum ether/EtOAc v/v 20:1); ^1H NMR δ: (400 MHz, $CDCl_3$): 7.46 (2H, d, J = 7.2), 7.38–7.31 (3H, m), 7.30 (1H, d, J = 7.2), 7.25–7.17 (2H, m), 7.16–7.15 (1H, m), 3.99 (1H, d, J = 14.0), 3.90 (1H, d, J = 14.0), 3.70 (1H, d, J = 6.0) 3.44 (1H, d, J = 6.0), 2.42 (3H, s); ^{13}C NMR δ: (100 MHz, $CDCl_3$): 169.8, 155.6, 137.1, 136.4, 134.3, 129.7, 128.8, 128.6, 128.4, 128.2, 127.8, 125.6, 63.8, 49.6, 42.8, 11.6; IR: ν_{max} (KBr)/cm^{-1}: 3065, 2925, 2851, 1459, 1379, 718; HRMS: calcd for $C_{19}H_{16}ClN_3O_3$ ($[M]^+$): 369.0880, found: 369.0876.

2.6. *cis*-2-[1-Benzyl-3-(3-methyl-4-nitroisoxazol-5-yl)-aziridin-2-yl]pyridine 3f

Yellow oil (41%); R_f: 0.1 (petroleum ether/EtOAc v/v 5:1); ^1H NMR δ: (400 MHz, $CDCl_3$): 8.42–8.41 (1H, m), 7.59 (1H, td, J = 8.0, J = 1.6), 7.50–7.45 (3H, m), 7.38–7.33 (2H, m), 7.30–7.26 (1H, m), 7.14–7.11 (1H, m), 4.01 (1H, d, J = 13.0), 3.95 (1H, d, J = 13.0), 3.86 (1H, d, J = 6.4), 3.64 (1H, d, J = 6.4), 2.42 (3H, s); ^{13}C NMR δ: (100 MHz, $CDCl_3$): 169.9, 155.6, 154.5, 149.3, 137.1, 136.6, 128.8, 128.3, 127.8, 123.0, 122.3, 63.9, 51.6, 41.9, 11.6; IR: ν_{max} (KBr)/cm^{-1}: 3060, 2916, 2851, 1603, 1508, 1379, 1150, 698; HRMS: calcd for $C_{18}H_{16}N_4O_3$ ($[M]^+$): 336.1222, found: 336.1229.

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