# Stereoselective synthesis of *N*-alkylaziridines from *N*-chloroamines

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**We report the first racemic and stereoselective synthesis of *cis*- and *trans*-*N*-alkylaziridines *via* *N*-chloroamines; using this methodology an *N*-3,4,5-trimethoxybenzylaziridine was synthesised and efficiently cleaved, affording the corresponding NH aziridine in high yield.**

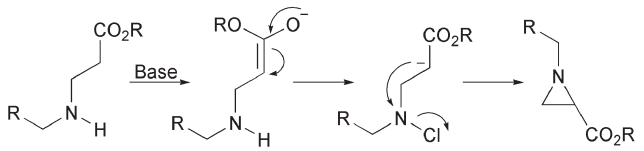
The development of protocols that afford difficult to synthesise *N*-alkylaziridines is a challenge yet to be addressed.[1] In this Communication we report that *N*-chloroamines can be used for the efficient synthesis of *N*-alkylaziridines. Our results demonstrate that, contrary to literature precedent, *N*-chloroamines are relatively stable, efficient, readily accessible starting materials that afford structurally diverse *N*-alkylaziridines that would, using conventional protocols, be available only *via* arduous, inefficient and laborious procedures.

Although *N*-chloroamines have been utilised for over 125 years,[2] they have only been employed in a small number of reaction types *i.e.* N-centered radicals,[3] Ritter,[4] Hoffman–Loffler reactions[5] and Stieglitz rearrangements.[6] Their lack of widespread use can be attributed to their reported instability,[7] *e.g.* in protonating media they decompose and the relatively weak N–Cl bond is readily cleaved (photolysis and/or thermal processes).

We considered that appending a chlorine onto a nitrogen induces a net polarisation of the N–Cl bond towards the chlorine. Incorporating this principle we speculated on the ability of *N*-chloroamines to act as efficient nitrogen centered electrophiles for heterocycle formation *via* intramolecular cyclisations (Scheme 1).

Apart from a report in 1961[8] on racemic *N*-*tert*-butyl-α-amino acids synthesis there are no reports of any intramolecular cyclisations that utilise *N*-chloroamines for aziridine synthesis.

In comparison to *N*-activated aziridines there are few procedures that afford *N*-alkylaziridines. These can be grouped into: addition of carbenes or ylids to imines;[9] addition of nitrenes to alkenes;[10] and nucleophile mediated 3-*exo*-tet cyclisations (Scheme 1).[11] The first two have significant environmental/experimental drawbacks




**Scheme 1** Proposed pathway to *N*-alkylaziridine synthesis.

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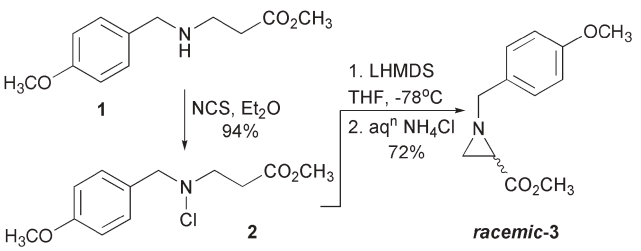
*i.e.* toxic/expensive metal salts or difficult to handle toxic Lewis acids. Furthermore, generating carbenoids or nitrenes from diazo species is, particularly on a large scale, potentially hazardous,[12] as is the synthesis/storage of the diazo precursors.[13]

It is apparent that alternative *N*-alkylaziridine syntheses are required.

Refluxing an acetonitrile solution of 4-methoxybenzylamine and methyl 3-bromopropionate afforded β-amino ester **1** in good yield (Scheme 2). Critical for the success of the proposed aziridination procedure, we undertook the *N*-chlorination of **1**. Stirring an ethereal solution of **1** and NCS afforded **2** in an excellent 94% yield. With **2** in hand, synthesis of racemic *N*-(4-methoxybenzyl) aziridine-2-carboxylic acid methyl ester **3** was attempted. Gratifyingly, following deprotonation of **2** racemic **3** was afforded in an unoptimised 72% yield (Scheme 2).[14] $^1$H-NMR analysis of the crude product **3** revealed that unreacted **2** comprised the majority of the mass balance (15–20%). Contrary to literature reports on different systems we could not find any evidence for the formation of base induced 1,2-elimination products *i.e.* (*E*)- and (*Z*)-alkanimines[15] or of products resulting from nitrene or imine formation/decomposition.

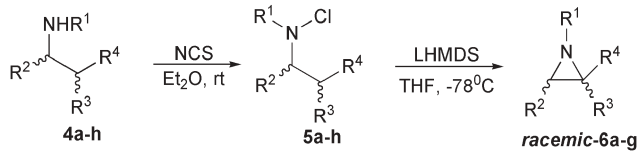
Confident that our protocol could be applied to the synthesis of a series of racemic *N*-alkylaziridines, we investigated the generality of the reaction. Secondary amines **4a–4h** were synthesised in excellent yields (84–99%) *via* aza-Michael reactions between 4-methoxybenzylamine, allylamine, *tert*-butylamine, cyclohexylamine and *tert*-butyl/methyl acrylate, methyl crotonate/tiglate and acrylonitrile (Table 1).[16] Subsequent *N*-chlorination (NCS) of **4a–4h** produced **5a–5h** in good to excellent yields (64–99%). In a finding worthy of note and in contrast to reports on *N*-chloroamine *instability*,[17] we were surprised by the stability of **5a–5h**. For example, no special precautions were required for their synthesis although on exceptionally sunny days the flask was wrapped in foil. Furthermore no special purification procedures or techniques were required for their chromatography on silica. Due to their ease of synthesis we did not attempt to synthesise and store the *N*-chloroamines. It is also worth bearing in mind the potential of *N*-chloroamines to have carcinogenic properties. Substituting




**Scheme 2** Synthesis of racemic **3** *via* *N*-chloroamine **2**.

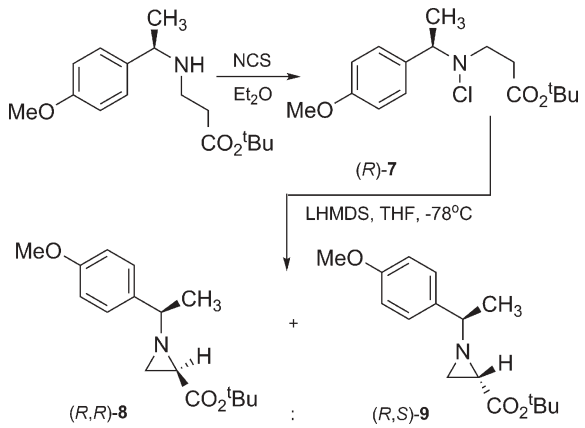
**Table 1** Yields for the individual reaction steps towards **6a–g**




| $R^1$ | $R^2$ | $R^3$ | $R^4$ | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 4-$MeOC_6H_4CH_2$ | H | H | $-CO_2Me$ | **4a** 89% | **5a** 94% | **6a** 72% |
| 4-$MeOC_6H_4CH_2$ | H | H | –CN | **4b** 84% | **5b** 93% | **6b** 70% |
| 4-$MeOC_6H_4CH_2$ | H | H | $-CO_2{}^tBu$ | **4c** 87% | **5c** 65% | **6c** 39% |
| 4-$MeOC_6H_4CH_2$ | Me | H | $-CO_2Me$ | **4d** 87% | **5d** 64% | **6d** 79% |
| Allyl | H | H | $-CO_2Me$ | **4e** 92% | **5e** 78% | **6e** 58% |
| *tert*-Bu | H | H | $-CO_2{}^tBu$ | **4f** 94% | **5f** 82% | **6f** 90% |
| 4-MeOBn | Me | H | $-CO_2{}^tBu$ | **4g** 97% | **5g** 64% | **6g** 63% |
| 4-MeOBn | H | Me | $-CO_2Me$ | **4h** 99% | **5h** 99% | — |

NCS for NIS or NBS failed to return *N*-haloamines that were suitable for cyclisation. Gratifyingly, when **5a–5g** were deprotonated the desired 3-*exo*-tet cyclisation reactions afforded unoptimised moderate (39%) to excellent yields (90%) of racemic *N*-alkylaziridines **6a–6g**. Of note, the cyclisation of **5g** (the secondary amine starting material for **5g** was synthesised *via* an aza-Michael reaction between *para*-methoxybenzylamine and *trans*-methyl crotonate), a β-methyl substituted ester was tolerated; racemic *trans*-**6g** ($J_{2,3}$ 2.8 Hz) was produced in a 63% yield. However attempted cyclisation of **5h** afforded the corresponding imine derived from a 1,2-elimination process. Although further studies are essential, these preliminary results suggest that: the protocol is substrate tolerant; the process is amenable to nitrogen substituent variation; the cyclisation procedure accommodates structurally diverse alkyl esters and that different electron-withdrawing moieties *i.e.* nitrile and ester groups are tolerated.

With these racemic results in hand we sought to extend our methodology to the asymmetric synthesis of *N*-alkylaziridines. *N*-chlorination of the precursor amine afforded (*R*)-(*para*-methoxy-α-methylbenzyl)-*N*-chloroamine **7**; its deprotonation and subsequent cyclisation gave a diastereomeric mixture (83 : 17, 72% yield) of aziridines which were assigned by $^1$H-NMR as (*R*,*R*)-**8** (major) and (*R*,*S*)-**9** (minor, Scheme 3). Purification of the major product resulted in a crystal suitable for X-ray analysis.‡ The structure (Fig. 1) clearly shows the favorable *trans*-disposition between the *N*-appended group and the ester on the aziridine ring and confirms the absolute stereochemistry as (*R*,*R*)-**8**.




**Scheme 3** Asymmetric synthesis of *N*-alkylaziridines.

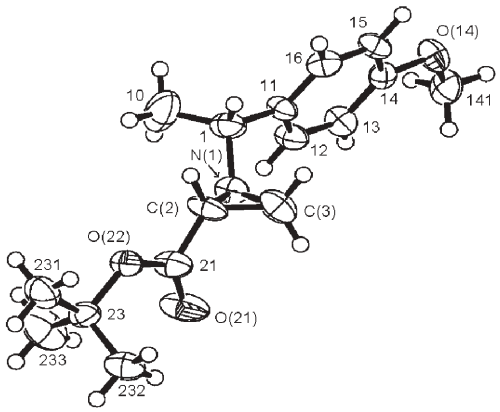
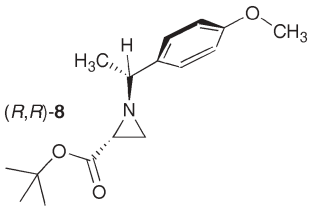



**Fig. 1** X-ray crystal structure of (*R*,*R*)-**8**.




Using (*R*)-*para*-methoxy-α-methylbenzylamine, phenyl vinyl sulfone and benzyl acrylate as Michael acceptors the corresponding amines were *N*-chlorinated and cyclised affording diastereomeric mixtures of aziridines **9** and **10** in 65% and 87% yields and 75 : 25 diastereomeric ratios respectively (Fig. 2, tentative major diastereomers shown).

Further studies, employing **7**, investigated the effect on the cyclisation reaction when alternative bases were employed. Substituting LHMDS (Scheme 3) with NaH, KH, BEMP, DBU, $Et_3N$ or NaOMe returned starting material **7**. However LDA, *tert*-BuOK, NaHMDS or KHMDS afforded poor to good yields (20–85%) and diastereoselectivities (50 : 50–81 : 19) of (*R*,*R*)-**8** and (*R*,*S*)-**9** compared with LHMDS. Similarly, raising the reaction temperature (Scheme 3) from −78 °C to RT had a relatively small effect on the yields (73 ± 8%) and diastereoselectivities (83 : 17–77 : 23) of the resulting (*R*,*R*)-**8** and (*R*,*S*)-**9**. In contrast to this, changing the solvent had a significant impact on both the yield and diastereoselectivity (Table 2). Acyclic and cyclic ethers (entries 2, 4 and 5), aromatics (entries 6 and 7) and the aryl ether anisole (entry 3) afforded substantially higher yields and/or diastereoselectivities than chlorinated solvents. Of note, either petrol or TBDME (entries 1 and 2 respectively) independently produced excellent diastereoselectivities and yields of (*R*,*R*)-**8** and (*R*,*S*)-**9** (93 : 7 and 89 : 11; 88% and 82% respectively).

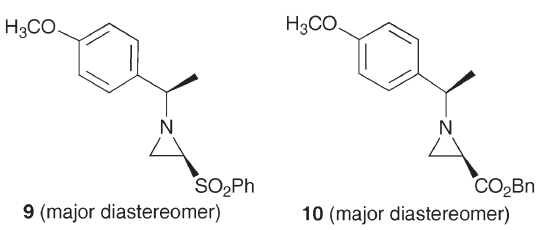
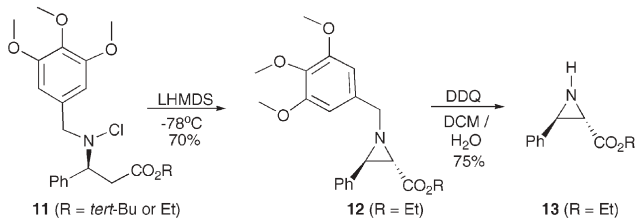



**Fig. 2** Asymmetric synthesis of **9** and **10**.

**Table 2** Probing for solvent effects during the cyclisation of **7**

| Entry | Solvent | Yield | **8** : **9** | Entry | Solvent | Yield | **8** : **9** |
|---|---|---|---|---|---|---|---|
| 1 | petrol | 88% | 93 : 7 | 7 | benzene | 67% | 78 : 22 |
| 2 | TBDME | 82% | 89 : 11 | 8 | DMF | 64% | 72 : 28 |
| 3 | anisole | 73% | 79 : 21 | 9 | dioxane | 57% | 80 : 20 |
| 4 | THF | 82% | 83 : 17 | 10 | neat | 57% | 57 : 43 |
| 5 | ether | 40% | 88 : 12 | 11 | 1,2-DCE | 15% | 77 : 23 |
| 6 | toluene | 70% | 85 : 15 | 12 | DCM | 10% | 71 : 29 |




**Scheme 4** Cleavage of the *N*-3,4,5-trimethoxybenzyl group off *trans*-**12**.

The cleavage of *N*-appended activating groups and even more so non-activating groups off aziridines requires harsh reagents and/or reaction conditions that often result in the partial or complete destruction of the heterocycle. We considered the synthesis of an oxidatively cleavable electron-rich *N*-benzyl substituted aziridine using the *N*-chlorination–cyclisation methodology reported here to offer a convenient solution to the problem. Reductive amination of the imine derived from 3,4,5-trimethoxybenzaldehyde and *tert*-butyl (3*S*)-3-amino-3-phenylpropionate followed by *N*-chlorination afforded **11** in an excellent 92% yield (Scheme 4). Disappointingly, all attempted cyclisations using **11** failed (1,2-elimination products resulted).[15] However the corresponding ethyl ester (R = Et, **11**), enolate generation and presumed $S_N2$ cyclisation afforded *trans*-**12** in a 70% yield. Critically, when *trans*-**12** was reacted with DDQ the *N*-(3,4,5-trimethoxybenzyl) substituent cleaved, returning *trans*-**13** in a 75% yield. Attempted oxidative cleavage using DDQ of the corresponding 4-methoxybenzyl group off (*R,R*)-**13** was slow and incomplete.

In conclusion, we have demonstrated that *N*-alkyl-β-amino esters and nitriles are efficiently transformed into the corresponding *N*-chloroamines and that these are convenient starting materials for the synthesis of structurally diverse racemic and optically active *N*-alkylaziridines. The regioselective ring opening of 2-substituted-*N*-alkylaziridines using a variety of reagents, *e.g.* triazole,[18] hydrogenation,[19] azide,[19] and halide anions,[19] corroborates their importance as valuable synthetic intermediates. Uniquely, we have also ascertained that electron-rich *N*-benzyl substituents can be efficiently installed/cleaved *via* exceptionally mild conditions, affording the corresponding NH aziridine in good yield.

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## Notes and references

‡ Crystal structure analysis of (*R,R*)-1-[1-(4-methoxyphenyl)-ethyl]-aziridine-2-carboxylic acid *tert*-butyl ester.

Crystal data: $C_{16}H_{23}NO_3$, $M$ = 277.4. Orthorhombic, space group $P2_12_12_1$ (no. 19), $a$ = 5.614(2), $b$ = 11.689(3), $c$ = 25.371(6) Å, $V$ = 1665.1(7) Å$^3$. $Z$ = 4, $D_c$ = 1.106 g cm$^{-3}$, $F(000)$ = 600, $T$ = 293(2) K, $\mu$(Mo-Kα) = 0.76 cm$^{-1}$, $\lambda$(Mo-Kα) = 0.71069 Å. Crystals are colourless needle-plates. Intensity data were measured on a Nonius CAD4 diffractometer (with monochromated radiation); 1400 reflections to $\theta_{max}$ = 20°, the limit of useful diffraction; 1240 unique reflections ($R_{int}$ 0.034), 685 'observed' with $I > 2\sigma_I$. Corrections were applied for Lorentz-polarisation effects, slight crystal deterioration, and to eliminate negative net intensities (by Bayesian statistical methods). Structure determined by direct methods in SHELXS[20] and refined by full-matrix least-squares, on $F^2$'s, in SHELXL.[20] At convergence, $wR_2$ = 0.139 and $R_1$ = 0.100 (A2) for all 1240 reflections weighted $w = [\sigma^2(F_o^2) + (0.0542P)^2]^{-1}$ with $P = (F_o^2 + 2F_c^2)/3$; for the 'observed' data only, $R_1$ = 0.056. The Flack parameter, $x$ = −3(5), allows no valid conclusions to be drawn about the absolute configuration, but the enantiomer shown corresponds with that prepared from known (*R*) material. CCDC 611802. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608504k

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14 A flame dried round bottomed flask was charged (under argon) with **1** (210 mg, 0.97 mmol) in anhydrous diethyl ether (10 mL) followed by NCS (251 mg, 1.88 mmol). The resulting suspension was stirred for 1 hour at ambient temperature after which time the white precipitate was removed *via* filtration. The resulting ether filtrate was concentrated *in vacuo* affording a clear oil which was purified *via* flash chromatography (silica, hexane : ether, 2 : 1) returning **2** (234 mg, 94%). A solution of **2** (150 mg, 0.58 mmol) in anhydrous THF (4 mL) was cooled to −78 °C (under argon); to this was added LHMDS (1.06 M in THF, 0.713 mL, 0.757 mmol). The reaction was stirred for 30 minutes at −78 °C and subsequently quenched with saturated $NH_4Cl$ solution. Extraction and purification of the product (silica, hexane : ethyl acetate, 1 : 1) afforded racemic-**3** as a clear oil (93 mg, 72%). $R_f$ 0.2 (ether–hexane 1 : 2). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (2H, d, $J$ 8.7), 6.85 (2H, d, $J$ 8.7), 3.78 (3H, s, $OCH_3$), 3.70 (3H, s, $OCH_3$), 3.47 (2H, m), 2.22 (1H, dd, $J$ 3.2, 1.2), 2.18 (1H, dd, $J$ 6.5, 3.2), 1.78 (1H, dd, $J$ 6.5, 1.2); $^{13}$C-NMR (125 MHz) $\delta$ 171.5, 159.2, 129.9, 129.7, 114.1, 63.5, 55.5, 52.5, 37.4, 34.6; IR ($\nu_{max}$/cm$^{-1}$) 1742, 1611.
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