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Highly *cis*-selective synthesis of iodo-aziridines using diiodomethyllithium and *in situ* generated *N*-Boc-imines†

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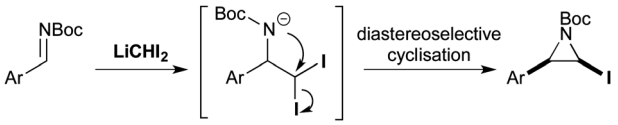
The first preparation of iodoaziridines is described. The addition of diiodomethyllithium to *N*-Boc-imines affords these novel aziridines in high yields. The reaction proceeds in one-pot *via* a highly diastereoselective cyclisation of an amino *gem*-diiodide intermediate.

Aziridines continue to provide both structural fascination,[1] and important synthetic intermediates for wide ranging applications in chemical synthesis.[2] Consequently, diverse synthetic methods for their preparation have been disclosed.[3] In recent years the functionalisation of intact aziridine rings has become important, allowing access to a variety of aziridine derivatives from single precursors. In particular, anionic functionalisation of aziridines,[4] in the absence of a stabilising group, has been mediated either by functional group exchange,[5] or by direct deprotonation at the most acidic site.[6] Recently, Vedejs and co-workers reported the palladium catalysed cross coupling of aziridine metal species, formed by Bu_3Sn–Li exchange, with aryl halides.[7] We envisaged that more efficient routes to suitably functionalised aziridines, that would enable regiocontrolled and diverse derivatisation of the intact ring, could find numerous applications in synthesis.

C-Heteroatom substituted aziridines can dramatically influence the reactivity and stability of the 3-membered ring.[8] Chloro-aziridines, in particular dichloroaziridines, often formed by the reaction of dichlorocarbenes and imines,[9,10] are widely used in the preparation of *N*-containing heterocycles.[8] Bromoaziridines are more difficult to access, and have been reported on only a few occasions. Ziegler first formed bromoaziridines by a Barton decarboxylation–bromination from aziridine carboxylates, affording a mixture of *cis*/*trans*-isomers.[11] These were used as radical precursors in the synthesis of mitomycin-like antitumour agents.[12] Yudin has reported bromoaziridines through an *N*-transfer approach, generating a nitrene under oxidative conditions,[13] as has Huang using $TsNBr_2$.[14] Additionally, Oshima reported the intermediacy of bromoaziridines in the preparation of silyl aziridines, proposing an *in situ* elimination of bromide.[15] Mono- and di-fluoroaziridines have also been recently reported.[16]



Scheme 1 Proposed route to iodoaziridines.

Iodoaziridines, on the other hand, are unknown in the literature to date. We chose to explore the possibility of forming iodoaziridines, as a potential reactive substrate for cross coupling, which should also provide precursors for anionic or radical functionalisation. Here we report the preparation of this new functional group, in high yields and excellent *cis*-stereoselectivity in one step from simple *N*-Boc-imine–sulfinic acid adducts.

We proposed an addition-cyclisation protocol to access iodoaziridines from imines using diiodomethyllithium, analogous to the aza-Darzens reaction (Scheme 1).[17,18] Recently Charette and Bull utilised diiodomethane anions at −78 °C to prepare alkyl diiodides by alkylation,[19] and to form styryl halides by alkylation/elimination,[20] but diiodomethyllithium remains an underutilised reagent.[21] Importantly, whereas in the aza-Darzens reaction itself the diastereochemistry of the aziridine product is determined in the initial addition, here, due to the symmetrical nature of the diiodomethyllithium nucleophile the cyclisation step would be diastereodetermining.

The stability of potential iodoaziridines was naturally a significant concern, due to potential loss of iodide amongst other potential decomposition routes. We elected to examine *N*-Boc imines to provide an electron-withdrawing group on *N* as well as offering potential for further functionalisation or ring opening.

Initial investigations concentrated on the addition of diiodomethyllithium to phenyl *N*-Boc imine to afford the amino-diiodide. Diiodomethyllithium was preformed by deprotonation of CH_2I_2 with LiHMDS at −78 °C prior to addition of the imine.[22] Both the imine and imine–HO_2STol adduct **1a** were examined, with the latter preferred for practical simplicity, generating the imine *in situ* by deprotonation with excess base.[23,24] Careful optimisation of the reaction conditions was undertaken, including the equivalents of base and CH_2I_2, the use of Lewis basic additives, as well as concentration and the solvent ratio (a mixture of THF and ether was essential).[19a] The optimal

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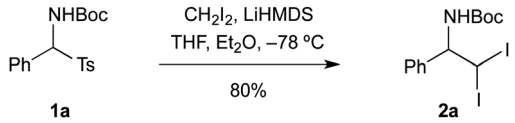
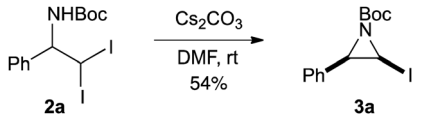
† Electronic supplementary information (ESI) available: Experimental and characterization data and NMR spectra (^1H and ^{13}C) for all novel compounds. See DOI: 10.1039/c2cc37029h



Scheme 2 Formation of amino-diiodide **2a**.



Scheme 3 Cyclisation to iodoaziridine **3a** promoted by Cs_2CO_3.

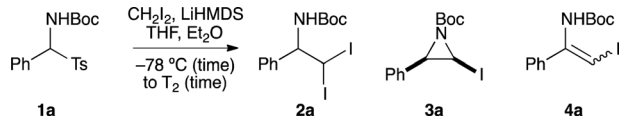
conditions (3.0 equiv. CH_2I_2, 2.6 equiv. LiHMDS, THF/Et_2O, −78 °C) provided amino-diiodide **2a** in 80% yield (Scheme 2).

We next assessed the conversion of diiodide **2a** to aziridine **3a** using a variety of bases and Lewis acids to promote the cyclisation. Under these conditions, multiple pathways could be conceived: the desired cyclisation may occur to form either *syn* or *anti*-aziridines, cyclisation to the oxazoline, or alternatively elimination to the vinyl iodide. Pleasingly, the use of Cs_2CO_3 in DMF produced an effective cyclisation, providing iodoaziridine **3a** (54% yield, Scheme 3).[25] Remarkably, aziridine **3a** was stable to isolation and could be purified on silica gel without decomposition.[26] Furthermore, exclusive formation of the *cis*-aziridine was observed indicating a highly stereoselective cyclisation step was occurring.

Having proved iodoaziridine **3a** was indeed a viable structure, the possibility of a one-pot synthesis was investigated. Cyclisation could be promoted by subsequent warming of the reaction mixture, after the initial addition of $LiCHI_2$ was complete, under otherwise similar reaction conditions. Subtle control of the reaction temperature profile proved to be critical.

The addition of $LiCHI_2$ to the generated imine occurred very rapidly at −78 °C,[27,28] but the intermediate was stable at this temperature (Table 1, Entry 1). Warming to rt by removing the flask from the dry ice bath led to inseparable mixtures of iodoaziridine **3a** with the elimination product **4a**. Cyclisation was observed to occur only slowly at −20 °C, with diiodide **2a** the major product after 60 min. At 0 °C the diiodide reacted completely to afford a 3 : 1 mixture of iodoaziridine **3a** and the elimination product iodide **4a**, and rapid warming to rt in a water bath gave an improved ratio (entries 2–4). Ultimately the

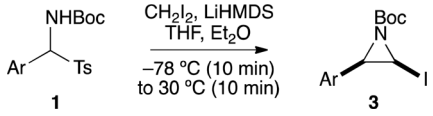
Table 1 Selected optimisation: one-pot preparation of iodoaziridines[a]



Entry	Time at −78 °C[b] (min)	T_2 (°C)	Time at T_2 (min)	Product ratio **2a** : **3a** : **4a**
1	60	—[c]	—	**2a** only[d]
2	30	−20	60	6 : 2 : 1
3	30	0	90	– : 3 : 1
4	20	rt	90	– : 10 : 1
5	10	30	10	**3a** only[e]

[a] Imine–HO_2STol adduct **1** (0.3 mmol), CH_2I_2, (3 equiv.), LiHMDS (2.6 equiv.), THF/Et_2O (3 : 1), −78 °C to 30 °C. [b] Time following addition of **1a**. [c] Reaction quenched at −78 °C. [d] As Scheme 2; yield 80%. [e] 83% yield.

Table 2 Scope of one-pot synthesis of iodoaziridines[a]



Entry	Ar	Yield (%)	d.r.[b]	
1	Ph	83	> 95 : 5	**3a**
2		88[c]	> 95 : 5	
3	4-Tolyl	96	> 95 : 5	**3b**
4[d]	2-Tolyl	89	90 : 10 (> 95 : 5)	**3c**
5	2-Napthyl	92	> 95 : 5	**3d**
6	4-*t*BuPh	67	> 95 : 5	**3e**
7	4-ClPh	51	> 95 : 5	**3f**
8[d]	2-ClPh	52	87 : 13 (88 : 12)[e]	**3g**
9	4-BrPh	42	> 95 : 5	**3h**
10	4-FPh	76	> 95 : 5	**3i**
11[f]	3-OMePh	77	> 95 : 5	**3j**
12	4-CF_3Ph	13	> 95 : 5	**3k**
13	3-Pyridyl	49	> 95 : 5	**3l**

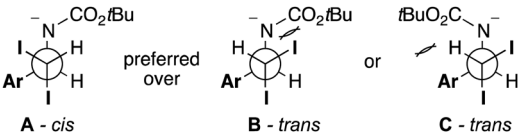
[a] Imine–HO_2STol adduct **1** (0.6 mmol), CH_2I_2, (3 equiv.), LiHMDS (2.6 equiv.), THF/Et_2O (3 : 1), −78 °C to 30 °C. [b] *d.r.* of crude mixture by ^{1}H NMR. Where > 95 : 5 is stated, the minor diastereoisomer could not be observed by ^{1}H NMR. *d.r.* of purified compound indicated in parentheses where relevant. [c] Reaction performed on a 3 mmol scale. [d] Warmed to 30 °C for 30 min as required to induce cyclisation. [e] Also contained diiodide **2 g** in crude mixture, which was isolated in 5% yield. [f] Purified on neutral alumina due to decomposition on silica gel.

rate of warming was shown to be crucial in avoiding elimination. Therefore the cyclisation was performed in a water bath at 30 °C, to ensure rapid and reproducible warming. This completely prevented the elimination pathway and iodoaziridine **3a** could be isolated cleanly in excellent yield (Table 1, entry 5, Table 2 entry 1).[29] Performing the reaction on a 3 mmol scale afforded similarly excellent yield and selectivity (Table 2, Entry 2).

Variation of the aromatic group of the imine with alkyl and napthyl substituents gave the corresponding iodoaziridines in high yields, and exclusively as the *cis*-isomers (Table 2, entries 3–6). The *ortho*-tolyl substrate displayed more reluctance to cyclise, requiring a longer time at the elevated temperature (30 min) to achieve complete cyclisation from the amino-diiodide (entry 4), presumably due to unfavourable steric interactions.

Next halogenated aromatics were examined, which were well tolerated by the reaction conditions (entries 7–10). With *ortho*-chlorophenyl (Entry 8) cyclisation was more significantly slowed presumably due to coordination of the lone pairs on the *ortho*-substituent with the lithium cation in the intermediate. Notably in this example the *trans*-iodoaziridine was observed.[30] All other examples were isolated in > 95 : 5 *cis*-selectivity by ^{1}H NMR.

The 3-methoxyphenyl bearing imine was also tolerant of the reaction conditions but required the short reaction times to prevent decomposition (Entry 11). As electron rich *N*-Boc aziridines are prone to S_N1-type opening, purification required chromatography on neutral alumina to prevent decomposition. Electron poor aryl-imines were successful (entries 12–13) but with lower yields due to increased amounts of elimination and other side product formation. Alkyl imines were generally not successful, for example with cyclohexyl imine-adduct (**1m**), only the corresponding diiodide (**2m**) was isolated in 29% yield. The use of CH_2Br_2 in the place of CH_2I_2 under otherwise identical



Scheme 4 Orientation for cyclisation; **A** preferred (Ar and I *cis*).

conditions with **1a** led to the formation of the corresponding bromoaziridine (**5**) with exclusive *cis*-stereochemistry in an unoptimised yield of 30%.

Our proposal for the *cis*-selectivity in forming the iodoaziridines is based on steric factors (Scheme 4).[31] The aryl and Boc groups are likely to adopt an *anti*-orientation preferentially, providing two conformations (A and B) with N and I in an *anti*-periplanar arrangement appropriate for cyclisation. We propose that an unfavourable interaction between the non-displaced iodide with the Boc group is dominant in the cyclisation transition state where the *N*-atom becomes sp^3 hybridised. Hence the non-displaced iodine prefers to adopt a position away from the bulk of the Boc group and so gauche to the Ph group, resulting in the *cis*-aziridine configuration.

In summary, we report the first examples of iodoaziridines. The use of diiodomethyllithium with careful temperature control allows either the isolation of the amino-diiodide or complete cyclisation to the iodoaziridine with very high *cis*-selectivity, and both with excellent yields. We are currently developing methods for the functionalisation of iodoaziridines to various aziridine derivatives, which will be reported in due course.

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25 Compound **3a** was assigned as the *cis*-aziridine on the basis of IR stretch (C=O; 1724 cm^{-1}) and characteristic ^1H NMR coupling constants (J = 5.4 for aziridine CH).
26 Iodoaziridine **3a** was stable to silica gel and in solution. On concentration the neat compound showed significant sensitivity to light leading to decomposition. Iodoaziridines were stored as stock solutions in dichloromethane at −20 °C. Under these conditions **3a** was stable for >4 weeks.
27 Low temperature is required for the initial addition to ensure the stability of $LiCHI_2$.
28 See ESI† for further details on ^1H NMR sampling studies into the rate of addition and cyclisation. This supports our mechanistic hypothesis of addition followed by cyclisation at elevated temperatures, rather than an alternative mechanism *via* diiodocarbene. Quenching the reaction at −78 °C with D_2O (forming **2a**) did not lead to any incorporation of deuterium in place of the CHI_2 proton, but partial incorporation at NH. This suggests that the intermediate diiodide is not deprotonated to the carbenoid under the reaction conditions.
29 A possible explanation for effect of rate of warming on product distribution is that elimination is caused by excess $LiCHI_2$ which decomposes rapidly on warming to non-basic species, preventing the undesired elimination reaction.
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