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Studies on the synthesis of α-iodoaziridines and improved conditions for the synthesis of alkyl-α-iodoaziridines using $ClMgCHI_2$

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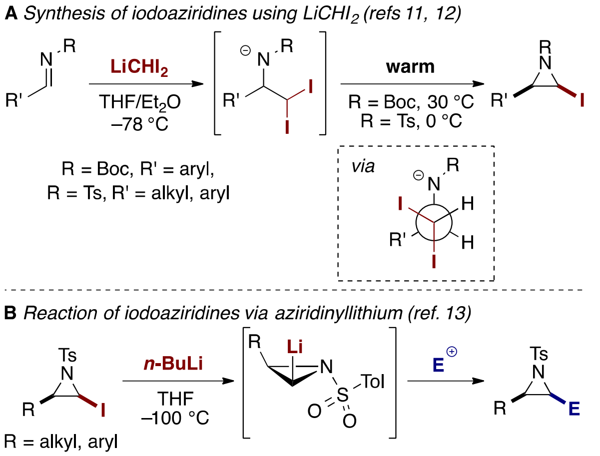
ABSTRACT

α-Iodoaziridines are unusual motifs and intriguing structures for further functionalisation of the intact aziridine. The preparation of *N*-protected α-iodoaziridines is achieved through an addition-cyclisation reaction of $LiCHI_2$ with imines. The effects of varying the *N*-group and using different carbenoids are investigated. Excellent *cis*-stereochemistry is achieved, except for *N*-carbamates containing aryl groups. Using the mixed carbenoid LiCHICl, the iodide leaving group is selected for cyclisation affording chloroaziridines only, as a *cis*/*trans* mixture. More convenient and higher yielding conditions for the preparation of alkyl *N*-Ts α-iodoaziridines are developed, using $ClMgCHI_2$. Additionally, the formation of the problematic primary alkyl α-iodoaziridines is achieved.

1. Introduction

Aziridines are important motifs in organic chemistry as a result of the inherent strain in the three-membered heterocycle.[1] This feature is central to their use as synthetic intermediates in ring opening processes to provide important nitrogen-containing compounds,[2,3] and also to the mode of biological action of aziridine containing natural products.[4] For the synthetic chemist the small ring structure of aziridines is a fascinating target for new methodology development, and there continues to be important advances in the stereoselective synthesis of aziridines.[5] Conceptually there are several strategies for the preparation of aziridine derivatives. These include the transfer of carbenoid reagents or equivalents to imines.[6] The direct nitrogen transfer to alkenes can be achieved using nitrenoid derivatives.[7] Aziridines can also be accessed by cyclisation of β-functionalised amines,[8] which may be formed effectively via addition of nucleophiles to α-haloimines.[9] An alternative, divergent strategy is to prepare an aziridine by one of these approaches, and then to couple that intact aziridine, forming a bond directly to the aziridine ring.[10] This has been achieved by metalation of aziridines and reaction with electrophiles,[11,12] as well as palladium-catalysed cross-coupling of the intact aziridines.[13]

Inspired by this latter approach, we hypothesised that iodo-substituted aziridines might provide interesting precursors for the further functionalisation of intact aziridine rings. Towards this goal, we have recently developed protocols for the synthesis of *N*-Boc[14] and *N*-Ts[15] α-iodoaziridines, the first examples of this functional group (Scheme 1A). Both of these methods employ the addition of diiodomethyllithium, formed via the deprotonation of diiodomethane with LiHMDS, to *N*-protected imines, often formed



Scheme 1. Synthesis of α-iodoaziridines and functionalisation via aziridinyllithium.

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in situ from their sulfinic acid adducts, followed by highly stereoselective cyclisation.

The formation of *N*-Boc α-iodoaziridines was successful for aryl substituted imines.[14] With *N*-Ts imines, both alkyl and aryl substituted α-iodoaziridines could be accessed in moderate to good yields, though unbranched, primary alkyl imines only afforded very low yields.[15a] The temperature at which cyclisation occurred varied depending on the nature of the *N*-protecting group, but excellent *cis*-selectivity was achieved in all cases. These α-iodoaziridines were shown to be stable on isolation and could be purified by chromatography when the stationary phase was judiciously selected.[15] Furthermore, we demonstrated that *N*-Ts α-iodoaziridines could be used to generate aziridinyllithium species by Li–I exchange (Scheme 1B).[16] The aziridinyllithium was then trapped with electrophiles, affording *N*-sulfonyl aziridine derivatives in high yields and with complementary regio- and stereochemistry to deprotonation approaches.

Halomethylmetal reagents, in particular chloromethyllithium, have received significant attention in synthetic chemistry, as they can display both nucleophilic and electrophilic reactivity.[17–19] Dihalomethylmetal reagents have been investigated to a lesser degree.[20–22] Integral to the approach to α-iodoaziridines has been the use of diiodomethyllithium.[14,15] Unlike traditional aza-Darzens reactions, whereby the diastereoselectivity of aziridine products is determined in the initial carbenoid addition step, here due to the symmetrical nature of $LiCHI_2$, the cyclisation step is diastereodetermining. We considered that using alternative reagents (changing either the nature of the *N*-group, or the nature of the carbenoid reagent ($MCHI_2$)), could afford a different stereochemical outcome, provide improved yields for the more challenging substrates, or provide insight into the factors that affect stereoselectivity.

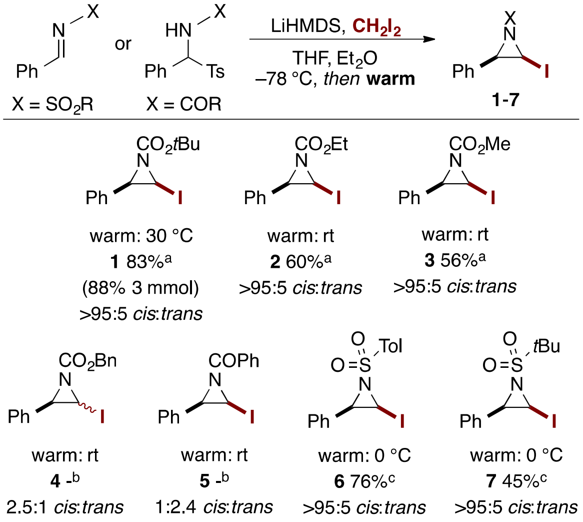
Here we report our investigations into the effect of variation of the *N*-protecting group and the carbenoid reagents employed in the synthesis of α-iodoaziridines, and relevance to the stereochemical outcome. We report an improved procedure for the preparation of alkyl substituted *N*-Ts α-iodoaziridines with improved yields, through the use of $ClMgCHI_2$, and study the problematic unbranched primary alkyl α-iodoaziridine examples.

2. Results and discussion

2.1. Role of *N*-protecting group

We first assessed the effect of changing the *N*-protecting group on the α-iodoaziridine reaction, using imines formed from benzaldehyde. Diiodomethyllithium was formed by deprotonation of CH_2I_2 with LiHMDS over 20 min in a THF/Et_2O mixture at −78 °C, prior to the addition of the imine–HSO_2Tol adduct. Within the carbamate series (2.4 equiv CH_2I_2, 2.6 equiv LiHMDS), the reaction with the *N*-Boc imine gave 83% isolated yield of α-iodoaziridine **1**.[14] The reaction required warming to 30 °C to give full cyclisation and prevent elimination from the intermediate diiodide.[23] Only the *cis*-α-iodoaziridine was observed. In moving to the ethyl and methyl carbamates, the products (**2** and **3**, respectively) were obtained in reduced yields, presumably due to attack of the nucleophile at the carbonyl. However, very high diastereoselectivity was maintained, despite the decrease in steric bulk; again only the *cis*–product was observed. Rapid warming from −78 °C to ambient temperatures was required to minimize the formation of unwanted side products and to ensure full cyclisation of the amino *gem*-diiodide intermediates. The reaction with phenyl carbamate yielded a complex mixture of products. The imine formed from *N*-benzyl carbamate also afforded a complicated mixture of products under the reaction conditions. Elimination of iodide from the *gem*-diiodide intermediate to form the corresponding vinyl iodide was a major reaction pathway. The Cbz-protected α-iodoaziridine **4** was observed in the ^1H NMR spectrum of the crude reaction mixture, as a mixture of diastereoisomers (*cis*:*trans*, 2.5:1), but could not be isolated (CHI: *cis*, δ 4.76, *J*=5.4 Hz vs *trans*, δ 4.31, *J*=1.9 Hz). In both cases, isolation of aziridine-like products proved problematic, with decomposition apparent on a variety of stationary phases. Interestingly, the use of the benzoyl *N*-protecting group (COPh) led to a reverse in the diastereoselectivity of the cyclisation step, with the *trans*-product now the major product **5** (*trans*:*cis*=2.4:1). Unfortunately, decomposition again occurred on attempted purification and the aziridine products could not be isolated.

Our hypothesis for the *cis*-stereochemical outcome of the cyclisation is that interactions of the non-displaced iodide with the *N*-protecting groups disfavour the *trans*-aziridine cyclisation transition state (Scheme 1A).[14] In all of the cases depicted in Scheme 2, we observed exclusively the *cis*-α-iodoaziridines, apart from when *N*-groups containing aromatic rings were employed (Cbz and benzylamide). This suggests a favourable π-π interaction between the aryl groups may be occurring, promoting formation of the *trans*-compound in these cases.



Scheme 2. Effect of *N*-protecting group on α-iodoaziridine formation. [a] Reaction conditions: imine–HO_2STol adduct (0.50–0.65 mmol), CH_2I_2 (3.0 equiv), LiHMDS (2.6 equiv), THF:Et_2O (3:1), −78 °C (10 min), *then warm* (10 min). [b] Product not isolated, unstable to chromatography. [c] Reaction conditions: imine (0.50 mmol), CH_2I_2 (3.4 equiv), LiHMDS (3 equiv), THF:Et_2O (3:1), −78 °C (10 min), *then warm* (15 min).

We next assessed bulky sulfonyl protecting groups, under slightly different reaction conditions; 1.0 equiv imine, 3.4 equiv CH_2I_2, 3.0 equiv LiHMDS. We had previously reported *N*-Ts α-iodoaziridine **6**, formed in 76% on warming the reaction mixture to 0 °C to promote cyclisation, exclusively as the *cis*-aziridine. The *tert*-butylsulfonyl protecting group, in similar fashion, also gave rise exclusively to the *cis*-α-iodoaziridine **7** in 45% yield.

2.2. Mixed halo-carbenoids: chloroiodomethyllithium

Reacting $LiCHBr_2$, in place of $LiCHI_2$, with imine–HSO_2Tol adduct **8** afforded *cis*-*N*-Boc bromoaziridine **9** in 30% yield (Scheme 3).[14] Deyrup demonstrated that chloroaziridines also show a complete preference for *cis*-stereochemistry.[20] However, mixed dihalocarbenoid systems of the form LiCHXY (X≠Y) have not been previously investigated, posing interesting questions about the reactivity of the proposed intermediate and the diastereoselectivity. Chloroiodomethane was chosen as a suitable carbenoid precursor to investigate this, due to cost and availability. Being unsymmetrical, the initial nucleophilic addition of LiCHICl would determine the relative stereochemistry of a particular product,