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A Convenient Synthesis of Chiral Nonracemic Vinyl Aziridines

Daniel Morton,[†] David Pearson,[‡,§] Robert A. Field,[†] and Robert A. Stockman*,[†]

School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich, NR4 7TJ, U.K., and Millenium Pharmaceuticals UK, Granta Park, Great Abington, Cambridge CB1 6ET, U.K.

r.stockman@uea.ac.uk

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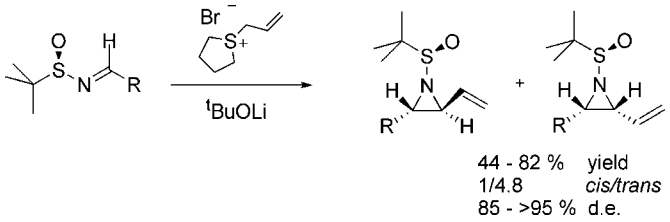
ABSTRACT



The preparation of a range of alkyl and aryl chiral vinyl aziridines was achieved in high yield and stereoselectivity, and with excellent diastereoselectivity, by reaction of *tert*-butylsulfinylimines with the ylide derived from *S*-allyl tetrahydrothiophenium bromide.

Vinyl aziridines are increasingly being exploited as versatile intermediates in organic syntheses. Elaboration via ring opening[1−3] or ring expansion[4] provides direct access to a host of structural motifs that are valuable in the synthesis of both natural and non-natural products.[5] The use of enantiomerically pure vinylaziridines as synthetic building blocks is particularly appealing.[6,7] In this paper, we disclose a convergent, flexible, and straightforward approach for the synthesis of chiral nonracemic vinyl aziridines. Employing an approach developed by Hou and Dai,[8] and recently extended within our laboratories,[9] reaction of allyl sulfur ylides with chiral *tert*-butylsulfinylimines provides access to a series of nonracemic chiral vinyl aziridines. Our previous work on the synthesis of chiral monosubstituted aziridines[10] exploited the high stereodirecting nature of the *tert*-butylsulfinyl group.[11] Herein, we disclose our initial findings on the reaction of chiral *tert*-butylsulfinyl imines with the ylide formed by deprotonation of *S*-allyl tetrahydrothiophenium bromide.

tert-Butylsulfinyl imines were prepared from the corresponding aldehydes using the procedures developed by Ellman et al.[12] In all instances, imines were prepared in high yield and as single enantiomers. To investigate the optimal conditions for the aziridination procedure, a range of solvents and bases were investigated. For these experiments the *tert*-

* To whom correspondence should be addressed. Fax: +44 (0) 1603 592003

[†] University of East Anglia.

[‡] Millenium Pharmaceuticals UK.

[§] Current address: Inpharmatica Ltd, 127 Science Park, Milton Road, Cambridge, CB4 0GD, U.K.

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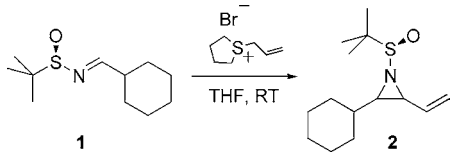
butlsulfinylcyclohexyl imine, **1**, was the chosen substrate. Table 1 summarizes the performance of nine bases in the vinyl aziridination reaction.

Table 1. Investigating the Effect of Base upon the Aziridination of *tert*-Butylsulfinylimines



entry	base	time (h)	yield (%)	cis/trans
1	^{t}BuLi	48	50	1/2
2	^{n}BuLi	24	trace	
3	NaH	24	0	
4	K_2CO_3	5	46	>1/50
5	Na_2CO_3	24	0	
6	Cs_2CO_3	4	58	>1/50
7	^{t}BuOK	2.5	65	1/4.8
8	^{t}BuONa	6	55	1/3.2
9	^{t}BuOLi	1.5	78	1/4.7

The stronger bases that prevailed in our previous investigations,[10] where sodium hydride and butyllithium were found to be the bases of choice, were found to be inefficient for this system (entries 1−3); with sodium hydride no aziridine formation was observed. In these cases, the [2,3]-sigmatropic rearrangement of the sulfur ylide was found to predominate. This is a known side reaction of allyl sulfur ylides,[13] in accordance with the findings of Sommellet and Hauser.[14] The weaker carbonates (Table 1, entries 4−6) effected the desired reaction with respectable levels of stereocontrol, in varying yields,[15] over a period of many hours. The use of *tert*-butoxides exhibited improved yields and provided acceptable levels of stereocontrol (Table 1, entries 7−9).

The reactivity of allyl sulfur ylides varies with solvent.[8] The results of the aziridination in 10 different solvent systems are summarized in Table 2. Significantly, the solvent in which we observe the highest chemical yield conversely offers the lowest stereochemical control. In DMSO, the cis/trans ratio is 1:1.2. It is believed that depression of the Sommellet−Hauser rearrangement and a stabilization of the proposed aziridination betaine intermediates, contribute to the increased yield and depletion of stereoselectivity.[16]

Optimal conditions for the aziridination reaction involve the use of lithium *tert*-butoxide to deprotonate the sulfur salt in THF at room temperature. This rapid reaction gives high yields and respectable stereocontrol (entry 2, Table 2.).

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(15) In THF with Na_2CO_3 as the base, none of the desired product was observed, this varied in other solvents. See the Supporting Information.

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Table 2. Effect of Solvent on the Conversion of **1** to **2** (1 equiv of **1**, 1.5 equiv of LiO^tBu, and 1.5 equiv of Sulfonium Salt Used in Each Case)

entry	solvent	time (h)	yield (%)[17]	cis/trans
1	DCM	12	8	<1/50
2	THF	1.5	78	1/4.7
3	DMF	12	35	1/2.3
4	DMA	6	66	1/2.4
5	DMSO	1.5	>95	1/1.2
6	MeCN	12	30	1/2.0
7	toluene	12	19	1/2.5
8	diethyl ether	24	28	>1/50
9	DME	24	30	>1/50
10	dioxane	24	25	>1/50

We then turned our focus to the scope of this reaction, carrying out the aziridination of a range of chiral *tert*-butylsulfinylimines, derived from aromatic, aliphatic and heterocyclic aldehydes. These results are summarized in Table 3. The aziridination of substituted sulfinyl imines generally proceeded in good yield (44−78%) with only particularly sensitive and unstable substrates resulting in less than 50% conversion (entry 5).[18] An improvement on earlier work,[10] both aliphatic and aromatic substrates undergo the aziridination in high yields, the use of a weaker base for the deprotonation reducing the enolization with aliphatic substrates previously encountered.[9]

Throughout this investigation, irrespective of solvent or base, aziridination of **1** had proceeded with over 95% diastereoselectivity. This exceptional facial selectivity is also evident over a wider range of substrates, borne out by the fact that in only three instances did the de drop below 90% (Table 3, entries 3, 9, and 11). This aspect of the reaction is thought to be due to the large steric interaction between the *tert*-butyl group and the attacking sulfonium ylide. The diastereoselectivity observed is greater than witnessed in previous work with trimethylsulfonium iodide.

For most substrates, aziridination was complete within 30 min, again, comparing favorably to previous sulfur ylide aziridinations.[16] Large (entries 4, 11, and 14), small (entries 1, 5, and 9), alkyl (entries 5−11), and aromatic substituents on the imines (entries 1−4) all displayed a significant predilection for the trans configuration. Reduced selectivities were observed with electron-deficient (entry 3), unstable (entry 9), and unreactive substrates (entry 13). There have

Scheme 1. Initial Addition Intermediates

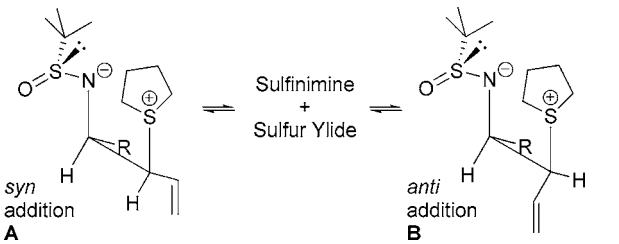
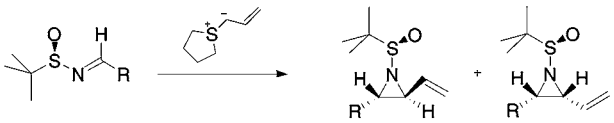
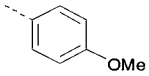
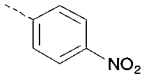
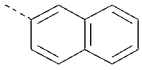
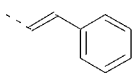


Table 3. Scope of the Aziridination of Chiral Sulfinyl Imines with Allyl Sulfur Ylides[a]



eEntry	R-group	time (min)	yield (%)[b]	*cis/trans*[c]	d.e (*trans*) (%)[d]
1		25	68	29:71	90
2		45	76	18:82	92
3		40	74	41:59	84
4		25	64	20:80	>95
5		35	44	20:80	90
6		30	67	18:82	>95
7		45	58	19:81	>95
8		30	62	17:83	>95
9		35	61	28:72	86
10		35	78	17:83	>95
11		40	54	12:88	88
12		25	55	33:67	>95
13		35	82	17:83	>95

[a] General procedure for the aziridination: 1 equiv of imine, 1.5 equiv of ylide, and 1.5 equiv of Li^{t}BuO, in THF at room temperature. [b] Yield of the purified product as a mixture of diastereomers. [c] Cis/trans ratio determined from the ^{1}H NMR of the crude reaction mixture. [d] de determined from ^{1}H NMR of the crude reaction mixture.

been a number of studies on the mechanistic aspects of the sulfur ylide ring forming reaction to explain the trans preference observed.[16,19] Inspection of the initial addition intermediates (Scheme 1) provides an explanation for the predominance of the trans isomer.

The reaction proceeds in two stages. The initial addition step is reversible and thought to proceed via a quasi [2 + 2] addition driven by electrostatic attraction, to form intermediates **A** and **B**.[19] The anti addition intermediate, **B**, is significantly more stable than the syn addition product, **A**, due to decreased gauche interactions. For ring closure to occur, rotation to an anti-periplanar configuration of *N* and *S* substituents is required. The transition from a high energy intermediate, **A**, to a significantly lower energy rotamer drives the equilibrium to the *anti*-periplanar configuration, while the rotation of the low energy intermediate, **B**, to a

(17) Yields quoted are of purified product.

(18) The aziridination of the sulfinylimines derived from *N*-methylpyrrole-2-carbaldehyde and pivaldehyde failed. Polymerization of the pyrrole moiety and steric clash of the *tert*-butyl groups are thought to be responsible.

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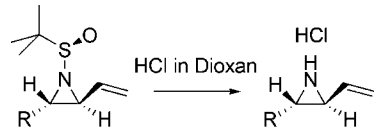
sterically more hindered rotamer is disfavored. This is believed to be the rate-determining step. Thus, ring closure gives a predominance of *trans*-aziridine.

To realize the full potential of the vinyl aziridines, opportunity for elaboration is required. Deprotection of the *tert*-butylsulfinylaziridines, to provide access to the *N*-H aziridines, would allow the subsequent conversion to a range of synthetically useful compounds. Various methods have been used to deprotect the *tert*-butylsulfinyl motif from amines: oxidation and subsequent cleavage,[20] removal using methyllithium[21] or Grignard reagents,[22] and acidic cleavage under anhydrous conditions[23] are but a few which failed on our substrates. Oxidation to the *tert*-butylsulfonyl (BUS) group[20] proved too harsh for the aziridines and resulted in decomposition. Methyllithium was too basic for our substrates and the reaction yielded a complex mixture of decomposition products with only trace amounts of the deprotected aziridine. However, we have discovered that through a modification of the published procedures it is possible to affect the deprotection. Cleavage using anhydrous HCl in dioxane was found to be the method of choice for the vinyl aziridines detailed in Table 3 (Scheme 2).

Scheme 2. Acidic Deprotection of *tert*-Butylsulfinylaziridines



Initially literature procedures for deprotection using Brønsted acids were investigated.[11] However, a 1:4 mixture of deprotected aziridine and ring-opened aziridine was isolated. Changing this reaction by omission of the methanol cosolvent and significantly increasing the dilution of the system (10 mg in 1 mL of dioxan) provided an effective deprotection strategy that the sensitive, highly reactive, vinyl aziridines could tolerate.[24] The deprotection proceeded in near-quantitative yields with no detectable loss in stereochemistry. The hydrochloride salts isolated circumvent previous stability issues associated with unprotected aziridines, and are stable at room temperature for a period of weeks.

In conclusion, the *tert*-butylsulfinyl group is an effective activating/directing group for access to enantiomerically pure vinyl aziridines directly from the corresponding imines. Heterocyclic, aromatic and aliphatic imines are all suitable substrates for this procedure. Good yields and stereoselectivity, simple procedures and the opportunity for separation of the isomers, all make this an attractive and direct procedure for the synthesis of chiral vinyl aziridines. The deprotection of these aziridines opens up the further opportunities for these highly substituted compounds. Exploration of the scope and stereocontrol of this reaction and the use of such aziridines to provide concise routes to more complex structures are ongoing and will be reported in due course.

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Supporting Information Available: General synthetic procedures and characterization and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) The deprotection reaction requires careful monitoring by TLC and use of freshly made saturated HCl gas in dioxan solution. The use of excess HCl in dioxan for extended periods (over 10 minutes) results in clean ring-opening of the aziridinium salt by chloride at the carbon bearing the vinyl group.