Tetrahedron Letters 49 (2008) 4768–4770

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of chiral non-racemic substituted vinyl aziridines

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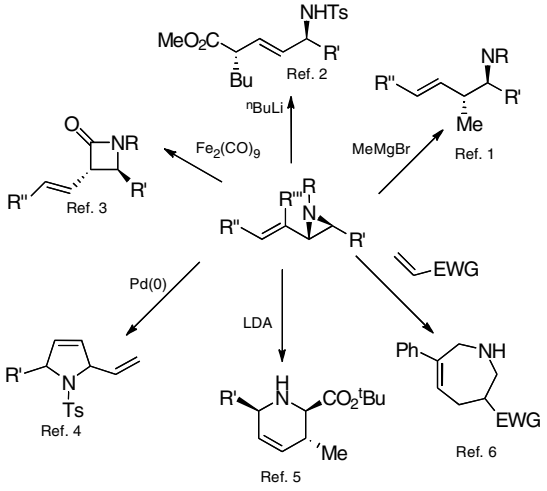
ARTICLE INFO

Article history:
Received 21 April 2008
Revised 14 May 2008
Accepted 20 May 2008
Available online 24 May 2008

ABSTRACT

Synthesis of a range of chiral non-racemic vinyl aziridines with varying substitutions on the alkene has been achieved by the reaction of (S_S)-*tert*-butylphenylsulfinimine with a range of ylides derived by deprotonation of substituted allyltetrahydrothiophenium salts. Yields of the substituted vinyl aziridines range from 0% to 90%, with trans:cis ratios between 1:1 and 0:100 and diastereomeric excesses of up to 99%.

There has been much interest in the synthesis of vinyl aziridines over the past two decades due to their highly functionalised nature and versatile reactivity. For example, vinyl aziridines have several sites at which nucleophiles can attack, and undergo ring-opening in S_N2[1] and S_N2'[2] modes with regioselectivity dictated by judicious choice of nucleophile. Vinyl aziridines can also be transformed into a wide range of heterocycles, including β-lactams,[3] pyrrolines,[4] tetrahydropyridines[5] and azepines[6] (Scheme 1).



Scheme 1. Synthetic applications of vinyl aziridines.

Synthetic approaches to vinyl aziridines include nitrenoid additions to 1,3-dienes,[7] conversion of vinyl epoxides,[8] reduction or alkylation of α–β unsaturated oximes,[9] intramolecular S_N2' substitutions,[10] olefination of oxo-aziridines[11] and carbenoid additions to imines.[12] However, since the pioneering work of Hou and Dai on the addition of ylides to activated imines,[13] this approach has become the most successful and general.[14] We have previously reported on the addition of tetrahydrothiophenium allylide to a range of activated imines,[15] including the chiral *tert*-butylsulfinimines.[16] Herein we report on the addition of sulfur allylides which bear substitution on the alkene[17] to a chiral non-racemic sulfinimine.

Substituted allyl sulfonium salts **1a**–**f** (Table 1) were formed by reaction of the corresponding allyl halide or tosylate with tetrahydrothiophene in dichloromethane for 3–5 days[17] (Method A) and, when necessary, with the addition of 1 equiv of silver tetrafluoroborate in order to push the reaction to completion (Method B). We have previously reported on the addition of allyltetrahydrothiophenium ylide to a range of chiral sulfinimines,[16] during which study we were able to ascertain that lithium *tert*-butoxide was the base of choice. In that study, we found that THF as solvent tended to give the best compromise of stereoselectivity and conversion, with DMSO giving the best conversion at the expense of trans:cis selectivity. In this study, we found that this generally remained the case.[18] It is very noticeable the effect that substitution of the alkene has on the rate of reaction of the ylide. In both THF and DMSO, the unsubstituted ylide **2a** reacts with (S_S)-*tert*-butylphenylsulfinimine in 30 min or less in both DMSO and THF. Substitution of the ylide, even with a simple methyl group (**2b**), effectively halts the reaction in THF at room temperature, and this trend is seen across the other substituents also. With the hindered ylides (**2b–d**) reaction was only seen in DMSO. The electronically activated ylide **2e** was able to react in THF, albeit significantly more slowly than in DMSO. The ylide derived from **2e** gave excellent trans:cis selectivity and diastereoselectivity. In general, while

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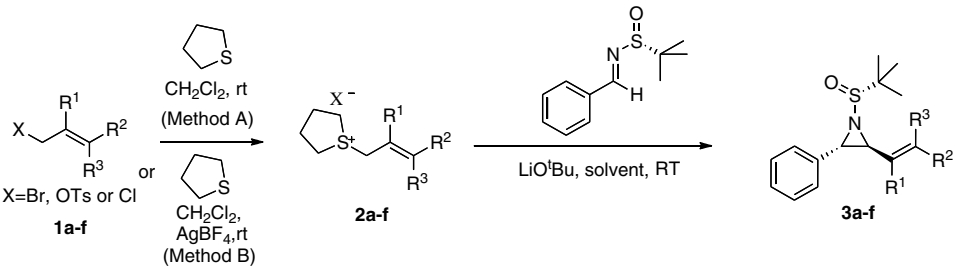
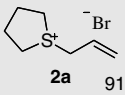
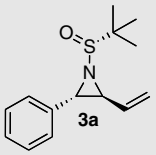
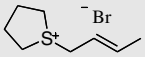
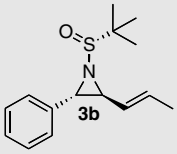
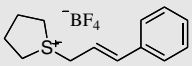
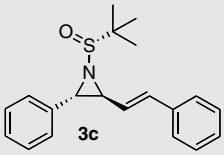
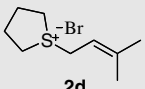
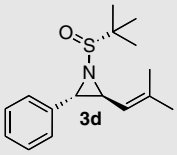
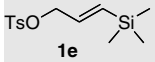
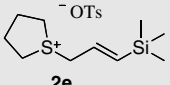
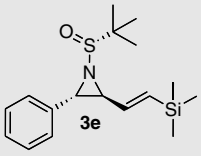
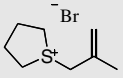
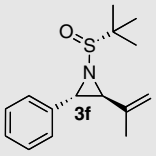
doi:10.1016/j.tetlet.2008.05.090

Table 1
Synthesis of substituted vinyl aziridines



Substrate	Salt formation method	Sulfonium salt	Aziridine product	Solvent	Time	Yield[a]	Cis:trans	dr of trans
Allyl bromide **1a**	**A**	 **2a** 91%[15]	 **3a**	THF DMSO	30 min 30 min	68% 75%	3:7 1:1	95:5 60:40
Crotyl bromide **1b**	**A**	 **2b** 94%[15]	 **3b**	THF DMSO	18 h 15 min	Trace 85%	– 1:2	– 60:40
Cinnamyl Chloride **1c**	**B**	 **2c** 76%[15]	 **3c**	THF DMSO	18 h 5 min	Trace 75%	– 2:3	– 51:49
Prenyl bromide **1d**	**A**	 **2d** 81%[15]	 **3d**	THF DMSO DMSO	24 h 2.5 h 18 h	Trace 39% 66%	– 3:7 3:7	– 68:32 68:32
 **1e**	**A**	 **2e** 68%	 **3e**	THF DMSO	18 h 3 h	90% 70%	1:12 5:6	100:0 50:50
 **1f**	**A**	 **2f** 47%[15]	 **3f**	THF DMSO	18 h 1 h	56% 63%	3:7 2:3	100:0 100:0

[a] Yields quoted are of the purified mixtures of diastereomers.

THF always gave better diastereoselectivities, the greater the steric bulk on the ylide and the closer the bulk is to the sulfur, the higher the diastereoselectivity became in DMSO, to the point where the 2-methyl ylide **2f** gives excellent levels of diastereoselectivity albeit with almost no trans:cis selectivity. The assignment of stereochemistry was by analogy with our previous work.[16a]

In conclusion, the addition of substituted sulfur allylides to *tert*-butylphenylsulfinimine gives a range of substituted chiral vinyl aziridines in good yields and moderate to excellent selectivities. Further studies on the exploitation of substituted vinyl aziridines as building blocks for synthesis are on-going in these laboratories and will be published in due course.

Acknowledgements

The authors thank Merck, Sharpe and Dohme and EPSRC for funding (K.C.).

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18. *General procedure for the synthesis of vinyl aziridines:* To a solution of sulfonium salt in DMSO (2 equiv, 0.16 M, 3 mL) under argon was added the imine (1 equiv), followed by lithium *tert*-butoxide (2 equiv). Progress of the reaction was monitored by TLC. Upon complete disappearance of the imine as monitored by TLC, the reaction was quenched by the addition of ice cold brine, and was stirred for 10 min. The reaction solution was extracted with diethyl ether (2×25 mL). The organic residues were then evaporated under reduced pressure and re-dissolved in 1:1 petroleum ether/diethyl ether and washed with brine before being dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by column chromatography over neutral alumina eluting with 1% ethyl acetate/petroleum ether gave the products. Aziridine **3a**: mp 75–76 °C. $[\alpha]_D^{23}$ −95 (*c* 1.0, $CHCl_3$). ν_{max} (thin film)/cm^{-1} 1601, 1460, 1355, 1080. MS (EI/CI): *m*/*z* [M+H] 250 (25%), 228 (100%). HRMS calcd for $C_{14}H_{20}NOS$ (M+H) 250.1265, found 250.1266. δ_H (400 MHz; $CDCl_3$) trans: 7.24 (5H, m), 6.20 (1H, ddd, *J* 17.0, 10.0, 9.5), 5.39 (1H, d, *J* 16.9), 5.28 (1H, d, *J* 10.3), 3.47 (1H, d, *J* 3.6), 3.09 (1H, dd, *J* 9.4, 3.6), 1.21 (9H, s). δ_C (100 MHz; $CDCl_3$) trans: 130.4, 126.4, 125.6, 124. 5, 119.6, 55.0, 48.1, 36.5, 20.6. Aziridine **3b**: $[\alpha]_D^{23}$ −51 (*c* 0.8, $CHCl_3$). ν_{max} (thin film)/cm^{-1} 1450, 1070; MS (EI/CI): *m*/*z* 264 [M+H, 100%]. HRMS calcd for $C_{15}H_{22}NOS$ (M+H), 264.1417, found 264.1418. δ_H (400 MHz; $CDCl_3$) trans: 7.3–7.2 (5H, m), 5.95 (1H, dq, *J* 15.2, 6.4), 5.60 (1H, dd, *J* 15.2, 9.2), 3.64 (1H, d, *J* 3.6), 3.0 (1H, dd, *J* 9.2, 3.6), 1.76 (3H, d, *J* 6.4), 1.14, (9H, s). δ_C (75 MHz; $CDCl_3$) trans: 135.8, 131.8, 126.6, 125.7, 123.5, 54.9, 48.2, 35.9, 20.6, 15.9. Aziridine **3c**: $[\alpha]_D^{23}$ −25 (*c* 0.1, $CHCl_3$). ν_{max} (thin film)/cm^{-1} 1430, 1350, 1050. MS (EI/CI): *m*/*z* 326 [M+H, 100%]. HRMS calcd for $C_{20}H_{24}NOS$ (M+H) 326.1573, found 326.1573. δ_H (400 MHz; $CDCl_3$) trans: 7.40–7.18 (10H, m), 6.72 (1H, d, *J* 15.6), 6.30 (1H, dd, *J* 15.6, 9.2), 3.76 (1H, d, *J* 3.6), 3.16 (1H, dd, *J* 9.2, 3.6), 1.21 (9H, s). δ_C (75 MHz; $CDCl_3$) trans: 136.9, 136.5, 135.5, 128.7, 128.6, 128.0, 127.9, 126.6, 126.4, 125.2, 57.4, 54.7, 44.4, 23.1. Aziridine **3d**: $[\alpha]_D^{23}$ −89 (*c* 0.9, $CHCl_3$). ν_{max} (thin film)/cm^{-1} 1450, 1350, 1100. MS (EI/CI): *m*/*z* 278[M+H, 100%]. HRMS calcd for $C_{16}H_{24}NOS$ (M+H) 278.1573, found 278.1571. δ_H (400 MHz; $CDCl_3$) trans: 7.4–7.2 (5H, m), 5.30 (1H, d, *J* 8.4), 3.63 (1H, d, *J* 4.0), 3.16 (1H, dd, *J* 8.4, 4.0), 1.79, (3H, s), 1.78 (3H, s), 1.21 (9H, s). δ_C (100 MHz; $CDCl_3$) trans: 142.4, 138.2, 129.6, 128.2, 127.7, 118.1, 57.0, 47.1, 38.4, 26.0, 23.0, 18.2. Aziridine **3e**: $[\alpha]_D^{23}$ −70 (*c* 0.25, $CHCl_3$). ν_{max} (thin film)/cm^{-1} 1450, 1350, 1230. MS (EI/CI): *m*/*z* 322 [M+H, 15%], 106 (83%), 90 (100%). HRMS calcd for $C_{17}H_{28}NOS^{28}Si$ (M+H) 322.1655, found 322.1658. δ_H (360 MHz; $CDCl_3$) trans: 7.40–7.32 (5H, m), 6.40 (1H, dd, *J* 18.4, 9.0), 6.18, (1H, d, *J* 18.4), 3.62 (1H, d, *J* 3.6), 3.22 (1H, dd, *J* 9.0, 3.6), 1.32 (9H, s), 0.00 (9H, s). δ_C (90 MHz; $CDCl_3$) trans: 141.2, 139.4, 138.5, 130.0, 129.4, 127.8, 58.8, 57.6, 46.3, 24.4, 0.0. Aziridine **3f**: $[\alpha]_D^{23}$ −15 (*c* 1.35, $CHCl_3$). ν_{max} (thin film)/cm^{-1} 1450, 1360, 1170. MS (EI/CI): *m*/*z* 264 [M+H, 28%], 145 (100%). HRMS calcd for $C_{15}H_{22}NOS$ (M+H) 264.1417, found 264.1415. δ_H (400 MHz; $CDCl_3$) trans: 7.33 (5H, m), 5.18 (2H, s), 3.59 (1H, d, *J* 4.0), 3.18 (1H, d, *J* 4.0), 1.93 (3H, s), 1.12 (9H, s). δ_C (100 MHz; $CDCl_3$) trans: 137.8, 133.5, 127.6, 127.3, 126.9, 115.6, 55.6, 49.5, 44.1, 21.2, 19.0.