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Direct synthesis of aliphatic vinyl aziridines

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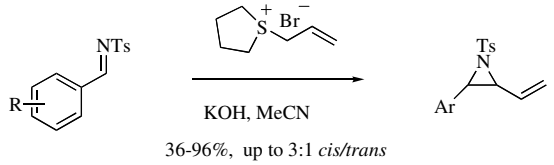
Abstract—The synthesis of vinyl aziridines, by the reactions of a range of diphenylphosphinyl and *p*-toluenesulfonyl alkyl aldimines with the ylide derived from *S*-allyl tetrahydrothiophenium bromide, are reported.

Vinyl aziridines are increasingly being utilised as useful building blocks for synthesis. Some recent examples of the versatility of vinyl aziridines include S_N2' ring opening with organo-cuprates,[1] conversion to amino-methylene cyclopropanes,[2] S_N2 ring opening to form amino-alcohols[3] and ring expansion to tetrahydropyridines[4] and azepines.[5]

As part of a programme directed at a number of natural product syntheses, we required a range of N-protected aliphatic vinyl aziridines. The recent work of Hou and Dai has shown that aryl aldimines react well with allyl sulfur ylides to form vinyl aziridines in good yield (Scheme 1).[6] In this paper we report the extension of this methodology to alkyl derived aldimines.

We initially investigated alkyl sulfonyl imines as substrates. These were synthesised from the corresponding aldehydes according to the procedure of Chemla et al.[7] or in the case of pivaldehyde, the method of Proctor and MacKay[8] was used. The results of our investigations into the aziridination of alkyl sulfonyl imines, with the sulfonium salt derived from tetrahydrothiophene and allyl bromide, are shown in Table 1. The alkyl sulfonyl imines were sensitive to hydrolysis, and thus were used immediately, without further purification. Several base/solvent combinations were tried for the aziridination reaction,[9] with the only successful conditions found to be deprotonation with butyllithium at low temperature.[10] The *s*-butyl, cyclohexyl and *t*-butyl tosylimines produced the desired product in 58%, 53% and 49% yields, respectively, after chromatography over silica gel (Table 1). The *n*-pentyl vinyl aziridine was formed in 51% yield, but was found to be unstable over a period of a day. Interestingly the reaction showed a preference for the formation of *trans* vinyl aziridines, which is in contrast to the findings of Hou and Dai on the aromatic substrates. Our conditions use much lower temperatures, and thus it is possible that the *trans* vinyl aziridines are the kinetically favoured products. The use of other, potentially more easily removed sulfonyl groups, such as *o*-nitrobenzenesulfonyl or trimethylsilylethanesulfonyl gave poor results (<5%), with large amounts of sulfonamide being isolated. We surmised that these sulfonyl groups were too electron withdrawing, thus leading to hydrolysis of the imine. The study was then turned to investigate the use of diphenylphosphinylimines as substrates for the aziridination.



Scheme 1.

The synthesis of *N*-diphenylphosphinylimines was carried out by conversion of the aldehyde to the corresponding oxime,[11] and subsequent conversion to the phosphinylimine following the procedure of Boyd et al.[12] Initially, *N*-diphenylphosphinylpivaldimine was reacted with the sulfonium salt derived from tetrahydrothiophene and allyl bromide with a range of bases and solvents.[9] Optimal conditions were found to be the use of potassium *tert*-butoxide in acetonitrile at room

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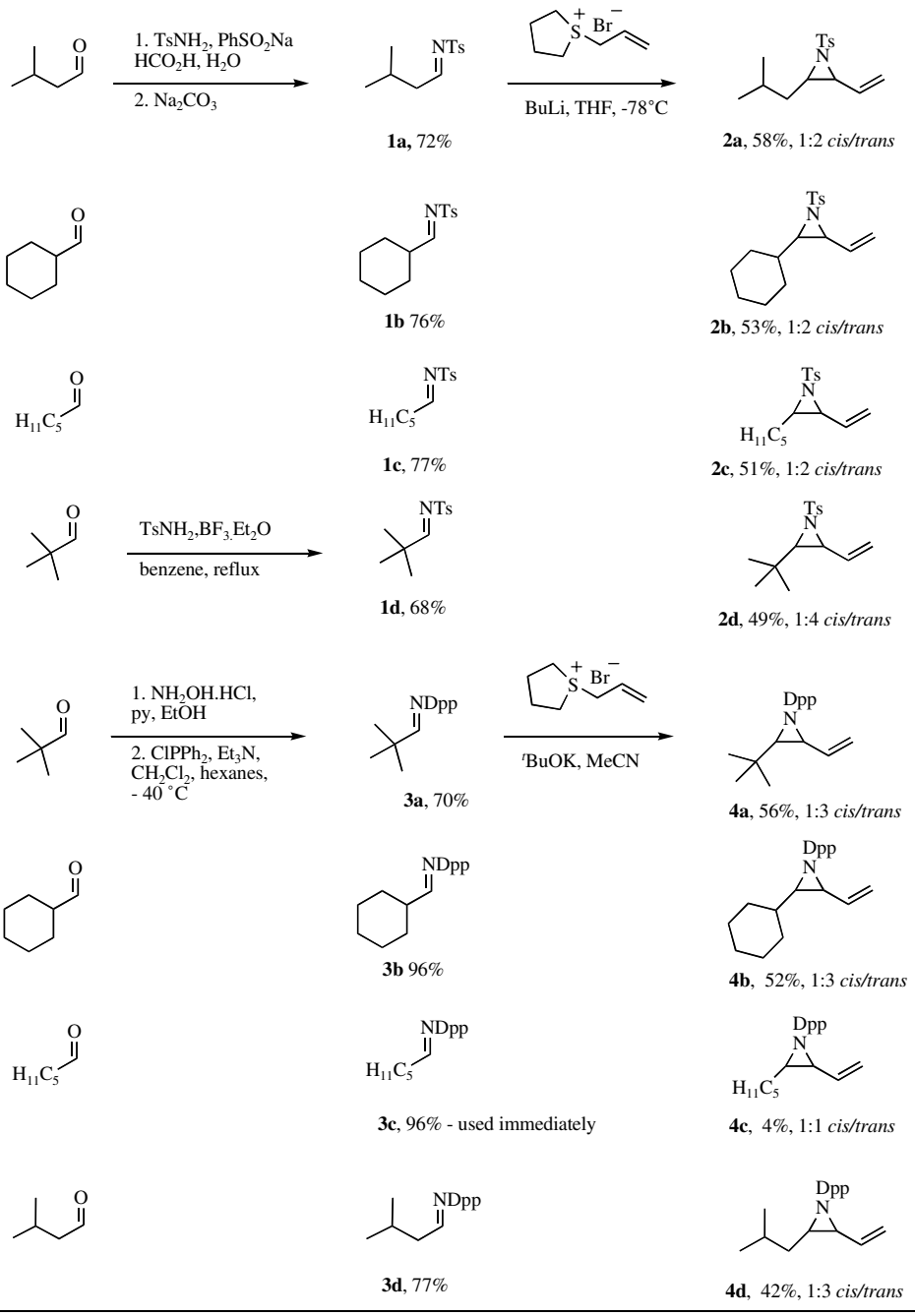
Table 1



All imines were used immediately without further purification. All vinyl aziridines were purified by column chromatography, and yields are of fully purified compounds characterised by ^{1}H and ^{13}C NMR, IR, MS and HRMS.

temperature, giving a yield of 56% with a 3:1 ratio of *trans* to *cis* products.[13] These optimised conditions were then used to convert aldimines **3** to vinyl aziridines **4**, as shown in Table 1. Yields for the transformation were generally similar to those found with the sulfonyl imines, ranging from 42% to 56%, with the *trans* product being favoured in all cases by a ratio of 3:1 except for the *n*-pentyl vinyl aziridine, which gave a 1:1 ratio of the *trans* to *cis* products, which were found to be unstable to chromatography, resulting in a disappointing yield of purified product. It should be noted that the *N*-Dpp imines are relatively unstable to hydrolysis, and were therefore used directly, although storage for a short period in a freezer is possible, except in the case of the *n*-pentyl derivative, which is unstable over a period of hours. The *N*-Dpp vinyl aziridines were purified by column chromatography over neutral alumina.

In conclusion, we have found that alkyl tosylimines and alkyl diphenylphosphinylimines can be transformed into

N-protected vinyl aziridines in a concise manner. The moderate yields and diastereoselectivity are partly offset by the simple procedures and high convergency of this approach, which should allow a wide variety of vinyl aziridines to be accessed. Studies on the use of these vinyl aziridines as synthetic building blocks for natural product synthesis, and use of chiral sulfinyl imines as substrates for the ylide aziridination[14] are on-going in these laboratories, and our results will be published in due course.

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9. Other bases/solvents tried include KOH, *t*-BuOK, NaH, DBU, KHMDS, acetonitrile, dichloromethane and DMF. The *trans* product preference for vinyl aziridine formation was also noted by Sweeney and co-workers on their studies of an aza-Darzens type reaction of diphenylphosphinyl imines with lithiated allyl bromide in the presence of zinc chloride: Cantrill, A. A.; Jarvis, A. N.; Osbourn, H. M. I.; Ouadi, A.; Sweeney, J. B. *Synlett* **1996**, 847; Hou and Dai also noted a preference for *trans* vinyl aziridination using aromatic diphenylphosphinyl imines with silylated sulfur ylide substrates: Hou, X.-L.; Yang, X.-F.; Dai, L.-X.; Chen, X.-F. *Chem. Commun.* **1998**, 747.
10. Typical procedure: To a solution of 1-allyl-tetrahydrothiophenium bromide (0.45 g, 2.19 mmol, 1 equiv) in anhydrous tetrahydrofuran (30 mL) at −78 °C under an atmosphere of argon, was added *n*-butyl lithium (1.05 mL of a 2.5 M solution in hexanes, 2.62 mmol, 1.2 equiv). The reaction mixture was stirred for 30 min, then re-cooled to −78 °C. A solution of *N*-cyclohexylmethylene-4-methylbenzenesulfonamide (0.58 g, 2.19 mmol) in anhydrous tetrahydrofuran (10 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred for 24 h. A saturated aqueous solution of ammonium chloride (30 mL) and ethyl acetate (30 mL) were added. The organic layer was separated, washed with brine (30 mL), dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification by column chromatography over silica gel (eluting with 12:1 hexane/ethyl acetate) gave *p-toluenesulfonyl-2-cyclohexyl-3-vinyl aziridine* (0.36 g, 1.17 mmol, 53%) as a colourless oil and as a 2:1 mixture of diastereoisomers (*trans* and *cis* aziridines); ν_{max}(thin film)/cm^{-1} 1327, 1161; ^{1}H NMR (400 MHz; $CDCl_3$; TMS), δ 7.82 (2H, d, *J* 8), 7.31 (2H, d, *J* 8), 6.15 (1H, ddd, *J* 17.2, 10 and 10, *trans* isomer), 5.62 (1H, ddd, *J* 18, 10.4 and 7.5, *cis* isomer), 5.49 (1H, d, *J* 17.2, *trans* isomer), 5.42 (1H, d, *J* 17.2, *cis* isomer), 5.54 (1H, d, *J* 10.4, *trans* isomer), 5.40 (1H, d, *J* 10.4, *cis* isomer), 3.36 (1H, dd, *J* 7.5 and 7.5, *cis* isomer), 3.12 (1H, dd, *J* 10 and 4.4, *trans* isomer), 2.82 (1H, dd, *J* 8 and 4.4, *trans* isomer), 2.62 (1H, dd, *J* 7.5 and 7.5, *cis* isomer), 2.44 (3H, s), 1.70–1.41 and 1.25–0.83 (11H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS), δ 136.9 (*cis* isomer), 132.1 (*trans* isomer), 131.6, 130.1, 129.4, 127.7, 121.6 (*trans* isomer), 121.2 (*cis* isomer), 53.0 (*trans* isomer), 51.2 (*trans* isomer), 50.5 (*cis* isomer), 45.6 (*cis* isomer), 39.5 (*trans* isomer), 35.7 (*cis* isomer), 30.3, 29.7, 25.9, 25.5, 25.3, 21.6; *m*/*z* (EI) 306 (M+1, 98%); HRMS: Found: 306.1526. $C_{17}H_{23}NO_2S$ (M+H) Requires 306.1528.
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13. Typical procedure: To a solution of *N*-cyclohexylmethylenediphenylphosphinamide (0.83 g, 2.66 mmol) and 1-allyltetrahydrothiophenium bromide (0.82 g, 3.99 mmol, 1.5 equiv) in anhydrous acetonitrile (30 mL) at room temperature under an atmosphere of argon, was added potassium *tert*-butoxide (0.45 g, 3.99 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 24 h, then concentrated in vacuo. Water (30 mL) and ethyl acetate (30 mL) were added. The organic layer was separated, washed with brine (30 mL), dried over anhydrous sodium sulfate and evaporated in vacuo. Purification by column chromatography over neutral alumina (eluting with 15:1–1:1 hexane/ethyl acetate) gave *1-diphenylphosphinyl-2-cyclohexyl-3-vinyl aziridine* (0.49 g, 1.40 mmol, 52%) as a colourless liquid and as a 3:1 mixture of diastereoisomers (*trans* and *cis* aziridines); ν_{max}(thin film)/cm^{-1} 1119, 960 (P=O); ^{1}H NMR (400 MHz; $CDCl_3$; TMS), δ 7.94–7.86 and 7.48–7.38 (10H, m), 6.04 (1H, ddd, *J* 17.2, 10 and 9, *trans* isomer), 5.78 (1H, ddd, *J* 16, 10 and 8, *cis* isomer), 5.39 (1H, dd, *J* 16 and 1.2, *cis* isomer), 5.27 (1H, dd, *J* 10 and 1.2, *cis* isomer), 5.21 (1H, dd, *J* 17.2 and 1.2, *trans* isomer), 5.02 (1H, dd, *J* 10 and 1.2, *trans* isomer), 3.28 (1H, ddd, J_{H-P} 16, *J* 8 and 7, *cis* isomer), 3.03 (1H, ddd, J_{H-P} 15.6, *J* 9 and 3.2, *trans* isomer), 2.68 (1H, ddd, J_{H-P} 16, *J* 7.2 and 3.2, *trans* isomer), 2.62 (1H, ddd, J_{H-P} 16, *J* 8 and 7, *cis* isomer), 1.70–1.54 and 1.29–0.75 (11H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS), δ 136.2 (*cis* isomer), 135.7 (*trans* isomer), 133.1, 131.7, 129.6, 128.2, 120.1 (*cis* isomer), 119.1 (*trans* isomer), 48.1 (*trans* isomer), 46.8 (*trans* isomer), 46.0 (*cis* isomer), 41.5 (*cis* isomer), 40.3 (*trans* isomer), 36.8 (*cis* isomer), 30.7, 30.3, 26.3, 25.9 and 25.7; *m*/*z* (EI) 352 (M+1, 100%); HRMS: Found: 352.1830 $C_{22}H_{26}NOP$ (M+H) Requires 352.1825.
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