Novel Synthesis of Chiral Unactivated 2-Aryl-1-benzylaziridines

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Received 6 February 2009

Abstract: Chiral (R_S,*R*)- and (R_S,*S*)-*N*-(*tert*-butylsulfinyl)-2-arylaziridines were transformed into (*R*)- and (*S*)-2-aryl-1-benzylaziridines via a short three-step procedure. Deprotection and ring opening of (R_S,*R*)- and (R_S,*S*)-*N*-sulfinyl-2-arylaziridines (95–99% de) in acid medium afforded 2-aryl-2-chloroethylamine hydrochlorides in high yield (83–90%). These intermediates were converted into the corresponding chiral *N*-(benzylidene)-β-aryl-β-chloro-amines in good yield (78–85%). Subsequent reduction of the synthesized aldimines afforded chiral 2-aryl-1-benzylaziridines in good to excellent yield (74–94%) and enantiomeric excess (83–99% ee). The enantiomeric purity of the chiral aldimines and aziridines was established by NMR spectroscopy using Pirkle alcohol as the chiral solvating agent.

Key words: chiral aziridines, asymmetric synthesis, ring opening, ring closure, haloimines

Chiral aziridines are important target compounds in organic chemistry and their synthesis remains a major challenge. Aziridines are divided into the class of 'activated' aziridines which have an electron-withdrawing N-substituent and 'unactivated' aziridines, such as *N*-alkyl- or *N*-benzylaziridines, which need to be quaternized to undergo ring-opening reaction.[2] 'Activated' and 'unactivated' aziridines can behave differently in terms of regioselectivity during nucleophilic ring-opening reactions,[3] and, therefore, the development of methodologies to transform chiral activated aziridines into unactivated aziridines with retention of the enantiomeric purity is of importance.[4]

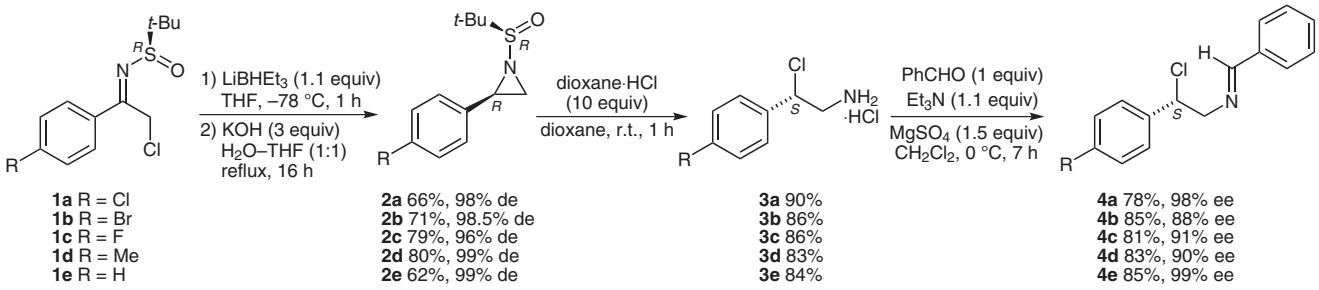
Chiral aziridines are mainly synthesized by ring closure of chiral amino alcohols,[5] ring opening of chiral epoxides with azide followed by ring closure,[5c,6] asymmetric aza-Darzens reaction,[7] asymmetric addition to azirines,[8] stereoselective nitrene addition to olefins,[9] aza-Payne rearrangement of 2,3-epoxy amines,[10] asymmetric addition of nucleophiles across α-haloimines,[11] and reaction of ylides with chiral imines.[12] Due to the ability of chiral aziridines to undergo a variety of synthetically useful transformations a broad range of chiral functionalized compounds can be obtained. Nucleophilic ring opening, the most thoroughly studied reaction of chiral aziridines,[13] is facilitated by the release of ring strain and affords enantiomerically pure β-substituted ethylamines.

In this paper, the convenient synthesis of chiral 2-aryl-1-benzylaziridines as potential precursors for nucleophilic ring opening to chiral biologically and synthetically important phenylethylamines,[14,15] is described with chiral 2-aryl-1-(*tert*-butanesulfinyl)aziridines as starting material. This transformation from chiral 'activated' aziridines to the corresponding enantiomerically pure 'unactivated' aziridines involves the efficient synthesis of two intermediates, namely 2-aryl-2-chloroethylamine hydrochlorides and the corresponding *N*-(benzylidene)-β-aryl-β-chloroamines.

Chiral (R_S,*R*)-*N*-(*tert*-butylsulfinyl)aziridines **2a–e** were prepared by reduction of (R_S)-*N*-*tert*-butanesulfinyl α-haloimines **1** with $LiBHEt_3$ in dry THF and subsequent treatment with KOH as reported earlier.[11a,16] These chiral aziridines **2a–e** were obtained highly diastereomerically enriched (dr 98:2 up to >99:1 as determined by ^1H NMR analysis) after recrystallization from Et_2O in 62–80% yield. The aziridines (R_S,*R*)-**2** were deprotected and regioselectively ring-opened by treatment with a saturated solution of dry HCl in dioxane while stirring for one hour at room temperature which afforded the (*S*)-2-aryl-2-chloroethylamine hydrochlorides **3** in high yield (83–90%, Scheme 1).[11a,b,17] These hydrochlorides **3** were then transformed into the corresponding (*S*)-*N*-(benzylidene)-2-aryl-2-chloroethylamines **4** in 78–85% yield by treatment with benzaldehyde in the presence of triethylamine and magnesium(II) sulfate in dichloromethane (Scheme 1).[18] The regiochemistry of the ring opening of aziridines **2** and the correct characterization of 2-aryl-2-chloroethylamine hydrochlorides **3** and the corresponding aldimines **4** was chemically ascertained by the synthesis of 2-azadiene **5** upon treatment of aldimine **4c** with potassium *tert*-butoxide in *tert*-butanol for one hour at room temperature (Scheme 2).

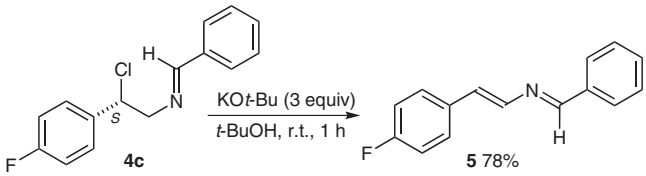
The enantiomeric purity of aldimines **4** was determined via an NMR technique using the chiral solvating agents (*R*)-**6** and (*S*)-**6** (Pirkle alcohol, Figure 1).[19] All initial attempts to use the recently developed macrocyclic chiral shift reagent Chirabite-AR (**7**) to determine the enantiomeric purities of aldimines **4** failed.[20] No NMR spectra showing chemical shift nonequivalences could by obtained upon addition of Chirabite-AR (**7**) to racemic aldimines **4** in $CDCl_3$. Compounds **4** were prepared in the same way from racemic *tert*-butanesulfinamide via racemic *N*-*tert*-butanesulfinyl α-haloimines **1** as described before. However, if one equivalent of (*R*)-Pirkle alcohol **6** [(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol] is added to racemic aldimine **4b**, a well-resolved spectral nonequivalence of the signals from each CH_2- and CH-proton of the

SYNLETT 2009, No. 8, pp 1265–1268
Advanced online publication: 08.04.2009
DOI: 10.1055/s-0028-1088125; Art ID: G05109ST



Scheme 1

two aldimine enantiomers is observed in the ^{1}H NMR spectrum (300 MHz, $CDCl_3$).



Scheme 2

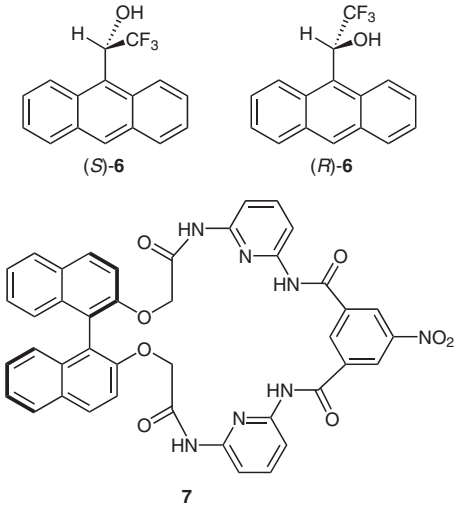
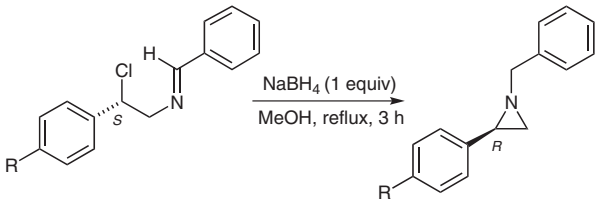


Figure 1 Chiral Pirkle alcohols **6** and Chirabite-AR® (**7**)

Analogously, upon addition of 5.5 equivalents of (*R*)-**6** to aldimine **4b**, a good separation of the corresponding signals for the asymmetrically prepared major enantiomer (*S*)-**4b** and its minor enantiomer (*R*)-**4b** was observed, allowing determination of the enantiomeric purity [88% ee for (*S*)-**4b**]. Similar NMR experiments with (*R*)- and (*S*)-Pirkle alcohol **6** were also carried out with the chiral aldimines **4a**,**c**–**e** for determination of the enantiomeric excess. In this way, it was observed that the unsubstituted aldimine **4e** (R = H) and the *p*-chloro-substituted derivative **4a** were enantiomerically pure (>98% ee) within the limits of the NMR technique, while some racemization occurred for the other *para*-substituted compounds **4b**–**d** (>88% ee). It is not clear, however, if this reduced enantiomeric purity is due to some racemization of the starting *N*-sulfinylaziridines **2b**–**d** prior to nucleophilic ring opening with HCl or results from the small contribution of a S_N1-type pathway during the nucleophilic ring opening.[21]

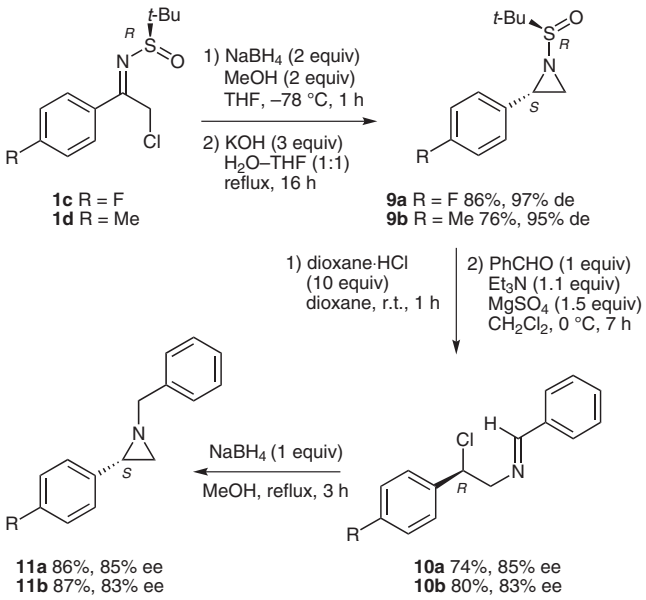
In the last step, the chiral (*R*)-2-aryl-1-benzylaziridines **8a**–**e** were synthesized in good yield (74–94%) by reduction of chiral aldimines **4a**–**e** with sodium borohydride in methanol under reflux (Scheme 3).[22,23] The β-chloroamines formed by nucleophilic addition of hydride were subsequently ring-closed by an internal nucleophilic substitution with a Walden inversion. The enantiomeric purity of 2-phenylaziridines **8** (88–99% ee) was again determined via NMR-experiments with (*R*)-**6** or (*S*)-**6**.



Scheme 3

These experiments demonstrated that the ring closure of (*S*)-*N*-(benzylidene)-β-aryl-β-chloroamines **4** to (*R*)-2-aryl-1-benzylaziridines **8** occurs via an S_N2-type pathway without further racemization. The absolute configuration of (*R*)-1-benzyl-2-phenylaziridine **8e** was confirmed by comparison of the optical rotation {(*R*)-**8e**: $[\alpha]_D$ –73.7 (*c* 0.76, EtOH)} with literature values {(*S*)-**8e**: $[\alpha]_D^{24}$ +69.2 (*c* 2.0, EtOH);[24] (*R*)-**8e**: $[\alpha]_D^{20}$ –49.4 (*c* 2.0, EtOH)}.[25]

The analogous transformation of the new (R_S,*S*)-*N*-(*tert*-butylsulfinyl)aziridines **9a**,**b**, prepared in high yields via the intrinsically more diastereoselective reduction of (R_S)-*N*-*tert*-butanesulfinyl α-chloroimines **1c**,**d** with $NaBH_4$,[11a] to chiral (*S*)-2-aryl-1-benzylaziridines **11** gave somewhat less satisfying results (Scheme 4). Deprotection of aziridines **9** and imination of the corresponding 2-aryl-2-chloroethylamine hydrochlorides afforded the aldimines **10** with a lower enantiomeric purity (83–85% ee) as determined via NMR experiments with (*R*)-**6**. Reduction of aldimines **10** with sodium borohydride in methanol under reflux efficiently resulted in ring closure to (*S*)-2-aryl-1-benzylaziridines **11** without further loss of the configurational integrity.



Scheme 4

In conclusion, a short synthesis of the unactivated (*R*)- and (*S*)-2-aryl-1-benzylaziridines **8** and **11** was developed in high yield and good to excellent enantiomeric purity via a three-step sequence from the activated (R_S,*R*)- and (R_S,*S*)-*N*-(*tert*-butylsulfinyl)-2-arylaziridines **1** and **9**. The enantiomeric purity of the intermediate *N*-(benzylidene)-β-aryl-β-chloroamines and aziridines was influenced by the *para*-substituent of the aryl group. The synthesis of chiral N-unactivated aziridines **8** and **11** is complementary to the access towards chiral N-activated aziridines **2** and **9**.

Acknowledgment

The authors are indebted to Ghent University (GOA) and the Research Foundation-Flanders (FWO-Vlaanderen) for financial support of this research.
The authors are indebted to Prof. D. M. Hodgson for addressing important suggestions regarding the ring opening of chiral aziridines **2**.

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(16) **(R_S,*R*)-*N*-(*tert*-Butylsulfinyl)-2-(4-methylphenyl)-aziridine (2d)**
Prepared according to a previously described method, see ref. 11a. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 9 H), 1.99 (d, *J* = 3.9 Hz, 1 H), 2.34 (s, 3 H), 2.97 (d, *J* = 7.2 Hz, 1 H), 3.09 (dd, *J* = 7.2, 3.9 Hz, 1 H), 7.13–7.20 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 22.8, 28.6, 34.7, 57.4, 126.3, 129.2, 134.6, 137.5. IR (ATR): ν_{max} = 1063, 1362, 1457, 1681, 2960, 3346 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 238(100) [M + H$^+$]. $[\alpha]_D$ –238.5 (*c* 1.15, CH_2Cl_2); mp 106.0–107.0 °C. Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90; S, 13.51. Found: C, 65.44; H, 8.35; N, 6.11; S, 13.28.

(17) **(*S*)-2-Chloro-2-(4-methylphenyl)ethylamine Hydrochloride (3d)**
Prepared according to a previously described method, see ref. 11a,b. ^{1}H NMR (300 MHz, D_2O): δ = 2.31 (s, 3 H), 3.19 (dd, *J* = 12.7, 4.4 Hz, 1 H), 3.26 (dd, *J* = 12.7, 8.7 Hz, 1 H), 4.93 (dd, *J* = 8.7, 4.4 Hz, 1 H), 7.26–7.32 (m, 4 H). ^{13}C NMR (75 MHz, D_2O): δ = 20.8, 45.8, 70.0, 126.6, 130.1, 137.1, 139.6. IR (ATR): ν_{max} = 1146, 1510, 1603, 2361, 2958 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 152/154(100), 170/172(20) [M + H$^+$]. $[\alpha]_D$ +52.6 (*c* 1.01, MeOH); mp 173.6–174.6 °C. Anal. Calcd for $C_9H_{13}NCl_2$: C, 52.45; H, 6.36; N, 6.80. Found: C, 52.52; H, 6.42; N, 6.57.

(18) **Preparation of (*S*)-*N*-Benzylidene-[2-chloro-2-(4-methylphenyl)ethyl]amine (4d)**
Triethylamine (0.09 g, 0.93 mmol) was added to a solution of (*S*)-2-chloro-2-(4-methylphenyl)ethylamine hydrochloride (**3d**, 0.15 g, 0.88 mmol), $MgSO_4$ (0.15 g, 1.27 mmol), and benzaldehyde (0.09 g, 0.88 mmol) in CH_2Cl_2 (15 mL). The reaction was stirred for 7 h at 0 °C. The suspension was subsequently filtered, and the solvent was evaporated. Diethyl ether (15 mL) was added and the obtained mixture was again filtered and evaporated, yielding **4d** which was purified by recrystallization from Et_2O (0.18 g); yield 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 4.02 (ddd, *J* = 12.5, 8.5, 1.1 Hz, 1 H), 4.21 (ddd, *J* = 12.5, 5.0, 1.7 Hz, 1 H), 5.24 (dd, *J* = 8.5, 5.0 Hz, 1 H), 7.16–7.45 and 7.72–7.76 (m, 9 H), 8.28 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 62.7, 69.0, 127.2, 128.3, 128.6, 129.3, 131.0, 135.8, 137.0, 138.3, 163.7. IR (ATR): ν_{max} = 1449, 1514, 1645, 2361, 2916 cm^{-1}. MS (ES, pos. mode): *m/z* (%): 258/260(100) [M + H$^+$]. $[\alpha]_D$ +55.8 (*c* 0.70, CH_2Cl_2); mp 79.4–80.4 °C. Anal. Calcd for $C_{16}H_{16}NCl$: C, 74.55; H, 6.26; N, 5.43. Found: C, 74.89; H, 6.37; N, 5.20.

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(23) **Preparation of (*R*)-1-Benzyl-2-(4-methylphenyl)-aziridine (8d)**
To a stirred solution of aldimine **4d** (0.12 g, 0.47 mmol) in MeOH (15 mL) was added $NaBH_4$ (0.02 g, 0.47 mmol), and the reaction mixture was brought to reflux for 3 h. Afterwards, a sat. soln of $NaHCO_3$ (10 mL) was added, and the organic solvent was evaporated. The resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$) and filtered to afford 1-benzyl-2-(4-methylphenyl)aziridine (**8d**, 0.09 g) in pure form after removal of the solvent in vacuo; yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (d, *J* = 6.6 Hz, 1 H), 1.97 (d, *J* = 3.3 Hz, 1 H), 2.32 (s, 3 H), 2.47 (dd, *J* = 6.6, 3.3 Hz, 1 H), 3.58 (d, *J* = 13.8 Hz, 1 H), 3.70 (d, *J* = 13.8 Hz, 1 H), 7.08–7.38 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 37.8, 41.4, 64.8, 126.1, 126.9, 127.8, 128.3, 129.0, 136.5, 137.1, 139.2. IR (ATR): ν_{max} = 1026, 1452, 1517, 2826, 3028 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 224(100) [M + H$^+$]. $[\alpha]_D$ –55.8 (*c* 1.01, CH_2Cl_2). Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.21; H, 7.83; N, 5.96.

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