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Enantiomerically Pure 2-Alkyl and 2,3-Dialkylaziridines from 2-Sulfinylimines

José L. García Ruano,* Antonio Lorente, Jesús H. Rodríguez Ramos*

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco 28049-Madrid, SPAIN

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Abstract: A new entry to optically pure aziridines from *N*-*p*-methoxyphenyl derivatives of 2-*p*-tolylsulfinylketimines is reported. The highly stereoselective reduction of the imines with DIBAL-H/ZnX_2 yielded the corresponding sulfinyl amines, which can be transformed into the *N*-Cbz derivatives through a two-step sequence involving reaction with BnO_2CCl and subsequent oxidation with CAN. These compounds were easily transformed into optically pure aziridines by reduction of the sulfinyl group, further methylation at sulfur, and final cyclization with base.
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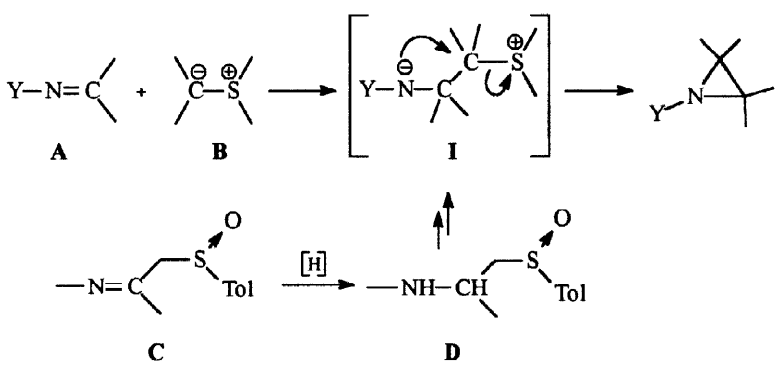
The wide scope of aziridines as building blocks in asymmetric synthesis of various types of organic molecules,[1] has stimulated a great interest in devising methods to obtain them in an enantiopure form to supplement the few available methods.[2] One of the more promising strategies is the aziridination through the reaction of an imine **A** with a sulfur ylide **B** (Scheme 1), which involves a stereocontrolled nucleophilic addition as a first step, followed by an intramolecular nucleophilic substitution of an R_2S group by an amide anion.[3]



Scheme 1

The sulfinyl group of the *N*-sulfinylimines **A** (Y=SOTol in Scheme 1) has been shown to be an efficient chiral auxiliary in this asymmetric synthesis of aziridines, but the scope of such a method remains uncertain due to the so far rather low availability of the enantiopure starting materials. Thus, one of the best methods, involving the reaction of lithium enolates of ethyl 2-bromoacetate with *N*-sulfinyl imines,[4] has been applied only to *N*-sulfinylbenzaldimine, whereas the reactions of sulfur ylides with the same electrophiles, have only been investigated on *N*-sulfinyl imines derived from aldehydes lacking α-hydrogens.[5] Although several papers

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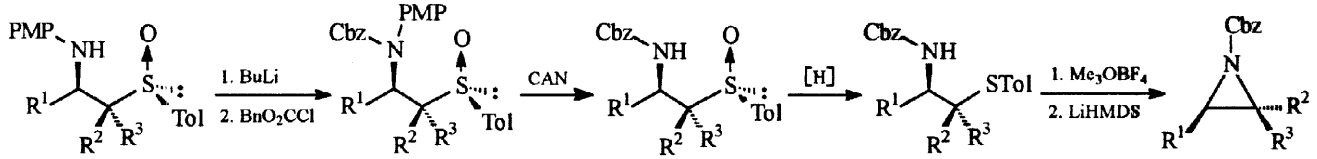
describing general methods to obtain sulfinylimines from any type of aldehyde and ketone have recently been published,[6] the above mentioned reactions have not been investigated on such substrates.

A more versatile second strategy would involve the synthesis of the intermediates **I** from the enantiomerically pure 2-sulfinylamines **D**, which in turn could be easily available by stereoselective reduction of the corresponding 2-sulfinylimines **C** (see Scheme 1). To our knowledge this second strategy, similar to that used to prepare epoxides from 2-sulfinylalcohols,[7] has never been investigated. In this paper, we describe the results obtained in this research.

Recently we have reported a general method to obtain enantiomerically pure acyclic 2-sulfinylketimines.[8] The reduction of such compounds with DIBAL-H/ZnX_2[9] has recently been shown to be an efficient general method to obtain 2-sulfinylamines in high enantiopurity.[10] The transformation of the amine into a carbamate derivative as well as that of the sulfinyl group into the sulfonium one (better leaving group), allows us to form aziridines according to the sequence shown in Scheme 2.[11]



	R^1	R^2	R^3				
1	*n*-Pr	H	H	**5** (80%)	**9** (65%)	**13** (90%)	**17** (70%)
2	Me	H	Et	**6** (87%)	**10** (53%)	**14** (85%)	**18** (55%)
3	Me	Et	H	**7** (87%)	**11** (52%)	**15** (60%)	**19** (42%)
4	*i*-Pr	H	H	**8** (70%)	**12** (65%)	**16** (80%)	**20** (45%)

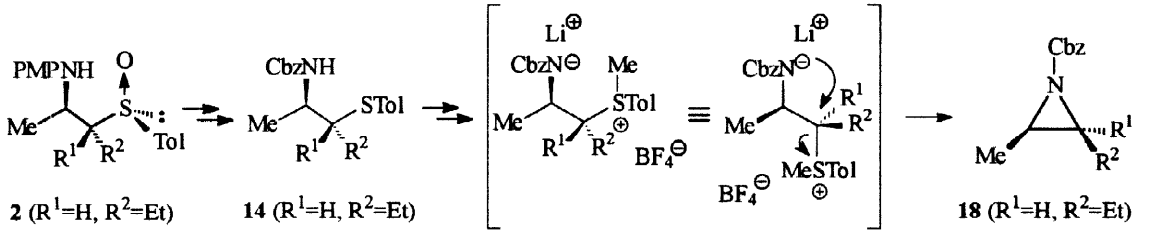
Scheme 2

Compounds **1-4** were obtained as single diastereoisomers by reaction of the corresponding *N*-*p*-methoxyphenyl-2-sulfinylimines[12] with DIBAL-H/ZnI_2 in CH_2Cl_2 at –48 °C for 1 h and at room temperature for an additional hour.[9,10] The removal of the *N*-*p*-methoxyphenyl group with cerium ammonium nitrate (CAN), had been reported only in the case of β-lactams[13] suggesting that such protecting group can only be efficiently eliminated for amide derivatives.[14] Although acetyl, benzoyl and *t*-butoxycarbonyl derivatives of compounds **1-4** could be easily prepared, their subsequent treatment with CAN did not afford the expected *N*-de-arylated compounds in good yield, mainly due to the concomitant oxidation of the sulfinyl group into the sulfonyl one. However, the use of *N*-benzyloxycarbonyl (Cbz) derivatives **5-8** as substrates for the CAN oxidation yielded better results, since this group allowed removal of the PMP substituent without affecting the sulfur moiety, affording compounds **9-12**.[15] The low reactivity of the aromatic amino group in **1-4** towards benzyl chloroformate was increased by previous deprotonation of amines with BuLi. This sequence for transformation of *N*-PMP derivatives into *N*-Cbz ones can be interesting from a synthetic point of view.

The reduction of the sulfoxides **9-12** with $BF_3.OEt_2$/NaI in CH_3CN, successfully used with other sulfinyl derivatives,[16] only gave high yields in the reactions leading to **13** and **14** (90 and 85%, respectively), the yield of **16** being lower (60%). Surprisingly, under the same conditions, compound **11** did not afford the expected sulfide **15**, the unprotected sulfenylamino derivative being the only isolated product. In this case, treatment of **11** with $(CF_3CO)_2O$ / NaI in acetone[17] yielded the desired sulfide **15** in 60% yield. The reaction of this reducing agent with **12** improved the yield up to 80%.

The final intramolecular cyclization of **13-16** into the aziridines **17-20** was carried out in moderate to high yields through a one-pot procedure consisting in the methylation at sulfenyl sulfur with Me_3OBF_4 followed by

treatment with LiHMDS in THF at –78 °C. Quenching the reaction mixture with water or aqueous saturated NH_4Cl solution resulted in recovery of the intermediate sulfonium salt which may be due to the increase of the medium polarity, allowing attack of the nucleophilic methyl *p*-tolyl sulfide (the by-product in the cyclization) onto the highly reactive aziridine ring. To obtain the heterocyclic compounds it was necessary to concentrate the reaction mixture to dryness, to extract the residue with diethyl ether and, after evaporation of the solvent, to carried out purification by chromatography. The aziridines **17-20** obtained were stable enough to be stored without decomposition.[18]



2 (R^1=H, R^2=Et) **14** (R^1=H, R^2=Et) **18** (R^1=H, R^2=Et)

3 (R^1=Et, R^2=H) **15** (R^1=Et, R^2=H) **19** (R^1=Et, R^2=H)

Scheme 3

The isolation of only one diastereoisomer of 2,3-dialkylaziridine **18** and **19** starting from **14** and **15** respectively, suggests that intramolecular cyclization must occur with inversion of the configuration at C-2, according to an internal S_N2 process. The *cis* and *trans* stereochemistry was unequivocally assigned to aziridines **18** and **19** on the base of their vicinal coupling constants. Therefore, taking into account that no step involved in the synthetic sequence affects the configuration at C-1, the *trans*-aziridine **19** must derive from a compound with the methyl and ethyl groups in a *syn* arrangement (**15**), whereas the *cis*-aziridine **18** must be obtained from the acyclic precursor bearing both alkyl groups with an *anti* relationship (**14**).

In summary, a new entry to the enantiomerically pure *N*-protected 2-alkyl and 2,3-dialkyl aziridines starting from *N*-*p*-methoxyphenyl-2-sulfinylimines is reported, involving as the key steps, in addition to the completely stereoselective reduction of the substrates with DIBAL-H/ZnI_2, the transformation of *N*-PMP amino derivatives into *N*-Cbz ones and the highly stereoselective elimination of the sulfur moiety according to an internal S_N2 process from the 2-aminosulfonium salts.

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11. The use of carbamate derivatives was necessary in order to prevent the competitive methylation of both sulfur and nitrogen atoms in a further step of the synthesis.
12. The use of *N*-benzyl derivatives instead the PMP ones as the starting materials in the sequence shown in Scheme 2 was not satisfactory because all the attempts of further debenzylation with H_2, Pd/C, in order to obtain the free amine (which would be transformed into the carbamate derivatives required for cyclization) were unsuccessful.
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14. Recently it has been reported that the use of CAN in a high excess is able to remove the PMP group of the compounds with amine structure (Bravo, P.; Farina, A.; Kukhar, V. P.; Markowski, A. L.; Meille, S. V.; Soloshonok, V. A.; Sorochinski, A. E.; Viaani, F.; Zanda, M.; Zappalà, C. *J. Org. Chem.* 1997, *62*, 3424).
15. **9**: $[\alpha]_D^{20}$+75.0 (*c* 1, CH_2Cl_2); ^{1}H NMR δ 7.55 and 7.28 (AA'BB' system, 4H), 7.32-7.25 (m, 5H), 5.88 (d, 1H, J = 8.4 Hz), 5.06 (s, 2H), 3.84 (m, 1H), 3.10 (dd, 1H, J = 7.8, 13.2 Hz), 2.94 (dd, 1H, J = 4.9, 13.2 Hz), 2.37 (s, 3H), 1.58 (m, 2H), 1.29 (m, 2H), 0.82 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 155.6, 141.3, 140.2, 136.3, 129.7, 128.2, 127.7, 127.6, 124.0, 66.2, 62.7, 47.2, 36.5, 21.1, 18.7, 13.4. **10**: $[\alpha]_D^{20}$+89.0 (*c* 1, CH_2Cl_2); ^{1}H NMR δ 7.60-7.22 (m, 9H), 5.58 (bs, 1H), 5.03 (s, 2H), 4.08 (m, 1H), 2.73 (m, 1H), 2.39 (s, 3H), 1.90-1.55 (m, 2H), 1.24 (d, 3H, J = 7.0 Hz), 1.02 (t, 3H, J = 7.4 Hz); ^{13}C NMR δ 155.3, 140.9, 138.4, 136.3, 129.5, 128.2, 127.7, 127.6, 124.6, 68.2, 66.2, 47.2, 21.1, 18.7, 18.5, 12.1. **11**: $[\alpha]_D^{20}$+50.5 (*c* 0.67, CH_2Cl_2); ^{1}H NMR δ 7.42-7.22 (m, 9H), 5.25 (d, 1H, J = 7.8 Hz), 5.13 (m, 2H), 4.17 (m, 1H), 2.77 (m, 1H), 2.40 (s, 3H), 1.81-1.52 (m, 2H), 1.38 (d, 3H, J = 7.1 Hz), 8.90 (t, 3H, J = 7.5 Hz); ^{13}C NMR δ 155.2, 140.1, 139.2, 136.3, 129.2, 128.1, 127.6, 123.7, 115.6, 70.1, 66.1, 47.3, 20.8, 15.6, 14.5, 11.5. **12**: $[\alpha]_D^{20}$+46.7 (*c* 0.53, CH_2Cl_2); ^{1}H NMR δ 7.67-7.22(m, 9H), 5.11 (s, 2H), 5.06 (d, 1H, J = 9.7 Hz), 3.74 (m, 1H), 2.97 (m, 2H), 2.41 (s, 3H), 1.86 (septuplet, 1 H, J = 5.7 Hz), 0.85 (m, 6H); ^{13}C NMR δ 155.8, 141.4, 139.9, 136.3, 129.6, 128.0, 127.8, 127.5, 127.3, 124.2, 66.1, 60.6, 51.6, 31.8, 21.0, 18.2, 17.5.
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18. **Synthesis of aziridines. General procedure.** *i*) *Preparation of sulfonium salt*: To a suspension of Me_3OBF_4 (0.19 g, 1.3 mmol, 2 equiv.) in CH_2Cl_2 (10 mL) was added a solution of the corresponding sulfenyl carbamate (0.64 mmol, 1 equiv.) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 2-4 h and filtered. The filtrate was evaporate to dryness and the residue was washed several times with anhydrous diethyl ether and dried. The resulting sulfonium salt was used for the next step as such. *ii*) *Cyclization*: THF (20 mL) was added to the preceding residue and the temperature was lowered to −78 °C. Then, a 1M solution of LiHMDS (0.7 mmol, 1.1 equiv.) was added and the reaction mixture was stirred at this temperature for 45 min. The mixture was concentrated to dryness and the residue was stirred with diethyl ether (40-50 mL) and filtered. The filtrate was concentrated and the product was purified by flash chromatography. HRMS analysis of **17-20** were satisfactory. **17**: $[\alpha]_D^{20}$−21.2 (*c* 2, CH_2Cl_2); ^{1}H NMR δ 7.34 (m, 5H), 5.13 (s, 2H), 2.44 (m, 1H), 2.32 (d, 1H, J = 6.1 Hz), 1.97 (d, 1H, J = 3.8 Hz), 1.55-1.35 (m, 4H), 0.95 (t, 3H, J = 7.8 Hz); ^{13}C NMR δ 163.4, 135,8, 128.4, 128.1, 128.0, 67.9, 38.1, 34.0, 31.7, 20.0, 13.7. **18**: $[\alpha]_D^{20}$−2.12 (*c* 0.94, CH_2Cl_2); ^{1}H NMR δ 7.34 (m, 5H), 5.11 (s, 2H), 2.57 (dq, 1H, J = 6.7, 5.8Hz), 2.38 (q, 1H, J = 6.7 Hz), 1.59-1.40 (m, 2H), 1.25 (d, 3H, J = 5.8 Hz), 1.05 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 163.9, 136.1, 128.4, 128.0, 127.9, 67.7. 43.9, 37.7, 20.7, 12.7, 11.3. **19**: $[\alpha]_D^{20}$−27.0 (*c* 0.94, CH_2Cl_2); ^{1}H NMR δ 7.37 (m, 5H), 5.13 (s, 2H), 2.31 (dq, 1H, J = 3.3, 5.7 Hz), 2.16 (dt, 1H, J = 3.3, 6.1 Hz), 1.71-1.31 (m, 2 H), 1.24 (d, 3H, J = 5.7 Hz), 1.00 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 162.0, 136.0, 128.4, 128.2, 128.1, 67.7, 46.1, 39.5, 24.5, 16.1, 10.9. **20**: $[\alpha]_D^{20}$+45.0 (*c* 1, CH_2Cl_2); ^{1}H NMR δ 7.34 (m, 5H), 5.12 (s, 2H), 2.30 (d, 1H, J = 6.2 Hz), 2.24 (ddd, 1H, J = 3.8, 6.2, 7.2 Hz), 2.01 (d, 1H, J = 3.8 Hz), 1.44 (m, 1H), 1.06 (d, 3H, J = 6.7 Hz), 0.95 (d, 3H, J = 6.9 Hz); ^{13}C NMR δ 163.5, 135.8, 128.4, 128.0, 127.8, 67.8, 44.2, 30.6, 19.6, 18.8.