Chemistry of Allylsulfones: A New Preparation of *N*-Diphenylmethylene-2-Vinyl-Substituted Cyclopropylamines

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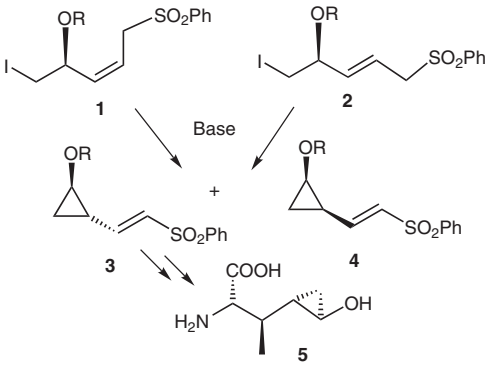
Abstract: A new methodology for the synthesis of *N*-diphenylmethylene-2-vinyl-substituted cyclopropylamines, starting from the allylsulfone **11**, is described. The starting material **11** can be obtained in both enantiomeric forms. The stereoselectivity of the cyclopropane formation has been studied by molecular modeling

Key words: cyclopropylamines, vinylsulfones, allylsulfones, cyclopropanes, Garner's aldehyde

The importance of the cyclopropylamine function in drugs such as ciprofloxacin (Ciprobay®) and moxifloxacin (Avalox®) and natural products as belactosin A,[1] together with increasing awareness of the importance of chirality in biological activity, make the asymmetric synthesis of cyclopropylamines an important area for research. In spite of this interest there are not many procedures for the synthesis of 2-substituted cyclopropylamines, the most widely used being the Curtius rearrangement,[2] cyclopropanation of N-protected enamines[3] or a Kulinkovich type reaction with dialkylamides.[4] Less exemplified is cyclopropanation with imine carbene complexes.[5] Our completely different approach to 2-vinyl-substituted amino-cyclopropanes is based upon the synthesis of cyclopropanols from allylsulfones which we have described previously (Scheme 1).[6] The vinylsulfone unit reactivity was exploited further and led to the synthesis of **5**, an amino acid analogue of glutamic acid.[10]

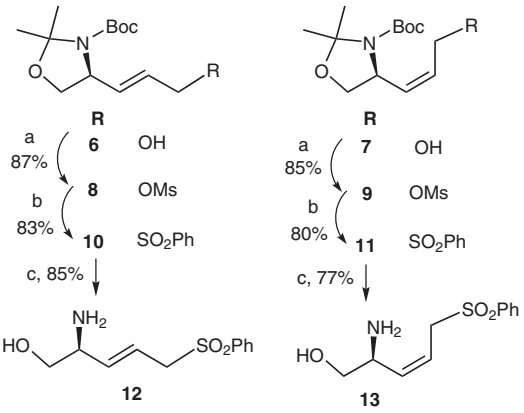
The methodology for cyclopropane formation consists of the treatment of allyl sulfones such as **1** or **2** with base, to give *trans*:*cis* cyclopropanols **3** and **4** diastereoselectively, in a ratio of 70:30 or 30:70 (depending upon the protecting groups) from **2**, and 95:5 independent of the protecting group from **1** (Scheme 1).

Due to the synthetic utility of 1,2-amino alcohols[8] and especially the use of Garner's aldehyde in the synthesis of natural and unnatural compounds with biological activity[9] we decided to apply our methodology to the synthesis of enantiomerically pure cyclopropylamines.



Scheme 1

The allylsulfones **12** and **13** were obtained by the procedure developed by our group[10] for the synthesis of allyl sulfones such as **1** or **2**, starting in this case from the previously described compounds **6** and **7** (Scheme 2).[11]



Scheme 2 *Reaction conditions*: a) MsCl, Et_3N, CH_2Cl_2, 0 °C; b) $NaSO_2Ph$, DMF, r.t.; c) MeOH, 2 N HCl, 40 °C, 12 h.

In order to apply our cyclopropane formation methodology it was necessary to protect the nitrogen with at least one electron-withdrawing group, due to the donor–acceptor character of the anticipated vinylcyclopropane products.[12] Deprotection of the acetonides of **10** and **11** under the usual conditions gave, in good yield, amino alcohols **12** and **13**. The nitrogen was protected with the standard protecting groups (Tosyl, Boc, Moc, alone or together

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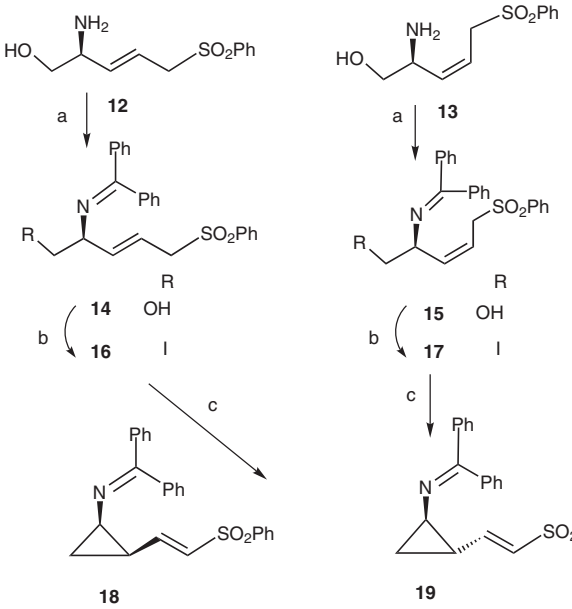
with a benzyl group) and the hydroxyl group converted to various leaving groups, but in no case did treatment with base lead to the desired cyclopropanes. With all these failures to produce the cyclopropane ring, we chose to protect the nitrogen as its diphenylmethylene derivative,[13] as used previously in the synthesis of the amino-cyclopropane moiety of belactosin by Armstrong et al.[1f] and in the synthesis of 1-amino-cyclopropane carboxylic acid in the preparation of azepines by Salaün et al.[14]

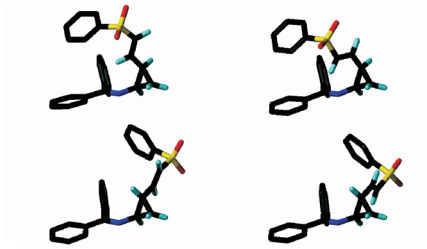
Compound **12** was protected as the diphenylmethylene derivative **14**, which was transformed without isolation (by reaction with iodide, PPh_3 and imidazole in dichloromethane) into the iodide **16**,[15] which in turn and without purification, was treated with HMDSNa to give the amino-cyclopropanes **18** and **19** stereoselectively in a 1:4 ratio. In order to increase the selectivity as we have done in the synthesis of cyclopropanols, compound **13** was synthesized analogously as for **12**, and transformed similarly into the iodide **17**. When this compound was submitted to the same conditions, only compound **19** was detected,[16] in good yield, and its structure and stereochemistry were determined by extensive NMR studies (Scheme 3).



Scheme 3 *Reaction conditions*: a) i. 2 M HCl; ii. $Ph_2C{=}NH$, CH_2Cl_2; b) I_2, PPh_3, imidazole, CH_2Cl_2; c) HMDSNa, THF, –78 °C, 38%, for the three steps.

We undertook a molecular modeling study to try to understand why the stereoselectivity was so much better for the (*Z*)-allylsulfone (such as **17**) than it had been for (*E*)-allylsulfones (such as **16**). Applying the same reasoning as we had previously found to work for the cyclopropanol formation,[7] we considered models for a late transition state for each of four possible reactions: formation of the *cis*- or *trans*-cyclopropane from either the *Z* or *E* precursor. The late transition state models were obtained by constraining the C1-C2-C3-C4 torsion in the products **18** and **19** to either 0° (for cyclization of **17**) or 180° (for cyclization of **16**), and performing a stochastic conformational[17] search including energy minimization of each conformer found with the MMFF94s forcefield.

With a torsional constraint of 400 kJ/mol, the models for the transition states for the cyclization of **16** to the *cis*- and *trans*-cyclopropane showed only a 1.4 kJ/mol difference in MMFF94s strain energy, while the transition state model for the cyclization of **17** to **19** was 5.4 kJ/mol lower in energy than that for cyclization of **17** to **18**. Very similar trends were observed with other values of the torsional constraint, suggesting that this effect is genuine, and it is easy to see in Figure 1 that the transition state model for cyclization of the *cis*-olefin **17** to the *cis*-cyclopropane **18** (upper right) is notably more crowded than the other three, with a particularly severe interaction between the vinylic proton and the imine nitrogen. It thus seems reasonable to propose that the reaction proceeds via a product-like transition state and that this poor steric interaction reduces practically to zero the amount of **17** that is converted to **18**, explaining the observed difference in stereoselectivity between cyclization of the *cis* precursor **17** and the *trans*-analogue **16**.



Late transition state models for:	
16 → 18	**17 → 18**
16 → 19	**17 → 19**

Figure 1

In conclusion, we have obtained chiral amino-cyclopropanes substituted with a vinyl sulfone, with high diastereoselectivity, which we attribute to a product-like transition state in which unfavorable interactions between C1 and the protected secondary amine are minimized. To the best of our knowledge this is the first time that amino-cyclopropanes have been synthesized in this way. The importance of 1,2-amino alcohols, the accessibility of both enantiomers of Garner's aldehyde and the versatility of the vinylsulfone group attached to the cyclopropane products make this procedure an excellent entry to the synthesis of this class of compound as building blocks for the synthesis of conformationally restricted amino acids.

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(16) **Data for Compound 19**: $[\alpha]_D^{20}$ –76.8 (*c* 1.45, $CHCl_3$). IR (film): ν_{max} = 3058, 2928, 1446, 1317, 1145, 1086, 801 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (m, 1 H, 3-Hα), 1.73 (dt, 1 H, *J* = 8.8, 4.4 Hz, 3-Hβ), 2.20 (m, 1 H, 2-H), 3.11 (ddd, 1 H, *J* = 4.4, 7.2, 9.2 Hz, 1-H), 6.33 (d, 1 H, *J* = 15.0 Hz, 2′-H), 6.46 (dd, 1 H, *J* = 9.2, 14.6 Hz, 1′-H), 7.10–7.61 (m, 13 H, Ar-), 7.84 (m, 2 H, H_{ortho}, -SO_2Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.8 (C-3), 26.1 (C-2), 46.3 (C-1), 127.4–129.1 (CH-Ar), 130.0 (C-2′), 133.1 (C_{para}, -SO_2Ph), 136.3 and 139.4 (C_{ipso}, -Ph), 141.0 (C_{ipso}, -SO_2Ph), 148.1 (C-1′), 168.7 (*C*Ph_2). MS: *m*/*z* (%) = 388 (30) [MH^+], 307 (15), 246 (35), 154 (100), 77 (55). HMRS: *m*/*z* calcd for $C_{24}H_{22}NSO_2$: 388.1371; found: 388.1321 [MH^+].

(17) The molecular modeling studies were carried out with Maestro v. 5.1.016 coupled to MacroModel v. 8.1.031, both supplied by Schrodinger, Inc. of Portland, OR, USA. Starting structures were built by sketching and were atom-typed automatically and energy-minimized using up to 5000 iterations of TNCG minimization to default convergence. The conformational search was carried out using the MCMM/Lowmode mixed method, with default settings based upon the automated setup procedure within Maestro. The conformational constraints were added manually and set to 25, 100 or 400 kJ/mol in three separate runs for each of the four models (*cis*- and *trans*-cyclopropane, and torsional constraint set to 0 or 180 degrees). The number of trials was set to 100 since at this value all the low-energy conformations were found at least 4 times. Minimizations were all achieved with up to 5000 iterations of TNCG optimization to default convergence, and all structures were successfully converged.