Synthesis of 6- and 7-Membered N-Heterocycles Using α-Phenylvinylsulfonium Salts

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Supporting Information Placeholder

Abstract: A concise synthesis of stereodefined C-substituted morpholines, piperazines, azepines and oxazepines in moderate to excellent yields (27% to 75%) is reported by reaction of 1,2- or 1,3-amino alcohol/1,2- or 1,3-diamine with an α-phenylvinylsulfonium salt. High levels of regio- and diastereoselectivity (from 2:1 to >20:1) are observed through judicious choice of base (Cs₂CO₃), and solvent (CH₂Cl₂). Reactions are performed at ambient temperature and open to air and do not require anhydrous solvent. The deprotection of the N-sulfonamide protecting groups (N-Ts and N-Ns) is also demonstrated. Factors affecting regio- and diastereocontrol are discussed.

The question “are we making the right molecules?” has hung over the pharmaceutical industry for many years. Njardarson analyzed all U.S. FDA approved small molecule drugs and found that 21% (71) contained saturated 6-membered N-heterocycles with an additional heteroatom. Clearly, morpholines and piperazines are in “the right molecules” category and this demand continues to stimulate new methods for their synthesis. Current state of the art methods for the synthesis of saturated N-heterocycles containing an additional heteroatom include Ti-mediated hydroamination/reduction, Pd-mediated carboamination, photoredox C-H arylation, nucleophilic substitution, Lewis acid catalyzed ring expansion of 3-oxetanone spirocycles, ammonium persulfate mediated S₃N₂-type ring opening of aziridines with halogenated alcohols and the SnAP reagents developed by Bode. The latter method is the most attractive in terms of generality, substitution patterns and lack of protecting groups that it can accommodate. However, the use of toxic tin reagents unfortunately detracts from the chemistry and its applicability in an industrial setting. Herein we report a new complementary method for the synthesis of di- and trisubstituted saturated N-heterocycles bearing an ethylene bridge. In order to access more substituted N-heterocycles we considered the use of vinylsulphonium salts, with either α- or β-substituents (5 and 6) (Scheme 1). However, for a successful process, the challenges of controlling both regioselectivity during the initial conjugate addition (attack through O vs. N), and


We have previously investigated the synthesis of saturated N-heterocycles bearing an additional heteroatom using vinylsulphonium salt 2 (Scheme 1). This methodology has proven to be versatile for the construction of N-heterocycles bearing an ethylene bridge. In order to access more substituted N-heterocycles we considered the use of vinylsulphonium salts, with either α- or β-substituents (5 and 6) (Scheme 1). However, for a successful process, the challenges of controlling both regioselectivity during the initial conjugate addition (attack through O vs. N), and
diastereoselectivity would need to be overcome. In this paper we describe our success in achieving these goals.

Table 1. Synthesis of substituted morpholines with 10.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>Yield (%)</th>
<th>Diastereomeric Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>67</td>
<td>13:1</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>(R)-Me</td>
<td>H</td>
<td>(S)-Ph</td>
<td>53</td>
<td>21:1</td>
</tr>
<tr>
<td>3</td>
<td>9c</td>
<td>(S)-Bn</td>
<td>H</td>
<td>H</td>
<td>59</td>
<td>8:1</td>
</tr>
</tbody>
</table>

(a) Isolated yields. (b) Diastereoselectivity was determined from ^1H NMR of the crude reaction mixtures.

Initially, we investigated the annulation of 1,2-aminoalcohols 9a-c with the known β-phenylvinylsulphonium salt 10. Treatment of 9a-c with DBU as a base, gave morpholines 11a-c in good yields and with complete regioselectivity (conjugate addition through O rather than N) (Table 1, entries 1-3). Although the initial results were promising these reactions suffered from several problems highlighting some of the challenges faced. Incomplete conversion was observed for all substrates, and a competing side reaction involving elimination of the intermediate sulfonium salt was also observed, leading to the isolation of side-products 12a-c. Furthermore, both morpholines 11b and 11c were formed as ~1:1 mixtures of diastereomers.

We then investigated α-phenylvinylsulphonium salt 13. Initial reaction screening focused on the (R)-alanine-derived N-tosyl protected amino alcohol 14. Treatment of 14 with 13, in the presence of DBU as the base (Table 2, entry 1) led to the formation of the desired compound 15, albeit in poor yield as a mixture of isomers. An improvement in yield was achieved through batch-wise addition of 13 (Table 2, entry 2). Preparative HPLC separation and analysis of the two major isomers by ^13C/HSQC NMR indicated that a 2:1 mixture of regioisomers had been formed. The relative stereochemistry of the major regioisomer was confirmed by X-ray crystallography (cis-15a) and the relative stereochemistry of the minor regioisomer was determined to be cis-15b through analysis of JHH coupling constants. These initial results also confirmed that excellent levels of diastereoselectivity were observed. Further optimization of the reaction conditions eventually revealed Cs2CO3/CH2Cl2 as the base and solvent of choice for this reaction. Pleasingly, this base and solvent system led to complete regioselectivity, with conjugate addition occurring through O, generating almost exclusively cis-15a (Table 2, entries 3-6, see SI for full optimisation table). Batch-wise addition of both Cs2CO3 and 13 was necessary to ensure that the reaction went to completion, due to competing decomposition of 13 under the reaction conditions over time. The operational simplicity of the reaction should also be noted, allowing the chemistry to be performed over short reaction times, open to air and on a gram scale (Table 2, entry 6).

Table 2. Optimization of reaction conditions with 13.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>13 (equiv.)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>Isomeric Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU (3.5)</td>
<td>1</td>
<td>24</td>
<td>rt</td>
<td>9</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>DBU (3.5)</td>
<td>2 x 1</td>
<td>24</td>
<td>0 then rt</td>
<td>45</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>Cs2CO3 (3.5)</td>
<td>1</td>
<td>24</td>
<td>rt</td>
<td>18</td>
<td>20:1</td>
</tr>
<tr>
<td>4</td>
<td>Cs2CO3 (3.5)</td>
<td>3</td>
<td>24</td>
<td>rt</td>
<td>64</td>
<td>20:1</td>
</tr>
<tr>
<td>5</td>
<td>Cs2CO3 (2 x 2)</td>
<td>3</td>
<td>6</td>
<td>rt</td>
<td>71</td>
<td>20:1</td>
</tr>
<tr>
<td>6</td>
<td>Cs2CO3 (2 x 2)</td>
<td>2 x 1</td>
<td>6</td>
<td>rt</td>
<td>76</td>
<td>20:1</td>
</tr>
</tbody>
</table>

(a) ^1H NMR yields of 15 calculated from the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. (b) Isomeric ratio represents the ratio of the two major isomers formed during the reaction (15a and 15b). (c) Isolated yield in parentheses. (d) Identical reaction performed on gram scale open to air using benzene/CH2Cl2 as the solvent gave 77% (72%) of 15. (See SI for full optimisation table).

With an optimized procedure in hand, the substrate scope of the reaction was then investigated (Scheme 3). Amino-alcohols derived from enantiopure amino acids valine 16a, phenylalanine 16b, tryptophan 16c and serine 16d all underwent the desired transformation to give morpholines 17a-d in excellent yields and with excellent regio/diastereoselectivity. Furthermore, 16a-c could be isolated as single isomers by recrystallization, albeit in slightly reduced yields. In contrast to substrates 17a-d, the tert-butyl ester morpholine 17e was formed as a 2:1 mixture of regioisomers, which we were unable to separate. More hindered substrates 16f and 16g also participated in the reaction to give the desired morpholines 17f and 17g in good yields, with excellent regioselectivities. Unfortunately, under these optimized conditions substrates bearing the following protecting groups - Boc, Cbz, Troc, Bn, COCl2, or unprotected nitrogen, failed, giving either unreacted starting material or polar compounds which could not be identified. However, the related nosyl15 protected amino-alcohol 16h was compatible, giving morpholine 17h in slightly lower yield and with lower regioselectivity in comparison to the
The methodology is also applicable to substrates 16i-k with substituents α to oxygen and/or nitrogen leading to the formation of di- and tri-substituted morpholines 17i-k in good yields and with moderate selectivities. For substrate 17k, excellent regioselectivity was achieved, but lower diastereoselectivity was observed. The synthesis of C-substituted piperazines was also possible starting from 1,2-diamine substrates 16l-n. The corresponding piperazines 17l-n were formed in good yields and with good diastereo- (17l) and regioselectivities (17m) for some substrates, but low diastereoselectivities for others (17n). Finally, the application of α-phenylvinlysulphonium salt 13 to the synthesis of substituted azepines and oxazepines was also conducted and the 7-membered heterocycles 17o and 17p were formed in moderate yields but very high regioselectivity.

Scheme 2. Rationale for the observed regio- and diastereoselectivity.

A rationale for the observed regio- and diastereoselectivities is proposed (Scheme 2). The observed regioselectivity results from a faster rate of reaction of the more nucleophilic oxygen nucleophile, despite its lower concentration [TsNH (pK_a 17 DMSO) vs. OH (pK_a 30 DMSO)]. The diastereoselectivity of this transformation is set during the S_N_Ar displacement, which proceeds through two diastereomeric transition states A and B. The major diastereomer results from placing all substituents in pseudo-equatorial positions (A) whilst the minor diastereomer results from placing the phenyl group in a pseudo-axial position (B). The cyclized product C then ring flips because of unfavourable gauche interactions to give the major isomer cis-15a. Although cis-15a has an unfavourable 1,3-diaxial interaction, this conformation is observed in solution [3J_HH PhCH (d, J 4.0 Hz)]. Conformer C would be expected to have one large 3J_HH (ax-ax) and one small coupling 3J_HH (ax-eq) which are not observed. We have observed similar effects in thiomorpholines previously.18

To demonstrate synthetic utility, N-Ts morpholine cis-15a was deprotected using a sodium/naphthalene reduction, and isolated as the hydrochloride salt 18 in excellent yield, as a single diastereoisomer. The S_N_Ar deprotection of N-Ns morpholine cis-17h with 2-mercaptoethanol and DBU was
also achieved leading to the HCl salt 18 in excellent yield. As signals overlapped in the $^1$H NMR of 18, it was Boc protected to give 19 which allowed the coupling constants to be measured; these showed a good correlation with the parent N-sulfonamides cis-15a and cis-17h.

**Scheme 3. Deprotection of morpholines.**

![Diagram of Scheme 3. Deprotection of morpholines.]

Conditions A: Na/naphthalene (3 equiv.), DME (0.1 m), –78 °C, 30 min. (B) 2-mercaptoethanol (2 equiv.), DBU (2 equiv.), acetone (0.2 m), rt, 30 min. (C) HCl (1 m in Et,O, 1.5 equiv.), rt, 5 min.

In conclusion, we have developed a highly practical route to stereodefined C-substituted morpholines, piperazines, azepines and oxazepines to excellent yields, using our recently developed α-phenylvinsulphonium salt 13. The method exhibits high levels of regio- and diastereoselectivity and is operationally simple. Reactions are conducted open to air, with non-anhydrous solvents, on gram-scale using readily available starting materials and reagents. The methodology enables rapid construction of spatially-defined substituents and heteroatoms in small molecules from flexible acyclic precursors – features which will resonate with drug discovery programs.

**ASSOCIATED CONTENT**

**SUPPORTING INFORMATION**

Experimental procedures and spectroscopic data for all novel compounds. The Supporting Information is available at DOI: 10.1021/……

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**Notes**

The authors declare no competing financial interests.

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**REFERENCES**

(3) 1,595 small molecule drugs analysed, of these, 640 contain N-heterocyclic rings. Within this data set, 21% (71 compounds) contain morpholine or piperazine rings.
TOC Graphical Abstract

\[
\begin{align*}
R^2_1 & \overset{XH}{\underset{\text{PG}}{\overset{\text{NH}}{\underset{\text{PG}}{\text{R}^1_1}}}} + \overset{\text{Ph}}{\overset{\text{S}}{\overset{\text{BPh}_4}{\text{S}}}} \\
& \overset{\text{C}_6\text{H}_5\text{CO}_3}{\overset{\text{CH}_2\text{Cl}_2}{\overset{\text{rt, 1-24 h}}{\text{Open Flask}}}} \\
& \overset{\text{Gram Scale}}{\overset{\text{Operationally Simple}}{\text{R}^2_1}} \overset{X}{\overset{\text{PG}}{\underset{\text{PG}}{\text{R}^1_1}}}
\end{align*}
\]

\(X = \text{O, N-PG, S}\)
\(n = 1, 2\)

17 Examples
2:1 to >20:1 isomeric ratio
(regio- and diastereoselectivity)