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

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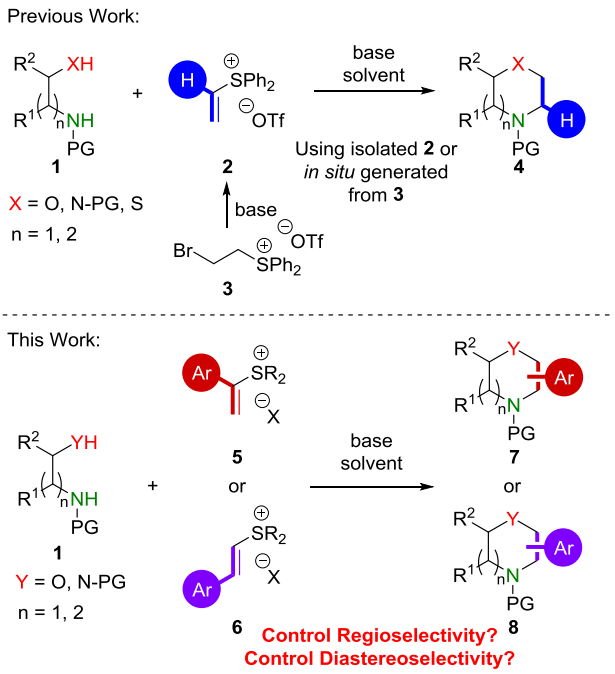
Supporting Information Placeholder

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 (Cs_2CO_3), and solvent (CH_2Cl_2). 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.[1] Njardarson analyzed all U.S. FDA approved small molecule drugs[2] and found that 21% (71)[3] 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,[4] Pd-mediated carboamination,[5] photoredox C-H arylation,[6] nucleophilic substitution,[7] Lewis acid catalyzed ring expansion of 3-oxetanone spirocycles,[8] ammonium persulfate mediated S_N2-type ring opening of aziridines with halogenated alcohols[9] and the SnAP reagents developed by Bode.[10] 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 a second heteroatom with very high regio- and diastereo-control, using our recently developed *α*-arylvinylsulfonium salt.[11]

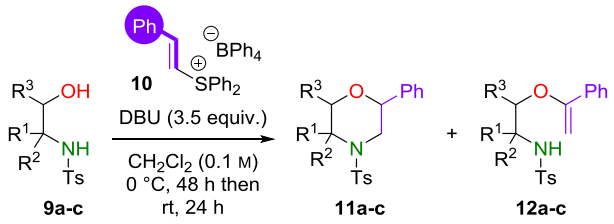
We have previously investigated the synthesis of saturated *N*-heterocycles bearing an additional heteroatom using vinylsulfonium salt **2** (Scheme 1).[7,12] This methodology has proven to be versatile for the construction of *N*-heterocycles bearing an ethylene bridge.[13] In order to access more substituted *N*-heterocycles we considered the use of vinylsulfonium 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

Scheme 1. Synthesis of saturated *N,X*-heterocycles using vinylsulfonium salts.



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.



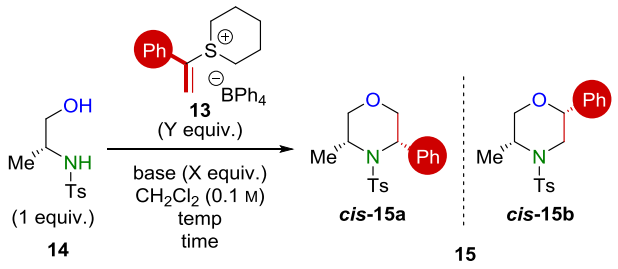
entry	substrate	R^1	R^2	R^3	**11** (%)[a]	**12** (%)[a]	dr[b]
1	**9a**	Me	Me	H	67	13	-
2	**9b**	(*R*)-Me	H	(*S*)-Ph	53	21	1.1:1
3	**9c**	(*S*)-Bn	H	H	59	8	1.5:1

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

Initially, we investigated the annulation of 1,2-amino-alcohols **9a-c** with the known *β*-phenylvinylsulfonium salt **10**.[14] 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*-phenylvinylsulfonium salt **13**.[11] 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 ^{13}C/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 $^3J_{HH}$ coupling constants. These initial results also confirmed that excellent levels of diastereoselectivity were observed. Further optimization of the reaction conditions eventually revealed Cs_2CO_3/CH_2Cl_2 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 Cs_2CO_3 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.

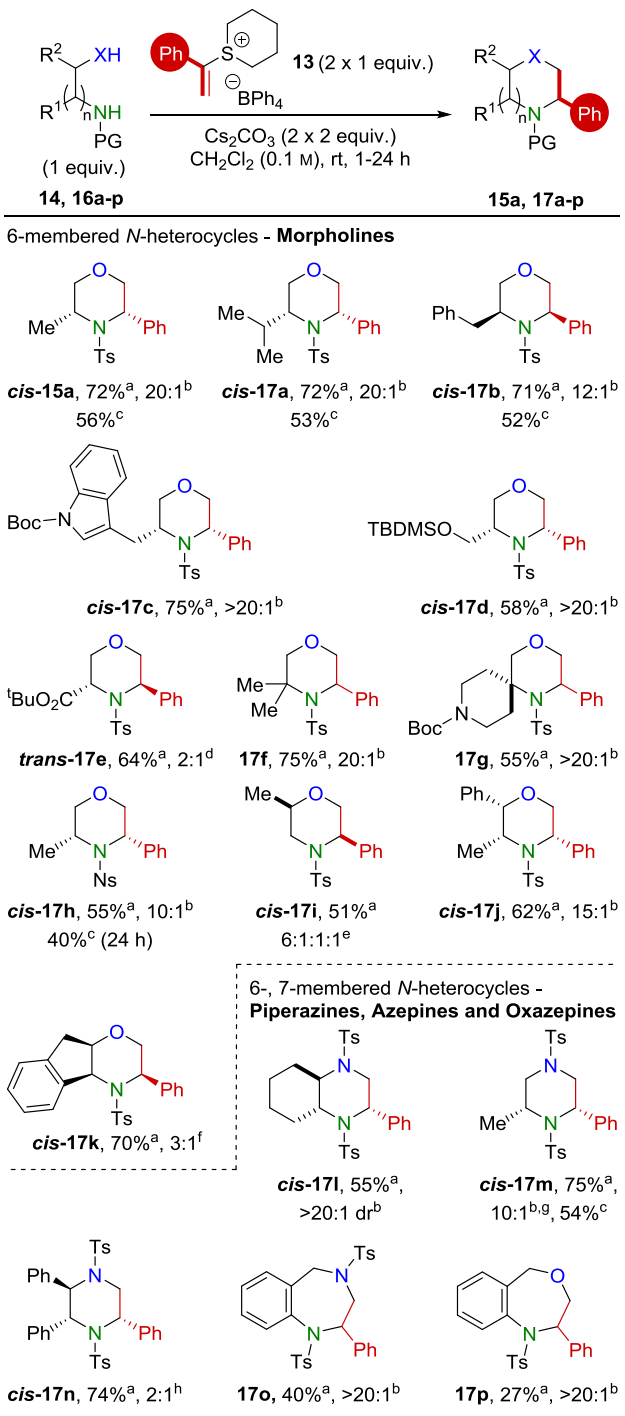


entry	base (equiv.)	**13** (equiv.)	time (h)	temp (°C)	**15** (%)[a]	isomeric ratio[b] **15a**:**15b**
1	DBU (3.5)	1.2	24	rt	9	2:1
2	DBU (3.5)	2 × 1	24	0 then rt	45	2:1
3	Cs_2CO_3 (3.5)	1.2	24	rt	18	20:1
4	Cs_2CO_3 (3.5)	3	24	rt	64	20:1
5	Cs_2CO_3 (2 × 2)	3	6	rt	71	20:1
6	Cs_2CO_3 (2 × 2)	2 × 1	6	rt	76 (73)[c,d]	20:1

(a) ^{1}H NMR yields of **15** calculated from the crude reaction mixture using 1,3,5-trimethyoxybenzene 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 bench CH_2Cl_2 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, $COCF_3$, or unprotected nitrogen, failed, giving either unreacted starting material or polar compounds which could not be identified. However, the related nosyl[15] protected amino-alcohol **16h** was compatible, giving morpholine **17h** in slightly lower yield and with lower regioselectivity in comparison to the

Scheme 3. Substrate scope.

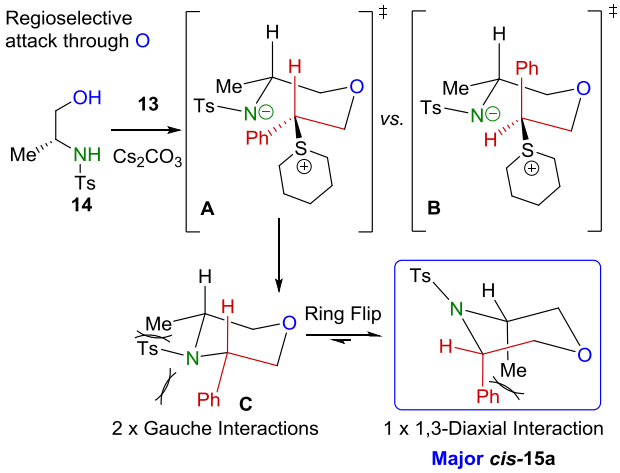


(a) Isolated yield after column chromatography. (b) Ratio of regioisomers determined from the 1H NMR of the crude reaction mixtures prior to purification. (c) Isolated yield after recrystallization to obtain a single regioisomer. (d) trans-17e was formed as a 1:1 mixture of diastereomers (see SI). The yield reported is the isolated yield after recrystallization which lead to an enrichment of the trans-17e diastereomer. (e) cis-17i was formed as a 6:1:1:1 mixture of regioisomers and diastereomers. (f) cis-17k was formed as a 3:1 mixture of diastereomers. (g) NOE and 3JHH analysis was used to confirm the relative stereochemistry of cis-17m. (h) cis-17n was formed as a 2:1 mixture of diastereomers as determined by analysis of 3JHH coupling constants (see SI).

tosyl protected amino-alcohol **14**.

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-phenylvinylsulfonium 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.

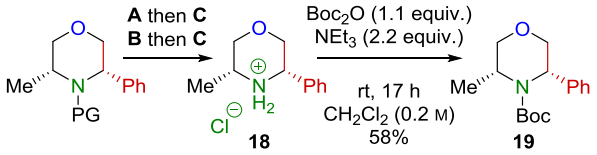


A rationale for the observed regio- and diastereoselectivities is proposed (Scheme 2). The observed regioselectivity results from a faster rate of reaction of the more nucleophilic oxygen nucleophile, despite its lower concentration [TsNH (pK_a 17 DMSO[16]) *vs.* OH (pK_a 30 DMSO[17])]. The diastereoselectivity of this transformation is set during the S_N2 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 [$^3J_{HH}$ PhC*H* (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_NAr deprotection of *N*-Ns morpholine ***cis*-17h** with 2-mercaptoethanol and DBU[19] 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.



PG = Ts ***cis*-15a**, **A** then **C**: 86% over 2 steps
PG = Ns ***cis*-17h**, **B** then **C**: 92% over 2 steps

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_2O, 1.5 equiv.), rt, 5 min.

In conclusion, we have developed a highly practical route to stereodefined *C*-substituted morpholines, piperazines, azepines and oxazepines in moderate to excellent yields, using our recently developed *α*-phenylvinylsulfonium 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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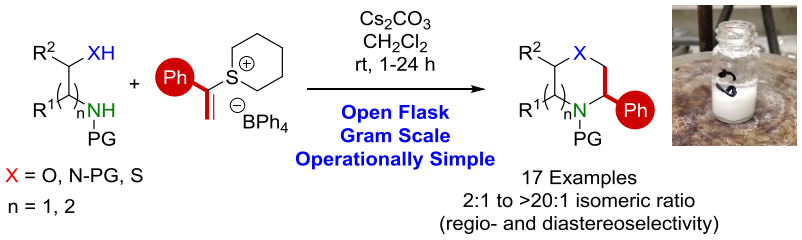
TOC Graphical Abstract



X = O, N-PG, S

n = 1, 2

17 Examples

2:1 to >20:1 isomeric ratio

(regio- and diastereoselectivity)