ORGANIC LETTERS

2009
Vol. 11, No. 2
257−260

Bromoethylsulfonium Salt—A More Effective Annulation Agent for the Synthesis of 6- and 7-Membered 1,4-Heterocyclic Compounds

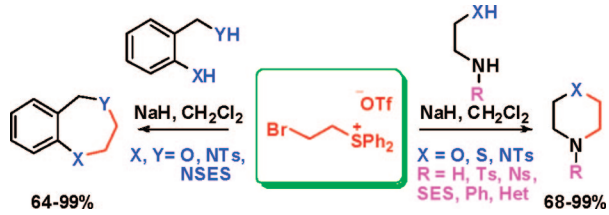
Muhammad Yar, Eoghan M. McGarrigle,* and Varinder K. Aggarwal*

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, United Kingdom

v.aggarwal@bristol.ac.uk

Received October 14, 2008

ABSTRACT

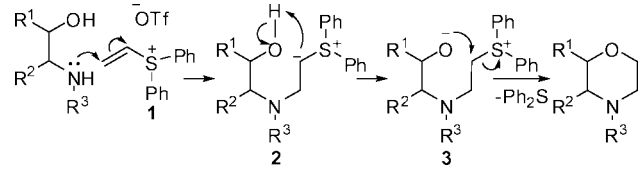


Reaction of bromoethylsulfonium salt with 1,2-/1,3-aminoalcohols gave six- and seven-membered rings in good-to-excellent yields. The reactions proceed through generation of a vinyl sulfonium salt followed by annulation to give 1,4-heterocyclic compounds such as morpholines and benzoxazepines in a simple procedure. The method accommodates a range of nitrogen substituents and the amino alcohol can be substituted by amino thiols and diamines to give thiomorpholines, piperazines and benzodiazepines.

Heterocyclic compounds particularly morpholines, thiomorpholines and piperazines are some of the most important biologically active compounds.[1] However, the synthesis of such compounds in an efficient and straightforward manner is not trivial. For instance when using 1,2-dihaloderivatives to create the heterocycle low yields and side-reactions are often reported.[2]

As part of our ongoing research into the chemistry of vinyl sulfonium salts[3] we recently reported an efficient method for the synthesis of these pharmacologically important components from β-heteroamino compounds.[4] A range of *N*-tosyl morpholines were synthesized in good yield from the reaction of β-amino alcohols with diphenyl vinyl sulfonium salt **1**. The proposed mechanism for the reaction is shown in Scheme 1. The cascade of events is initiated by

Scheme 1. Proposed Mechanism for Morpholine Synthesis Using Vinyl Sulfonium Salt **1**



(1) For a review see: (a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641–662. For recent examples see: (b) Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, 2100–2106. (c) D'hooghe, M.; Vanlangendonck, T.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 4678–4681. (d) Pedrosa, R.; Andrés, C.; Mendiguchía, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 8854–8863. (e) Wilkinson, M. C. *Tetrahedron Lett.* **2005**, *46*, 4773–4775. (f) Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045–1047.

(2) (a) Chiu, H.; Lin, Y. C.; Cheng, C. Y.; Tsai, M. C.; Yu, H. C. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 383–393. (b) Kashima, C.; Harada, K. *J. Chem. Soc., Perkin. Trans. 1* **1988**, 1521–1526. (c) Liang, P. H.; Hsin, L. W.; Cheng, C. Y. *Bioorg. Med. Chem.* **2002**, *10*, 3267–3276. (d) Sakai, K.; Yoneda, N. *Chem. Pharm. Bull.* **1981**, *29*, 1554–1560. (e) Bhatt, U.; Just, G. *Helv. Chim. Acta* **2000**, *83*, 722–727.

10.1021/ol8023727 CCC: $40.75
Published on Web 12/12/2008

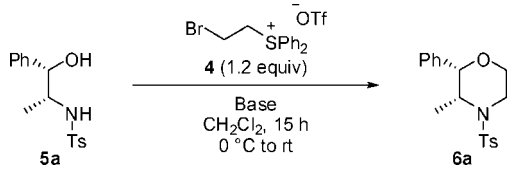
nucleophilic attack of the amide on the electrophilic sulfonium salt which forms an intermediate sulfur ylide **2**.[5] A proton transfer unmasks a second electrophilic center and creates a potent nucleophile, leading to the heteroatom displacing the sulfide from **3** and forming the desired heterocyclic product.

Although this method was highly effective for a range of *N*-tosyl amino alcohols, it suffers from the need to prepare and isolate the sensitive, oily vinyl sulfonium salt—an especially challenging problem on a large scale. We now report that in fact this annulation chemistry can be conducted with the stable crystalline salt **4** which is easily prepared on a large scale, and that the reaction is no longer limited to tosyl sulfonamides. Furthermore, we have extended the scope of this annulation reaction to include the pharmacologically important 7-membered ring heterocycles (e.g., benzodiazepines).

As noted above, the main problem associated with the annulation reaction shown in Scheme 1 was the sensitive nature of the oily vinyl sulfonium salt **1**. Since the vinyl sulfonium salt is generated by base from bromoethylsulfonium salt **4** and base is employed in the annulation reaction we wondered whether the sulfonium salt **4** could be used directly in the process. This would have a major advantage since the salt **4** is a free-flowing crystalline material, easy to handle, facile to prepare on a large scale, and now commercially available.[6]

Initial investigations focused on identifying a suitable base for the proposed in situ protocol (Table 1) using the easily

Table 1. Optimization of the Base in the Annulation Protocol Using the Bromoethyl Sulfonium Salt **4**

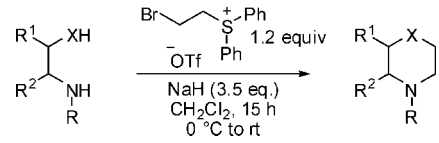


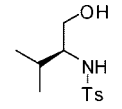
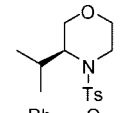
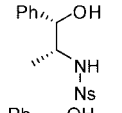
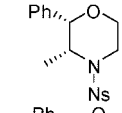
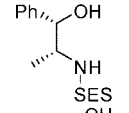
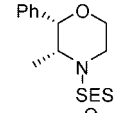
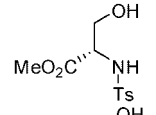
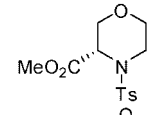
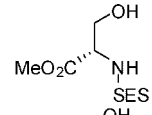
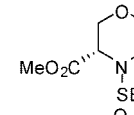
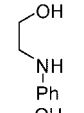
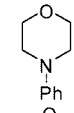
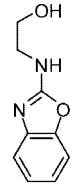
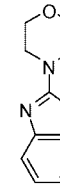
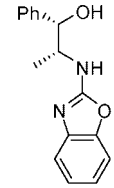
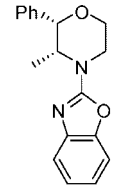
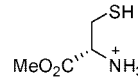
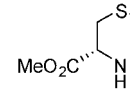
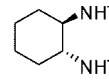
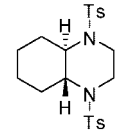
entry	base	equiv	yield (%)
1	Et_3N	6	30
2	DBU	6	74
3	NaH	6	72
4	DBU	3.5	86
5	**NaH**	**3.5**	**87**
6	DBU	3.1	77
7	NaH	3.1	71

accessible norephedrine-derived sulfonamide **5a** as a model substrate. The required morpholine **6a** was obtained in good yield using bases such as NaH and DBU (entries 2 and 3) but not with Et_3N (entry 1), which had been the base of choice in our earlier studies using **1**. The poor performance is presumably due to Et_3N not promoting a clean elimination process in the conversion of bromoethyl sulfonium salt to the vinyl sulfonium salt. The yields were further optimized by adjusting the number of equivalents of base and it was found that 3.5 equiv gave the best yields (entries 4 and 5).

Having found suitable conditions, the scope of this new methodology was explored (Table 2). As with the method

Table 2. Scope of the Annulation Reaction Using Bromoethyl Sulfonium Salt **4**



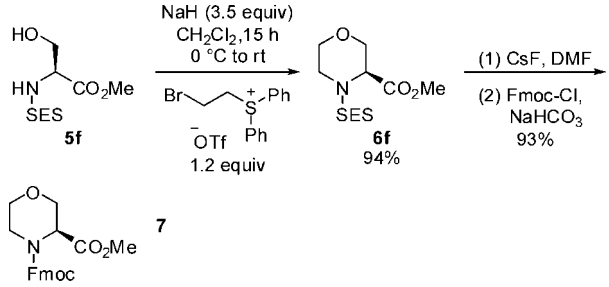
entry	substrate		product		yield (%)
1		**5b**		**6b**	93
2		**5c**		**6c**	89 [a]
3		**5d**		**6d**	93
4		**5e**		**6e**	93
5		**5f**		**6f**	94
6		**5g**		**6g**	92 [b]
7		**5h**		**6h**	92 [c]
8		**5i**		**6i**	68 [d]
9		**5j**		**6j**	99
10		**5k**		**6k**	98

[a] 2.5 equiv of **4**. [b] 2.5 equiv of **4** and 5 equiv of NaH. [c] 2.5 equiv of **4** and 7.5 equiv of NaH. [d] 3.75 equiv **4** and 7.5 equiv of NaH.

using preformed **1**, *N*-sulfonyl-protected amino alcohols were converted into morpholines in good-to-excellent yields (entries 1, 2 and 4). However the methodology is no longer

limited to tosyl sulfonamides.[7] For instance, the more easily cleaved SES group[8] was also found to be suitable, giving access to *N*-SES-substituted morpholines (entries 3 and 5). The SES-protected morpholine **6f** (from entry 5, Table 2) was easily converted to the Fmoc-protected morpholine **7**, an important building block for a range of biologically active compounds (Scheme 2).[9] In a broad ranging study of the

Scheme 2. Application of Methodology to the Synthesis of Fmoc-Morpholine (3*S*) Carboxylate **7**



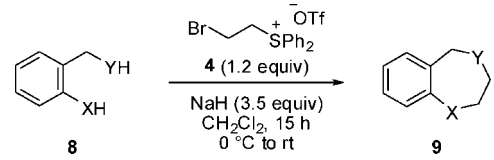
range of N-substituents[10] that were compatible with the annulation process it was discovered that *N*-aryl groups could successfully be employed. Thus treatment of *N*-aromatic and *N*-heteroaromatic β-amino alcohols with bromoethyl sulfonium salt and NaH in CH_2Cl_2 yielded the required morpholines in good-to-excellent yields (entries 6, 7 and 8). Morpholines with *N*-aromatic and *N*-heteroaromatic groups are common motifs in molecules of pharmaceutical interest,[1] and this new methodology provides a facile route for their preparation.

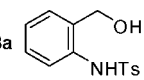
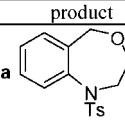
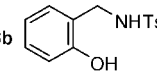
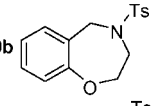
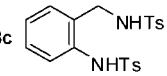
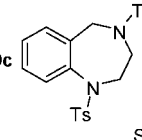
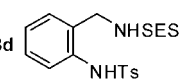
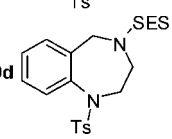
This simple method was also effective for the synthesis of thiomorpholines[11] and piperazines from β-amino thiol and bis-tosylamides, respectively, in excellent yields (entries 9 and 10). Moreover, no chromatography was required for the purification of thiomorpholine, which was isolated as its HCl salt after the work up. It is noteworthy that no racemization of potentially labile chiral centers bearing acidic protons was detected under these mild conditions (entries 4, 5 and 9).

Although one can draw a plausible mechanism involving successive S_N2 displacements of diphenylsulfide and bromide from **4**, we believe that the reactions proceed through formation of vinyl sulfonium salt **1** followed by conjugate addition to **1** as in Scheme 1. Indeed, by monitoring the reaction using ^{1}H NMR, **1** was clearly identified.[12]

Finally, after the successful application of this methodology to the synthesis of 6-membered 1,4-heterocyclic compounds, its extension to the synthesis of more challenging 7-membered heterocycles[13] **9** was explored. Such compounds, especially when fused to an aromatic group, represent a "privileged motif" in medicinal chemistry.[14−18] For example, the 1,4-benzodiazepine family show a broad spectrum of therapeutic activity[19] including dampening of the central nervous system (e.g., valium), muscle relaxant, antibiotic, antiulcer, anti-HIV agent, and Ras farnesyltransferase inhibitors. We therefore targeted tetrahydro 1,4-benzodiazepines and 1,4-benzoxazepines in our study. Gratifyingly, employing *N*-tosyl 1,3-amino alcohols and 1,3-diamines in this simple protocol yielded 1,4-oxazepines and 1,4-diazepines in moderate-to-excellent yields (Table 3). The

Table 3. Synthesis of 1,4-Benzoxazepines and 1,4-Benzodiazepines



entry	substrate	product	yield (%)
1	**8a** 	**9a** 	99 [a]
2	**8b** 	**9b** 	64
3	**8c** 	**9c** 	99
4	**8d** 	**9d** 	99

[a] 2.2 equiv of bromoethyl sulfonium salt and 5.5 equiv of NaH are used.

(3) For vinyl sulfonium salts see: (a) Kokotos, C. G.; McGarrigle, E. M.; Aggarwal, V. K. *Synlett* **2008**, 2191–2195. (b) Unthank, M. G.; Tavassoli, B.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 1501–1504. (c) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7066–7069; *Angew. Chem.* **2006**, *118*, 7224−7227. (d) Kim, K.; Jimenez, L. S. *Tetrahedron: Asymmetry* **2001**, *12*, 999–1005, and references therein. (e) Wang, Y.; Zhang, W.; Colandrea, V. J.; Jimenez, L. S. *Tetrahedron* **1999**, *55*, 10659–10672. For epoxidation reactions of butadienylsulfonium salts, see: (f) Rowbottom, M. W.; Mathews, N.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3927–3929. For recent examples of the application of vinyl phosphonium salts see: (g) Kumarn, S.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2006**, 3211–3213.

(4) (a) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784–3786. *Angew. Chem.* 2008, *120*, 3844−3846; For an application see: (b) Hansch, M.; Illa, O.; McGarrigle, E. M.; Aggarwal, V. K. *Chem. Asian J.* **2008**, *3*, 1657–1663.

(5) For a recent review on the use of ylides in reactions that form rings other than 3-membered rings see: Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937–948.

(6) This salt is now commercially available from Aldrich.

(7) Nucleophiles with *two acidic protons on the same atom* have been shown to react with vinyl sulfonium salts to give 3-membered rings (e.g., primary amines give aziridines): see ref 4a and (a) Gosselck, J.; Béress, L.; Schenk, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 596–597; *Angew. Chem.* **1966**, *78*, 606. (b) Johnson, C. R.; Lockard, J. P. *Tetrahedron Lett.* **1971**, *12*, 4589–4592. (c) Takaki, K.; Agawa, T. *J. Org. Chem.* **1977**, *42*, 3303–3304. (d) Matsuo, J.; Yamanaka, H.; Kawana, A.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 392–393. Where the nucleophile can be resonance-stabilized forming an enolate, 5-membered rings have also been obtained: (e) Braun, H.; Huber, G. *Tetrahedron Lett.* **1976**, *17*, 2121–2124. (f) Batty, J. W.; Howes, P. D.; Stirling, C. J. M. *J. Chem. Soc., Perkin 1* **1973,** 65–68; ref 7b.

(8) Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099–2102.

mixed *N*-tosyl/*N*-SES 1,3-diamine **8d** was also employed and again the 1,4-diazepine **9d** was formed in excellent yield. This heterocycle bears orthogonally protected amines which can be deprotected and derivatized as required.

In summary, a new protocol for the efficient synthesis of 6- and 7-membered heterocyclic compounds from readily available amino alcohols/thiols and diamines has been described. This methodology shows considerable scope as a wide range of amino substituents can be used in the reaction. Bromoethyl sulfonium salt **4** was employed as an effective reagent to generate vinyl sulfonium salt **1** in situ for this simple annulation reaction. Pharmacologically important morpholines, thiomorpholines, piperazines, benzoxazepines and benzodiazepines were obtained in good-to-excellent yields using this practical, mild procedure.

Acknowledgment. M.Y. thanks the Higher Education Commission of Pakistan for support of a studentship. V.K.A. thanks the Royal Society for a Wolfson Research Merit Award, the EPSRC for a Senior Research Fellowship, and Merck for research support. We thank Dr. Matt Unthank (GSK, Tonbridge, UK) for helpful discussions.

Supporting Information Available: Experimental procedures and characterization data including NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8023727

(9) (a) Sladojevich, F.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2007**, *72*, 4254–4257. (b) Levin, J. I.; Chen, J. M.; Laakso, L. M.; Du, M.; Du, X.; Venkatesan, A. M.; Sandanayaka, V.; Zask, A.; Xu, J.; Xu, W.; Zhang, Y.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4345–4349. (c) Almstead, N. G.; Bradley, R. S.; Pikul, S.; De, B.; Natchus, M. G.; Taiwo, Y. O.; Gu, F.; Williams, L. E.; Hynd, B. A.; Janusz, M. J.; Dunaway, C. M.; Mieling, G. E. *J. Med. Chem.* **1999**, *42*, 4547–4562. (d) Chiba, J.; Machinaga, N.; Takashi, T.; Ejima, A.; Takayama, G.; Yokoyama, M.; Nakayama, A.; Baldwin, J. J.; McDonald, E.; Saionz, K. W.; Swanson, R.; Hussain, Z.; Wong, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 41–45.

(10) In our previous study, it was found that amides and carbamates were not compatible with this methodology. See ref 4a for details.

(11) In the case of 1,2-aminothiols primary amines can be employed without aziridine formation since the more nucleophilic thiol adds to the vinyl sulfonium salt first.

(12) Mechanistically it is unclear why 3.5 equiv of NaH are required, but the use of less NaH gave lower yields of cyclized product, together with protonated **2** [see ref 4a].

(13) For leading references on 7-membered heterocycles see: Bremner, J. B.; Samosorn, S. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2008; Vol. 19, Chapter 7.

(14) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65–85.

(15) Lee, S.-C.; Park, S. B. *Chem. Commun.* **2007**, 3714–3716.

(16) Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem.* **1996**, *39*, 3539–3546.

(17) Ishihara, Y.; Hirai, K.; Miyamoto, M.; Goto, G. *J. Med. Chem.* **1994**, *37*, 2292–2299.

(18) Welmaker, G. S.; Sabalski, J. E. *Tetrahedron Lett.* **2004**, *45*, 4851–4854.

(19) See reference 14 for leading references.