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ARTICLE *in* ANGEWANDTE CHEMIE INTERNATIONAL EDITION · SEPTEMBER 2008

Impact Factor: 11.26 · DOI: 10.1002/anie.200800373 · Source: PubMed

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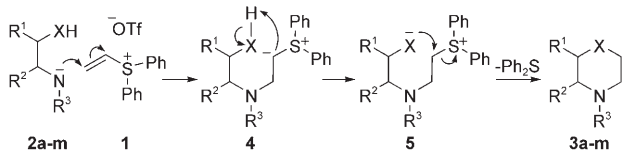
DOI: 10.1002/anie.200800373

An Annulation Reaction for the Synthesis of Morpholines, Thiomorpholines, and Piperazines from β-Heteroatom Amino Compounds and Vinyl Sulfonium Salts**

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

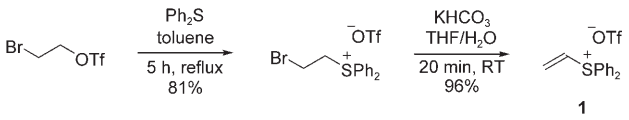
The nitrogen-containing heterocycles comprising morpholines, thiomorpholines, and piperazines are some of the most important pharmacophores in medicinal chemistry.[1] However, the direct synthesis of such compounds by alkylation of β-amino alcohols/thiols/amines with 1,2-dihalo derivatives is often fraught with low yields and side reactions.[2] 1,2-Dihalogen derivatives are generally poor electrophiles and reactions are often accompanied by competing elimination processes. A solution to this problem is to carry out a three-step sequence employing an α-halogen acid halide as the electrophile.[3] Following amide formation and intramolecular alkylation, reduction finally furnishes the required heterocycles. Herein, we describe the application of a novel concept to prepare these pharmacologically important heterocycles from β-amino alcohols/thiols/amines in one step and high yield.

We reasoned that soft electrophiles operating under less basic conditions would minimize competing elimination pathways and therefore considered the possibility of employing Michael acceptors. This led us to vinyl onium salts (e.g., **1**). We expected that, following conjugate addition of one of the heteroatoms, an ylide **4** would be generated that could undergo proton transfer with the other heteroatom (Scheme 1). The heteroatom anion generated, **5**, would then attack the onium ion electrophile to effect ring-closure and produce the required heterocycle. Although vinyl onium salts have been employed in three-component coupling reactions with nucleophiles and electrophiles,[4] their potential to react according to the pathway shown in Scheme 1 has not previously been recognized.[5]



Scheme 1. Proposed annulation reaction for heterocycle synthesis mediated by vinyl sulfonium salt **1**.

Of the readily available vinyl onium salts, it was thought that sulfonium and phosphonium would be better at promoting the conjugate addition step than ammonium since the ylide intermediate is better stabilized.[6] However, to promote cyclization leaving group ability of the onium is critical and this falls in the order S > N ≫ P.[7] These considerations led us to examine vinyl sulfonium salts, and in particular diphenyl vinyl sulfonium salt **1**.[4c,8] This salt was easily prepared through a modified procedure as shown in Scheme 2.[9] In this modification, the conventional 5 day reflux has been replaced by a 5 h reflux using toluene in place of CH_2Cl_2 and the Ag_2O base has been replaced with inexpensive $KHCO_3$ in a THF/H_2O mixture. After a short reaction time clean elimination occurred with this base although after a few hours the product of water addition began to be observed.[10]



Scheme 2. Synthesis of diphenyl vinyl sulfonium salt **1**.

A range of amino alcohols **2a–f** bearing sulfonamide residues[11] with different degrees of substitution and stereochemistry were tested (Table 1, entries 1–6). In all cases morpholines **3a–f** were obtained in very high yield. This novel process is especially noteworthy for its simplicity of reaction conditions (Et_3N, CH_2Cl_2, RT) and workup. Evaporation of the reaction mixture and simple chromatography allowed easy separation of the nonpolar by-product (Ph_2S) from the polar morpholine. Although limited to sulfonamides, the use of the more easily cleaved nosylamide is noteworthy (Table 1, entry 6).

No such limitations applied to the reactions of β-aminothiols. A range of β-aminothiols **2g–i** bearing different levels of functionality and substitution were smoothly converted into the corresponding thiomorpholines in near quantitative yield (Table 1, entries 7–9). The products were easily isolated in this case by an acid/base wash to give essentially pure material.

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[**] 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 and the EPSRC for a Senior Research Fellowship.

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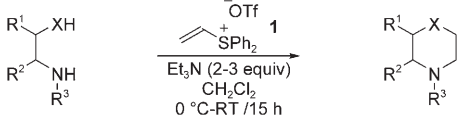
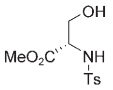
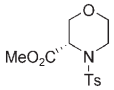
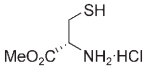
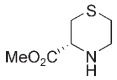
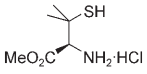
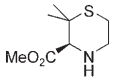
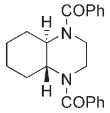
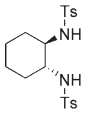
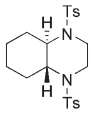
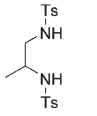
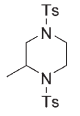
Table 1: Synthesis of morpholines, thiomorpholines, and piperazines using diphenyl vinyl sulfonium salt **1**.



Entry	Substrate		Product		Yield [%][a]
1		**2a**		**3a**	94
2		**2b**		**3b**	96
3		**2c**		**3c**	97
4		**2d**		**3d**	96
5		**2e**		**3e**	98
6		**2f**		**3f**	98
7		**2g**		**3g**	98
8		**2h**		**3h**	96
9	 **2i**	**2i**		**3i**	94
10		**2j**		**3j**	98[b]
11		**2k**		**3k**	91
12		**2l**		**3l**	99[c]
13		**2m**		**3m**	98[c]

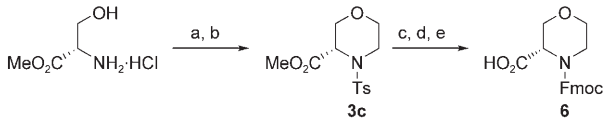
[a] Yields of isolated products. [b] Isolated after benzoylation (see Supporting Information for details). [c] DBU (2 equiv) was used as a base.

Piperazines were also effectively synthesized by using this process starting from 1,2-diamines **2j**,**k** or the corresponding tosylamide analogues **2l**,**m** (Table 1, entries 10–13). In the case of cyclohexanediamine, benzoylation of the piperazine was carried out to assist isolation and purification of the product (Table 1 entry 10). For the 1,2-bis-sulfonamides it was found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave higher yields that Et_3N.

Substrates with potentially epimerizable stereogenic centers (Table 1, entries 3, 8, and 9) did not undergo any detectable racemization, presumably because of the mild reaction conditions employed.

The mechanism of this novel process is believed to be as shown in Scheme 1. In the case of the morpholine synthesis, the question of which nucleophile added first was demonstrated by the isolation of the intermediate sulfonium salt protonated **5f** (X = O, R^1 = Ph, R^2 = Me, R^3 = Ns) which clearly showed that sulfonamide adds first to the vinyl sulfonium salt **1**. In the case of the β-aminothiols we believe that the thiol adds first because in the corresponding reactions of unprotected β-amino alcohols, aziridines were formed from initial reaction of the primary amine to the vinyl sulfonium salt.[12]

Finally, the synthetic utility of this methodology is illustrated in a short, highly efficient synthesis of morpholine-(3*S*)-carboxylic acid,[13] an important motif in a broad range of biologically active molecules.[14] Thus, sulfonamide protection[15] of L-serine methyl ester hydrochloride (95%), followed by reaction with diphenyl vinyl sulfonium salt **1** gave the required morpholine **3c** in 97% yield. Detosylation,[16] 9-fluorenylmethoxycarbonyl (Fmoc) protection and hydrolysis[13] of the ester gave the morpholine amino acid **6**, suitably protected for standard coupling reactions, in 84% overall yield (Scheme 3) and without any racemization along the reaction sequence.



Scheme 3. Synthesis of the enantiopure Fmoc morpholine-(3*S*)-carboxylic acid **6.** a) TsCl (1.1 equiv), NEt_3 (2.4 equiv), 95%; b) **1**, NEt_3 (2 equiv), CH_2Cl_2, 0 °C–RT, 15 h, 97%; c) PhOH (2 equiv), 45% HBr in CH_3COOH, 16 h, RT, 94%; d) Fmoc-Cl (1.1 equiv), $NaHCO_3$ (3 equiv), 99%; e) 5 M HCl, dioxane, 16 h, reflux, 98%.

In conclusion, we have developed a new strategy for the concise synthesis of morpholines, thiomorpholines, and piperazines from the corresponding β-amino alcohols/thiols/amines. This simple, one-step protocol avoids any redox processes making it compatible with a much broader range of functional groups. The bis-electrophile employed to form the heterocycles is diphenyl vinyl sulfonium triflate **1**. This study represents the first occasion where the potential of a vinyl sulfonium salt to act as a bis-electrophile to form a six-membered ring has been recognized and then utilized with considerable success. Indeed, we believe that this novel protocol will become the method of choice for the synthesis of these pharmacologically important heterocycles.

Received: January 24, 2008
Published online: April 11, 2008

Keywords: annulation · heterocycles · morpholines · vinyl sulfonium salts · ylides

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

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

[3] a) K. E. Henegar, M. Cebula, *Org. Process Res. Dev.* **2007**, *11*, 354 – 358; b) E. Brenner, R. M. Baldwin, G. Tamagnan, *Org. Lett.* **2005**, *7*, 937 – 939; c) A. Meinzer, A. Breckel, B. A. Thaher, N. Manicone, H.-H. Otto, *Helv. Chim. Acta* **2004**, *87*, 90 – 105; d) J. Prabhakaran, V. J. Majo, J. J. Mann, J. S. Dileep Kumar, *Chirality* **2004**, *16*, 168 – 173; e) naphthol derivatives: Jpn. Kokai Tokkyo Koho, Patent JP 57163356, **1982**; f) A. Viso, R. F. de La Pradilla, A. Flores, A. García, M. Tortosa, M. L. López-Rodríguez, *J. Org. Chem.* **2006**, *71*, 1442 – 1448.

[4] For vinyl sulfonium salts see: a) M. G. Unthank, N. Hussain, V. K. Aggarwal, *Angew. Chem.* **2006**, *118*, 7224 – 7227; *Angew. Chem. Int. Ed.* **2006**, *45*, 7066 – 7069; b) K. Kim, L. S. Jimenez, *Tetrahedron: Asymmetry* **2001**, *12*, 999 – 1005, and references therein; c) Y. Wang, W. Zhang, V. J. Colandrea, L. S. Jimenez, *Tetrahedron* **1999**, *55*, 10659 – 10672; for epoxidation reactions of butadienylsulfonium salts see: d) M. W. Rowbottom, N. Mathews, T. Gallagher, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3927 – 3929; for recent examples of the application of vinyl phosphonium salts see: e) S. Kumarn, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2006**, 3211 – 3213.

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

[6] The pK_a values of the following bromide salts in DMSO at 25 °C are: $PhCH_2SBu_2$ (18.8), $PhCH_2PBu_3$ (21.9), and $PhCH_2NEt_3$ (30.8). See J.-P. Cheng, B. Liu, Y. Zhao, Y. Sun, X.-M. Zhang, Y. Lu, *J. Org. Chem.* **1999**, *64*, 604 – 610.

[7] V. K. Aggarwal, J. N. Harvey, R. Robiette, *Angew. Chem.* **2005**, *117*, 5604 – 5607; *Angew. Chem. Int. Ed.* **2005**, *44*, 5468 – 5471.

[8] This was found to be generally superior to dialkylvinyl sulfonium salts. See Supporting Information for further details.

[9] This salt, and its precursor, will soon be commercially available from Aldrich.

[10] Nucleophiles, including H_2O, have been reported to add to the vinyl sulfonium salt in the presence of base. W. von E. Doering, K. C. Schreiber, *J. Am. Chem. Soc.* **1955**, *77*, 514 – 520.

[11] These were more successful than primary amine (unprotected), amide, or carbamate groups. See Supporting Information for further details.

[12] See ref. [5d] and Supporting Information for further details of aziridine formation from unprotected β-amino alcohols.

[13] F. Sladojevich, A. Trabocchi, A. Guarna, *J. Org. Chem.* **2007**, *72*, 4254 – 4257.

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

[15] J. E. Baldwin, A. C. Spivey, C. J. Schofield, J. B. Sweeney, *Tetrahedron* **1993**, *49*, 6309 – 6330.

[16] L. Sannamu, N. Kosaku, A. Haruhiko, K. Tetsuo, N. Izumiya, *Int. J. Pept. Protein Res.* **1986**, *27*, 44 – 50.

