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Substituted 1,4-Benzoxazepines, 1,5-Benzoxazocines, and N- and S-Variants

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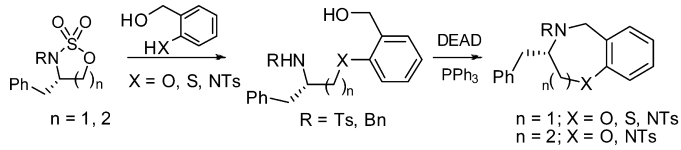
ABSTRACT

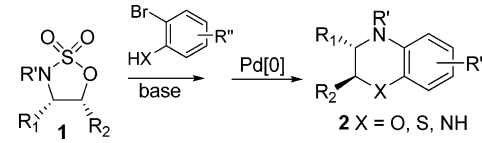


Nucleophilic cleavage of enantiomerically pure 1,2-cyclic sulfamidates with phenol, aniline, and thiophenol nucleophiles, followed by a Mitsunobu reaction, including use of a *o*-quinomethide variant of this process, provides an entry to substituted 1,4-tetrahydrobenzoxazepines, benzothiazepines, and benzodiazepines. Application of this methodology to 1,3-cyclic sulfamidates affords a parallel entry to the analogous substituted 1,5-benzoxazocines and 1,5-benzodiazocines.

Cyclic sulfamidates **1**, which are readily available in enantiomerically pure form,[1] provide the basis of a flexible entry to a range of substituted heterocyclic scaffolds.[2] These include benzofused systems **2**, representing substituted tetrahydrobenzoxazines, benzothiazines, and quinoxalines, and the sequence outlined in Scheme 1 provides a general entry to these heterocyclic targets.[3]

More generally, these structures represent "rule of three"[4] compatible fragments, and we were interested to extend the scope of this chemistry to provide access to other, heterocyclic targets with medicinal potential.

Scheme 1. Synthesis of Enantiomerically Pure Benzoxazines, Benzothiazines, and Quinoxalines



The corresponding seven-ring variants (tetrahydrobenzoxazepines, benzothiazepines, and benzodiazepines) have also attracted a great deal of interest from the pharmaceutical sector,[5] and in this paper we report the application of cyclic

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(1) Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581–2616.

(2) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811–814. Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727–4730. Bower, J. F.; Szeto, P.; Gallagher, T. *Chem. Commun.* **2005**, 5793–5795. Bower, J. F.; Chakthong, S.; Švenda, J.; Williams, A. J.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2006**, *4*, 1868–1877. Bower, J. F.; Riis-Johannessen, T.; Szeto, P.; Whitehead, A. J.; Gallagher, T. *Chem. Commun.* **2007**, 728–730. Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2007**, *5*, 143–150. Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 4909–4912. Bower, J. F.; Williams, A. J.; Woodward, H. L.; Szeto, P.; Lawrence, R. M.; Gallagher, T. *Org. Biomol. Chem.* **2007**, *5*, 2636–2644. Nguyen, H. N.; Wang, Z. J. *Tetrahedron Lett.* **2007**, *48*, 7460–7463. Xiong, Z. M.; Gao, D. H. A.; Cogan, D. A.; Goldberg, D. R.; Hao, M. H.; Moss, N.; Pack, E.; Pargellis, C.; Skow, D.; Trieselmann, T.; Werneburg, B.; White, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1994–1999. Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238–3241. So, S. M.; Yeom, C. E.; Cho, S. M.; Choi, S. Y.; Chung, Y. K.; Kim, B. M. *Synlett* **2008**, 702–706.

(3) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283–3286.

(4) Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. *Drug Discovery Today* **2003**, *8*, 876–877. "Rule of three" is a fragment-based variant of Lipinski's "rule of five": Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25. Lipinski, C. A. *J. Pharmacol. Toxicol. Methods* **2000**, *44*, 235–249.

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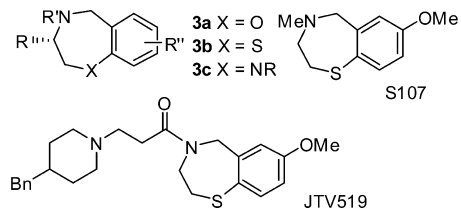
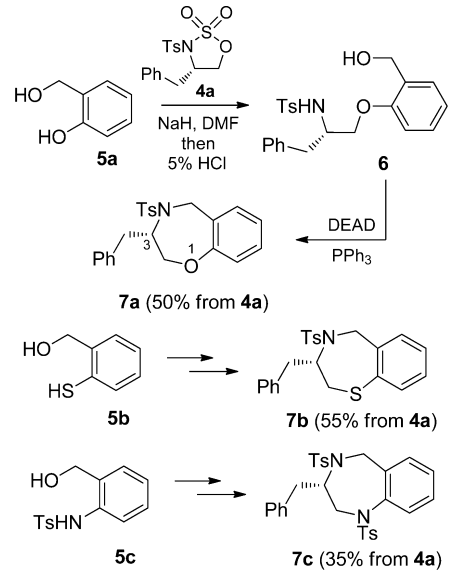
sulfamidates to the synthesis of seven- and eight-ring heterocyclic systems based on a departure from the chemistry outlined in Scheme 1. There is currently significant interest in targets based on 1,4-benzofused heterocycles of general structure **3a**−**c**; for example, the tetrahydro-1,4-benzothiazepines S107 and JTV519 are being evaluated for treating conditions linked to stabilization of cardiac ryanodine receptors (RyR1), which leak Ca^{2+} when subjected to stress.[6]



Utilizing an electrophilic 1,2-sulfamidate, our approach to 1,4-benzoxazepines, thiazepines, and diazepines **3a**−**c** is outlined in Scheme 2 and is based on use of an aryl-based nucleophile carrying an adjacent benzylic alcohol. Treatment of the *N*-sulfonyl 1,2-cyclic sulfamidate **4a**[7] with (2-hydroxymethyl)phenol **5a** gave adduct **6** which underwent smooth cyclization under Mitsunobu conditions[8,9] to provide 3-benzyl-substituted tetrahydro-1,4-benzoxazepine **7a** in 50% overall yield. [Note that the synthesis of **7a** (and **7c**) has recently been reported also using a Mitsunobu reaction to construct the seven-membered ring.[9] However, all of the examples cited employ a highly acidic TsNH nucleophile (as in **6**). It is, however, possible to exploit *o*-quinomethide reactivity (see below) and extend the scope of the nitrogen nucleophile used under Mitsunobu conditions.] alb/alb

Similar transformations were achieved using (i) thiophenol **5b** to give 3-substituted 1,4-benzothiazepine **7b** and (ii) *N*-sulfonyl aniline **5c** to give 3-substituted 1,4-benzodiazepine **7c**.[10] It is appropriate to point out that free anilines ($ArNH_2$) are not, in our hands, generally effective nucleophiles toward cyclic sulfamidate electrophiles. These problems are, however, readily overcome using *N*-sulfonyl (e.g., **5c**) or *N*-carbamoyl variants.

Scheme 2. Synthesis of Substituted 1,4-Benzoxazepines, Benzothiazepines, and Benzodiazepines



While the cyclization of, e.g., **6** to **7a** is a conventional Mitsunobu reaction (i.e., requiring an acidic NH), an equivalent overall transformation was achieved using the corresponding *N*-benzyl cyclic sulfamidate **4b** with aniline **5c** (Scheme 3). Using standard Mitsunobu conditions, the *N*-benzyl amine **8b** cyclized to give 3-substituted 1,4-benzodiazepine **9b**, the structure of which was confirmed by X-ray crystallography.

Clearly adduct **8b** does not incorporate a sufficiently acidic NH for the usual Mitsunobu mechanism to operate, but Nikam[11] has demonstrated that in the presence of a suitable activator (here PPh_3, DEAD) benzylic alcohols react via an *o*-quinomethide intermediate as a direct result of the presence of an *ortho*-positioned ether or aniline. Interestingly, while the corresponding phenolic adduct **8a** (Scheme 3) was prepared in excellent yield, this substrate did not cyclize

(5) Examples of these heterocycles abound in the literature and in the patent literature. A recent example is BMS-214662, an enantiomerically pure 1,4-benzodiazepine that is a highly apotopic farnesyltransferase inhibitor displaying potent antitumor activity. Hunt, J. T.; Ding, C. Z.; Batorsky, R.; Bednarz, M.; Bhide, R.; Cho, Y.; Chong, S.; Chao, S.; Gullo-Brown, J.; Guo, P.; Kim, S. H.; Lee, F. Y. F.; Leftheris, K.; Miller, A.; Mitt, T.; Patel, M.; Penhallow, B. A.; Ricca, C.; Rose, W. C.; Schmidt, R.; Slusarchyk, W. A.; Vite, G.; Manne, V. *J. Med. Chem.* **2000**, *43*, 3587–3595. Reid, T. S.; Beese, L. S. *Biochemistry* **2004**, *43*, 6877–6884.

(6) (a) Bellinger, A. M.; Mongillo, M.; Marks, A. R. *J. Clin. Invest.* **2008**, *118*, 445–453. Bellinger, A. M.; Reiken, S.; Dura, M.; Murphy, P. W.; Deng, S. X.; Landry, D. W.; Nieman, D.; Lehnart, S. E.; Samaru, M.; LaCampagne, A.; Marks, A. R. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2198–2202. Bellinger, A. M.; Reiken, S.; Carlson, C.; Mongillo, M.; Liu, X. P.; Rothman, L.; Matecki, S.; Lacampagne, A.; Marks, A. R. *Nat. Medicine* **2009**, *15*, 325–330.

(7) Cyclic sulfamidates **4a/b** and **10** provide a useful and validated test bed for demonstrating chemistry in this area. Clearly **4a/b** and **13** lack a substituent at the reacting center, but our experience[3] is that phenols, anilines, and thiophenols are effective nucleophiles towards a range of other and more substituted cyclic sulfamidates and that chemistry demonstrated with **4a/b** and **10** is not limited in terms of its further application and scope. For this reason, our focus was on the range of heterocyclic scaffolds available rather than the substitution pattern associated with each individual substrate. In addition, the enantiomeric purity of adducts such as **6** and **7a**−**c** is based on this earlier experience where loss of stereochemical integrity at a nonreacting center was never observed. By analogy, we have assumed that **12b** derived from **10** is also a single enantiomer.

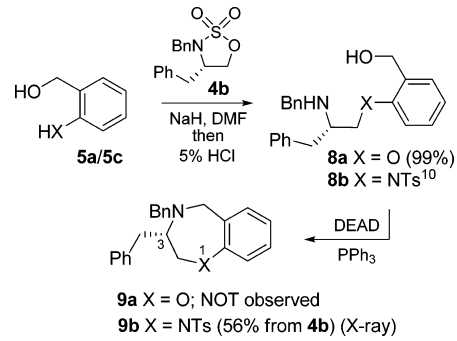
(8) For recent examples of conventional (i.e., using acidic NH nucleophiles) Mitsunobu cyclizations to generate medium ring benzofused heterocycles, see: Banfi, L.; Guanti, A. B. G.; Lecinska, P.; Riva, R. *Org. Biomol. Chem.* **2006**, *4*, 4236–4240. Banfi, L.; Basso, A.; Guanti, G.; Kielland, N.; Repetto, C.; Riva, R. *J. Org. Chem.* **2007**, *72*, 2151–2160. For a very recent entry to benzoxazepines via an alternative (but related) double displacement, see: Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257–260.

(9) Mishra, J. K.; Panda, G. *J. Comb. Chem.* **2007**, *9*, 321–338. This group employed (i) an intermolecular Mitsunobu alkylation (using a 2-amino alcohol) and (ii) a Mitsunobu cyclization of an NHTs nucleophile to achieve medium ring formation. An example of a 1,4-benzodiazocine (compare the 1,5-isomer **12b** described here) was also reported.

(10) Sulfonyl migration from the aniline nitrogen to the other nitrogen center within the initial adduct (resulting from reaction of **4a** with **5c**) was observed. Varying amounts of sulfonyl migration (from the aniline moiety and depending on the workup conditions) also accompanied formation of **8b** and **11b**. See Supporting Information.

(11) Nikam, S. S.; Kornberg, B. E.; Rafferty, M. F. *J. Org. Chem.* **1997**, *62*, 3754–3757.

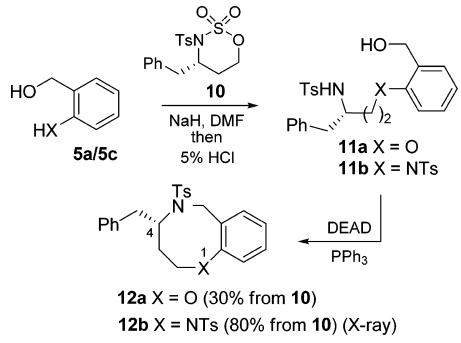
Scheme 3. *N*-Benzyl Amines as Nucleophiles under Mitsunobu Conditions



under the Mitsunobu conditions that proved successful for conversion of **8b** to **9b**. Degradation of **8a** occurred, and 1,4-benzoxazepine **9a** was not observed. We suggest that this serves to indicate the level of activation necessary to achieve seven-ring formation using an *o*-quinomethide-mediated mechanism.

The enantiomerically pure 4-substituted 1,3-cyclic sulfamidate **10** (readily prepared from (*S*)-phenylalanine) reacted with phenol **5a** and *N*-sulfonyl aniline **5c** to provide adducts **11a** and **11b**, which then cyclized to provide the 4-substituted 1,5-benzoxazocine **12a** and the 4-substituted 1,5-benzodiazocine **12b** in 30% and 80% overall yields, respectively. The eight-membered ring structure of **12b** was verified by X-ray crystallography (Scheme 4).

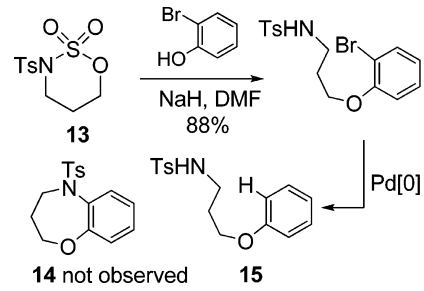
Scheme 4. 1,5-Benzoxazocine and 1,5-Benzodiazocine Synthesis



Our earlier studies (outlined in Scheme 1) relied on Pd(0)-mediated amination to establish the benzofused six-membered ring. Extending this methodology to a seven-ring analogue would extend the chemistry described above and provide access to substituted 1,5-benzoxazepines, thiazepines, and diazepines, but we have encountered difficulties in achieving this objective.[12]

While initial cleavage of the simple unsubstituted cyclic sulfamidate **13** was successful under basic conditions using 2-bromophenol, attempts to achieve seven-ring cyclization under a variety of Pd(0) conditions to provide 1,5-benzoxazepine **14** failed; the only product observed was **15**, the result of C−Br bond reduction (Scheme 5).[13]

Scheme 5. Attempts to Access the 1,5-Benzoxazepine Scaffold



In summary, the chemistry reported here underpins further the synthetic utility of 1,2- and 1,3-cyclic sulfamidates as versatile entry points to biologically and medicinally important heterocyclic scaffolds. By exploiting the reactivity of cyclic sulfamidates (coupled with the ability to generate an *o*-quinomethide intermediate that participates in the Mitsunobu reaction), access to specifically substituted seven- and eight-ring benzofused heterocycles using enantiomerically pure precursors is allowed. These now encompass 1,4-benzoxazepines, thiazepines, and diazepines, and eight-ring variants (1,5-benzoxazocines and 1,5-benzodiazocines) are also accessible.

Acknowledgment. We thank Dr. Mairi Haddow (University of Bristol) for crystallographic determinations, and J.R. thanks the Thailand Research Fund for the award of a Royal Golden Jubilee Scholarship through Professor Boonsong Kongkathip. Financial support from the Center for Innovation in Chemistry (PERCH−CIC), Commission on Higher Education, Thai Ministry of Education is also acknowledged.

Supporting Information Available: Experimental details and spectroscopic data for all new compounds and crystallographic details of **9b** and **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Pd-mediated amination has been successfully exploited to generate seven-membered rings. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350. Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546. Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35–37. Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311–2314. Qadir, M.; Priestley, R. E.; Rising, T.; Gelbrich, T.; Coles, S. J.; Hursthouse, M. B.; Sheldrake, P. W.; Whittall, N.; Hii, K. K. *Tetrahedron Lett.* **2003**, *44*, 3675–3678. Omar-Amrani, R.; Schneider, R.; Fort, Y. *Synthesis* **2004**, 2527–2534. Kitamura, Y.; Hashimoto, A.; Yoshikawa, S.; Odaira, J.; Furuta, T.; Kan, T.; Tanaka, K. *Synlett* **2006**, 115–117.

(13) In addition to use of NTs as the substrate for Pd(0)-mediated amination (see Scheme 5), NBn and NCO_2Et variants were evaluated without success. C−Br reduction (cf. **15**) remained the major pathway observed for these *ortho*-bromo phenolic ethers in attempts to generate a seven-membered ring.