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Synthesis and Structural Analysis of a New Class of Azaspiro[3.3]heptanes as Building Blocks for Medicinal Chemistry

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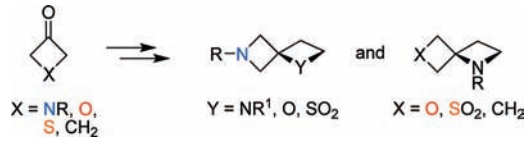
ABSTRACT



Straightforward access toward previously unreported substituted, heterocyclic spiro[3.3]heptanes is disclosed. These spirocyclic systems may be considered as alternatives to 1,3-heteroatom-substituted cyclohexanes, which are otherwise insufficiently stable to allow their use in drug discovery. Conformational details are discussed on the basis of X-ray crystallographic structures.

We have documented that oxetanes[1] and 2,6-diazaspiro[3.3]heptanes[2] can be used advantageously to fine-tune physicochemical and biochemical properties of druglike structures.[3] These have been shown to be surrogates for piperazines, morpholine, thiomorpholine, and piperidine; in general, all of the surrogates display a trend toward higher metabolic stability and aqueous solubility as well as lower lipophilicity. Herein, we describe the synthesis of an array of 1,6-substituted azaspiro[3.3]heptanes. This significantly extends the substitution pattern of accessible spiro[3.3]heptanes, rendering them useful for drug discovery.

Piperazines and morpholines are commonly employed saturated heterocycles in medicinal chemistry. The saturated six-membered ring scaffolds possess inherent limitations with respect to the relative positioning of the endocyclic heteroatoms. Thus, although the 1,4-heteroatom substitution pattern in six-membered cycles is chemically stable, the alternative 1,3 relationship, for example in 1,3-oxazinane (Figure 1, X

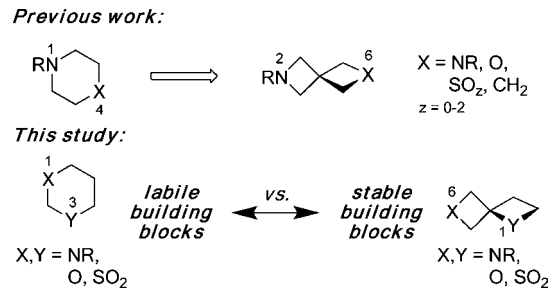


Figure 1. 1,6-Heteroatom-substituted spiro[3.3]heptanes as alternatives to 1,3-heteroatom-substituted cyclohexanes.

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(1) (a) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736–7739. (b) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Märki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512–4515. (c) Wuitschik, G.; Carreira, E. M.; Rogers-Evans, M.; Müller, K. Oxetan-3-one: chemistry and synthesis. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K.; Braish, T., Eds.; CRC Press: Boca Raton, 2008; pp 217−229. (d) Details can be found in: Wuitschik, G. Oxetanes in Drug Discovery. Ph.D. Thesis, ETH Zürich, Zürich, 2008. (e) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, in press. (f) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, in press.

(2) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, in press.

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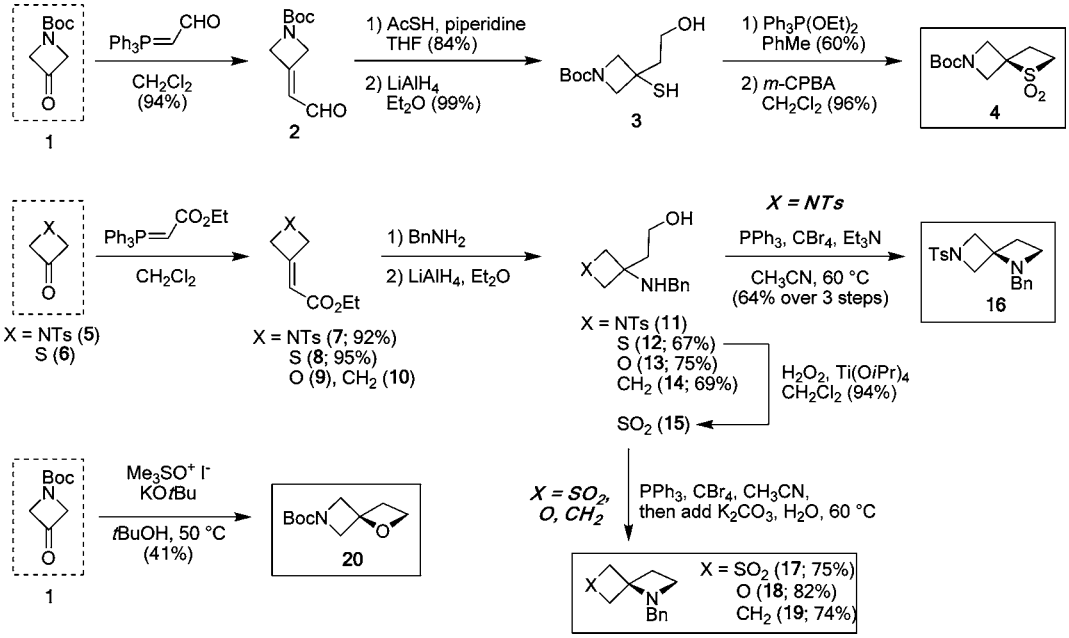
Scheme 1. Synthesis of Spirocyclic Building Blocks

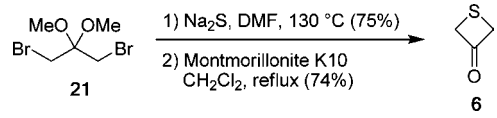


= O, Y = NH), can lead to chemically unstable systems of rather limited use for drug design. Consequently, structures incorporating these heteroatom relationships are hardly seen in the context of drug discovery.[4] The spiro[3.3]heptane scaffold provides an opportunity to position heteroatoms in a relationship that mimics that in the six-membered ring, and it can thus be considered as a surrogate without the associated instability. Surprisingly, the 1,6-heteroatom-substituted spiro[3.3]heptane ring systems have little precedence. The only example in the literature is a *N*-piperonyl substituted 6-oxa-1-azaspiro[3.3]heptane from our own work.[1b,5] We therefore turned our attention to the synthesis and analysis of a series of novel azaspirocyclic frameworks.

With the exception of spirocycle **20**, 1,6-heteroatom-substituted spiro[3.3]heptanes **4** and **16**−**19** can be prepared from their corresponding four-membered cyclic ketones[6] following the same general strategy (Scheme 1). Thus, ketone **1** underwent condensation with $Ph_3P{=}CHCHO$ to furnish **2** in 94% yield. Conjugate addition of thioacetic acid[7] (84% yield) followed by reduction with $LiAlH_4$[8] provided thiol alcohol **3** in 99% yield. Standard conditions for Appel or Mitsunobu reactions failed to deliver the desired thietane from **3**; however, the use of diethoxytriphenylphosphorane[9] effected ring closure to produce the corresponding thietane (60%), which following oxidation with *m*-CPBA delivered **4** (96%).

Spirocyclic compounds **16**−**19** were synthesized from the corresponding α,β-unsaturated esters **7**−**10**.[10] Compounds **7** and **8** were readily obtained from *N*-tosylazetidin-3-one (**5**)[11] and thietan-3-one (**6**),[12] respectively. Previous syntheses of ketone **6** were rather low yielding and difficult to reproduce with larger amounts of material; therefore, we developed a new synthesis from commercially available dibromide **21** (Scheme 2). On a multigram scale, **21** was treated with sodium sulfide in hot DMF. The resulting thietan-3-one dimethyl ketal was subjected to montmorillonite K10 clay in refluxing CH_2Cl_2 to afford **6** after recrys-

Scheme 2. Synthesis of Thietan-3-one



(3) For other recent work of oxetanes in the field of drug discovery, see: (a) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259–3262. (b) Duncton, M. A. J.; Estiarte, M. A.; Johnson, R. J.; Cox, M.; O'Mahony, D. J. R.; Edwards, W. T.; Kelly, M. G. *J. Org. Chem.* **2009**, *74*, 6354–6357.

(4) Patents: for hexahydropyrimidines, consider: (a) Kodumuru, V. WO 2007/046867, 2007. (b) Faucher, N. E.; Martres, P.; Meunier, S. WO 2009/047240, 2009. Hemiaminals: (c) Aquino, C. J.; Chong, P. Y.; Duan, M.; Kazmierski, W. M. WO 2004/055011, 2004. (d) Guillemont, J. E. G.; Pasquier, E. T. J. WO 2005/070924, 2005. (e) Ballhause, H.; Engelhardt, G.; Landgraf, C. A.; Mayer, N.; Roth, W.; Schumacher, K.; Prox, A. EP 413302, 1990. (f) Schriewer, M.; Grohe, K.; Krebs, A.; Pedersen, U.; Schenke, T.; Haller, I.; Metzger, K. G.; Endermann, R.; Zeiler, H.-J. EP 391132, 1989. Thioaminals: (g) Bateson, J. H.; Gilpin, M. L. WO 1998/039311, 1998.

(5) The *N*-piperonyl-substituted system was prepared in order to facilitate the various analyses.

(6) For an overview of the chemistry of these ketones, see: Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29–60.

(7) Granvogl, M.; Christlbauer, M.; Schieberle, P. *J. Agric. Food Chem.* **2004**, *52*, 2797–2802.

(8) Trost, B. M.; Schinski, W. L.; Chen, F.; Mantz, I. B. *J. Am. Chem. Soc.* **1971**, *93*, 676–684.

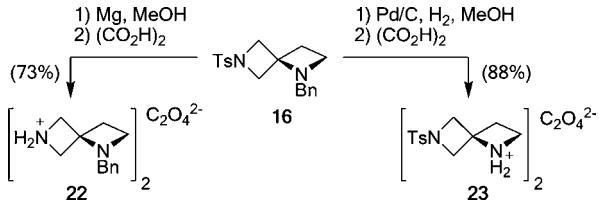
(9) (a) Robinson, P. L.; Kelly, J. W.; Evans, S. A. *Phosphorus Sulfur* **1987**, *31*, 59–70. (b) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 5210–5219.

tallization from pentane, the only purification step en route to **6**. It is interesting to mention that in contrast to the cleavage of the dimethyl ketal of oxetan-3-one,[1a] formation of **6** from its acetal can be conducted at high concentrations and is complete within 3 h.

Amino alcohols **11**−**14** were obtained in high yields following conjugate addition of *N*-benzylamine and ester reduction. In the case of thietane **12**, oxidation to sulfone **15** (H_2O_2/Ti(O*i*Pr)$_4$)[13] prior to ring closure was found to be necessary. Cyclization using PPh_3/CBr_4 and base (Et_3N or K_2CO_3) then provided **16**−**19**. Oxetane **20** was obtained in one step from protected azetidin-3-one **1** using a "double Corey−Chaykovsky" methylene insertion reaction.[14] Subsequent to their preparation, stability tests have revealed that **16**−**18**, **24**, and **25** remained essentially unaffected under stirring with 0.5 M HCl in THF/H_2O for several hours, as assayed by ^{1}H NMR spectroscopy and reisolation of the starting material.

In order to showcase the utility of the synthetic sequences and because we anticipate use of these novel modules, 1,6-diazaspiro[3.3]heptane **16**[15] was conveniently prepared on a preparative scale (15 g). The fact that the nitrogens are orthogonally protected in **16** enable different groups to be appended at each locus. Thus, it is readily converted to the monoprotected oxalate salts **22** and **23** (Scheme 3) that in turn can be directly used for many amine functionalization reactions such as arene aminations, as previously reported by us on a 2,6-diazaspiro[3.3]heptane.[16] It is worth noting that these ammonium salts are bench-stable compounds that can be stored for several months without noticeable change.

Scheme 3. Formation of Stable Oxalate Salts



In parallel with the synthetic efforts toward these novel building blocks, we are interested in examining and defining the conformational preferences of these unusual ring systems. In this regard, we have embarked on the preparation of derivatives that could be crystallized and subjected for X-ray crystallographic analysis. To our delight, *N*-benzyl-protected sulfone **17** solidified upon standing and was successfully crystallized from hexanes/CH_2Cl_2. Spirocyclic compounds **4** and **20** were transformed into the corresponding crystalline *p*-bromobenzoates **24** and **25** (Scheme 4). 6-Oxa-1-azaspiro[3.3]heptane **18** and **23** were also tranformed into crystalline amides **27** and **26**.

Scheme 4. Synthesis of *p*-Bromobenzoates for X-ray Crystallographic Analysis

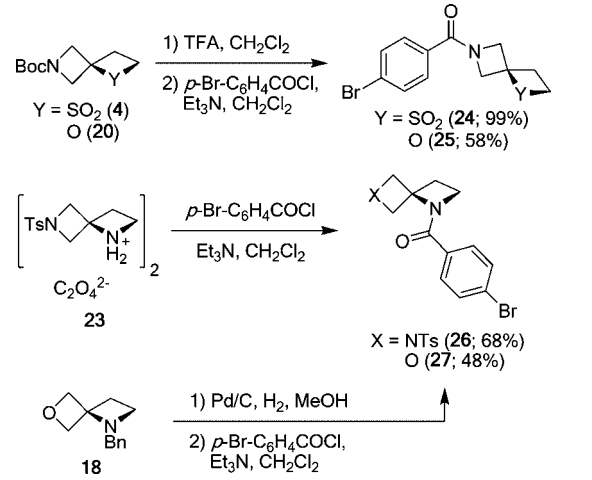


Figure 2 displays the crystal structures of compound pairs **24**/**25** and **26**/**27** as well as of *N*-benzylamine **17**. Marked ring puckering is observed for the azetidine ring ($\varphi = 27°$) in **17** and the dioxothietane rings of **17** ($\varphi = 28°$) and **24** ($\varphi = 21°$); all other four-membered heterocycles in this study can be considered essentially flat (ring puckering <7°).

It has been shown that carboxamides of azetidines tend to be pyramidalized,[17] a trend we also observed in the solid-state structure of **24** and **25**. In the case of **24**, the sum of the three valence angles around the nitrogen atom (θ) is 344.7°, a noticeable discrepancy from 360° for the ideal planar amide. The hinge angle α, defined as the angle between the C−N−C plane and the N−C(carbonyl) bond, was calculated for **24** to be 148.4°, differing greatly from the ideal 180° for planar amide groups. The amide group geometry in **25** follows this tendency as well ($\theta = 354.2°$, $\alpha = 160.9°$). If the amide is situated in the 1-position of the

(10) For compound **9**, see ref 1. Cyclobutane **10** is known; see, e.g.: Afzal, M.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, *93*, 937–945.

(11) (a) Katritzky, A. R.; Cundy, D. J.; Chen, J. *J. Heterocycl. Chem.* **1994**, *34*, 271–275. (b) Axenrod, T.; Watnick, C.; Yazdekhasti, H. *J. Org. Chem.* **1995**, *60*, 1959–1964. (c) Singh, A.; Sikder, N.; Sikder, A. K. *Indian J. Chem.* **2005**, *44B*, 2560–2563.

(12) (a) Mayer, R.; Funk, K. F. *Angew. Chem.* **1961**, *73*, 578–579. (b) Kozikowski, A. P.; Fauq, A. H. *Synlett* **1991**, 783–784. (c) Maheshwari, K. K.; Berchtold, G. A. *J. Chem. Soc. D, Chem. Commun.* **1969**, 13.

(13) Hutton, C. A.; Jaber, R.; Otaegui, M.; Turner, J. J.; Turner, P.; White, J. M.; Bacskay, G. B. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1066–1071.

(14) (a) Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 5133–5134. For an enantioselective synthesis of oxetanes, see: (b) Sone, T.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1677–1680.

(15) Although the preparation of **16** was not reported, it was suggested as a bifunctional scaffold: Stocks, M. J.; Wilden, G. R. H.; Pairaudeau, G.; Perry, M. W. D.; Steele, J.; Stonehouse, J. P. *Chemmedchem* **2009**, *4*, 800–808.

(16) Burkhard, J.; Carreira, E. M. *Org. Lett.* **2008**, *10*, 3525–3526.

(17) See, for example: (a) Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191–15199. (b) For a general discussion about nonplanar amides, consider: Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169–182.

(18) Ohwada, T.; Okamoto, I.; Shudo, K.; Yamaguchi, K. *Tetrahedron Lett.* **1998**, *39*, 7877–7880.

(19) See ref 18: *N*-tosylaziridine ($\theta = 291.2°$, $\alpha = 120.5°$), *N*-tosylazetidine ($\theta = 338.8°$, $\alpha = 142.75°$).

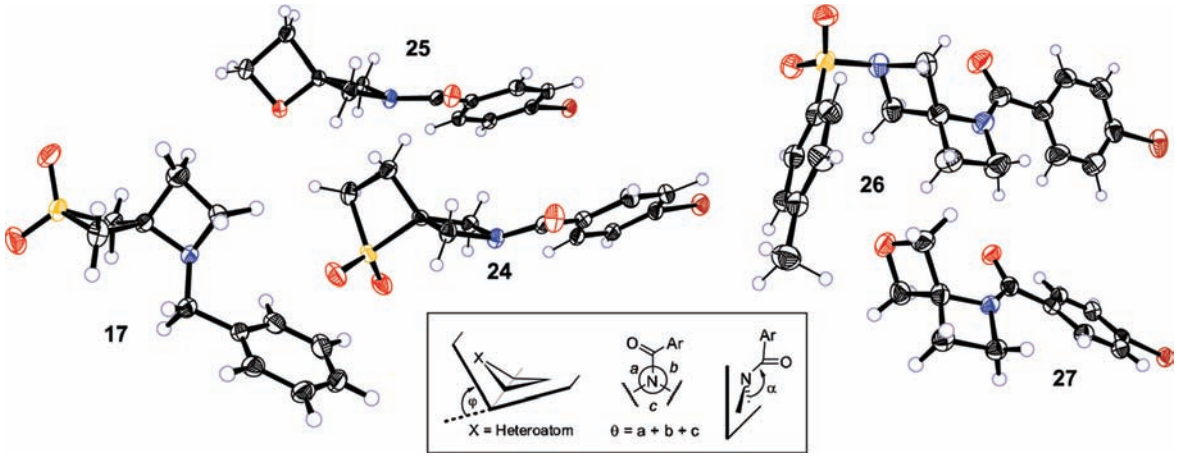


Figure 2. Determined X-ray structures of different azaspiro[3.3]heptanes. Structures are represented in the ORTEP format with ellipsoids at 50% probability. The definition of angles Φ, φ, and α is illustrated in the box.

spiro[3.3]heptane framework, we observe twisting to a much lesser extent (for **27**: $\theta = 357.7°$, $\alpha = 168.1°$; for **26**: $\theta = 359.8°$, $\alpha = 176.5°$).

The geometry of the nitrogen in sulfonamides is typically pyramidal, and the conformational preferences are quite different from carboxamides.[18] Compound **26** adopts a conformation in its solid state, where the pyramidalization of the nitrogen is pronounced ($\theta = 333.3°$, $\alpha = 137.3°$), placing this compound between *N*-tosylaziridine and *N*-tosylazetidine.[19]

In summary, we have prepared novel building blocks of the spiro[3.3]heptane family from simple ketones, namely the 3-oxo derivatives of azetidine, oxetane, cyclobutane, and thietane. Access to the latter was granted after the development of a new scalable procedure. Furthermore, stable 1,6-diazaspiro[3.3]heptane ammonium oxalate salts were prepared. The various azaspirocycles were converted to crystalline derivatives, of which crystal structures were determined and analyzed, especially for conformations around the nitrogen atom of amides and sulfonamides. With rapid syntheses and detailed structural information available, we expect these building blocks to find wide applications in the field of drug discovery in much the same way oxetanes and 2,6-diazaspiro[3.3]heptanes have.[20]

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Supporting Information Available: Experimental procedures and characterization for all new compounds. Crystallographic information files (CIF) for **17**, **24**, **25**, **26**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) A search of the recent patent literature produces a sizable listing. A selection of these include: China: US 2009163512; Novartis: WO 2009077367, WO 2009068682; Boehringer Ingelheim: WO 2009070485; Schering: WO 2009061699, WO 2009058856, WO 2009055331; Syngenta: US 2009068140; Sanofi Aventis: EP 2007-291010; Santhera: WO 2009010299; Vertex: WO 2009006315; Merck: WO 2008156726. (b) Oxetan-3-one is now commercially available from multiple sources, e.g. Synthonix, Inc. (see advertisement in *Chem. Eng. News* **2009**, *87* (42)).