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Synthesis of Novel Azaspiro[3.4]octanes as Multifunctional Modules in Drug Discovery

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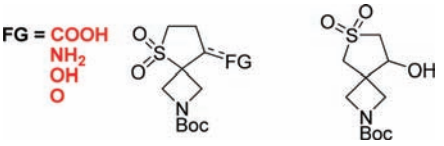
ABSTRACT



Step-economic and scalable syntheses of novel thia-azaspiro[3.4]octanes are reported. These spirocycles and some related intermediates can serve as uncharted multifunctional modules for drug discovery chemistry.

The identification of novel building blocks through design and synthesis constitutes a critical role for organic chemistry in the drug discovery process. We have recently described a collection of spirocylic building blocks,[1−3] which provide entry into novel chemical, pharmacological, and proprietary space. In line with these interests we continue to expand the collection of spirocycles by exploring new structures. Characteristics of these "compact modules" are that they should have tunable polarities affecting the phys-chem and safety parameters as well as that they should be amenable to vectorization. The latter provides ready shape diversity, a feature critical to contemporary compound collections looking to access poorly or uncharted 3D-macromolecular biological targets. In this context, our recent pursuits have included thia-azaspiro[3.4]octanes (Figure 1). The concept driving our interest in these structures initially was their similarity to the parent diazaspiro[3.3]heptanes[2b,c] and newly developed azaspiro[3.3]heptane scaffolds[2a] in our group (Figure 1) and the fact that these position functional groups and attendant exit vectors in a cambered environment. Additionally, we reasoned that the inclusion of a heteroatom, such as sulfur, particularly in its oxidized state, at different positions of the spirocycle would serve to generate uncharted spiro[3.4]octanes that intuitively resembled "drug-like" fragments. Herein, we report convenient constructions of the novel thia-azaspirocyclic systems.

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(1) For oxetanes and related spirocycles, see: (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, FL, 2008; pp 217−229. (d) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227–3246. (e) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052–9067.

(2) For azaspiro[3.3]heptanes, see: (a) Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780–783. (b) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524–3527. (c) Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944–1947. (d) Burkhard, J.; Carreira, E. M. *Org. Lett.* **2008**, *10*, 3525–3526.

(3) For other recent related work, see: (a) Xu, R.; Czarniecki, M.; de Man, J.; Pan, J.; Qiang, L.; Root, Y.; Ying, S.; Su, J.; Sun, X.; Zhang, Y.; Yu, T.; Zhang, Y.; Hu, T.; Chen, S.-H. *Tetrahedron Lett.* **2011**, *52*, 3266–3270. (b) Meyers, M. J.; Muizebelt, I.; van Wiltenburg, J.; Brown, D. L.; Thorarensen, A. *Org. Lett.* **2009**, *11*, 3523–3525. (c) 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. (d) 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.

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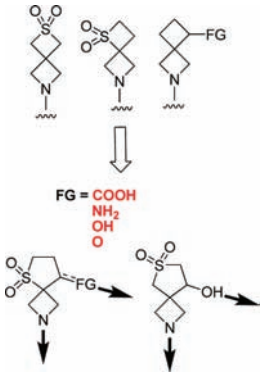


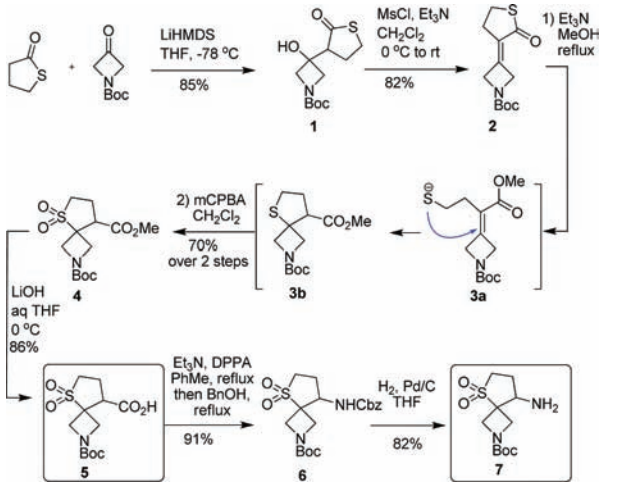
Figure 1. Azaspiro[3.4]octanes incorporating sulfones shown with exit vectors.

The first targets for synthesis were 8-functionalized 5-thia-2-azaspiro[3.4]octanes **5** and **7** (Scheme 1) from commercially available 1-*N*-Boc-3-azetidinone[4] as a starting point. Thus, aldol addition of 4-butyrothiolactone with 1-*N*-Boc-3-azetidinone produced adduct **1** on an 8-g scale in 85% yield. Subsequent dehydration provided conjugated thiolactone **2** (82%). The key spirocyclization was then realized upon exposure of **2** to alkaline methanol solution, which produced **3b**. We hypothesize the observed formation of **3b** from **2** proceeds by methanol-triggered opening of the thiolactone[5] followed by intramolecular conjugate addition onto the unsaturated ester in **3a**. After removal of volatiles, the unpurified spirocyclic ester **3b** was directly subjected to oxidation with mCPBA to afford sulfone **4** in 70% yield (two steps). Saponification furnished the corresponding acid **5** (86%). When **5** was subjected to the Curtius rearrangement protocol, orthogonally protected bisamine **6** was isolated in 91% yield. Finally, after hydrogenolytic removal of the Cbz-group, amine **7** was obtained in 82% yield.

In order to render the new spirocycles more versatile, further manipulations were investigated that permitted installation of carbonyl and alcohol groups. However, attempts to implement Barton's decarboxylative oxygenation[6] method on acid **5** were unsuccessful, despite the clean formation of the intermediate thiopyridone adduct. Examination of ketone derivatives under conditions leading to Bayer–Villiger rearrangement did not meet with success. Our attention was then shifted to developing a de novo route analogous to the approach to thiolanes reported by Warren.[7]

As shown in Table 1, the first step in the implementation of Warren's method was to access an efficient sulfenylation

Scheme 1. Synthesis of Spirocyclic Modules **5** and **7**



to reach key intermediates **8a** or **8b**. Although access to **8a** was possible by conversion of commercially available 1-*N*-Boc-3-azetidinone into the corresponding homologous enol ether, which was then subjected to the sulfenylation with BnSCl to provide the required aldehyde **8a**, this two-step protocol provided **8a** in only 16% poor yield (entry 1, Table 1). Formation of the corresponding enol ether under the Peterson conditions[8] did not lead to improvements (entry 2, Table 1), and the attempted preparation of silyl enol ether of the parent aldehyde[9] was unsatisfactory as well (entries 3 and 4,[10] Table 1). Furthermore, the formation of silyl ketene acetal of the parent ester[11] was not detected (entry 5, Table 1); rather C-silylation was exclusively observed. The direct sulfenylation of the enolate derived from the parent ester with BnSSBn, by using LiHMDS as a base, yielded an unknown product (entry 6, Table 1). However, ester enolization with LDA allowed direct sulfenylation to give BnS-ester **8b** in 40% yield (entry 7, Table 1). The yield could be improved to 53% with the addition of HMPA as a cosolvent (entry 8, Table 1).[12] It should be emphasized that, unlike 1-*N*-Boc-3-azetidinone, the chemistry of 1-*N*-Boc-3-azetidinecarboxaldehyde and methyl 1-*N*-Boc-3-azetidinecarboxylate is not well-documented. Thus the enolization studies provide important opportunities for this class of building blocks.

Ester **8b** underwent Claisen condensation to provide ketoester **9** in 84% yield (Scheme 2). Although the reduction to 1,3-diol **10** proceeded cleanly with DIBAL, the yield was modest. Following the Warren conditions,[7] treatment of BnS-1,3-diol **10** with TsCl in pyridine smoothly produced spirocyclic alcohol **13** at room temperature. We hypothesize that the reaction proceeds by [1,4]-SBn participation

(4) (a) From PharmaBlock, catalog no. PB00003. (b) For the chemistry of the ketone, see: Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29–60.

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(7) Eames, J.; Kuhnert, N.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1504–1510.

(8) Magnus, P.; Roy, G. *Organometallices* **1982**, *1*, 553–559.

(9) From Apollo Scientific Ltd., catalog no. OR15687.

(10) Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *Chem. Commun.* **2002**, 1628–1629.

(11) From Apollo Scientific Ltd., catalog no. OR42009.

(12) For HMPA as cosolvent, see: Grieco, P. A.; Flynn, D. L.; Zelle, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 6414–6417.

Table 1. Screening for an Efficient Sulfenylation to Reach Key Intermediate

8a: X = CHO
8b: X = COOMe

entry	starting material	conditions	product	total yield
1	R_1, R_2 = -O-	1) $Ph_3P^+Cl^-CH_2OMe$ 2) BnSCl	**8a**	16%
2	R_1, R_2 = -O-	1) $TMSCH_2OMe$ 2) KH 3) BnSCl	**8a**	15%
3	R_1 = CHO R_2 = H	1) TMSCl, Et_3N 2) BnSCl	**8a**	trace
4	R_1 = CHO R_2 = H		N.D.[a]	-[b]
5	R_1 = CO_2Me R_2 = H	TMSCl, LDA	N.D.[a]	-[b]
6	R_1 = CO_2Me R_2 = H	BnSSBn, LiHMDS	N.D.[a]	-[b]
7	R_1 = CO_2Me R_2 = H	BnSSBn, LDA	**8b**	40%
8	R_1 = CO_2Me R_2 = H	BnSSBn, LDA, HMPA	**8b**	53%

[a] Not desired product. [b] The yield was not determined.

and debenzylation with the chloride generated *in situ*.[7] Finally, oxidation with *m*CPBA furnished sulfonyl alcohol **14** in 67% yield, and subsequent oxidation with DMP proceeded very well to provide the corresponding sulfonyl ketone **15**.

We next examined the construction of 6-thia-2-azaspiro-[3.4]octanes (**20** and **21**, Scheme 3). The aldol addition reaction involving $BnSCH_2CHO$[13] and protected azetidine ester produced adduct **16** on gram scale in acceptable yield. Azetidine **16** underwent stepwise reduction (DIBAL-$NaBH_4$) to afford 1,3-diol **17**. Subsequent treatment of 1,3-diol **17** with TsCl in pyridine produced a mixture of tosylate **18** along with desired spirocyclic thiolane **19**. The complete conversion of the intermediate tosylate into the spirocyclic thiolane could be smoothly realized (50% for **19** overall from **16**) by heating in DMF. Finally, oxidation with mCPBA gave sulfone alcohol **20** in excellent yield. Parikh–Doering oxidation[14] of **19** proceeded well to provide the corresponding sulfenyl ketone **21** in 63% yield.

In summary, we have described the synthesis of six new multifunctional modules through the use of highly step-economic sequences. The syntheses of 5-thia-2-azaspiro-[3.4]octanes **5** and **7** were accomplished in five and seven steps, respectively. Sulfone alcohol **14** (five steps) and ketone **15** (six steps) are also conveniently accessed. Finally, alcohol **20** and ketone **21** were prepared in six steps each. We anticipate these building blocks will be welcome additions as novel scaffolds to the drug discovery tool box.

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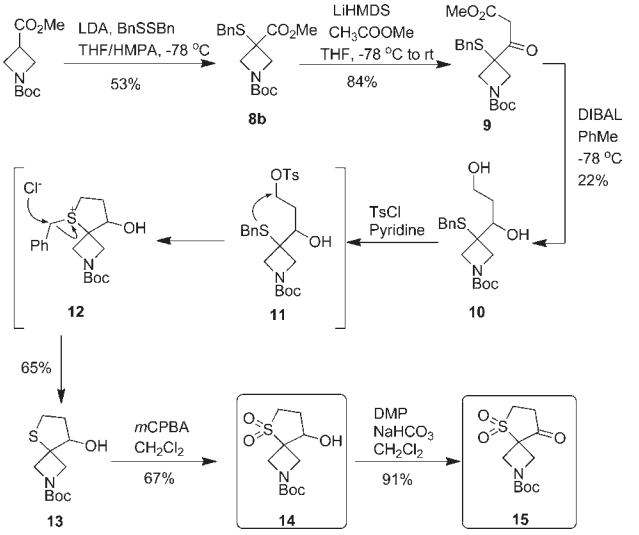
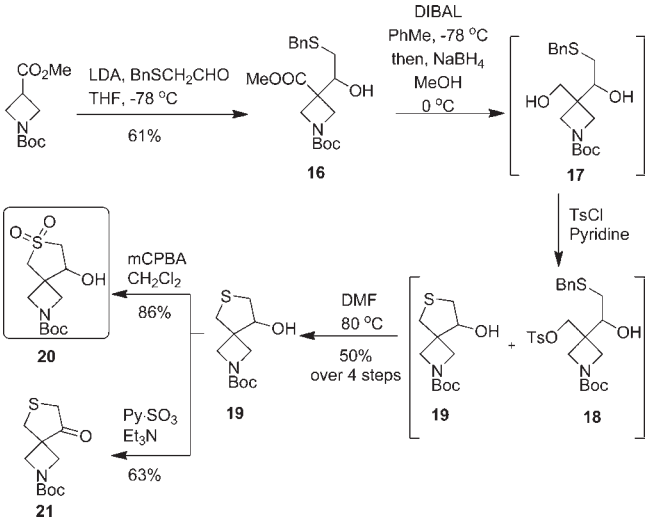
Scheme 2. Synthesis of Spirocyclic Modules **14** and **15**



Scheme 3. Synthesis of Spirocyclic Modules **20** and **21**



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