ORGANIC LETTERS

2013
Vol. 15, No. 18
4766–4769

Construction of Multifunctional Modules for Drug Discovery: Synthesis of Novel Thia/Oxa-Azaspiro[3.4]octanes

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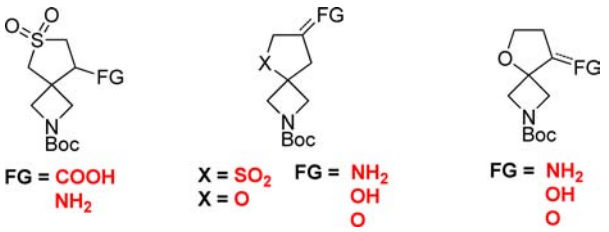
Received July 26, 2013

ABSTRACT



New classes of thia/oxa-azaspiro[3.4]octanes are synthesized through the implementation of robust and step-economic routes. The targeted spirocycles have been designed to act as novel, multifunctional, and structurally diverse modules for drug discovery. Furthermore, enantioselective approaches to the spirocycles are reported.

Recently we have documented research efforts aimed at new classes of spirocyclic ring systems designed to expand the palette of tailored module scaffolds available to medicinal chemists, which constitute an important role for synthetic chemistry in the drug discovery process. An essential component for this process[1] is to provide access to specific molecular topologies with functional group diversity, essential for generating leads that discriminate among biological targets, therefore promoting the selectivity and enhancing the safety profile of the final candidates. In recent endeavors involving spirocyclic modules for drug discovery, we have described the generation of angular azaspiro[3.3]heptanes and the first collection of thia-azaspiro[3.4]octanes (Figure 1, structures **I** and **II**);[2] herein we report the expansion of the azaspiro[3.4]octane family to include complementary structures (Figure 1, structures **III**, **IV**, and **V**).

We have previously reported 6-thia-2-azaspiro[3.4]octanes incorporating alcohols.[2b] The utility of these scaffolds would be significantly enhanced by the design of the spirocyclic scaffold with additional functional groups, leading to a collection of molecules with variable exit vectors. By virtue of the 1,3 relationship between sulfur and FG in **III** (Figure 1), it would be possible to utilize 1,3-dipolar cycloadditions as a convergent means to prepare

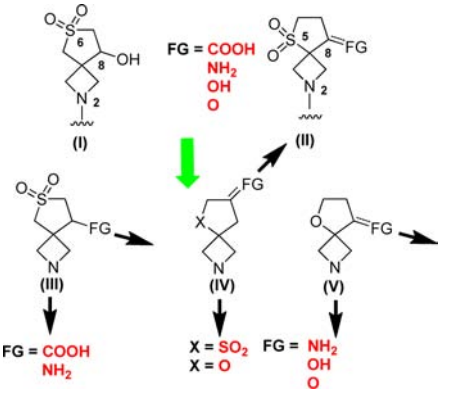


Figure 1. Evolution of azaspiro[3.4]octanes incorporating sulfones and oxygens shown with variable exit vectors.

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(1) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010**, *1*, 80.
(2) (a) For the new azaspiro[3.3]heptanes, see: Burkhard, J. A.; Guérot, C.; Knust, H.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 66–69. (b) For the thia-azaspiro[3.4]octanes, see: Li, D. B.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 6134–6136.

10.1021/ol402127b
Published on Web 08/30/2013

an ester, as a variable domain to access other groups, such as carboxylic acids and amines.

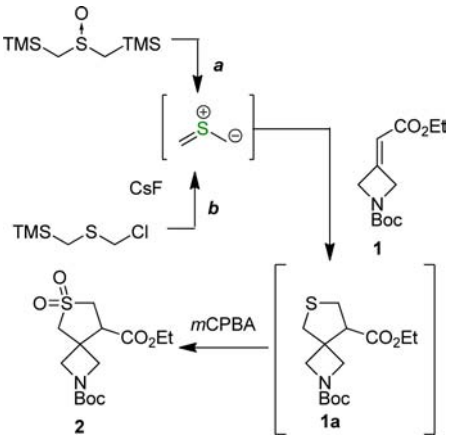
Conjugated ester **1** was prepared quantitatively by Wittig olefination[3] of *N*-Boc azetidin-2-one on gram scale (Table 1). The azetidine product obtained **1** was then subjected to the 1,3-dipolar cycloaddition reactions with thiocarbonyl ylid generated in situ through either of two ways involving the use of sulfoxide or sulfide precursors. In the first series of attempts, heating bis(trimethylsilylmethyl)sulfoxide resulted in a sila-Pummerer rearrangement[4] (Table 1, entry 1), which in the presence of **1** yielded 1,3-dipolar cycloadduct **1a** as an inseparable mixture, including largely unreacted **1** (*ca.* 30% conversion). After subsequent oxidation with *m*CPBA, sulfone ester **2** was then isolated and fully characterized (29% yield over two steps). Examination of various solvents for this transformation did not prove helpful. For example, although HMPA has been recommended as optimal in certain related cases (Table 1, entry 2), we did not record an improvement.[4b] We next scrutinized the use of thiocarbonyl ylid formed *in situ* from chloromethyl trimethylsilylmethyl sulfide. Treatment of the latter with CsF in CH_3CN/HMPA at 80 °C for 30 h (Table 1, entry 3)[5] led to *ca.* 80% conversion and a 49% overall yield following subsequent oxidation of the cycloadduct with *m*CPBA (Table 1, entry 3). It is worth noting that the results of entry 3 constitute the first example of a β,β-disubstituted conjugated ester as a dipolarophile, reacting with a thiocarbonyl ylid to form the corresponding β,β-disubstituted thiolane in a useful yield.

Following construction of the 6-thia-2-azaspiro[3.4]octane, we proceeded to elaborate the scaffold (Scheme 1). Saponification of ester **2** proceeded smoothly to furnish the corresponding acid **3**, as the first of the targeted modules. Subsequent implementation of a Curtius rearrangement provided orthogonally protected bisamine **4**, which was then unmasked to produce amine **5** in 78% yield after reductive deprotection.

Further modification in the thiolane of the 5-thia-2-azaspiro[3.4]octanes[2b] (Figure 1, structures **II** → **IV**) is a fascinating way to generate the new type modules with two exit vectors in a different tilted direction. Thus the new modules **11** and **12** were designed and synthesized as shown in Scheme 2.

Ester **1** underwent modified Woodward thiolane cyclization (thia-Michael addition−Dieckmann cyclization)[6] to provide an inseparable (and inconsequential) mixture

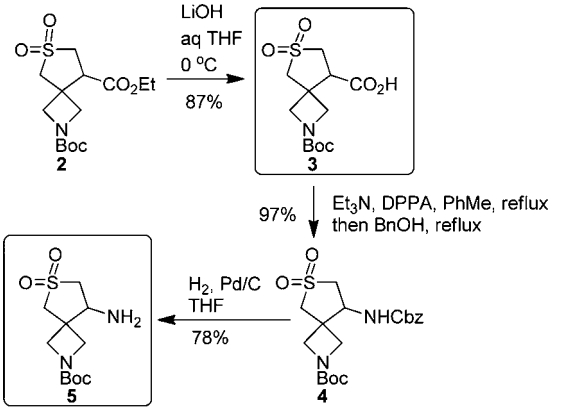
Table 1. Optimization of 1,3-Dipolar Cycloadditions



entry	path	conditions	conversion (^{1}H NMR)	yield of **2**[a]
1	**a**	CH_3CN, 80 °C, 4 h	*ca.* 30%	29%
2	**a**	HMPA, 100 °C, overnight	*ca.* 15%	13%
3	**b**	CH_3CN/HMPA (10:1), 80 °C, 30 h	*ca.* 80%	49%

[a] Total yield after the oxidation with *m*CPBA.

Scheme 1. Synthesis of Spirocyclic Modules **3** and **5**



of the two spirocyclic ketoesters **6a** and **6b**, which were directly subjected to Krapcho decarboxylation to sulfenyl ketone **7** in 62% yield over two steps. Reduction of ketone **7** with $NaBH_4$ proceeded well to provide the corresponding alcohol **8** (89%). Transformation of **8** to **9** was achieved employing Mitsunobu inversion,[7] giving **9** as an inseparable mixture, whose subsequent oxidation with *m*CPBA furnished the corresponding sulfonyl imide **10** in 38% yield over two steps. Following protecting group removal by treatment of **10** with hydrazine, targeted amine **11** was

(3) (a) Collier, P. N. *Tetrahedron Lett.* **2009**, *50*, 3909–3911. (b) For a similar example of **1** prepared by the Wittig olefination, see: Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944–1947.

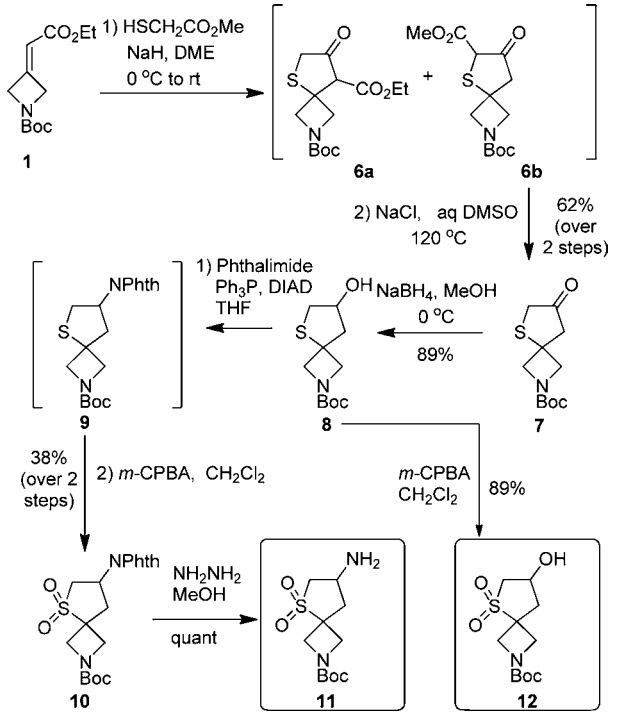
(4) (a) Aono, M.; Hyodo, C.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1986**, *27*, 4039–4042. (b) Aono, M.; Terao, Y.; Achiwa, K. *Heterocycles* **1995**, *40*, 249–260.

(5) (a) For 1,3-dipolar cycloaddition with thiocarbonyl ylid in acetonitrile under heating conditions, see: Karlsson, S.; Högberg, H.-E. *Org. Lett.* **1999**, *1*, 1667–1669. (b) For the first report on 1,3-dipolar cycloaddition with thiocarbonyl ylid in acetonitrile, see: Hosomi, A.; Matsuyama, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1986**, 1073–1074.

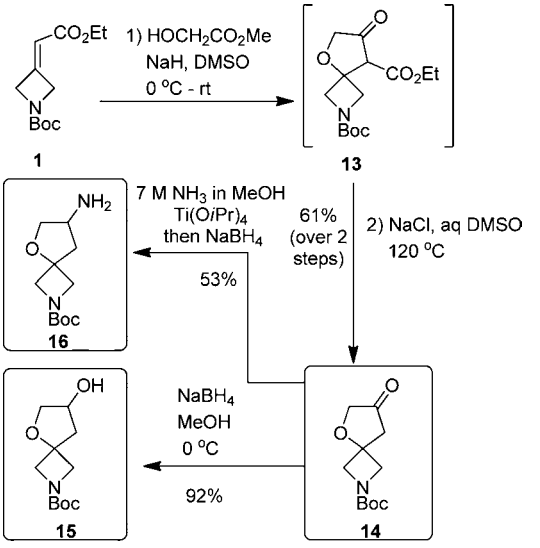
(6) (a) Liu, H.-J.; Ngooi, T. K. *Can. J. Chem.* **1982**, *60*, 437–439. (b) Woodward, R. B.; Eastman, R. H. *J. Am. Chem. Soc.* **1946**, *68*, 2229–2235.

(7) Sen, S. E.; Roach, S. L. *Synthesis* **1995**, 756–758.

Scheme 2. Synthesis of Spirocyclic Modules **11** and **12**



Scheme 3. Synthesis of Spirocyclic Modules **14**–**16**



isolated in quantitative yield. The oxidation of **8** with *m*CPBA produced the sulfonyl alcohol **12** in 89% yield.

The tandem conjugate addition–Dieckmann cyclization protocol described in the preceding paragraph[8] offered opportunities for the construction of oxa-azaspiro[3.4]-octanes. The sequence starting with **1** and methyl glycolate smoothly provided the desired spirocyclic ketoester **13** (Scheme 3), which, without purification, was subjected to Krapcho decarboxylation to form oxa-azospirocyclic ketone **14** in 61% yield over two steps.[9] Its reduction with $NaBH_4$ furnished the corresponding alcohol **15**. Compound **14** could also be subjected to reductive amination conditions (7 M NH_3 in MeOH and titanium(IV) isopropoxide, followed by $NaBH_4$)[10] to afford amine **16**[11] in 53% yield. The concise approach thus provides access to three 5-oxa-2-azaspiro[3.4]octane modules **14**–**16** in two to three steps. The synthetic routes to the building blocks described above provide access to racemates. Since, at the outset, it is not clear which enantiomer will be optimal in a given drug discovery program, we have found that it is most practical to carry out chromatographic resolution, thereby providing access to the two enantiomers. The subsequent identification of a promising subunit in a targetted project generates incentive for studies aimed at developing enantioselective approaches. We describe one of these below.

In order to examine whether scaffold construction was amenable to a more precise spatial vectorization, we also examined a route to provide **16** enantioselectively. In this respect, the addition of a vinylmagnesium bromide solution to *N*-Boc-3-azetidinone quantitatively afforded the vinyl alcohol **17**, which was subjected to *O*-allylation to give diene **18** in 93% yield (Scheme 4). Subsequent preparation of the corresponding dihydrofuran proceeded smoothly to furnish enol ether **19** (89%) via the cascade involving [Ru]-catalyzed ring-closing metathesis and olefin isomerization.[12] Asymmetric hydroboration with (−)-Ipc_2BH[13] at low temperature followed by oxidative workup converted spirocyclic dihydrofuran **19**[14] into alcohol (−)-(*R*)-**15** in 74% yield with 90% ee.[15] Mitsunobu inversion of the secondary alcohol with phthalimide and subsequent exposure to hydrazine were utilized for the production of the corresponding amine (−)-(*S*)-**16** in 74% overall yield and without any loss in configuration.[15] The absolute configuration was unambiguously confirmed by an X-ray diffraction analysis after the derivatization of chiral amine **16** to its carbamide **21** (ORTEP format with ellipsoids at 50% probability).

Finally, the last modules targeted for construction were 8-functionized 5-oxa-2-azaspiro[3.4]octanes (Scheme 5).

(8) Bunnage, M. E.; Davies, S. G.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 2763–2776 and references therein.

(9) The synthesis of spirocyclic module **14** has been recently reported by using one [Au]-catalytic spirocyclization protocol; see: Painter, T. O.; Bunn, J. R.; Schoenen, F. J.; Douglas, J. T.; Day, V. W.; Santini, C. *J. Org. Chem.* **2013**, *78*, 3720–3730.

(10) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463–1471.

(11) This spirocyclic module has been registered by WuXi AppTec Co., Ltd. with CAS no.1250998-24-3; However no information is currently available for its synthesis.

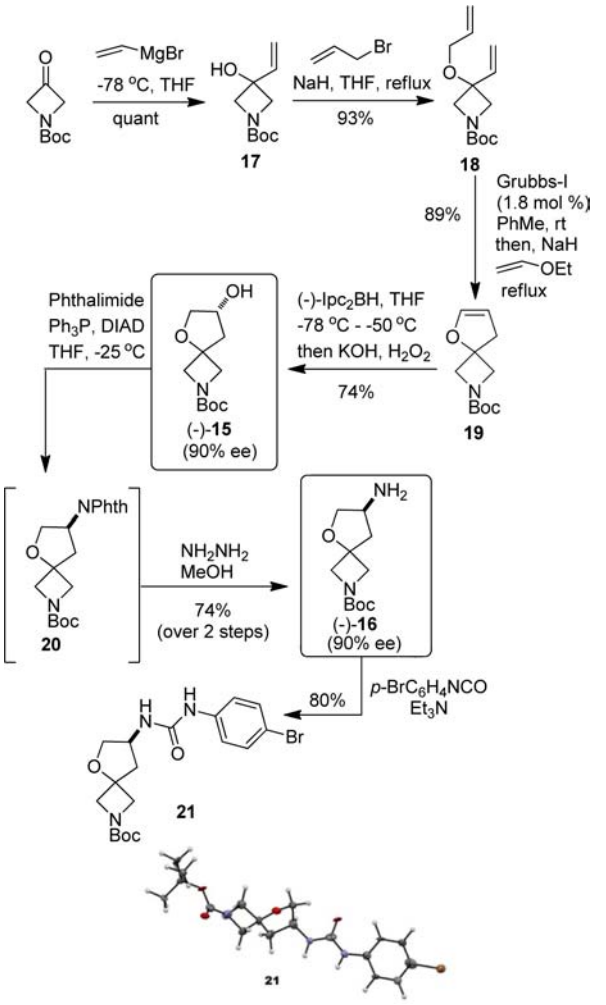
(12) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672–7687.

(13) (a) For preparation of (−)-Ipc_2BH, see: Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945–947. (b) For asymmertric hydroboroation of 2,3-dihydrofuran, see: Brown, H. C.; Gupta, A. K.; Rangaishenvi, M. V.; Prasad, J. V. N. V. *Heterocycles* **1989**, *28*, 283–294.

(14) Intermediate **19** has been recently prepared by using one different synthetic approach; see: Kumar, S.; Thornton, P. D.; Painter, T. O.; Jain, P.; Downard, J.; Douglas, J. T.; Santini, C. *J. Org. Chem.* **2013**, *78*, 6529–6539.

(15) The determinations of enantiomeric excess of (−)-(*R*)-**15** and (−)-(*S*)-**16** were performed on a Jasco2080Plus SFC after UV-detectable derivatization to the corresponding benzoates or benzamides.

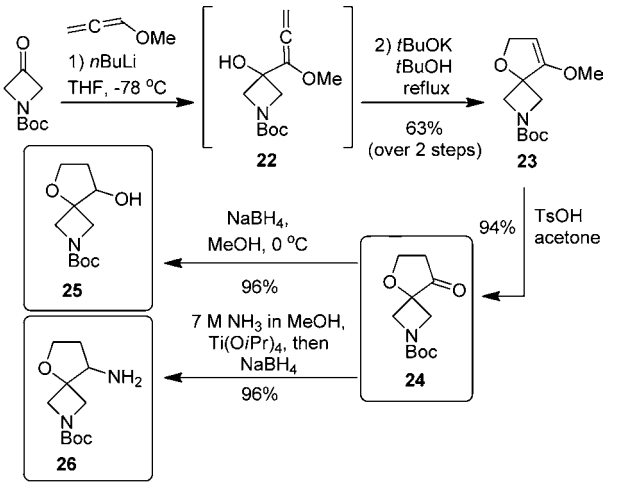
Scheme 4. Enantioselective Synthesis of Spirocyclic Modules **15** and **16**



Through the use of Magnus' allene cyclization method,[16] construction of the spirocyclic system is effected as shown in Scheme 5. Addition of lithiated methoxyallene[17] to *N*-Boc-3-azetidinone cleanly produced adduct **22** on gram scale, which was sufficiently pure for subsequent spirocyclization (*t*BuOK/*t*BuOH, cat. dicyclohexyl-18-crown-6) to form the spirocyclic enol ether **23** in 63% yield over two

(16) Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746–7747.
(17) For preparation of methoxyallene, see: Anderson, K. R.; Atkinson, S. L. G.; Fujiwara, T.; Giles, M. E.; Matsumoto, T.; Merifield, E.; Singleton, J. T.; Saito, T.; Sotoguchi, T.; Tornos, J. A.; Way, E. L. *Org. Process Res. Dev.* **2010**, *14*, 58–71.

Scheme 5. Synthesis of Spirocyclic Modules **24**–**26**



steps. Next, its treatment with TsOH in acetone proceeded in 94% yield to give ketone **24**. Following reduction with $NaBH_4$ and reductive amination,[10] alcohol **25** and amine **26** were produced.

In summary, we have disclosed approaches for the construction of novel azaspiro[3.4]octanes as multifunctional modules amenable for further elaboration in drug discovery. Ten designed modules were prepared in up to 6 steps, and access to two of these in enantioenriched form is reported. The compact nature of these novel modules coupled with inherent tunable physicochemical properties will enable their potential targeting both inside and outside of the brain for drug discovery projects, as well as assure a novel intellectual property position. Our current endeavors in this direction will be revealed in due course.

Acknowledgment. Dr. W. B. Schweizer and Mr. M. Solar at ETH-Zürich are acknowledged for X-ray structure determination. We are grateful to F. Hoffmann-La Roche, the Swiss National Science Foundation, and ETH-Zürich for the generous support of the research program.

Supporting Information Available. Experimental procedures, compound characterization data, and crystallographic information file (CIF) for **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.