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Synthesis of Novel Angular Spirocyclic Azetidines

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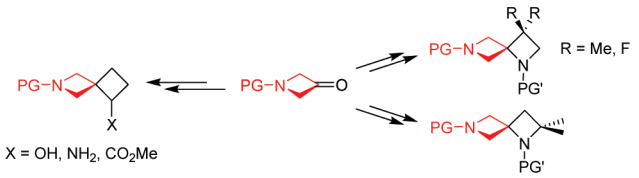
ABSTRACT



The syntheses of a variety of novel angular azaspiro[3.3]heptanes are reported. *gem*-Difluoro and *gem*-dimethyl variants of the angular 1,6-diazaspiro[3.3]heptane module were prepared in high yields using efficient sequences. Additionally, a practical one-pot synthesis of 5-oxo-2-azaspiro[3.3]heptanes and subsequent conversions into functionalized derivatives are described. The methods reported are amenable to the synthesis of these building blocks for drug discovery as members of a library or individually on a preparative scale.

The design and synthesis of novel, readily manipulated building blocks is of fundamental importance in modern drug discovery. In an effort to explore uncharted chemical and pharmacological space,[1] the preparation of novel spirocyclic scaffolds has recently been the subject of significant interest.[2] Functionalized azaspiro[3.3]heptanes are especially attractive scaffolds because they offer the potential of wide variability in relative spatial disposition of functional groups and attendant vectors. As shown in Figure 1, the linear 2-azaspiro[3.3]heptane modules (**1**−**3**) possess exit vectors in geometrically opposing directions; by contrast angular modules, such as 1,6-diazaspiro[3.3]heptane **4** and **5**−**8**, position two exit vectors in a tilted arrangement. Of the possible variants of azaspiro[3.3]heptanes, linear scaffolds such as 2,6-azaspiro[3.3]heptanes **1**,[3] 6-oxo-2-azaspiro-[3.3]heptanes **2**, and other spirocyclic derivatives **3**[4] have been covered in the literature. In contrast, angular frameworks have only been described by our group.[5] Because we anticipate wide potential for the use of scaffold **4** in medicinal chemistry, we envisaged extending the profile of **4** by incorporation of a variety of substituents on the underlying

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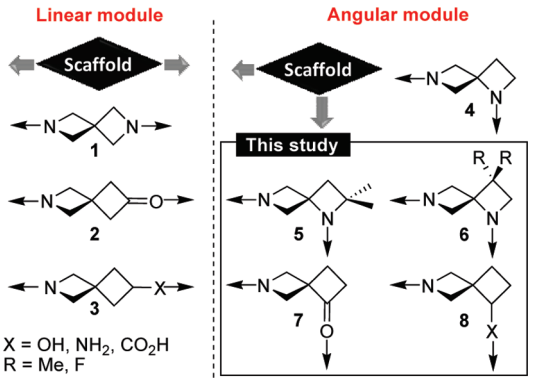
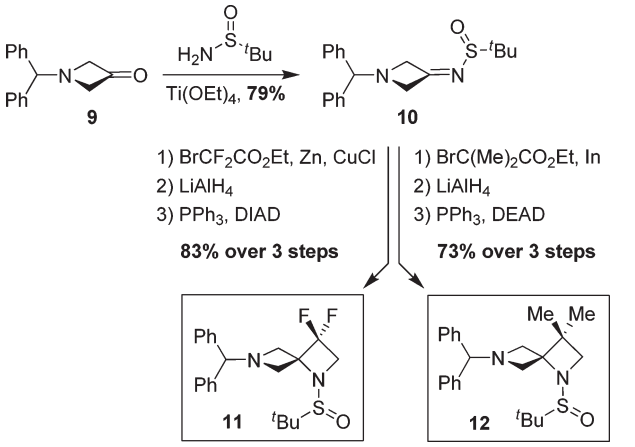


Figure 1. Representation of linear and angular azaspiro-[3.3]heptanes.

scaffold, such as *gem*-difluoro and -dimethyl groups by virtue of their frequency of use in medicinal chemistry.[6,7] We wish to report the syntheses of novel angular 3,3- and 2,2-*gem*-disubstituted 1,6-diazaspiro[3.3]heptanes **5** and **6**, as well as 5-oxo-2-azaspiro[3.3]heptane **7** and derivatives **8** of the underlying scaffold. These are derived from a common precursor azetidin-3-one.

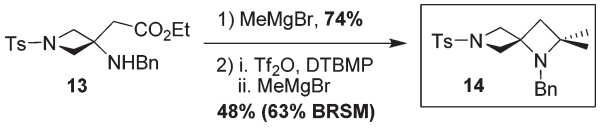
N-*tert*-Butylsulfinyl imines are known for their high stability and electrophilicity compared to other imine derivatives; consequently they enable the facile addition of a wide range of nucleophiles across C=N.[8] We decided to take advantage of these properties to prepare 3,3-disubstituted 1,6-diazaspiro[3.3]heptanes **11** and **12**. $Ti(OEt)_4$ mediated condensation of commercially available *N*-benzhydryl azetidin-3-one **9** and racemic *tert*-butylsulfinamide gave *N*-sulfinyl imine **10** in good yield (Scheme 1).[9] The Reformatsky addition has been frequently employed for the preparation of α,α-difluoro-*β*-amino acids, α,α-difluoro-*β*-lactams, and 3,3-difluoroazetidines.[10] For example, their synthesis was recently reported via reaction of the Reformatsky reagent derived from ethyl bromodifluoroacetate and *N*-*tert*-butylsulfinyl aldimines;[11] however, to the best of our knowledge, no such reactivity has been observed with ketimines. The only case where an *N*-*tert*-butylsulfinyl ketimine was used in a Reformatsky reaction involved unsubstituted acetate enolates.[12]

Scheme 1. Synthesis of 3,3-*gem*-difluoro- and 3,3-*gem*-Dimethyl-1,6-diazaspiro[3.3]heptanes



Ketimine **10** underwent addition of ethyl bromodifluoroacetate in the presence of activated Zn and CuCl at 60 °C to quantitatively afford the corresponding ester. Subsequent ester reduction and ring closure through the implementation of Mitsunobu cyclization afforded 3,3-*gem*-difluoroazetidine **11** in excellent yield. In a similar fashion, 3,3-dimethyl-1,6-diazaspiro[3.3]heptane **12** was prepared. Indium-mediated Reformatsky reaction of ketimine **10** and ethyl 2-bromo-2-methylpropanoate yielded a separable mixture of ester (56%) and *β*-lactam (28%) products. Both were converted individually to the targeted 3,3-dimethylazetidine **12**, using similar conditions as described above. To the best of our knowledge, the enolate additions described above constitute the first additions involving a *N*-*tert*-butylsulfinyl ketimine and a Reformatsky reagent derived from ethyl bromodifluoroacetate and ethyl 2-bromo-2-methylpropanoate.

Scheme 2. Synthesis of 2,2-*gem*-dimethyl-1,6-diazaspiro-[3.3]heptane



In order to access 2-substituted 1,6-diazaspiro[3.3]heptane, such as **5**, a modified approach was required (Scheme 2). Base-mediated cyclization of previously reported *β*-amino

(6) For *gem*-difluoromethylene compounds, see: (a) Yamazaki, T.; Taguchi, T.; Ojima, I. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: 2009; Chapter 1, pp 3−46. (b) Reddy, V. P.; Perambuduru, M.; Alleti, R. In *Advances in Organic Synthesis*; Bentham Science: 2006; Vol. 2, pp 327−351.

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(8) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(9) Ketimine **10** proved to be stable enough to be purified by column chromatography on silica and could be stored in the freezer for months with no evidence of decomposition.

(10) Boyer, N.; Gloanec, P.; De Nanteuil, G.; Jubault, P.; Quirion, J. C. *Eur. J. Org. Chem.* **2008**, 4277 and references cited therein.

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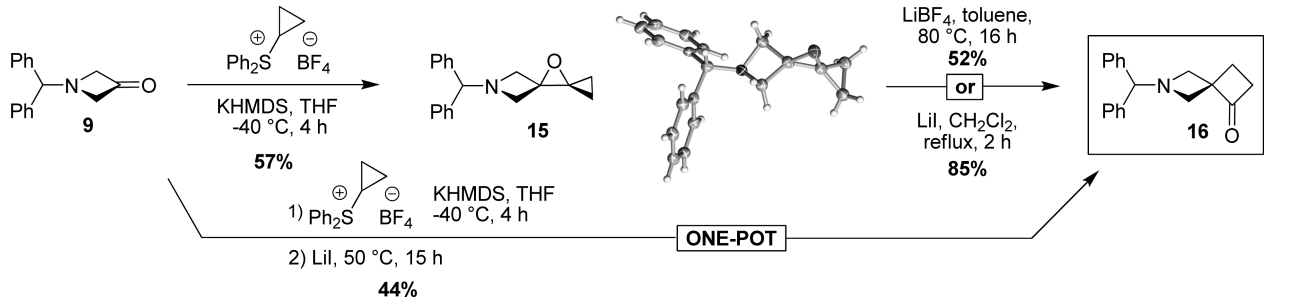
(12) Brinner, K.; Doughan, B.; Poon, D. J. *Synlett* **2009**, 991.

Scheme 3. Synthesis of 5-oxo-2-azaspiro[3.3]heptane **16**

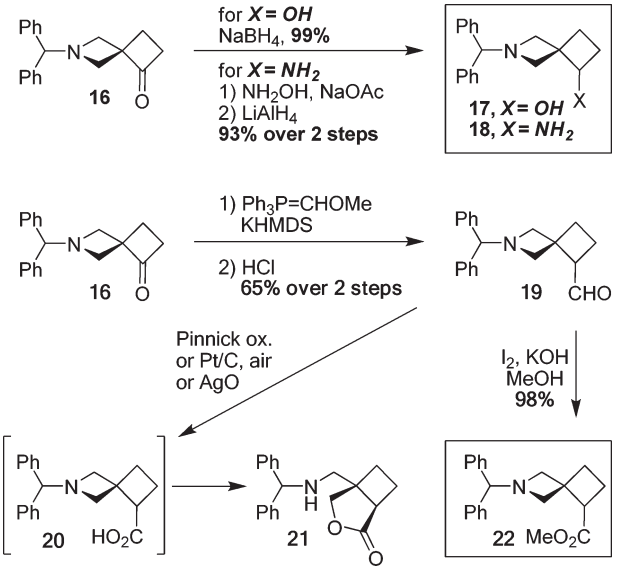


ester **13**[5] into the corresponding β-lactam (**28**, see Supporting Information (SI)) by treatment with MeMgBr proceeded in good yield. Attempts to effect additions to the intermediate β-lactam so as to generate **14**, using modified Bouveault reaction, with $ZrCl_4$ and MeMgBr were unsuccessful.[13] However, application of conditions recently reported for the conversion of β-lactams to *tert*-alkylamines[14] proved fruitful. Thus, one-pot reductive bisalkylation of the β-lactam (**28**, see SI) with MeMgBr afforded 2,2-*gem*-dimethylazetidine **14** in 48% yield (63% based on recovered starting material).

Syntheses of potential isosteres of the parent diazaspiroheptanes for medicinal chemistry, such as the novel angular modules 5-oxo-2-azaspiro[3.3]heptane **7** and its derivatives **8**, were then targeted. Application of the Trost method for the synthesis of cyclobutanones was envisaged to furnish **16**[15] with *N*-benzhydryl azetidin-3-one as the starting material (Scheme 3).[16] Initially, when **9** was allowed to react with cyclopropyldiphenylsulfonium tetrafluoroborate under standard conditions (KOH in DMSO) no product was isolated and we only observed decomposition. Similar results were obtained with KO^{t}Bu in toluene. Interestingly, the use of KHMDS in THF at −40 °C led to complete conversion of the azetidin-3-one to intermediate oxaspiropentane **15**.[17] The unpurified product was then submitted to rearrangement upon exposure to $LiBF_4$ to afford the required cyclobutanone **16** in modest yield (26%). The reaction was also carried out with azetidin-3-ones incorporating a variety of protecting groups (i.e., *N*-Boc and *N*-Ts), giving the corresponding cyclobutanones within the same range of yield. In order to improve the yield of this transformation, the reaction conditions for each step were scrutinized. Addition of cyclopropyl sulfonium tetrafluoroborate to the *N*-benzhydryl azetidin-3-one **9** delivered the highly strained 6-aza-8-oxa-dispiro[2.0.3.1]octane **15**, which was, surprisingly, sufficiently stable for isolation (57% yield) and characterization (see X-ray structure). The second step was then carried out with purified material to determine if it could be further optimized. The rearrangement reaction utilizing lithium tetrafluoroborate gave the desired cyclobutanone **16** in 52% yield. The use of substoichiometric quantities of lithium iodide resulted in a dramatic improvement, as the reaction was complete within 2 h and gave the 5-oxo-2-azaspiro-[3.3]heptane **16** in 85% yield. Finally, for practical reasons, a sequential one-pot synthesis was attempted, and it proved successful as no yield loss was observed in the overall formation of **16** (44% yield). The reaction can be easily conducted on large scale up to 20 g, making this transformation a highly efficient process.

In subsequent investigations, manipulations of the carbonyl were performed so as to access useful building modules for medicinal chemistry as shown in Scheme 4. Alcohol **17**

Scheme 4. Derivatization of 5-oxo-2-azaspiro[3.3]heptane



(13) Denton, S. M.; Wood, A. *Synlett* **1999**, 55.

(14) Xiao, K. J.; Luo, J. M.; Ye, K. Y.; Wang, Y.; Huang, P. Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 3037.

(15) While the manuscript was in preparation, *tert*-butyl 5-oxo-2-azaspiro[3.3]heptane-2-carboxylate was reported to be commercially available (from WuXi AppTec, publication date on SciFinder: 10/27/2010), showcasing the importance of this new scaffold. No experimental details are available.

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was easily obtained in quantitative yield by reduction of **16** with sodium borohydride. Additionally, the corresponding amine **18** was also prepared by sequential reductive amination via the intermediate oxime. The synthesis of carboxylic acid **20** was then undertaken by conversion of cyclobutanone **16** into the corresponding homologous aldehyde **19**. At this stage, aldehyde **19** was subjected to the Pinnick oxidation conditions; however, instead of the expected acid **20**, lactone **21** was the isolated product (76% yield). We hypothesized that acidic conditions had led to protonation of the azetidine, which subsequently triggered lactone formation. Therefore, oxidation reaction conditions under neutral conditions were examined. Treatment of aldehyde **19** with AgO[18] or air in the presence of Pt/C[19] produced lactone **21** in 50% and 95% yield, respectively. ^{1}H NMR studies of the reaction revealed the intermediate formation of carboxylic acid **20** which undergoes rearrangement to lactone **21** within 24 h, due to the zwitterionic nature of the amino acid. Consequently, the corresponding methyl ester **22** was successfully prepared by an alkaline iodine oxidation[20] in 98% yield.

In summary, we showcase the utility of the azetidin-3-ones to access a wide range of new synthetically useful azaspiro[3.3]heptanes. We have thus expanded the diversity of 1,6-diazaspiro[3.3]heptane modules and have described the synthesis of *gem*-difluoro and *gem*-dimethyl substituted azetidines. We also report a one-pot synthesis of 5-oxo-2-azaspiro[3.3]heptane and its transformation into several useful derivatives. With rapid scalable syntheses of these novel functionalized angular modules described herein, we expect these building blocks to find a wide range of applications in drug discovery.

Acknowledgment. André Alker (F. Hoffmann-La Roche AG, Basel) is acknowledged for the determination of the X-ray structure.

Supporting Information Available. Experimental procedures and characterization for all new compounds. Crystallographic information file (CIF) for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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