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# Synthesis of *tert*-Butyl 6-Oxo-2-azaspiro[3.3]heptane-2-carboxylate

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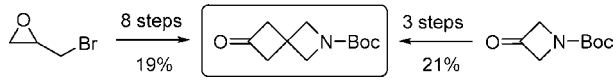
## ABSTRACT




**Two efficient and scaleable synthetic routes to previously unknown bifunctional *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate are described. This compound and related intermediates described herein are useful for further selective derivation on the azetidine and cyclobutane rings providing a convenient entry point to novel compounds accessing chemical space complementary to piperidine ring systems.**

Recent analysis of druglike chemical space has revealed that relatively few structural frameworks dominate the vast array of potential chemical diversity.[1] A lack of structural diversity in chemical libraries limits the potential for identifying lead matter for drug discovery. Thus there is a need to identify novel, readily accessible synthetic templates as novel pharmacophores.

Of the ∼1350 small molecule FDA approved drugs, 137 contain a piperidine moiety and 73 contain a piperazine moiety.[2] Identification of piperidine and piperazine structurally complementary surrogates provides the potential for expanding druglike chemical space and diversity. Indeed, 2,6-diazaspiro[3.3]heptanes have recently drawn significant interest in the pharmaceutical industry as a structural surrogate for the piperazine ring system.[3] Whereas 2,6-diazaspiro[3.3]heptanes have been known since the 1930s[4] and have been the subject of significant interest in the synthetic community,[5] it is remarkable that a corresponding bifunctional piperidine surrogate such as *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (**1**) had not been described in the literature at the time of this work. During the preparation of this manuscript, a milligram scale synthesis of closely related synthetic intermediates 6-(benzyloxy)-2-azaspiro[3.3]heptane (**2**) and *tert*-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (**11**) was reported in a patent for GPR119 modulators.[6]

In this report, we describe two efficient and scaleable syntheses of *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (**1**) and related synthetic intermediate 6-(benzyloxy)-2-azaspiro[3.3]heptane (**2**) useful for preparation of various 2,5-disubsituted and 2,6-disubstituted 2-azaspiro[3.3]heptanes (Figure 1). Synthetic scaffolds **1** and **2** permit the use of various synthetic methods, such as α-alkylation, Wittig reactions, addition of Grignard reagents, condensation reactions, N-acylations, N-alkylations, sulfonylations, and the

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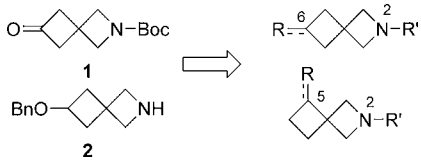


**Figure 1.** Potential synthetic applications of *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (**1**) and 6-(benzyloxy)-2-azaspiro-[3.3]heptane (**2**).

like, to incorporate moieties in the 2-, 5-, and 6-positions in any order appropriate to access the targets of choice.

This novel, conformationally rigid 2-azaspiro[3.3]heptane template provides a complementary structural surrogate for 4-substituted piperidine, homopiperidine, and 4-methylene-piperidine ring systems (Figure 2). An overlay of molecular

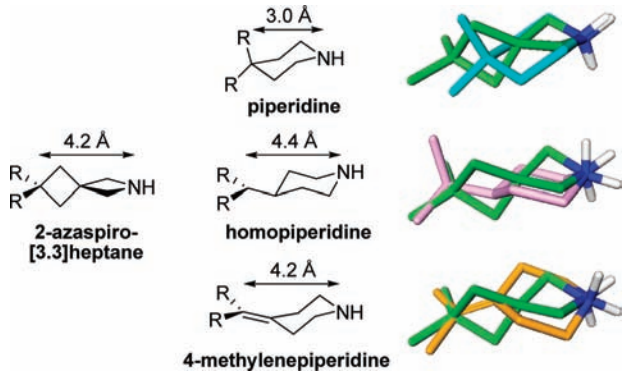


**Figure 2.** Comparison of 2,6-diazaspiro[3.3]heptane, 2-azaspiro[3.3]-heptane (green), piperidine (blue), homopiperidine (pink), and 4-methylenepiperidine (orange) ring systems.

models of these systems reveals similar spatial positioning of substituents in the location corresponding to the 6-position but somewhat different spatial trajectories.[7] For example, the 2-azaspiro[3.3]heptane ring system is approximately 1 Å longer than a similarly substituted piperidine ring but similar in length to the corresponding homopiperidine and 4-methylene ring systems. Furthermore, the trajectory of the 6-position substituents of the 2-azaspiro[3.3]heptane is slightly different than the piperidine-based surrogates. Thus, a bifunctional 2-azaspiro[3.3]heptane ring system provides a means to probe novel chemical space complementary to these ring systems commonly found in approved drugs.

We envisioned that the previously unknown 6-oxo-2-azaspiro[3.3]heptane ring system could be accessed from construction of either end of the spiro ring system (Figure 3). Our first approach involved the stepwise construction of the cyclobutane ring **3** from 1,3-dibromopropane

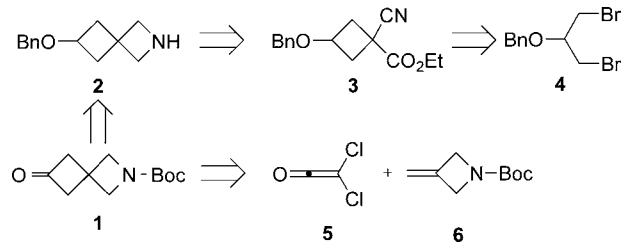
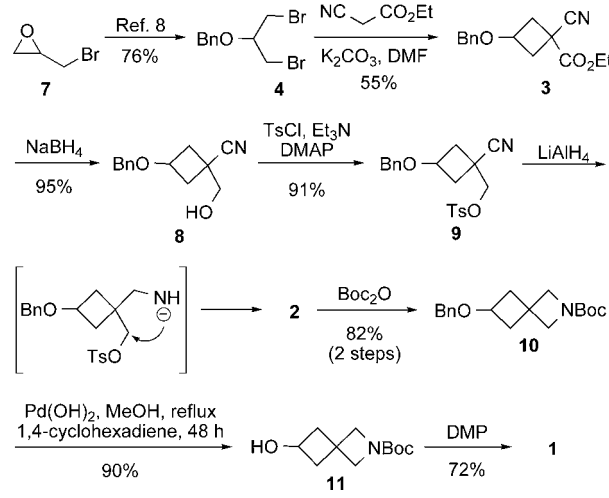


**Figure 3.** Retrosynthesis of 6-oxo-azaspiro[3.3]heptane **1**.

derivative **4** followed by formation the azetidine ring of **2** and conversion to **1** in seven steps overall. Our second generation synthesis shortened this sequence utilizing a [2 + 2] cycloaddition of 1,2-dichloroketene **5** and azetidine olefin **6**.

Our first approach to the 2-azaspiro[3.3]heptane ring system is shown in Scheme 1. 1,3-Dibromopropane derivative **4**, readily

**Scheme 1.** Synthesis of **1** and Related Intermediates



available from inexpensive epibromohydrin **7**,[8] was condensed with ethyl cyanacetate in the presence of potassium carbonate[9] to give α-cyanoester cyclobutane **3** as a 4:1 mixture of diastereomers in modest yield. Reduction of **3** with sodium borohydride gave alcohol **8** followed by conversion to the tosylate **9** in excellent yields. Nitrile intermediate **9** was reduced with lithium aluminum hydride to furnish the primary amine, which spontaneously displaced the tosyl group to ring close[9] and form the azaspiro[3.3]heptane derivative **2**, which was

(7) Molecular overlays were prepared from structures minimized using *MacroModel, version 9.0*; Schrodinger, LLC: New York, 2005 (OPLS 2005 force-field, with GB/SA water solvation model). The homopiperidine derivative was subjected to a conformational search to identify the global minimimum conformation. Distances indicated are C—N distances determined from minimized structures.

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isolated crude. To facilitate isolation and purification, the amine was protected with Boc anhydride to give bis-protected, bifunctional azaspiro[3.3]heptane intermediate **10** in good yield over the two steps. The benzyl group was then removed under transfer hydrogenation conditions to give alcohol **11** in good yield. Finally, oxidation of compound **11** with Dess−Martin periodinane (DMP) gave the desired Boc-protected 6-oxo-2-azaspiro[3.3]heptane **1** in good yield.

This sequential route provides access to compound **1** in eight steps and 19% overall yield, as well as synthetically useful, orthogonally protected 2-azaspiro[3.3]heptane **10** in six steps and 30% yield and related 2-azaspiro[3.3]heptane analogs **2** and **11**.

Confirmation of the structure of 6-oxo-2-azaspiro[3.3]heptane **1** was obtained by X-ray crystallographic analysis of crystals obtained from ethyl acetate and heptane (Figure 4).

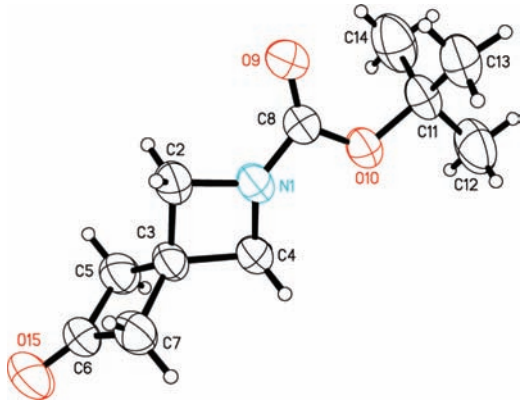
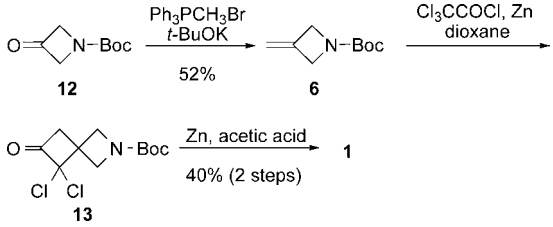



**Figure 4.** X-ray plot of 6-oxo-azaspiro[3.3]heptane **1**.

A more concise, but similarly yielding, three-step synthesis of 2-azaspiro[3.3]heptane **1** utilizing a [2 + 2] cycloaddition with dichloroketene is shown in Scheme 2.

**Scheme 2.** Synthesis of **1** via [2 + 2] Cycloaddition




Wittig reaction of *N*-Boc-azetidin-3-one **12** proceeded in modest yield to give olefin **6**. Initial attempts to carry out the subsequent [2 + 2] cycloaddition reaction were unsuccessful. Generation of the dichloroketene from dichloroacetyl chloride and triethylamine[11] gave complicated reaction mixtures with no evidence of the cycloaddition product **13**. Despite successful reports using trichloroacetyl chloride and zinc−copper couple in 1,2-dimethoxyethane on similar cycloadditions to generate spirocyclobutanes,[12] we were only successful using zinc powder[11,13] in dioxane. It is important to note that a slow exotherm develops while the reaction is slowly warmed from 0 to 25 °C.[14] In order to maintain efficient reaction conversion, it is important to maintain the reaction temperature between room temperature and 30 °C. If the reaction temperature exceeds 30 °C, significant loss of the Boc group is observed.

Without further purification, the crude dichloroketone **13** was dechlorinated in the presence of zinc and acetic acid[10] to give the desired 2-azaspiro[3.3]heptane **1** in modest yield after chromatography. This concise route provided 51 g of compound **1** in three steps and 21% overall yield. Notably, the cycloaddition chemistry was successfully carried out on 100 g scale in 2.5 L of solvent and could be further optimized to improve the yield.

In conclusion, two scaleable syntheses of the novel 6-oxo-2-azaspiro[3.3]heptane ring system exemplified by compound **1** have been described. The first route, depicted in Scheme 1, is very practical, beginning with inexpensive epibromohydrin, and permits access to several 2-azaspiro[3.3]heptane intermediates in reasonable yield. The second route, depicted in Scheme 2, provides rapid and scaleable access to compound **1** in just three steps from readily available but considerably more expensive *N*-Boc-azetidin-3-one. Compound **1** and related intermediates **2**, **10**, and **11** described herein are useful for further selective derivation on the azetidine and cyclobutane rings providing access to novel 2,5- and 2,6-disubsituted compounds accessing chemical space complementary to piperidine, homopiperidine, and 4-methylenepiperidine ring systems.

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

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(14) We have noticed in similar [2 + 2] reactions using zinc-copper couple that a violent exotherm may develop, especially when using THF as the solvent.

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