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 \sim 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-2azaspiro[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

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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-methylenepiperidine 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-2azaspiro[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



available from inexpensive epibromohydrin 7,⁸ was condensed with ethyl cyanacetate in the presence of potassium carbonate⁹ 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 close⁹ 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.



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 triethylamine¹¹ gave complicated reaction mixtures with no evidence of the cycloaddition product **13**. Despite successful reports using trichloroacetyl chloride and

l, 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.
l, Without further purification, the crude dichloroketone 13 was deablering the maintain the reaction conversion.

dechlorinated in the presence of zinc and acetic acid¹⁰ to give the desired 2-azaspiro[3.3]heptane **1** in modest yield after chromatog-raphy. 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.

zinc-copper couple in 1,2-dimethoxyethane on similar

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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