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3-Benzyl-3-azabicyclo[3.1.1]heptan-6-one: A Promising Building Block for Medicinal Chemistry

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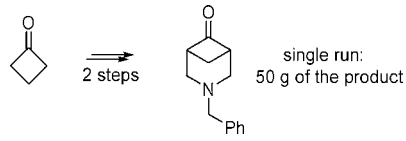
ABSTRACT



An efficient two-step multigram synthesis of the previously unknown 3-benzyl-3-azabicyclo[3.1.1]heptan-6-one is described. The compound is shown to be a promising building block for further selective derivatization of the cyclobutane ring providing novel conformationally restricted piperidine derivatives.

Conformational restriction is an effective tool used in medicinal chemistry to improve/modify pharmacological characteristics of drug candidates.[1] As the result of fixation of the functional groups in a biologically active conformation, the sterically restricted compounds are often more efficient and selective ligands for various targets, thus displaying pronounced biological activity. On the other hand, compounds comprising conformationally restricted units usually possess higher metabolic stability compared to that of the nonrestricted analogues.[2] However, the corresponding conformationally restricted building blocks are often obtained through multistep and low-yield synthetic procedures,[3] so that their up-scaled production is limited. In this context, the development of new synthetic strategies for facile large-scale preparation of the conformationally restricted synthons of cheap and commercially available starting materials is of particular interest.

The piperidine motif is seldom-used in drug discovery. For example, of the ∼1350 small molecule FDA-approved drugs, 136 contain a piperidine moiety.[4] Herein, we report a highly effective two-step multigram preparation of novel 3-benzyl-3-azabicyclo[3.1.1]heptan-6-one (**1**) and its ap-

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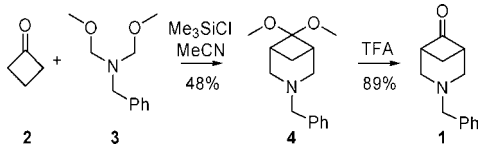
plication in the synthesis of the conformationally restricted piperidine derivatives.

The double Mannich reaction of cyclic ketones with *N*,*N*-bis(alkoxymethyl)alkylamine[5] reagents is a facile strategy to prepare bicyclic piperidine analogues. Since the first report in 2006, a number of publications on the double Mannich annulation of cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone with *N*,*N*-bis(alkoxymethyl)alkylamine reagents has appeared.[6] However, to the very best of our knowledge, so far absolutely nothing is known about the corresponding reaction of the simplest stable cyclic ketone, cyclobutanone (**2**).[7] Therefore, we have become interested in performing this transformation.

Indeed, heating the mixture of cyclobutanone (**2**) and *N*,*N*-bis(methoxymethyl)benzylamine (**3**) in acetonitrile in the presence of Me_3SiCl afforded the bicyclic compound **4** in 48% yield (Scheme 1). Acidic hydrolysis of the ketal moiety in **4** smoothly provided ketone **1** in 89% yield.

Scheme 1. Synthesis of 3-Benzyl-3-azabicyclo[3.1.1]heptan-6-one (**1**)



The structure of ketone **1** was proven by an X-ray diffraction study (Figure 1). Importantly, the synthesis of

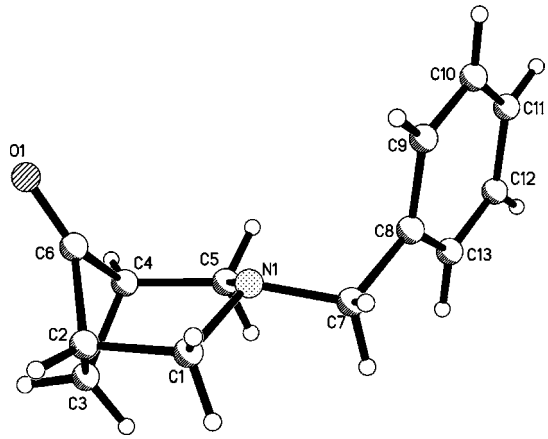
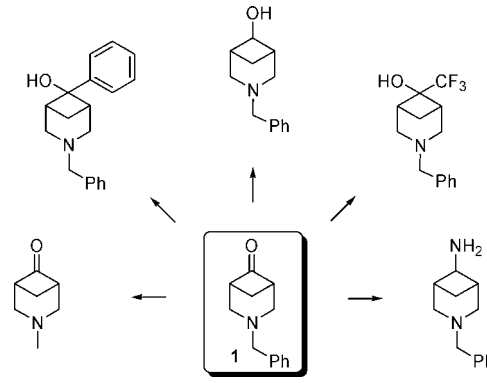


Figure 1. X-ray crystal structure of ketone **1**.

compound **1** was easily up-scaled, so that 50 g of the pure product was prepared in a single batch.

Next, several representative transformations of ketone **1** were performed in order to show its feasibility as a starting compound in the synthesis of various pharmacologically relevant intermediates (Scheme 2).

Scheme 2. Representative Modifications of Ketone **1**



The building blocks depicted in Scheme 2 can be considered as conformationally restricted analogues of 4-substituted piperidines, frequently occurring in approved drugs (Figure 2).

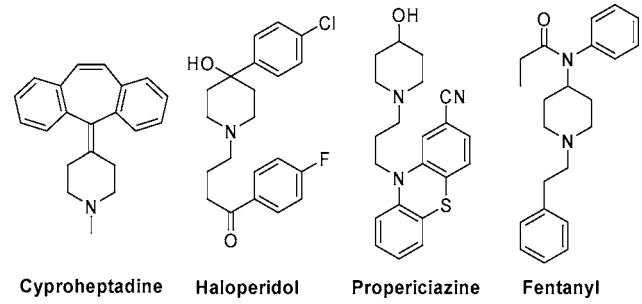


Figure 2. Some marketed pharmaceuticals possessing the 4-substituted piperidine moiety.

First, an applicability of the benzyl moiety in compounds **1** and **4** as an *N*-protecting group, which provides an access to various *N*-substituted piperidines, was demonstrated. Thus, the synthesis of the simplest *N*-alkyl ketone **5** was pursued.

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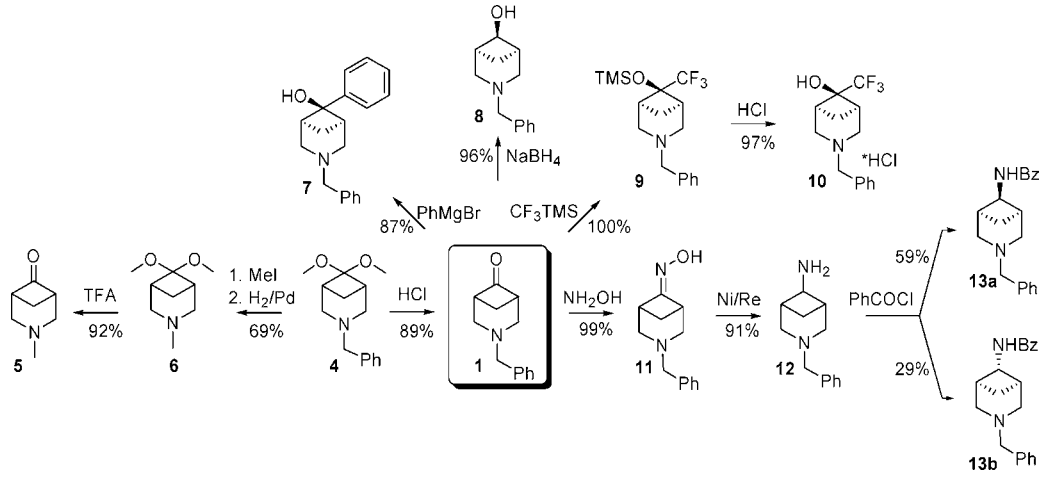
Scheme 3. Synthesis of Conformationally Restricted Piperidine Analogues **5**, **7**, **8**, **10**, and **12**



Alkylation of the tertiary amine **4** with MeI followed by a hydrogenation of the benzyl group in the corresponding quaternary salt, using 10% palladium on charcoal as the catalyst, gave ketal **6** in 69% yield. Acidic cleavage of the ketal moiety in **6** smoothly provided *N*-methyl ketone **5** in 92% yield (Scheme 3).

Next, several modifications of the carbonyl group in compound **1** were performed. An addition of PhMgBr to ketone **1** in THF at −50 °C gave alcohol **7** in 87% yield. As expected, a nucleophilic attack of the Grignard reagent at the carbonyl group in **1** occurred at the less sterically hindered side to give the product **7** as a single isomer. Similarly, reduction of the carbonyl group in **1** with $NaBH_4$ in MeOH at −50 °C afforded alcohol **8** as the sole isomer in 96% yield. An addition of CF_3TMS to ketone **1** in the presence of NBu_4F in THF[8] at room temperature quantitatively gave the corresponding trifluoroethanol derivative **9**. Again, the formation of only one isomer was observed. Acidic cleavage of the TMS group in **9** smoothly provided the CF_3-substituted alcohol **10** in 97% yield.

Finally, the synthesis of diamine **12** from ketone **1** was performed. The reaction of **1** with NH_2OH in water gave the corresponding oxime **11** in 99% yield. Reduction of the oxime group in **11** using Raney nickel alloy afforded pure amine **12** in 91% yield as a mixture of two stereoisomers. If needed, the isomeric derivatives of **12** substituted at the primary amino can be readily separated. For example, representative amide coupling of amine **12** with PhCOCl provided the corresponding orthogonally protected diamines **13a**/**13b**, which were easily separated by flash column chromatography.

The structures of the compounds **7**, **10**, and **13a** were determined by X-ray analysis (Figure 3). The stereoconfiguration of alcohol **8** was established by NOESY experiments (Supporting Information).

In summary, we have developed a two-step synthesis of novel 3-benzyl-3-azabicyclo[3.1.1]heptan-6-one (**1**) from cyclobutanone in 43% overall yield; 50 g of ketone **1** was easily prepared in a single batch. Compound **1** is a promising

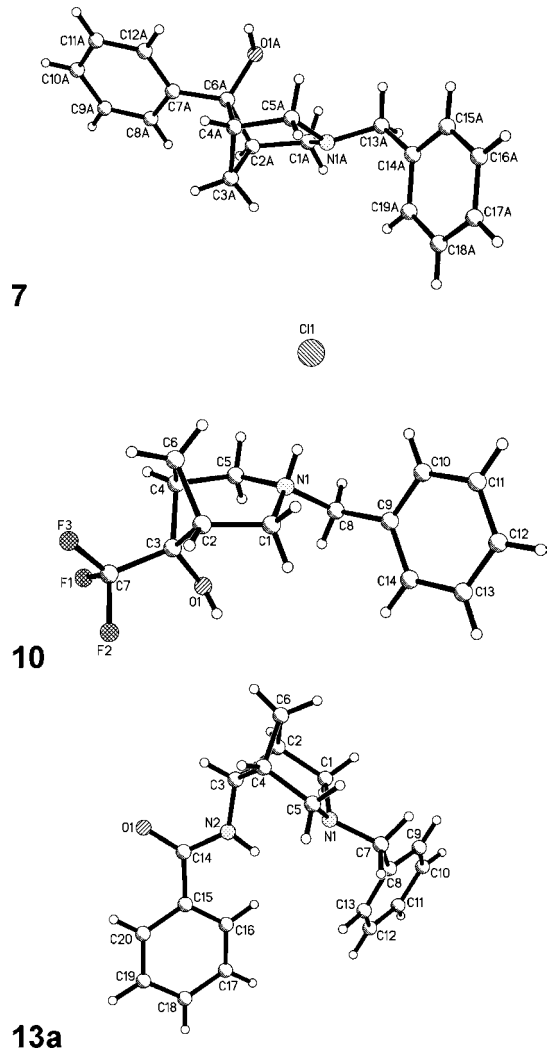


Figure 3. X-ray crystal structures of the compounds **7**, **10**, and **13a**.

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building block suitable for the preparation of conformationally restricted piperidine derivatives. The representative 4-substituted piperidines **5**, **7**, **8**, **10**, and **12** were conveniently prepared from **1** by routine transformations. With rapid scalable synthesis, we expect compound **1** and its related derivatives described herein to find wide applications in the field of drug discovery as piperidine analogues.

Supporting Information Available: Experimental procedures, crystallographic data, structure description, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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