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A practical synthesis of [$^{13}C_4$] *N*-benzylpiperazine from [$^{13}C_2$] glycine

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ABSTRACT

A high yielding gram-scale synthesis of [$^{13}C_4$] *N*-benzylpiperazine for use as a convenient and versatile building block in isotope labeling studies of clinical drug candidates is reported.

Efficient methods for isotope labeling of clinical drug candidates are very important for metabolic studies in the development of new drugs.[1] It is desirable to have the label located at a relatively stable part of the molecule to avoid fragmentation of the labeled moiety as a result of metabolic degradation. Four or more labeled atoms are normally required for accuracy in spectroscopic measurements, as well as a high isotopic purity of the labeled final compound. Furthermore, it is advantageous to use a labeling strategy that allows for facile introduction of the labeled moiety without modification of the established synthetic route and that also allows use of the same labeled moiety for analog structures.

Piperazines are frequent motifs in several drugs, for example among the antipsychotics Abilify®, Seroquel®, Zyprexa®, and Geodon®, which were among the top 40 selling drugs on the US market in 2010, as well as Levaquin® and Viagra® (Fig. 1).[2] The piperazine ring is most often a stable part of the molecule and offers a convenient location for the introduction of four ^{13}C atoms. However, [$^{13}C_4$] piperazine is not commercially available and often requires difficult monoprotection in order for it to become a useful building block.

Herein, we report an efficient synthesis of [$^{13}C_4$] *N*-benzylpiperazine as a versatile building block which could be used for facile introduction of a ^{13}C-labeled piperazine moiety. Common methods start from acetic acid derivatives and overall yields are generally modest.[3] To our knowledge, the selection of alternative commercially available ^{13}C-labeled starting materials is somewhat limited. Therefore, we have developed a scheme starting from readily available [$^{13}C_2$] glycine, which provides the title compound in high overall yield.

There are already some procedures reported for the preparation of ^{13}C-labeled piperazines. Previous examples suffer from limited applicability, for example, unsubstituted[4] or *N*-methylpiperazine.[3a] We identified the need for a monoprotected unit in order to widen the scope of piperazine labeling chemistry. We opted for a UV-active and hydrophobic benzyl substituent as the *N*-protecting group, which was to be introduced early in the synthetic sequence, thus facilitating spectroscopic analysis, and purification and isolation of intermediates. The benzyl group can be removed later by catalytic hydrogenation after derivatization of the second piperazine nitrogen atom.

We synthesized the target compound **8** by combining two [$^{13}C_2$] glycine units, one of which was *N*-benzylated glycine ester 4 (Scheme 1), and the other was *N*-Boc-protected glycine **5** (Scheme 2). Compound **4** was prepared in four steps via reductive amination,[5] *N*-Boc-protection,[6] esterification, and Boc-removal. The first two steps were performed in a one-pot, two-step manner to avoid isolation of the zwitterionic form of **1** and compound **2** was easily isolated via acid–base extraction. Chromatographic purification was not required for this or any of the following intermediates **3** and **4**, and they could be isolated in good yields by extractive means.

Compound **5** was prepared in one step via Boc-protection of glycine and was coupled with compound **4** using standard coupling conditions.[7] Compound **6** underwent spontaneous ring-closure after Boc-deprotection and subsequent treatment with aqueous base. The resulting diketopiperazine **7** was reduced by $LiAlH_4$ in refluxing THF,[4] affording target compound **8** in nearly 40% overall yield and over 98% isotopic purity. This procedure could easily be executed on a multigram scale and also provides

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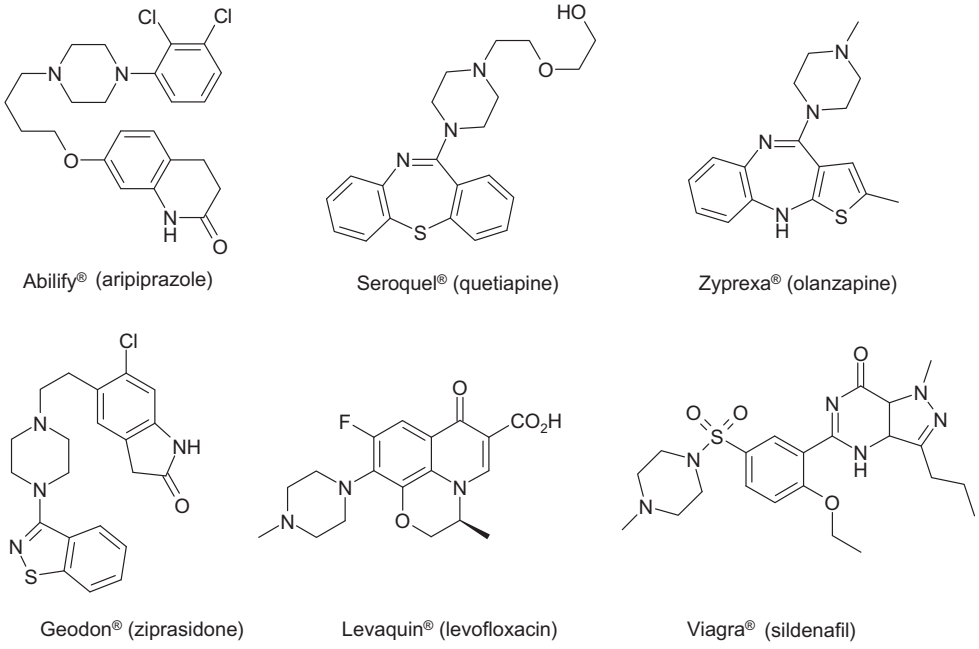
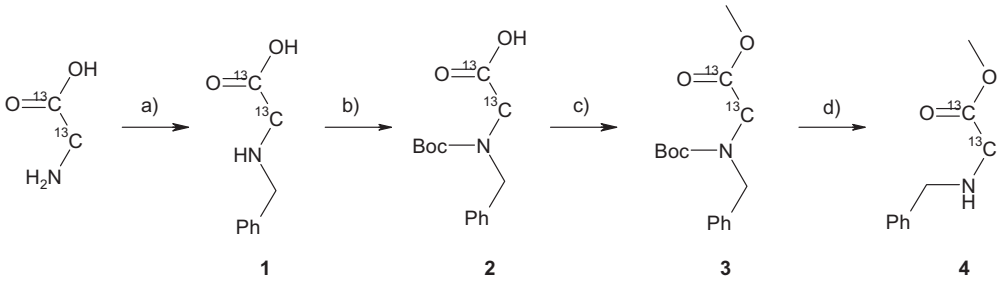
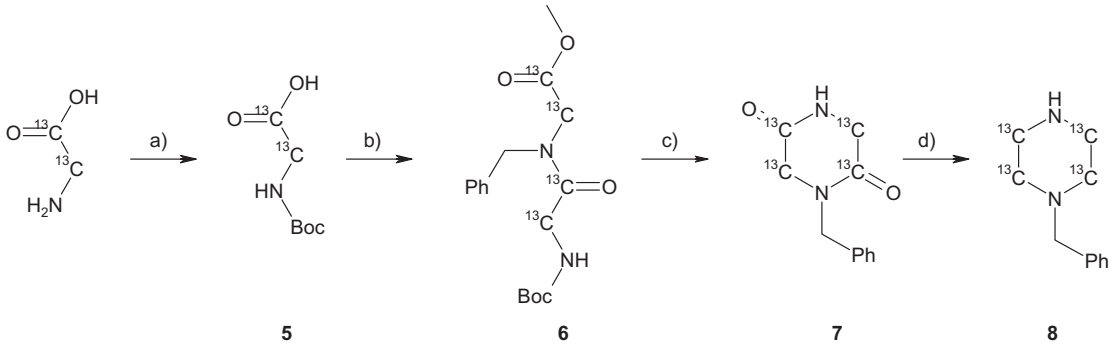


Figure 1. Top selling drugs containing N,N′-disubstituted piperazines.



Scheme 1. Synthesis of **4**. Reagents and conditions (a) benzaldehyde, Et_3N, MeOH, rt, 3 h then $NaBH_4$, overnight, 99%; (b) $(Boc)_2O$, 1,4-dioxane, Et_3N, rt, 2 h, 82% (c) MeI, Cs_2CO_3, DMF, rt, overnight, 88% (d) TFA, CH_2Cl_2, rt, 2 h, 99%.



Scheme 2. Synthesis of **8**. Reagents and conditions (a) $(Boc)_2O$, 1,4-dioxane/H_2O, Et_3N, rt, overnight, 83%; (b) HBTU, DIPEA, CH_2Cl_2, rt, 10 min then **4**, rt, 2 h, 80%; (c) TFA, CH_2Cl_2, rt, overnight then satd aq $NaHCO_3$, rt, 15 min, 90%; (d) $LiAlH_4$, THF, reflux, 2 h, 73%.

the option of introducing, for example, ^{15}N-labeling from [^{15}N] glycine or D-labeling by using $LiAlD_4$ in the final reduction step.

In conclusion, we have reported a reliable and simple procedure for the preparation of [$^{13}C_4$] *N*-benzylpiperazine, which could serve as a versatile building block for labeled piperazine-containing drug candidates.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.084.

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