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Synthesis of ^{15}N-labeled heterocycles *via* the cleavage of C–N bonds of anilines and glycine-^{15}N†

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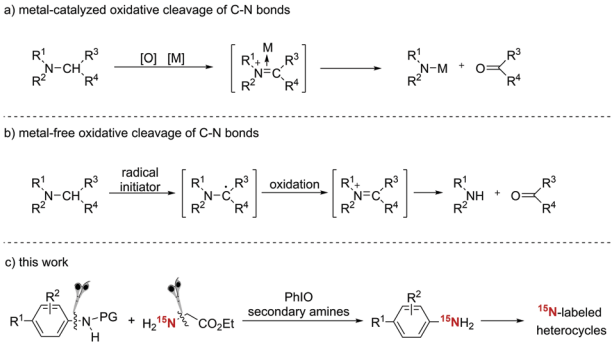
A nitrogen replacement process that directly incorporates the ^{15}N atom of glycine-^{15}N into anilines was reported. The process involves a Csp^2–N bond cleavage of anilines driven by dearomatization and a Csp^3–N bond cleavage of glycine-^{15}N driven by aromatization. A variety of ^{15}N-labeled aromatic heterocycles can be prepared *via* this process.

The cleavage of C–N bonds is one of the most important topics in chemistry because it provides a convenient approach to generate nitrogen or/and carbon sources to facilitate the synthesis of the desired compounds from simple and available starting materials. Compared with the cleavage of the activated C–N bonds such as diazonium salts,[1] ammonium salts,[2] and strained azaheterocycles,[3–5] the cleavage of unactivated C–N bonds of aromatic or aliphatic amines is not easily achievable due to the high C–N bond dissociation energy. In recent years, oxidative cleavage of unactivated C–N bonds has drawn particular attention and made great progress. For example, the groups of Huang,[6] Su,[7] Li,[8] Jiang,[9] and Yin[10] have reported the successful examples of the transition metal catalysed oxidative cleavage of C–N bonds *via* the similar imine/iminium intermediates (Scheme 1a).[11] But notwithstanding these advances, the development of a metal-free oxidative cleavage method for the unactivated C–N bonds under mild conditions is seldom explored, especially for the C–N bonds of primary amines. In the present metal-free cleavage process, the iminium intermediates are normally formed from the radical C–H activation and oxidation (Scheme 1b).[12]

Incorporation of a ^{15}N atom in biologically active molecules is an important method in studying the pharmacokinetics and metabolism of compounds at various stages of drug development.[13] Simultaneously ^{15}N labels is required to enhance the MRI signals[14] by hyperpolarization techniques[15] and has been employed for synthesis of a wide range of small biomolecules used *in vivo* to probe metabolism and function.[16] Thus it is of great significance to develop effective method to introduce a ^{15}N atom into pharmaceutical molecules and biomolecules. ^{15}N-labeled anilines are the key precursors to ^{15}N-labeled aromatic heterocycles. ^{15}N-labeled anilines are normally prepared by the reduction of ^{15}N-labeled nitrobenzene using H^{15}NO$_3$ as nitrogen source,[17] or the Hofmann rearrangement of ^{15}N-labeled benzamide using ^{15}NH$_4$NO$_3$ or ^{15}NH$_4$Cl as nitrogen source.[18] The need for harsh conditions and the use of explosive reagents make many of these methods unsuitable for practical applications. Glycine-^{15}N, an important isotopic labeling amino acid, is widely used as tracer for detecting metabolism or as precursor to other ^{15}N-labeled amino acids. In connection with our recent research on the dearomatization of anilines,[19] we originally conceived that glycine-^{15}N might be ready to undergo an imine exchange reaction with the dearomatized intermediate of anilines. Subsequent aromatization to restore the aromaticity of the imine exchange product might drive a rearrangement to form ^{15}N-labeled anilines.



Scheme 1 Oxidative cleavage of C–N bonds.

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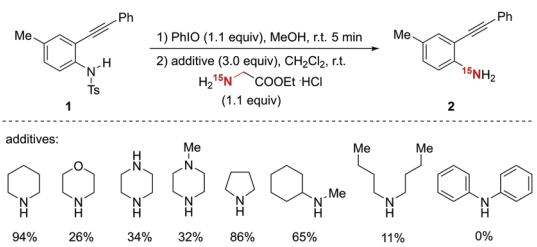
Herein, we report a nitrogen replacement process that directly incorporates the ^{15}N atom of glycine-^{15}N into anilines *via* a Csp^2–N bond cleavage of anilines driven by dearomatization and a Csp^3–N bond cleavage of glycine-^{15}N driven by aromatization. A variety of ^{15}N-labeled aromatic heterocycles can be prepared by using glycine-^{15}N as the nitrogen source (Scheme 1c).

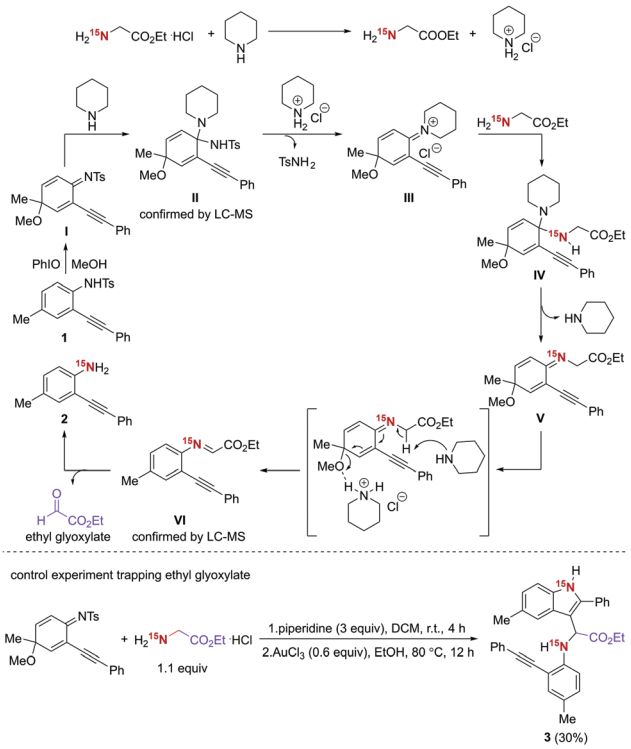
The main challenge to implementation of this tactic was the realization of an efficient imine exchange reaction between the dearomatized intermediate of anilines with glycine-^{15}N because of the multifunctional structural features of the dearomatized intermediate. In an initial test, MeOH was removed *in vacuo* after the oxidative dearomatization of 4-methyl-2-(2-phenylethynyl) benzenamine **1**, and CH_2Cl_2 was used as the solvent for the reaction of the crude dearomatization product with ethyl glycinate-^{15}N. No reaction occurred in the absence of catalyst. The addition of a variety of Lewis acids did not promote the imine exchange reaction but promote a [1,2] methyl group migration and cyclization of the dearomatized intermediate leading to the formation of 4-methyl substituted indoles.[20] Because secondary amines have been widely used to activate α,β-unsaturated compounds *via* an iminium intermediate,[21] 1 equivalent of piperidine was added to promote the imine exchange reaction. To our delight, the formation of ^{15}N-labeled 4-methyl-2-(2-phenylethynyl)benzenamine **2** was obtained in 45% yield. Screening of the ratio of reagents and solvents indicated that, when 3 equivalents of piperidine was employed, the commercial ethyl glycinate-^{15}N hydrochloride could be directly used and the reaction in CH_2Cl_2 at room temperature gave rise to **2** in 94% yield. A variety of secondary amines were then examined, piperidine proved to be the best promoter for the formation of ^{15}N-labeled product **2** (Scheme 2).

A tentative pathway for the piperidine-promoted reaction is depicted in Scheme 3. The inert Csp^2–N bond in 2-alkynylanilines is converted to the C=N bond in 2-alkynylcyclohexadienimine intermediate **I** through oxidative dearomatization. Condensation of piperidine with **I** forms an iminium intermediate **III** that then reacts with ethyl glycinate-^{15}N to generate the second cyclohexadienimine intermediate **V**. Aromatization might be a great driving force to drive a rearrangement to restore the aromaticity and convert the Csp^3–N bond in ethyl glycinate-^{15}N to the C=N bond in the *N*-aryl imine intermediate **VI**. Subsequent hydrolysis of the imine group produces ^{15}N-labeled 2-alkynylanilines.

There is some evidence to support the hypothesized pathway. The analysis of the reaction mixture by LC–MS confirmed the generation of intermediates **II** and **VI**. To capture the ethyl glyoxylate generated from the hydrolysis of intermediate **VI**, 0.6 equivalents of $AuCl_3$ was added into the reaction mixture. Compound **3** which is supposed to be formed by the reaction of two molecules of product **2** with the ethyl glyoxylate was obtained.

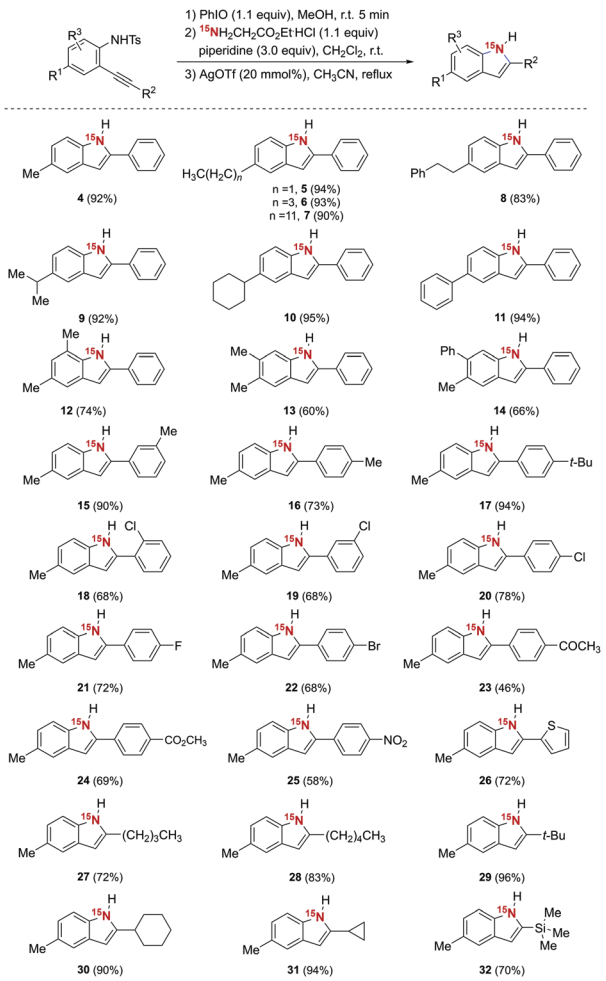


Scheme 2 Evaluation of secondary amines as promoters.



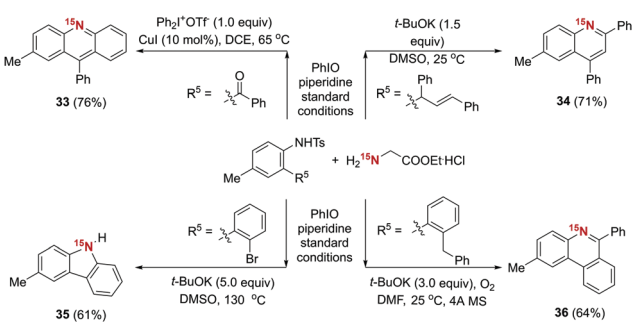
Scheme 3 Tentative reaction pathway.

In the presence of 20 mol% of AgOTf, ^{15}N-labeled 4-methyl-2-(2-phenylethynyl)benzenamine was converted to ^{15}N-labeled indole **4** in an almost quantitative yield. Under the established conditions, the scope for the transformation of 2-alkynylanilines to ^{15}N-labeled indoles was investigated (Scheme 4). The length of the linear alkyl group at the C4 position of 2-alkynylanilines had no influence on the transformation. For example, the reactions of 4-ethyl, 4-butyl and 4-dodecyl-2-(phenylethynyl)aniline gave rise to the corresponding products **5**, **6** and **7** in 94%, 93% and 90% yield, respectively. In addition to the linear alkyl group, isopropyl, cyclohexyl, or phenyl groups can be the *para*-substituent in the 2-alkynylanilines. The steric hindrance caused by the second methyl group or a phenyl group at the C6 or the C5 position of 2-alkynylanilines tended to diminish the yield of compounds **12**, **13** and **14**. A range of functional groups on the benzene ring of the alkynyl moiety were compatible with the reaction conditions. An electronic effect of the functional groups was observed. Reactions with electron-rich substituents such as the methyl or the *tert*-butyl group gave higher yields than those with electron-deficient groups such as the nitro or the carbonyl group or the halogen atoms. Reaction of substrates bearing a thienyl, alkyl, cycloalkyl, or TMS group at the 2-alkynyl moiety proceeded smoothly leading to the formation of the corresponding 2-substituted ^{15}N-labeled indoles in moderate to good yield.



Scheme 4 The scope of transformation of 2-alkynylanilines to ^{15}N-labeled indoles.

In addition to the ^{15}N-labeled indoles, this transformation could also be used in the synthesis of many other ^{15}N-labeled heterocycles. For example, as shown in Scheme 5, by using the corresponding 2-substituted anilines as substrates, the ^{15}N-labeled acridine **33**, quinoline **34**, carbazole **35**, and phenanthridine **36** could be prepared through the nitrogen replacement process and subsequent condensation or cyclization reactions. When the R^5 group is a butyl group or a hydrogen atom, the reaction under the standard conditions was complex.



Scheme 5 Synthesis of ^{15}N-labeled heterocycles.

In summary, we have developed a nitrogen replacement process that directly incorporates the ^{15}N atom of glycine-^{15}N into anilines. The process involves a Csp^2–N bond cleavage of anilines driven by dearomatization and a Csp^3–N bond cleavage of glycine-^{15}N driven by aromatization. A variety of ^{15}N-labeled aromatic heterocycles including indoles, acridines, quinolines, carbazoles and phenanthridines can be prepared *via* this process. The extension of this method to other aniline system and the application of this strategy to the synthesis of useful ^{15}N-labeled molecules are in progress.

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Conflicts of interest

There are no conflicts to declare.

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