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Novel synthesis of benzofuran- and indol-2-yl-methanamine derivatives

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ABSTRACT

We report on a novel synthesis towards benzofuran-2-yl-methanamine and indol-2-yl-methanamine derivatives by using *ortho*-methoxy and *ortho*-nitro substituted phenylacetic acids as starting material, respectively. For each compound series, a key intermediate bearing the oxazole-4-carboxylic acid methylester moiety was produced. Refluxing the *ortho*-methoxy series in HBr/HAc produced the desired benzofuran-2-yl-methanamines. Accordingly, for the synthesis of indoles the nitro-group was first reduced and refluxing these intermediates in HCl gave the corresponding indol-2-yl-methanamines. The method worked well with electron donating substituents. Limitations regarding electron withdrawing substituents are discussed. This straightforward synthetic procedure can be a useful approach to generate a variety of substituted benzofuran-2-yl-methanamine and indol-2-yl-methanamine compounds by starting from readily available phenylacetic acid derivatives.

Benzofurane and indole scaffolds are present in a huge number of chemical entities including compounds showing interesting biological activities, among them are compounds of natural origin.[1–3] In line with this notion, chemical components or building blocks bearing the benzofurane and indole moiety are of significant importance in synthetic strategies leading to the desired structures.

In the present Letter we report on the discovery of a novel straightforward synthesis towards benzofuran-2-yl-methanamines and indol-2-yl-methanamines, respectively. These products were coincidentally obtained in our recent medicinal chemistry project towards the preparation of (1*H*)-pyrazin-2-ones.[4] Herein, the original synthetic approach involved 1-amino-3-(aryl)propan-2-ones (α-aminoketones, e.g., **1**, Scheme 1 A) as key intermediates. These α-aminoketones were typically produced from phenylacetic acid derivatives (**1a**) by reaction with methyl-2-isocyanoacetate to build their corresponding oxazole-4-carboxylic acid methylesters **1b**.[5] Subsequently, the acidic cleavage of the oxazole moiety was used as a suitable method to avoid dimerization of the (non-protonated) α-aminoketones.[4] However, by refluxing methyl 5[(2-methoxyphenyl)methyl]oxazole-4-carboxylate **2b** in HBr we obtained benzofuran-2-yl-methanamine **2** in good yield and high purity instead of the expected 1-amino-3-(*o*-methoxyphenyl) propan-2-one (Scheme 1 B).[6] In line with this notion, comparable procedures involving HBr via cleavage of *ortho*-methoxy groups were employed for the synthesis of other benzofurane derivatives.[7–12]

Consequently, the observation that **2** could be produced from **2a** prompted us to also investigate the method for the synthesis of some analogue indole derivatives. In fact, when *o*-nitrophenylacetic acid **7a** was employed as starting material, indol-2-yl-methanamine **7** could be produced accordingly (upon reduction of the nitro to the aniline moiety, Scheme 1C).[13]

A large variety of methods is available for the synthesis of benzofurane- and indole derivatives in general (for recent reviews see literature[14,15]). However, only a few methods have been reported for the preparation of heteroaryl-2-yl-methanamines.[3,16,17] While most of the relevant publications regarding the preparation and applications of heteroaryl-2-yl-methanamines (mostly for drug discovery projects) can be found in patent literature from commercial entities,[18] some have been published by academic researchers. For instance, Russo et al.[16] developed a Sonogashira–Linstrumelle reaction starting from 2-iodophenol leading to benzofuran-2-yl-methanamines. Recently, a chemoenzymatic preparation of benzofuran-2-yl-ethanamines was published.[3] Likewise, only a few methods are available for the synthesis of indol-2-yl-methanamines.[16] However, these methods often involve drawbacks such as

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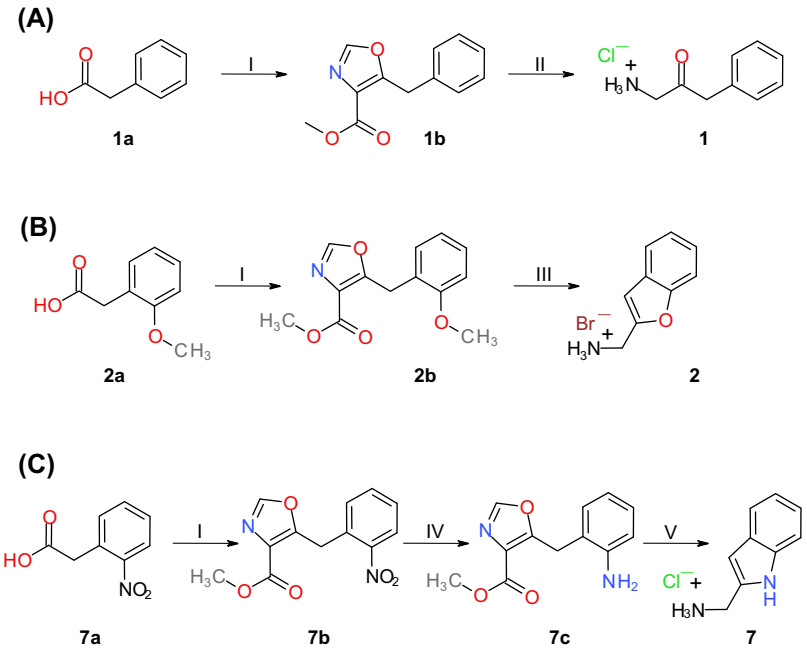
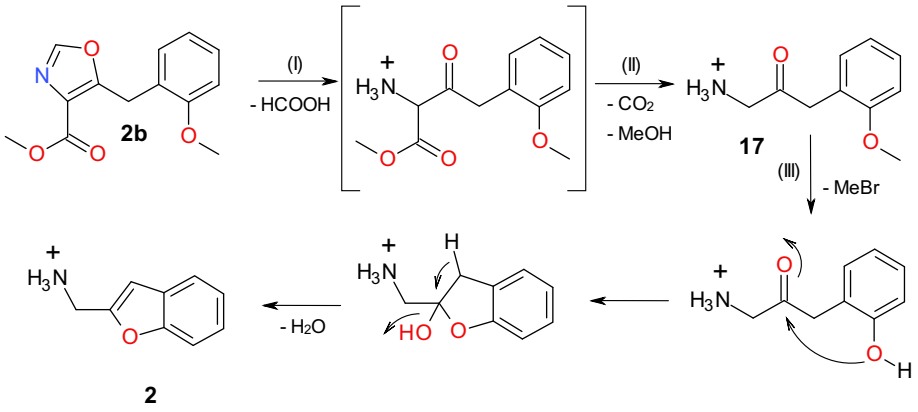


Scheme 1. (A) Synthesis of α-aminoketones as key intermediates in our recent project towards the synthesis of (1*H*)-pyrazin-2-ones; (B) preparation of benzofuran-2-yl-methanamine by using *o*-methoxyphenylacetic acid as starting material; (C) preparation of indol-2-yl-methanamine by using *o*-nitrophenylacetic acid as starting material. Reactants and conditions **I**: 1. CDI, 2. methyl-2-isocyanoacetate; **II**: HCl, reflux; **III**: HBr, reflux; **IV**: Pd/C, cyclohexene, microwave heating; **V**: HCl, reflux.

expensive amounts of catalysts, prolonged reaction times, tedious work-up procedures or limited availability of starting material with the desired decoration.

Regarding the present method, the formation of heteroaryl-2-yl-methanamines from the oxazole moiety is discussed in Scheme 2 exemplified by the synthesis of compound **2** starting from **2b** (the mechanism for building the oxazole moiety from arylacetic acid **2a** by reaction with methyl-2-isocyanoacetate has been published elsewhere[5]). We propose that the reaction towards the formation of benzofuran-2-yl-methanamine starts by acid mediated degradation of the oxazole ring in **2b** (Scheme 2). Ester cleavage and subsequent decarboxylation produce the protonated α-aminoketone. When HBr is used a cleavage of the methoxy-ether occurs to form the free phenol-function. Subsequently, the benzofurane ring in **2** is build by means of a Knoevenagel-reaction. In line with this notion, when HCl was employed (instead of HBr) the reaction produces 1-amino-3-(2-methoxyphenyl)propan-2-one-HCl (**17**, Scheme 2). This indicates that the methoxy moiety remains stable under these conditions. In turn, refluxing α-aminoketone **17** in HBr yielded the respective benzofuran-2-yl-methanamine **2** hence providing further evidence for the proposed reaction mechanism.

Thus, we became interested in the question if this procedure could lead to a general synthetic method towards substituted benzofuran-2-yl-methanamines and indol-2-yl-methanamines, respectively. Therefore, in order to characterize this reaction in more detail for each series, we investigated the application for a set of substituted phenylacetic acids as starting material. Accordingly, the method was successfully applied to the synthesis of the benzofuran-2-yl-methanamines **2**–**6** and indol-2-yl-methan-



Scheme 2. Proposed reaction mechanism exemplified for the formation of benzofuran-2-yl-methanamine **2** starting from key intermediate methyl-5-[(2-methoxyphenyl)methyl]oxazole-4-carboxylate (compound **2b**). Reactants and conditions **I/II**: reflux, HCl, MeOH; **III**: reflux, HBr, HAc. A comparable mechanism is discussed for the formation of the indol-2-yl-methanamines, for example, **7** by using the corresponding methyl-5-[(2-aminophenyl)methyl]oxazole-4-carboxylate **7c** and HCl, not shown).