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Highly efficient one-pot amination of carboxylate-substituted nitrogen-containing heteroaryl chlorides via Staudinger reaction

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ABSTRACT

An efficient one-pot method for the synthesis of *tert*-butyl 6-aminonicotinate (**5**) is described. The key transformation involves displacement of the chloro group in *tert*-butyl 6-chloronicotinate (**2**) with azide followed by a Staudinger reaction. The scope of this methodology is further extended for the synthesis of a series of carboxylate-substituted heteroaryl amines. In particular, we synthesized *tert*-butyl carboxylate-substituted amino-pyridine, -pyridazine, and -pyrazine. In addition to one-pot conversion, short reaction time, simplicity of operation, ease of purification, and good yields are the key advantages of this methodology.

Aminonicotinic acid is a commonly used building block in the synthesis of many bioactive molecules,[1] providing access to chemical diversity with amine and carboxylate functionality. In particular, 6-aminonicotinic acid is an important building block toward many pharmacologically active compounds which exhibit antidiabetic,[2] anticancer,[3] and antiinflammatory[4] activity (Fig. 1). Some of these compounds act as a modulator for kinases wherein the amine is derivatized to an amide and is involved in hydrogen bond donor and acceptor interactions via the NH in amide and the nitrogen in pyridine.[2a,5] Recently, in one of our ongoing programs methyl 6-aminonicotinate was coupled with a carboxylic acid to obtain the amide scaffold (**1a**, Fig. 2).[6] Subsequent hydrolysis of the methyl

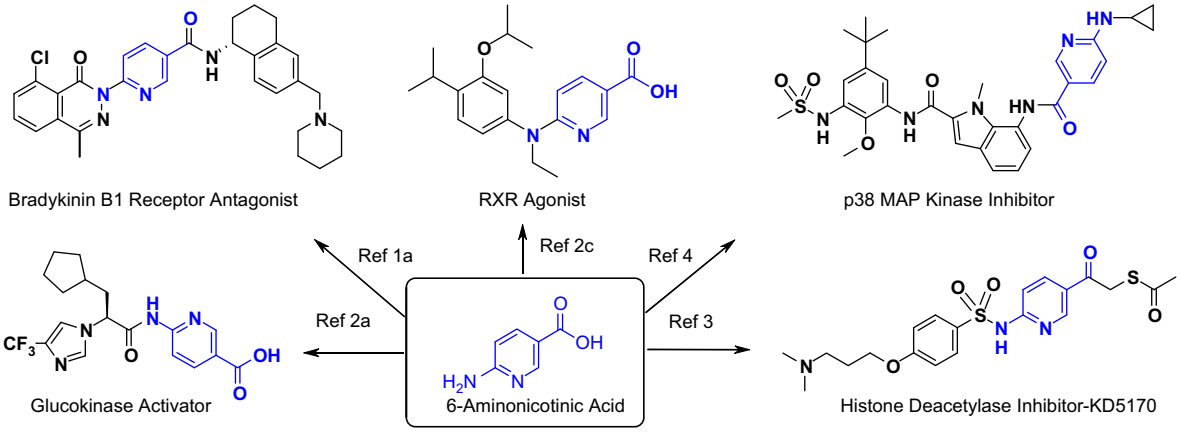

Figure 1. Representative bioactive compounds bearing 6-aminonicotinic acid as a structural fragment.

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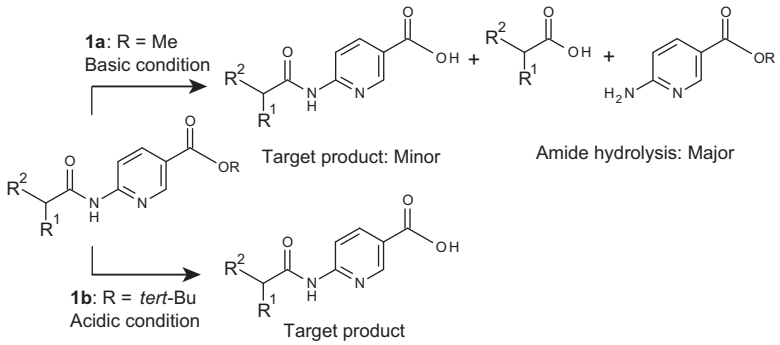


Figure 2. Hydrolysis of nicotinate derivative.

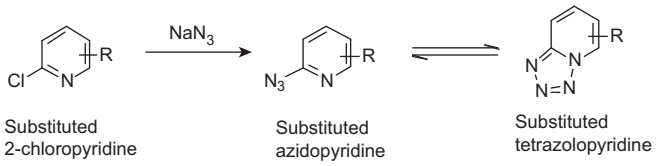
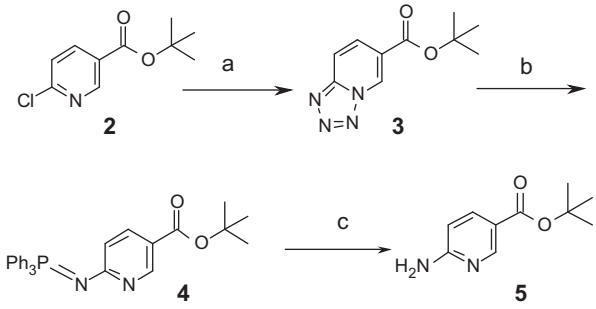


Figure 3. Reaction of sodium azide with substituted 2-chloropyridin.



Scheme 1. Reagents and conditions: (a) NaN_3 (2 equiv), DMSO, 120 °C, 10 h, 97%; (b) triphenylphosphine (2 equiv), DMSO, 120 °C, 2 h, 93%; (c) DMSO, 1 N HCl, 90 °C, 2 h, 90%.

ester functionality in **1a** using sodium or lithium hydroxide at room temperature afforded the nicotinic acid derivative as a target product, unfortunately in very low yield (15–20% yield). It was observed that the amide hydrolysis was a major side reaction for **1a** under basic conditions. To circumvent this issue we sought to employ *tert*-butyl 6-aminonicotinate in place of methyl 6-aminonicotinate to synthesize the hydrolytically-labile amide scaffold **1b**, which would allow for exclusive hydrolysis of the *tert*-butyl ester under acidic conditions. While this manuscript was under preparation, an article appeared describing the synthesis of 2, 4-, 5-, and 6-aminonicotinic acid *tert*-butyl esters from the corresponding chloro derivative via aminolysis with hydrazine hydrate as a key step.[7] Herein, we report a facile, one-pot methodology for the synthesis of *tert*-butyl 6-aminonicotinate and various carboxylate-substituted heteroaryl amines.

Our initial attempt to access the target product involved the nucleophilic displacement of the chloro group in *tert*-butyl 6-chloronicotinate (**2**)[8] employing either ammonium hydroxide or neat ammonia.[9] Reactions were found to be inefficient even though carried out in sealed tube with heating for several hours. Next, we tried the copper-catalyzed direct amination of *tert*-butyl 6-chloronicotinate (**2**) with sodium azide[10a] and trimethylsilylazide[10b] as amine source.

However, these reactions gave the desired product in low yield along with side products.[10] Alternatively, we sought to obtain the desired amine from **2** by displacement of chlorine with azide followed by a Staudinger reaction. Under typical Staudinger conditions, azide derivatives are reduced by triphenylphosphine (PPh_3) to access iminophosphoranes, which generate amine products upon hydrolysis under acidic conditions.[11] However, it has been reported in the literature that 2-chloropyridine reacts with sodium azide to give the corresponding azido-pyridine and tetrazolo[1,5-*a*]pyridine (Fig. 3).[12] The equilibrium of these products is governed by several factors such as the nature of substituents (R), solvent, and reaction temperature.[12c,12d]

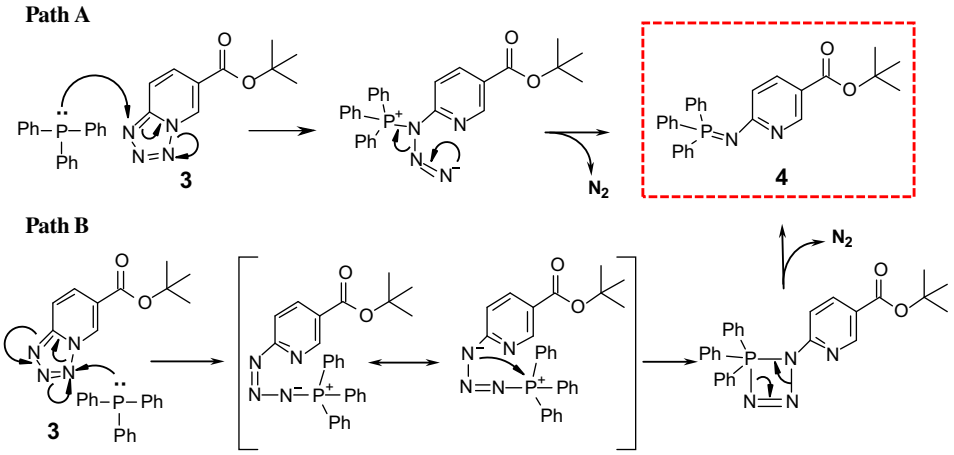


Figure 4. Putative mechanism for the formation of iminophosphorane **4**.