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Supramolecular Anion Recognition Mediates One-Pot Synthesis of 3-Amino-[1,2,4]-triazolo Pyridines from Thiosemicarbazides

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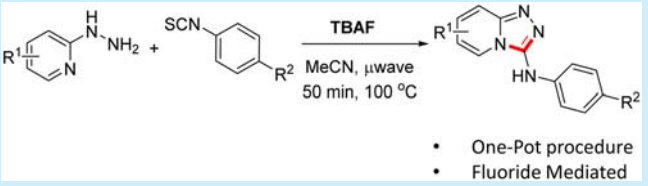
Supporting Information

ABSTRACT: A facile one-pot synthesis of 3-amino-[1,2,4]-triazolo[4,3-*a*]pyridines from thiosemicarbazides through anion mediated synthesis is reported. Thiosemicarbazides derived from 2-hydrazino pyridine, 5-chloro 2-hydrazino pyridine, and 2-hydrazine quinoline were formed in situ as anion receptors in the presence of TBAF. Under microwave heating, thiosemicarbazides furnished the triazolo pyridines in good to moderate yields. The formation of the thiosemicarbazides hydrogen bonding anion receptors was critical in cascading the reaction toward the formation of the triazolo pyridines.



Triazolo pyridines are an important class of organic molecules for medicinal chemistry and are associated with a broad range of biological activity.[1,2] [1,2,4]Triazolo pyridine analogues display potent activity against p38 mitogen activated protein kinase (MAKP); a key enzyme in regulating proinflammatory mediators such as IL1-β and TNF-α. Selective inhibitors of p38 are of therapeutic interest for the treatment of chronic obstructive pulmonary disease (COPD).[3] [1,2,4]-Triazolo pyridine analogues also function as inhibitors of Akt1 and Akt2 kinases involved in the regulation of survival, proliferation, and growth of cells,[4] and of JAK2, a critical target for oncology.[5] However, detailed investigation into their biological function has been hampered due to limited suitable methodologies for their synthesis. A number of multistep methods have been reported, usually involving highly toxic desulfurizing reagents.[6] Recently Swinnen and co-workers[7] reported a synthesis, starting from thiosemicarbazides, using polymer-supported Mukaiyama's reagent. They proposed a reaction mechanism via a highly reactive carbodiimide intermediate that undergoes cyclization to yield the triazolo pyridine core. Herein, we report the synthesis of 3-amino-[1,2,4]-triazolo[4,3-*a*]pyridine analogues (Table 1), starting from 2-hydrazino pyridines in a one-pot synthesis involving tetrabutylammonium fluoride (TBAF) as a reagent.[8] This approach was inspired by our interest in employing supramolecular structures in synthetic chemistry,[9a,b] where *in situ* formation of thiosemicarbazide based anion receptors is a key step. Hydrogen bonding receptors, such as urea, thioureas, squaramides, and amides, are commonly used in supramolecular anion chemistry and in organocatalysis.[10,11] However, the use of such structures as *"reagents"* in organic synthesis is not widely explored; the exception being the use of thiourea in the preparation of guanidinium structures (via thiouronium formation). TBAF is widely employed in organic synthesis as a F^- source and as a mild base. It is known to act as a catalyst for the reduction of aldehydes and ketones using hydrosilanes and also for the chemoselective reduction reactions of phthalimides and imidazolidine-2,4-diones.[12] We have used TBAF to activate aryl amines toward converting CO_2 to HCO_3, via the formation of HF_2^-.[13] TBAF is used in fluorine mediated homocoupling of aryl halides[14] and as a mild base for the elimination reaction of bromoalkenes to alkynes.[15] Herein we demonstrate that the formation of triazolo pyridines by simply mixing 2-hydrazino pyridines with TBAF and isothiocyanates in one pot under microwave irradiation.

Thiosemicarbazides recognize anions through hydrogen bonding where significant color changes can occur due to deprotonation of a "thiourea proton" by basic anions.[16−18] This was confirmed using NMR spectroscopy and X-ray crystallography.[16,24] On further investigation, we discovered that treatment with dry TBAF could convert the thiosemicarbazide into a new product upon standing. The reaction mixture yielded crystals suitable for X-ray crystal structure analysis, which showed the successful formation of the [1,2,4]triazolo pyridine product.

In order to investigate the scope, we used three different hydrazinopyridine starting materials, namely 2-hydrazino-pyridine, 5-chloro-2-hydrazinopyridine, and 2- hydrazino-quinoline (Table 1). For each substrate, we investigated the TBAF mediated cyclization reaction with eight different isothiocyanates, bearing either an electron-withdrawing (EW) and electron-donating (ED) substituent on the phenyl ring. In the case of 2-hydrazino pyridine, all of the eight isothiocyanates furnished the expected [1,2,4]-triazolo[4,3-*a*]pyridine amine derivatives. Irrespective of the nature of the substituent on the

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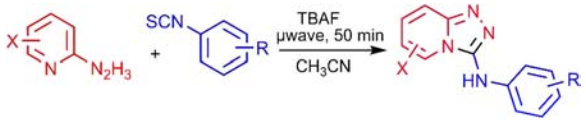
Table 1. Reaction Conditions of 3-Amino-1,2,4-triazolo[4,3-*a*]pyridines



X-N_2H_3	R-NCS	TBAF (equiv)	yield (%)[a]	product
		1.1	27	
		2.1	56	1
		1.1	55	2
		1.1	60	3
		1.1	76	4
		1.1	73	5
		1.1	20	6
		1.1	26	7
		1.1	29	8
		1.1	26	
		3.1	56	9
		2.1	14	10
		2.1	18	11
		3.1	42	12
		3.1	38	13

[a]Isolated yield. All reactions were carried out under microwave irradiation in a sealed vial. TBAF was dried over P_2O_5 under vacuum.

phenyl ring of the isothiocyanate, all of the reactions furnished the desired triazolo pyridines, after 50 min of microwave irradiation, at 100 °C. However, it is noteworthy that the thiosemicarbazides formed in situ from isothiocyanates possessing an electron-withdrawing substituent tended to undergo cyclization much more efficiently (e.g., **1**−**5**). In fact, the more electron-rich isothiocyanates (e.g., **6**−**8**) gave substantially lower yields, as summarized in Table 1. For these reactions, the thiosemicarbazide intermediates were obtained in *ca.* 15−30% yields upon isolation using automatic SiO_2 column chromatography. Because of this drawback, we performed these reactions with increasing amounts (1.1, 2.1, 3.1, and 4.5 equiv) of TBAF, but in general, no significant improvement in yield was observed. Only for the formation of *para*-nitro derivative **1** was there a noticeable enhancement, where the yield of **1** increased from 27% to 56% upon using 2.1 equiv of TBAF.

Expanding upon the above-mentioned studies, we extended this methodology to 5-chloro-2-hydrozino pyridine and 2-hydrazino quinolone using the same eight isothiocyanate derivatives. The 5-chloro-2-hydrazino pyridines furnished the triazole analogues **9**, **10**, and **11**, Table 1. However, irrespective of the equivalents of TBAF employed, no conversion to the triazole was observed with the remaining five isothiocyanates. In fact, for all of these reactions, the corresponding thiosemicarbazides were obtained as the major products. This suggests that the nature of the substituents on both the pyridinyl and phenyl component of the thiosemicarbazides plays a critical role in the cyclization process, with electron-withdrawing groups on the pyridine ring lowering the yield of the cyclization process. Similar to the 5-chloro derivatives, the more sterically challenging 2-hydrazino quinoline also yielded only three triazolo pyridines. In the case of **12**, an increase in the equivalents of TBAF from 1.1 to 3.1 equiv resulted in an improved yield of the triazole to 38%, with the 4-CF_3 and 3,5-di-CF_3 triazoles being observed.

To probe the mechanism, we investigated the reaction using ^{1}H NMR spectroscopy ($(CD_3)_2SO$, 600 MHz), where the thiosemicarbazide exhibited characteristic signals for the "thiourea" protons, resonating between 10.2 and 8.1 and 10.4−8.2 ppm, depending on the nature of the aryl group. Treatment of the thiosemicarbazide with TBAF resulted in the disappearance of the thiourea proton, suggesting fluoride-mediated deprotonation is the initial step, as shown in Figure 2a. The resulting organic anion undergoes cyclization *in situ* with loss of sulfur to form the desired triazole, which has a new NH-proton appearing between 8.5 and 10.2 ppm, Figure 1b. This would suggest that the mechanism involves (a) the formation of the thiosemicarbazide, (b) anion recognition, and (c) deprotonation of the thiourea.

Gratifyingly, this process could also be followed by X-ray crystallography, as single crystals for X-ray structure analysis were isolated and resolved for the deprotonated thiosemicarbazides, elemental sulfur, and 6 of the 14 1,2,4-triazolo pyridines products.[24] Some of these structures are shown in Figure 2, clearly demonstrating the successful formation of the desired products from all of the hydrazine starting materials.

Further analysis of the synthesis showed that additional equivalents of TBAF were required to promote the ring closing of the triazolo adducts **9** and **12**. This raises the interesting possibility that TBAF may have a dual role in the reaction, functioning both as a base to deprotonate the thiosemicarbazides and as a desulfurizing agent to promote the cyclization process. In the literature, desulfurization is accomplished using toxic heavy metals oxides such as Pb_2O_4, $HgCl_2$, $Hg(OAc)_2$, HgO, methyl iodide, or highly reactive acid halides such as phosgene and thionyl chloride.[20,21] In some reactions photo-

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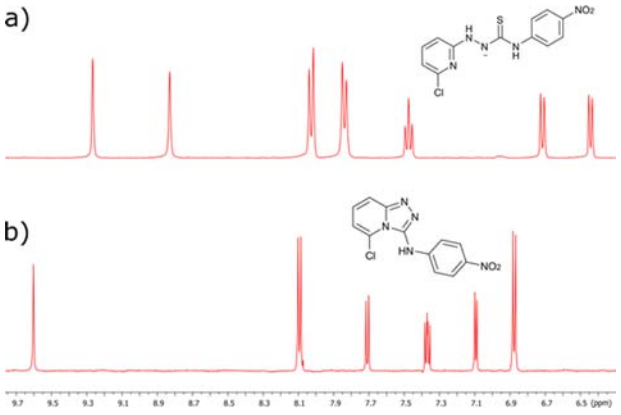


Figure 1. (a) ^{1}H NMR ($(CD_3)_2SO$, 600 MHz) of **9b** (deprotonated) and (b) **9**.

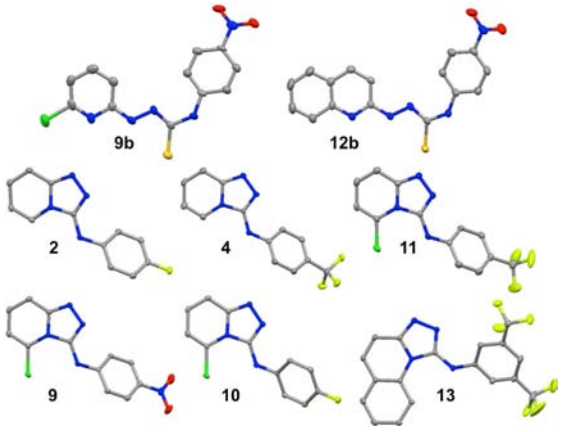


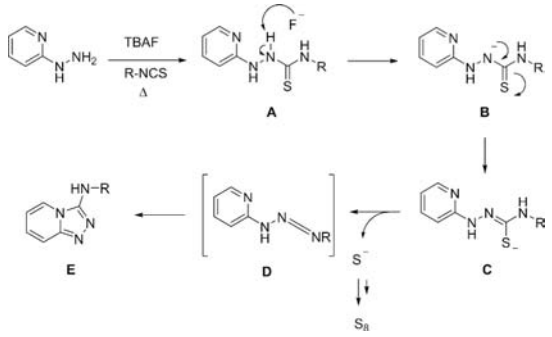
Figure 2. Solid state crystal structures.

irradiation in the presence of benzophenone promotes desulfurization.[22] Because of this, additional control experiments were performed. First, the synthesis of thiosemicarbazides was attempted in the absence of TBAF in order to determine if F^- was necessarily required for the cyclization reaction (Table 1, Supporting Information). These studies found that, irrespective of the substituent on the phenyl ring of the isothiocyanate, the thiosemicarbazides were only isolated as the prime product. Moreover, when the reactions were performed for 180 min, only thiosemicarbazide formation was observed and no cyclized product was isolated, demonstrating that the deprotonation process was an essential part of the synthesis of the desired products.

With this in mind, we also explored the use of other anions such as AcO^-, Cl^-, $H_2PO_4^-$, and OH^-. However, F^- showed by far the best conversion of the thiosemicarbazides to the triazoles. The remaining anions showed either poor conversions or hardly any at all, the order of reactivity being: $F^- > AcO^- > H_2PO_4^- > OH^- > Cl^-$. This further confirms the importance of the deprotonation step, as Cl^- is not normally not considered a "good" anion for the deprotonation of ureas and thioureas.[23] Hence, it is clearly evident from our results that F^- is mediating the in situ formation of the triazolo pyridines.

Based on these results, a plausible reaction mechanism for the triazolo pyridine synthesis is illustrated in Scheme 1; the first step involves the formation of thiosemicarbazide **A**. This is followed by anion recognition, in situ deprotonation of the thiosemicarbazide by F^-, and the generation of **B** which is

Scheme 1. Proposed mechanism for the formation of 1,2,4-Triazolo Pyridyl-3-amines



evident from both NMR and X-ray crystal structure analysis. Subsequent desulfurization to a carbodiimide intermediate **D** and intramolecular cyclization afford the 1,2,4-triazole **E**.

In conclusion, we have successfully developed a novel, efficient, transition-metal-free, one-pot protocol for the synthesis of biologically relevant 3-amino-[1,2,4]-triazolo[4,3-*a*]pyridines. Control experiments provided insight into the critical role of the F^- anion in the reaction as a base for deprotonation of the *in situ* formed thiosemicarbazide, which is the key step for the cyclization to the triazole core. We show that the substituents on both aryl starting materials have a major effect on the yield of the cyclization reaction, where EW-substituents tend to furnish improved yields of triazoles over ED groups. This methodology can be applied and extended to a variety of hydrazino pyridines to produce a broad range of 1,2,4-triazolo pyridyl amines in an efficient manner. Further expansion of the substrate scope is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03645.

Experimental procedures; HRMS analysis data of all new compounds (PDF)
NMR characterization (PDF)

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Notes

The authors declare no competing financial interest.

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