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Base-Mediated Hydroamination of Propargylamine: A Regioselective Intramolecular 5-*exo-dig* Cycloisomerization en Route to Imidazole-2-thione

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Supporting Information

ABSTRACT: An intramolecular transition-metal-free base-mediated hydroamination of propargylamine with isothiocyanates has been achieved. This atom-economical, regioselective intramolecular 5-*exo-dig* cycloisomerization was utilized for the one-pot synthesis of diversely substituted imidazole-2-thione and spiro-cyclic imidazolidine-2-thione. The reaction goes to completion at room temperature via propargylthiourea and 65−97% isolated yields were obtained.

The hydroamination reaction is a direct addition of nitrogen and hydrogen on carbon−carbon multiple bonds.[1] Hydroamination poses a significant challenge due to repulsion between a nitrogen lone pair and the olefin/alkyne π system, and it is also difficult to control the regioselectivity (Markovnikov vs anti-Markovnikov) of hydroamination.[2] Hydroamination reactions can be classified as acid-catalyzed,[3] base-catalyzed,[4] radical-mediated,[5] and transition-metal-catalyzed hydroaminations.[6] Among these, transition-metal-catalyzed hydroamination reactions are the most popular and extensively studied due to lower activation energy and wide substrate scope as compared to other methods.[7] Many research groups have used hydroamination as a key step for the total synthesis of natural products.[8]

Van der Eycken et al. reported $AgNO_3$-mediated diversity-oriented synthesis of 2-iminoimidazolines (Scheme 1A). They have used this methodology for the total synthesis of 2-aminoimidazole alkaloids of the naamine family.[9] Recently, a one-pot protocol based on an Ag(I)-catalyzed cycloisomerization of propargylurea, derived from secondary propargylamine and isocyanate, was developed for making a 2-imidazolone core (Scheme 1B).[10] Fokin and co-workers reported the construction of imidazolones via a Rh(II)-catalyzed transannulation reaction of 1-sulfonyl-1,2,3-triazoles with heterocumulenes (Scheme 1C).[11]

Knochel et al. reported the base-catalyzed hydroamination of alkyne with substituted aniline and heterocyclic amines using catalytic $CsOH{\cdot}H_2O$ in NMP.[12] Intramolecular reaction of 2-(2-alkynyl)anilines under the above conditions gave access to 2-substituted indoles.[13] Imidazole-2-thione core is a key structural component of several bioactive molecules, and large numbers of synthetic approaches have been reported for the formation of this core.[14] But synthesis of imidazole-2-thiones by hydroamination reaction of propargylamine remains an unexplored field. Apart from biological importance of imidazole-2-thiones[15] they can be used for the generation of novel *N*-heterocyclic carbenes (NHCs).[16] Inspired by metal-[17] and base-catalyzed hydroamination reactions,[18] we saw an opportunity to develop a hydroamination of propargyl(thio)urea which will give us an easy access to imidazole-2-(thio)ones. All our efforts in this context have been summarized in this exercise.

To begin, we explored the transition-metal catalyst for a reaction between propargylamine[19] and isothiocyanate. When propargylamine **1a** was reacted with phenyl isothiocyanate at room temperature in the presence of 15 mol % of $AgNO_3$ in acetonitrile, to our disappointment it did not result in formation of any of the possible product (Scheme 1A); instead, we observed decomposition of the starting materials. Although it is well established in the literature that hydroamination of propargylguanidine using a catalytic amount of $AgNO_3$ affords 2-iminoimidazoline in almost quantitative yield by *5-exo-dig* heterocyclization.[9] In the present case, sulfur in propargylthiourea **2a** might be poisoning the catalyst, thus inhibiting the hydroamination reaction. A similar observation was made by Van der Eycken et al.[9] where they failed to carry out guanylation and cyclization simultaneously with the Ag (I) catalyst in the presence of di-Boc-protected thiourea, probably due to the formation of insoluble silver sulfide (Scheme 1).

Next we turned our attention toward base-catalyzed hydroamination. The results of this study are summarized in Table 1.When propargylamine **1a** was treated with phenyl isothiocyanate in DMF using K_2CO_3 as a base, we observed formation of 33% of cyclized product **3a** (Table 1, entry 7).

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Scheme 1. Transition-Metal-Catalyzed Routes to Imidazole Derivatives

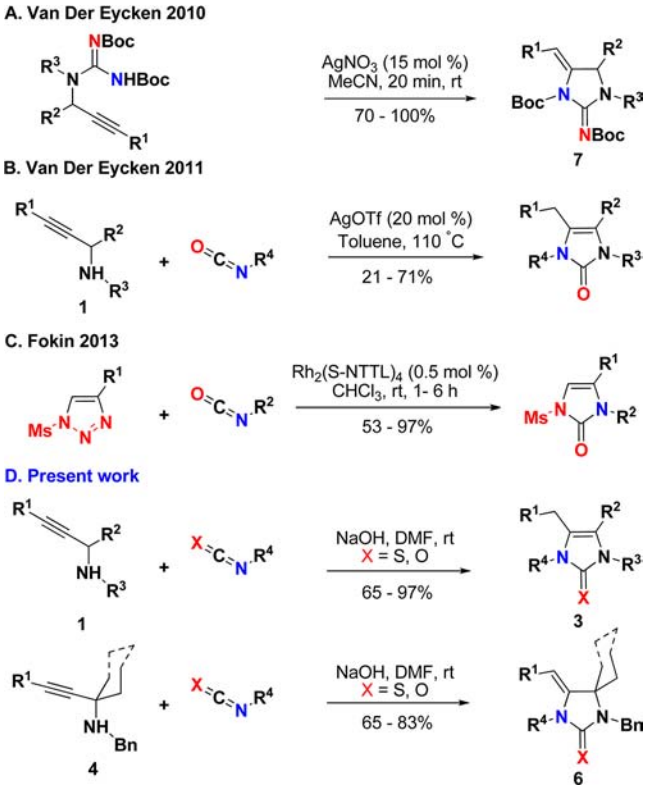
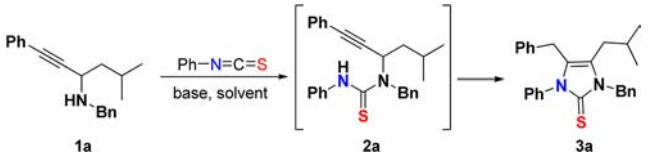


Table 1. Optimization of Reaction Conditions for the One-Pot Synthesis of Imidazolidine-2-thione



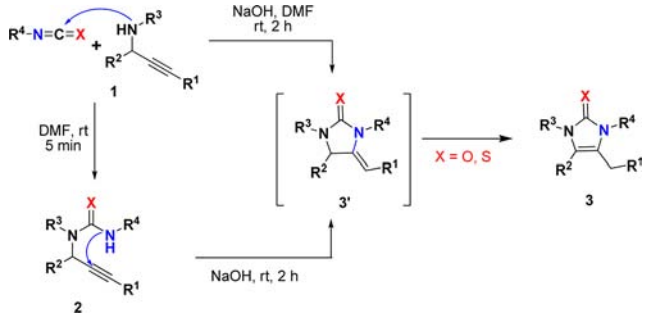
entry[a]	solvent	base	equiv	time (h)	yield[b] (%)
1	DMF			12	(96)[c]
2	THF	NaOH[d]	1.0	5	88
3	THF	K_2CO_3	1.0	12	18
4	THF	Et_3N	1.0	4	42
5	THF	NaO^{t}Bu	1.0	3	90
6	THF	NaH	1.0	12	13
7	DMF	K_2CO_3	1.0	12	33
8	DMF	NaOMe	1.0	3	66
9	DMF	NaOH[d]	0.2	8	65
10	DMF	NaOH[d]	1.0	2	97
11	DMF	NaO^{t}Bu	1.0	2	94
12	Toluene	NaOH[d]	1.0	12	75

[a]All of the reactions were performed at 25 °C with propargylamine (1.0 mmol), PhNCS (1.0 mmol), base (1.0 mmol), and solvent (5 mL). [b]Isolated yields after column chromatography. [c]Isolated yield of **2a**. [d]Powderd NaOH gave the best results.

When this reaction was done in DMF without base, propargylthiourea **2a** was formed as a sole product (Table 1, entry 1). The above two observations emphasize the role of a base in the hydroamination of propargylthiourea. Change of solvent to THF only gave 18% of the desired **3a** (Table 1, entry 3). Use of organic base Et_3N resulted in the formation of **3a** in moderate yield (Table 1, entry 4). Use of strong base NaH afforded **3a** in poor yield (Table 1, entry 6). Our aim was to optimize this base-mediated hydroamination reaction in a manner amenable for exclusive formation of **3a**. To our delight when the reaction was carried out using NaO^{t}Bu as a base in THF, desired product **3a** was obtained in 90% yield (Table 1, entry 5). The yield of **3a** was increased to 94% when DMF was used as a solvent (Table 1, entry 11). The product **3a** was exclusively formed by regioselective intramolecular 5-*exo-dig* cycloisomerization of propargylthiourea which was confirmed by spectroscopic tools. In presence of NaOMe, **3a** was obtained in moderate yield (66%) (Table 1, entry 8). Hydroamination when carried out in the presence of powdered NaOH in DMF afforded imidazole-2-thione **3a** in 97% yield (Table 1, entry 10). The reaction was sluggish when only 0.2 equiv of powdered NaOH was used and only 65% of **3a** was isolated (Table 1, entry 9). The superbasic KOH/DMSO system has been employed in hydroamination of various aryl acetylenes with nitrogen heterocycles.[20] Powdered NaOH also gave desired product **3a** when THF and toluene were used as solvent (Table 1, entries 2 and 12), showing that this reaction is not dependent on the superbasic nature mediated by base and solvent.

In order to understand the mechanism of the hydroamination reaction, while performing the experiments the utmost care was taken to avoid the metal contamination throughout the reaction (see the Supporting Information). When this reaction was carried out in DMF without base, propargylthiourea **2a** was isolated (Table 1, entry 1). The structure of intermediate **2a** was determined by (^{1}H, ^{13}C, HRMS, IR) spectral data. Base was not required for the first step, and it did not accelerate the reaction because the intermediate (**2a** and **2b**) was formed without base in less than 5 min at 0 °C (Scheme 2), which was confirmed by taking the

Scheme 2. Proposed Mechanism for Hydroamination Reaction



NMR of crude reaction mixture. When the isolated **2a** was treated with NaOH in DMF, clean product **3a** was formed (Scheme 2). The above experiments revealed that base was not required for the formation of propargyl(thio)urea, but it was necessary for the hydroamination reaction of propargyl(thio)-urea to form imidazole-2-(thi)ones.

After establishing and optimizing the conditions for the hydroamination reaction, the scope of this reaction was explored, as illustrated in (Scheme 3). Various propargylamines smoothly reacted with a variety of isothiocyanates to give imidazole-2-thiones in excellent yields. The electron-withdrawing groups as well as electron-donating groups present on the phenyl isothiocyanate were well tolerated, and the

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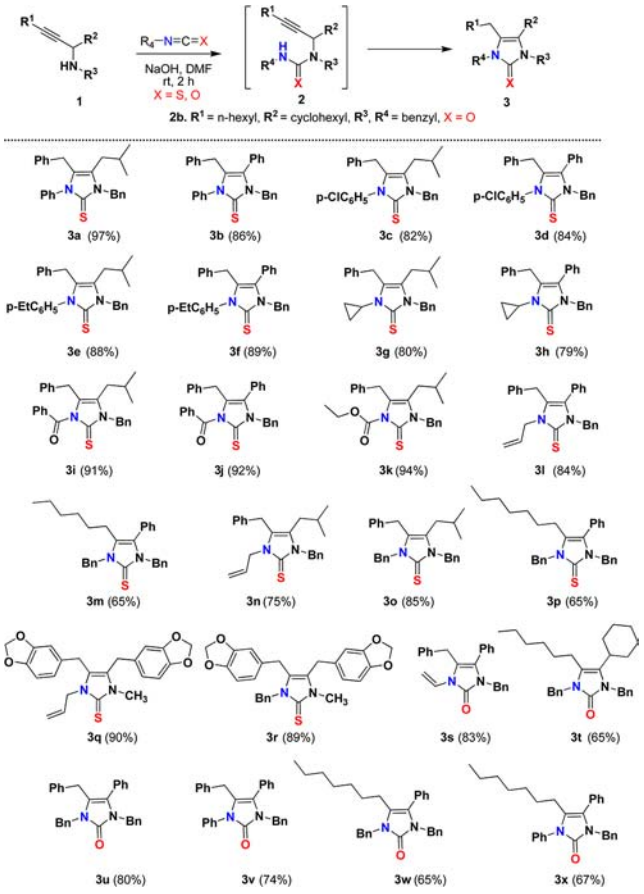
Scheme 3. One-Pot Synthesis of Imidazole-2-(thi)ones[a]



[a]Reaction conditions: All of the reactions were performed with propargylamine (1.0 mmol), R_4NCX (1.0 mmol), NaOH (1.0 mmol) and DMF (5 mL) at 25 °C.

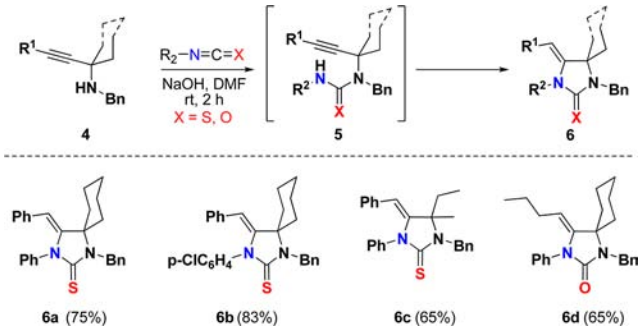
desired imidazole-2-thione **3c–f** were formed in excellent yields. Cyclopropyl isothiocyanate also reacted smoothly to provide **3g** and **3h**. The structure of the hydroamination product was unambiguously established by single crystal X-ray analysis of compound **3g** (see the Supporting Information).[21] Next, the scope of the reaction was explored by reacting benzoyl isothiocyanate with propargylamine, and a clean hydroamination reaction was observed as **3i** and **3j** were formed in excellent yields. Isothiocyanate was prepared from ethyl chloroformate; the reaction also worked efficiently to furnish **3k**. Allyl isothiocyanate reacted ably to form **3l**.

Remarkably, this protocol was further extended to unactivated propargylamines prepared from aliphatic alkynes and products, **3m** and **3p** were formed in moderate to good yields. Additionally, reaction of allyl and benzyl isothiocyanate with propargylamine gave **3q** and **3r**.

This method was equally efficient for hydroamination of propargylamine with isocyanate, and imidazole-2-ones **3s**, **3u**, and **3v** were prepared in good yields. Reaction of propargylamine prepared from aliphatic alkynes gave product **3t**, **3w**, and **3x**. In this case, the reaction proceeds via intermediate **2**, which is proved by isolation of intermediate **2b**, and the structure of **2b** was unambiguously established by single-crystal X-ray analysis (see the Supporting Information).

Further exploration of the substrate scope revealed that propargylamine **4** was also suitable for the hydroamination reaction (Scheme 4).[22] Gratifyingly the reaction of **4** proceeded

Scheme 4. Scope of the Hydroamination Reaction[a]



[a]Reaction conditions: All the reactions were performed with propargylamine (1.0 mmol), R_2NCX (1.0 mmol), NaOH (1 mmol), and DMF (5 mL) at 25 °C.

smoothly with various aryl isothiocyanates under the optimized reaction condition to give corresponding spiro cyclic imidazolidine-2-thione **6a** and **6b** in highly regio- and stereoselective manner. These hydroamination reactions proceed through intermediate **5**, with a complete control over the stereochemistry. The exocyclic double bond formed was confirmed to be *Z*-isomer by single crystal X-ray analysis of **6b** (see Supporting Information).[21] Similarly **6c** and **6d** were synthesized in moderate yields.

In summary, we have developed a base catalyzed hydroamination of propargyl(thio)urea at ambient temperature. Wide varieties of iso(thio)cyanate and propargyl amines have participated in this reaction and an array of novel imidazole-2-(thi)ones are synthesized, which could be used as precursors for the formation of novel *N*-heterocyclic carbenes (NHCs). A plethora of propargylamines are accessible via A^3 coupling reaction. We foresee that this reaction which has four diversity points, can become a valuable tool for synthesizing biologically interesting imidazole-2-(thi)ones.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) CCDC 999252 (**6b**), CCDC 1025563 (**2b**), and CCDC 999253 (**3g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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