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Selective Access to 4-Substituted 2-Aminothiazoles and 4-Substituted 5-Thiocyano-2-aminothiazoles from Vinyl Azides and Potassium Thiocyanate Switched by Palladium and Iron Catalysts

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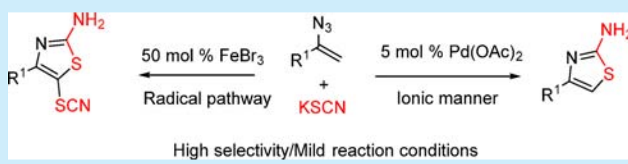
Supporting Information

ABSTRACT: A highly selective construction of 4-substituted 2-aminothiazoles and 4-substituted 5-thiocyano-2-aminothiazoles, respectively, catalyzed by palladium(II) acetate and promoted by iron(III) bromide from vinyl azides and potassium thiocyanate has been developed. Use of readily available starting materials, high selectivity, as well as mild reaction conditions make this practical method particularly attractive.



2-Aminothiazoles and their derivatives are one of the most important aza-heterocycles widely found in natural products and pharmaceutical compounds. The broad spectrum biological activities exhibited by this structure include anticancer,[1] antiviral,[2] antimicrobial,[3] antiprion,[4] anti-inflammatory,[5] and psychotropic activities.[6]

The most widely used synthetic method to access 2-aminothiazoles is the Hantzsch cyclocondensation of α-halocarbonyl compounds with thiourea.[7] Many other strategies to synthesize 2-aminothiazoles have also been developed.[8] However, traditional methods to synthesize 2-aminothiazoles often suffer from low yields, harsh reaction conditions, and less environmentally friendly reagents. In particular, there are no prior examples covering the direct synthesis of 4-substituted 5-thiocyano-2-aminothiazoles, although organic thiocyanates not only exhibit insecticidal and other biological activities[9] but also can easily be transformed to sulfur-containing compounds such as thiols,[10] sulfides,[11] and sulfur heterocycles.[12] The only reported method for the synthesis of 5-thiocyano-2-aminothiazoles is a stepwise synthesis starting from bromination of 2-aminothiazoles followed by thiocyanation of 5-bromo-2-aminothiazoles by inorganic thiocyanates.[13] Thus, the discovery of new, direct, and general synthetic routes to such heterocycles remains a formidable challenge.

Vinyl azides have been widely used as versatile synthons for the synthesis of aza-heterocycles.[14] Vinyl azides can react smoothly with incipient anions with the elimination of molecular nitrogen.[15] They can also produce iminyl radicals when radicals attack vinyl azides.[16] It is known that the thiocyanate anion can be easily oxidized by hypervalent iodine reagents, CAN, or other oxidants to afford the thiocyanate radical.[17] We envisioned that 2-aminothiazoles could be achieved by the reaction of vinyl azides and potassium thiocyanate with transition metals serving as the oxidants.

During the course of our study on the reactions of vinyl azides and potassium thiocyanate with various transition metals, we found that the reaction of α-azidostyrene and potassium thiocyanate with $Pd(OAc)_2$ in *n*-propanol gave 4-phenyl-2-aminothiazole **3a** in 90% yield. The most favorable reaction conditions for the formation of **3a** were established by further investigation of a number of experimental variables such as catalysts, reaction temperature, solvents, equivalents of catalysts, and potassium thiocyanate (Table S1, Supporting Information). The reaction proceeded smoothly to give the corresponding product **3a** in 90% yield by the catalytic use (0.05 equiv) of $Pd(OAc)_2$ under mild reaction conditions without any other additives (entry 10, Table S1).

Surprisingly, we obtained the unexpected 4-phenyl-5-thiocyanato-2-aminothiazole **4a** accompanied by a trace amount of **3a** when $FeSO_4{\cdot}7H_2O$ was used as the catalyst (entry 1, Table S2, Supporting Information). No corresponding product was observed in the absence of transition-metal salts. A range of other metal catalysts were screened (entries 2–6, Table S2), and application of $FeBr_3$ behaved the best in the conversion (entry 6, Table S2). In order to investigate the effects of solvents on this reaction, various solvents (entries 6–10, Table S2) were tested. The conversion was achieved in 92% yield without the detection of **3a** by using CH_3CN as the solvent instead of *n*-propanol (entry 9, Table S2). In addition, the conversion was maintained when a smaller amount of $FeBr_3$ was applied (entry 11, Table S2). The reaction was also assessed under different reaction temperatures and with different equivalents of potassium thiocyanate, but there was no improvement in the conversion (entries 14–18, Table S2).

With the optimized reaction conditions in hand, the scope of the reaction was studied using a set of vinyl azides. For the $Pd(OAc)_2$-catalyzed reaction, various substituted vinyl azides bearing several functional groups worked well with potassium thiocyanate to provide the desired 4-substituted 2-amino-

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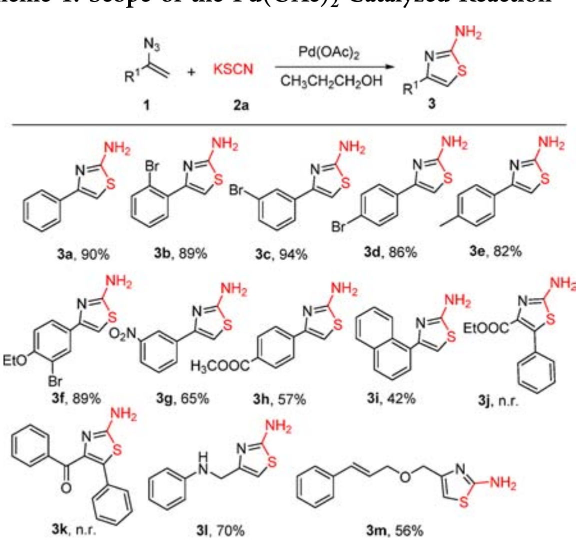
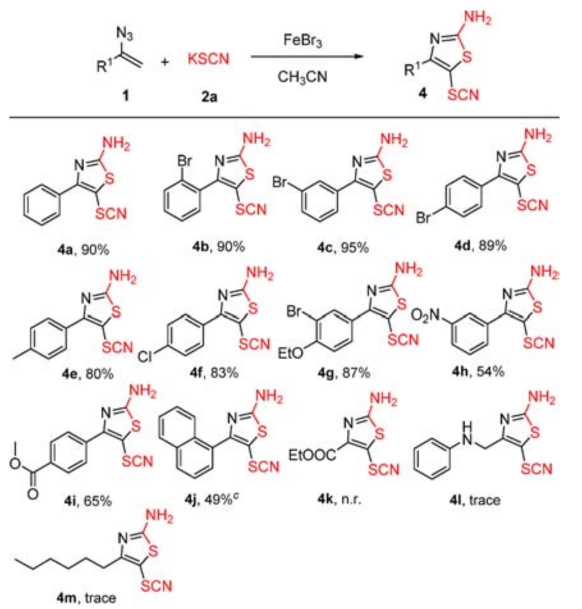
thiazoles in relatively high yields without the detection of 4-substituted 5-thiocyano-2-aminothiazoles (Scheme 1). The

Scheme 1. Scope of the Pd$(OAc)_2$-Catalyzed Reaction[a,b]



[a]Reactions were carried out in *n*-propanol (2.0 mL) with **1** (1 mmol, 1.0 equiv), **2a** (3 mmol, 3.0 equiv), and Pd$(OAc)_2$ (0.05 mmol, 0.05 equiv), 80 °C, 12 h. [b]Isolated yield.

Scheme 2. Scope of the $FeBr_3$-Promoted Reaction[a,b]



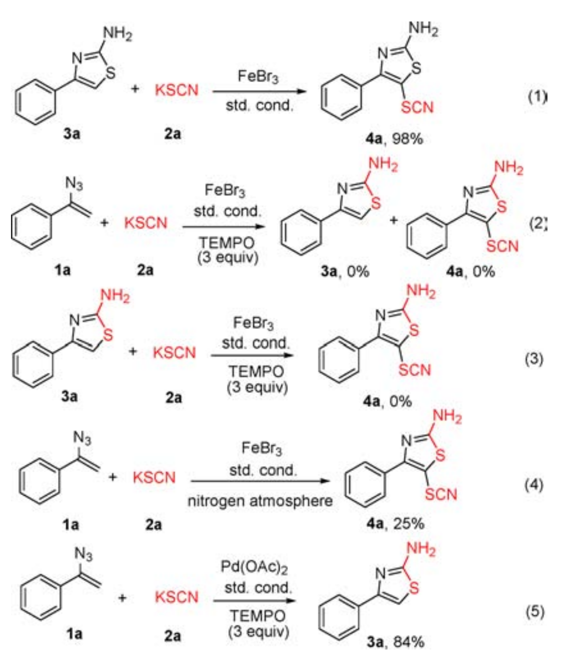
[a]Reactions were carried out in CH_3CN (2.0 mL) with **1** (1 mmol, 1.0 equiv), **2** (3 mmol, 3.0 equiv), and $FeBr_3$ (0.5 mmol, 0.5 equiv), 80 °C, 12 h. [b]Isolated yield. [c]Refluxed under 100 °C for 24 h.

reaction efficiencies were not significantly affected by the substituted groups at different positions of the phenyl ring of vinyl azides (**3b** compared to **3c**,**d**, Scheme 1). Generally, substrates with electron-withdrawing groups on the phenyl ring performed a little worse (**3g**,**h** compared to **3a**, Scheme 1). When electron-withdrawing groups, such as the ester group and benzoyl group, were directly linked to the α-position of vinyl azides, there was totally no reaction (**3j**,**k**, Scheme 1). In addition, other aromatic motifs such as 1-naphthyl (**3i**, Scheme 1) and alkyl substitution (**3l**,**m**, Scheme 1) at the α-position of vinyl azides were also successfully incorporated. Notably, substrates bearing the carbon−carbon double bond were also compatible with the reaction (**3m**, Scheme 1), which can hardly be synthesized by the traditional Hantzsch-type condensation of α-halocarbonyl compounds with thiourea because application of the halogen reagents in preparing α-halocarbonyl compounds is destructive to unsaturated carbon−carbon bonds.

Then the scope of the $FeBr_3$-promoted reaction was examined (Scheme 2). Vinyl azides with various substituted phenyl groups (**4a**−**i**, Scheme 2) or other aromatic motifs (**4j**, Scheme 2) were well tolerated without the detection of 4-substituted 2-aminothiazoles. However, substrates with electron-withdrawing groups (**4k**, Scheme 2) and alkyl groups (**4l**, **4m**, Scheme 2) at the α-position of vinyl azides were not compatible with the reaction, probably due to their low activities. *N*-(2-Azidoallyl)aniline readily reacted with potassium thiocyanate under the standard conditions of the Pd$(OAc)_2$-catalyzed reaction (**3l**, Scheme 1) but performed poorly under the standard conditions of the $FeBr_3$-promoted reaction (**4l**, Scheme 2). The problem was considered to be the free-radical thiocyanation on the phenyl ring of *N*-(2-azidoallyl)aniline,[17e] decomposition of *N*-(2-azidoallyl)aniline, and other resulting side reactions in the $FeBr_3$-promoted reaction.

To gain insight into the possible mechanism of the selective access to 4-substituted 2-aminothiazoles and 4-substituted 5-thiocyano-2-aminothiazoles, a series of experiments were conducted. Since a mixture of 4-substituted 2-aminothiazoles and 4-substituted 5-thiocyano-2-aminothiazoles was detected at the very beginning of the $FeBr_3$-promoted reaction, we envisioned that 4-substituted 2-aminothiazoles might be the key intermediate of the $FeBr_3$-promoted reaction. When **3a** was subjected to the standard conditions of the $FeBr_3$-promoted reaction, we obtained **4a** as the sole product in 98% yield (eq 1, Scheme 3), which further confirmed that the key intermediate

Scheme 3. Investigation of the Reaction Mechanism



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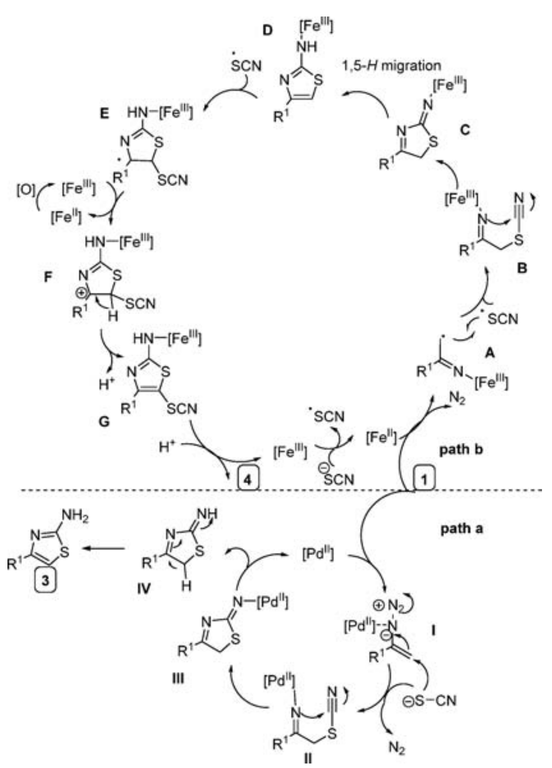
4-substituted 2-aminothiazoles were generated in the $FeBr_3$-promoted reaction. Then, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added as a radical scavenger to demonstrate the difference between these two catalytic systems. Neither **3a** nor **4a** was detected when TEMPO was added to the reaction of α-azidostyrene under the standard conditions of the $FeBr_3$-promoted reaction (eq 2, Scheme 3), which indicated that the pathway of α-azidostyrene to the intermediate **3a** of the $FeBr_3$-promoted reaction probably proceeded via a free-radical mode. Furthermore, when TEMPO was added to the reactions of **3a** under the standard conditions of the $FeBr_3$-promoted reaction, the reaction was also totally suppressed (eq 3, Scheme 3), which indicated that the conversion of the intermediate **3a** to **4a** was also through a free-radical path. In addition, the low yield obtained in the control reaction under the nitrogen atmosphere indicated that oxygen was critical to the turnover of the catalytic cycle of the $FeBr_3$-promoted reaction (eq 4, Scheme 3). However, when TEMPO was added to the reactions of α-azidostyrene under the standard conditions of the $Pd(OAc)_2$-catalyzed reaction (eq 5, Scheme 3) the yield was not significantly influenced, which suggested that the $Pd(OAc)_2$-catalyzed reaction was not through a radical pathway but probably in an ionic manner.

The structures of the 4-substituted 2-aminothiazoles and 4-substituted 5-thiocyano-2-aminothiazoles were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. On the basis of the above experimental results and previous related reports, plausible mechanisms for the highly selective transformations of these two catalytic systems were proposed. For the $Pd(OAc)_2$-catalyzed reaction (path a, Scheme 4), initial coordination of palladium(II) to the azide group provides palladium(II)−azide complex **I**, increasing the electrophilicity of the pendant olefin.[18] The nucleophilic attack of potassium thiocyanate expels N_2 to produce the intermediate **II**, and its intramolecular nucleophilic attack to the cyano group gives cyclized intermediate **III**. Protonation of intermediate **III**, followed by aromatization, would generate 4-substituted 2-aminothiazoles.

Scheme 4. Proposed Reaction Pathway



The $FeBr_3$-promoted reaction (path b, Scheme 4) was thought to be initiated by one-electron oxidation of thiocyanate anion by iron(III) bromide, giving thiocyanate radical with the release of reduced iron(II) species. Vinyl azide **1** was reduced by iron(II) species to afford iminyl iron(III) radical **A** with the elimination of molecular nitrogen.[19] Thiocyanate radicals add readily to radical **A** to produce alkylideneaminoiron(III) **B**, which undergoes an intramolecular nucleophilic attack to afford cyclized intermediate **C**. Then 1,5-*H* migration of intermediate **C** generates 2-aminothiazole intermediate **D**, which can be easily converted to 4-substituted 2-aminothiazoles by protonation. Thiocyanate radicals attack the electron-rich site of the 2-aminothiazole intermediate **D** to yield radical **E**, which was further oxidized by the iron(III) species to form cation **F** with oxygen serving as a co-oxidant.[20] Deprotonation of cation **F**, followed by protonation, yields the target 4-substituted 5-thiocyano-2-aminothiazoles with the regeneration of iron(III) species.

In conclusion, we have demonstrated a novel and efficient protocol to access 4-substituted-2-aminothiazoles and 4-substituted-5-thiocyano-2-aminothiazoles switched by palladium and iron catalysts from vinyl azides and potassium thiocyanate. Further investigation of the reaction mechanism showed that this reaction probably proceeded through an ionic pathway and a radical pathway, respectively, to afford different products in the presence of palladium(II) acetate and iron(III) bromide. The use of readily available starting materials, high selectivity, and mild reaction conditions make this method quite attractive. Further studies on the scope, mechanism, and synthetic applications of this reaction are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02152.

Experimental procedures, optimization of the reaction conditions, characterization, and spectra data of the final products (PDF)

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Notes

The authors declare no competing financial interest.

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