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COMMUNICATION

Transition-metal-free cross-coupling of thioethers with aryl(cyano)iodonium triflates: a facile and efficient method for the one-pot synthesis of thiocyanates

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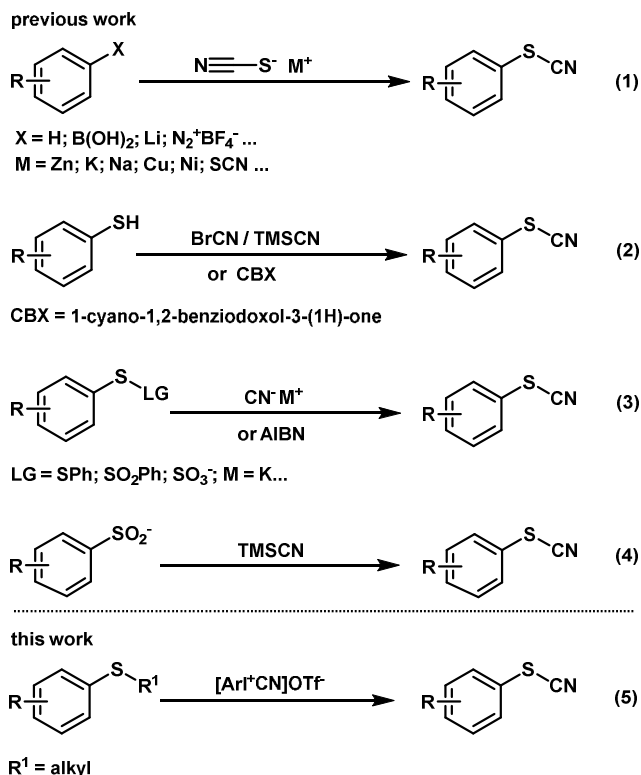
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A novel transition-metal-free cross-coupling method for the one-step synthesis of thiocyanates via the C–S bond cleavage of readily available thioethers with aryl(cyano)iodonium triflates as the cyanating agent is developed. This process features relatively broad substrate scopes, less-toxic hypervalent iodine reagents, mild operating conditions, excellent functional group compatibilities, and affords various thiocyanates in moderate to good yields.

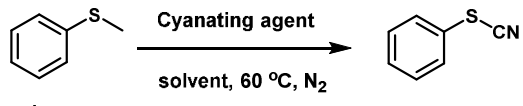
Organic thiocyanates are well-known in the area of organosulfur chemistry and have attracted considerable attention, since they are not only the substructures or building blocks of bioactive natural products¹ and pesticides,² but also the versatile synthetic precursors and useful intermediates for the synthesis of sulfur-containing compounds such as thiols,³ thioethers,⁴ disulfides,⁵ trifluoromethyl sulfides⁶ and thiocarbamates.⁷ On the one hand, thiocyanates can usually be obtained by the nucleophilic or electrophilic thiocyanation of the corresponding organic molecules with stoichiometric amounts of inorganic thiocyanates (Scheme 1, eqn. (1)),⁸ which commonly requires more careful control of the reaction conditions to avoid the undesirable formation of isothiocyanates. On the other hand, the cyanation of sulfur-containing compounds, such as thiol derivatives (Scheme 1, eqn. (2)⁹ and (3)¹⁰) and arylsulfinate salts (Scheme 1, eqn. (4)),¹¹ provides a beneficial complement and perfection for the aforementioned transformation. However, most of these cyanation methods are confronted with various drawbacks and limitations, including the utilization of highly poisonous and notorious cyanating agents (*e.g.* KCN, CuCN, Zn(CN)₂ and TMSCN), the pre-functionalization or pre-activation of substrates and harsh reaction conditions.

In the past few years, great achievements have been made in the efficient introduction of C≡N moieties via alternative cyano sources¹² into molecules. More recently, Wang and co-workers¹³ reported an efficient method for iron(II)-catalyzed direct cyanation of arenes with aryl(cyano)-iodonium triflates as the cyanating agents, which were developed by Stang and co-workers.¹⁴ Herein, we report a one-step, metal-free synthetic route to the synthesis of thiocyanates between readily available thioethers and aryl(cyano)-iodonium triflates as the cyano source under mild conditions (Scheme 1, eqn.

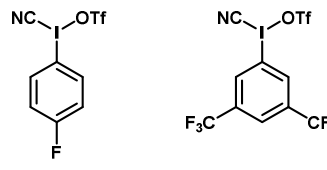


Scheme 1 Existing methods to prepare aryl thiocyanates.

(5)). This protocol offers several advantages of relatively broad substrate scopes and the utilization of less-toxic hypervalent iodine reagents as the cyanide source. To the best of our knowledge, the present study is the first example of accessing the thiocyanates via the unusual C–S bond cleavage of thioethers under metal-free condition, although the cleavage of C–S bonds has been extensively studied with a vast range of transition-metal catalysts.¹⁵

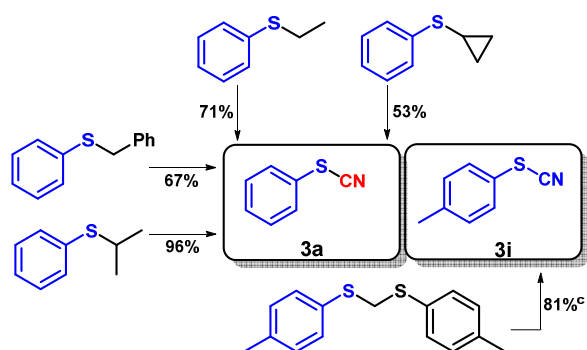
Table 1 Optimization of the reaction conditions^a


Entry	Solvent (1mL)	Cyanating agent	Yield ^b (%)
1	DMF	2a	0
2	THF	2a	0
3	Toluene	2a	65
4	DCM	2a	69 ^c
5	CH ₃ CN	2a	77
6	CH ₃ CN	2b	93



^a The reactions were conducted with 0.5 mmol of **1a** and 0.75 mmol of **2a-b** for 12 h. ^b Isolated yields. ^c Stirred at 40 °C.

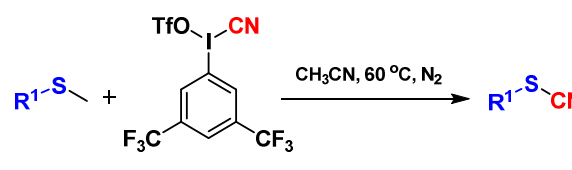
We initiated our studies by investigating the reaction of thioanisole (**1a**) and 1.5 equiv of 4-fluorophenyl(cyano)iodonium triflate (**2a**) in various commonly used organic solvents for 12 h under nitrogen atmosphere. To our delight, it was found that with CH₃CN as the solvent, the reaction provided a 77% yield of the desired product (Table 1, entry 5). In contrast, none of the expected product was formed in DMF and THF (Table 1, entries 1 and 2), or relatively low yields of product were obtained in toluene and DCM (Table 1, entries 3 and 4). Further improvement in the yield was achieved by replacing 4-fluorophenyl(cyano)iodonium triflate (**2a**) with 3,5-di(trifluoromethyl)phenyl(cyano)iodonium triflate (**2b**) as the cyanating agent (Table 1, entry 6). Consequently, the reaction condition described in entry 6 was selected as the standard condition for investigation of the reaction scope.

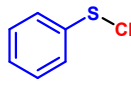
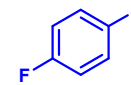
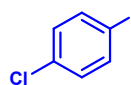
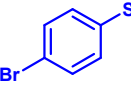
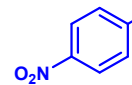
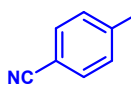
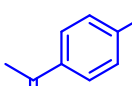
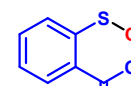
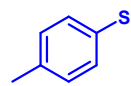
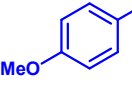
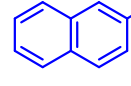
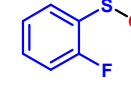
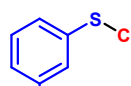
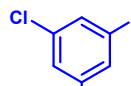
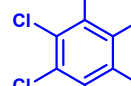



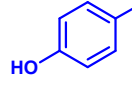
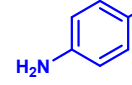
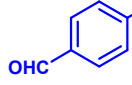


^a The reactions were proceeded in the standard condition.

^b Isolated yields. ^c The yield was calculated based on one side.

Scheme 2 Diversity in C-S bond cleavage^{a,b}

Table 2 Scope of thioether derivatives^{a,b}


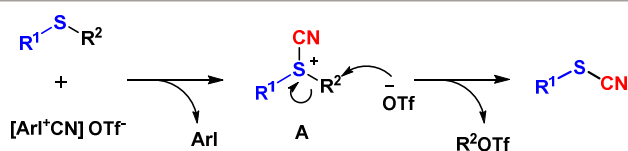
		
3a 93%	3b 88%	3c 75%
		
3d 62%	3e 43%	3f 59%
		
3g 20%	3h 57%	3i 71%
		
3j 69%	3k 42%	3l 71%
		
3m 63%	3n 59%	3o 6%
		
3p 36%	3q 68%	3r 22%
		
3s 0%	3t 0%	3u 0%

^a The reactions were conducted with 0.5 mmol of **1a-u** and 0.75 mmol of **2b** for 12 h. ^b Isolated yields.

To assess the ability and efficiency of Csp³-S bond cleavage in this protocol, various alkyl phenyl sulfides, such as ethyl, isopropyl, benzyl, cyclopropane and phenyl sulfides were subsequently reacted with 3,5-di(trifluoromethyl)phenyl(cyano)iodonium triflate (**2b**) under the above-optimized reaction condition, and the results are summarized in Table 2. In all cases studied, the reaction proceeded smoothly to afford the corresponding thiocyanates **3a** and **3i** in moderate to excellent yields under metal-free condition.

With the highly efficient condition in regard to the cleavage of S-CH₃ bond in hand, we next commit to explore the scope of this reaction with respect to a variety of thioether derivatives. As shown in Table 3, the thioanisole derivatives bearing electron-donating substituents, gave slightly better yields than

those bearing electron-withdrawing substituents, such as nitryl (**3e**), cyano (**3f**). Gratifyingly, diverse functional groups, including halides (**3b**, **3c** and **3d**), cyano (**3f**), acetyl (**3g**), ester (**3h**), nitro (**3e**), alkyl (**3i**) and alkoxy (**3j**), were very well tolerated under the optimal reaction condition, furnishing the desired products in generally moderate to excellent yields. However, thioanisoles containing an active hydrogen atom such as OH, NH₂, or aldehyde did not undergo the same reactions (**3s**, **3t** and **3u**). Furthermore, the position of attached substituent groups on the phenyl ring did not affect the efficiency of this transformation (**3b**, **3i** and **3m**). In addition to mono-substituted thioanisoles, bis-substituted thioanisole was also compatible with this novel reaction, generating the corresponding thiocyanate (**3n**) in 59% yield. It was noteworthy that a miserable yield of 6% was observed when pentachlorothioanisole (**1o**) was employed as substrate, possibly due to its poor solubility in acetonitrile. Besides the substituted thioanisole derivatives, the reactions of 2-(methylthio)thiophene (**1q**), and 2-(methylthio)pyridine (**1r**) with 3,5-di(trifluoromethyl)phenyl(cyano)iodonium triflate (**2b**) under standard condition were also investigated, and the desired thiocyanate products **3q** and **3r** were obtained in 68% and 22% yields, respectively. Finally, we also detected this reaction with alkyl thioethers under the standard condition, and the expected thiocyanate (**3p**) could be isolated in a relatively low yield of 36%.



Scheme 3 Proposed mechanism for the reaction.

On the basis of a previous report by Sanford and co-workers,¹⁶ a possible mechanism is depicted in Scheme 2. Initially, the oxidation of thioethers with aryl(cyano)iodonium triflates gives rise to the corresponding sulfonium salts **A** and aryl iodides. After subsequent nucleophilic substitution of **A** with triflate (OTf⁻), the expected thiocyanate products could be released with alkyl triflate as byproduct to finish the reaction. To prove our mechanistic hypothesis, we repeated the model reaction (Table 1, entry 6), and to our delight, the existence of MeOTf (R² = Me) and 1-iodo-3,5-bis(trifluoromethyl)benzene could be observed in the crude mixture by GC-MS analysis. Furthermore, when the reaction of thioanisole (**1a**) and 3,5-di(trifluoromethyl)phenyl(cyano)iodonium triflate (**2b**) was carried out in CDCl₃, we could also observe the generation of MeOTf and 1-iodo-3,5-bis(trifluoromethyl)benzene by ¹³C NMR analysis. These observations lend very strong support to our mechanistic proposal.

In summary, we have developed a transition-metal-free transformation of readily available thioethers into the corresponding thiocyanates through the Csp³-S bond cleavage. This process features relatively broad substrate scopes, less-toxic hypervalent iodine reagents, mild operating conditions, excellent functional group compatibilities, and affords various thiocyanates in moderate to good yields. Notably, this protocol is not only complementary to existing methods of thiocyanate formation, but also offers an opportunity to extend the applications of less-toxic hypervalent iodine reagents in organic synthesis. Further investigations on related reactions involving hypervalent iodine reagents for the

preparation of other useful sulfur-containing compounds are still underway in our laboratory.

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Notes and references

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 † Electronic Supplementary Information (ESI) available: Detailed synthetic procedures and characterization of new compounds. See DOI: 10.1039/c000000x/

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