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Copper-Catalyzed Intermolecular Trifluoromethylthiocyanation of Alkenes: Convenient Access to CF_3-Containing Alkyl Thiocyanates

Zhaoli Liang, Fei Wang, Pinhong Chen, and Guosheng Liu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of OrganicChemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

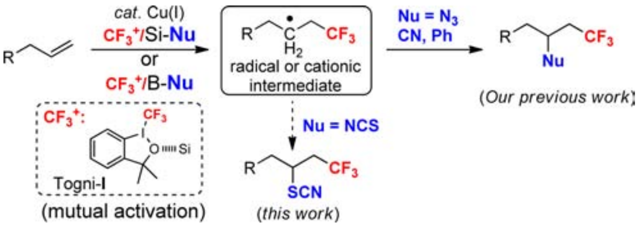
Ⓢ *Supporting Information*

ABSTRACT: A highly selective and efficient approach for the direct trifluoromethylthiocyanation of alkenes has been developed using trimethylsilyl isothiocyanate (TMSNCS) as the thiocyanating agent and Togni reagent as the CF_3 source in the presence of copper(I) catalyst. Both activated and unactivated alkenes work well to deliver various CF_3-containing thiocyanates.

Organic thiocyanates are prevalent moieties in bioactive compounds with antimicrobial[1] or antiproliferative activitiy[2] as well as versatile building blocks to access various heterocyclic compounds.[3] For instance, α-thiocyanato carbonyl compounds are considered as intermediates in the synthesis of several types of thiazoles. Therefore, much effort has been focused on the development of efficient methods for the introduction of the thiocyano group into small molecules. Traditional nucleophilic substitution of alkyl halides[4] and alcohols[5] is one of the most widely used methods for the synthesis of thiocyanates, and the isothiocyanate anion (NCS^-) can also undergo electrophilic reaction with allylic silanes[6] and carbonyl compounds[7] in the presence of oxidant. However, large excess amounts of strong oxidants and toxic metal thiocyanates are generally required. Owing to the unique properties of the trifluoromethyl group in pharmaceuticals and agrochemicals,[8] we envisioned that if CF_3 and a thiocyanate group could be simultaneously introduced into a carbon−carbon double bond, the vicinal trifluoromethyl thiocyanated compounds could be obtained efficiently from simple alkenes. Herein, we report a novel copper-catalyzed intermolecular trifluoromethylthiocyanation of alkenes to deliver vicinal CF_3-substituted alkyl thiocyanates.

Recently, the copper-catalyzed trifluoromethylation of alkenes allowing the effective formation of sp^3 C−CF_3 bonds has attracted much attention,[9−11] and a range of new transformations have been developed from various research groups with metal catalysts or metal-free reaction conditions. In these reports, a series of CF_3 reagents, including nucleophlic, electrophilic trifluoromethyl reagents and trifluoromethanesulfinate salts etc., were proven to be the efficient CF_3 source. Recent mechanistic studies revealed that the reaction was initiated from a CF_3 radical or CF_3 cation using DFT calculation by Li and co-workers[12] or experimental investigation by Sodeoka and co-workers.[13] Our group recently disclosed that the mild electrophilic CF_3 reagent, ether type Togni-I reagent, could be used as an efficient CF_3 reagent to achieve difunctionalization of alkenes through a mutual activation model between Togni-I reagent and silicon or boron reagents. Several successful intermolecular functionalization reactions of alkenes, such as trifluoromethylazidation, trifluoromethylcyanation, and trifluoromethylarylation, have been developed (Scheme 1).[14] Among them, the reaction was initiated from a CF_3 radical, and a carbon radical was involved. We speculated that if this carbon radical could be trapped by thiocyanate in the presence or absence of a metal catalyst, the final trifluoromethylthiocyanation might be expected to give vicinal CF_3 thiocyanation product from alkenes.

Scheme 1. Copper-Catalyzed Intermolecular Trifluoromethylation of Alkenes



In order to test the above hypothesis, trimethylsilyl isothiocyanate (TMSNCS) was used as a Lewis acid to test the reaction of **1a** with the ether-type Togni-I reagent in the presence of copper catalyst (Table 1). We were delighted to find that the reaction indeed gave the desired product **2a** in 70% yield (entry 1). In contrast to previous studies, the ester type Togni-II reagent was also effective and provided slightly better yield than Togni-I (entry 2). The excellent yield (90%) was obtained by increasing the amount of CF_3^+ reagent (entry 3). Further solvent screening indicated that various solvents were suitable for this transformation, but the polar solvent was better than nonpolar solvent (entries 3−9). The best yield

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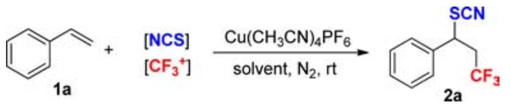
Table 1. Optimization of the Reaction Conditions[a,b]



entry	[NCS]	[CF_3^+]	solvent	yield (%)
1[c]	TMSNCS	Togni-I	DMA	70
2[c]	TMSNCS	Togni-II	DMA	73
3	TMSNCS	Togni-II	DMA	90
4	TMSNCS	Togni-II	THF	47
5	TMSNCS	Togni-II	EtOH	80
6	TMSNCS	Togni-II	toluene	42
7	TMSNCS	Togni-II	CH_3CN	78
8	TMSNCS	Togni-II	CH_2Cl_2	48
9	TMSNCS	Togni-II	DMSO	98
10[d]	TMSNCS	Togni-II	DMSO	96[e]
11[f]	TMSNCS	Togni-II	DMSO	0
12[d]	NaSCN	Togni-II	DMSO	37
13[d]	KSCN	Togni-II	DMSO	30
14[d]	NH_4SCN	Togni-II	DMSO	29

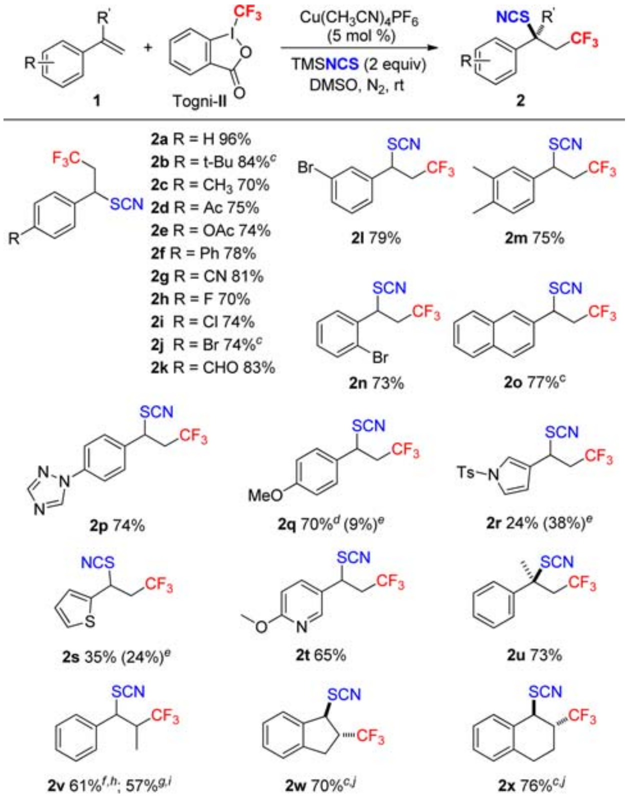
[a] Reaction conditions: **1a** (0.1 mmol), TMSNCS (0.2 mmol), Togni reagent (0.15 mmol), $Cu(CH_3CN)_4PF_6$ (10 mol %) in 0.5 mL of solvent. [b] ^{19}F NMR yield using *N,N*-dimethyltrifluoroacetamide as an internal standard. [c] Togni reagent (1.1 equiv). [d] $Cu(CH_3CN)_4PF_6$ (5 mol %). [e] Isolated yield. [f] Without Cu catalyst.

(98%) was given in the solvent of DMSO (entry 9). Delightfully, there is no significant drop of the yield when the catalyst loading was lowered to 5 mol % (entry 10). No reaction occurred in the absence of copper catalyst (entry 11). Notably, the reaction of cyanate salts, such as NaSCN, KSCN, and NH_4SCN, also afforded the desired product **2a**, but with low yields (29%−37%, entries 12−14).

With the optimized conditions in hand, we first explored the substrate scope of styrenes. As shown in Scheme 2, styrenes (**1a**−**p**) with different substituents on the aromatic ring, including electron-donating and electron-withdrawing groups, can be transformed into the corresponding products **2a**−**p** in good to excellent yields. A variety of functional groups, such as halogen, ester, ether, nitrile, ketone, aldehyde, and triazole, were well tolerated under these reaction conditions. Among them, 2-vinylnaphthalene gave product **2o** in 77% yield using (bath)CuI catalyst, in which low yield was obtained with $Cu(CH_3CN)_4PF_6$. However, when more electron-rich styrenes, such as *p*-methoxystyrene (**1q**), 1-tosyl-3-vinyl-1*H*-pyrrole (**1r**), and 3-vinylthiophene (**1t**), were used as substrates, the reaction provided the mixture of C−S bond-forming products **2q**−**s** and C−N bond-forming products, and the selectivities were dependent on the electron property of aromatic rings and reaction time.[15] In contrast, the electron-deficient 2-methoxy-5-vinylpyridine (**1t**) only gave the C−S bond-forming product **2t** selectively. Remarkably, the 1,1-disubstituted styrene (**1u**) and 1,2-disubstituted styrene (**1v**) were also suitable for the reaction to give desired products **2u** and **2v** in moderate yields, and both *E*-**1v** and *Z*-**1v** gave the same product **2v** with a similar dr ratio (2−4:1). For the cyclic styrenes (**1w**−**x**), the *trans* products (**2w**−**x**) were obtained with excellent diastereoselectivity (30:1).

Inspired by the above results, we turned our attention to more challenging unactivated alkenes (Scheme 3). First, monosubstituted terminal alkenes were surveyed, which successfully afforded the corresponding products (**4a**−**f**) in moderate to good yields in which unprotected phenol group

Scheme 2. Substrate Scope of the Styrenes[a,b]

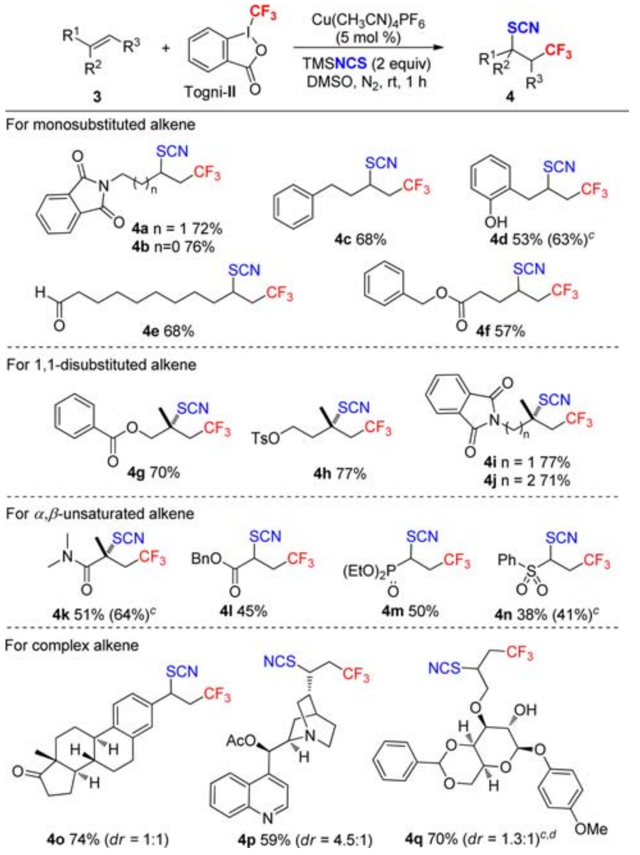


[a] Reaction conditions: **1** (0.2 mmol), TMSNCS (2 equiv), [CF_3^+] (1.5 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol %) in DMSO (1 mL). [b] Isolated yield. [c] (Bath)CuI as catalyst. [d] Reaction time is 10 min. [e] Isolated yield of C−N bond-forming side product in parentheses. [f] *Z*-*β*-Methylstyrene. [g] *E*-*β*-Methylstyrene. [h] dr = 4:1. [i] dr = 2:1. [j] dr = 30:1. Bath =2,9-dimethyl-1,10-phenanthroline.

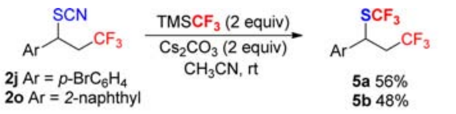
and aldehyde group were tolerated (**3d**,**e**). Second, 1,1-dialkyl-substituted olefins (**3g**−**j**) were also suitable for this transformation to give **4g**−**j** in good yields. Again, good functional group tolerance was observed. Third, electron-deficient alkenes, such as *α*,*β*-unsaturated amide, carbonyl ester, phosphoric ester, and sulfone, were proven to be also good candidates for the reaction to deliver CF_3-containing alkylthiocyanate compounds (**4k**−**n**) in moderate yields. The structure of compound **4k** was confirmed by X-ray analysis (see the Supporting Information). Finally, in order to explore the application in organic synthesis, more complex alkenes, containing estrone (**3o**), cinchonine (**3p**), and sugar (**3q**) motifs, were surveyed. The reactions proceeded smoothly to afford the corresponding products **4o**−**q** in good yields, albeit in low stereoselectivities, which indicated a promising route toward the modification of active compounds in later stages.

Finally, further transformation of trifluoromethylthiocyanation products was studied. On the basis of the diverse reactivity of thiocyanate group, for instance, the thiocyanate group can be smoothly converted into another prevalent lipophilic group SCF_3 in the presence of $TMSCF_3$ and Cs_2CO_3. Both **2j** and **2o** were converted to **5a** and **5b** in moderate yields, respectively (eq 1). In particular, the thiocyanate group could be transformed to tetrazoles **5c** through a classical Click reaction in 92% yield (eq 2), which probably act as a metabolically stable surrogate for the carboxy group.[16] Routinely, compound **2a** was reduced with $LiAlH_4$ and then exposed under air to give the

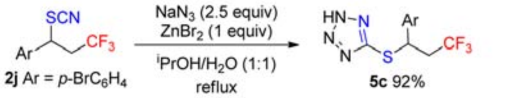
Scheme 3. Substrate Scope of Unactivated Alkenes[a,b]



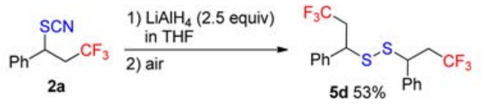
[a] Reaction conditions: **3** (0.2 mmol), TMSNCS (2 equiv), [CF_3^+] (1.5 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol %) in DMSO (1 mL). [b] Isolated yield. [c] (Bath)CuI as catalyst. [d] [CF_3^+] (3 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol %), 2 days.



(1)



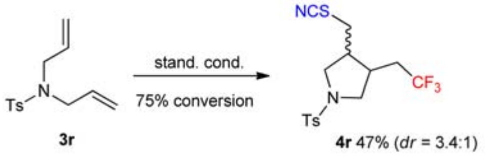
(2)



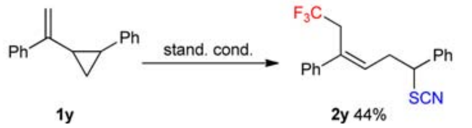
(3)

disulfide product **5d** in 53% yield, which is vital for the stabilization of peptide structures (eq 3).

(4)



(5)



(6)

To gain more insight into the reaction mechanism, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added as a radical scavenger. The trifluoromethylthiocyanation reaction was partly inhibited, and the Tempo addition to benzylic radical and CF_3 radical was observed to give **5e** (26%) and **5f** (62%), respectively (eq 4). In addition, when diene substrate **3r** was subjected to the standard conditions, the cyclization product **4r** was obtained only with moderate dr value (eq 5). The reaction of the radical clock substrate **1y** also provided the ring-opening product **2y** in moderate yield (eq 6). These observations revealed that a benzylic radical generated from addition of CF_3 radical to alkenes was involved in the reaction. Finally, the electronic effect of styrenes was also evaluated under the standard conditions, and a much smaller Hammett ρ value of 0.019 was obtained (see the Supporting Information), which excluded the possibility of carbon cation and was consistent with the benzylic radical property.

In summary, an efficient copper-catalyzed intermolecular trifluoromethylthiocyanation of alkenes has been developed. This reaction provides a general and straightforward way to construct various CF_3-containing thiocyanates under mild conditions. These products can be easily converted into the corresponding sulfur derivatives. More importantly, simple alkenes can be used as substrates, and a wide range of functional groups are tolerated.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectral data for all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gliu@mail.sioc.ac.cn.

Notes

The authors declare no competing financial interest.

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