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Radical Cyanotrifluoromethylation of Isocyanides: Step-Economical Access to CF_3-Containing Nitriles, Amines, and Imines

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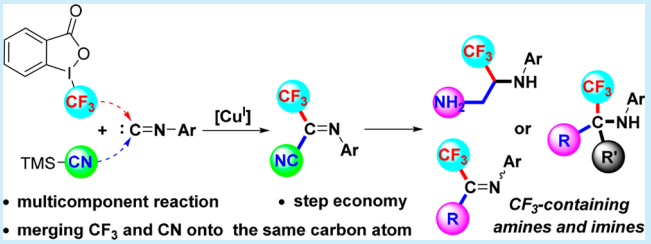
Supporting Information

ABSTRACT: A novel copper-catalyzed radical cyanotrifluoromethylation has been achieved through a multicomponent reaction of isocyanides, Togni's reagent, and trimethylsilyl cyanides, affording trifluoroacetimidoyl nitriles in good yields. This reaction demonstrates a unique feature of merging two valuable functional groups—trifluoromethyl (CF_3) and cyan (CN)—onto the same C atom. The transformation proceeds by the initial addition of the CF_3 radical to isocyanide and the subsequent intermolecular C−CN formation. The products can be successfully transformed to a series of CF_3-containing amines and imines that may serve in the synthesis of valuable pharmaceuticals and agrochemicals.



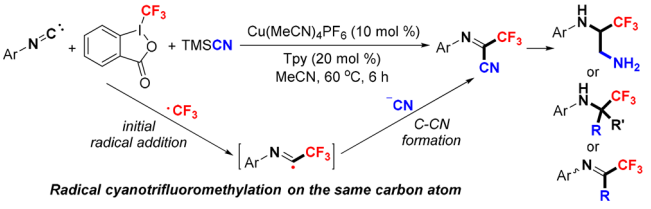
Difunctionalization of unsaturated bonds has emerged as a powerful tool in organic chemistry, because it allows the merging of two different functional groups into a single precursor via a single operation, thus significantly improving molecular complexity with excellent step economy.[1] Difunctionalization involving trifluoromethylation is an important transformation for rapidly introducing the trifluoromethyl moiety into the target molecules, which are commonly found in biologically active compounds, as well as pharmaceuticals and agrochemicals.[2−5] Recently, cyanotrifluoromethylation, which combines trifluoromethylation and cyanation, has become increasingly attractive, because it affords various valuable compounds containing CF_3 and CN groups.[3−5] Most of these reactions involved substrates with unsaturated C−C bonds, such as alkenes[3] and alkynes,[4] so that the two functional groups were combined into two vicinal C atoms. However, cyanotrifluoromethylation of a single C atom has not been reported so far.

Isocyanides are an important class of C1 synthons in modern organic synthesis and exhibit a unique characteristic:[6,7] they not only react with electrophiles, nucleophiles,[7e,8] and radicals,[7f,9] but also can be inserted into metal−carbon and metal−heteroatom bonds in transition-metal-catalyzed reactions.[7a−d,10] In recent years, the reactions of isocyanide substrates with fluorine reagents have attracted much attention,[11] and most of these reactions proceed via the initial addition of the fluorine-containing radical to isocyanide, followed by intramolecular cyclization. However, much less progress has been made toward the radical difunctionalization of isocyanides via a multicomponent merging strategy, especially, cyanotrifluoromethylation.

Multicomponent reactions (MCRs) are particularly appealing as step-economical reactions, because they can simultaneously combine three or more fragments into new frameworks, via a one-pot process.[12] Following the report on the Passerini and Ugi reactions,[13] diverse MCRs of isocyanides have been widely explored,[14] while few radical MCRs have been developed. Recently, we reported radical cascade reactions to furnish trifluoromethylated nitriles[15a] and trifluoroethyl isoquinolines.[15b]

Taking advantages of Togni's reagent,[16] here, we report a cooperative copper-catalyzed radical cyanotrifluoromethylation of isocyanides, Togni's reagent, and trimethylsilyl cyanides, giving trifluoroacetimidoyl nitriles in good yields (see Scheme 1). This multicomponent reaction accomplishes the difunctionalization of a single C atom in isocyanide and incorporates CF_3 and CN groups. Moreover, the cyanotrifluoromethylation product can readily convert to a wide range of CF_3-substituted amines and imines via one-step transformations.

Scheme 1. Radical Cyanotrifluoromethylation of Isocyanides to Access CF_3-Containing Compounds



For the initial investigation, isocyanide **1a** was chosen as the model substrate (see Table 1). This substrate was treated with the commonly used CF_3 reagent **2a** and TMSCN in the presence of 10 mol % $Cu(OAc)_2$ in 1,2-dichloroethane (DCE)

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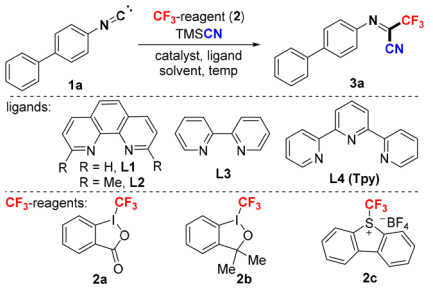
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	solvent[b]	temperature (°C)	yield[c] (3a, %)
1	$Cu(OAc)_2$		DCE	rt	21
2	$Cu(OAc)_2$	L1	DCE	rt	31
3	$Cu(OAc)_2$	L1	DCM	rt	27
4	$Cu(OAc)_2$	L1	THF	rt	20
5	$Cu(OAc)_2$	L1	DMSO	rt	17
6	$Cu(OAc)_2$	L1	toluene	rt	20
7	$Cu(OAc)_2$	L1	MeCN	rt	48
8	$Cu(OAc)_2$	L1	MeCN	60	64
9	$Cu(OAc)_2$	L1	MeCN	80	61
10	$Cu(OTf)_2$	L1	MeCN	60	54
11	CuOAc	L1	MeCN	60	51
12	CuCl	L1	MeCN	60	44
13	CuI	L1	MeCN	60	47
14	CuCN	L1	MeCN	60	36
15	$Cu(MeCN)_4PF_6$	L1	MeCN	60	68
16[d]	$Cu(MeCN)_4PF_6$	L1	MeCN	60	65
17[e]	$Cu(MeCN)_4PF_6$	L1	MeCN	60	60
18	$Cu(MeCN)_4PF_6$	L2	MeCN	60	64
19	$Cu(MeCN)_4PF_6$	L3	MeCN	60	58
20	$Cu(MeCN)_4PF_6$	L4	MeCN	60	71
21[f]	$Cu(MeCN)_4PF_6$	L4	MeCN	60	67
22[g]	$Cu(MeCN)_4PF_6$	L4	MeCN	60	ND

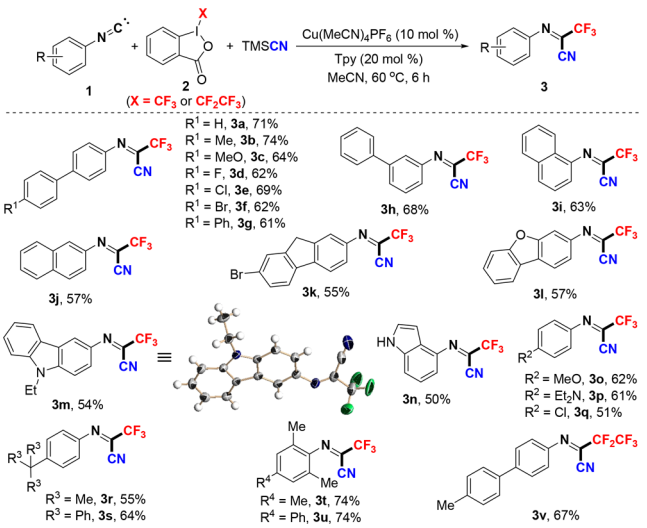
[a]Reaction conditions: isocyanide **1a** (0.2 mmol), **2a** (0.3 mmol), TMSCN (0.4 mmol), catalyst (0.02 mmol), ligand (0.04 mmol), solvent (2 mL), 6 h under Ar, unless noted. [b]Legend: DCE, 1,2-dichloroethane; DCM, dichloromethane; THF, tetrahydrofuran; DMSO, dimethyl sulfoxide; and MeCN, aceotrnitrile. [c]Isolated yield. [d]$Cu(MeCN)_4PF_6$ (0.04 mmol) and **L1** (0.08 mmol) were used. [e]$Cu(MeCN)_4PF_6$ (0.01 mmol) and **L1** (0.02 mmol) were used. [f]**2b** was used instead of **2a**. [g]**2c** was used instead of **2a**.

at room temperature for 12 h. Interestingly, both the valuable functional groups CF_3 and CN were introduced onto the C atom of the isocyanide group to give cyanotrifluoromethylation product **3a** in 21% or 31% isolated yields without or with ligand **L1**, respectively (entries 1 and 2 in Table 1). Screening of various common solvents revealed that MeCN gave the best result, furnishing **3a** in 48% yield (entries 3–7 in Table 1). Increasing the reaction temperature to 60 °C improved the product yield to 64% (entries 8 and 9 in Table 1). Among the [Cu^I] and [Cu^{II}] catalysts that were further tested, $Cu(MeCN)_4PF_6$ was determined to be the best one (entries 10–15 in Table 1). Next, we examined the impact of catalyst and ligand loading, and found that the yield of **3a** did not improve upon increasing/decreasing the amount of catalyst and ligand (entries 16 and 17 in Table 1).

With the aim of obtaining a satisfactory yield, the ligand effect was further investigated (entries 18–20 in Table 1). The results show that the tridentate ligand terpyridine (Tpy) **L4** had a positive effect on this transformation, giving **3a** in 71% yield (entry 20 in Table 1), which might arise from the formation of a more stable Tpy-chelated copper intermediate. Finally, replacing the CF_3 reagent **2a** with **2b** led to a similar yield of **3a**, while using **2c** did not give the desired product (entries 21 and 22 in Table 1). Thus, the optimized reaction conditions were established as $Cu(CH_3CN)_4PF_6$ (10 mol %), Tpy (20 mol %), TMSCN (2.0 equiv), and Togni's reagent **2a** (1.5 equiv) in MeCN at 60 °C for 6 h under an argon atmosphere.

Under the optimal conditions, we next explored the substrate scope of this cyanotrifluoromethylation (Scheme 2). First, a variety of substituted biphenyl isocyanides were

Scheme 2. Substrate Scope of Isocyanides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), TMSCN (0.4 mmol), $Cu(MeCN)_4PF_6$ (0.02 mmol), Tpy (0.04 mmol), MeCN (2 mL), 60 °C, 6 h, under Ar. [b]Isolated yield.

examined. Various substituent groups, including Me, MeO, F, Cl, Br, and phenyl, were compatible with the reaction conditions, and the corresponding products **3b–3g** were isolated in 61%–74% yields. The *meta*-isocyanobiphenyl group worked well in the reaction and generated the desired product **3h** in 68% yield. With *ortho*-isocyanobiphenyl, however, only a small amount of the desired product was formed, as detected by gas chromatography–mass spectroscopy (GC-MS), because of the feasibility of intramolecular cyclization.[11]

Naphthyl isocyanides participated in the cyanotrifluoromethylation reaction, providing the corresponding products **3i** and **3j** in moderate yields. Fluorenyl isocyanide was also effective for this reaction and generated the desired product **3k** in 55% yield. Moreover, heterocyclic isocyanides derived from dibenzo[*b*,*d*]furan, 9-ethyl-9*H*-carbazole, and 1*H*-indole could be cyanotrifluoromethylated under the optimized conditions to afford the corresponding products **3l–3n** in moderate yields. The structure of **3m** determined by single-crystal X-ray diffraction (XRD) analysis (see the Supporting Information (SI)) was consistent with the NMR-based structure, indicating that the obtained products were formed as pure *E*-stereoisomers.

Next, we evaluated the suitability of phenyl isocyanides with various substituents on the benzene ring for this reaction. Reactions with isocyanides bearing MeO, Et_2N, and Cl groups at the *para*-position of the benzene ring proceeded well to give

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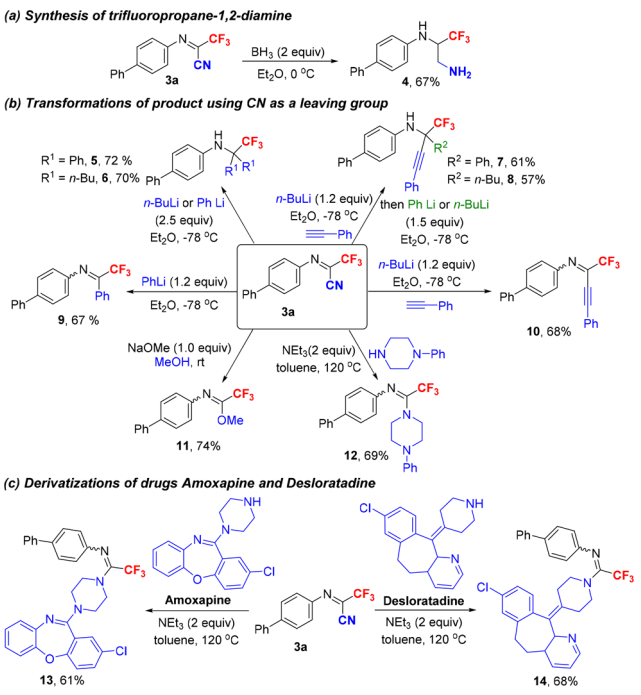
the desired products **3o**−**3q**, as did the *t*-Bu or trityl-substituted phenyl isocyanides to afford **3r** or **3s**. Multi-substituted phenyl isocyanides were also tolerated in the reaction, providing the desired products **3t** and **3u** in good yields. However, phenyl isocyanides with strongly electron-withdrawing groups (CF_3 or NO_2) showed unsatisfactory reactivity in this transformation, as did the alkyl isocyanides, such as benzyl or *t*-butyl substituted isocyanides, which might be due to the instability of the corresponding imidoyl radical intermediates.

To verify the flexibility of the cyanotrifluoromethylation, a hypervalent iodine reagent **2** with perfluoroethyl substituent was synthesized and subjected to the reaction with isocyanide under the optimized conditions. The desired product **3v** was isolated in 67% yield, clearly demonstrating that the method is a powerful tool to access perfluoroalkylatomidoyl nitriles. In addition, we also successfully performed one reaction at larger scale (2 mmol of **1a**) and isolated product **3a** (0.35 g) in 63% yield.

To further investigate the synthetic value of our protocol, various downstream transformations of product **3a** were investigated. As indicated in Scheme 3a, BH_3 was found to

Scheme 3. Transformations of Product and Derivations of the Drugs Amoxapine and Desloratadine



be effective to reduce **3a** to CF_3-substituted 1,2-diamine **4** (67% yield), which is useful in the synthesis of natural products, biologically active compounds, and ligands containing 1,2-diamine skeletons.[17]

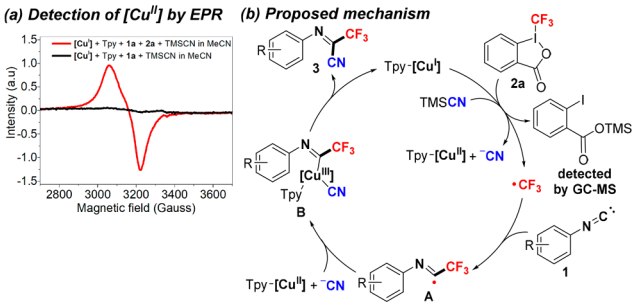
As indicated in Scheme 3b, the treatment of the cyanotrifluoromethylation product **3a** with excess lithium reagents produced amines **5** and **6** with two phenyl or two *n*-butyl groups in good yields. Amines containing two different groups such as **7** and **8** could also be generated by a one-pot reaction, wherein imine intermediate generated in the reaction with (phenylethynyl)lithium, and then converted to **7** or **8** after further reaction with Ph-Li or *n*-Bu-Li (61% or 57% yields).

Through carefully controlling the amount of the lithium reagents, phenyl- or phenylethynyl-substituted imines **9** and **10** could be readily obtained from **3a** in 67% and 68% yields, respectively. Moreover, iminoether **11** was generated in 74% yield upon the treatment of **3a** with NaOMe in MeOH. The substituted benzamidine **12** was also readily obtained in the reaction of **3a** with *N*-phenylpiperazine. Because of the high reactivity of imine group, the diverse conversions of the resulting imine products might be further applied in the synthesis of valuable pharmaceuticals and agrochemicals containing CF_3.

Amoxapine is a new antidepressant, which has neuroleptic and antidepressive effects.[18a] Desloratadine is a long-lasting and nonsedating antihistamine commonly used for the treatment of seasonal allergies and chronic hives.[18b] Via a similar transformation, the drugs Amoxapine and Desloratadine could also react with **3a** to afford the corresponding imine derivatives **13** and **14** in 61% and 68% yields, respectively (Scheme 3c). These results demonstrate the usefulness of our methodology in the derivatization of drugs to incorporate CF_3 and imine groups.

To obtain insight into the mechanism of cyanotrifluoromethylation, a stoichiometric amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used as the radical inhibitor. The results indicate that the cyanotrifluoromethylation was completely inhibited, and the TEMPO−CF_3 adduct was obtained in 44% yield (see the SI), suggesting that the cyanotrifluoromethylation might involve a radical pathway. Moreover, we tried to detect [Cu^{II}] intermediate using electron paramagnetic resonance (EPR). Under standard conditions to form **3a**, the EPR signal of [Cu^{II}] could be clearly seen (see the red line in Scheme 4a),[19] while the signal

Scheme 4. EPR Studies and Proposed Mechanism



of [Cu^{II}] could not be detected in the absence of **2a** (Scheme 4a, black line). The results indicate that [Cu^{II}] intermediate formed in the cyanotrifluoromethylation, which further demonstrates that a single electron transfer process occurred in the cyanotrifluoromethylation.

On the basis of the above experimental results and previous mechanistic studies of cyanotrifluoromethylation of alkenes,[3,5] we propose a plausible mechanism for this transformation, as outlined in Scheme 4b. First, CF_3 reagent **2a** and TMSCN are activated by the Tpy-[Cu^{I}] catalyst to generate the Tpy-[Cu^{II}], $^{-}$CN anion, and the active CF_3 radical along with the formation of trimethylsilyl 2-iodobenzoate (detected by GC-MS). The active CF_3 radical adds to the N=C: bond of isocyanide **1** to give imidoyl radical **A**,[11c,g] which might attach to Tpy-[Cu^{II}] with $^{-}$CN anion to give Tpy-[Cu^{III}] intermediate **B**.[2j,3b] Finally, **B** might undergo reductive

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elimination to furnish the product **3** with the regenerated catalyst Tpy-[Cu^{I}].

In summary, we have developed a novel copper-catalyzed radical cyanotrifluoromethylation via the multicomponent reaction of isocyanides, Togni's reagent, and trimethylsilyl cyanides in good yields and with excellent regioselectivity. This multicomponent reaction has achieved the difunctionalization of isocyanide and incorporated CF_3 and CN groups onto the single C atom, providing direct access to trifluoroacetimidoyl nitriles. Mechanistic investigations demonstrated that the reaction proceeded via the addition of the CF_3 radical to isocyanide and the following intermolecular C−CN bond formation. Downstream transformations of the product, especially the one-step access to CF_3-substituted amines and imines, indicated the usefulness of this protocol for the synthesis of important CF_3-containing compounds, which may be important intermediates of pharmaceuticals and agrochemicals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02328.

Detailed experimental procedures, characterization data of products (NMR, HRMS, etc.), spectra of the products (PDF)

Accession Codes

CCDC 1856875 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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