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Copper-Catalyzed Trifluoromethylalkynylation of Isocyanides

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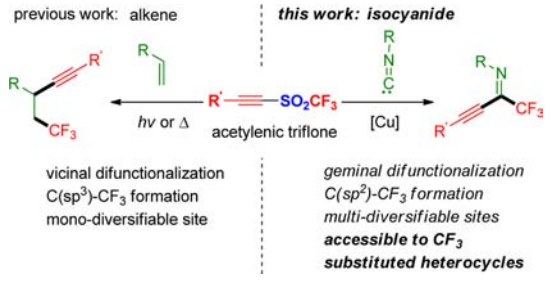
Supporting Information

ABSTRACT: The title reaction proceeds with acetylenic triflones and isocyanides under mild conditions using copper as a catalyst. This transformation provides an efficient access to (*E*)-*N*-alkyl trifluoromethyl alkynyl ketoimines, which are useful building blocks for the synthesis of CF_3-containing N-heterocycles, propargylamines, etc.

The last two decades have witnessed remarkable progress in trifluoromethylation reactions due to the great importance of trifluoromethyl-containing molecules in pharmaceutical and agrochemical studies.[1] From the view of bond-forming efficiency, trifluoromethylation with installation of additional function groups is more attractive than those transformations in which only one C−CF_3 bond is formed. Simultaneous C−CF_3 and C−X (X = O,[2] N,[3] C,[4] etc.) formation across the C−C double bond has been extensively studied using Umemoto's or Togni's reagent. However, the transformability of the resulting CF_3-substituted alkanes is limited depending on the nature of the substituent X. Undoubtedly, alkyne is one of the most versatile functionalities for further transformations.[5] In 1996, Fuchs reported an elegant work on trifluoromethylalkynylation of alkenes with acetylenic triflones in which the SO_2 unit was released under radical conditions (left, Scheme 1).[6] Further study using acetylenic triflone as a trifluoromethylalkynylating agent is not reported in the literature.[7]

Scheme 1. Trifluoromethylalkynylation Using Acetylenic Triflone



On the other hand, isocyanide (RNC) is widely applied in different types of reactions, such as the well-known Passerini and Ugi multicomponent reactions,[8] transition-metal-catalyzed imidoylations,[9] as well as radical-chain reactions.[10] The result of isocyanide-involved reactions is that two groups are added geminally to the divalent carbon to form normal tetravalent imine derivatives as stable products or reactive intermediates. Early research demonstrated that isocyanide was an ideal class of one-carbon synthon used for perfluoroalkyliodination by insertion to $C_nF_{2n+1}I$ through imidoyl radical intermediate.[11] Recent independent research by Studer, Zhou, and Yu employed biaryl isocyanides in sequential trifluoromethylation and intramolecular arylation through homolytic aromatic substitution (HAS) to construct heteroarenes.[12]

Inspired by Fuchs' work,[6] a relevant desulfonylative trifluoromethylalkynylation taking place on the geminal carbon of isocyanide is designed. In this hypothesized process, isocyanide formally replaces the sulfone moiety (SO_2) in acetylenic triflones to produce *N*-alkyl trifluoromethyl alkynyl ketoimines which are multidiversifiable synthons for the synthesis of CF_3-containing N-heterocycles of pharmaceutical importance (e.g., celecoxib, a nonsteroidal anti-inflammatory drug, and DPC 961,[13] a potential non-nucleoside reverse transcriptase inhibitors of HIV-1). The previous method of preparing trifluoromethyl alkynyl ketoimines mainly depends on coupling of alkynes with in situ generated trifluoroacetimidoyl halides which are moisture sensitive.[14] Moreover, they are not accessible by condensation of trifluoroacetyl acetylenes with amines due to the competing Michael addition.[15] Thus, this unprecedented trifluoromethylalkynylation of isocyanides (right, Scheme 1) will provide a practical synthesis of *N*-alkyl trifluoromethyl alkynyl ketoimines.

We commenced the study with a reaction between cyclohexyl isocyanide **1a** and phenylacetylenic triflone **2a** under argon. As shown in Table 1, $Cu(OAc)_2$ (20 mol %) was essential for the formation of the desired ketoimine **3a** in MeCN as a solvent (entries 1−3). Only a complicated reaction mixture of unidentified products was detected in the absence of $Cu(OAc)_2$. Other copper-, manganese-, zinc-, and palladium-based catalysts were ineffective or less efficient for this transformation (see details in the Supporting Information). Performing the reaction in other solvents including dioxane, ether, THF, or dichloromethane gave much lower yields of **3a** (entries 4−7). Lowering the initial reaction temperature to 0 °C and then warming gradually to 15 °C could improve the yield of **3a** to 78%, determined by ^{19}F NMR of the crude product (entry 8). When

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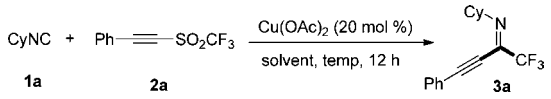
Table 1. Optimization of the Reaction Conditions[a]



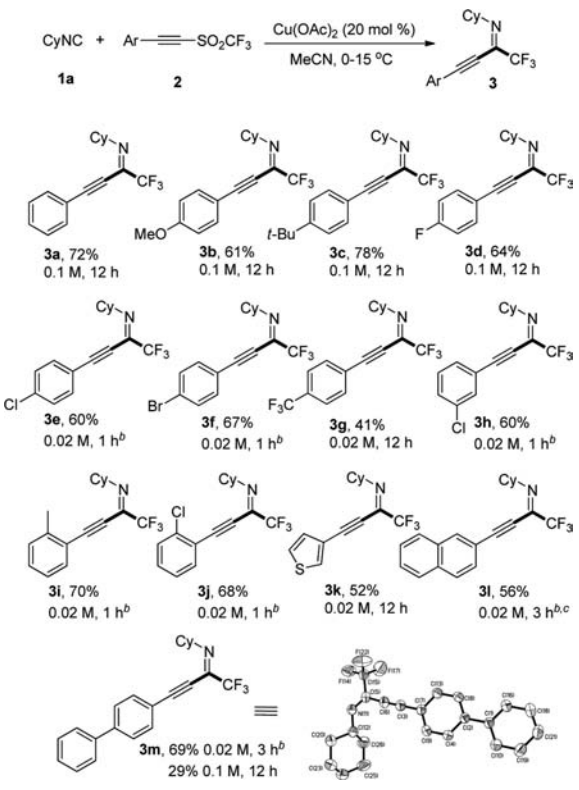
entry	catalyst	solvent	temp (°C)	yield[b] (%)
1	$Cu(OAc)_2$	MeCN	25	63
2		MeCN	25	0
3	NaOAc[c]	MeCN	25	0
4	$Cu(OAc)_2$	dioxane	25	40
5	$Cu(OAc)_2$	ether	25	23
6	$Cu(OAc)_2$	THF	25	8
7	$Cu(OAc)_2$	CH_2Cl_2	25	29
8	$Cu(OAc)_2$	MeCN	0−15	78 (72)[d]
9[e]	$Cu(OAc)_2$	MeCN	0−15	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), $Cu(OAc)_2$ (20 mol %), MeCN (1.0 mL), 12 h, in Ar. [b]The yield of **3a** was determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard. [c]0.2 equiv. [d]Isolated yield in the parentheses. [e]In O_2.

the reaction was conducted in O_2, the formation of **3a** was completely inhibited (entry 9).

With the optimized reaction conditions established, the scope of acetylenic triflones was examined first (Scheme 2). During substrate exploration, it was found the isolating yields of **3** could be improved at lower concentration for most of the substrates (**3e**−**m**).[16] Functional groups of varied electronic nature including OMe, Me, *t*-Bu, F, Cl, and Br tolerated the reaction conditions well to furnish the corresponding *N*-cyclohexyl trifluoromethyl arylalkynyl ketoimines in 60−78% yields.

Scheme 2. Scope of Acetylenic Triflones[a]

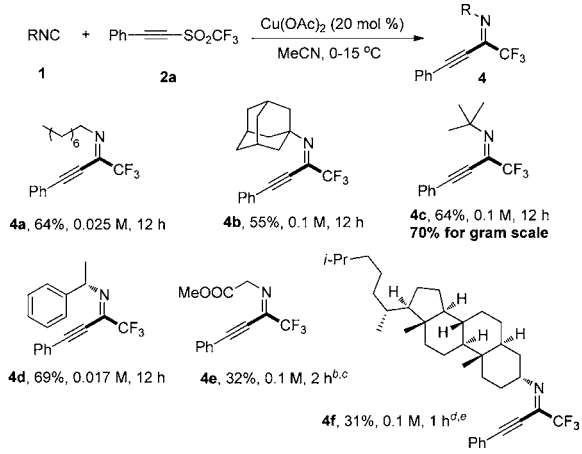


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), $Cu(OAc)_2$ (20 mol %), MeCN, isolated yields of **3**. [b]At 0 °C. [c]4.0 equiv of **1a**.

However, extreme electron-deficient CF_3-substituted acetylenic triflone gave **3g** in a significant lower yield of 41%. *o*-Chloro-substituted product **3j** was obtained in even higher yield (68%) than those analogues with chloride on *meta* (**3h**, 60%) or *para* (**3e**, 60%) positions, indicating that addition of the imidoyl moiety at the acetylenic carbon far away from the aryl ring was more likely taking place (vide infra). Thienyl- and naphthyl-substituted acetylenic triflones were also applicable in the current desulfonylative trifluoromethylalkynylation reaction (**3k**, **3l**). Most importantly, only one isomer was detected in all of these reactions. The configuration of the ketoimine product was determined unambiguously to be the *E*-form by the crystal structure of *p*-phenyl-substituted **3m**.

Then, the generality of isocyanides was investigated (Scheme 3). Besides secondary isocyanide **1a**, primary and tertiary

Scheme 3. Scope of Isocyanides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), $Cu(OAc)_2$ (20 mol %), MeCN, isolated yields of **4**. [b]At 0 °C. [c]50 mol % of $Cu(OAc)_2$. [d]In 1,4-dioxane. [e]At 25 °C.

isocyanides were also viable in this transformation, delivering the corresponding (*E*)-*N*-alkyl trifluoromethyl alkynyl ketoimines **4a**−**c** in 55−64% yields. Optically pure amine derived isocyanide with an alkyl alpha-chiral center was also tested. No racemization took place during the reaction by careful HPLC analysis of the product **4d**, which could be used for further diastereoselective transformations at the imidoyl carbon. Methyl 2-isocyanoacetate reacted with **2a** to give product **4e** from the desired difunctionalization reaction rather than [3 + 2] annulation,[17] albeit in low yield at higher catalyst loading. The reaction of cholesterol-derived isocyanide with **2a** was run in dioxane due to its poor solubility in CH_3CN, and the corresponding ketoimine **4f** was obtained in 31% yield. Notably, gram-scale synthesis of **4c** was achieved successfully, demonstrating the synthetic practicality of the reaction. Unfortunately, when aryl isocyanide was applied, no desired product could be isolated in the complicated reaction mixture.

The ketoimine products containing multiple functionalities including imine, alkyne, and CF_3 are versatile building blocks for the synthesis of more complicated F-bearing molecules (Scheme 4). For example, when **4c** reacted with *n*-BuLi at −78 °C in ether, 1,1-difluoromethylene product **5**, as a result of S_N2'-type reaction, was isolated in 71% yield together with neglectable amount of secondary propargylamine **6** (2% ^{19}F NMR). Intriguingly, the chemoselectivity was completely inversed by

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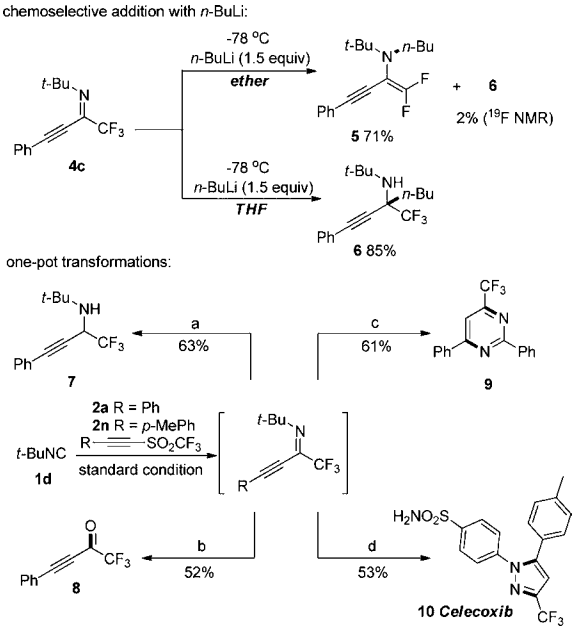
Scheme 4. Diversified Transformations of Trifluoromethyl Alkynyl Ketoimines[a]

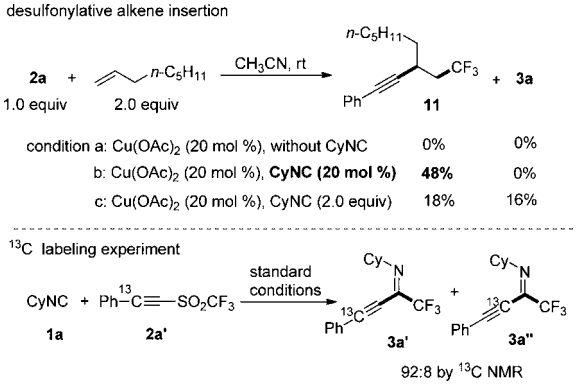


[a]Reaction conditions: (a) $NaBH_3CN$ (1.5 equiv), HOAc (1.5 equiv), MeCN, rt, 4 h; (b) 0.5 M H_2SO_4 (1.5 equiv), THF, rt, 30 min; (c) benzamidine hydrochloride hydrate (3 equiv), $NaHCO_3$ (6 equiv), MeCN, 120 °C, 24 h; (d) step 1: 4-hydrazinobenzene-1-sulfonamide hydrochloride (1 equiv), DMSO/H_2O, rt, 2 h; step 2: $Cu(OAc)_2$ (20 mol %), NEt_3 (1 equiv), DMSO/H_2O, rt, 1 h.

simply changing the reaction solvent to THF, delivering **6** exclusively in 85% yield. Although the exact reason for the excellent selectivity controlled by solvent was not clear at this stage, it provided a practical route to 1,1-difluoroenamine and trifluoromethyl propargyl amine from the common substrate.[18] Selective one-pot reduction of the imine moiety was realized by adding $NaBH_3CN$ and HOAc directly to the reaction mixture of *t*-BuNC (**1d**) and **2a**, generating secondary propargyl amine **7** in 63% total yield. Hydrolysis of the ketoimine intermediate in acidic media led to related trifluoromethyl alkynyl ketone **8** in modest yield. In addition, both of the alkyne and imine functionalities could react with bisnucleophiles to provide trifluoromethyl-substituted heterocycles. For instance, 2,6-diphenyl-4-(trifluoromethyl)pyrimidine **9** was synthesized in one pot through condensation of the crude reaction mixture with benzamidine in the presence of $NaHCO_3$ in good isolating yield.[19] More importantly, regioselective condensation of 4-hydrazinobenzene-1-sulfonamide hydrochloride with unpurified ketoimine intermediate by sequential nucleophilic addition and cyclization under the help of extra 20 mol % of $Cu(OAc)_2$ and 1 equiv of NEt_3 to furnish celecoxib **10**, a nonsteroidal anti-inflammatory drug, in a 53% total yield from acetylenic triflone **2n**.[20]

To gain insights into the reaction mechanism, a control experiment between **1a** and **2a** in the presence of 1.2 equiv of TEMPO was performed under otherwise identical conditions. Neither **3a** nor CF_3 adduct of TEMPO was detected in ^{19}F NMR of the reaction mixture. Actually, even 5 mol % of TEMPO was enough to shut off the reaction. When 2.0 equiv of 1-octene was present as a competitive radical trap of isocyanide **1a**,[6a,21] 18% of alkene difunctionalization product **11** and 16% of isocyanide insertion product **3a** were detected by ^{19}F NMR together with unidentified byproducts (Scheme 5). However, when the amount of isocyanide dropped to 20 mol %, only the alkene

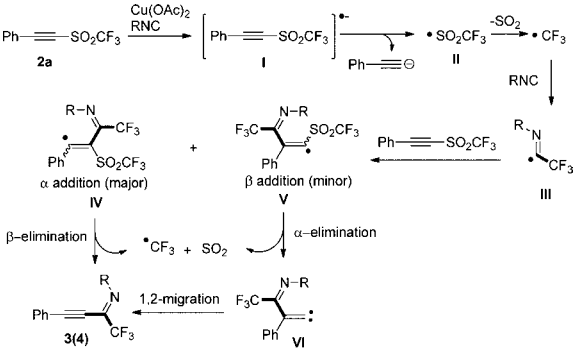
Scheme 5. Mechanistic Studies



insertion product **11** was produced in 48% NMR yield. Interestingly, none of the products were formed in the absence of isocyanide **1a**, indicating the importance of the $Cu(OAc)_2$/isocyanide combination for the initiation of the reaction (see the Supporting Information for details). These results of radical trap experiments as well as the fact that the reaction can be inhibited by O_2 suggested that trifluoromethyl radical was involved in this reaction. Finally, substrate **2a**′ with one of the acetylenic carbons ^{13}C labeled was used in a standard reaction with **1a**.[6b] The corresponding ^{13}C-labeled products **3a**′ and **3a**″ were produced in a ratio of about 92:8 determined by ^{13}C NMR, demonstrating that 1,2-aryl migration was a minor reaction pathway.

Based on these observations, a plausible mechanism was proposed in Scheme 6. Initially, the complex of $Cu(OAc)_2$ and

Scheme 6. Proposed Mechanism



isocyanide promotes the decomposition of acetylenic triflone to trifluoromethyl radical and SO_2 via intermediate **II** probably through single electron transfer (SET). Subsequently, trifluoromethyl radical is trapped by isocyanide to form imidoyl radical **III** which prefers the more stable *E* configuration. Addition of the imidoyl radical to acetylenic triflone at α or β carbon may take place. Both the ^{13}C-labeling experiment and the substitution effect on the phenyl ring agree with α-addition as a major pathway. β-Elimation of intermediate **IV** delivers the desired ketoimine product and regenerates the trifluoromethyl radical via species **II**. β-Addition followed by α-elimination gives carbene intermediate **VI**. 1,2-Phenyl migration furnishes the same product, however, which is a minor process indicated by ^{13}C-labeled product **3a**″.

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In summary, we developed a novel copper-catalyzed trifluoromethylalkynylation of aliphatic isocyanides with arylacetylenic triflones to generate (*E*)-*N*-alkyl trifluoromethyl alkynyl ketoimines under mild conditions. This is a new type of isocyanide-involved difunctionalization incorporation of trifluoromethylation. The resulting ketoimine products are versatile building blocks easily convertible to trifluoromethyl-substituted N-heterocycles, propargylamines, etc. Mechanistic studies reveals that isocyanide is not only a reactant in this transformation but also responsible for the initial trifluoromethyl radical formation under the aid of $Cu(OAc)_2$.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for products. 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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