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Trichloroisocyanuric Acid Promoted Cascade Cyclization/Trifluoromethylation of Allylic Oximes: Synthesis of Trifluoromethylated Isoxazolines

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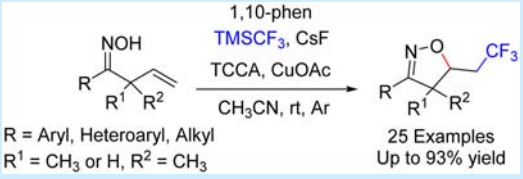
Supporting Information

ABSTRACT: Cheap and commercially available trichloroisocyanuric acid has been used to promote trifluoromethylation by using $TMSCF_3$ as the trifluoromethyl source. The method provides a novel and efficient protocol for the construction of CF_3-containing 4,5-dihydroisoxazoles from allylic oximes in good to excellent yields.



Isoxazolines are important structural motifs existing in numerous natural products,[1] pharmaceuticals,[2] and agrochemicals.[3] They also serve as important building blocks in organic synthesis as well as chiral ligands in asymmetric catalysis.[4] Therefore, it is not surprising that many efforts have been devoted to the construction of the isoxazoline scaffold over the past decades.[5] On the other hand, the incorporation of fluorinated moieties, particularly the CF_3 group, into drug candidates can significantly alter their lipophilicity, metabolic stability, and bioavailability owing to the unique properties of the CF_3 group.[6] Thus, the synthesis of CF_3-containing compounds has attracted considerable research interest in recent years. To date, a series of trifluoromethylating reagents have been developed and successfully employed to introduce the CF_3 group into organic compounds.[7]

Recently, CF_3-substituted isoxazolines have been proven to exhibit remarkable biological activities (Figure 1).[7d,8] Therefore, it is highly desirable to develop efficient methods for the synthesis of CF_3-containing isoxazoline compounds. However, efficient methods for the introduction of the CF_3 group into isoxazolines have previously been scarce.[7d,9] A general synthetic approach toward CF_3-containing isoxazolines involves the cyclization/trifluoromethylation of β,γ-unsaturated oximes. For instance, Liang's and Chen's groups successively reported the synthesis of CF_3-containing isoxazolines from β,γ-unsaturated oximes compounds by using Togni's reagent and Umemoto's reagent as the trifluoromethylating reagents, respectively.[7d,9c] However, these protocols suffer from moderate yields of the products, high price, and nonavailability of the trifluoromethylating reagents on large scale in industry. Therefore, it is highly desirable to develop new protocols for incorporation of the CF_3 group into isoxazolines.

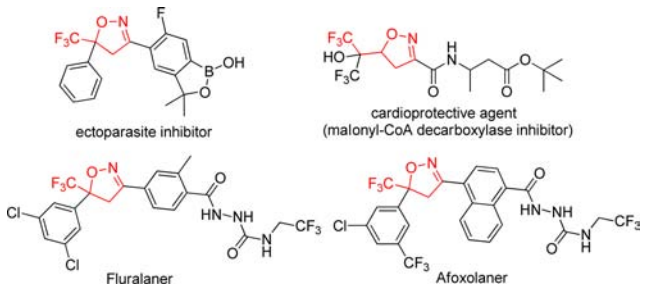


Figure 1. Examples of biologically active CF_3-containing isoxazolines.

Trichloroisocyanuric acid (TCCA) is used as a versatile and innocuous oxidant or chlorinating reagent with high stability in industry.[10] In the realm of synthetic organic chemistry, TCCA has been widely applied in a variety of reactions due to its low price, ready availability, environmentally benign attributes, and ability to serve as a source of three chlorine atoms for a variety of reactions.[11] However, the TCCA-promoted strategy to achieve highly functionalized fluorine-containing compounds is quite limited (Scheme 1).[12] Until now, only halofluorination of alkenes and trifluoromethylthiolation promoted by TCCA have been reported. TCCA-mediated trifluoromethylation of allylic oximes remains unexplored. Herein, we report the TCCA-promoted cyclization/trifluoromethylation of allylic oximes by using $TMSCF_3$ as trifluoromethyl source, which provided a concise and efficient method for preparation of trifluoromethyl-substituted 4,5-dihydroisoxazoles.

We initially tested the feasibility of the cyclization/trifluoromethylation of oxime **1a** with $TMSCF_3$ in the presence of CsF, CuCl, and TCCA in CH_3CN under argon atmosphere. After brief optimization of the mole ratio of the reactants, we

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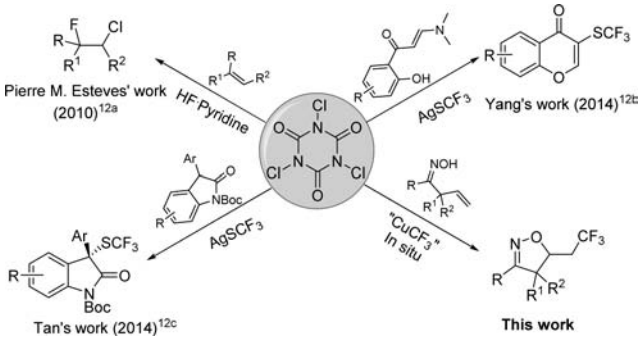
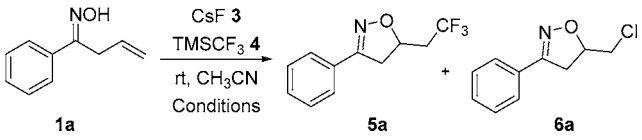
Scheme 1. TCCA-Promoted Reactions To Access Fluorine-Containing Compounds



found that the mole ratio of 1:3:3.6:3.6:0.5 for oxime **1a**/CuCl/CsF/$TMSCF_3$/TCCA seemed to be the best one to give the product **5a** in 60% yield and the byproduct **6a** in 32% yield, which was then used to optimize other reaction conditions.

Because of their high efficiency and the relatively low cost, copper salts are usually used to promote trifluoromethylation via in situ formation of $CuCF_3$.[13] Thus, we screened other copper salts such as CuCN, CuI, $CuCl_2$, and $Cu(OAc)_2$ (Table 1, entries 2–5). When CuCN was used in the reaction, no

Table 1. Optimization of Reaction Conditions[a]



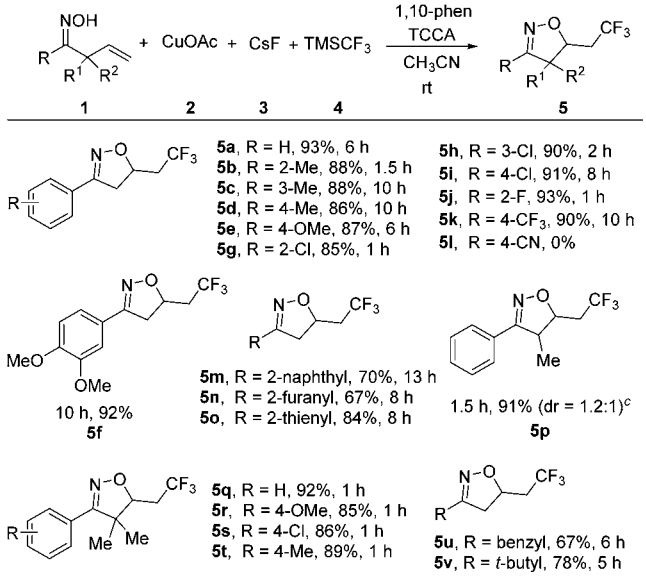
			yield[b] (%)	
entry	copper salt **2**	additive (equiv)	**5a**	**6a**
1	CuCl	TCCA (0.5)	60	32
2	CuCN	TCCA (0.5)	trace	trace
3	CuI	TCCA (0.5)	24	51[c]
4	$CuCl_2$	TCCA (0.5)	nd	98
5	$Cu(OAc)_2$	TCCA (0.5)	nd	97
6	CuOAc	TCCA (0.5)	51	nd
7	CuOAc	TCCA (0.67)	82	nd
8	CuOAc	TCCA (0.84)	32	54
9	CuOAc	*N*-Cl-phthalimide (2.0)	80	nd
10	CuOAc	NCS (2.0)	19	66
11[d]	CuOAc	TCCA (0.67)	93	nd
12[d]		TCCA (0.67)	nd	trace
13[d]	CuOAc		nd	nd

[a]All reactions were carried out by using 0.3 mmol of **1a**. [b]Isolated yields. [c]Yield for 5-(iodomethyl)-3-phenyl-4,5-dihydroisoxazole (**6aa**). [d]3 equiv of 1,10-phen was added to the reaction mixture. nd = not detected.

reaction occurred (Table 1, entry 2). When $CuCl_2$ and $Cu(OAc)_2$ were used, only chlorinated byproduct **6a** was obtained in almost quantitative yields. CuI led to the desired product **5a** in only 24% yield, while another iodinated byproduct **6aa** instead of chlorinated **6a** was formed in 51% yield. Encouragingly, the addition of CuOAc made the reaction produce solely the product **5a** in 51% yield without formation of any byproducts, and 40% of starting material was recovered (Table 1, entry 6). Encouraged by this result, the amount of TCCA was increased to 0.67 equiv, and the yield of **5a** reached 82% (Table 1, entry 7). Unfortunately, the yield of **5a** was not elevated any more when the amount of TCCA was further increased (Table 1, entry 8). Other additives such as *N*-chlorophthalimide or NCS were also examined in the reaction, but the yield of **5a** was not improved (Table 1, entries 9 and 10). Considering that in situ produced $CuCF_3$ may be unstable, 1,10-phenanthroline was added to form a complex [(phen)-$CuCF_3$] to stabilize in situ formed $CuCF_3$ according to the literature.[14] To our delight, the yield of **5a** was greatly increased to 93% (Table 1, entry 11). Finally, the effects of CuOAc and TCCA on the reaction were studied. It was found that both of them were essential to the reaction because no desired product **5a** was observed in the absence of CuOAc or TCCA (Table 1, entries 12 and 13).

With the optimal reaction conditions in hand, we next explored the scope of the reactions with a variety of β,γ-unsaturated oximes **1**. As shown in Scheme 2, all of the

Scheme 2. Substrate Scope of Reaction[a,b]



[a]All reactions were carried out using 0.3 mmol of **1a**, 0.67 equiv of TCCA, 3 equiv of CuOAc, 3 equiv of 1,10-phen, 3.6 equiv of $TMSCF_3$, 3.6 equiv of CsF, and 8 mL of CH_3CN. [b]Isolated yields. [c]The ratio of diastereomers was determined by crude ^1H NMR and ^{19}F NMR.

aromatic oximes **1** with electron-donating or electron-withdrawing groups on their phenyl rings afforded the desired isoxazolines **5a–k** in excellent yields (85–93%), except for 4-cyano-substituted oximes **1l**, which gave a complex mixture. Naphthal- and heteroaryl-substituted substrates were also transformed into the desired products **5m,o** in good yields. The reaction could also be applied to aliphatic oximes such as **1u** and **1v**, which produced **5u** and **5v** in 67% and 78% yields, respectively. The oximes with different allylic groups produced the products **5q–5t** in good yields (85–92%), and substrates **1p** gave a mixture of diastereoisomers **5p** (dr =1.2:1) in 91% yield.

In order to further examine the generality of the reaction, compounds **1w–y** were exposed in the optimized reaction conditions (Scheme 3). The bis-oxime **1w** afforded the monotrifluoromethylated product **5w** instead of the bis-trifluoromethylated one. When oxime **1x** was used in the reaction, no trifluoromethylated product was produced, and

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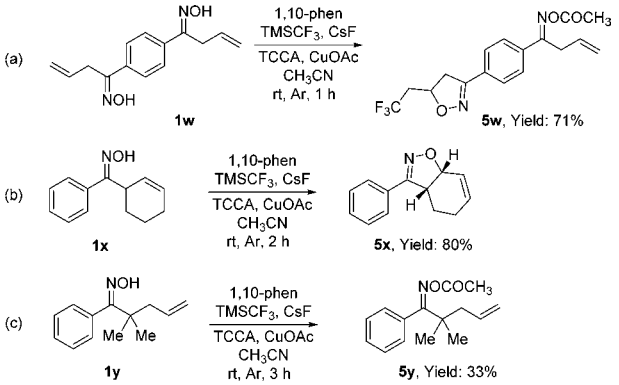
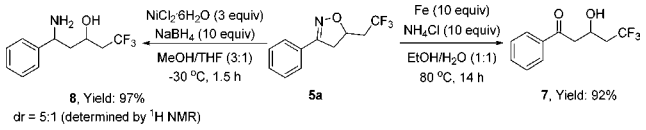
Scheme 3. Scope of Other Substrates



only isomerized product **5x** was obtained in 80% yield. If oxime **1y** was applied as substrate, acetoxylation at the hydroxyl group occurred to give the product **5y** instead of the desired cyclization/trifluoromethylation reaction.

Isoxazolines are often used as important synthetic building blocks in organic synthesis.[4a,c,f] To demonstrate the synthetic utility of trifluoromethylation products, further transformation of isoxazolines was examined. For instance, **5a** was applied to reductive ring-opening reactions (Scheme 4). When **5a** was

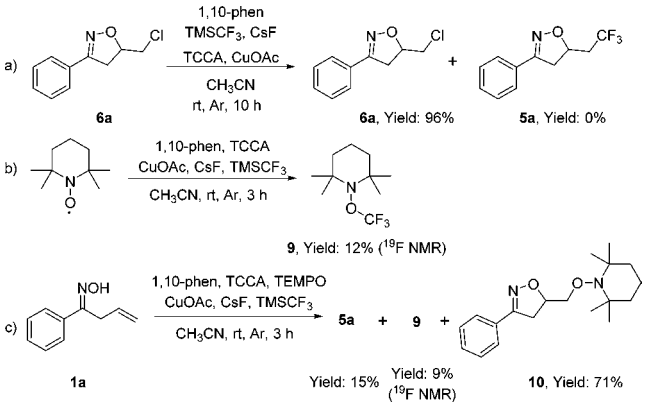
Scheme 4. Synthetic Applications of Current Method



reacted with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$, 1,3-amino alcohol **8** was obtained in 97% yield. If **5a** was stirred with Fe and NH_4Cl in $EtOH/H_2O$, *β*-hydroxy ketone **7** could be obtained in 92% yield. During these ring-opening reactions, the trifluoromethyl groups remained unchanged.

To probe the reaction mechanism, some control experiments were conducted as shown in Scheme 5. Chlorinated product **6a** was obtained as a byproduct at the beginning of our studies. Thus, the pure **6a** was exposed to the standard reaction conditions, but there was no trifluoromethylated product **5a** formed. These indicated that desired product **5a** did not come from the byproduct **6a** (Scheme 5, a). In the second experiment, the substrate oxime **1a** was taken away, and

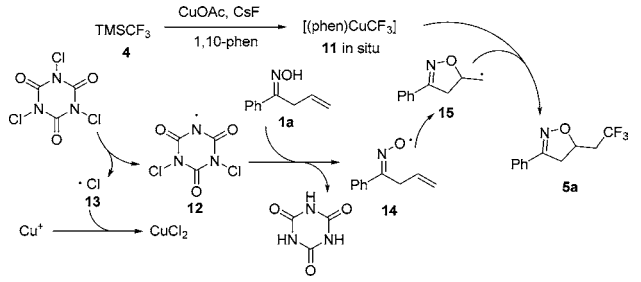
Scheme 5. Control Experiments for Mechanism



TEMPO was added into the reaction mixture under the standard reaction conditions. TEMPO−CF_3 adduct **9** was obtained only in 12% yield (Scheme 5, b). This meant the trifluoromethyl radical was not the major intermediate in the reaction. However, when TEMPO was added into the reaction mixture with oxime **1a** as substrate, products **5a** and **9** were formed in 15% and 9% yield, respectively; another product **10** was obtained in 71% yield. This meant that radical **15** was the major intermediate (Scheme 5, c).

Consequently, a mechanism was suggested on the basis of experimental results and the literature[5e,i,15] (Scheme 6). As

Scheme 6. Proposed Mechanism



illustrated in Scheme 6, when $TMSCF_3$ was stirred with CuOAc, CsF, and 1,10-phenanthroline, a complex **11** was formed first.[14] Addition of TCCA and oxime **1a** into the reaction mixture produced radical **12**, which abstracted a proton from the hydroxyl group in oxime **1a** to produce radical **14**. TCCA was finally converted into isocyanuric acid, which was detected from the reaction mixture. Cyclization of radical **14** gave another carbon radical **15**, which abstracted a trifluoromethyl group from complex **11** to give the final product **5a**.

In conclusion, cheap and commercially available trichloroisocyanuric acid has been used to promote the first trifluoromethylation by using $TMSCF_3$ as the CF_3 source. Allylic oximes were efficiently converted to trifluoromethylated 4,5-dihydroisoxazoles in good to excellent yields by cascade cyclization/trifluoromethylation. The related products, trifluoromethyl-containing 4,5-dihydroisoxazoles, could be easily converted into 1,3-amino alcohol and *β*-hydroxy ketone by reductive ring-opening reactions. Further studies on TCCA-promoted trifluoromethylation reactions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03582.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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