LETTERS

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

Weigang Zhang,[†] Yingpeng Su,[†][©] Ke-Hu Wang,[†] Lili Wu,[†] Bingbing Chang,[†] Ya Shi,[†] Danfeng Huang,[†] and Yulai Hu^{*,†,‡}[©]

[†]College of Chemistry and Chemical Engineering, Northwest Normal University, 967 Anning East Road, Lanzhou 730070, P. R. China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

Supporting Information

ABSTRACT: Cheap and commercially available trichloroisocyanuric acid has been used to promote trifluoromethylation by using TMSCF₃ 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.

I soxazolines 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 CF₃ group, into drug candidates can significantly alter their lipophilicity, metabolic stability, and bioavailability owing to the unique properties of the CF₃ group.⁶ Thus, the synthesis of CF₃-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 CF₃ group into organic compounds.⁷

Recently, CF₃-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 CF₃-containing isoxazoline compounds. However, efficient methods for the introduction of the CF₃ group into isoxazolines have previously been scarce.^{7d,9} A general synthetic







approach toward CF₃-containing isoxazolines involves the cyclization/trifluoromethylation of β , γ -unsaturated oximes. For instance, Liang's and Chen's groups successively reported the synthesis of CF₃-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 CF₃ group into 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 TCCApromoted cyclization/trifluoromethylation of allylic oximes by using TMSCF₃ as trifluoromethyl source, which provided a concise and efficient method for preparation of trifluoromethylsubstituted 4,5-dihydroisoxazoles.

We initially tested the feasibility of the cyclization/ trifluoromethylation of oxime 1a with TMSCF₃ in the presence of CsF, CuCl, and TCCA in CH₃CN 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, CuCl₂, and Cu(OAc)₂ (Table 1, entries 2–5). When CuCN was used in the reaction, no



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** 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 CuCF₃ may be unstable, 1,10-phenanthroline was added to form a complex [(phen)-CuCF₃] to stabilize in situ formed CuCF₃ 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 $\beta_i \gamma$ -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 TMSCF₃, 3.6 equiv of CsF, and 8 mL of CH₃CN. ^{*b*}Isolated yields. ^{*c*}The ratio of diastereomers was determined by crude ¹H NMR and ¹⁹F 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 4cyano-substituted oximes 11, 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

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





reacted with NaBH₄ in the presence of NiCl₂·6H₂O, 1,3-amino alcohol **8** was obtained in 97% yield. If **5a** was stirred with Fe and NH₄Cl in EtOH/H₂O, 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 6awas 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 5aformed. 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





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^{Se,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 TMSCF₃ as the CF₃ 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 TCCApromoted 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.or-glett.6b03582.

Experimental procedures and compound characterization (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: huyl@nwnu.edu.cn. ORCID [®]

Yingpeng Su: 0000-0002-4396-4198 Yulai Hu: 0000-0002-9630-4150

Notes

The authors declare no competing financial interest.

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