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Elemental tellurium mediated synthesis 2-(trifluoromethyl)oxazoles using trifluoroacetic anhydride as reagent

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An elemental tellurium mediated synthesis of 2-(trifluoromethyl)oxazoles from the reaction of acetophenone oxime acetates with trifluoroacetic anhydride has been developed. This new tandem cyclization proceeds in good to excellent yields *via* a SET reduction followed by a 5-*endo*-trig pathway. Some of the title compounds showed fungicidal and insecticidal activities.

The oxazole scaffold is a prominent and privileged chemical entity that is found in a wide variety of natural products and synthetic biologically active compounds.[1-3] In fact, molecules derived from oxazole exhibit excellent pharmacological properties such as COX-2 inhibitory activity,[4] antiinflammatory activity,[5] anticancer activity,[6, 7] antidiabetic activity,[8] and antifungal activity[9, 10] (Figure 1). Therefore, there is continuing interest in the development of more general and versatile synthetic methodologies for the construction and chemical modification of oxazoles.[11-13]

On the other hand, introduction of the trifluoromethyl (-CF_3) group onto heterocyclic rings often gives rise to significant changes in the chemical and physical properties of a potential drug candidate due to displaying increased bioavailability, membrane and metabolic stability, etc.[14-19] Therefore, the development of efficient methods for the construction of 2-trifluoromethylated oxazoles and their derivatives would be of particular interest as the effect of trifluoromethyl introduction on this motif.

In this context, several methods have been introduced in recent years for the preparation of 2-(trifluoromethyl)oxazoles, often based on multiple steps through trifluoroacetamide[20-24] (Scheme 1a) or trifluoroacetate[25-27] (Scheme 1b) intermediates followed by coupling or cyclization, or rearrangement reaction.[28, 29] Although these previous contributions represent important developments, these approaches are not convenient for product diversification. These procedures also revealed some drawbacks such as limited availability of the starting materials, or multistep reaction processes.

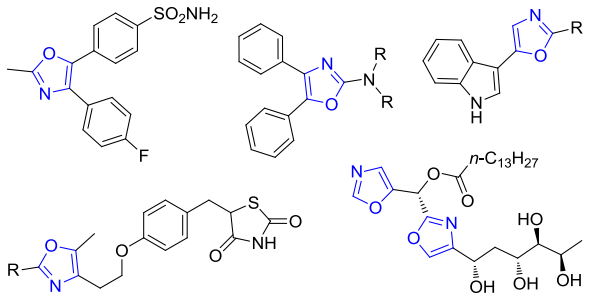
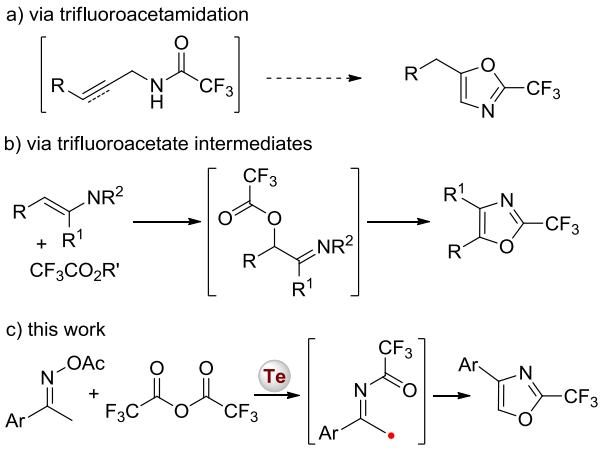


Figure 1. Examples of biologically relevant oxazoles.



Scheme 1. Strategies for the preparation of 2-(trifluoromethyl)oxazoles.

Tellurium is mainly used in metallurgy, electronics, chemical industry, and glass. There are very rare examples of organic synthesis that are mediated by elemental tellurium or

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† Footnotes relating to the title and/or authors should appear here.
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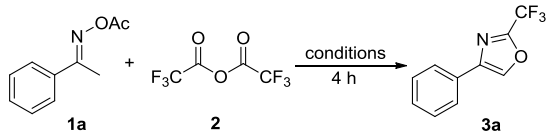
organotellurium reagent.[30-32] On the other hand, oxime acetates have emerged as readily accessible and versatile building blocks for the synthesis of nitrogen-containing heterocyclic compounds catalyzed by copper,[33-38] cobalt,[39] and iron complexes.[40] Recognizing the semimetallic character of tellurium, we envisioned that tellurium could be utilized as a single electron transfer (SET) reagent to generate iminium radical from oxime acetates, which subsequently may undergo cyclization to afford 2-(trifluoromethyl)oxazole products (Scheme 1c). We were interested in developing an efficient method for synthesis of trifluoromethylated heterocyclic compounds that utilised only readily available and inexpensive fluorinating reagents.[41-44] Here, we report a new method for the synthesis of 2-(trifluoromethyl)oxazoles through elemental tellurium mediated reaction of oxime acetates with trifluoroacetic anhydride.

Table 1. Optimization of the reaction conditions [a]



1a 2 3a

Entry	Promoter (equiv)	Additive (equiv)	Solvent	Tem. (℃)	Yield (%) [b]
1	–	–	Toluene	120	0
2	O_2	–	Toluene	120	0
3	S_8 (1)	–	Toluene	120	0
4	Se (1)	–	Toluene	120	2
5	Te (1)	–	Toluene	120	38
6	Te (1)	I_2 (0.2)	Toluene	120	98
7	–	I_2 (0.2)	Toluene	120	1
8	Te (0.2)	I_2 (0.2)	Toluene	120	75
9	Te (0.2)	I_2 (1)	Toluene	120	32
10	CuI (1)	I_2 (0.2)	Toluene	120	5
11	$Ni(COD)_2$ (1)	I_2 (0.2)	Toluene	120	0
12	$Pd(PPh_3)_4$ (1)	I_2 (0.2)	Toluene	120	0
13	Zn (1)	I_2 (0.2)	Toluene	120	0
14	Te (1)	I_2 (0.2)	Diglyme	120	9
15	Te (1)	I_2 (0.2)	Dioxane	120	8
16	Te (1)	I_2 (0.2)	DMSO	120	0
17	Te (1)	I_2 (0.2)	DMF	120	0
18	Te (1)	I_2 (0.2)	Toluene	120	86 [c]
19	Te (1)	I_2 (0.2)	Toluene	100	73

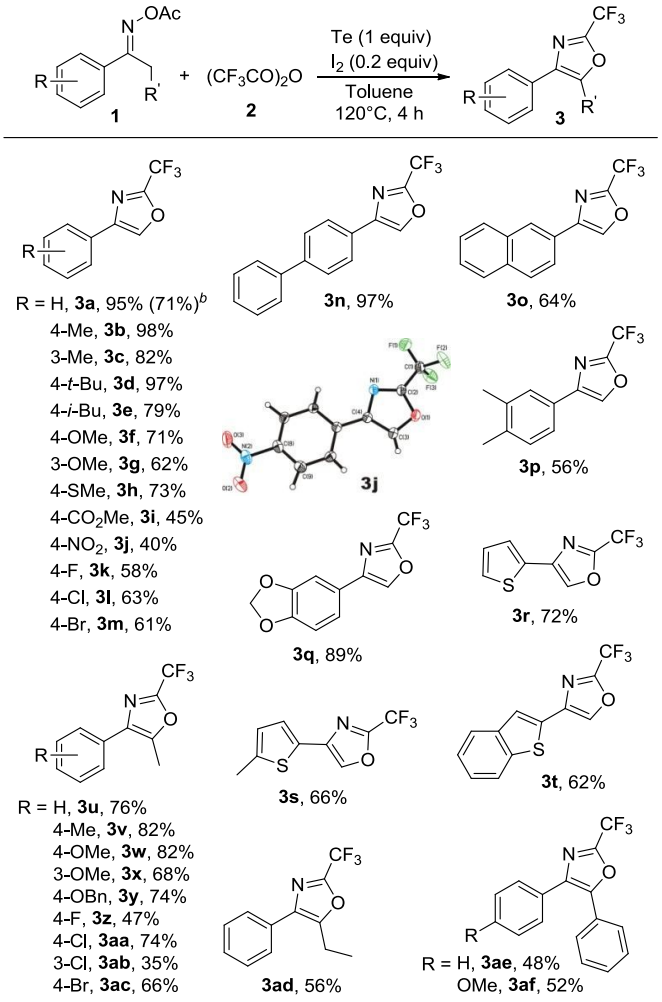
[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.20 mmol), solvent (1.0 mL), under N_2 atmosphere; [b] The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard; [c] The reaction was conducted under an air atmosphere.

To test the above hypothesis, we investigated the reaction of acetophenone oxime acetate (**1a**) with trifluoroacetic anhydride (**2**) in the presence of various promoters (Table 1). In the absence of a promoter, complete recovery of the starting material was observed after 4 hours at 120 °C (entry 1). It was recognized that oxygen, sulfur, as well as selenium do not show reactivity at 120 °C (entries 2–4), whereas at the same temperature, tellurium do mediate the desired reaction (entry 5). Since the addition of molecular iodine could promote oxidative cyclization reaction,[45-47] 0.20 equiv of I_2 was used as additive for the reaction. Gratifyingly, the desired product 4-phenyl-2-(trifluoromethyl)oxazole **3a** was generated in 98% NMR yield (entry 6). The reaction could not be performed with I_2 alone, thus implying that tellurium was essential (entry 7). The essential role of tellurium combining with iodine for the reaction was further verified by lowering Te loading to 0.2 equiv or increasing I_2 loading to 1 equiv and observing a significant decrease in the yield of **3a** (75% and 32% yield; entries 8 and 9, respectively). Transition-metal catalysts were also examined, and it was found that CuI, $Ni(COD)_2$, $Pd(PPh_3)_4$, and Zn were ineffective for this reaction (entries 10–13). A solvent screen was then carried out and low conversions were observed in diglyme, dioxane, DMSO, and DMF (entries 14–17). Interestingly, product **3a** was formed in slightly lower yield when the reaction was carried out under an air atmosphere (entry 18). It was also found a significant decrease in reactivity when the reaction temperature was reduced to 100 °C (entry 19).

Under the optimized reaction conditions, the scope and limitation of the cyclization of oxime acetates with trifluoroacetic anhydride were investigated (Table 2). Acetophenone oxime acetate derivatives bearing electron-donating groups such as methyl, *tert*-butyl, *iso*-butyl, methoxy, and methylmercapto underwent successful cyclization in good to excellent yield (**3b**–**3h**, 62–98%). Moreover, product **3a** was isolated in 71% yield (1.52 g) upon performing the reaction on a 10.0 mmol scale. Acetophenone oxime acetate derivatives containing electron-withdrawing substituents including ester, nitro, fluoro, chloro, and bromo also underwent successful cyclization, giving the 2-(trifluoromethyl)oxazoles in moderate yields, with no cleavage of aryl–halide bond observed (**3i**–**3m**, 40–63%). The structure of **3j** was also unequivocally confirmed by single-crystal X-ray analysis. Furthermore, 4-acetyl-biphenyl oxime acetate and 2-acetylnaphthalene oxime acetate also afforded good yields of products **3n** (97%) and **3o** (64%), respectively. The cyclization worked fine for the disubstituted acetophenone oxime acetate to furnish **3p** in 56% yield. The heteroaromatic substrates such as benzo[*d*][1,3]dioxole, thiophene, and benzo[*b*]thiophene oxime acetates efficiently underwent cyclization with **2** to afford the corresponding products **3q**–**3t** in 62–89% yields.

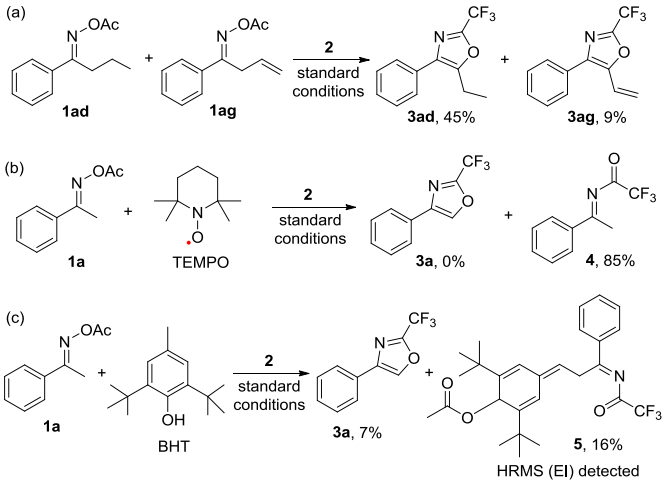
In addition, oxime acetates derived from other aromatic ketones such as propiophenone, butyrophenone, and 1-(4-methoxyphenyl)-2-phenylethanone reacted smoothly with **2** under the standard conditions to afford the 4,5-disubstituted 2-(trifluoromethyl)oxazoles **3u**–**3af** in 35–82% yields. Importantly, a broad range of functional groups such as methoxy (**3w**, **3x**, and **3af**), benzyloxy (**3y**), and halo (**3z**–**3ac**) were well tolerated.

Table 2. Synthesis of 2-(trifluoromethyl)oxazoles 3 [a]



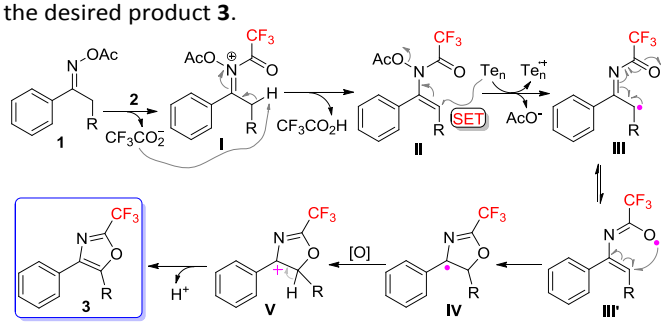
[a]Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol, 2.0 equiv), Te (1.0 mmol, 2.0 equiv), I_2 (0.20 mmol, 0.20 equiv), toluene (4.0 mL), 120 °C, 4 h, N_2; Isolated yields; [b]Performed on 10.0 mmol scale.

In order to gain insight into the mechanism of the cyclization of oxime acetates with trifluoroacetic anhydride, a series of control experiments and radical trapping were rationally designed and performed. A competition between butyrophenone oxime **1ad** and allyl *p*-tolyl ketone oxime **1ag** toward **2** resulted in preferential reaction of **1ad** (Scheme 2a). This observation implied that more stable allyl radical, which suffers from a higher activation energy for further *endo* cyclization, may be generated during the reaction with **1ag**. When the reaction of acetophenone oxime acetate (**1a**) was carried out in the presence of a radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), none of the desired product **3a** was detected (Scheme 2b). Instead, the trifluoroacetylated product **4** was formed in 85% yield. This result indicates that the reaction might proceed via a radical process. When BHT was used as a radical trap, low yield of product **3a** was observed. Trapping of the adduct **5** formed by the combination of trifluoroacetylated imine and BHT once again confirms that the reaction follows a radical mechanism (Scheme 2c).



Scheme 2. Mechanistic experiments.

Based on the above studies, a plausible reaction mechanism of the present 2-(trifluoromethyl)oxazoles formation is depicted in Scheme 3. The electrophilic trifluoroacetylation of acetophenone oxime acetates **1** with **2** gave intermediate **I**, which smoothly underwent β-H elimination to furnish trifluoroacetylated enamide derivatives **II**. A SET reduction of **II** by the reducing elemental tellurium and subsequent AcO^- elimination afforded a alkyl radical intermediate **III**. Upon isomerization of **III** to an alkoxyl radical **III'**, followed by a 5-*endo* cyclization would generate the radical intermediate **IV**. Finally, the oxidation of **IV** with tellurium species or I_2 gave the carbocation intermediate **V**, which upon deprotonation furnish the desired product **3**.



Scheme 3. Proposed mechanism for the formation of 3.

To evaluate biological activities of the title compounds, a general screening on their bactericidal and insecticidal activities was performed (See Supporting Information). The results revealed that some of 2-(trifluoromethyl)oxazoles displayed potent fungicidal activities against wheat powdery mildew (WPM) and corn rust (CSR), and insecticidal activities against plutella xylostella.

In conclusion, we have demonstrated that elemental tellurium can promote synthesis of 2-(trifluoromethyl)oxazoles from the reaction of acetophenone oxime acetates with trifluoroacetic anhydride. Mechanistic studies demonstrated

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that a radical pathway (SET reduction) and a 5-*endo*-trig cyclization is operative under the reaction conditions. This protocol represents an extremely simple and efficient method for the synthesis of trifluoromethylated oxazoles, notable synthetic targets, from readily available starting materials with exclusive selectivity and good to excellent yields. Some of the title compounds exhibited potent fungicidal and insecticidal activities. Efforts to further expand the scope of this reaction, and develop new reaction are currently ongoing in our laboratories.

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Conflicts of interest

There are no conflicts to declare.

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