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One-Pot Synthesis of Trifluoromethylated Iodoisoxazoles via the Reaction of Trifluoroacetohydroximoyl Chloride with Terminal Alkynes and *N*-Iodosuccinimide

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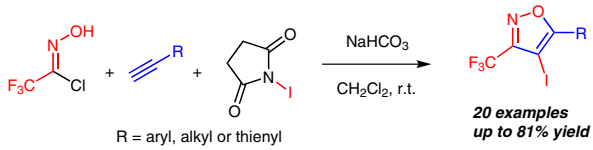

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Abstract Trifluoromethylated iodoisoxazoles have been synthesized by the reaction of trifluoroacetohydroximoyl chloride, alkynes, and N-iodosuccinimide in a one-pot reaction under metal-free and mild conditions. An array of iodoisoxazole compounds with a wide range of functionalities was obtained in moderate to good yields. The iodine-substituted isoxazoles render versatile reaction sites for subsequent conversion. Plausible pathways are proposed based on the control experiments.

Key words alkynes, cycloaddition, trifluoromethylated iodoisoxazoles, hydroximoyl chloride, synthetic methods

Isoxazoles and their derivatives have been found in numerous natural products and drug molecules,[1] such as muscimol and ibotenic acid.[2] They are also used in human cloning agonists including dopamine D4 receptors, $GABA_A$ antagonist, analgesic, anti-inflammatory, and ulcerogenic, etc (Figure 1).[3] Substituted isoxazole exhibits desirable biological activity as it has long been a desirable chemotype for medicinal chemistry.[3b,4]

There are a number of reported methods of synthesizing isoxazoles, such as the reaction of 1,1,1-trihalo-4-methoxy-4-phenylbut-3-en-2-one with hydroxylamine(Scheme 1, eq. 1),[5a] α-benzotriazolyl-α,β-unsaturated ketones with hydroxylamine (Scheme 1, eq. 2),[5b] trifluoroacetylacetone with hydroxylamine (Scheme 1, eq. 3),[5c] reaction of alkyne with *N*-hydroxy imine (Scheme 1, eq. 4 and 5).[6] Recently, Larock reported a method for the synthesis of iodine- or bromine-substituted isoxazoles via the electrophilic cyclization of 2-alkyn-1-one *O*-methyl oximes with ICl, I_2, Br_2, or PhSeBr (Scheme 2).[7]

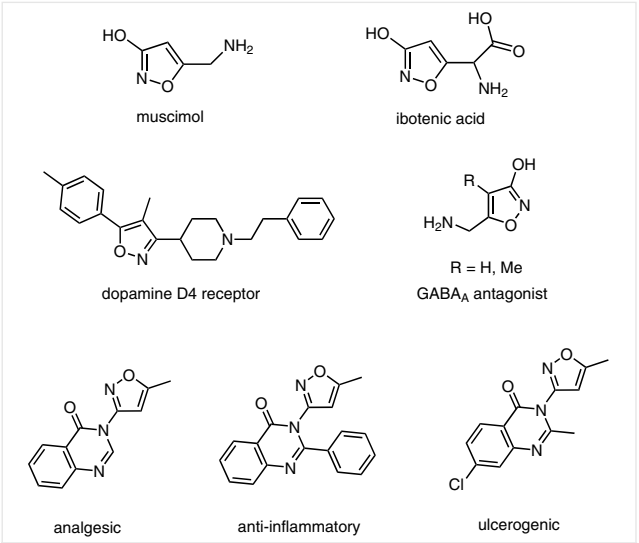
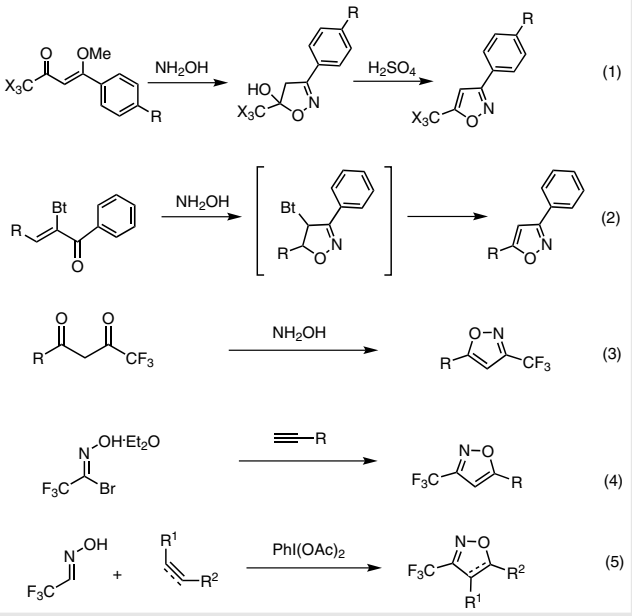
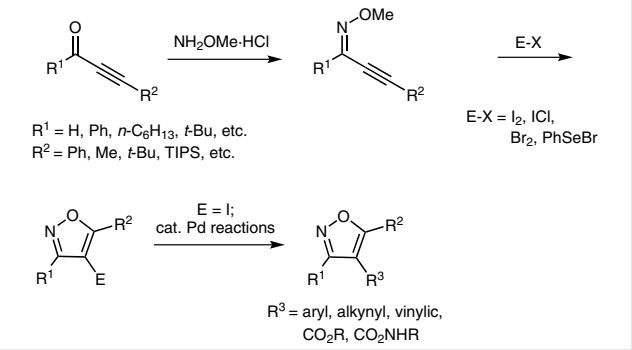


Figure 1 Natural products and drug molecules containing isoxazole

Although fluorine is uncommonly involved in natural products and biological processes, an increasing number of studies have revealed that the introduction of fluorine in a specific position of organic compounds sometime can alter their physical and biological activity dramatically.[8] For example, trifluoromethylated organic compounds have been widely used in medicinal chemistry.[9] Our laboratory's research focuses on using trifluoroacetimidoyl halide as a synthetic block. Recently we reported the results of using



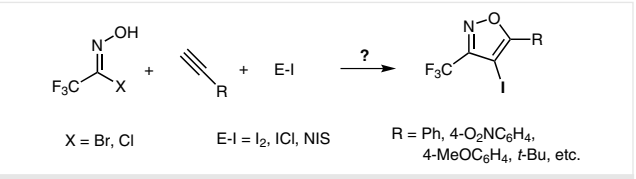
Scheme 1 Traditional methods for synthesis of isoxazole



Scheme 2 Synthesis of halogenated isoxazole

fluorinated imide halide as a starting material to synthesize trifluoromethylated quinoxaline and other heterocyclic compounds via Sonogashira reaction catalyzed by palladium/copper system.[10]

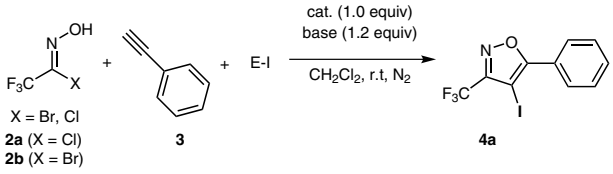
Based on our previous experiences of using fluorinated imidoyl halides as a reactant, we decided to apply one of the most commonly used fluorinated building blocks, trifluoroacetaldehyde, as starting material to synthesize fluorine-containing and halogenated *N*-hydroxy imide halogen.[11] Trifluoromethylated iodoisoxazole compounds were synthesized via one-pot reaction of fluorinated *N*-hydroxy imide halogen with alkyne and iodine electrophilic reagents which could be further transformed to more complex trifluoromethylated isoxazole substrates through the conversion of the carbon iodine bond.[12] This strategy is exemplified in Scheme 3.



Scheme 3 Synthesis of trifluoromethylated iodoisoxazoles

The initial reaction was carried out with 1.0 equivalent of **2b**, 1.2 equivalent of phenylacetylene, 1.2 equivalents of Et_3N, 1.0 equivalent of CuI, and 2.0 equivalent of ICl in dichloromethane (CH_2Cl_2) at room temperature. The corresponding 4-iodoisoxazole was obtained in 13% overall yield (Table 1, entry 1). Then I_2 or *N*-iodosuccinimide (NIS) was selected as iodine electrophile, and it was found that NIS was the better option (Table 1, entries 2 and 3). When CuBr and tetramethylethylenediamine (TMEDA) were used as catalyst and base, the reaction yield was 34% (Table 1, entry

Table 1 Optimization of the Reaction Conditions[a]



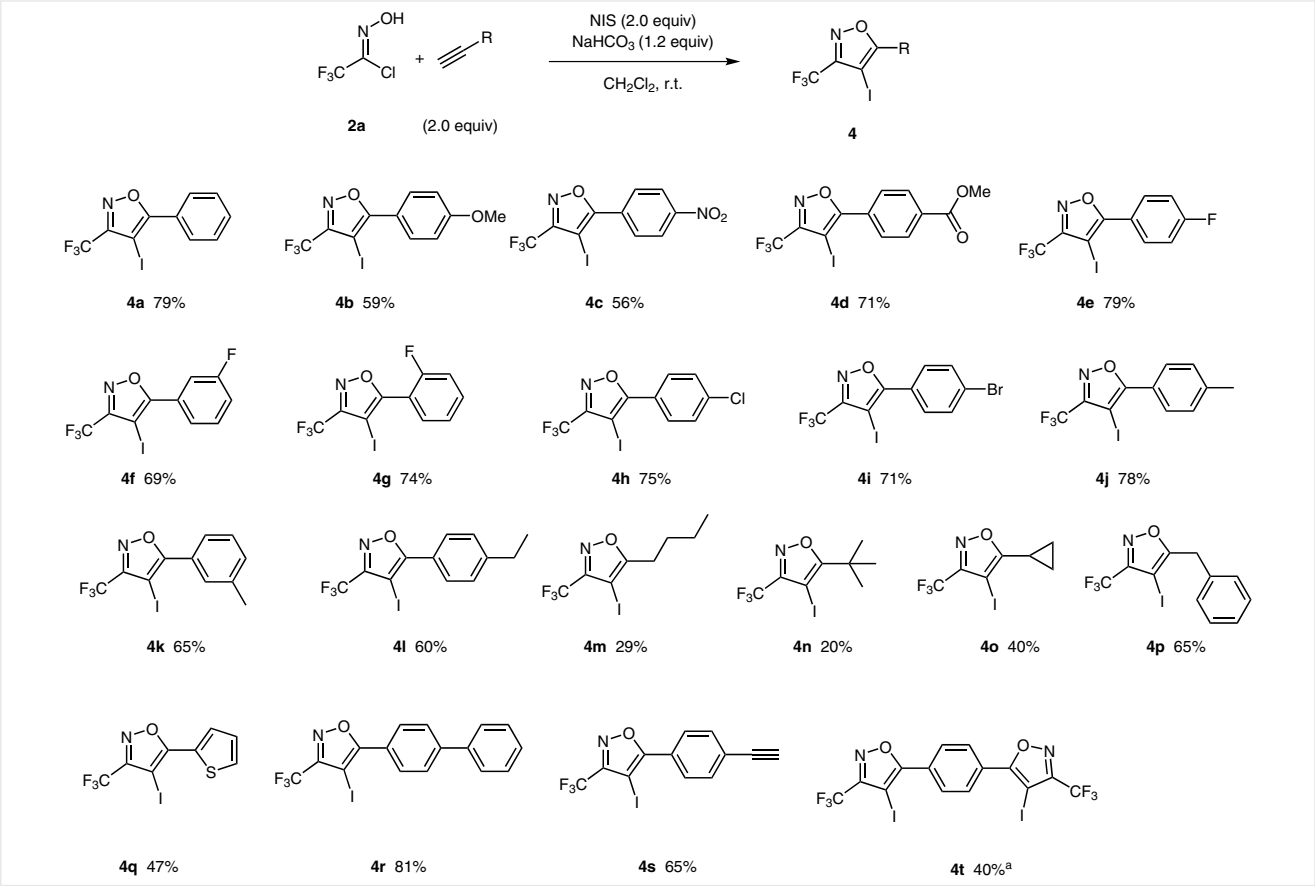
Entry	**2a**/**2b**	E-I	Catalyst	Base	Yield (%)[b]
1	**2b**	ICl	CuI	Et_3N	13
2	**2b**	I_2	CuI	Et_3N	9
3	**2b**	NIS	CuI	Et_3N	21
4	**2b**	NIS	CuBr	TMEDA	34
5	**2a**	I_2	CuBr	$NaHCO_3$	4
6	**2a**	NIS	Cu	$NaHCO_3$	74
7	**2a**	NIS	CuCl	$NaHCO_3$	40
8	**2a**	NIS	CuBr	$NaHCO_3$	69
9	**2a**	NIS	$Cu(OAc)_2$	$NaHCO_3$	70
10[c]	**2a**	NIS	CuBr	$NaHCO_3$	68
11[d]	**2a**	NIS	CuBr	$NaHCO_3$	79
12[e]	**2a**	NIS	CuBr	$NaHCO_3$	81
13	**2a**	NIS	CuBr	Na_2CO_3	81
14	**2a**	NIS	CuBr	Cs_2CO_3	49
15	**2a**	NIS	–	$NaHCO_3$	79
16	**2a**	NIS	–	Na_2CO_3	72
17	**2b**	NIS	–	$NaHCO_3$	71

[a] Reaction conditions: at room temperature, 0.2 mmol of **2a**/**2b**, 0.4 mmol of phenylacetylene, 1.2 equiv of base,1.0 equiv of catalyst were added to 2.0 equiv of E-I, followed by addition of 4 mL of CH_2Cl_2.
[b] Yields were based on ^{19}F NMR with PhF as an internal standard.
[c] Conditions: 3.0 equiv NIS were used.
[d] Conditions: 3.5 equiv NIS were used.
[e] Conditions: 4.0 equiv NIS were used.

4). When **2a** was used as a starting material, $NaHCO_3$ and I_2 were selected as the inorganic base and electrophilic reagent, the yield was only 4% (Table 1, entry 5). The combination of **2a**/$NaHCO_3$/NIS/Cu achieved the best result as the yield reached 74% (Table 1, entry 6). However, it was found that when CuCl was used as catalyst, the yield was reduced to only 40% (Table 1, entry 7). Furthermore, when CuBr or $Cu(OAc)_2$ was applied as catalysts, the yields increased to 69% or 70%, respectively (Table 1, entries 8 and 9). The yields were found to increase with the increasing of the amount of NIS (Table 1, entries 10–12). When the stronger base Cs_2CO_3 was used, the yield dropped (Table 1, entry 14). Interestingly, the reaction was found proceeded better in the absence of catalyst (Table 1, entries 15–17). Finally, we determined the optimal reaction's condition as using NIS as electrophilic reagent and $NaHCO_3$ as base and reacting at room temperature.

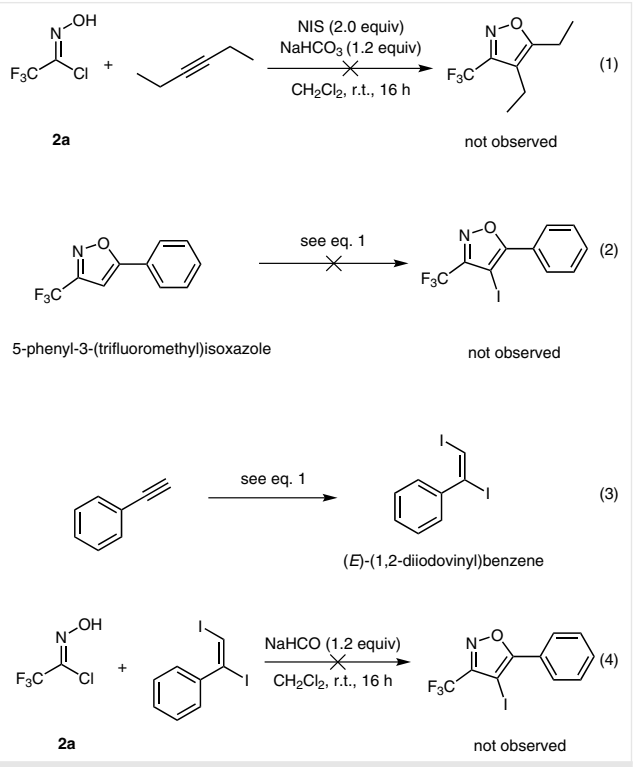
With the optimized conditions in hand, a range of alkynes were examined to evaluate the reaction.[13] As shown in Scheme 4, this protocol was efficient with various arynes bearing electron-donating groups such as methyl, ethyl, and methoxy, affording the corresponding iodine-substituted products in good yields (**4b**,**j**–**l**). When the substituents on the benzene ring were electron-withdrawing groups, such as nitro, ester, fluorine, chlorine, and bromine, the yields were also very good (**4c**–**i**). The substituents on the phenyl ring have little influence on the product yield regardless of *ortho*, *meta*, or *para* positions (**4e**–**g**,**j**,**k**). The yield declined when the aliphatic alkynes were used (**4m**–**o**). The reaction was also compatible with benzyl substituted alkyne (**4p**). 2-Ethynylthiophene could also be effectively converted into iodoisoxazole analogue with moderate efficiency (**4q**). 4-Phenylphenylethyne readily furnished the corresponding iodoisoxazole in good yield (**4r**). When 1,4-diethynylbenzene was used, both single cycloaddition product and bicyclic adducts were generated (**4s**,**t**).

In order to gain some insight into the reaction mechanism, some controlled experiments were carried out. When **2a** was reacted with 3-hexyne, the expected cycloaddition product was not formed (Scheme 5, eq. 1). If isoxazole was reacted with NIS under the same reaction conditions the iodoisoxazole product was not observed (Scheme 5, eq. 2), which means that the isoxazole is not an intermediate in the reaction. Without **2a**, the reaction of phenyl acetylene alone, 1, 2-diiodovinylbenzene was formed as the main



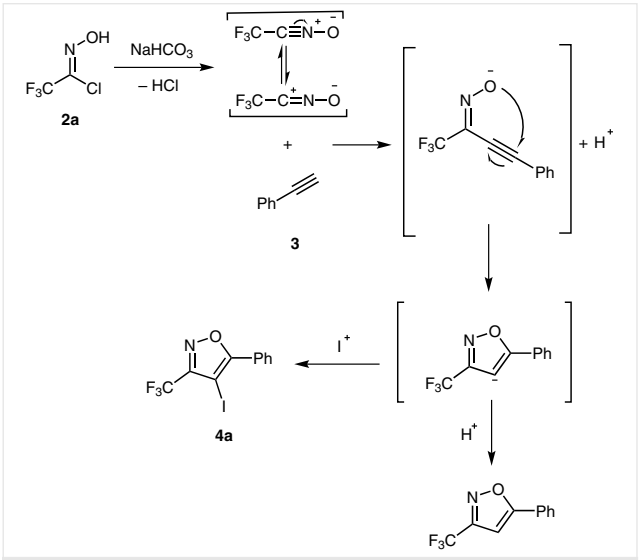
Scheme 4 Substrate scope for iodinated isoxazole. *Reaction conditions*: **2a** (1 mmol), alkyne (2 mmol), NIS (2 mmol), $NaHCO_3$ (1.2 mmol), CH_2Cl_2 (6 mL), r.t. Isolated yields. [a] 0.25 equiv 1,4-diethynylbenzene were used.

product under the same reaction conditions (Scheme 5, eq. 3).[14] Reaction of 1,2-diiodovinylbenzene with **2a** failed to produce iodoisoxazole (Scheme 5, eq. 4).



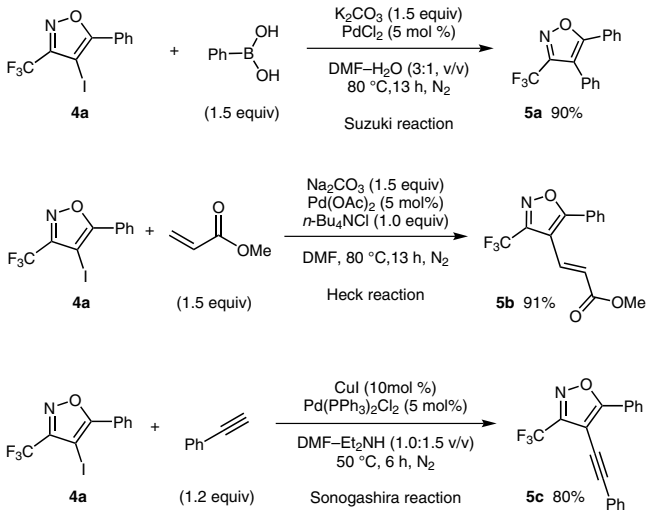
Scheme 5 Control experiments

On the basis of the above control experiments, a tandem pathway is proposed for this novel reaction.[12] As shown in Scheme 6, 2a reacts with $NaHCO_3$ to give 1,3-dipolar intermediate. The terminal alkyne **3**attacks the carbocation of the 1,3-dipolarintermediate to form the corresponding oxime anion and proton. The subsequent intramolecular attack of the oxime anion on the triple bond gives the isoxazole anion. Finally, reaction of proton or iodo cation with the isoxazole anion affords the iodoisoxazole or the isoxazole (20% yield).



Scheme 6 Proposed mechanism for this reaction

To demonstrate the value of the trifluoromethyliodoisoxazole products **4**, a number of reactions were carried out utilizing this iodoisoxazole as starting material. As expected, the iodo group in **4a** was smoothly converted into the corresponding aryl, alkenyl, or alkynyl groups under Suzuki,[15] Heck,[15] or Sonogashira[7b] cross-coupling conditions (Scheme 7).



Scheme 7 Transformation of iodoisoxazole derivatives

In summary, trifluoromethyl *N*-hydroxyimino halide can be used as a building block for introducing fluoro and iodo groups into the isoxazole. The incorporated iodo group can facilitate the synthesis of trifluoromethy isoxazole derivatives, making it useful in synthetic pharmaceutical chemistry.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562115.

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(13) **Typical Procedure for the Synthesis of Compound 4a**
To a dry reaction tube, **2a** (147 mg, 1.0 mmol), phenylacetylene (204 mg, 2.0 mmol), $NaHCO_3$ (101 mg, 1.2 mmol), NIS (450 mg, 2.0 mmol), and CH_2Cl_2 (6 mL) was added successively at room temperature under N_2 atmosphere. Then the reaction was stirred at room temperature. By the end (monitored by ^{19}F NMR), the system was diluted with water, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane) affording **4a** (268 mg, yield 79%); white solid; mp 102–103 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12–7.93 (m, 2 H), 7.55 (d, *J* = 6.1 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.67 (s, 3 F). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.35 (s), 157.56 (q, *J* = 36.5 Hz), 131.70 (s), 129.09 (s), 127.92 (s), 126.03 (s), 119.41 (q, *J* = 272.5 Hz), 49.70 (s). HRMS (EI): *m*/*z* calcd for $C_{10}H_5F_3INO$ $[M]^+$: 338.9368; found: 338.9362. IR (KBr): ν = 2956, 1476, 1446, 1255, 1187, 1143, 1006, 960 cm^{-1}.

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