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# NIS-Mediated Oxidative Cyclization of *N*-(2-Trifluoromethyl-3-alkynyl) hydroxylamines: A Facile Access to 4- Trifluoromethyl-5-acylisoxazoles†

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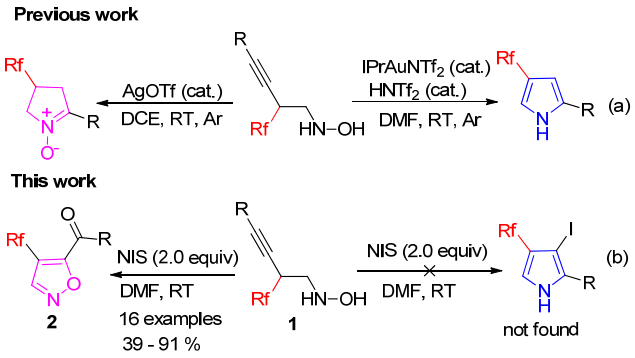
A novel NIS-mediated oxidative cyclization of *N*-(2-trifluoromethyl-3-alkynyl)hydroxylamines was developed, which provides a facile access to 4-trifluoromethyl -5-acylisoxazoles in 39-91% yields. Various types of commonly used electrophilic halogen source such as ICl, $I_2$, NIS, NBS and NCS at different temperature in various solvents were investigated. It was found that the NIS acts as both oxidant and electrophile for the present sequential transformation. The scope, mechanism and application of this NIS-mediated domino reaction for further synthetic transformation were studied.

## Introduction

Isoxazole is one of important heterocycles possessing a remarkable variety of synthetic applications.[1] Moreover, isoxazole skeleton was widely found in many bioactive natural products and pharmaceutical drugs such as valdecoxib, leflunomide, and cloxacillin.[2] Owing to its importance, a variety of methods have been developed for the preparation of isoxazoles,[1c,3] among which the predominant methods include [3+2] cycloaddition reactions between alkynes and nitrile oxides, the reactions of hydroxylamine with 1,3-dicarbonyl compounds, or unsaturated carbonyl compounds, or unsaturated nitriles. However, these methods often require high temperature, strong bases or mineral acids and afford poor regioselectivity. Therefore, the development of novel and efficient methods from readily available materials are highly desirable. On the other hand, trifluoromethyl substituted five-membered heterocycles have received considerable attention in past years,[4] owing that the introduction of $CF_3$ group would enhance and modify their original biological activities.[5] However, to the best of our knowledge, the methods for synthesis of perfluoroalkyl substituted isoxazoles have been rarely explored.[6]

Very recently, we have demonstrated a novel divergent cyclizations of *N*-(2-(perfluoroalkyl)-3-alkynyl)hydroxylamines **1** by subtle choice of transition-metal catalysts, leading to two important perfluoroalkyl substituted nitrogen containing heterocycles such as cyclic nitrones and pyrroles (Scheme 1a).[7] As an alternative to transition metal-catalysts,[8] iodine have been frequently utilized to mediate electrophilic cyclizations for synthesis of diverse carbocycles and heterocycles.[9] The iodine catalyst often behaves very similar to gold catalyst in some aspects, especially in those cyclization of functionalized alkynes containing adjacent nucleophilic centers. With this knowledge in mind, and as part of our ongoing program to develop diversity-oriented reactions[10] from identical starting material(s), we envisaged that compound **1** might be able to undergo similar tandem dehydrative cyclization process by using iodine instead of gold(1) as electrophile to afford the corresponding iodo-substituted pyrroles. However, to our surprise, unexpected perfluoroalkyl substituted isoxazole was isolated in moderate to good yields, when compound **1** was subjected to the solution of NIS in DMF, in which NIS serves as an oxidant for this oxidative cyclization(Scheme 1b).

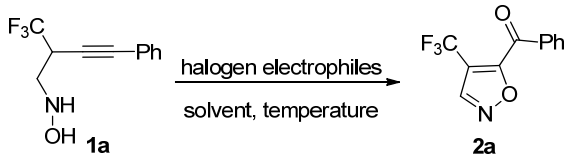



**Scheme 1.** Our previous work (a) and the present work (b).

## Results and Discussion

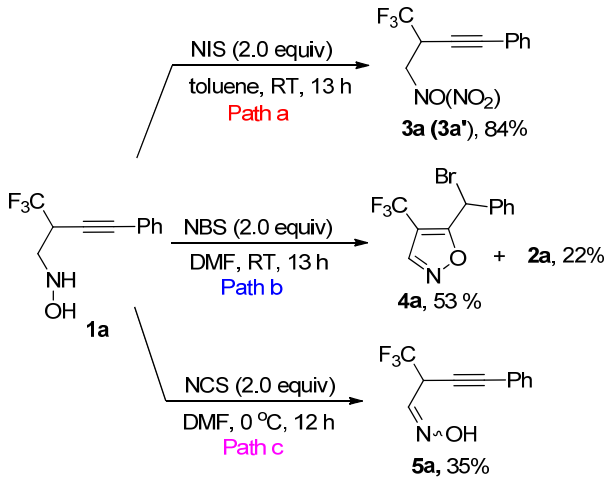
Initially, a series of common used electrophilic halogen source such as ICl, $I_2$, NIS, NBS and NCS at different temperature in various solvents were investigated (Table 1 and Scheme 2). The reaction was sluggish when using ICl or molecule $I_2$ as electrophiles[3e,3f] in dichloromethane at ambient temperature, and the corresponding isoxazole **2a** was obtained in very low yields (Table 1, entries 1-2). These results indicated that ICl and $I_2$ are ineffective for the present oxidative cyclization, despite they are effective for electrophilic

**Table 1.** Screening reaction conditions[a]




| Entry | Electrophile | Solvent | Temp | Time | **2a**(%)[b] |
|---|---|---|---|---|---|
| 1 | 1.2 ICl | DCM | rt | 12h | 5 |
| 2 | 1.2 $I_2$ | DCM | rt | 12h | 7 |
| 3 | 1.2 $I_2$ | DMF | rt | 12h | 16 |
| 4 | 2.0 $I_2$ | DMF | rt | 13h | 32 |
| 5 | 2.0 $I_2$ | DMF | 0 °C | 13h | 40 |
| 6 | 2.0 NIS | DMF | 0 °C | 15h | 75 |
| **7** | **2.0 NIS** | **DMF** | **rt** | **15h** | **83(79)[c]** |
| 8 | 2.5 NIS | DMF | rt | 15h | 74 |
| 9 | 2.0 NIS | DMAC | rt | 14h | 76 |
| 10 | 2.0 NIS | THF | rt | 12h | 54 |
| 11 | 2.0 NIS | $CH_3CN$ | rt | 12h | 10 |
| 12 | 2.0 NIS | DMSO | rt | 12h | 12 |

[a] [**1a**] = 0.1 M. [b] All reactions were quenched at specified reaction temperature by using saturated $Na_2S_2O_3$ after the substrate was consumed completely. Solution NMR yields using $CH_2Br_2$ as the internal reference. [c] Yield of isolated product are shown in parentheses. [d] DMAC = *N*, *N*-dimethylacetamide.

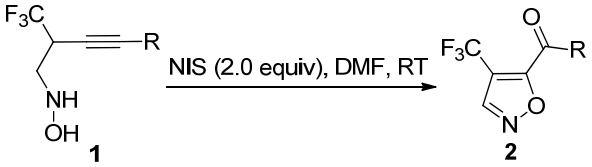



**Scheme 2.** Diverse transformation of **1a**.

cyclization of 2-alkyn-1-one *O*-methyl oximes.[3e,3f] Product diversity heavily relies on the electrophilic halogen source, solvent and reaction temperature. After numerous attempts, NIS was found to be the best oxidant and polar, coordinating solvent N, N-dimethylformamide (DMF) is the best solvent, leading to substituted isoxazole **2a** in 79% isolated yield (Table 1, entry 7). The use of more amounts of NIS could not improve the yield (Table 1, entry 8). Interestingly, hydroxylamine **1a** reacts with NIS at room temperature in non-polar solvent such as toluene, DCM to afford a mixture of nitroso (nitro) compounds **3a** (**3a'**) in 1:1 ratio as predominant products in 84% isolated yield (Scheme 2, Path a). However, the treatment of hydroxylamine **1a** with NBS in DMF afforded bromomethylated isoxazole **4a** in 53% isolated yield as the major product (Scheme 2, Path b). Oxime **5a** could be isolated as two inseparable isomers in 35% yield from the complicated reaction mixture, when the reaction was performed in DMF at 0°C with the use of NCS as the reagent. It is noteworthy that no any cyclization product **2a** could be detected under this reaction condition (Scheme 2, Path c), indicating that the reaction pattern heavily depends on the reactivity of electrophilic halogen source [11] and the choice of reactions conditions.

With the optimal reaction conditions in hand, the scope of this oxidative cyclization process was examined by variation of the R group on the alkyne moiety and the results are outlined in Table 2. Both electron-donating and electron-withdrawing substituted aryl groups were well tolerated, providing the desired 4-trifluoromethyl-5-acyl disubstituted isoxazoles in moderate to good yields (Table 2, entries 1–11). The reaction also displays well tolerance of various substitution patterns (*o*-, *m*-, and *p*-) (Table 2, entries 6–8). The structure of isoxazole **2i** was unambiguously confirmed by X-ray crystallography (Figure 1).[12] Notably, substituting the alkynyl unit with a pyridine heterocycle (**1m**) resulted in lower yield and the reaction requires much longer time. We attribute the lower yield and low reactivity to the basic pyridine moiety (Table 2, entry 12). This result is also consistent with the fact that isoxazole **2a** could not be formed when bases were added to the reaction mixture. In the case of alkyne bearing cyclopropyl group or electron rich heteroaryl group such as thiophen-2-yl, the reaction became complicated and the corresponding isoxazole **2n** and **2o** could be separated in 33%, 47% isolated yield, respectively (Table 2, entries 13-14). It is also noteworthy that no desired product was obtained when alkyne bearing TMS group (**1p**) or terminal alkyne (**1q**) was used as substrate (Table 2, entries 15–16).

**Table 2.**Substrate scope of hydroxylamines **1**[a]




| Entry | R (1) | Time(h) | Yield (%) |
|---|---|---|---|
| 1 | 4-Me$C_6H_4$ (**1b**) | 13 | **2b** (65) |
| 2 | 4-MeO$C_6H_4$ (**1c**) | 13 | **2c** (81) |
| 3 | 4-Cl$C_6H_4$ (**1d**) | 16 | **2d** (77) |
| 4 | 4-Br$C_6H_4$ (**1e**) | 16 | **2e** (60) |
| 5 | 4-$CF_3C_6H_4$ (**1f**) | 13 | **2f** (75) |
| 6[c] | 4-$NO_2C_6H_4$ (**1g**) | 16 | **2g** (65) |
| 7[c] | 3-$NO_2C_6H_4$ (**1h**) | 13 | **2h** (91) |
| 8 | 2-$NO_2C_6H_4$ (**1i**) | 13 | **2i** (86) |
| 9 | 4-C$NC_6H_4$ (**1j**) | 13 | **2j** (74) |
| 10 | 4-$CO_2MeC_6H_4$ (**1k**) | 12 | **2k** (75) |
| 11 | 1-Naphthyl (**1l**) | 12 | **2l** (65) |
| 12 | 2-Pyridinyl (**1m**) | 36 | **2m** (39) |
| 13 | Cyclopropyl (**1n**) | 15 | **2n** (33) |
| 14 | Thiophen-2-yl (**1o**) | 15 | **2o** (47) |
| 15 | TMS (**1p**) | 13 | -- |
| 16 | H (**1q**) | 13 | -- |

[a] Unless otherwise specified, the rection was carried out by using **1** (0.2 mmol), NIS (2.0 equiv.) in 2 mL of DMF at room temperature. [b] Yield of the isolated product. [c] reaction was performed at 0 °C.

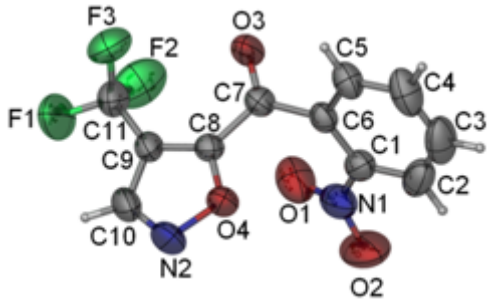
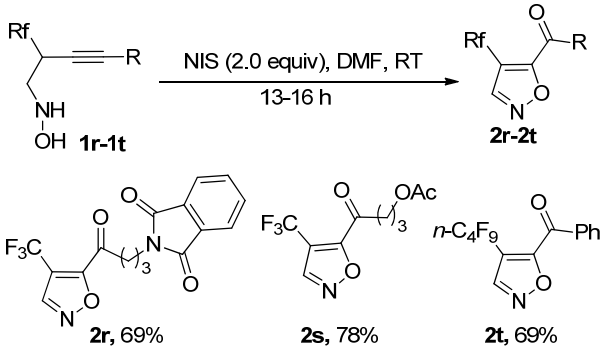



**Figure 1. ORTEP depiction of compound 2i**

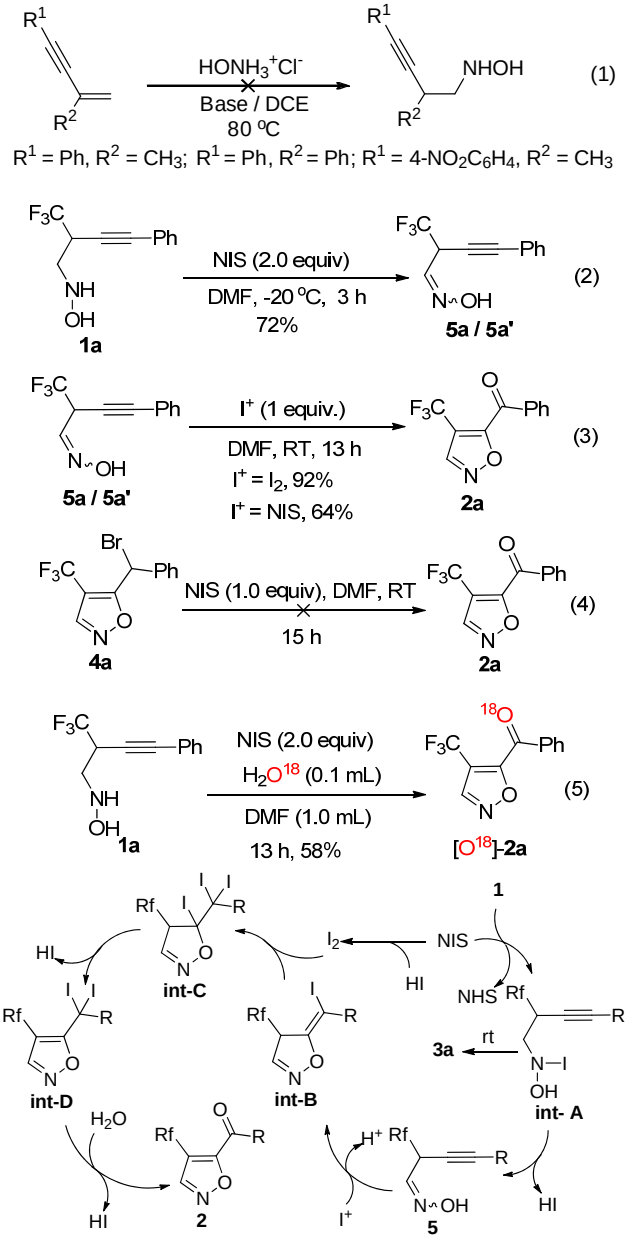
However, the reaction also works well for those substrates bearing alkyl groups containing ester and amide functional groups under the optimal reaction conditions, leading to the desired isoxazoles **2r** and **2s** in 69% and 78% isolated yields, respectively (Scheme 3). It is noteworthy that other perfluoroalkyl groups such as *n*-$C_4F_9$ could also be well introduced and the corresponding isoxazole **2t** was obtained in 69% isolated yield.




**Scheme 3.** NIS mediated reaction of **1r-1t**.

To probe whether the trifluoromethyl group is important for inducing the present cyclization, three 1,3-conjugaed enynes bearing methyl or phenyl group instead of trifluoromethyl group were synthesized and subjected to the reaction with hydroxylamine hydrochloride under different reaction conditions including using various base or elevating reaction temperature, however, no desired nucleophilic addition products were detected. These results indicated that 1,3-conjugaed enynes bearing perfluoroalkyl group at double bond position is crucial to nucleophilic addition leading to *N*-(2-(trifluoromethyl)-3-alkynyl)hydroxylamines **1** [Eq.(1)]. Our previous work have demonstrated that 1,3-conjugaed enynes bearing an electron-withdrawing group such as alkoxycarbonyl instead of a trifluoromethyl group react smoothly with hydroxylamines to afford 2,3-dihydroisoxazoles via tandem inter- and intramolecular nucleophilic addition[13], which again indicate that $CF_3$ is a unique electron-withdrawing group.

To gain insight into this oxidative cyclization, some control experiments were then carried out. Oxime **5a** could be isolated in 72% yield as a mixture of *Z*/*E* stereoisomers by treatment of hydroxylamine **1a** with NIS in DMF at -20 °C for 3 h, followed by quenching with saturated aqueous $Na_2S_2O_3$ [Eq.(2)]. Oxime **5a** underwent facile cyclization with the use of 1.0 equivalent of NIS or $I_2$ to afford isoxazole **2a** in 64% and 92% isolated yield, respectively [Eq.(3)]. These results indicated that the oxime **5a** is most probably the key intermediate for the oxidative cyclization of compound **1**. In the contrast, no reaction occurred and 100% of **4a** was recovered, when bromomethylated isoxazole **4a** was subjected to the optimal reaction conditions [Eq.(4)], which provide strong support that the plausible reaction pathway through the corresponding halomethylated isoxazole **4a** could be ruled out. To examine where the oxygen atom in ketone group of **2a** is from, a control reaction was carried out in DMF containing $H_2O^{18}$. The corresponding $O^{18}$-labeled product [$O^{18}$]-**2a** was obtained in 58% yield [Eq.(5)], indicating that the oxygen atom of the ketone originated from water rather than from molecular dioxygen.[11]

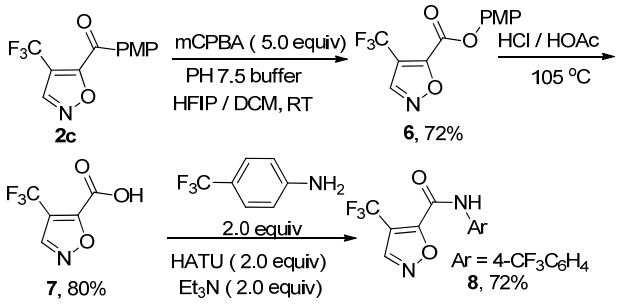



**Scheme 4.** Plasusible mechanism.

Based on the above controlled experiments, a plausible reaction mechanism that accounts for this NIS-mediated oxidative cyclization of hydroxylamine **1** was outlined in

Scheme 4. Initially, the hydroxylamine **1** was selectively oxidized by NIS to produce hydroxylhaloamine **int-A**, which would produce the isolable oxime **5** with the elimination of HI.[14] Those two *Z*/*E* isomers of oxime **5** could mutually isomerize under acid condition. The $I^+$ mediated electrophilic cyclization of *Z*-oxime **5** would then generate intermediate **int-B** via a *5-exo-dig* cyclization mode. The electrophilic addition of molecular $I_2$ to double bond of **int-B** afforded intermediate triiodo **int-C**, which upon aromatization would afford the diiodomethylated **int-D** via the elimination of one molecule of HI. Finally, the **int-D** would easily undergo hydrolysis to give the product isoxazole **2**.

The synthetic utility was showcased by using representative product **2c** as precursor for further synthetic transformation to compounds of type **8** which may be useful for further applications in the field of agrochemicals and pharmaceuticals (Scheme 5). The regioselective Bayer-Villiger oxidation[15] of **2c** by *m*-CPBA produced the ester **6** in 72% isolated yield. The corresponding carboxylic acid **7** was then prepared in 80% yield through the hydrolysis under acid conditions.[16] Subsequent condensation of acid **7** with 4-trifluoromethyl aniline with the use of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) as coupling reagent produced the final product **8**.[17]




**Scheme 5.** Synthetic utility of **2c**

## Conclusions

In summary, we have developed a novel NIS-mediated oxidative cyclization of *N*-(2-trifluoromethyl-3-alkynyl) hydroxylamine under mild conditions, which provide a facile route to various 4-trifluoromethyl-5-acylisoxazoles. Moreover, NIS plays a dual role in the present transformation, serving simultaneously as an oxidant and an electrophile to mediate the cyclization. The synthetic utility of this method for further synthetic transformation is also demonstrated. The salient features of this novel method include the readily available starting materials, the ease of operation, the synthetically usefulness and new reaction pathway.

## Experimental section

**Representative Procedure for the Synthesis of Phenyl(4-(trifluoromethyl)isoxazol-5-yl)methanone (2a).**

To a solution of N-(4-phenyl-2-(trifluoromethyl)but-3-yn-1-yl) hydroxylamine **1a** (46 mg, 0.2 mmol) in DMF(2.0 mL), NIS (90.0 mg, 0.4 mmol) was added at room temperature, the reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$ (2.0 mL), Then extracted with ethyl acetate (3x4.0 mL) and the combined organic extracts were dried over $MgSO_4$. After filtration and evaporation, the residue was purified by flash column chromatography on silica gel to afford **2a**. [Eluent: petroleum ether : ethyl acetate = 50:1 ].

Colorless oil. 79% isolated yield.$^1$H NMR (400 MHz, $CDCl_3$) $^1$H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.04 (d, *J* = 7.7 Hz, 2H), 7.72 (t, *J* = 7.3 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 2H).$^{19}$F NMR (377 MHz, $CDCl_3$) δ -57.31. $^{13}$C NMR (100 MHz, $CDCl_3$) δ 180.58, 164.66, 148.35 (q, *J* = 2.6 Hz), 135.18, 134.47, 130.23, 129.02, 120.21 (q, *J* = 268.1 Hz), 114.87 (q, *J* = 40.9 Hz). MS (70 eV): m/z (%): 241 ($M^+$, 1.99), 46 (100). HRMS calcd for $C_{11}H_6F_3NO_2$: 241.0351, found: 241.0353.

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Electronic Supplementary Information (ESI) available: Copies of NMR spectra of all new compounds See DOI: 10.1039/b000000x/

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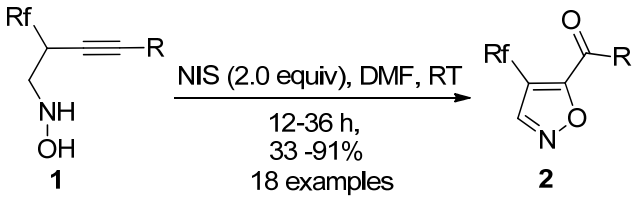


**NIS mediated sequential procedure involving oxidation and electrophilic cycloisomerization of *N*-(2-trifluoromethyl-3-alkynyl) hydroxylamines for 4-trifluoromethyl-5-acylisoxazole synthesis has been developed.**