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Tandem Synthesis of 3-Halo-5-Substituted Isoxazoles from 1-Copper(I) Alkynes and Dihaloformaldoximes

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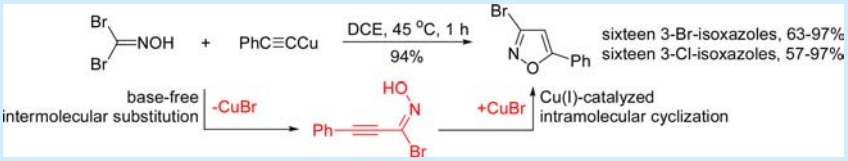
Supporting Information



ABSTRACT: A tandem synthesis of 3-halo-5-substituted isoxazoles has been developed from 1-copper(I) alkynes and dihaloformaldoximes under base-free conditions. Thus, 1,3-dipolar cycloaddition and all its drawbacks can now be avoided completely.

The isoxazoles are a large family of heterocycles that are found in numerous natural products and synthetic compounds.[1] As shown in Figure 1, 3-halo-5-substituted isoxazoles (**1** and **2**) are very important members due to the substitution of halogen atoms on the ring. Many of them not only have novel medicinal properties[2] but also are versatile intermediates in organic synthesis.[3−5]

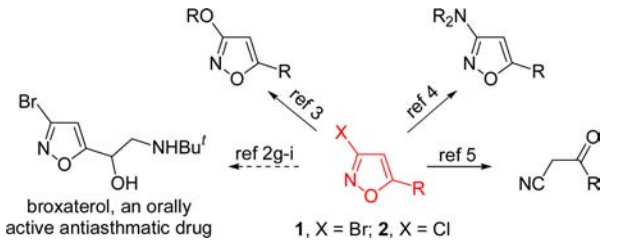


Figure 1. Applications of 3-haloisoxazoles.

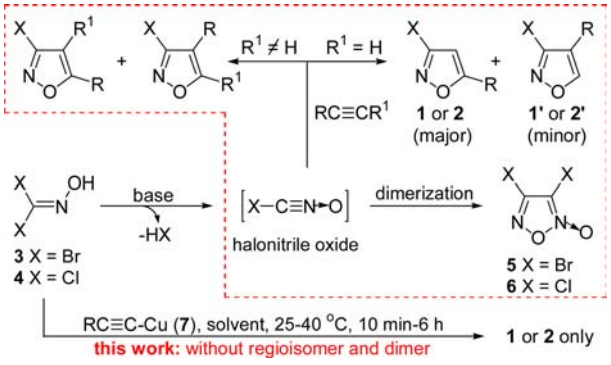
Investigation showed that 1,3-dipolar cycloaddition (1,3-DPCA) of an alkyne with nitrile oxide is the most popular method for the synthesis of substituted isoxazoles.[1,6] Although nitrile oxides are carefully generated *in situ* by dehydrohalogenation of α-halo-oximes or by dehydrogenation of oximes, their extremely high reactivity often leads to two drawbacks: poor regiocontrol in the products and dimerization of the nitrile oxide.[1,6,7] As shown in Scheme 1, when dihaloformaldoxime (**3** or **4**) is used as a substrate, the isoxazole **1** or **2** is synthesized with the same drawbacks. But, this is the only practical method for the synthesis of such products to date.

Herein, we would like to report a novel tandem synthesis of **1** or **2** from 1-Cu(I) alkynes (**7**) and **3** or **4**. Since the method does not involve a 1,3-DPCA and the intermediacy of a halonitrile oxide, all drawbacks of a 1,3-DPCA are avoided completely.

In the literature, early improvements to this type of 1,3-DPCA were focused on ways to reduce the formation rate of the nitrile oxide by using weak bases, low temperatures, and slow addition of a reactant (α-halo-oxime or base). Yet, these approaches have no significant impact on the 1,3-DPCA when **3** or **4** is used as a substrate[2f,3d,4d,6i,8] because these geminal dihalides generate the corresponding halonitrile oxides at a rate too fast for the reactants to be controlled. Recently, several Cu(I)-catalyzed procedures have been reported to optimize the 1,3-DPCA of terminal alkynes.[9] As shown in Scheme 2, terminal alkyne **8** was initially converted into a 1-Cu(I) acetylide intermediate **7**, whereafter the reactivity and regioselectivity of the triple bond were enhanced. Unfortunately, when we treated the mixture of **3** and phenylethyne (**8a**) with the same catalytic system, 3-bromo-5-phenylisoxazole (**1a**) was obtained as a single regioisomer in only 51% yield accompanied by some dimer **5**. This may be caused by fast formation of the bromonitrile oxide in an aqueous $KHCO_3$ solution.

To further reduce the rate of bromonitrile oxide formation, we tried to use powdered $KHCO_3$ in an organic solvent. Thus,

Scheme 1. 1,3-DPCA and This Work



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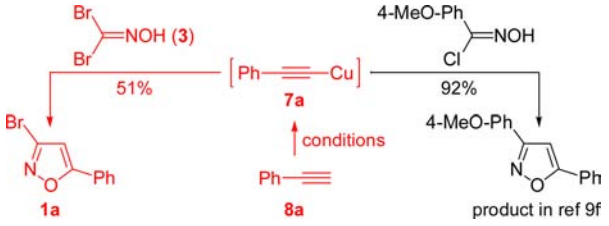
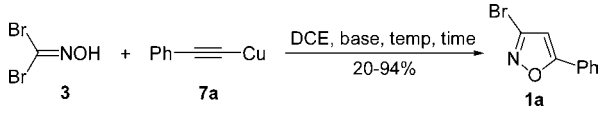
Scheme 2. Cu(I)-Catalyzed 1,3-DPCA[a]



[a]The conditions in ref 9f were used: $CuSO_4·5H_2O$ (2 mol %), NaAsc (10 mol %), $KHCO_3$ (4.3 equiv), H_2O/*t*-BuOH (1:1), rt, 4 h.

the premade **7a** was employed as a substrate because it could not be generated from **8a** and $CuSO_4·5H_2O$/NaAsc (sodium ascorbate)[9f] in an organic solvent. As shown in Table 1, the

Table 1. Reactions by Using 7a as a Substrate[a]



entry	base	3:7a (by mole)	temp (°C)	time (h)	1a (%)[b]
1	$KHCO_3$	1.2:1	25	12	76
2	CsF	1.2:1	25	12	76
3	K_2CO_3	1.2:1	25	12	73
4	K_3PO_4	1.2:1	25	12	70
5	NaOAc	1.2:1	25	12	68
6	Bu_4NOAc	1.2:1	25	12	20
7	–	1.2:1	25	12	93
8	–	1.2:1	35	7.5	93
9	–	1.2:1	45	1.0	94
10	–	1.2:1	50	0.5	85
11	–	1:1	45	1.0	75
12	–	1.1:1	45	1.0	80
13	–	1.5:1	45	1.0	94
14	–	2:1	45	1.0	94

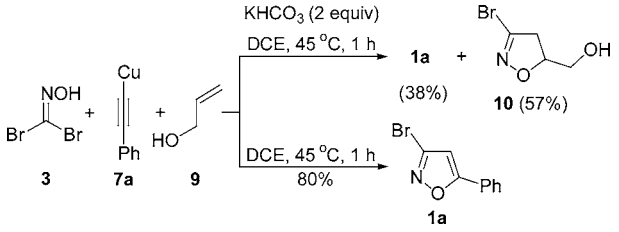
[a]The mixture of **3** and **7a** (0.5 mmol) in $ClCH_2CH_2Cl$ (1 mL) was stirred in a stoppered glass tube. [b]The isolated yields.

yield of **1a** was increased to 76% after a mixture of **3**, **7a**, and $KHCO_3$ in DCE was stirred for 12 h (entry 1). Similar results were observed by using different insoluble bases (entries 1–5). To our great surprise, **1a** was obtained in 93% yield under base-free conditions (entry 7). The reaction time was reduced significantly by increasing the temperature, but the yield of **1a** was not influenced (entries 7–9). No dimer **5** was detected even when a large excess of **3** was employed (entries 13–14). These results strongly suggested that the base-free reactions did not proceed by way of 1,3-DPCA and a bromonitrile oxide.

To prove our hypothesis, two competitive experiments were run as shown in Scheme 3. In the presence of $KHCO_3$, the reaction of **3**, **7a**, and **9** gave two products **1a** and **10**. However, the same reaction gave **1a** as a single product in the absence of $KHCO_3$. These results clearly indicated that the first experiment was a 1,3-DPCA, with bromonitrile oxide as an intermediate, while the latter experiment went through an unknown mechanism.

Luckily, a small amount of an intermediate was separated when the reaction of **3** and **7a** was performed at 20 °C. Its structure was assigned as (*E*)-1-bromo-3-phenylpropynal oxime [(*E*)-**11**] by NMR spectra and single crystal X-ray diffraction analysis (Figure 2). As shown in Scheme 4, (*E*)-**11** was

Scheme 3. Two Competitive Experiments



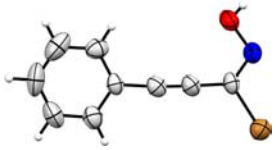
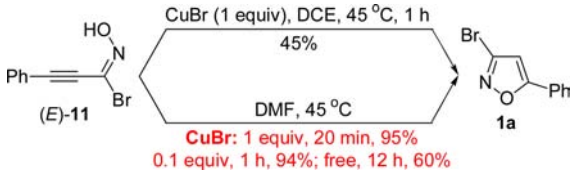


Figure 2. Structure of intermediate (*E*)-**11**.

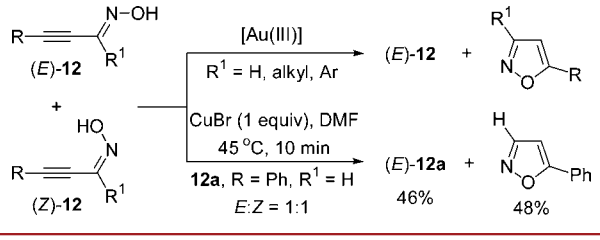
Scheme 4. Cu(I)-Catalyzed Cyclization of (*E*)-11



converted into **1a** smoothly in the presence of CuBr in DCE, but in only 45% yield. Realizing that the commercial CuBr is a polymer with much lower catalytic activity than that of *in situ* generated CuBr, the coordinating solvent DMF was used to give **1a** in 95% yield within 20 min. Further experiments indicated that this conversion was a Cu(I)-catalyzed cyclization, and use of 0.1 equiv of CuBr was sufficient to produce excellent results.

Recently, several gold(III)-catalyzed intramolecular cyclizations of propynal or propynone oximes (**12**) have been reported for the synthesis of isoxazoles (Scheme 5).[10] They

Scheme 5. Chemoselective Cyclization of *E*/*Z*-Oximes



showed high regioselectivity in the products formed, but their precusor substrates (**12**) were associated with some drawbacks: they needed to be preprepared as an *E*/*Z*-mixture; but, only one isomer (*cis*-position between hydroxyl and alkynyl) underwent the cyclization with the other isomer having to be separated off before or after the cyclization. When the *E*/*Z*-mixture (1:1) of 3-phenyl-propynal oxime (**12a**) was used as the substrate under our conditions, only the *Z*-isomer underwent the cyclization, with almost quantitative recovery of the *E*-isomer.

Based on the above results, a possible tandem pathway was proposed as shown in Scheme 6. Under the base-free conditions, the formation of bromonitrile oxide by dehydrochlorination of **3** was inhibited. Therefore, **3** underwent a

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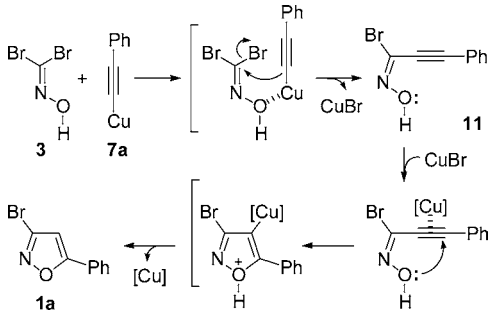
Scheme 6. A Possible Tandem Pathway

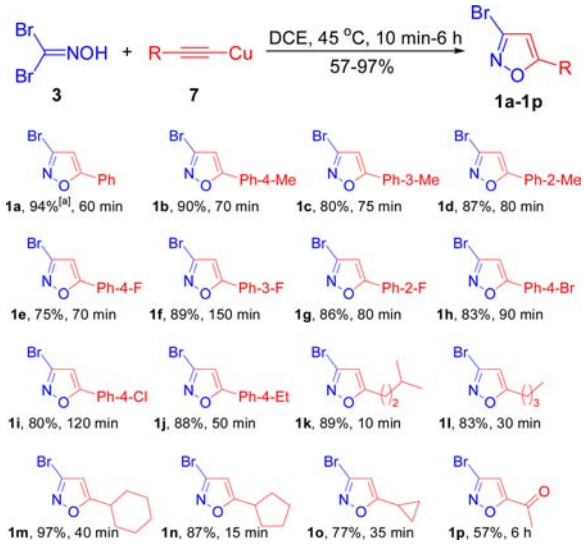


nucleophilic addition−elimination with **7a** to selectively give (*E*)-**11** as an intermediate. Then, (*E*)-**11** carried out a Cu(I)-catalyzed intramolecular cyclization to give **1a**. In this pathway, the Cu(I) ion may play three important roles: (a) the triple bond in **7a** is polarized by the Cu(I) to increase its reactivity and regioselectivity;[11] (b) the (*E*)-configuration of **11** is well controlled by coordination of the Cu(I) with oxime; (c) the cyclization of (*E*)-**11** is catalyzed by the Cu(I). Thus, this new pathway has the convenience of intermolecular substitution and the good regioselectivity of intramolecular cyclization.

As shown in Table 2 (see: SI), many solvents can be used for the reaction of **3** and **7a**. Noncoordinating solvents usually give better yields of **1a** (entries 1−4) than coordinating solvents (entries 5−9). The yield of **1a** is reduced significantly in the presence of a ligand, which may also function as a base (entries 10−13). Finally, entry 1 was assigned as our standard conditions.

The scope of this method was tested with dibromoformaldoxime (**3**) as shown in Scheme 7. All tested products

Scheme 7. Scope of 4-Br-5-Substituted Isoxazoles

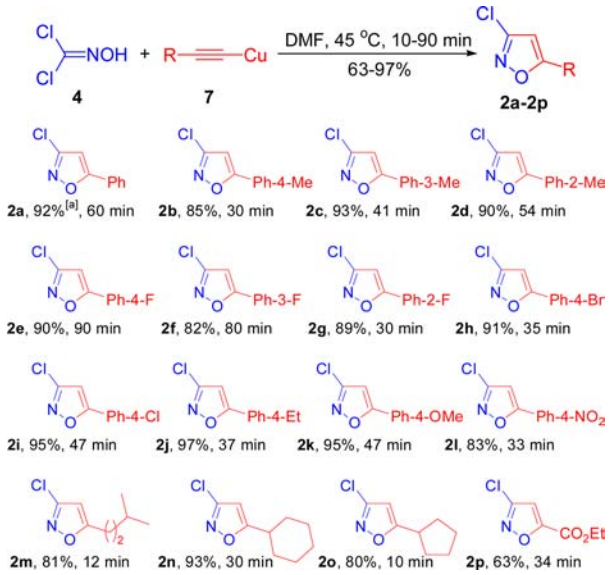


[a]Separated yields were obtained.

(**1a−1p**) were obtained in good-to-excellent yields by simply stirring the mixture of **3** and **7** in DCE. The reactions of arylethynes bearing electron-donating groups were mainly influenced by steric effects (see: **1b−1d**), while those bearing electron-withdrawing groups were mainly influenced by electronic effects (see: **1e−1g**). Alkylethynes usually gave the products in higher yields with shorter reaction times (see: **1k−1o**) compared to arylethynes. But, (4-methoxyphenyl)ethyne (**7q**) and (4-nitrophenyl)ethyne (**7r**) gave unsatisfactory results. It seems that **7q** has very low nucleophilicity because it gave a complicated mixture with 1,4-diarylbutadiyne (an oxidative coupling product) as a major product. The substrate **7r** gave a very low yield of the expected product even with a prolonged reaction time (24 h). This problem may be caused by the fact that both the substrate and product have very poor solubility in DCE. Therefore, it was difficult to convert one solid into another solid. On a 1.5-g scale, **1a** was prepared in 85% yield without optimization.

Unfortunately, the product **2a** was obtained in only 30% yield from dichloroformaldoxime (**4**) and **7a** under similar conditions, which may be caused by the lower reactivity of **4**. Since the 1-copper(I) alkyne usually has a polymeric structure and its reactivity can be enhanced by using coordinating solvents to dissociate its polymeric structure,[12] this problem was resolved easily by using DMF as a solvent. As shown in Scheme 8, **2a** was obtained in 92% yield within 1 h and all other

Scheme 8. Scope of 4-Cl-5-Substituted Isoxazoles



[a]Separated yields were obtained.

desired products (**2a−2p**) were obtained in good-to-excellent yields. It is noteworthy that **7q** and **7r** gave the expected products **2k** and **2l** in excellent yields. It seems that the use of **4** as a substrate achieved higher efficiency (shorter time and higher yield) than that of **3**. On a 1.5-g scale, **2k** was prepared in 90% yield without optimization.

In summary, a highly regioselective tandem synthesis of 3-halo-5-substituted isoxazoles has been developed. To the best of our knowledge, our method offers a second practical pathway for the synthesis of such products besides 1,3-DPCA. A possible mechanism and functions of Cu(I) were proposed. The method may find wide use because it proceeds under extremely convenient conditions.

■ ASSOCIATED CONTENT

Supporting Information

Experiments, characterization, ^{1}H and ^{13}C NMR spectra for all products and CIF file for (*E*)-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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