Synthesis of 3,4,5-Trisubstituted Isoxazoles in Water via a [3+2]-Cycloaddition of Nitrile Oxides and 1,3-Diketones, β-Ketoesters, or β-Ketoamides: Base-mediated and Keto-enol-controlled Mechanism

Md Imran Hossain,[1] Md Imdadul H. Khan,[1] Seong Jong Kim,[2] Hoang V. Le[1,*]

[1] Department of BioMolecular Sciences and Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, Mississippi 38677, USA

[2] Natural Products Utilization Research Unit, United States Department of Agriculture, Agricultural Research Service, University, Mississippi 38677, USA

ABSTRACT: A selective [3+2]-cycloaddition reaction of nitrile oxides and 1,3-diketones, β-ketoesters, or β-ketoamides in water without the need of a metal catalyst is described. The selectivity of the reaction can be controlled by the polarity of solvents in the presence of an appropriate base. The optimized reaction condition circumvents other reactions, such as O-imidoylation or hetero [3+2]-cycloaddition. The reaction happens fast in water to provide an environment friendly access to 3,4,5-trisubstituted isoxazoles, specifically acyl-substituted, ester-substituted, or amide-substituted isoxazoles, which are important structures found in numerous bioactive natural products and pharmaceuticals.

Key words: 3,4,5-Trisubstituted isoxazoles; trifluoromethyl-substituted isoxazoles; acyl-substituted isoxazoles; ester-substituted isoxazoles; amide-substituted isoxazoles

Introduction

Isoxazoles are a privileged class of five-membered heterocycles, which are found in numerous bioactive natural products[1,2] and synthetic small molecule drugs,[3,4] and are used as important precursors for the synthesis of β-hydroxy carbonyls and γ-amino alcohols.[1] Isoxazoles, appearing in 33 patents from the year of 2016 to 2018,[3] is an important drug class due to their wide range of biological activities, such as anticancer,[5] antibiotic,[6,7] antimicrobial,[8] antifungal,[9] and anti-inflammatory.[10] Therefore, new methods to develop efficient, high-yield, and green routes to isoxazoles are always highly desirable.

New accesses to 3,4,5-trisubstituted isoxazoles, particularly the ones that leverage diverse chemical libraries, are exciting as current methods are limited. One commonly used route is the cycloaddition of alkynes and nitrile oxides with heat.[11–16] While 3,5-disubstituted isoxazoles can be easily accessed by the route from terminal alkynes, 3,4,5-trisubstituted isoxazoles requires high degree of substitution on non-terminal alkynes to activate them for a decent yield, thus

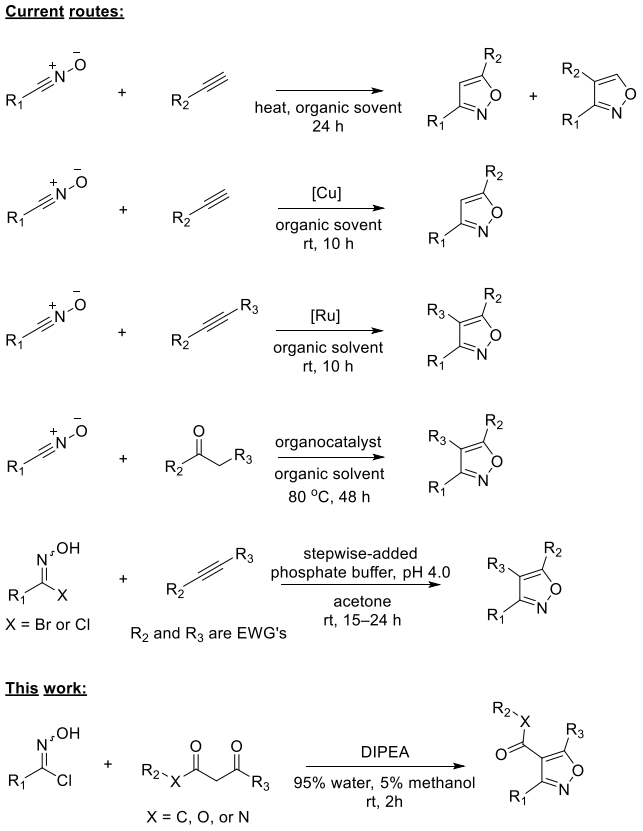


Figure 1. Routes to isoxazoles

limiting the scope of the substrates of this route. The cycloaddition of alkynes and nitrile oxides can be carried out without catalysts in high temperature conditions; however, the regioselectivity on the products is very poor.[17,18] Copper catalysts can help bring the reaction condition to room temperature and improve both the regioselectivity and yields; however, they only worked for the reaction with terminal alkynes to produce 3,5-disubstituted isoxazoles.[19,20] The synthesis of 3,4,5-trisubstituted isoxazole from highly substituted non-terminal alkynes remain challenging for copper catalysts. Ruthenium (II) catalysts have been shown to help the reaction proceed smoothly at room temperature, producing high yields and regioselectivity for both 3,5-disubstituted and 3,4,5-trisubstituted isoxazoles.[21,22] In a similar fashion, Palladium catalysts were used for an electrophilic intramolecular cyclization of alkynes and aldoximes to produce 3,4,5-trisubstituted isoxazole, but the scope of the substrates of the method was limited as substituted 2-alkyne-1-one *O*-methyl oximes needed to be synthesized independently.[23] In addition, the use of expensive and environmentally unfriendly metal catalysts is generally discouraged.

Dehalogenation of hydroximoyl chloride in the presence of a strong base to generate nitrile oxides and a follow-up cycloaddition with 1,3-diketones, β-ketoesters or β-ketoamides are a commonly used 2-step route to 3,4,5-trisubstituted isoxazoles.[24,25] Xiao Zhou et al. recently reported a direct access to 3,4,5-trisubstituted isoxazoles via an enolate-mediated 1,3-dipolar cycloaddition of β-functionalized ketones with nitrile oxides using organocatalyst.[26,27] This enolate-mediated cycloaddition, however, requires long reaction time in organic solvents at high temperature.

More importantly, recently, a water-assisted cycloaddition of nitrile oxides and alkenes or alkynes under mild acidic conditions was reported.[30] This reaction was carried out in 0.1 M phosphate buffer at pH 4.0, room temperature for 15–24 h and generated 3,5-disubstituted isoxazolines and 3,4,5-trisubstituted isoxazoles in good yields without using any metal catalysts. Development of organic reactions in water not only is environmentally friendly, but also finds significant applications in biological systems (e.g., click reactions, bio-conjugation, and bio-orthogonal chemistry). For example, due to its high aqueous tolerance and easy preparation under mild basic condition, a facile, copper-free, [3+2] biorthogonal cycloaddition between nitrile oxide and strained alkenes has become popular in ligation chemistry;[29] however, the alkenes need to be highly strained in order to this reaction to happen without the need for an additional metal catalyst.

As part of our lab's effort to find new environmentally friendly accesses to heterocycles, herein we report a synthesis of 3,4,5-trisubstituted isoxazoles in water via a [3+2]-cycloaddition of nitrile oxides and 1,3-diketones without the need of a metal catalyst (**Figure 1**). We also show that the cycloaddition reaction in aqueous media proceeds though keto tautomer, whereas in organic solvents, the side reaction proceeds through enol tautomer. The equilibriums of keto-enol tautomerization of β-diketones, β-ketoesters, and β-ketoamides were observed to follow Meyer's rule,[28] where the tautomeric equilibrium shifted towards the keto tautomer with increasing solvent polarity. In addition, electron withdrawing substituents such as trifluoromethyl group on β-diketones favored enol tautomer. In aqueous medium, β-diketones and their derivatives mostly remained in keto forms, which are more polar than their enol counterparts and more stable in polar solvents.

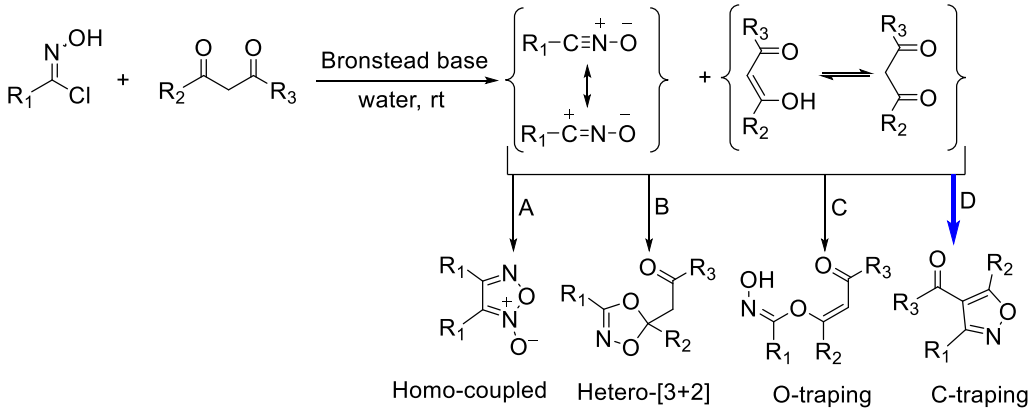
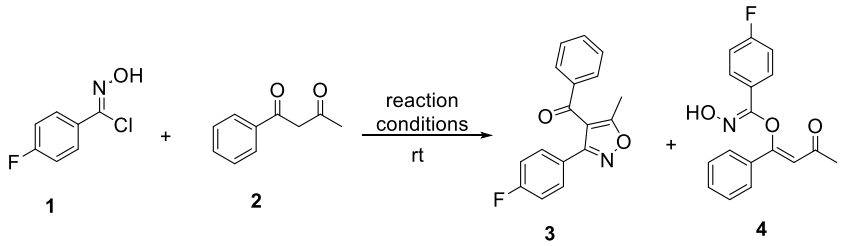


Figure 2. Possible products of the reaction between nitrile oxide and 1,3-ketones

Table 1. Optimization of reaction conditions to synthesize isoxazoles **3**[a]



Entry	Base	Solvents	Time (h)	Yield (%)	
				3	**4**
1	DBU	95% methanol, 5% water	18	-	-
2	S-Proline	95% methanol, 5% water	18	-	-
3[b]	$NaHCO_3$	2% methanol, 98% water	3	14	55
4[b]	Na_2CO_3	2% methanol, 98% water	3	52	33
5	TEA	2% methanol, 98% water	2	54	22
6	TEA	95 % methanol, 5% water	2	68	19
7	TEA	CH_2Cl_2	2	50	28
8	TEA	Isopropanol	2	57	30
9	DIPEA	$CHCl_3$	1	43	52
10	DIPEA	CH_2Cl_2	1	17	81
11	DIPEA	95 % methanol, 5% water	1	89	-
12	DIPEA	5% methanol, 95% water	1	98	-
13[c]	DIPEA	98 % methanol, 2% water	5	95	-
14	DIPEA (10 mol %)	5% methanol, 95% water	2	-	70
15	-	95 % methanol, 5% water	2	-	95
16[d]	DIPEA (10 mol %)	Phosphate buffer (pH 7.4), 5% methanol	2	7	76

[a] Unless otherwise noted, the reactions were performed with 0.5 mmol of **1**, 0.5 mmol of **2**, and 3 equivalents of DIPEA in 15 mL indicated solvents at room temperature for indicated time. Yields are calculated from NMR spectra of the crude product using acetonitrile as internal standard. [b] Four equivalents of $NaHCO_3$ and Na_2CO_3. [c] Two equivalent of DIPEA and 45 mL of the solvent mixture. [d] 10 mol% of DIPEA. TEA = Triethylamine, DIPEA= N,N-Diisopropylethylamine, DBU= 1,8-Diazabicyclo(5.4.0)undec-7-ene

Results and Discussion

Planning of the reaction to proceed in water at room temperature presented us several challenges. Foremost, the nitrile oxides, often generated by dehalogenation of hydroximoyl chloride in situ in a basic condition or dehydration of nitroalkanes,[31] are highly reactive and readily dimerize (**Figure 2**, path A). Therefore, we have to find a good condition to stabilize the nitrile oxides for a certain amount time to undergo [3+2]-dipolar cycloaddition with 1,3-diketones. Hetero atomic [3+2] cyclization is also a possibility[31] (**Figure 2**, path B). In addition, there is a native competition between O-trapping and C-trapping products of the nitrile oxides (**Figure 2**, paths C and D), which need to be controlled carefully to form the C-trapping isoxazole products that we wanted.

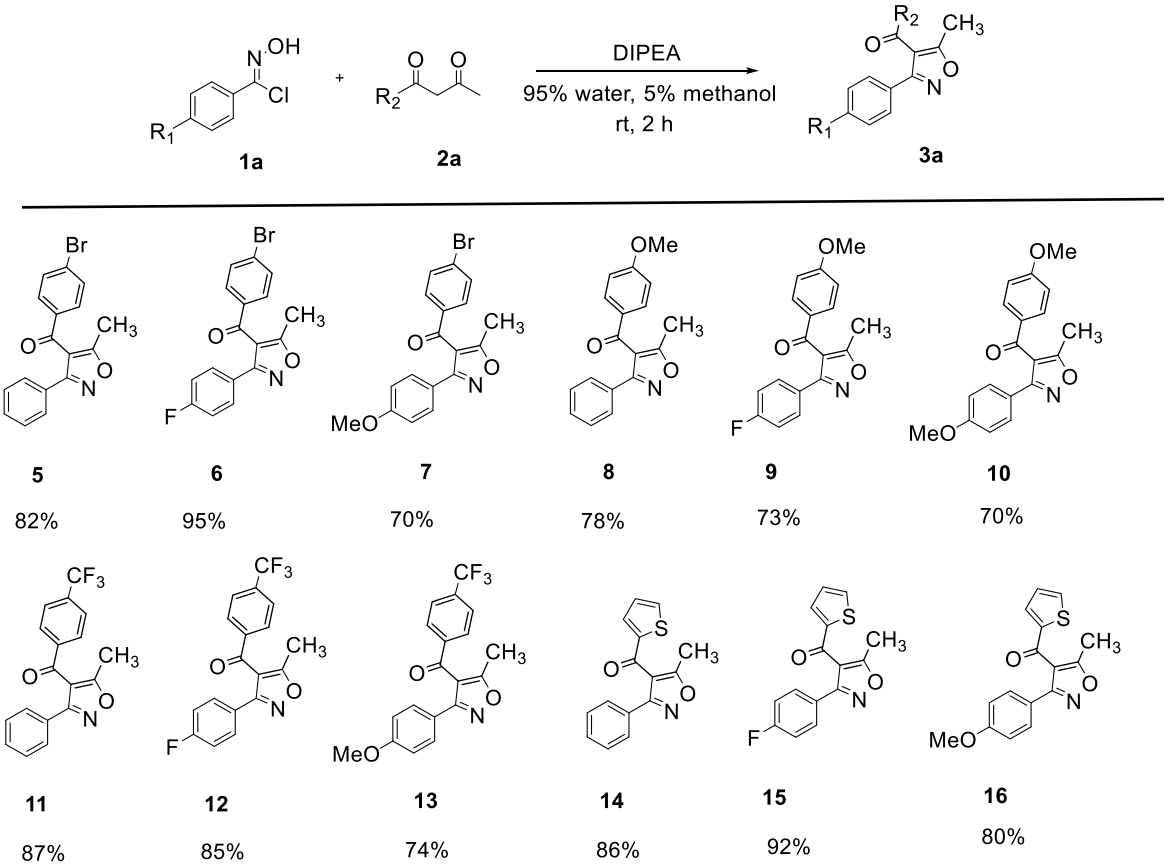
We chose compounds **1** and **2** as the starting substrates and water-methanol mixture as the aqueous medium, and carried out the reactions at room temperature. A series of organic and inorganic bases were screened in various combinations of water-methanol mixtures and other solvents. The results are summarized in **Table 1**.

In our first attempt, DBU or S-proline in 5% water, 95% methanol yielded a complex mixture of compounds that were not easy to distinguish (**Table 1**, entries 1 and 2). Inorganic bases $NaHCO_3$ and Na_2CO_3 in 98% water, 2% methanol produced only 14% and 52% of isoxazoles **3**, respectively, and 55% and 33% of compound **4**, respectively, after 3 hours (**Table 1**, entries 3 and 4). Trimethylamine (TEA) in 98% water, 2% methanol afforded 54% of **3** and 22% of **4** after 2 hours (**Table 1**, entry 5). However, TEA with decreased water content from 98% to 5% improved both the yield (68%) and selectivity (3.6 times) of **3** (**Table 1**, entry 6). Similar yields and selectivity of **3** were obtained when TEA was used in either dichloromethane (50%; 1.8 times) or isopropanol (57%; 1.9 times) as solvents (**Table 1**, entries 7 and 8). Diisopropylethylamine (DIPEA) in chloroform neither improved the yield (43%) nor selectivity (0.8 times) of **3** (**Table 1**, entry 9). In dichloromethane, DIPEA furnished even lower yield (17%) and selectivity (0.2 times) of **3** (**Table 1**, entry 10). Interestingly, in 95% methanol, 5% water, DIPEA gave **3** in 89% yield in 1 hour, while in 95% water, 5% methanol, DIPEA gave **3** in 98% yield in 1 hour, the highest yield of our screening in the shortest reaction time (**Table 1**, entries 11 and 12). The reaction furnished a similar yield (95%) with reduced equivalence of DIPEA and reactant concentration (2 equivalent and 0.001M, respectively); however, this condition required longer reaction time (5 hour) to complete (**Table 1**, entry 13). We observed high selectivity of compound **4** when we reduced the amount of DIPEA to 10 mol% in 95% water, 5% methanol (**Table 1**, entry 14) or with no DIPEA in 95% methanol, 5% water (**Table 1**, entry 15) in excellent yields (70% and 95%, respectively). Compound **4** was also formed almost exclusively in phosphate buffer (pH 7.4), 5% methanol with 10 mol% of DIPEA (**Table 1**, entry 16).

With the optimized reaction condition for the formation of isoxazoles **3** (DIPEA, 95% water, 5% methanol, room temperature), we explored the scope of substrates for both the oximes and β-ketones. First, we carried out the reactions between various phenyl hydroximoyl chlorides and 1,3-diketones (**Figure 3**). To ensure completion, all reactions were run for 2 hours regardless of the electron withdrawing or electron donating substituents on the benzene rings. Overall, electron donating substituents on phenyl hydroximoyl chloride or on phenyl 1,3-diketones produced comparatively lower yields than those of electron withdrawing groups. For example, the reaction afforded from 70% to 74% yield when one of the reactants contained a *para*-substituted methoxy group (compounds **7**–**10** and **13**),

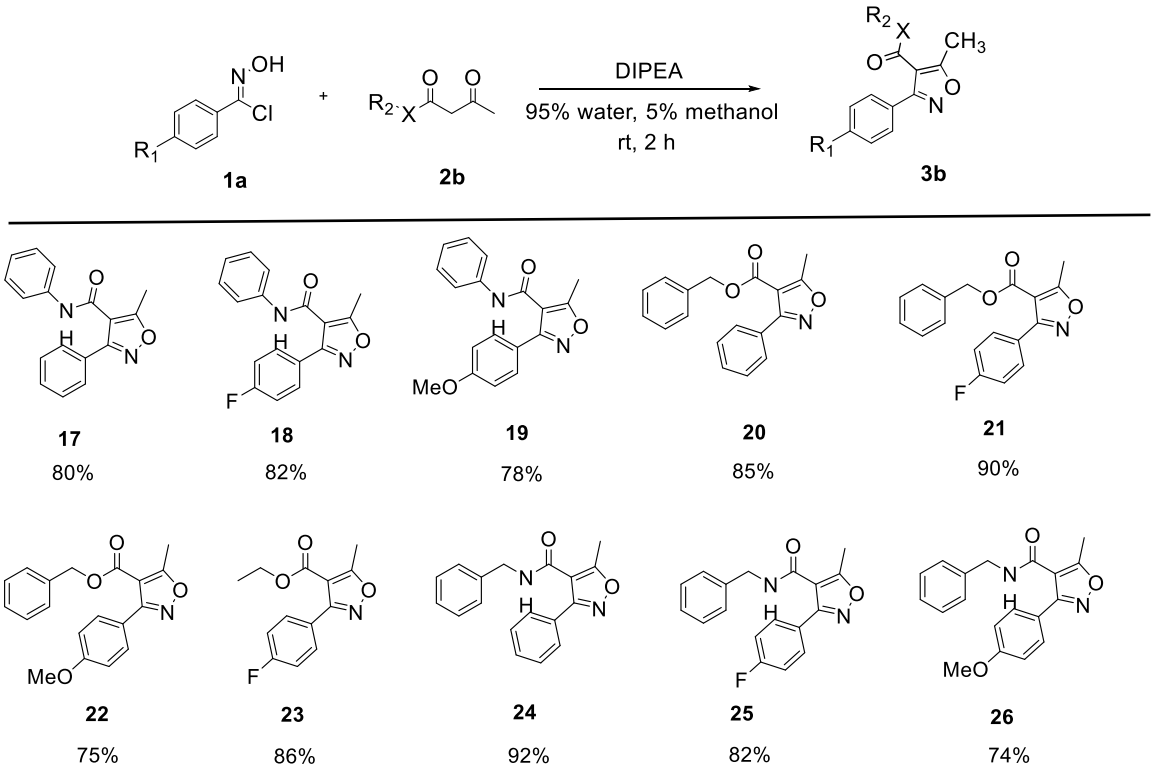
whereas the reaction afforded from 82% to 95% yield when one of the reactants contained a *para*-substituted Br, F, or CF_3 group, or contained a thiophene ring (compounds **5**, **6**, **11**, **12**, **14**, and **15**).

We also carried out the reactions between various phenyl hydroximoyl chlorides and β-ketoesters or β-ketoamides with the optimized reaction condition. Phenyl, benzyl, and ethyl β-ketoesters or β-ketoamides reacted smoothly with phenyl hydroximoyl chloride and gave the corresponding isoxazoles **3b** in excellent yields (**Figure 4**). These yields of β-ketoesters and β-ketoamides were observed compatible those of 1,3-diketones, suggesting β-ketoesters and β-ketoamides also favor the keto form more than the enol form in the keto-enol tautomerization, thus pushing the reaction toward the C-trapping path of the cycloaddition (**Figure 2**, path D).



Unless otherwise noted, the reactions were performed with 0.5 mmol of **1a**, 0.5 mmol of **2a**, and 3 equivalents of DIPEA in 15 mL of 95% water, 5% methanol at room temperature for 2 hours. The yields were calculated after isolation and purification of products.

Figure 3. Reactions between various phenyl hydroximoyl chlorides and 1,3-diketones



Unless otherwise noted, the reactions were performed with 0.5 mmol of **1a**, 0.5 mmol of **2b**, and 3 equivalents of DIPEA in 15 mL of 95% water, 5% methanol at room temperature for 2 hours. The yields were calculated after isolation and purification of products.

Figure 4. Reactions between various phenyl hydroximoyl chlorides and β-ketoesters or β-ketoamides

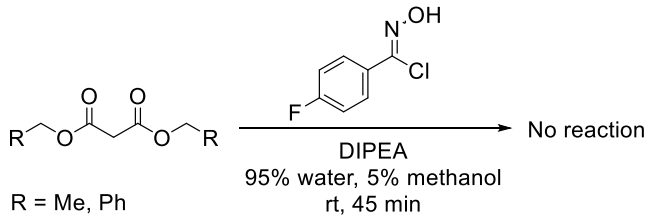


Figure 5. Reactions between 4-fluorophenyl hydroximoyl chloride and diethyl malonate or dibenzyl malonate did not proceed.

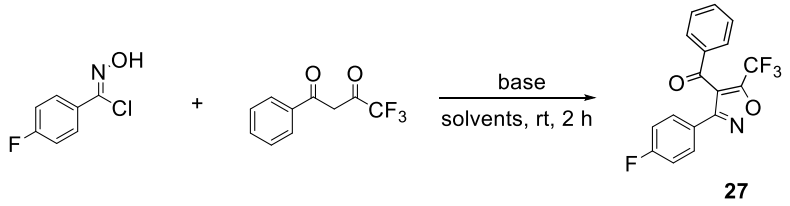
We also carried out the reactions between the phenyl hydroximoyl chloride that gave the best yield, 4-fluorophenyl hydroximoyl chloride, and diethyl malonate or dibenzyl malonate under the optimized reaction condition; however, the reactions did not proceed (**Figure 5**). We suspected the increased electron donating effect on both sides of the 1,3-diketones in diethyl malonate or dibenzyl malonate made the methylene group less acidic, thus DIPEA was not able to deprotonate the methylene for the nucleophilic addition and successive cyclization to happen.

The scope of substrates was further explored with a strong electron withdrawing group, such as trifluoromethyl, instead of methyl, in the 1,3-diketones (**Table 2**). The reaction between 4-fluorophenyl hydroximoyl chloride and 4,4,4-trifluoro-1-phenyl-1,3-butanedione under the optimized reaction condition gave a complex mixture of products with only a trace amount of the expected product **27** being detected (**Table 2**, entry 1). Meanwhile, some of 4,4,4-trifluoro-1-phenyl-1,3-butanedione starting material remained unreacted. We suspected the lower solubility of 4,4,4-trifluoro-1-phenyl-1,3-butanedione in water was responsible for the low yield of the reaction. Since trifluoromethyl-substituted isoxazoles are particularly desirable in drug discovery, we decided to optimize the

reaction conditions to synthesize the trifluoromethyl-substituted isoxazole **27**. We varied the solvent mixtures and the bases, but keep the reaction temperature at room temperature and reaction time at 2 hours, as these are the highlights of our synthetic method. The results are shown in **Table 2**. First, we varied the percentage of methanol in the solvent mixture with water to increase the solubility of 4,4,4-trifluoro-1-phenyl-1,3-butanedione. As the percentage of methanol increased from 5% to 50%, 75%, and 95%, the yield of **27**, with DIPEA as the base, increased from trace amount to 40% (**Table 2**, entries 1–4). With dichloromethane as the solvent, DIPEA also gave **27** in 40% yield (**Table 2**, entry 5). When TEA was used as the base, isopropanol resulted in **27** in 40% yield (**Table 2**, entry 9); meanwhile, dichloromethane, benzene, and 5% water, 95% methanol mixture gave much lower yields (**Table 2**, entries 6–8).

We also carried out other reactions between various phenyl hydroximoyl chlorides and trifluoromethyl 1,3-diketones with DIPEA in 5% water, 95% methanol (**Figure 6**). The reactions proceeded smoothly and produced the expected products; however, the yields were also just 35–40%. Overall, even though the low solubility issue of trifluoromethyl 1,3-diketone in water was solved with the increased percentage of methanol, or with the use of dichloromethane or isopropanol, the reactions to synthesize trifluoromethyl-substituted isoxazoles produced lower yields than those of methyl-substituted isoxazoles. The low yields may be due to the electron withdrawing effect of the trifluoromethyl group, which shifts the keto-enol equilibrium towards the enol form, thus hindering the reaction progress toward the C-trapping path of the cycloaddition (**Figure 2**, path D).

Table 2. Optimization of reaction conditions to synthesize trifluoromethyl-substituted isoxazole **27**[a]



27

Entry	Base	Solvents	Yield of **27** (%)
1	DIPEA	95% water, 5% methanol	Trace
2	DIPEA	50% water, 50% methanol	Trace
3	DIPEA	25% water, 75% methanol	30
4	DIPEA	5% water, 95% methanol	40
5	DIPEA	dichloromethane	40
6	TEA	5% water, 95% methanol	22
7	TEA	dichloromethane	20
8	TEA	benzene	5
9	TEA	isopropanol	40

[a] Unless otherwise noted, the reactions were performed with 0.5 mmol of 4-fluorophenyl hydroximoyl chloride, 0.5 mmol of 4,4,4-trifluoro-1-phenyl-1,3-butanedione, and 3 equivalents of bases in 15 mL of the indicated solvents at room temperature for 2 hours

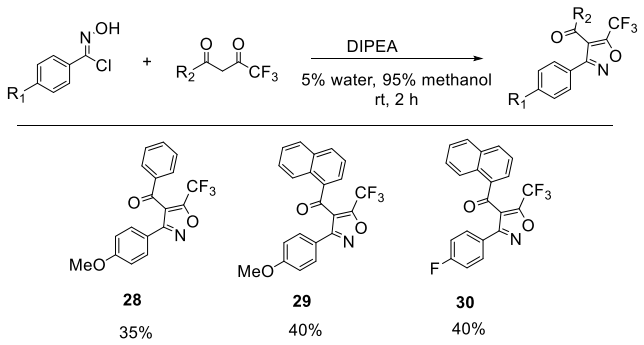


Figure 6. Scope of trifluoro methyl diketones in the reactions with phenyl hydroximoyl chloride

These results about electronegative substituents and solvent polarity matched with previous observations.[32,33] The electronegative substituents would increase the degree of enolization,[31,34] and solvents polarity would have little effect to the keto-enol tautomerization of the 1,3-diketones that contain an electron withdrawing group.[31] We observed the effect of solvent polarity on the keto-enol equilibrium of 1,3-diketones and their base-mediated [3+2] cycloaddition reactions via nuclear magnetic resonance (NMR) spectroscopy. ^{1}H NMR spectra of 1-phenyl-1,3-butanedione in $CDCl_3$ and in methanol-d_4 indicated that the enol tautomer was predominant in $CDCl_3$ while the keto tautomer was predominant in methanol-d_4, which is a more polar solvent (**Figure 7**). These observations helped explain why with DIPEA, **4** was formed predominantly in nonpolar solvents like in chloroform and dichloromethane (**Table 1**, entries 9–10), but **3** was formed exclusively in polar solvents like in water and methanol (**Table 1**, entries 11–13). A plausible mechanism for the formation of **3** (C-trapping product) vs. the formation of **4** (O-trapping product) is shown in **Figure 8**. In the presence of DIPEA and a nonpolar solvent like dichloromethane, the 1,3-diketone mostly formed an enolate ion **II**, which added to the carbocation of nitrile oxide or underwent a substitution reaction with hydroximoyl chloride to form the O-trapping product **4** (**Figure 8**). Meanwhile, in the presence of DIPEA and a polar solvent like water, the 1,3-diketone was likely to be deprotonated to form a stable carbanion predominantly, which added to the carbocation of nitrile oxide and gave the C-trapping intermediate **V**, followed by cyclization and dehydration to form compound **3** (**Figure 8**). In the small presence of DIPEA (10 mol%) or no presence of DIPEA, even in polar solvents like water and methanol, 1,3-diketone was not able to be deprotonated to form the carbanion, thus the O-trapping product **4** was formed either exclusively or predominantly due to the possible substitution reaction between the enol form and hydroximoyl chloride (**Table 1**, entries 14–16).

To see whether compound **4** can be transformed into **3** in a basic condition, we stirred compound **4** in the presence of DIPEA in a water-methanol mixture overnight. However, no changes of **4** were observed.

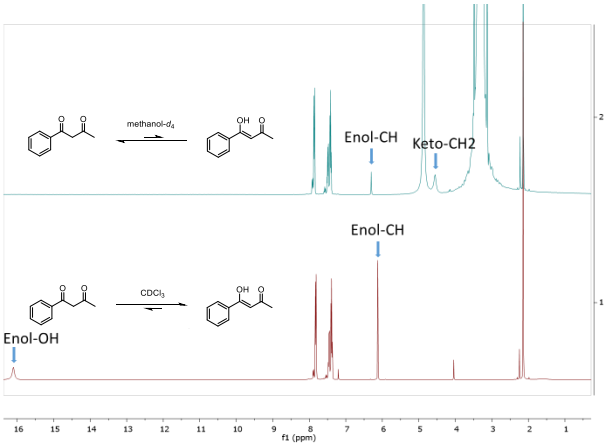


Figure 7. ^{1}H NMR spectra of 1-phenyl-1,3-butanedione in methanol-d_4 (top) in $CDCl_3$ (bottom)

Conclusion

We have developed a fast, water-assisted synthesis of 3,4,5-trisubstituted isoxazoles at room temperature via a [3+2] cycloaddition between 1,3-diketones and nitrile oxides. This efficient reaction method can be equally applicable for β-ketoesters and β-ketoamides. We also optimized the reaction conditions for the selectivity of C-trapping or O-trapping products

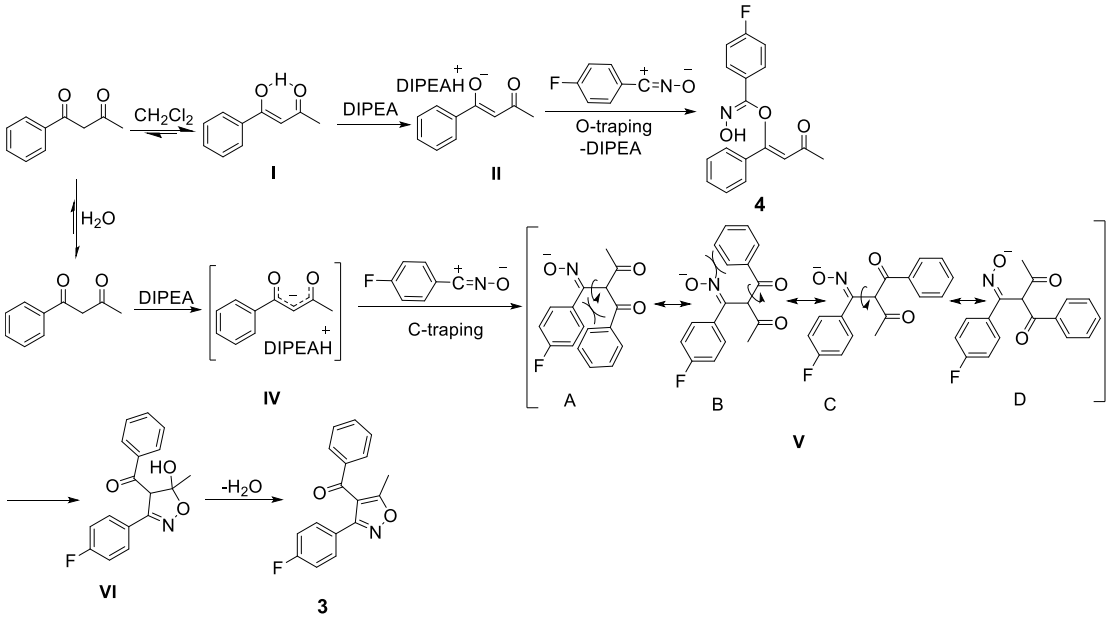


Figure 8. A plausible mechanism of the formation of compounds **3** and **4** in the presence of DIPEA in polar and nonpolar solvents

and proposed a plausible mechanism for their formation and selectivity. We also optimized the reaction conditions for trifluoromethyl-substituted isoxazoles. This method is environmentally friendly and produces high yields in fast reaction time. One limitation of this method is that it can only produce acyl-substituted, ester-substituted, or amide-substituted isoxazoles (with 1,3-diketones, β-ketoesters, or β-ketoamides as the starting materials, respectively). However, if those specific isoxazoles are the synthetically targeted ones, this method would be ideal comparing to the current methods with alkynes as the starting materials since the corresponding ketone-alkynes, ester-alkynes, or amide-alkynes need to be made independently via many challenging steps.[35] Acyl-substituted, ester-substituted, or amide-substituted isoxazoles are important structures found in numerous bioactive natural products and pharmaceuticals. For example, the antibiotic drugs oxacillin, cloxacilllin, and flucloxacillin are amide-substituted isoxazoles and share similar 3,4,5-trisubstituted isoxazole structures to the compounds synthesized in this report.

ASSOCIATED CONTENT

Supporting Information

Materials and methods, NMR spectroscopy, and mass spectrometry.

The Supporting Information is available free of charge at: https://onlinelibrary.wiley.com/

AUTHOR INFORMATION

Corresponding Author

* hle@olemiss.edu

AUTHOR CONTRIBUTIONS

M.I.H. carried out all the synthesis, optimization of reaction conditions, and mechanistic studies. M.I.H.K. and S.J.K. contributed to the characterization of the compounds. H.V.L. designed the project and supervised the overall coordination of the research. M.I.H. and H.V.L. wrote the manuscript. All authors approved the final version.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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REFERENCES

(1) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. Synthesis of Natural Products via Isoxazoles. *Synthesis (Stuttg).* **1987**, No. 10, 857–869.

(2) Rahbœk, L.; Christophersen, C. The Isoxazole Alkaloids; Elsevier, 2001; Vol. 57, pp 185–233.

(3) Zhu, J.; Mo, J.; Lin, H. zhi; Chen, Y.; Sun, H. peng. The Recent Progress of Isoxazole in Medicinal Chemistry. *Bioorganic Med. Chem.* **2018**, *26* (12), 3065–3075.

(4) Sysak, A.; Obmińska-Mrukowicz, B. Isoxazole Ring as a Useful Scaffold in a Search for New Therapeutic Agents. *Eur. J. Med. Chem.* **2017**, *137*, 292–309.

(5) Jensen, M. R.; Schoepfer, J.; Radimerski, T.; Massey, A.; Guy, C. T.; Brueggen, J.; Quadt, C.; Buckler, A.; Cozens, R.; Drysdale, M. J.; et al. NVP-AUY922: A Small Molecule HSP90 Inhibitor with Potent Antitumor Activity in Preclinical Breast Cancer Models. *Breast Cancer Res.* **2008**, *10* (2), R33.

(6) Hong, Y. L.; Hossler, P. A.; Calhoun, D. H.; Meshnick, S. R. Inhibition of Recombinant Pneumocystis Carinii Dihydropteroate Synthetase by Sulfa Drugs. *Antimicrob. Agents Chemother.* **1995**, *39* (8), 1756–1763.

(7) Luckner, P.; Brandsch, M. Interaction of 31 β-Lactam Antibiotics with the H+/Peptide Symporter PEPT2: Analysis of Affinity Constants and Comparison with PEPT1. *Eur. J. Pharm. Biopharm.* **2005**, *59* (1), 17–24.

(8) Ali, K. A.; Hosni, H. M.; Ragab, E. A.; El-Moez, S. I. A. Synthesis and Antimicrobial Evaluation of Some New Cyclooctanones and Cyclooctane-Based Heterocycles. *Arch. Pharm. (Weinheim).* **2012**, *345* (3), 231–239.

(9) Brown, G. D.; Denning, D. W.; Gow, N. A. R.; Levitz, S. M.; Netea, M. G.; White, T. C. Hidden Killers: Human Fungal Infections. *Sci. Transl. Med.* **2012**, *4* (165), 165rv13-165rv13.

(10) Talley, John J.; Malecha, James W.; Bertenshaw, Stephen; Graneto, Matthew J.; Carter, Jeffery S.; Li, Jinglin; Nagarajan, Srinivasan; Brown, D. L. . et al. Substituted Benzenesulfonamide Derivatives as Prodrug of COX-2 Inhibitor. PCT Int. Appl. (1997), WO 9738986 A1 19971023.

(11) Radhakrishna, A. S.; Sivaprakash, K.; Singh, B. B. Iodobenzene Dichloride - An Efficient Reagent for Preparation of Nitrile Oxides from Aldoximes. *Synth. Commun.* **1991**, *21* (15–16), 1625–1629.

(12) Moriya, O.; Nakamura, H.; Kageyama, T.; Urata, Y. Synthesis of Isoxazolines and Isoxazoles from Aldoximes by the Use of Sodium Bromite with Organotin Halide. *Tetrahedron Lett.* **1989**, *30* (30), 3987–3990.

(13) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. Generation of Nitrile Oxides from Oximes Using t -BuOI and Their Cycloaddition. *Org. Lett.* **2011**, *13* (11), 2966–2969.

(14) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. Oxidation of Oximes to Nitrile Oxides

with Hypervalent Iodine Reagents. *Org. Lett.* **2009**, *11* (7), 1539–1542.

(15) Zhao, G.; Liang, L.; Wen, C. H. E.; Tong, R. In Situ Generation of Nitrile Oxides from NaCl–Oxone Oxidation of Various Aldoximes and Their 1,3-Dipolar Cycloaddition. *Org. Lett.* **2019**, *21* (1), 315–319.

(16) Bourbeau, M. P.; Rider, J. T. A Convenient Synthesis of 4-Alkyl-5-Aminoisoxazoles. *Org. Lett.* **2006**, *8* (17), 3679–3680.

(17) Fouli, F. A.; Habashy, M. M.; El-Kafrawy, A. F.; Youseef, A. S. A.; El-Adly, M. M. 1,3-Dipolar Cycloaddition of Arylnitrile-N-Oxides with Methyl 3-Aryl-Prop-2-Yn-Oates and 1-Aryl-3-Phenyl-Prop-2-Yn-1-Ones. *J. far Prakt. Chemie* **1987**, *329* (6), 1116–1122.

(18) Jäger, V.; Colinas, P. A. Nitrile Oxides; 2003; pp 361–472.

(19) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, *127* (1), 210–216.

(20) Hansen, T. V.; Wu, P.; Fokin, V. V. One-Pot Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles. *J. Org. Chem.* **2005**, *70* (19), 7761–7764.

(21) Oakdale, J. S.; Sit, R. K.; Fokin, V. V. Ruthenium-Catalyzed Cycloadditions of 1-Haloalkynes with Nitrile Oxides and Organic Azides: Synthesis of 4-Haloisoxazoles and 5-Halotriazoles. *Chem. - A Eur. J.* **2014**, *20* (35), 11101–11110.

(22) Grecian, S.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles. *Angew. Chemie Int. Ed.* **2008**, *47* (43), 8285–8287.

(23) Waldo, J. P.; Larock, R. C. The Synthesis of Highly Substituted Isoxazoles by Electrophilic Cyclization: An Efficient Synthesis of Valdecoxib. *J. Org. Chem.* **2007**, *72* (25), 9643–9647.

(24) Mirzaei, Y. R.; Weaver, M. J.; Steiger, S. A.; Kearns, A. K.; Gajewski, M. P.; Rider, K. C.; Beall, H. D.; Natale, N. R. R. Improved Synthesis of 3-Aryl Isoxazoles Containing Fused Aromatic Rings. *Tetrahedron* **2012**, *68* (50), 10360–10364.

(25) Liu, B.; Liu, G.; Xin, Z.; Serby, M. D.; Zhao, H.; Schaefer, V. G.; Falls, H. D.; Kaszubska, W.; Collins, C. A.; Sham, H. L. Novel Isoxazole Carboxamides as Growth Hormone Secretagogue Receptor (GHS-R) Antagonists. *Bioorg. Med. Chem. Lett.* **2004**, *14* (20), 5223–5226.

(26) Zhou, X.; Xu, X.; Shi, Z.; Liu, K.; Gao, H.; Li, W. Enolate-Mediated 1,3-Dipolar Cycloaddition Reaction of β-Functionalized Ketones with Nitrile Oxides: Direct Access to 3,4,5-Trisubstituted Isoxazoles. *Org. Biomol. Chem.* **2016**, *14* (23), 5246–5250.

(27) Li, W.; Zhou, X.; Shi, Z.; Liu, Y.; Liu, Z.; Gao, H. Enolate-Mediated 1,3-Dipolar Cycloaddition Reactions of Allyl Ketones with Nitrile Oxides: Direct Access to 3,5-Disubstituted Isoxazolines. *Org. Biomol. Chem.* **2016**, *14* (42), 9985–9988.

(28) Meyer K.H. No Title. *Ann.* **1911**, *380*, 220–242.

(29) Gutsmiedl, K.; Wirges, C. T.; Ehmke, V.; Carell, T. Copper-Free "Click" Modification of DNA via Nitrile Oxide−Norbornene 1,3-Dipolar Cycloaddition. *Org. Lett.* **2009**, *11* (11), 2405–2408.

(30) Kesornpun, C.; Aree, T.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. Water-Assisted Nitrile Oxide Cycloadditions: Synthesis of Isoxazoles and Stereoselective Syntheses of Isoxazolines and 1,2,4-Oxadiazoles. *Angew. Chemie - Int. Ed.* **2016**, *55* (12), 3997–4001.

(31) Sloop, J. C.; Bumgardner, C. L.;

Washington, G.; Loehle, W. D.; Sankar, S. S.; Lewis, A. B. Keto-Enol and Enol-Enol Tautomerism in Trifluoromethyl-β-Diketones. *J. Fluor. Chem.* **2006**, *127* (6), 780–786.

(32) Arslan, N. B.; Özdemir, N. Direct and Solvent-Assisted Keto–Enol Tautomerism and Hydrogen-Bonding Interactions in 4-(m-Chlorobenzylamino)-3-Phenyl-4,5-Dihydro-1H-1,2,4-Triazol-5-One: A Quantum-Chemical Study. *J. Mol. Model.* **2015**, *21* (1), 19.

(33) Cook, A. G.; Feltman, P. M. Correction to Determination of Solvent Effects on Keto−Enol Equilibria of 1,3-Dicarbonyl Compounds Using NMR. *J. Chem. Educ.* **2010**, *87* (7), 678–679.

(34) Geraldes, C. F. G. C.; Barros, M. T.; Maycock, C. D.; Silva, M. I. The Preferential Direction of Enolization of Some Asymmetric 1,3-Dicarbonyl Compounds in Solution: A Study by Multinuclear NMR Spectroscopy. *J. Mol. Struct.* **1990**, *238*, 335–346.

(35) Roscales, S.; Bechmann, N.; Weiss, D. H.; Köckerling, M.; Pietzsch, J.; Kniess, T. Novel Valdecoxib Derivatives by Ruthenium(II)-promoted 1,3-Dipolar Cycloaddition of Nitrile Oxides with Alkynes – Synthesis and COX-2 Inhibition Activity. *Medchemcomm* **2018**, *9* (3), 534–544.

TABLE OF CONTENT

An environmentally friendly access to 3,4,5-trisubstituted isoxazoles, specifically acyl-substituted, ester-substituted, or amide-substituted isoxazoles, via a [3+2]-cycloaddition of nitrile oxides and 1,3-diketones, β-ketoesters, or β-ketoamides, respectively.