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TEMPO-Mediated Selective Synthesis of Isoxazolines, 5-Hydroxy-2-isoxazolines, and Isoxazoles via Aliphatic δ-C(sp3)-H Bond Oxidation of Oximes

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Abstract: Selective synthesis of three different bioactive heterocycles; isoxazolines, 5-hydroxy-2-isoxazolines and isoxazoles from the same starting material using TEMPO (2,2,6,6-Tetramethylpiperidin-1-oxyl) as a radical initiator is reported. Selectivity was achieved using different oxidants with TEMPO. The reaction goes through a 1,5-HAT (hydrogen atom transfer) process resulting in products with good yields. This strategy offers a straightforward route to three different heterocycles from oximes via radical-mediated C(sp^3)-H oxidation.

Introduction

Selective and direct functionalization of non-activated sp^3 carbon atoms is a longstanding challenge in organic synthesis.[1] Reactivity of aliphatic C–H bonds decreases with increasing distance from the closest reactive functional group (e.g., carbonyl group), and hence regioselective functionalization of remote aliphatic C–H bonds is very difficult.[2] In this context, radical-mediated functionalization is a method of choice in recent years as it has a significant advantage over other $2e^-$ processes (e.g., rearrangement, fragmentation etc).[3] Over the past years, radical-mediated functionalization of C(sp^3)-H bonds *via* 1,5-hydrogen atom transfer (HAT) has been well studied.[4] Direct functionalization is one of the most atom and step-economical, especially for the synthesis of complex moiety from a simple precursor.[5]

Isoxazoles and isoxazolines are the five-member nitrogen-containing heterocycles that contain two electronegative atoms (N and O) in 1, 2 relationships. Thus, these scaffolds could take part in hydrogen bonds, donor-acceptor interactions with various enzymes and receptors.[6] Currently, various life-saving drugs contain isoxazoles and isoxazolines moieties (Figure 1A)[7] and 5-hydroxy-2-isoxazolines have been utilized as a versatile synthon possibly because it can be easily transformed into various functional groups like isoxazoles, β-enaminones, 1,3-diketones, γ-amino alcohols, and *N*-aryl-β-lactams, etc.[8–10] Isoxazoles are also extensively used as 1,3-dicarbonyl equivalents in natural product synthesis.[11] These heterocycles are generally synthesized *via* [3 + 2] dipolar cycloaddition of nitrile oxide and olefins (Figure 1B).[12] Although this strategy works well in most of the cases, it has disadvantages such as (i) nitrile oxide is prepared from unstable hydroxamoyl chlorides[13] or by the hydrolysis of nitroalkanes,[14] usually under harsh conditions; and (ii) poor-regioselectivity with unbiased olefins,[15] which leads to difficulties in separating the two regio-isomers. Given the relevance of isoxazoles and isoxazolines in organic and medicinal chemistry and the limitations of the existing synthesis method, it is highly desirable to find a new and efficient complementary method. In this context, radical-mediated direct functionalization methods can be valuable as it offers broad substrate scope, easy separation of regio-isomers, and mild reaction conditions.

Chiba and co-workers have developed a radical-mediated protocol for the synthesis of isoxazolines.[16] This protocol was limited to only the synthesis of *di*-substituted isoxazolines (Figure 2). Later, an improved system was developed for the synthesis of isoxazolines using selectfluor/Bu_4NI by Liu and co-workers.[17] Other than these, there is no report on the divergent synthesis of isoxazoles and isoxazolines from oximes *via* the 1,5-HAT process.

Here, we have developed conditions based on a different strategy to synthesize three different heterocycles using mild conditions and cheap inorganic oxidants. This methodology also covers a broad range of substrates scope with moderate to excellent yields with good selectivity. Further, our method can also be elegantly controlled with the help of oxidants.

Results and Discussion

As an initial approach to synthesize isoxazoline **2a**, we used TEMPO as a radical initiator and $K_2S_2O_8$ as the oxidant in the presence of oxime **1a** as a model substrate in acetonitrile (MeCN) solvent at 50 °C. We observed that 3.0 equiv. of $K_2S_2O_8$ and 0.4 equiv. of TEMPO could produce a mixture of isoxazoline

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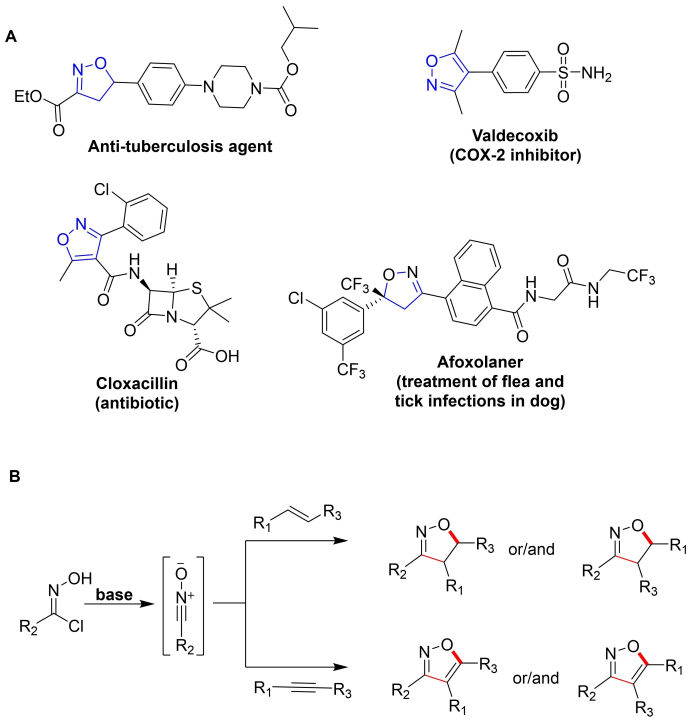


Figure 1. A) Examples of bioactive molecules containing isoxazole and isoxazoline. **B**) [3 + 2] Dipolar cycloaddition of nitrile oxides and olefins.

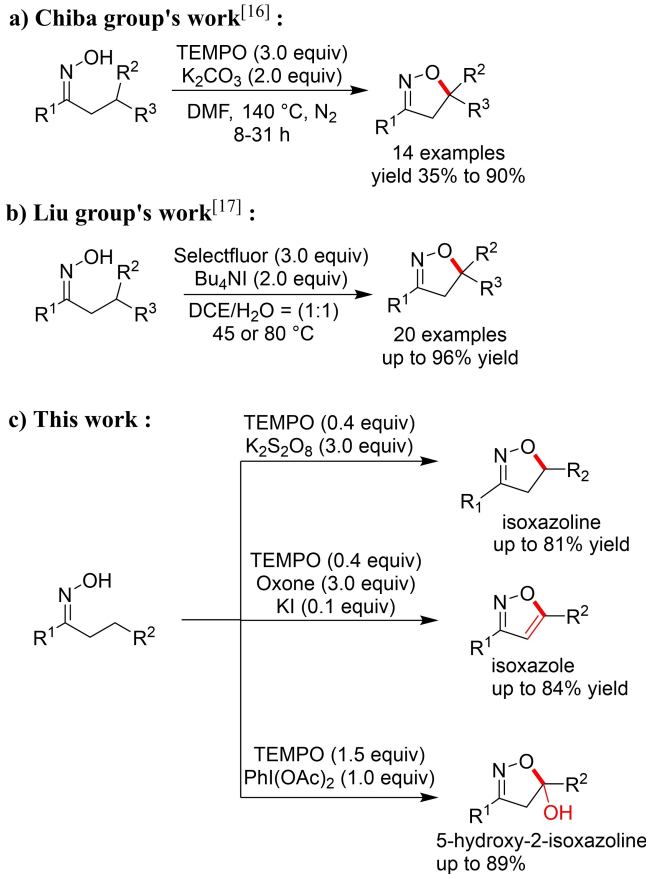
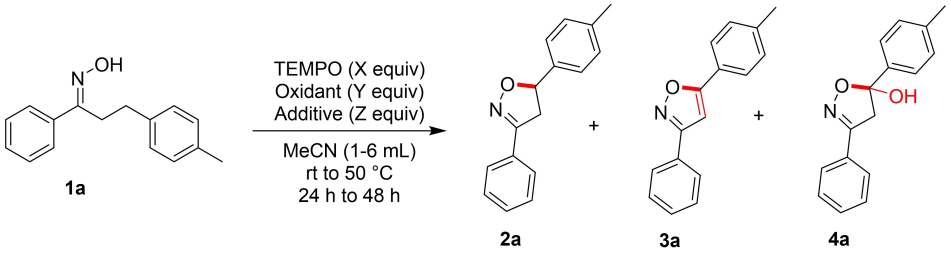


Figure 2. Previous literature report and this work.

2a and isoxazole **3a** in 4.0 mL of MeCN (Table 1, entry 4). We first investigated the effect of the solvent amount in the product formation (Table 1, entry 1–8). We obtained the maximum yield of isoxazoline when we used 6.0 mL of MeCN (75% isoxazoline **2a**; 15% isoxazole **3a**) (Table 1, entry 6). Different solvents like DMF, DCE, and 1,4-Dioxane were also screened, but the results were not satisfactory (see Supporting Information, SI). Interestingly, with 30 equiv. of water, the formation of isoxazoline **2a** could be enhanced to 83% (entry 13). Water was found to be critical to increase the yield, which might be due to the increased solubility of $K_2S_2O_8$. Therefore, the optimized reaction conditions for the isoxazolines (**2a**) synthesis were oxime **1a** (1.0 equiv, 0.2 mmol), TEMPO (0.4 equiv), $K_2S_2O_8$ (3.0 equiv) and H_2O (30 equiv) in MeCN (6.0 mL) at 50 °C for 30 h (Table 1, entry 13).

We noted that decreasing the solvent volume increased the formation of isoxazole **3a** (Table 1, entry 1–3), although the overall yield was low. We hypothesized that by varying different oxidants under low solvent volume, *in situ*, we could oxidize isoxazoline **2a** to isoxazole **3a**. Thus, it would give us a protocol for a one-pot synthesis of isoxazole **3a** from oxime 1a. To test this, we started with 2.0 mL of MeCN and observed an improved yield of **3a** up to 55% using $K_2S_2O_8$ (5.0 equiv) (Table 1, entry 15). Different oxidants like $NaIO_4$ and oxone ($KHSO_5 \cdot 0.5KHSO_4 \cdot 0.5\ K_2SO_4$) were screened, but the yield of **3a** did not improve any further. However, when a combination of oxone (2.0 equiv) and KI (0.1 equiv) was used, the conversion was increased to 99% (Table 1, entry 18) with the product ratio of 41:58 (**2a**:**3a**). We got the best yield of isoxazole (88%) using 3.0 equiv. of oxone and 0.1 equiv. of KI (Table 1, entry 20). This result is in line with hypoiodite mediated oxidative reaction

Table 1. Optimization conditions for the synthesis of **2a**, **3a**, **4a** from oxime **1a**.[a]



Entry	TEMPO [equiv]	Oxidant [equiv]	Solvent [mL]	Additive [equiv]	Time [h]	Yield[b] [%] **2a**	Yield[b] [%] **3a**	Yield[b] [%] **4a**
1	0.4	$K_2S_2O_8$ (3)	1	–	30	30	43	-
2	0.4	$K_2S_2O_8$ (3)	2	–	30	25	54	-
3	0.4	$K_2S_2O_8$ (3)	3	–	30	34	52	–
4	0.4	$K_2S_2O_8$ (3)	4	–	30	43	50	–
5	0.4	$K_2S_2O_8$ (3)	5	–	30	65	22	–
6	0.4	$K_2S_2O_8$ (3)	6	–	30	75	15	–
7	0.4	$K_2S_2O_8$ (3)	7	–	30	70	7	–
8	0.4	$K_2S_2O_8$ (3)	8	–	30	41	27	–
12	0.4	$K_2S_2O_8$ (3)	6	H_2O (60)	30	67	17	–
13	0.4	$K_2S_2O_8$ (3)	6	H_2O (30)	30	83 (81)[c]	8	–
14	0.4	$K_2S_2O_8$ (3)	6	H_2O (20)	30	71	17	–
15	0.4	$K_2S_2O_8$ (5)	2	–	48	25	55	–
16	0.4	$NaIO_4$ (3)	2	–	48	60	19	–
17	0.4	Oxone (1.5)	2	–	48	34	5	–
18	0.4	Oxone (2)	2	KI (0.1)	48	41	58	–
19	0.4	Oxone (2.5)	2	KI (0.1)	48	19	78	–
20	0.4	Oxone (3)	2	KI (0.1)	48	5	88 (84)[c]	–
21	0.4	$PhI(OAc)_2$ (1)	6		24	3	1	39
22	1.5	$PhI(OAc)_2$ (0.5)	6	–	24	1	5	50
23	1.5	$PhI(OAc)_2$ (1)	6	–	24	2	0	73 (70)[c]
24	1.5	$PhI(OAc)_2$ (1.5)	6	–	24	2	2	38

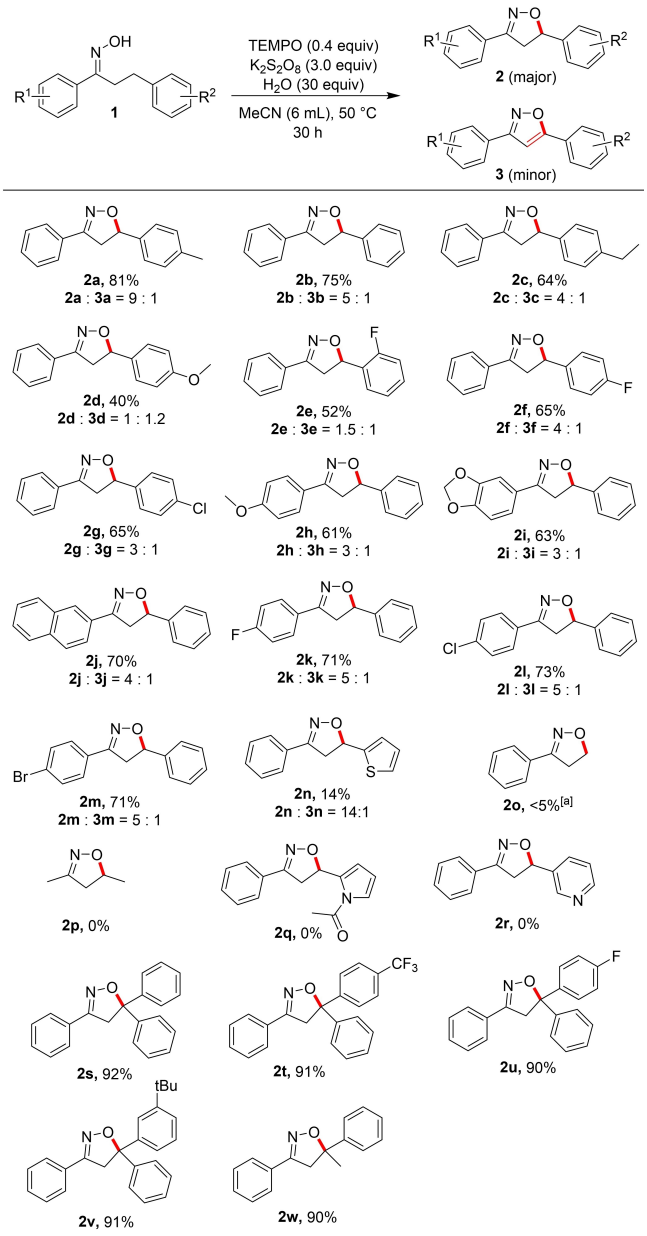
[a] Reaction conditions: **1a** (0.2 mmol), TEMPO (0.4–1.5 equiv), oxidant (1.0–5.0 equiv) in MeCN (1.0–6.0 mL) at 25 °C or 50 °C for 24 h–48 h. Entry (1–14), (15–20), and (21–24) reactions were carried out for 30 h, 48 h and 24 h respectively. [b] Yields were calculated by ^{1}H NMR using 1,1,2,2 tetrachloroethane as an internal standard. [c] Isolated yields are given in parenthesis.

was already reported using the oxone-KI system, where the generation of the activated iodine species was crucial for the transformation.[18]

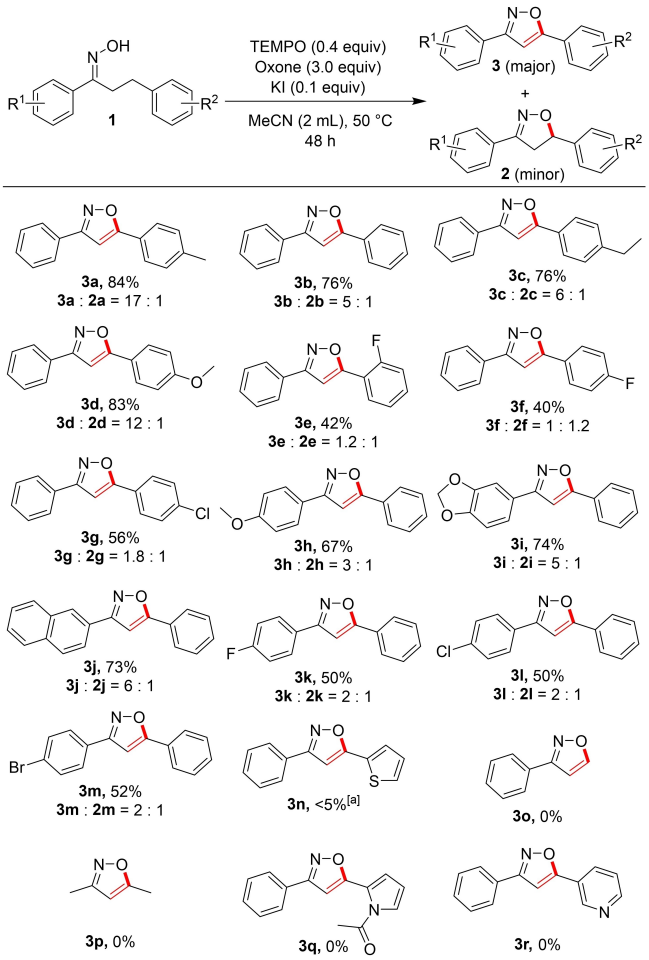
A new product 5-hydroxy-2-isoxazoline **4a** was obtained when $PhI(OAc)_2$ was used as an oxidant. The formation of **4a** was found to be very selective in the presence of $PhI(OAc)_2$. Our first trial reaction produced 39% of **4a** with the combination of 0.4 equiv. of TEMPO and 1.0 equiv. of $PhI(OAc)_2$ at room temperature under N_2 atmosphere (Table 1, entry 21). We found the best yield of **4a** up to 73% using 1.5 equiv. of TEMPO and 1.0 equiv. of $PhI(OAc)_2$ (Table 1, entry 23).

With the optimized experimental conditions for all the three heterocycles **2a**, **3a**, and **4a**, we decided to define the substrate scope of isoxazoline **2a** and the limitations of the reaction. The results are summarized in Scheme 1. Oxime **1** bearing both electron-donating and electron-withdrawing substitutions on the phenyl ring produced moderate to good yields. Various substitutions at the R^1 of oximes like *p*-methoxy, *p*-fluoro, *p*-chloro, and *p*-bromo (**1h**, **1k**, **1l**, **1m**) produced corresponding isoxazolines (**2h**, **2k**, **2l**, **2m**) with a yield ranging from 61% to 73%. Oxime containing naphthyl ring (**1j**) and 3,4-(methylenedioxy)benzene ring (**1i**) afforded desired products in 70% and 63% respectively. Oximes with substitution at the R^2 of the phenyl ring (**1c**, **1f**, **1g**), when reacted with the optimized conditions, also gave the corresponding isoxazoline (**2c**, **2f**, **2g**) in good yields. However, low yields and selectivity were found in the case of oxime containing *p*-methoxy (**1d**) and *o*-fluoro (**1e**) substitution. Particularly, when the substitution was *p*-methoxy, the reaction produced significantly more isoxazole **3d** than isoxazoline **2d**. This could be attributed to *in situ* oxidation of **2d** to **3d** because of the high reactivity of the phenyl ring being substituted with an electron donating group (-OMe). When the phenyl ring was substituted with thiophene moiety, corresponding isoxazoline **2n** was isolated in very less yield. The reaction of oxime **1o** was very sluggish. Oxime **1p**, **1q**, and **1r** when reacted under the standard conditions, did not yield the expected product. These results can be correlated to the stability of the radical intermediate (benzylic radicals are more stable than alkyl radicals), which is important for the product formations. Various substituted oximes containing tertiary methine moieties (**1s**–**1w**) produced corresponding isoxazolines (**2s**–**2w**) in excellent yields (single isomer).

Optimized conditions for the isoxazoles synthesis also work well on different derivatives of oximes (Scheme 2). The reaction produced the best yield when the R^2 side of the oximes was substituted with electron-donating groups. Oximes **1a**–**1d** gave



Scheme 1. Scope of the Synthesis of Isoxazoline **2** from Oxime **1**: [Reaction conditions: **1** (0.2 mmol), TEMPO (0.4 eq), $K_2S_2O_8$ (3.0 eq), water (30 eq) in MeCN (6.0 mL) at 50 °C for 30 h. Ratios (2:3) were calculated from the isolated yields. [a] ^{1}H NMR yield was recorded].



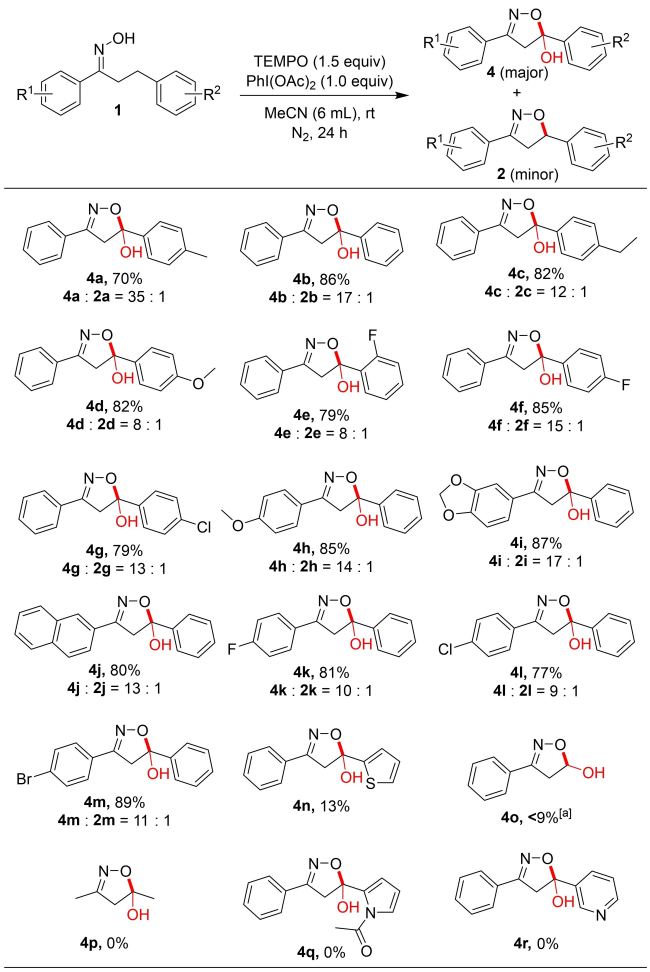
Scheme 2. Scope of the Synthesis of Isoxazole **3** from Oxime **1**: [Reaction conditions: **1** (0.2 mmol), TEMPO (0.4 eq), oxone (3.0 equiv), KI (0.1 eq) in MeCN (2.0 mL) at 50 °C for 48 h. Ratios (3:2) were calculated from the isolated yields. [a] ^{1}H NMR yield was recorded].

corresponding isoxazoles **3a**–**3d** in the range of 76–84% yields. The reaction furnished low yields and selectivity when electron-withdrawing groups were present at the R^2 position.

Fluorinated isoxazoles **3e** and **3f** were obtained in 42% and 40% yields, respectively. It is worth noting that the substitution effect is less prominent on product formation when the substitutions are present on the R^1 side of the phenyl ring than the R^2 side. Oxime containing naphthyl (**1j**) and 3,4-(methylenedioxy)benzene (**1i**) group afforded the products **3j** and **3i** in 73% and 74% yields respectively with good selectivity. Oximes containing (at R^1 side) fluorine, chlorine, and bromine (**1k**–**1m**) all reacted smoothly to give moderate yields of **3k**–**3m**. Alkyl oximes (**1o**, **1p**), pyrrole and pyridyl substituted oximes (**1q**, **1r**), when reacted with the standard conditions, failed to yield the expected products.

The reaction conditions developed here work well with various oximes **1** to produce 5-hydroxy-2-isoxazoline **4** (Scheme 3). Different substituted oximes (R^1 and R^2) were well tolerated and gave high yields with good selectivity. Various 5-hydroxy-2-isoxazoline bearing substitutions at the R^2 side like *p*-ethyl (**4c**), *p*-methoxy (**4d**), *o*-fluoro (**4e**), *p*-fluoro (**4f**) and *p*-chloro (**4g**) were obtained in high yields and selectivity. Oximes bearing substitutions at the R^1 position of the phenyl ring also proceeded efficiently to furnish the corresponding products **4h**–**4m**.

Thiophene derived hydroxy isoxazoline **4n** was obtained in 13% yield with the standard reaction conditions. The reaction was uncontrolled in case of oxime **1o** and the product formation was <9% (^{1}H-NMR yield). No detectable product formation was observed with oximes **1p**, **1q**, and **1r**. In general,



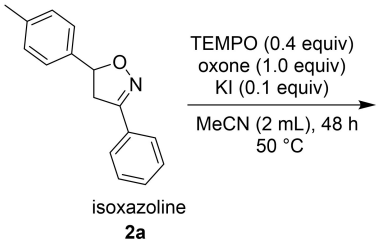
Scheme 3. Scope of the reaction: Synthesis of 5-hydroxy-2-isoxazoline **4** from oxime **1**: [Reaction conditions: **1** (0.2 mmol), TEMPO (1.5 eq), $PhI(OAc)_2$ (1.0 eq), in MeCN (6.0 mL) at room temperature for 24 h under N_2 atmosphere. Ratios (4:2) were calculated from the isolated yields. [a] ^1H NMR yields].

the conditions developed for the synthesis of **4** were less influenced by different substituents, unlike in the radical-mediated synthesis of isoxazole **3** and isoxazoline **2**.

Background experiments were carried out to justify our hypothesis for the *in situ* oxidation of isoxazoline **2** to isoxazole **3**. Isoxazoline **2a** was taken as a starting compound for the experiment. Isoxazole **3a** was obtained in 84% when **2a** was subjected to the conditions: TEMPO (0.4 equiv), oxone (1.0 equiv), KI (0.1 equiv) in 2.0 mL of MeCN at 50 °C. Product **3a** was found in much lower yield (4%) when the reaction was carried out using only oxone (Table 2, entry 2). When the same reaction was performed without KI, yield of **3a** was 60% (Table 2, entry 3). Isoxazole **3a** was formed <1% in the presence of only 0.4 equivalent of TEMPO (Table 2, entry 4). These results suggest that oxone alone cannot promote the oxidation of **2a** to **3a**. It is also highlighting the essential role of TEMPO and KI.

The oxidation reaction may follow a single electron oxidation pathway similar to the report of Wu *et al.*, where they

Table 2. Background study: Oxidation of isoxazoline to isoxazole.[a,b]

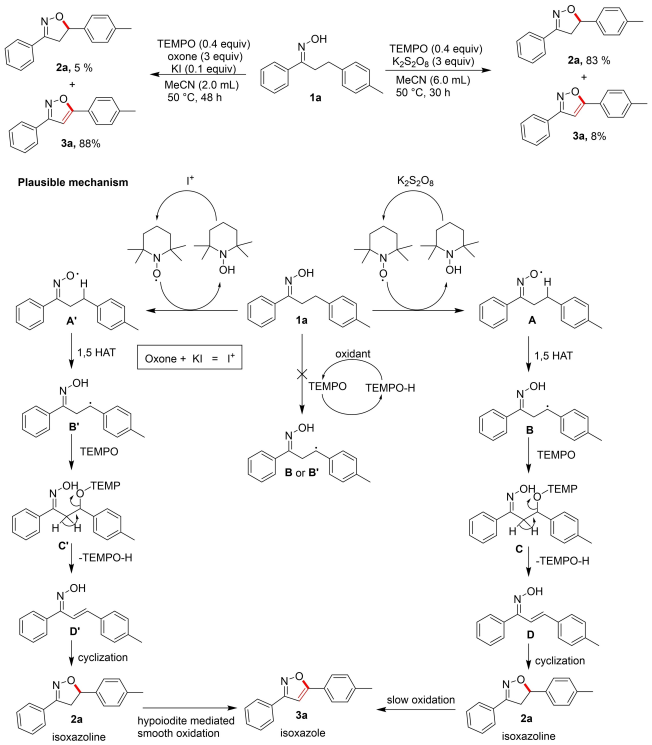


Entry	Deviation from the standard condition[a]	Yield[b] [%]
1	–	84
2	oxone (1.0 equiv)	4
3	without KI	60
4	TEMPO (0.4 equiv)	<1

[a] Reaction conditions: **1a** (0.2 mmol), TEMPO (0.4 eq), oxone (1.0 eq) and KI (0.1 eq) in MeCN (2.0 mL) at 50 °C for 48 h. [b] ^1H NMR yields were calculated using equivalents amount of 1,1,2,2 tetrachloroethane as an internal standard.

showed an efficient oxidation strategy to convert isoxazoline to isoxazole using nitric oxide (NO).[19]

A plausible mechanism is proposed for the divergent synthesis of isoxazoline **2a** and isoxazole **3a** from oxime **1a**, as shown in Scheme 4. In the case of isoxazoline synthesis, in the first step, TEMPO generates an iminoxyl radical **A** in the presence of $K_2S_2O_8$ from oxime **1a**. Radical **A** undergoes a 1,5-



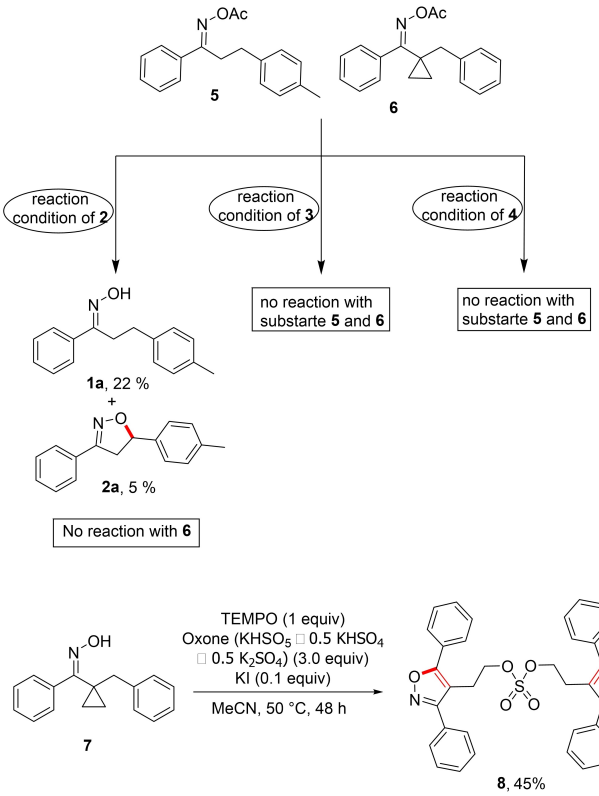
Scheme 4. Plausible mechanism for the divergent synthesis of **2a** and **3a** from oxime **1a**.

hydrogen atom transfer (HAT) reaction to give the corresponding carbon center radical **B**, which further reacts with TEMPO and after elimination produces **D**. Finally, **D** takes part in cyclization to give isoxazoline **2a**.

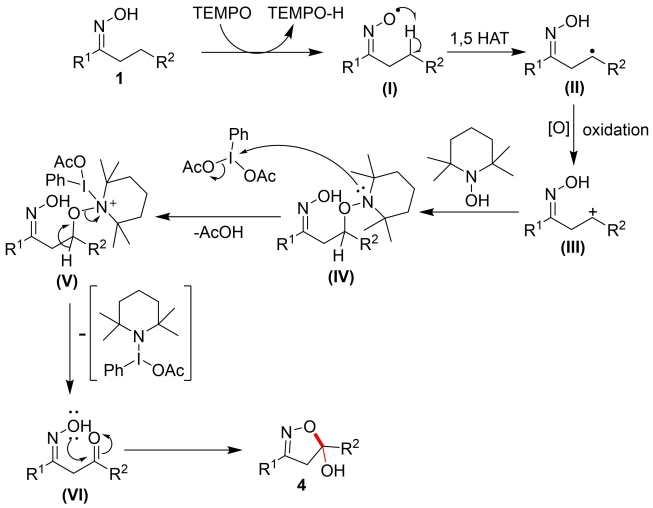
In the case of isoxazole synthesis, I^+ might be involved in the key oxidation step.[18] At the initial stage of the reaction, TEMPO generates an iminoxyl radical **A′** with the help of oxone/KI (Scheme 4). Intermediate **A′** would be likely to follow a similar route (**A′** to **D′**) to produce isoxazoline **2a**. Next, hypoiodite mediated oxidation occurs to give isoxazole **3a** (Scheme 4 and Table 2). Efficient *in situ* oxidation of **2a** to **3a** is hypothesized as the key step in this reaction.

To gain more insight into the reaction mechanism, we have carried out reactions with acetyl protected oximes. When acetyl protected oxime **5** was subjected to the standard reaction condition for the synthesis of **2**, the reaction produces a mixture of products, oximes **1a** and isoxazolines **2a** in low yields (Scheme 5). The reaction did not proceed when oxime **6** was treated with reaction condition used to make **2**. No reactions occurred when the acetyl protected oximes **5** and **6** were treated with reaction conditions used to make **3** and **4**. When oxime **7** was subjected to the standard reaction conditions of isoxazole synthesis, it yielded dimeric-isoxazole derivative **8** by radical-mediated ring-opening of cyclopropane (Scheme 5). These results clearly indicate the importance of *O*-radical formation in the reaction (intermediate **A** or **A′**, Scheme 4) and support the involvement of 1,5 HAT step. Also, these results ruled out the possibility of direct benzylic radical formation (**B** or **B′**, Scheme 4) from the oxime **1a**.

Our result shows that 1.5 equivalents of TEMPO is necessary to get the best yield that may be correlated to the source of extra oxygen, which is crucial for the formation of 5-hydroxy-2-isoxazoline **4**. A plausible mechanistic route is proposed, as shown in Scheme 6. In the presence of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), oxime **1** produced an oxygen-centered radical (**I**), which subsequently undergoes 1,5-HAT, oxidation reaction and produces intermediate (**III**). This reacts with TEMPO-H to form intermediate (**IV**). Then, the intermediate (**IV**) may react with $PhI(OAc)_2$ to give intermediate (**V**) that takes part in an elimination reaction and forms intermediate (**VI**), which, after an intramolecular cyclization reaction, provides the final product **4**.[20]



Scheme 5. Mechanism study: Evidence of radical based pathway [Reaction conditions: 0.2 mmol of **5**, **6** is used for the reactions. Yields were calculated from the crude reaction mixture, using equivalent amount of tetrachloroethane].



Scheme 6. Possible mechanistic route for the synthesis of 5-hydroxy-2-isoxazoline **4** from oxime **1**.

Conclusion

In summary, an efficient synthesis protocol for three heterocycles, 2-isoxazolines, 5-hydroxy-2-isoxazolines, and isoxazoles have been developed using TEMPO and a combination of oxidants from the same oxime. Inexpensive inorganic peroxides $K_2S_2O_8$ and oxone ($KHSO_5 \cdot 0.5\ KHSO_4 \cdot 0.5\ K_2SO_4$) have been used for the synthesis of 2-isoxazolines and isoxazoles. We also report an efficient synthesis protocol for 5-hydroxy-2-isoxazolines, a versatile synthon to obtain various value-added functional moieties such as isoxazole and γ-amino alcohols. Finally, the synthesis of isoxazole is shown using in situ radical-mediated oxidation of isoxazoline.

Experimental Section

General Information

Dry solvents were used for the reaction development. Reagents were purchased from commercial suppliers (Alfa Aesar, Spectrochem, Sigma-Aldrich, and TCI). Reactions were performed in a dried

glassware with a magnetic stirring bar placed inside. Merck silica gel (230–400 mesh) was used for the flash column chromatography. Ethyl acetate and hexane mixture was used as an eluent system to purify all the compounds. Buchi rotary evaporator was used to concentrate the organic solutions. The yields were calculated from the products obtained after column purification. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Jeol and 500 MHz Bruker. Proton chemical shifts are reported in ppm downfield from relative to the residual ^{1}H signal of $CDCl_3$ (δ 7.26 ppm) and DMSO-d_6 (δ 2.50 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.16 ppm) and in DMSO-d_6 (δ 39.52 ppm). Coupling constants (*J*) are measured in hertz (*Hz*).

General Procedure for the Synthesis of Oximes 1

All oximes were prepared according to the reported literature procedure.[21] To a solution of ketone (1.0 equiv) in EtOH (0.5 M) was added hydroxylamine hydrochloride (1.5 equiv) and NaOAc (2.0 equiv). The reaction mixture was then stirred at room temperature or heated at 60 °C until the ketone was consumed as monitored by TLC (TLC Silica gel 60 F254). The solvent was evaporated, and the residue was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with 1.0 N aqueous HCl and brine. Organic layer was dried over Na_2SO_4 and concentrated in a rotary evaporator. Purification of the crude product by flash column chromatography using hexane/ethyl acetate as eluent afforded the corresponding oxime.

General Procedure for the Synthesis of Isoxazolines 2 from Oximes 1

Oxime **1** (0.2 mmol, 1.0 equiv), TEMPO (0.08 mmol, 0.4 equiv), $K_2S_2O_8$ (0.6 mmol, 3.0 equiv), and H_2O (6.0 mmol, 30 equiv) in MeCN (6.0 mL) were added to an oven-dried glass tube equipped with a magnetic stir bar. Next, the tube was placed in a pre-heated oil-bath at 50 °C. The mixture was stirred at the same temperature for 30 h. Water was added, and the mixture was extracted with ethyl acetate (3 times). The combined organic layer was dried over Na_2SO_4. Solvent was removed in a rotary evaporator. The crude product was then purified by flash column chromatography on silica gel (mesh 230 400) using hexane and ethyl acetate (97:3 to 94:6) as eluents to afford the corresponding isoxazoline derivatives.

General Procedure for the Synthesis of Isoxazoles 3 from Oximes 1

Oxime **1** (0.2 mmol, 1.0 equiv), TEMPO (0.08 mmol, 0.4 equiv), oxone (0.6 mmol, 3.0 equiv), and KI (0.02 mmol, 0.1 equiv) in MeCN (2.0 mL) were added to an oven-dried glass tube equipped with a magnetic stir bar. The tube was placed in a pre-heated oil-bath at 50 °C. The mixture was stirred at the same temperature for 48 h. Water was added, and the mixture was extracted with ethyl acetate (3 times). The combined organic layer was dried over sodium sulphate. The solvent was removed in a rotary evaporator. The crude product was purified by flash column chromatography using silica gel (mesh 230 400). Hexane and ethyl acetate (98:2 to 94:6) as eluents were used to afford the corresponding isoxazole derivatives.

General Procedure for the Synthesis of 5-Hydroxy-2-Isoxazolines 4 from Oximes 1

Oxime **1** (0.2 mmol, 1.0 equiv), TEMPO (0.3 mmol, 1.5 equiv), and $PhI(OAc)_2$ (0.2 mmol, 1.0 equiv) in MeCN (6.0 mL) were added to an oven-dried glass tube equipped with a magnetic stir bar. The reaction was continued for 24 h under N_2 atmosphere. Water was added, and the mixture was extracted with ethyl acetate (3 times). The combined organic layer was dried over sodium sulphate. Rotary evaporator was used to remove the solvent. The crude product was then purified by flash column chromatography using silica gel (mesh 230 400). Hexane and ethyl acetate (93:7 to 89:11) as eluents were used to afford the corresponding 5-hydroxy-2-isoxazoline derivatives.

General Procedure for the Synthesis of Acetyl Protected Oximes 5 and 6

Oxime (1.0 equiv) and acetyl chloride (1.5 equiv) were dissolved in dichloromethane, and the mixture was cool with an ice-bath. Triethylamine (1.5 equiv) was added dropwise. The reaction mixture was brought to room temperature and stirring was continued for 4 hours. Water was added to the reaction mixture, and the organic phase was separated. The organic phase was washed with saturated NH_4Cl, aqueous Na_2CO_3 solution, and brine. The organic layer was dried over sodium sulphate and evaporated in rotary evaporator. The residue was purified by column chromatography using hexane and ethyl acetate (93:7) as eluent.

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Conflict of Interest

The authors declare no conflict of interest.

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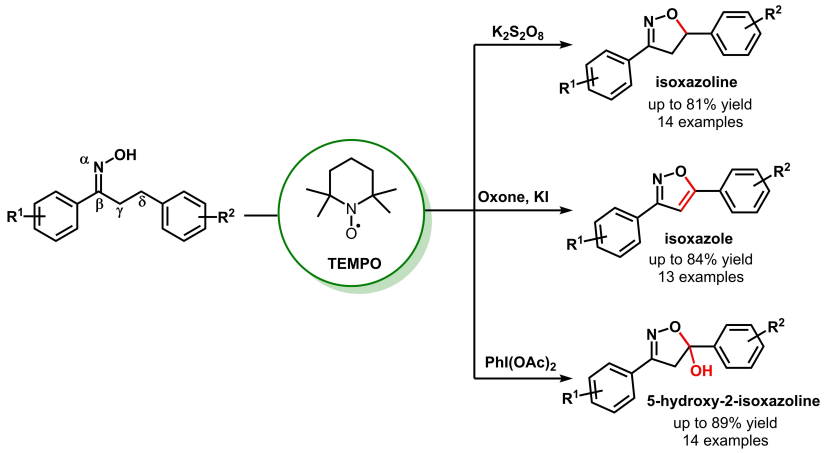

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TEMPO-Mediated Selective Synthesis of Isoxazolines, 5-Hydroxy-2-isoxazolines, and Isoxazoles via Aliphatic δ-C(sp3)-H Bond Oxidation of Oximes

Three heterocycles from one starting material: A divergent method for the synthesis of isoxazolines, isoxazoles, and 5-hydroxy-2-isoxazolines from oximes is developed using TEMPO as a radical initiator. Oxidants control the selectivity of the product formations.