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**Authors:** Hideo Togo and Taro Imai



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# One-pot Preparation of 3-Arylisoxazole-4,5-dicarboxylates from Benzylic Chlorides via Aldehydes, Oximes, and Nitrile *N*-Oxides with Acetylenedicarboxylates

**Taro Imai[a] and Hideo Togo*[1]**

**Keywords:** Benzylic halide / Isoxazole / NMO / Oxone® / Acetylene

Various diethyl 3-arylisoxazole-4,5-dicarboxylates were efficiently, smoothly, and quickly prepared in good to moderate yields by the successive treatment of benzylic chlorides and alkyl *p*-tosylates with NMO, hydroxylamine•hydrochloride, and then Oxone® in the presence of diethyl acetylenedicarboxylates under mild and transition-metal-free conditions.

[a] Graduate School of Science, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522 Japan
Fax: 81-43-290-2792
E-mail: togo@faculty.chiba-u.jp
Homepage: http://reaction-2.chem.chiba-u.jp/index.html
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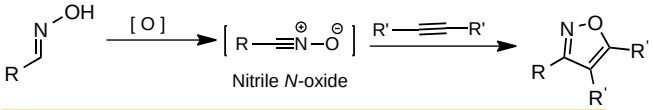
## Introduction

Some nitrogen-containing heteroaromatics are very important because of their potent biological activities.[1] Isoxazoles, in particular, are one of the most important nitrogen-containing heteroaromatics.[2] Isoxazole derivatives possessing anti-inflammatory,[2b] antimicrobial,[2c] anticancer,[2d] and antinociceptive[2e] activities are known. Therefore, extensive synthetic studies of isoxazoles have been carried out, and the most typical preparation method is the 1,3-dipolar cycloaddition of nitrile *N*-oxides to alkynes, as shown in Scheme 1. Recent reports for the preparation of isoxazoles via nitrile *N*-oxides with alkynes are as follows:[3] the preparation of 3-(difluoromethyl)isoxazoles with difluoromethyl nitrile *N*-oxide and alkynes,[3b] the preparation of 3-arylisoxazoles with aldoximes, alkynes, and alkyl nitrites,[3c] the preparation of 3,4-disubstituted and 3,4,5-trisubstituted isoxazoles with aldoximes, alkynes, and (diacetoxyiodo)benzene,[3d] the preparation of 3-(trifluoromethyl)isoxazoles with (trifluoromethyl)hydroximoyl bromide and alkynes,[3e] the preparation of 3,4,5-trisubstituted isoxazoles with nitrile *N*-oxides and ketones in the presence of 1,1,3,3-tetramethylquanidine,[3f] the preparation of 3,5-disubstituted isoxazoles with aldoximes, alkynes, and Oxone®($2KHSO_5•KHSO_4•K_2SO_4$) in the presence of $3,5\text{-}Me_2C_6H_3I$ (cat.),[3g] and the preparation of 3,5-disubstituted isoxazoles with aldoximes, alkynes, and [bis(trifluoroacetoxy)iodo]benzene.[3h] As other preparation methods for isoxazoles, the preparation of 3,5-disubstituted isoxazoles with ynones and trimethylsilylazide[3i] and the preparation of 3,5-diarylisoxazoles with 1,3-diaryl-1-thioketo-3-ketopropanes or 1,3-diaryl-3-thiomethyl-2-propen-1-ones and hydroxylamine[3j] were reported. On the other hand, as examples of transition-metal-catalyzed methods, the preparation of 3,5-disubstituted isoxazoles with ethynylarenes, *t*-BuONO, and $Sc(OTf)_3$ (cat.),[3k] the preparation of 3,5-disubstituted isoxazoles with hydroxyimino acids, alkenes, Oxone®, and $Ru(bpy)_3Cl_2$ (cat.),[3l] the preparation of 4-borylated 3,5-disubstituted isoxazoles with oximes of ynones, HBcat, and IPrAuTFA (cat.),[3m] the preparation of 3,5-disubstituted isoxazoles with *N*-hydroxyimidoyl chlorides, terminal alkynes, and $Cu(Phen)(Ph_3P)_2NO_3$ (cat.),[3n] and the preparation of 3,5-disubstituted isoxazoles with homopropargylic alcohols, *t*-BuONO, and $Fe(OTf)_3$ (cat.)[3o] were reported.




**Scheme 1**. Conventional Mehtod for Preparation of Isoxazoles

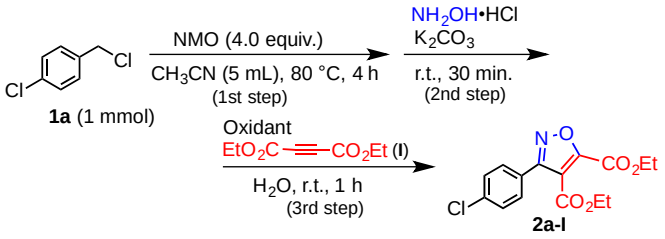
We also reported the preparation of 3,5-disubstituted isoxazoles with high regioselectivity in one pot by the treatment of terminal alkynes with *n*-BuLi, aromatic aldehydes, molecular iodine, and then hydroxylamine through the formation of propargyl alkoxides and α-alkynyl ketones.[4] On the other hand, we reported the one-pot conversion of methylarenes into aromatic aldehydes via benzylic bromides through the Wohl-Ziegler bromination of methylarenes, and the subsequent $S_N2$ and E2 reactions with *N*-methylmorpholine *N*-oxide (NMO).[5a] Based on the results for oxidation of benzylic bromides with NMO[5a] and benzylic chlorides with NMO[5b], here we would like to report one-pot preparation of 3-arylisoxazoles and 3-alkylisoxazoles from benzylic chlorides and alkyl *p*-tosylates by the treatment with NMO, hydroxylamine•hydrochloride, and Oxone® in the presence of acetylene derivatives. To the best of our knowledge, the transformation of benzylic halides into 3-arylisoxazoles and related reactions have never been reported.

## Results and Discussion

At first, *p*-chlorobenzyl chloride **1a** (1.0 mmol) was treated with NMO (4.0 mmol) in acetonitrile at 80 °C for 4 h to form *p*-chlorobenzaldehyde (1st step).[5a] Then, $NH_2OH•HCl$ (2.0 mmol) and $K_2CO_3$ (1.0 mmol) were added and the mixture was stirred at room temperature for 30 min to form the corresponding oxime quantitatively (2nd step). Once the oxime was formed, Oxone® (1.1 mmol), diethyl acetylenedicarboxylate (**I**) (1.5 mmol), and water (5 mL) were added and the obtained mixture was stirred at room temperature for 1 h (3rd step) to give diethyl 3-(4'-chlorophenyl)isoxazole-4,5-dicarboxylare **2a-I** in 54% yield, as shown in Table 1 (entry 1). When the reaction with **1a** was carried out under the same procedure and conditions without the addition of water at the 3rd step, the yield of isoxazole **2a-I** was dramatically decreased to 6% (entry 2) due to the insolubility of Oxone®. After

the same oxidation of **1a** with NMO, treatment of the formed aldehyde with reduced amounts of $NH_2OH$•HCl (1.2 mmol) and $K_2CO_3$ (0.6 mmol) at room temperature for 30 min and the subsequent treatment with Oxone® (1.1 mmol) and **I** (1.5 mmol) without water and with water (5 mL) at room temperature for 1 h gave isoxazole **2a-I** in 0% and 88% yields, respectively (entries 3, 4). Thus, the addition of water at the 3rd step is quite important to form isoxazole **2a-I**. The same treatment of **1a** with $NH_2OH$•$H_2O$ (1.2 equiv.) alone instead of $NH_2OH$•HCl and $K_2CO_3$ under the same procedure and conditions at the 2nd step slightly reduced the yield of isoxazole **2a-I** to 81% (entry 5). On the other hand, the same treatment of **1a** under the same procedure and conditions using reduced amounts of Oxone® (1.2 mmol) and **I** (1.2 mmol) with water at the 3rd step reduced the yield of isoxazole **2a-I** to 68% (entry 6). Thus, the treatment of **1a** (1 mmol) with NMO (4.0 equiv.) in acetonitrile under refluxing conditions for 4 h, and the subsequent treatment with $NH_2OH$•HCl (1.2 equiv.) and $K_2CO_3$ (0.6 equiv.) at room temperature for 30 min, followed by the treatment with Oxone® (1.5 equiv.), **I** (1.5 equiv.), and water (5 mL) at room temperature for 1 h gave the best yield of isoxazole **2a-I** (entry 4). When other oxidants, such as 30% hydrogen peroxide, 70% *t*-butyl hydrogen peroxide (TBHP), di-*t*-butyl peroxide (DTBT), $Na_2S_2O_8$, benzoyl peroxide (BPO), and (diacetoxyiodo)benzene (DIB) were used instead of Oxone® under the same procedure and conditions, isoxazole **2a-I** was not obtained at all (entries 7~12). Thus, Oxone® plays an important role in the present one-pot preparation of isoxazole **2a-I** from the oxime. On the other hand, when *p*-chlorobenzyl bromide and *p*-chlorobenzyl iodide instead of *p*-chlorobenzyl chloride **1a** were treated under the same procedure and conditions, isoxazole **2a-I** was obtained in 56% and 0% yields, respectively (entries 13, 14). Thus, benzyl bromide showed moderate reactivity, whereas benzyl iodide was not effective in the present reaction at all.

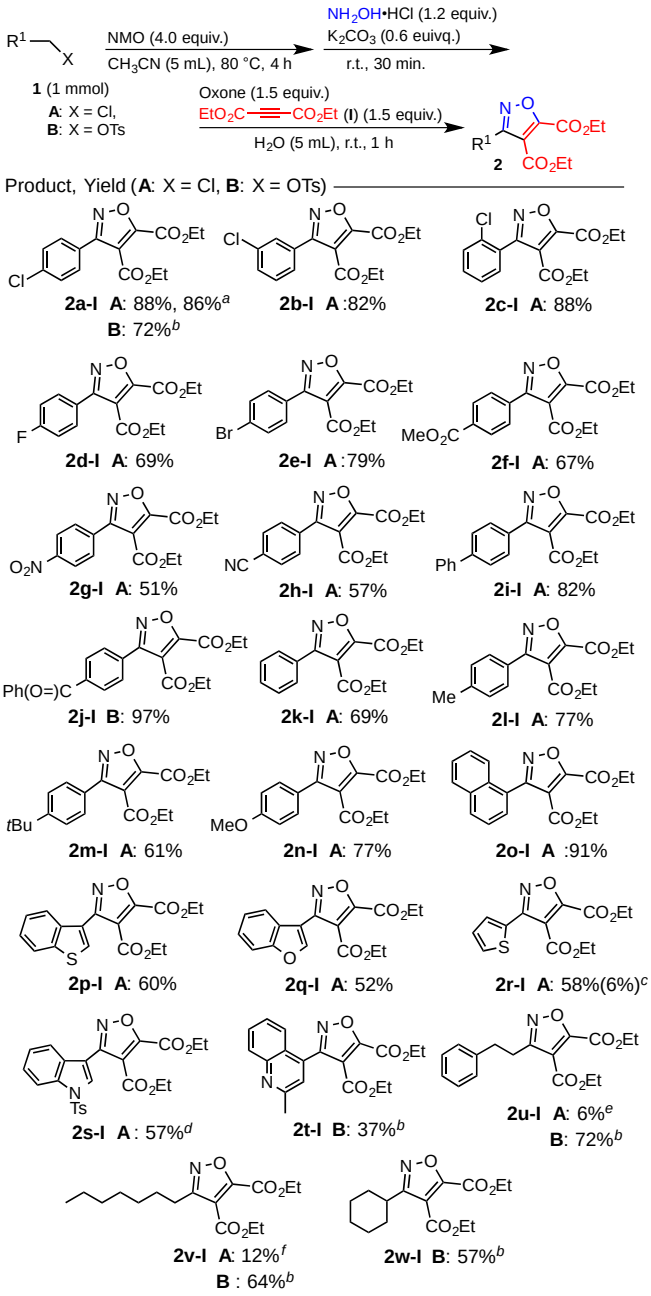
**Table 1.** Optimization for One-pot Transformation of *p*-Chlorobenzyl Chloride **1a** to Isoxazole **2a-I**



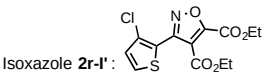

| Entry | $NH_2OH$•HCl (equiv.) | $K_2CO_3$ (equiv.) | Oxidant (equiv.) | **I** (equiv.) | $H_2O$ (mL) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 2.0 | 1.0 | Oxone® (1.1) | 1.5 | $H_2O$ (5) | 54 |
| 2 | 2.0 | 1.0 | Oxone® (1.1) | 1.5 | - | 6 |
| 3 | 1.2 | 0.6 | Oxone® (1.1) | 1.5 | - | 0 |
| 4 | 1.2 | 0.6 | Oxone® (1.5) | 1.5 | $H_2O$ (5) | 88 |
| 5[a,b] | 1.2 | - | Oxone® (1.5) | 1.5 | $H_2O$ (5) | 81 |
| 6 | 1.2 | 0.6 | Oxone® (1.2) | 1.2 | $H_2O$ (5) | 68 |
| 7 | 1.2 | 0.6 | 30% $H_2O_2$ (1.5) | 1.5 | $H_2O$ (5) | 0 |
| 8 | 1.2 | 0.6 | 70% TBHP (1.5) | 1.5 | $H_2O$ (5) | 0 |
| 9 | 1.2 | 0.6 | DTBP (1.5) | 1.5 | - | 0 |
| 10 | 1.2 | 0.6 | $Na_2S_2O_8$ (1.5) | 1.5 | $H_2O$ (5) | 0 |
| 11 | 1.2 | 0.6 | BPO (1.5) | 1.5 | - | 0 |
| 12 | 1.2 | 0.6 | DIB (1.5) | 1.5 | - | 0 |
| 13[c] | 1.2 | 0.6 | Oxone® (1.5) | 1.5 | - | 56 |
| 14[d] | 1.2 | 0.6 | Oxone® (1.5) | 1.5 | - | 0 |

[a] $NH_2OH$ (50% in water) was used instead of $NH_2O$•HCl. [b] 3rd step reaction was carried out for 2 h. [c] *p*-Chlorobenzyl bromide was used instead of *p*-chlorobenzyl chloride **1a**. [d] *p*-Chlorobenzyl iodide was used instead of *p*-chlorobenzyl chloride **1a**.

**Table 2.** One-pot Transformation of Benzylic Chlorides or Alkyl *p*-Tosylates **1** into Isoxazoles **2**



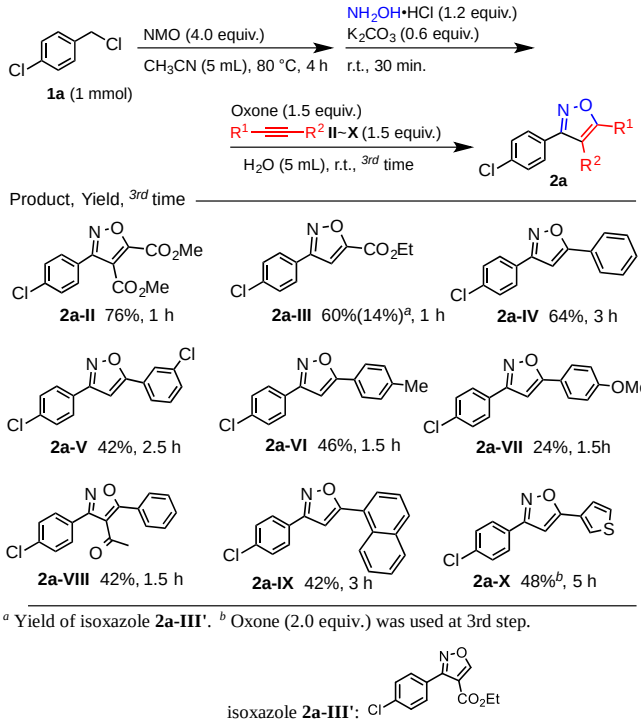

[a] **1a** (10 mmol) was used. [b] 1st step reaction was carried out for 2 h. [c] Yield of isoxazole **2r-I'**. [d] 2nd step reacion conditions : $NH_2OH$ (2.4 equiv.) and $K_2CO_3$ (1.2 equiv.) were used, and the mixture was stirred at r.t. for 60 h. [e] 1st step reaction was carried out for 5 h. [f] 1st step reaction was carried out for 4 h.



As a gram-scale experiment, successive treatment of *p*-chlorobenzyl chloride **1a** (10 mmol) with NMO (1st step), $NH_2OH$•HCl and $K_2CO_3$ (2nd step), and then Oxone® (15 mmol), **I** (15 mmol), and water (3rd step) under the same procedure and conditions provided isoxazole **2a-I** in 86% yield, as shown in Table 2.

Based on those results, various benzylic chlorides, such as *m*-chlorobenzyl chloride **1b**, *o*-chlorobenzyl chloride **1c**, *p*-fluorobenzyl chloride **1d**, *p*-bromobenzyl chloride **1e**, *p*-(methoxycarbonyl)benzyl chloride **1f**, *p*-nitrobenzyl chloride **1g**, *p*-cyanobenzyl chloride **1h**, *p*-phenylbenzyl chloride **1i**, benzyl chloride **1k**, *p*-methylbenzyl chloride **1l**, *p*-*t*-butylbenzyl chloride **1m**, *p*-methoxybenzyl chloride **1n**, and (naphthalen-1-yl)methyl chloride **1o**, were treated with NMO, $NH_2OH$•HCl and $K_2CO_3$, and then Oxone®, **I**, and water under the same procedure and conditions to form the corresponding isoxazoles **2b-I**~**2i-I** and **2k-I**~**2o-I** in good to moderate yields, respectively, as shown in Table 2. As regards heteroaromatic groups, when (benzothiophen-3-yl)methyl chloride **1p**, (benzofuran-3-yl)methyl chloride **1q**, (thiophene-2-yl)methyl chloride **1r**, and (1-tosylindole-3-yl)methyl chloride **1s**, were also treated with NMO, $NH_2OH$•HCl and $K_2CO_3$, and then Oxone®, **I**, and water under the same procedure and conditions, the corresponding isoxazoles **2p-I**~**2s-I** were obtained in moderate yields, respectively, as shown in Table 2. On the other hand, when aliphatic chlorides, such as 3-(phenyl)propyl chloride **1u** and 1-octyl chloride **1v**, were treated with NMO, $NH_2OH$•HCl and $K_2CO_3$, and then Oxone®, **I**, and water under the same procedure and conditions, the corresponding isoxazoles **2u-I** and **2v-I** were obtained in only 6% and 12% yields, respectively, as shown in Table 2. The reason why the yields of isoxazoles **2u-I** and **2v-I** were low is that the first transformation of alkyl chlorides into the corresponding aldehydes with NMO did not proceed effectively due to the low reactivity of the alkyl chlorides toward NMO. Therefore, for alkyl groups, (3-phenyl)propyl *p*-tosylate **1u'**, 1-octyl *p*-tosylate **1v'**, and (cyclohexyl)methyl *p*-tosylate **1w'** were treated with NMO, $NH_2OH$•HCl and $K_2CO_3$, and then Oxone®, **I**, and water under the same procedure and conditions to form the corresponding isoxazoles **2u-I**~**2w-I** in good to moderate yields, respectively, as shown in Table 2, although the same treatment of neopentyl *p*-tosylate did not generate the corresponding isoxazole at all. Similarly, for aromatic groups, when *p*-chlorobenzyl *p*-tosylate **1a'**, (*p*-benzoyl)benzyl *p*-tosylate **1j'**, and (2-methylquinoline-4-yl)methyl *p*-tosylate **1t'** were treated with NMO, $NH_2OH$•HCl and $K_2CO_3$, and then Oxone®, **I**, and water under the same procedure and conditions, the corresponding isoxazoles **2a-I**, **2j-I,** and **2t-I** were obtained in good to moderate yields, respectively. Then, other acetylene derivatives, such as dimethyl acetylenedicarboxylate (**II**), ethyl propiolate (**III**), phenylacetylene (**IV**), (*m*-chlorophenyl)acetylene (**V**), (*p*-methylphenyl)acetylene (**VI**), (*p*-methoxyphenyl)acetylene (**VII**), 4-phenyl-3-butyn-2-one (**VIII**), (naphthalene-1-yl)acetylene (**IX**), and (thiophen-3-yl)acetylene (**X**), were used instead of diethyl acetylenedicarboxylate (**I**). *p*-Chlorobenzyl chloride **1a** was treated with NMO in acetonitrile under refluxing conditions for 4 h, and then with $NH_2OH$•HCl and $K_2CO_3$ at room temperature for 30 min. This was followed by the reaction with Oxone®, acetylene derivatives (**II**~**X**), and water at room temperature for 1 h~5 h to give isoxazoles **2a-II**~**2a-X** in good to moderate yields, except **2a-VII**, as shown in Table 3. This is because electron-rich alkynes, such as (*p*-methoxyphenyl)acetylene (**VII**), reacted with active species, the chloro cation formed by the reaction of chloride ion and Oxone® at the 3rd reaction step and the formation of nitrile *N*-oxide from oxime was disturbed.[6]

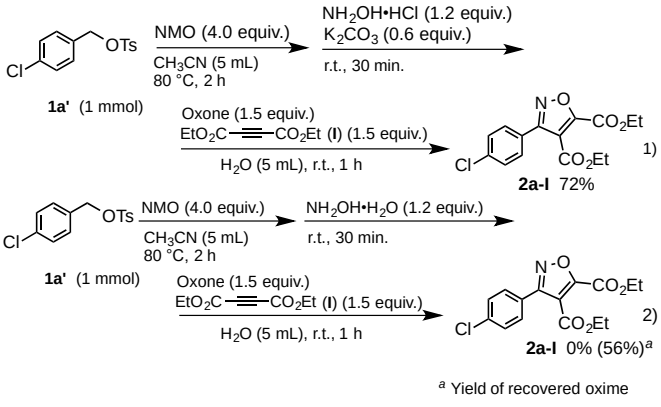
**Table 3.** One-pot Transformation of *p*-Chlorobenzyl Chloride **1a** into Isoxazoles **2a**




[a] Yield of isoxazole **2a-III'**. [b] Oxone (2.0 equiv.) was used at 3rd step.

isoxazole **2a-III'**:

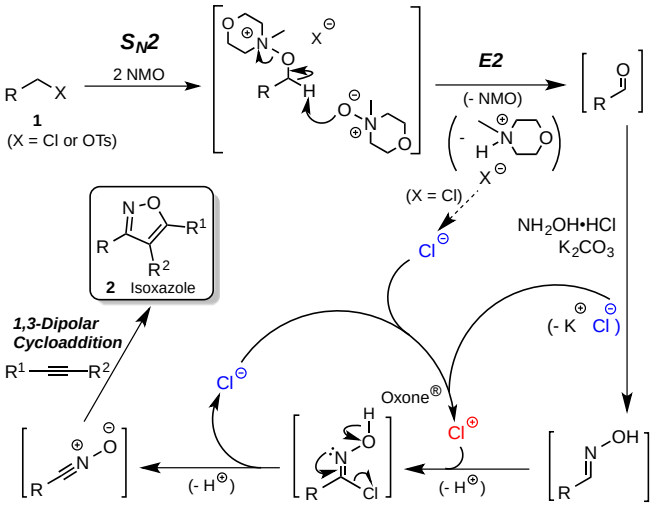
To understand the role of chloride ion derived from benzylic chloride and/or $NH_2OH$•HCl in the present one-pot preparation of 3-arylisoxazoles **2** from benzylic chlorides **1**, *p*-chlorobenzyl *p*-tosylate **1a'** instead of *p*-chlorobenzyl chloride **1a** was used. Thus, when *p*-chlorobenzyl *p*-tosylate **1a'** was treated with NMO, $NH_2OH$•HCl and $K_2CO_3$, and then Oxone®, **I**, and water under the same procedure and conditions, isoxazole **2a-I** was obtained in 72% yield, as shown in Scheme 2 (eq. 1). However, when *p*-chlorobenzyl *p*-tosylate **1a'** was treated with NMO, $NH_2OH$•$H_2O$, and then Oxone®, **I**, and water under the same procedure and conditions, isoxazole **2a-I** was not obtained at all (eq. 2). Thus, chloride ion plays an important role in the oxidation of the oxime to nitrile *N*-oxide in the presence of Oxone®, where the formed nitrile *N*-oxide reacts with diethyl acetylenedicarboxylate (**I**) to give isoxazole **2a-I**.[7]




[a] Yield of recovered oxime

**Scheme 2.** Reaction with *p*-Chlorobenzyl *p*-Tosylate **1a'**

A possible reaction pathway is shown in Scheme 3. Benzylic chlorides react with NMO through an $S_N2$ reaction and a subsequent E2 reaction to form aromatic aldehydes (1st step).[5] The formed aromatic aldehydes react smoothly with $NH_2OH$•HCl in the presence of $K_2CO_3$ to form oximes (2nd step). Then, the oximes are oxidized to nitrile *N*-oxides by a chloro cation that is formed by the reaction of chloride ion and Oxone®,[7] and the formed nitrile *N*-oxides react with acetylene derivatives to form isoxazoles. Here, chloride ion derived from benzylic chlorides and/or $NH_2OH$•HCl probably works as a catalyst for the formation of nitrile *N*-oxides from oxime in the presence of Oxone®.




**Scheme 3.** Possible Reaction Pathway

## Conclusions

A variety of benzylic chlorides and alkyl *p*-tosylates were treated with NMO, and then hydroxylamine•hydrochloride and potassium carbonate, followed by the reaction with Oxone® in the presence of acetylene derivatives to give 3-arylisoxazoles and 3-alkylisoxazoles in one pot under mild and transition-metal-free conditions. The key step of the present reaction is the oxidation of benzylic chlorides and alkyl *p*-tosylates by NMO to the corresponding aldehydes and the chloride-catalyzed oxidation of oximes to nitrile *N*-oxides by Oxone®. We believe the present method would be useful for the preparation of various 3-aryl- and 3-alkylisoxazole derivatives due to its simple operation using easily available substrates and reagents in one pot.

### Experimental Section

$^1$H NMR spectra were measured on 400 MHz spectrometers. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the □ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. $^{13}$C NMR spectra were measured on 100 MHz spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). Characteristic peaks in the infrared (IR) spectra were recorded in wave numbers, cm$^{-1}$. High-resolution mass spectra were recorded by Thermo Fisher Scientific Exactive Orbitrap mass spectrometers. Melting points were uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (60F-254). The products were purified by column chromatography on neutral silica gel 60N (63–210 mesh).

**General Procedure for Preparation of Isoxazoles 2 from Benzylic Chlorides or Alkyl *p*-Tosylates 1 with NMO, $NH_2OH$•HCl, and Oxone® in the presence of Acetylene Derivatives:**

To a solution of 4-chlorobenzyl chloride **1a** (161.03 mg, 1.0 mmol) in $CH_3CN$ (5.0 mL) in a 50 mL screw-capped flask was added *N*-methylmorpholine *N*-oxide (468.6 mg, 4.0 mmol) at room temperature. The mixture was stirred at 80 °C for 4 h. Then, hydroxylamine hydrochloride (83.4 mg, 1.2 mmol) and $K_2CO_3$ (82.9 mg, 0.6 mmol) were added, and the obtained mixture was stirred at room temperature for 0.5 h. After that, $H_2O$ (5.0 mL), diethyl acetylenedicarboxylate (239.0 µL, 1.5 mmol), and Oxone® (922.1 mg, 1.5 mmol) were added to the mixture at room temperature. The obtained mixture was stirred at room temperature for one hour. The resulting mixture was quenched with sat. aq. $Na_2S_2O_3$ and extracted with AcOEt (3 × 10 mL). The organic layer was washed with brine and dried over $Na_2SO_4$. Purification of the residue by short column chromatography on neutral silica gel (hexane/AcOEt = 10:1) gave diethyl 3-(4'-chlorophenyl)isoxazole-4,5-dicarboxylate **2a** (284.9 mg, 88%).

**Diethyl 3-(4'-chlorophenyl)isoxazole-4,5-dicarboxylate (2a-I)**.[8] Colorless Oil (284.9 mg, 88% yield): IR (neat) 2985, 1732, 1272, 1065, 731 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.33 (t, *J* = 7.2 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 14.0, 62.5, 62.9, 115.7, 125.4, 129.1, 129.5, 136.9, 156.0, 159.9, 160.2, 161.1; HRMS (APCI) Calcd for $C_{15}H_{15}O_5NCl(M+H)^+$ 324.0633, Found 324.0628.

**Diethyl 3-(3'-chlorophenyl)isoxazole-4,5-dicarboxylate (2b-I)**. Colorless Oil (266.4 mg, 82% yield): IR (neat) 2985, 1733, 1300, 1067, 755 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.33 (t, *J* = 7.0 Hz, 3H), 1.44 (t, *J* = 7.3 Hz, 3H), 4.39 (q, *J* = 7.0 Hz, 2H), 4.48 (q, *J* = 7.3 Hz, 2H), 7.41 (dd, *J* = 8.2, 7.7 Hz, 1H), 7.49 (dt, *J* = 8.2, 1.4 Hz, 1H), 7.60 (dt, *J* = 7.7, 1.4 Hz,1H), 7.72 (t, *J* = 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 13.9, 62.5, 62.9, 115.8, 126.4, 128.3, 128.6, 130.0, 130.6, 134.7, 155.9, 159.9, 160.0, 160.9; HRMS (APCI) Calcd for $C_{15}H_{15}O_5NCl$ $(M+H)^+$ 324.0633, Found 324.0634.

**Diethyl 3-(2'-chlorophenyl)isoxazole-4,5-dicarboxylate (2c-I)**.[8] Colorless Oil (285.6 mg, 88 % yield): IR (neat) 2985, 1732, 1304, 1081, 758 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.14 (t, *J* = 7.0 Hz, 3H), 1.45 (t, *J* = 7.3 Hz, 3H), 4.23 (q, *J* = 7.0 Hz, 2H), 4.51 (q, *J* = 7.3 Hz, 2H), 7.39 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.43-7.50 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.5, 13.9, 61.7, 63.0, 116.0, 126.7, 126.8, 129.5, 131.2, 131.4, 133.5, 156.1, 159.7, 160.5, 160.9; HRMS (APCI) Calcd for $C_{15}H_{15}O_5NCl(M+H)^+$ 324.0633, Found 324.0629.

**Diethyl 3-(4'-fluorophenyl)isoxazole-4,5-dicarboxylate (2d-I)**. Colorless Oil (211.1 mg, 69% yield): IR (neat) 2998, 1736, 1448, 1276, 844 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.32 (t, *J* = 7.2 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 7.17 (t, *J* = 8.8 Hz, 2H), 7.72 (dd, *J* = 8.8, 5.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.7, 13.8, 62.3, 62.8, 115.6, 115.9 (d, $J_{C-F}$ = 21.9 Hz), 123.1 (d, $J_{C-F}$ = 3.8 Hz), 130.3 (d, $J_{C-F}$ = 9.5 Hz), 155.9, 159.7, 160.2, 161.1, 164.0 (d, $J_{C-F}$ = 251.8 Hz); HRMS (APCI) Calcd for $C_{15}H_{15}O_5NF$ $(M+H)^+$ 308.0929, Found 308.0925.

**Diethyl 3-(4'-bromophenyl)isoxazole-4,5-dicarboxylate (2e-I)**. Colorless Oil (289.8 mg, 79% yield): IR (neat) 2984, 1732, 1272, 1063, 831 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.33 (t, *J* = 7.2 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 7.58~7.63 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.7, 13.8, 62.4, 62.8, 115.5, 125.1, 125.8, 129.6, 131.9, 155.8, 159.8, 160.2, 161.0; HRMS (APCI) Calcd for $C_{15}H_{15}O_5NBr$ $(M+H)^+$ 368.0128, Found 368.0128.

**Diethyl 3-[4'-(methoxycarbonyl)phenyl]isoxazole-4,5-dicarboxylate (2f-I)**. Colorless Oil (232.1 mg, 67% yield): IR (neat) 2986, 1723, 1273, 1065, 756 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.31 (t, *J* = 7.2 Hz, 3H), 1.44 (t, *J* = 7.2 Hz, 3H), 3.96 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 7.79 (d, *J*

= 8.5 Hz, 2H), 8.14 (d, *J* = 8.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.7, 13.8, 52.2, 62.4, 62.8, 115.7, 128.1, 129.7, 131.0, 131.8, 155.7, 159.8, 160.2, 160.8, 166.0; HRMS (APCI) Calcd for $C_{17}H_{18}O_7N$ $(M+H)^+$ 348.1078, Found 324.1077.

**Diethyl 3-(4'-nitrophenyl)isoxazole-4,5-dicarboxylate (2g-I)**. Colorless Solid (170.1 mg, 51% yield): mp 74-75 °C; IR (neat) 2916, 1729, 1524, 1289, 855 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.33 (t, *J* = 7.0 Hz, 3H), 1.45 (t, *J* = 7.3 Hz, 3H), 4.39 (q, *J* = 7.0 Hz, 2H), 4.50 (q, *J* = 7.3 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 8.34 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.9, 14.0, 62.7, 63.2, 115.5, 123.9, 129.6, 133.2, 149.1, 155.9, 159.7, 160.7, 160.8; HRMS (APCI) Calcd for $C_{15}H_{15}O_7N_2$ $(M+H)^+$ 335.0874, Found 335.0871.

**Diethyl 3-(4'-cyanophenyl)isoxazole-4,5-dicarboxylate (2h-I)**:Colorless Solid (187.1 mg, 60% yield); mp 91-93 °C; IR (neat) 2993, 2230, 1735, 1449, 1276, 844 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.33 (t, *J* = 7.2 Hz, 3H), 1.44 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.50 (q, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 14.0, 62.6, 63.2, 114.4, 115.4, 118.0, 129.1, 131.4, 132.5, 155.8, 159.9, 160.6, 160.7; HRMS (APCI) Calcd for $C_{16}H_{15}O_5N_2$ $(M+H)^+$ 315.0975, Found 315.0974.

**Diethyl 3-(biphenyl-4'-yl)isoxazole-4,5-dicarboxylate (2i-I)**. Colorless Solid (299.6 mg, 82% yield): mp 78-79 °C; IR (neat) 2981, 1727, 1283, 1071, 734 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.35 (t, *J* = 7.2 Hz, 3H), 1.44 (t, *J* = 7.2 Hz, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 8.34 (dd, *J* = 7.2, 7.0 Hz, 2H), 7.63 (d, *J* = 7.0 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 13.9, 62.3, 62.8, 116.0, 125.7, 127.0, 127.3, 127.8, 128.4, 128.8, 139.8, 143.3, 155.9, 159.4, 160.7, 161.4; HRMS (APCI) Calcd for $C_{21}H_{20}O_5N$ $(M+H)^+$ 366.1336, Found 366.1335.

**Diethyl 3-(4'-benzoylphenyl)isoxazole-4,5-dicarboxylate (2j-I)**. Colorless Oil (381.4 mg, 97% yield): IR (neat) 2984, 1731, 1660, 1272, 699 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.34 (t, *J* = 7.2 Hz, 3H), 1.45 (t, *J* = 7.2 Hz, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.50 (q, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.82-7.85 (m, 4H), 7.91 (d, *J* = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 14.0, 62.5, 63.0, 115.9, 128.2, 128.4, 130.0, 130.2, 130.6, 132.8, 136.9, 139.2, 155.9, 160.0, 160.4, 161.0, 195.8; HRMS (APCI) Calcd for $C_{22}H_{20}O_6N$ $(M+H)^+$ 394.1285, Found 394.1285.

**Diethyl 3-phenylisoxazole-4,5-dicarboxylate (2k-I).**[8] Colorless Oil (198.7 mg, 69% yield): IR (neat) 2984, 1733, 1302, 1138 1066 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.31 (t, *J* = 7.2 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 4,38 (q, *J* = 7.2 Hz, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 7.45-7.51 (m, 3H), 7.70 (d, *J* = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.7, 13.9, 62.3, 62.8, 116.0, 126.9, 128.1, 128.7, 130.5, 156.0, 159.4, 161.1, 161.3; HRMS (APCI) Calcd for $C_{15}H_{16}O_5N$ $(M+H)^+$ 290.1023, Found 290.1018.

**Diethyl 3-(4'-methylphenyl)isoxazole-4,5-dicarboxylate (2l-I)**.[8] Colorless Solid (233.4 mg, 77% yield); mp 44-46 °C: IR (neat) 2923, 1737, 1447, 1274, 826 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.33 (t, *J* = 7.2 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.47 (q, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.6, 13.7, 21.1, 62.1, 62.6, 115.9, 123.9, 127.7, 129.3, 140.7, 155.9, 159.1, 160.1, 161.3; HRMS (APCI) Calcd for $C_{16}H_{18}O_5N$ $(M+H)^+$ 304.1179, Found 304.1175.

**Diethyl 3-[4'-(*tert*-butyl)phenyl]isoxazole-4,5-dicarboxylate (2m-I)**. Yellow Oil (211.8 mg, 61% yield): IR (neat) 2965, 1734, 1302, 1270, 1065 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.33 (t, *J* = 7.2 Hz, 3H), 1.35 (s, 9H), 1.43 (t, *J* = 7.2 Hz, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.47 (q, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 13.9, 31.1, 34.8, 62.3, 62.8, 116.0, 124.0, 125.8, 127.7, 153.9, 156.1, 159.2, 160.9, 161.5; HRMS (APCI) Calcd for $C_{19}H_{24}O_5N$ $(M+H)^+$ 346.1649, Found 346.1649.

**Diethyl 3-(4'-methoxyphenyl)isoxazole-4,5-dicarboxylate (2n-I)**.[8] Yellow Oil (246.6 mg, 77% yield): IR (neat) 2985, 1733, 1611, 1254, 750 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.33 (t, *J* = 7.0 Hz, 3H), 1.43 (t, *J* = 7.3 Hz, 3H), 3.86 (s, 3H), 4.38 (q, *J* = 7.0 Hz, 2H), 4.47 (q, *J* = 7.3 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 13.9, 55.2, 62.3, 62.7, 114.1, 115.8, 119.1, 129.5, 156.0, 159.2, 160.6, 161.3, 161.5; HRMS (APCI) Calcd for $C_{16}H_{18}O_6N$ $(M+H)^+$ 320.1129, Found 320.1129.

**Diethyl 3-(naphthalen-1'-yl)isoxazole-4,5-dicarboxylate (2o-I)**.[8] Colorless Oil (307.5 mg, 91% yield): IR (neat) 2983, 1732, 1300, 1095, 776 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 0.85 (t, *J* = 7.3 Hz, 3H), 1.46 (t, *J* = 7.3 Hz, 3H), 4.04 (q, *J* = 7.3 Hz, 2H), 4.53 (q, *J* = 7.3 Hz, 2H), 7.48-7.62 (m, 4H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.0, 13.6, 61.5, 62.7, 117.0, 124.2, 124.5, 124.6, 126.1, 126.7, 127.9, 128.1, 130.4, 131.1, 133.1, 156.0, 159.8, 159.9, 161.2; HRMS (APCI) Calcd for $C_{19}H_{18}O_5N$ $(M+H)^+$ 340.1179, Found 340.1179.

**Diethyl 3-(benzo[b]thiophen-3'-yl)isoxazole-4,5-dicarboxylate (2p-I)**. Yellow Solid (206.2 mg, 60% yield): mp 105-107 °C; IR (neat) 2984, 1731, 1277, 1105, 756 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.41 (t, *J* = 7.3 Hz, 3H), 1.44 (t, *J* = 7.3 Hz, 3H), 4.48 (q, *J* = 7.3 Hz, 2H), 4.49 (q, *J* = 7.3 Hz, 2H),7.38-7.45 (m, 2H),7.84-7.89 (m, 2H), 7.93 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 13.9, 62.6, 63.0, 115.1, 122.2, 124.6, 124.8, 126.1, 126.9, 127.6, 139.1, 140.3, 155.9, 156.0, 160.1, 161.1; HRMS (APCI) Calcd for $C_{17}H_{16}O_5NS$ $(M+H)^+$ 346.0744, Found 346.0745.

**Diethyl 3-(benzofuran-3'-yl)isoxazole-4,5-dicarboxylate (2q-I)**. Pale Yellow Solid (181.1 mg, 55% yield): mp 63-65 °C; IR (neat) 3648, 1735, 1289, 1191, 755 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.42 (t, *J* = 7.3 Hz, 3H), 1.44 (t, *J* = 7.3 Hz, 3H), 4.49 (q, *J* = 7.3 Hz, 2H), 4.49 (q, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.51 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.9, 14.0, 62.5, 63.0, 109.8, 111.6, 114.9, 122.0, 123.5, 126.4, 127.4, 142.9, 152.9, 155.1, 155.7, 159.7, 160.6; HRMS (APCI) Calcd for $C_{17}H_{16}O_6N$ $(M+H)^+$ 330.0972, Found 330.0971.

**Diethyl 3-(thiophen-2'-yl)isoxazole-4,5-dicarboxylate (2r-I)**. Pale Yellow Oil (170.9 mg, 58% yield): IR (neat) 2983, 1731, 1273, 1193, 714 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.39 (t, *J* = 7.3 Hz, 3H), 1.43 (t, *J* = 7.3 Hz, 3H), 4.43 (q, *J* = 7.3 Hz, 2H), 4.47 (q, *J* = 7.3 Hz, 2H), 7.14 (dd, *J* = 5.2, 3.9 Hz, 1H), 7.50 (d, *J* = 5.2, 1.1 Hz, 1H), 7.64 (dd, *J* = 3.9, 1.1 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.8, 13.8, 62.4, 62.8, 114.9, 127.2, 127.7, 128.9, 129.6, 155.7, 155.8, 159.7, 161.0; HRMS (APCI) Calcd for $C_{13}H_{14}O_5NS$ $(M+H)^+$ 296.0587, Found 296.0583.

**Diethyl 3-(1-tosylindol-3'-yl)isoxazole-4,5-dicarboxylate (2s-I).** Colorless Solid (277.0 mg, 57% yield): mp 83-85 °C; IR (neat) 2920, 1748, 1364, 1176, 752 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.39 (t, *J* = 7.3 Hz, 3H), 1.44 (t, *J* = 7.3 Hz, 3H), 2.35 (s, 3H), 4.45 (q, *J* = 7.3 Hz, 2H), 4.49 (q, *J* = 7.3 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.32-7.42 (m, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.28 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.9, 14.0, 21.5, 62.6, 63.0, 109.3, 113.3, 115.1, 122.5, 124.3, 125.6, 127.0, 127.9, 128.1, 130.0, 134.6, 134.7, 145.5, 155.1, 156.3, 160.0, 161.2; HRMS (APCI) Calcd for $C_{24}H_{23}O_7N_2S$ $(M+H)^+$ 483.1220, Found 483.1220.

**Diethyl 3-(2'-methylquinolin-4'-yl)isoxazole-4,5-dicarboxylate (2t-I)**. Colorless Oil (131.1 mg, 37% yield): IR (neat) 2985, 2939, 1736, 1281, 1098 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 0.88 (t, *J* = 7.0 Hz, 3H), 1.47 (t, *J* = 7.0 Hz, 3H), 2.81 (s, 3H), 4.06 (q, *J* = 7.0 Hz, 2H), 4.54 (q, *J* = 7.0 Hz, 2H), 7.42 (s, 1H), 7.50 (dd, *J* = 7.7, 7.5 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.74 (dd, *J* = 8.4, 7.5 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.3, 14.0, 25.3, 62.0, 63.3, 116.6, 123.0, 124.2, 124.5, 126.7, 129.2, 130.0, 133.4, 147.9, 156.0, 158.3, 159.7(2C), 160.9; HRMS (APCI) Calcd for $C_{19}H_{19}O_5N_2$ $(M+H)^+$ 355.1288, Found 355.1284.

**Diethyl 3-phenethylisoxazole-4,5-dicarboxylate (2u-I)**. Colorless Oil (229.2 mg, 72% yield): IR (neat) 2983, 2359, 1726, 1268, 1098 cm$^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.36 (t, *J* = 7.3 Hz, 3H), 1.42 (t, *J* = 7.3 Hz, 3H), 3.00-3.04 (m, 2H), 3.16-3.20 (m, 2H),

4.35 (q, *J* = 7.3 Hz, 2H), 4.46 (q, *J* = 7.3 Hz, 2H), 7.20-7.24 (m, 3H), 7.28-7.32 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.9(2C), 27.4, 33.8, 61.7, 62.9, 113.8, 126.3, 128.3, 128.4, 140.2, 156.8, 160.5, 161.2, 162.6; HRMS (APCI) Calcd for $C_{17}H_{20}O_5N$ $(M+H)^+$ 318.1336, Found 318.1335.

**Diethyl 3-heptylisoxazole-4,5-dicarboxylate (2v-I)**. Colorless Oil (199.3 mg, 64% yield): IR (neat) 2929, 2857, 2362, 1729, 1098 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 0.88 (t, *J* = 6.7 Hz, 3H), 1.28-1.43 (m, 14H), 1.69 (quin, *J* = 7.6 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.45 (q, *J* = 7.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 14.0(3C), 22.6, 25.4, 27.7, 28.8, 29.1, 31.6, 61.7, 62.9, 114.0 156.9, 160.7, 160.9, 163.4; HRMS (APCI) Calcd for $C_{16}H_{26}O_5N$ $(M+H)^+$ 312.1805, Found 312.1802.

**Diethyl 3-cyclohexylisoxazole-4,5-dicarboxylate (2w-I)**. Colorless Oil (156.5 mg, 53% yield): IR (neat) 2932, 2855, 1730, 1266, 1100 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.21-1.42 (m, 3H), 1.37 (t, *J* = 7.3 Hz, 3H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.52-1.62 (m, 2H), 1.72-1.76 (m, 1H), 1.83-1.87 (m, 2H), 1.98-2.01 (m, 2H), 3.00 (tt, J = 11.8, 3.4 Hz, 1H), 4.37 (q, *J* = 7.3 Hz, 2H), 4.44 (q, *J* = 7.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 13.7(2C), 25.5, 25.9, 31.0, 35.6, 61.5, 62.6, 113.7, 156.7, 160.3, 160.7, 166.7; HRMS (APCI) Calcd for $C_{15}H_{22}O_5N$ $(M+H)^+$ 296.1492, Found 296.1492.

**Dimethyl 3-(4'-chlorophenyl)isoxazole-4,5-dicarboxylate (2a-II).**[8,9] Colorless Solid (223.5 mg, 76% yield): mp 80-81 °C (lit.,[9] mp 84-85 °C); IR (neat) 2962, 1726, 1445, 1268, 831 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 3.91 (s, 3H), 4.02 (s, 3H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 53.1, 53.4, 115.6, 125.3, 129.1, 129.5, 136.9, 156.3, 159.7, 160.3, 161.5; HRMS (APCI) Calcd for $C_{13}H_{11}O_5NCl$ $(M+H)^+$ 296.0320, Found 296.03180.

**Ethyl 3-(4'-chlorophenyl)isoxazole-5-carboxylate (2a-III)**.[10] Colorless Solid (186.5 mg, 60% yield): mp 129-130 °C; IR (neat) 1725, 1592, 1282, 827, 763 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 1.44 (t, *J* = 7.3 Hz, 3H), 4.47 (q, *J* = 7.3 Hz, 2H), 7.23 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 14.1, 62.4, 107.1, 125.0, 126.9, 128.3, 132.3, 156.6, 161.2, 162.0; HRMS (APCI) Calcd for $C_{12}H_{11}O_3NCl$ $(M+H)^+$ 252.0422, Found 252.0421.

**3-(4'-Chlorophenyl)-5-phenylisoxazole (2a-IV)**.[11,12] Colorless Solid (163.6 mg, 64% yield): mp 173-174 °C (lit.,[12] mp 177-179 °C); IR (neat) 1592, 1445, 1422, 1091, 766 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 6.81 (s, 1H), 7.44-7.52 (m, 5H), 7.79-7.85 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 97.3, 125.8, 127.2, 127.6, 128.0, 129.0, 129.2, 130.4, 136.0, 162.0, 170.7; HRMS (APCI) Calcd for $C_{15}H_{11}ONCl$ $(M+H)^+$ 256.0524, Found 256.0522.

**5-(3'-Chlorophenyl)-3-(4"-chlorophenyl)isoxazole (2a-V)**. Pale Yellow Solid (121.9 mg, 42% yield): mp 135-137 °C; IR (neat) 1559, 1426, 1103, 819, 795 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 6.84 (s, 1H), 7.44-7.45 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.70-7.75 (m, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.82-7.83 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 98.1, 123.9, 125.9, 127.3, 128.0, 128.8, 129.2, 130.3, 130.4, 135.1, 136.2, 162.1, 169.2; HRMS (APCI) Calcd for $C_{15}H_{10}ONCl_2$ $(M+H)^+$ 290.0134, Found 290.0131.

**3-(4'-Chlorophenyl)-5-(4"-methylphenyl)isoxazole (2a-VI)**. Colorless Solid (124.1 mg, 46% yield): mp 194-196 °C; IR (neat) 2919, 1491, 1428, 1092, 807 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 2.42 (s, 3H), 6.75 (s, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 21.5, 96.7, 124.5, 125.8, 127.7, 128.0, 129.2, 129.7, 135.9, 140.7, 161.9, 170.9; HRMS (APCI) Calcd for $C_{16}H_{13}ONCl$ $(M+H)^+$ 270.0680, Found 270.0790.

**3-(4'-Chlorophenyl)-5-(4"-methoxyphenyl)isoxazole (2a-VII)**. Colorless Solid (68.6 mg, 24% yield): mp 173-175 °C; IR (neat) 2934, 1611, 1496, 1251, 836 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 3.88 (s, 3H), 6.69 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 55.4, 95.9, 114.4, 120.1, 127.4, 127.7, 128.0, 129.1, 135.9, 161.2, 161.9, 170.7; HRMS (APCI) Calcd for $C_{16}H_{13}O_2NCl$ $(M+H)^+$ 286.0629, Found 286.0627.

**4-Acetyl-3-(4'-chlorophenyl)-5-phenylisoxazol (2a-VIII)**. Colorless Solid (125.5 mg, 42% yield): mp 107-108 °C; IR (neat) 1691, 1419, 1090, 944, 838 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 2.22 (s, 3H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.52-7.58 (m, 3H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.80 (dd, *J* = 8.0, 1.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 31.5, 117.0, 126.7, 126.8, 128.5, 128.9, 129.0, 130.2, 131.5, 136.5, 161.1, 170.9, 195.0; HRMS (APCI) Calcd for $C_{17}H_{13}O_2NCl$ $(M+H)^+$ 298.0629, Found 298.0627.

**3-(4'-Chlorophenyl)-5-(naphthalen-1"-yl)isoxazole (2a-IX)**. Yellow Solid (128.4 mg, 42% yield): mp 98-100 °C; IR (neat) 1559, 1426, 1080, 819, 795$cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 6.91 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.57-7.64 (m, 3H), 7.86-7.90 (m, 3H), 7.65 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 101.5, 125.0, 125.1, 125.3, 126.6, 127.6, 127.7, 127.8, 128.3, 128.8, 129.4, 130.4, 131.2, 133.9, 136.2, 161.9, 170.9; HRMS (APCI) Calcd for $C_{19}H_{13}ONCl$ $(M+H)^+$ 306.0680, Found 306.0679.

**3-(4'-Chlorophenyl)-5-(thiophen-3"-yl)isoxazole (2a-X)**. Colorless Solid (125.6 mg, 48% yield): mp 167-169 °C; IR (neat)1615, 1415, 1091, 787, 695 $cm^{-1}$; $^1$H-NMR ($CDCl_3$ : 400 MHz) $\delta$ = 6.66 (s, 1H), 7.43-7.47 (m, 4H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.84 (dd, *J* = 2.5, 1.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 97.3, 125.8, 127.2, 127.6, 128.0, 129.0, 129.2, 130.4, 136.0, 162.0, 170.7; HRMS (APCI) Calcd for $C_{13}H_9ONClS$ $(M+H)^+$ 262.0088, Found 262.0086.

**Supporting Information**: (see footnote on the first page of this article): Copies of the $^1$H NMR and $^{13}$C NMR spectra of all isoxazoles **2**.

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**Keywords**: Benzylic halide / Isoxazole / NMO / Oxone® / Acetylene

[1] (A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, "*Comprehensive Heterocyclic Chemistry III*", Elsevier, 2008.

[2] *Isoxazoles*: (a) D. Giomi, F. M. Cordero, F. Machetti, "*Five-membered Rings with Two Heteroatoms, each with their Fused Carbocyclic Derivatives*", p.365-p.485, Chap. 4.03, Vol. 4, Eds. by A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, "*Comprehensive Heterocyclic Chemistry III*", Elsevier, 2008. (b) G. Daidone, D. Raffa, B. Maggio, F. Plescia, V. M. C. Cutuli, N. G. Mangano, A. Caruso, A. *Arch. Pharm. Pharm. Med. Chem*., 1999, **332**, 50-54. (c) T. H. Al-Tel, R. A. Al-Qawasmeh, R. Zaarour, *Eur. J. Med. Chem*., 2011, **46**, 1874-1881. (d) W. Li, D. Hwang, D. Chen, C. Shen, C. Huang, T. Chen, C. Lin, Y. Chang, Y. Lo. H. Tseng, C. Lin, J. Song, H. Chen, S. Chen, S. Wu, C. Chen, *J. Med. Chem*., 2003, **46**, 1706-1715. (e) P. Ratcliffe, J. Maclean, L. Abernnethy, T. Clatkson, M. Dempster, A. M. Easson, D. Edwards, K. Everett, H. Feilden, P. Littlewood, D. McArthur, D. McGregor, H. MeLuskey, O. Nimz, L. A. Nisbet, R. Palin, H. Tracey, G. Walker, *Bioorg. Med. Chem. Lett*., 2011, **21**, 2559-2563.

[3] Recent review: (a) A. Sysak, B. Obminska-Mrukowicz, *Eur. J. Med. Chem*., 2017, **137**, 292-309. Recent reports: *for 1,3-dipolar cycloaddition of nitrile oxides* (b) A. Khutorianskyi, B. Chalyk, P. Borysko, A. Kondratiuk, P. K. Mykhailiuk, *Eur. J. Org. Chem*., 2017, 3935-3940. (c) K. S. Kadam, T. Gandhi, A. Gupte, A. K. Gangopadhyay, R. Sharma, *Synthesis*, 2016, **48**, 3996-4008. (d) A. Singhal, S. K. R. Parumala, A. Sharma, R. K. Peddinti, *Tetrahedron Lett*., 2016, **57**, 719-722. (e) J. Poh, C. Garcia-Ruiz, A. Zuniga, F. Meroni, D. C. Blakemore, D. L. Browne, S. V. Ley, *Org. Biomol. Chem*., 2016, **14**, 5983-5991.

(f) X. Zhou, X. Xu, Z. Shi, K. Liu, H. Gao, W. Li, *Org. Biomol. Chem*., 2016, **14,** 5246-5250. (g) A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev, V. V. Zhdankin, *Org. Lett.*, 2013, **15**, 4010-4013. (h) A. M. Jawalekar, E. Reubsaet, F. P. J. T. Rutjes, F. L. van Delft, *Chem. Commun.*, 2011, **47,** 3198-3200. *Others*; (i) G. R. Kumar, Y. K. Kumar, M. S. Reddy, *Chem. Commun*., 2016, **52**, 6589-6592. (j) B. Raghava, G. Parameshwarappa, A. Acharya, T. R. Swaroop, K. S. Rangappa, H. Ila, *Eur. J. Org. Chem*., 2014, 1882-1892. *With transition metals*; (k) P. Sau, S. K. Santra, A. Rakshit, B. K. Patel, *J. Org. Chem.*, 2017, **82**, 6358-6365. (l) T. D. Svejstrup, W. Zawodny, J. J. Douglas, D. Bidgeli, N. S. Sheikh, D. Leonori, *Chem. Commun*., 2016, **52**, 12302-12305. (m) K. N. Tu, J. J. Hirner, S. A. Blum, *Org. Lett*., 2016, **18**, 480-483. (n) M. D. R. B. Maiti K. Chanda, *Tetrahedron Lett*., 2016, **57**, 5514-5517. (o) P. Gao, H. Li, X. Hao, D. Jin, D. Chen, X. Yan, X. Wu, X. Song, X. Liu, Y. Liang, *Org. Lett*., 2014, **16**, 6298-6301.

[4] R. Harigae, K. Moriyama, H. Togo, *J. Org. Chem*., 2014, **79**, 2049-2058.

[5] Conversion of methylarenes into aromatic aldehydes with NBS and NMO: (a) M. Tabata, K. Moriyama, H. Togo, *Eur. J. Org. Chem*., 2014, 3402-3410. Conversion of benzylic chlorides into secondary benzylic amines with NMO and $NaBH_4$ under irradiation with ultrasonic cleaner (b) B. Khumraksa, W. Phakhodee, M. Pattarawarapan, *RSC Adv.*, 2014, ***4***, 20454-20458.

[6] (a) Oxidative α□chlorination of α,β□enones with KCl and Oxone® : P. K. Dieter, L. E. Nice, S. E. Velu, *Tetrahedron Lett*., 1996, **37**, 2377-2380. (b) oxidation of disulfides to thiosulfates with KCl and Oxone® : P. Natarajan, *Tetrahedron Lett*., 2015, **56**, 4131-4134. (c) light-induced oxidative chlorination of hydrocarbons with KCl and Oxone® : M. Zhao, W. Lu, *Org. Lett*., 2017, **19**, 4560-4563.

[7] (a) Formation of isoxazoles from oximes and alkynes with KCl and Oxone® : L. Han, B. Zhang, M. Zhu, J. Yan, *Tetrahedron Lett*., 2014, **55**, 2308-2311.

[8] A. Singhal, S. K. R. Parumala, A. Sharma, R. K. Peddinti, *Tetrahedron Lett*., **2016**, *57*, 719-722.

[9] S. Bhosale, S. Kurhade, U. V. Prasad, V. P. Palle, D. Bhuniya, *Tetrahedron Lett*. **2009**, *27*, 3948-3951.

[10] R. D. Jadhav, H. D. Mistry, H. Motiwala, K. S. Kadam, S. Kandre, A. Gupte, A. K. Gangopadhyay, R. Sharma, *J. Heterocyclic Chem.*, **2013**, *50*, 774-780.

[11] A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev, V. V. Zhdankin, *Org. Lett.* **2013**, *15*, 4010-4013.

[12] S. Tang, J. He, Y. Sun, L. He, X. She, *Org. Lett.*, **2009**, *11*, 3982-3985.

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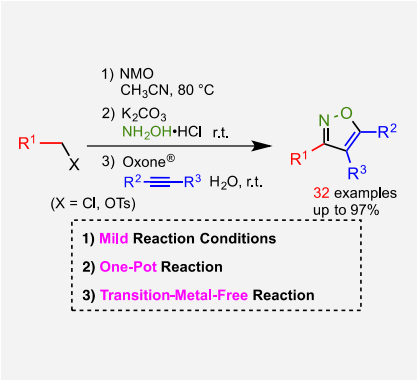
## Entry for the Table of Contents ((Please choose one layout.))

## Layout 1:

((Key Topic))

Benzylic chlorides were treated with NMO, and then $NH_2OH$•HCl, followed by the reaction with Oxone® in the presence of acetylenedicarboxylates to give the corresponding 3-arylisoxazole-4,5-dicarboxylates in good to moderate yields in one pot under transition-metal-free conditions.

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One-pot Preparation of 3-Arylisoxazole-4,5-dicarboxylates from Benzylic Chlorides via Aldehydes, Oximes, and Nitrile *N*-Oxides with Acetylenedicarboxylates

Keywords: Benzylic halide / Isoxazole / NMO / Oxone® / Acetylene

## Supporting Information

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