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Regioselective Cycloaddition

# Hypervalent Iodine(III) Reagent Mediated Regioselective Cycloaddition of Aldoximes with Enaminones

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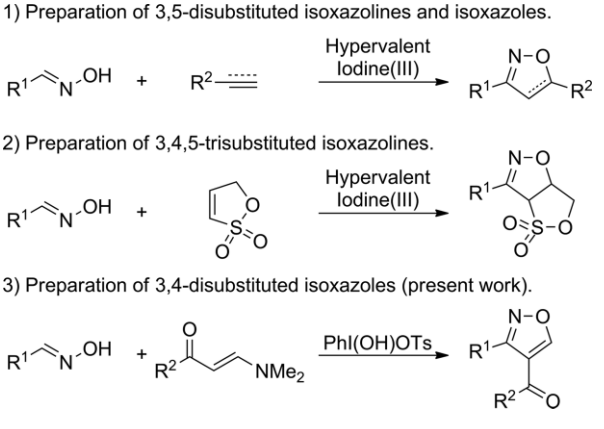
**Abstract:** An efficient oxidative cycloaddition of enaminones with nitrile oxides generated in situ from respective aldoximes using hypervalent iodine reagents has been developed. Reactions of various aldoximes with enaminones in the presence of [hydroxy(tosyloxy)iodo]benzene involved the regioselective cycloaddition reaction resulting in the formation of the 3,4-disubstituted isoxazoles in moderate to good yields. Structures of several isoxazole products were confirmed by a single X-ray crystallography.

## Introduction

1,3-Dipolar cycloaddition reaction is an important chemical transformation used for the construction of various heterocyclic compounds.[1] In particular, the oxidative cycloaddition of nitrile oxide species generated from aldoximes or related derivatives with unsaturated substrates represents an efficient procedures for preparation of isoxazoles or isoxazolines, which have nitrogen and oxygen atoms in a five-membered ring and are commonly found in natural products, medicinal drugs, and bioactive compounds.[2] The generation of nitrile oxide species from aldoximes or related derivatives under various synthetic conditions has been explored by many research groups.[2a,2c,2f,2h]

Organohypervalent iodine compounds have been known as broadly efficient and sustainable reagents, which have been widely used in the various oxidative reactions.[3] Numerous oxidative reactions or oxidative cycloaddition of aldoximes using hypervalent iodine(III) reagents have been explored.[4] Previously, some research groups including our group reported that reactions of aldoximes with unsaturated substrates using hypervalent iodine(III) reagents such as (diacetoxyiodo)benzene,[5] [bis(trifluoroacetoxy)iodo]benzene,[6] iodosylbenzene,[7] (dichloroiodo)benzene,[8] [hydroxy(tosyloxy)iodo]benzene,[9] or 2-[hydroxy(trifluoromethanesulfonyloxy)iodobenzoic acid[10] could allow the oxidative cycloaddition reactions to produce the corresponding isoxazolines, isoxazoles, or oxadiazoles. Recently, the catalytic hypervalent iodine(III) species mediated oxidative cycloaddition of aldoximes using alkenes or alkynes to form the isoxazoles or isoxazolines have been reported.[11] In previously reported cycloadditions of aldoximes with alkenes or alkynes using hypervalent iodine(III) species, most obtained compounds were 3,5-disubstituted products as major isomers (Scheme 1, Equation 1).[6a,6d,12] Previously, our research group reported that the oxidative cycloaddition of aldoximes using heterocyclic alkenes gave the corresponding 3,4,5-trisubstituted products in moderate to good yields (Scheme 1, Equation 2).[9b,11b] However, to the best of our knowledge, hypervalent iodine(III) reagent mediated regioselective synthesis of 3,4-disubstituted isoxazoles from aldoximes with unsaturated compounds has not been developed. On the other hand, enaminones are versatile unsaturated substrates used in the generation of heterocyclic compounds.[13] In particular, the useful cycloaddition strategies of various substrates using enaminones via the elimination of the amino groups have been reported.[13d,13f,13g,14] Herein, we report the hypervalent iodine(III) reagent mediated regioselective cycloaddition of aldoximes




Scheme 1. Hypervalent iodine(III) compounds mediated regioselective cycloaddition of aldoximes.

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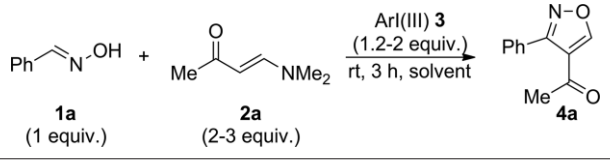
with enaminones to produce 3,4-disubstituted isoxazoles which structures are potentially important for bioactive compounds (Scheme 1, Equation 3).

## Results and Discussion

In the initial study of our experiment, we investigated the regioselective cycloaddition of benzaldoxime **1a** (1 equiv.) with enaminone **2a** (3 equiv.) using [hydroxy(tosyloxy)iodo]benzene, Koser's reagent, **3a** (2 equiv.) in various solvents at room temperature for 3 hours (Table 1, entries 1–7). We have found that dichloromethane is the best solvent for the formation of the desired isoxazole product **4a** (entry 1). The regioselectivity of the obtained structure **4a** was confirmed by X-ray crystallography (Figure 1, see in the Supporting Information for details). Screening of other iodine reagents **3** and Lewis acid, $AlCl_3$, instead of iodine reagent has indicated that Koser's reagent **3a** is an appropriate oxidant for this regioselective cycloaddition (entries 1, 8–14). Finally, decreasing the amount of enaminone **2a** or Koser's reagent **3a** led to a slightly suppressed product yield (entries 15 and 16).

Table 1. Optimization of regioselective cycloaddition of benzaldoxime **1a** with enaminone **2a** using iodine reagents **3**.[a]




| Entry[a] | Solvent | Iodine reagent **3** | **4a** Yield [%][b] |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | PhI(OH)OTs **3a** | 94 (92) |
| 2 | $CHCl_3$ | PhI(OH)OTs **3a** | 90 |
| 3 | $ClCH_2CH_2Cl$ | PhI(OH)OTs **3a** | 76[c] |
| 4 | Heptane | PhI(OH)OTs **3a** | 11[c] |
| 5 | MeCN | PhI(OH)OTs **3a** | 80[c] |
| 6 | AcOEt | PhI(OH)OTs **3a** | 32[c] |
| 7 | MeOH | PhI(OH)OTs **3a** | 91 |
| 8 | $CH_2Cl_2$ | $PhI(OAc)_2$ **3b** | 49[c] |
| 9 | $CH_2Cl_2$ | $PhI(OCOCF_3)_2$ **3c** | 8[c] |
| 10 | $CH_2Cl_2$ | PhIO **3d** | 16[c] |
| 11 | $CH_2Cl_2$ | KI **3e** | 0[c] |
| 12 | $CH_2Cl_2$ | $I_2$ **3f** | 0[c] |
| 13 | $CH_2Cl_2$ | PhI **3g** | 0[c] |
| 14 | $CH_2Cl_2$ | –[d] | 0[c] |
| 15[e] | $CH_2Cl_2$ | PhI(OH)OTs **3a** | 76[c] |
| 16[f] | $CH_2Cl_2$ | PhI(OH)OTs **3a** | 82 (67)[c] |

[a] Reaction conditions: benzaldoxime **1a** (1 equiv.), enaminone **2a** (2–3 equiv.), and iodine(III) reagent **3** (1.2–2 equiv.) in a solvent was stirred for 3 hours at room temperature. [b] Yields of product **4a** determined from $^1H$ NMR spectra of reaction mixtures are shown (number in parenthesis is isolated yield of **4a**). [c] Benzaldoxime **1a** was recovered from reaction mixture. [d] $AlCl_3$ was used instead of iodine reagent **3**. [e] 2 equiv. of **2a** was used. [f] 1.2 equiv. of **3a** was used.

In the next step, we investigated the reaction of various substituted aldoximes **1** with enaminone **2a** using optimized conditions leading to the formation of the corresponding 3,4-disubstituted isoxazole products **4** (Table 2). In general, the reaction of substituted benzaldoximes **1** with either electron-donating or electron-withdrawing groups under optimized conditions

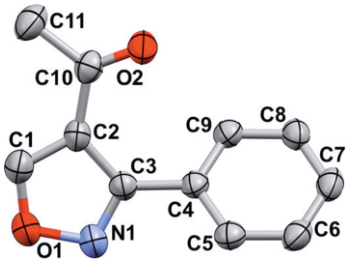
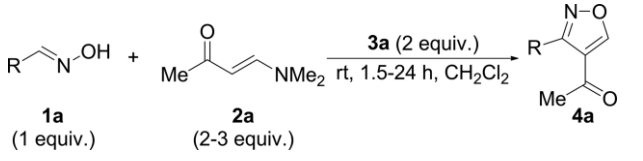



Figure 1. X-ray crystal structure of compound **4a**.

gave the respective desired products **4a–p** in moderate to good yields (entries 1–16). In the reaction of *ortho*-substituted benzaldoximes **1d** or **1i**, the desired corresponding isoxazoles **4d**, **4i** were obtained in moderate to good yields (entries 4, 9). However, performing the reaction of 4-(methylthio)benzaldoxime **1q** afforded the desired product **4q** in 34 % yield. During this reaction, competitive sulfide oxidation was probably involved in the reaction mixture.[15] The structures of isoxazoles **4p** and **4q** were established by X-ray crystallography (Figure 2, see in the Supporting Information for details). The reaction of enaminone **2a** with naphthyl aldoximes **1r, s** or heterocyclic aldoximes **1t, u** also proceeded efficiently producing the de-

Table 2. Preparation of 3,4-isoxazoles from various aldoximes **1** with **2a**.[a]




| Entry | **1,** R | Time [h] | **4** Yields [%][b] |
|---|---|---|---|
| 1 | **1a**, Ph | 3 | **4a**, 92 (85)[c] |
| 2 | **1b**, 4-$MeC_6H_4$ | 1.5 | **4b**, 74 |
| 3 | **1c**, 2,4-$Me_2C_6H_3$ | 24 | **4c**, 95 |
| 4 | **1d**, 2,6-$Me_2C_6H_3$ | 24 | **4d**, 59 |
| 5 | **1e**, 4-$MeOC_6H_4$ | 3 | **4e**, 72 |
| 6 | **1f**, 4-$ClC_6H_4$ | 3 | **4f**, 85 |
| 7 | **1g**, 3-$ClC_6H_4$ | 3 | **4g**, 97 |
| 8 | **1h**, 2-$ClC_6H_4$ | 6 | **4h**, 81 |
| 9 | **1i**, 2,6-$Cl_2C_6H_3$ | 3 | **4i**, 91 |
| 10 | **1g**, 4-$BrC_6H_4$ | 24 | **4j**, 90 |
| 11 | **1k**, 4-$NO_2C_6H_4$ | 24 | **4k**, 76 |
| 12 | **1l**, 3-$NO_2C_6H_4$ | 3 | **4l**, 98 |
| 13 | **1m**, 4-$NCC_6H_4$ | 24 | **4m**, 94 |
| 14 | **1n**, 4-$MeO_2CC_6H_4$ | 6.5 | **4n**, 82 |
| 15 | **1o**, 4-$AcOC_6H_4$ | 24 | **4o**, 81 |
| 16 | **1p**, 4-$PhC_6H_4$ | 3 | **4p**, 74 |
| 17 | **1q**, 4-$MeSC_6H_4$ | 24 | **4q**, 34 |
| 18 | **1r**, 2-Naphthyl | 24 | **4r**, 88 |
| 19 | **1s**, 1-Naphthyl | 24 | **4s**, 88 |
| 20 | **1t**, 5-Benzodioxole | 24 | **4t**, 83 |
| 21 | **1u**, 5-$NO_2$furyl | 24 | **4u**, 93 |
| 22 | **1v**, Propyl | 24 | **4v**, 46 |
| 23 | **1w**, $PhCH_2CH_2$ | 24 | **4w**, 56 |
| 24 | **1x**, (*E*)-PhCH=CH | 3 | **4x**, 62 |

[a] Reaction conditions: aldoxime **1** (1 equiv.), enaminone **2a** (3 equiv.), and Koser's reagent **3a** (2 equiv.) in a dichloromethane was stirred for 24 hours at room temperature. [b] Yields of isolated yield of **4**. [c] Large scale reaction: aldoxime **1a** (1 mmol; 1 equiv.), enaminone **2a** (3 mmol; 3 equiv.), and Koser's reagent **3a** (2 mmol, 2 equiv.) in a dichloromethane was stirred for 3 hours at room temperature.

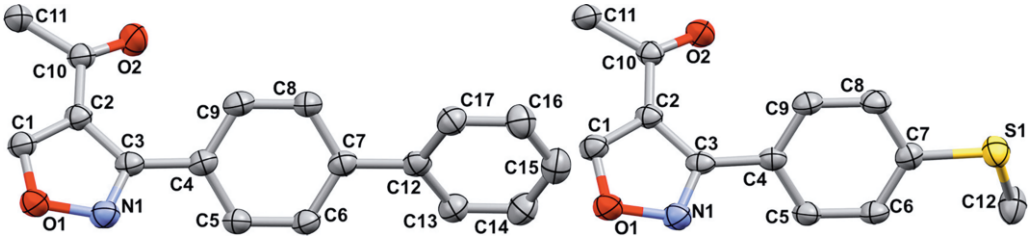
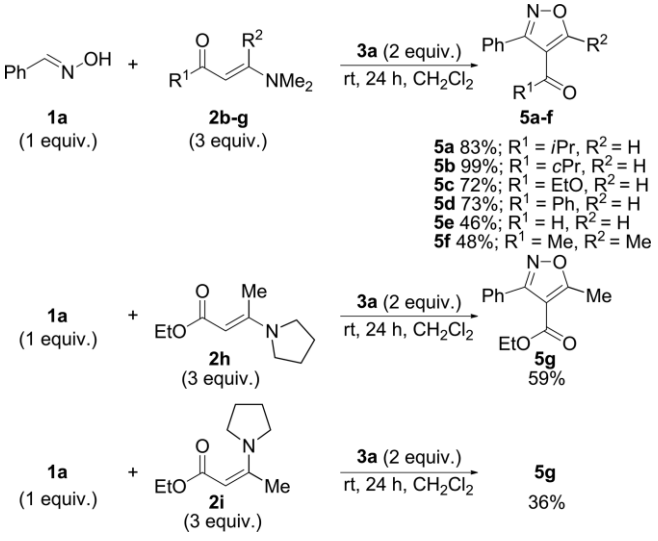



Figure 2. X-ray crystal structures of **4p** and **4q**.

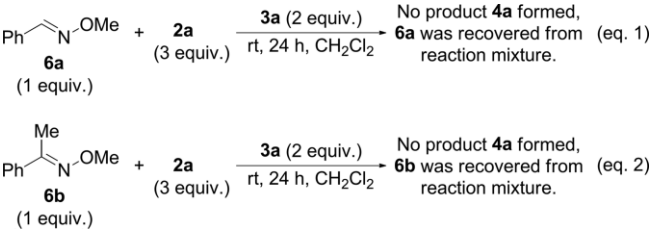
sired products **4r–u** in good yields (entries 18–21). When using the aliphatic aldoximes **1v, w** or cinnamaldoxime **1x** under optimized conditions, the corresponding isoxazoles **4v–x** were obtained in moderate yields (entries 22–24). In particular, the scale up reaction of **1a** could be also applicable under optimized conditions to give the desired product **4a** in 85 % yield.

Using the optimized conditions, we attempted to perform the regioselective cycloaddition of benzaldoxime **1a** with various enaminones **2b–g** (Scheme 2). In general, the reaction of enaminones **2b–e** with isopropyl, cyclopropyl, ethoxy, or phenyl group instead of methyl group gave the corresponding isoxazoles **5a-d** in good yields. When performing the reaction using enaminal **2f** under the same conditions, the desired product **5e** was received in 46 % yield. In the reaction of β-methyl-substituted enaminone **2g**, the respective isoxazole **5f** was obtained in 48 %. The reaction using (*E*)- or (*Z*)-β-methyl-substituted enaminones with cyclic amino group **2h**, **2i** also proceeded smoothly to give the 3,4,5-trisubstituted isoxazole **5g** in moderate yields.



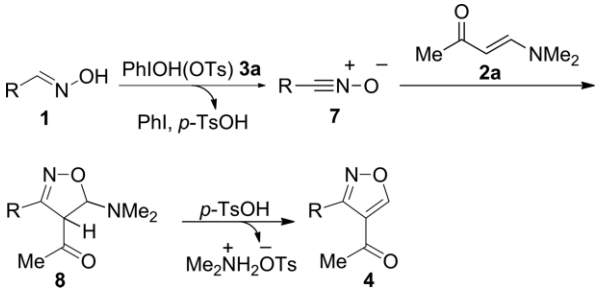

Scheme 2. Oxidative cycloaddition of **1a** using various enaminones **2b–i**.

For understanding the reaction mechanism, we performed several blank experiments. Based on previously reported reactions, nitrile oxide species were probably generated from the aldoxime and hypervalent iodine(III) reagent in the reaction mixture.[9b,11a,16] The reaction using protected benzaldoxime, *o*-methyl oxime **6a**, under optimized conditions did not proceed, and **6a** was recovered from reaction mixture (Scheme 3, Equation 1). This result indicated that the ligand exchange reaction between Koser's reagent and the hydroxy group of the aldoxime is important in this reaction. Next, the reaction using acetophenone oxime **6b** under optimized conditions did not proceed, and **6b** was recovered from the reaction mixture (Equation 2).[17] This result implies that the oxidation step of aldoxime is required in this cycloaddition.




Scheme 3. Control experiment.

Based on these observations and related literature reports of reactions of aldoxime species using hypervalent iodine(III) reagents, we suggested a regioselective cycloaddition reaction mechanism (Scheme 4).[9,16b] Firstly, the aldoxime **1** reacts with Koser's reagent **3a** to generate the nitrile oxide species **7** in the reaction mixture. Subsequently, the 1,3-dipolar reaction between nitrile oxide **7** and enaminone **2a** are involved in the reaction to produce the cyclized compound **8** followed by β-elimination of dimethylamine group to give the final 3,4-disubstituted isoxazoles **4**.[13g,14,18]




Scheme 4. Proposed reaction mechanism.

## Conclusions

In summary, we have developed the cycloaddition of aldoximes with enaminones using Koser's reagent. Our procedure produced the desired regioselective isoxazole compounds in moderate to good yields. This regioselective cycloaddition probably initially involved the 1,3-dipolar reaction between the gener-

ated nitrile oxide and enaminone followed by β-elimination of dialkylamine to afford the desired 3,4-disubstituted isoxazoles.

## Experimental Section

**General Experimental Remarks**: All reactions were performed under dry argon atmosphere with flame-dried glassware. Dichloromethane was distilled immediately prior to use. All commercial reagents were ACS reagent grade and used without further purification. All employed aldoximes and enaminones were commercially available from reagent companies. Melting points were determined in an open capillary tube with a Mel-temp II melting point apparatus. Infrared spectra were recorded on a PerkinElmer 1600 series FT-IR spectrophotometer. $^1$H NMR spectra were recorded on a Varian Inova 500 and 300 MHz NMR spectrometer; $^{13}$C NMR spectra were recorded on Varian Inova 500 and Varian 300 MHz NMR spectrometers at 125 and 75 MHz, respectively. Chemical shifts are reported in parts per million (ppm). $^1$H and $^{13}$C chemical shifts are referenced relative to the tetramethylsilane. X-ray crystal analysis was performed by Rigaku RAPID II XRD Image Plate using graphite-monochromated Mo-$K_\alpha$ radiation ($\lambda$ = 0.71073 Å) at 173 K. Please see the supporting information or the cif file for more detaied crystallography information.

**General Procedure for Preparation of isoxazoles:** Aldoxime **1** (0.250 mmol) and enaminone **2** (0.750 mmol) were added to a solution of Koser's reagent **3a** (196 mg, 0.500 mmol) in dichloromethane (2 mL). The reaction was stirred at room temperature for 1.5–24 h. After completion of the reaction, 5 % aqueous $Na_2S_2O_3$ (5 mL) was added, and the mixture was extracted with dichloromethane. The organic phase was dried with anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by column chromatography (hexane/ethyl acetate = 9:1 to 1:1) afforded analytically pure products **4** and **5**.

**1-(3-Phenylisoxazol-4-yl)ethan-1-one (4a):**[19] Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 43 mg (92 %) of product **4a**, isolated as a white solid: m.p. 78.0–78.8 °C (lit.[19] m.p. 83.0 °C); IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3366, 3127, 3091, 3006, 2923, 2852, 1685, 1560, 1445, 1387; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.00 (s, 1H), 7.72–7.65 (m, 2H), 7.54–7.42 (m, 3H), 2.44 (s, 3H); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 190.4, 163.4, 160.8, 130.3, 129.4, 128.4, 127.4, 120.9, 29.7; HRMS (APCI-positive ionization): calcd. for $C_{11}H_{10}NO_2$ ([M + H]$^+$): 188.0712, found 188.0727.

Single crystals of product **4a** suitable for X-ray crystallographic analysis were obtained by slow evaporation of dichloromethane solution. For details on crystal structure of compound **4a** see the CIF file in Supporting Information. CCDC 1942937.

**1-(3-(*p*-Tolyl)isoxazol-4-yl)ethan-1-one (4b):** Reaction of (*E*)-4-methylbenzaldehyde oxime **1b** (34 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 37 mg (74 %) of product **4b**, isolated as a white solid: m.p. 86.3–88.0 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3372, 3057, 2918, 2849, 1690, 1556, 1417, 1381; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.97 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 2.41 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 190.4, 163.3, 160.7, 140.4, 129.2, 129.0, 124.3, 120.8, 29.7, 21.4; HRMS (APCI-positive ionization): calcd. for $C_{12}H_{12}NO_2$ ([M + H]$^+$): 202.0868, found 202.0876.

**1-(3-(2,4-Dimethylphenyl)isoxazol-4-yl)ethan-1-one (4c):** Reaction of (*E*)-2,4-dimethylbenzaldehyde oxime **1c** (37 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 51 mg (95 %) of product **4c**, isolated as a white solid: m.p. 86.0–86.9 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3363, 3094, 3008, 2924, 2859, 1696, 1563, 1385, 1361; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.01 (s, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.13 (s, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 2.37 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.6, 162.7, 160.6, 139.9, 136.9, 133.2, 129.6, 126.5, 124.3, 122.2, 29.2, 21.3, 19.7; HRMS (APCI-positive ionization): calcd. for $C_{13}H_{14}NO_2$ ([M + H]$^+$): 216.1025, found 216.1036.

**1-(3-(2,6-Dimethylphenyl)isoxazol-4-yl)ethan-1-one (4d):** Reaction of 2,6-dimethylbenzaldehyde oxime **1d** (37 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 32 mg (59 %) of product **4d**, isolated as a white solid: m.p. 96.7–97.9 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3359, 3093, 2955, 2925, 2858, 1685, 1565, 1466, 1386; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.09 (s, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 2.13 (s, 3H), 2.09 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.6, 163.1, 159.7, 137.1, 129.6, 127.6, 127.2, 122.1, 28.7, 20.2; HRMS (APCI-positive ionization): calcd. for $C_{13}H_{14}NO_2$ ([M + H]$^+$): 216.1025, found 216.1032.

**1-(3-(4-Methoxyphenyl)isoxazol-4-yl)ethan-1-one (4e):** Reaction of (*E*)-4-methoxybenzaldehyde oxime **1e** (38 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 39 mg (72 %) of product **4e**, isolated as a white solid: m.p. 95.4–96.7 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3371, 3056, 2965, 2917, 2849, 1693, 1613, 1425, 1383, 1255, 1036; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.97 (s, 1H), 7.68 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 2.46 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 190.4, 163.4, 161.1, 160.3, 130.8, 120.6, 119.4, 113.7, 55.3, 29.7; HRMS (APCI-positive ionization): calcd. for $C_{12}H_{12}NO_3$ ([M + H]$^+$): 218.0817, found 218.0825.

**1-(3-(4-Chlorophenyl)isoxazol-4-yl)ethan-1-one (4f):**[20] Reaction of (*E*)-4-chlorobenzaldehyde oxime **1f** (39 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 47 mg (85 %) of product **4f**, isolated as a white solid: m.p. 111.7–112.1 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3345, 3113, 3077, 2923, 2856, 1691, 1577, 1413, 1383, 1095; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.01 (s, 1H), 7.68 (d. *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 2.49 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 190.0, 163.6, 159.9, 136.5, 130.8, 128.6, 125.8, 120.5, 29.7; HRMS (APCI-positive ionization): calcd. for $C_{11}H_9{}^{35}ClNO_2$ ([M + H]$^+$): 222.0322, found 222.0332.

**1-(3-(3-Chlorophenyl)isoxazol-4-yl)ethan-1-one (4g):** Reaction of (*E*)-3-chlorobenzaldehyde oxime **1g** (39 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 54 mg (97 %) of product **4g**, isolated as a white solid: m.p. 118.3–119.6 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3351, 3123, 3092, 2924, 2853, 1689, 1557, 1409, 1390, 1121; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.02 (s, 1H), 7.72 (d. *J* = 1.5 Hz, 1H), 7.60 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.49–7.45 (m, 1H), 7.42–7.37 (m, 1H), 2.48 (s, 3H); $^{13}$CNMR (75 MHz, $CDCl_3$): $\delta$ = 190.0, 163.7, 159.7, 134.2, 130.3, 129.6, 129.5, 129.1, 127.7, 120.6, 29.7; HRMS (APCI-positive ionization): calcd. for $C_{11}H_9{}^{35}ClNO_2$ ([M + H]$^+$): 222.0322, found 222.0333.

**1-(3-(2-Chlorophenyl)isoxazol-4-yl)ethan-1-one (4h):** Reaction of (*E*)-2-chlorobenzaldehyde oxime **1h** (39 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 45 mg (81 %) of product **4h**, isolated as a white solid: m.p. 62.1–62.6 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3365, 3139, 3095, 2924, 2854, 1685, 1563, 1437, 1387, 1118; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.01 (s, 1H), 7.55–7.34 (m, 4H), 2.34 (s, 3H);

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 189.9, 162.1, 158.9, 133.8, 131.2, 131.0, 129.7, 127.4, 126.8, 122.1, 28.9; HRMS (APCI-positive ionization): calcd. for $C_{11}H_9{}^{35}ClNO_2$ ([M + H]$^+$): 222.0322, found 222.0331.

**1-(3-(2,6-Dichlorophenyl)isoxazol-4-yl)ethan-1-one (4i):**[21] Reaction of (*E*)-2,6-dichlorobenzaldoxime **1i** (48 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 58 mg (91 %) of product **4i**, isolated as a white solid: m.p. 107.4–108.8 °C (lit.[21] m.p. 118–120 °C); IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3350, 3134, 3091, 3066, 2925, 2857, 1688, 1567, 1424, 1391, 1095; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.09 (s, 1H), 7.44 (d. *J* = 7.5 Hz, 1H), 7.41–7.36 (m, 2H), 2.35 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 189.4, 162.7, 156.8, 135.3, 131.5, 128.0, 127.1, 121.8, 28.8; HRMS (APCI-positive ionization): calcd. for $C_{11}H_8{}^{35}Cl_2NO_2$ ([M + H]$^+$): 255.9932, found 255.9945.

**1-(3-(4-Bromophenyl)isoxazol-4-yl)ethan-1-one (4j):** Reaction of (*E*)-4-bromobenzaldehyde oxime **1j** (50 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 60 mg (90 %) of product **4j**, isolated as a white solid: m.p. 111.5–112.1 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3348, 3111, 3082, 3068, 2925, 2854, 1692, 1575, 1408, 1380; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.02 (s, 1H), 7.64–7.58 (m, 4H), 2.49 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 190.3, 163.9, 160.2, 131.8, 131.2, 126.5, 125.1, 120.7, 29.9; HRMS (APCI-positive ionization): calcd. for $C_{11}H_9{}^{79}BrNO_2$ ([M + H]$^+$): 265.9817, found 265.9828.

**1-(3-(4-Nitrophenyl)isoxazol-4-yl)ethan-1-one (4k):**[21] Reaction of (*E*)-4-nitrobenzaldehyde **1k** (42 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 44 mg (76 %) of product **4k**, isolated as a white solid: m.p. 182.5–183.3 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3365, 3137, 3083, 3066, 2845, 1691, 1562, 1510, 1420, 1350, 856; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.08 (s, 1H), 8.33 (d, *J* = 9.5 Hz, 2H), 7.94 (d, *J* = 9.5 Hz, 2H), 2.56 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 189.8, 163.9, 159.2, 148.9, 133.7, 130.7, 123.4, 120.5, 29.7; HRMS (APCI-positive ionization): calcd. for $C_{11}H_9N_2O_4$ ([M + H]$^+$): 233.0562, found 233.0567.

**1-(3-(3-Nitrophenyl)isoxazol-4-yl)ethan-1-one (4l)**: Reaction of (*E*)-3-nitrobenzaldehyde oxime **1l** (42 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 57 mg (98 %) of product **4l**, isolated as a light yellow solid: m.p. 118.7–119.3 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3359, 3094, 2927, 2854, 1685, 1560, 1539, 1428, 1390, 1349, 861; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.11 (s, 1H), 8.65 (t, *J* = 1.5 Hz, 1H), 8.35 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.70–7.61 (m, 1H), 2.56 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 189.7, 163.9, 159.0, 147.9, 135.3, 129.2, 129.0, 124.8, 124.6, 120.2, 29.5; HRMS (APCI-positive ionization): calcd. for $C_{11}H_9N_2O_4$ ([M + H]$^+$): 233.0562, found 233.0576.

**4-(4-Acetylisoxazol-3-yl)benzonitrile (4m):** Reaction of (*E*)-4-(hydroxyamino)methyl) benzonitrile **1m** (37 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 50 mg (94 %) of product **4m**, isolated as a white solid: m.p. 181.3–181.7 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3370, 3134, 3090, 3057, 2922, 2232, 1689, 1577, 1421, 1386; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.08 (s, 1H), 7.87 (d, *J* = 7.1 Hz, 2H), 7.75 (d, *J* = 7.1 Hz, 2H), 2.54 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 189.8, 163.9, 159.4, 131.9, 130.2, 120.4, 118.3, 113.9, 29.6; HRMS (APCI-positive ionization): calcd. for $C_{12}H_9N_2O_2$ ([M + H]$^+$): 213.0664, found 213.0667.

**Methyl 4-(4-acetylisoxazol-3-yl)benzoate (4n):** Reaction of methyl (*E*)-4-((hydroxyimino)methyl) benzoate **1n** (45 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 50 mg (82 %) of product **4n**, isolated as a white solid: m.p. 116.2–117.4 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3371, 3093, 3005, 2916, 2849, 1705, 1689, 1559, 1413, 1119; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.06 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 3.94 (s, 3H), 2.49 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.0, 166.5, 163.8, 160.1, 131.8, 131.6, 129.5, 129.5, 120.7, 52.3, 29.7; HRMS (APCI-positive ionization): calcd. for $C_{13}H_{12}NO_4$ ([M + H]$^+$): 246.0766, found 246.0779.

**4-(4-Acetylisoxazol-3-yl)phenyl acetate (4o):** Reaction of (*E*)-4-((hydroxyimino)methyl)phenyl acetate **1o** (45 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 50 mg (81 %) of product **4o**, isolated as a white solid: m.p. 83.5–84.3 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3366, 3131, 3091, 2926, 2854, 1748, 1685, 1560, 1419, 1365, 1165, 1111; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.00 (s, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 2.47 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (300 MHz, $CDCl_3$): $\delta$ = 190.2, 169.1, 163.7, 160.0, 152.2, 130.8, 124.9, 121.6, 120.6, 29.7, 21.2; HRMS (APCI-positive ionization): calcd. for $C_{13}H_{12}NO_4$ ([M + H]$^+$): 246.0766, found 246.0774.

**1-(3-([1,1′-Biphenyl]-4-yl)isoxazol-4-yl)ethan-1-one (4p):** Reaction of (*E*)-([1,1′-biphenyl]-4-carbaldehyde oxime **1p** (49 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 49 mg (74 %) of product **4p**, isolated as a white solid: m.p. 146.8–147.7 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3353, 3126, 3083, 2926, 2856, 1692, 1572, 1446, 1411; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.00 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.50–7.42 (m, 1H), 7.37 (t, *J* = 6.9 Hz, 1H), 2.47 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 190.5, 163.7, 160.6, 143.2, 140.4, 130.0, 129.0, 127.9 127.3, 127.2, 126.3, 120.9, 29.9; HRMS (APCI-positive ionization): calcd. for $C_{17}H_{14}NO_2$ ([M + H]$^+$): 264.1025, found 264.1032.

Single crystals of product **4p** suitable for X-ray crystallographic analysis were obtained by slow evaporation of dichloromethane solution. For details on crystal structure of compound **4p** see the CIF file in Supporting Information. CCDC 1942938.

**1-(3-(4-(Methylthio)phenyl)isoxazol-4-yl)ethan-1-one (4q):** Reaction of (*E*)-4-(methylthio)benzaldehyde **1q** (42 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 20 mg (34 %) of product **4q**, isolated as a white solid: m.p. 93.1–94.8 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3363, 3099, 2924, 2854, 1685, 1573, 1411, 1379, 736; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.99 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 2.52 (s, 3H), 2.47 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.3, 163.5, 160.3, 141.8, 129.7, 125.6, 123.6, 120.7, 29.8, 15.2; HRMS (APCI-positive ionization): calcd. for $C_{12}H_{12}NO_2S$ ([M + H]$^+$): 234.0589, found 234.0592.

Single crystals of product **4q** suitable for X-ray crystallographic analysis were obtained by slow evaporation of dichloromethane solution. For details on crystal structure of compound **4q** see the CIF file in Supporting Information. CCDC 1942939.

**1-(3-(Naphthalen-2-yl)isoxazol-4-yl)ethan-1-one (4r):** Reaction of (*E*)-2-naphthaldehyde oxime **1r** (43 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 52 mg (88 %) of product, isolated as a white solid: m.p. 93.5–95.1 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3373, 3091, 3056, 2925, 2854, 1691, 1561, 1434, 1394, 862, 831, 822; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.00 (s, 1H), 8.26 (s, 1H), 7.94–7.89 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.57–7.48 (m, 2H), 2.43 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.3, 163.6, 160.7, 133.9, 132.8, 129.5, 128.6, 127.9, 127.7, 127.2, 126.5, 126.2, 124.7,

120.9, 29.7; HRMS (APCI-positive ionization): calcd. for $C_{15}H_{12}NO_2$ ([M + H]$^+$): 238.0868, found 238.0879.

**1-(3-(Naphthalen-1-yl)isoxazol-4-yl)ethan-1-one (4s):** Reaction of (*E*)-1-naphthaldehyde oxime **1s** (43 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 52 mg (88 %) of product **4s**, isolated as a white solid: m.p. 139.8–141.1 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3364, 3090, 3060, 2923, 2854, 1685, 1564, 1423, 1383, 803; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.11 (s, 1H), 8.13–7.97 (m, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.62–7.54 (m, 3H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.49–7.44 (m, 1H), 2.06 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.5, 162.0, 159.7, 133.4, 131.8, 130.5, 128.5, 128.1, 127.1, 126.4, 125.2. 125.0, 124.7, 123.0, 29.1; HRMS (APCI-positive ionization): calcd. for $C_{15}H_{12}NO_2$ ([M + H]$^+$): 238.0868, found 238.0869.

**1-(3-(Benzo[d][1,3]dioxol-5-yl)isoxazol-4-yl)ethan-1-one (4t):** Reaction of piperonaldoxime **1t** (41 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 48 mg (83 %) of product **4t**, isolated as a white solid: m.p. 133.2–133.6 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3339, 3091, 3025, 2908, 1673, 1562, 1466, 1397, 1260, 1242, 1150; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.97 (s, 1H), 7.25 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.19 (d, *J* = 1.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.03 (s, 2H), 2.47 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.4, 163.6, 160.3, 149.4, 147.6, 123.9, 120.8, 120.6, 109.8, 108.3, 101.5, 29.8; HRMS (APCI-positive ionization): calcd. for $C_{12}H_{10}NO_4$ ([M + H]$^+$): 232.0610, found 232.0626.

**1-(3-(5-Nitrofuran-2-yl)isoxazol-4-yl)ethan-1-one (4u):** Reaction of (*E*)-5-nitrofuran-2-carbaldehyde oxime **1u** (39 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 52 mg (93 %) of product **4u**, isolated as a yellow solid: m.p. 133.7–135.9 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3363, 3165, 3120, 2926, 2854, 1687, 1557, 1542, 1406, 1359, 1346; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.11 (s, 1H), 7.81 (d, *J* = 3.9 Hz, 1H), 7.42 (d, *J* = 3.9 Hz, 1H), 2.61 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 189.3, 164.2, 150.1, 143.9, 120.5, 118.2, 112.1, 29.6; HRMS (APCI-positive ionization): calcd. for $C_9H_7N_2O_5$ ([M + H]$^+$): 223.0355, found 223.0366.

**1-(3-Propylisoxazol-4-yl)ethan-1-one (4v):** Reaction of butyraldoxime **1v** (24 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 18 mg (46 %) of product **4v**, isolated as a clear oil; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3356, 3101, 2966, 2936, 2876, 1680, 1577, 1413, 1363; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.87 (s, 1H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.48 (s, 3H), 1.72 (sext, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.3, 162.0, 161.5, 119.9, 29.9, 28.8, 20.3, 13.3; HRMS (APCI-positive ionization): calcd. for $C_8H_{12}NO_2$ ([M + H]$^+$): 154.0868, found 154.0880.

**1-(3-Phenethylisoxazol-4-yl)ethan-1-one (4w):** Reaction of (*E*)-3-phenylpropanal oxime **1w** (37 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 30 mg (56 %) of product **4w**, isolated as a white solid: m.p. 52.8–53.9 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3353, 3104, 3064, 3028, 2934, 2865, 1685, 1578, 1412, 1363; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.85 (s, 1H), 7.33–7.25 (m, 4H), 7.23–7.18 (m, 1H), 3.24 (dd, *J* = 10.5 Hz, 8.3 Hz, 2H), 3.01 (dd, *J* = 10.5 Hz, 8.3 Hz, 2H), 2.48 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.8, 162.6, 161.4, 140.8, 128.5, 128.4, 126.2, 120.4, 33.6, 29.1, 27.6; HRMS (APCI-positive ionization): calcd. for $C_{13}H_{14}NO_2$ ([M + H]$^+$): 216.1025, found 216.1032.

**(E)-1-(3-Styrylisoxazol-4-yl)ethan-1-one (4x):** Reaction of *trans*-cinnamaldehyde oxime **1x** (37 mg, 0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) according to the general procedure afforded 33 mg (62 %) of product **4x**, isolated as a white solid: m.p. 94.9–96.3 °C; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3345, 3068, 3026, 2925, 2854, 1682, 1565, 1408, 1362, 854; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.91 (s, 1H), 7.68 (d, *J* = 16.8 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 16.8 Hz, 1H), 7.41–7.36 (m, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 2.52 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 190.9, 162.9, 158.2, 137.3, 135.9, 129.1, 128.8, 127.4, 120.0, 113.6, 29.4; HRMS (APCI-positive ionization): calcd. for $C_{13}H_{12}NO_2$ ([M + H]$^+$): 214.0808, found 214.0879.

**2-Methyl-1-(3-phenylisoxazol-4-yl)propan-1-one (5a):** Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and (*E*)-1-(dimethylamino)-4-methylpent-1-en-3-one **2b** (106 mg, 0.750 mmol) according to the general procedure afforded 45 mg (84 %) of product **5a**, isolated as a light yellow oil; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3361, 3090, 2974, 2934, 2875, 1688, 1558, 1444, 1387; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.98 (s, 1H), 7.67 (dd, *J* = 8.3 Hz, 1.8 Hz, 2H), 7.51–7.43 (m, 3H), 3.06 (sept, *J* = 7.0 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 197.7, 162.4, 161.3, 130.2, 129.3, 128.3, 127.5, 119.3, 39.9, 18.8; HRMS (APCI-positive ionization): calcd. for $C_{13}H_{14}NO_2$ ([M + H]$^+$): 216.1025, found 216.1032.

**Cyclopropyl(3-phenylisoxazol-4-yl)methanone (5b)**: Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and 1-cyclopropyl-3-(dimethylamino)-2-propen-1-one **2c** (104 mg, 0.750 mmol) according to the general procedure afforded 53 mg (99 %) of product **5b**, isolated as a yellow oil; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3337, 3090, 3011, 2926, 2854, 1685, 1557, 1448; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.06 (s, 1H), 7.72–7.67 (m, 2H), 7.51–7.43 (m, 3H), 2.18–2.11 (m, 1H), 1.23 (dt, *J* = 7.5 Hz, 3.5 Hz, 2H), 0.96 (dq, *J* = 8.0 Hz, 3.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 193.5, 162.6, 160.7, 130.2, 129.4, 128.3, 127.6, 121.5, 20.8, 12.1; HRMS (APCI-positive ionization): calcd. for $C_{14}H_{14}NO_2$ ([M + H]$^+$): 214.0868, found 214.0881.

**Ethyl-3-phenylisoxazole-4-carboxylate (5c):**[22] Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and ethyl-*N*,*N*-dimethylamino-acrylate **2d** (107 mg, 0.750 mmol) according to the general procedure afforded 42 mg (72 %) of product **5c**, isolated as a yellow oil; IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3450, 3066, 3101, 2984, 2940, 1719, 1565, 1448, 1387; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.01 (s, 1H), 7.77 (dd, *J* = 8.0 Hz, 2.0 Hz, 2H), 7.52–7.43 (m, 3H), 4.29 (q, *J* = 7.0 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1, 161.3, 160.9, 130.2, 129.5, 128.2, 127.3, 113.0, 61.1, 14,1; HRMS (APCI-positive ionization): calcd. for $C_{12}H_{12}NO_3$ ([M + H]$^+$): 218.0817, found 218.0827.

**3-Phenylisoxazole-4-carbaldehyde (5d):**[19] Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one **2e** (131 mg, 0.750 mmol) according to the general procedure afforded 45 mg (73 %) of product **5d**, isolated as a light yellow solid: m.p. 77.9–81.4 °C (lit.[22] m.p. 82–83 °C); IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3313, 3128, 3064, 2931, 1652, 1557, 1448, 1387; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.78 (s, 1H), 7.84 (dd, *J* = 8.3 Hz, 1.3 Hz, 2H), 7.68 (dd, *J* = 8.5 Hz, 1.5 Hz, 2H), 7.60 (t, *J* = 7.8 Hz, 1H) 7.49–7.38 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 187.5, 162.7, 161.5, 137.9, 133.6, 130.2, 129.4, 129.0, 128.8, 128.5, 127.4, 119.2.

**3-Phenylisoxazole-4-carbaldehyde (5e):**[23] Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and 3-(dimethylamino)-acrolein **2f** (74 mg, 0.750 mmol) according to the general procedure afforded 20 mg (46 %) of product **5e**, isolated as a white solid: m.p. 45.5–46.9 °C (lit.[23] m.p. 41–42 °C); IR (neat) cm$^{-1}$: $\tilde{\nu}$ = 3375, 3125, 3093, 2926, 2854, 2751, 1696, 1559, 1448, 1384; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 10.0 (s, 1H), 9.09 (s, 1H), 7.80 (dd, *J* = 7.5 Hz, 2.0 Hz, 2H), 7.57–7.50 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 182.7, 165.2, 160.5, 130.8, 129.1, 129.0, 126.7, 121.0; HRMS (APCI-positive ionization): calcd. for $C_{10}H_8NO_2$ ([M + H]$^+$): 174.0555, found 174.0573.

**1-(5-Methyl-3-phenylisoxazol-4-yl)ethan-1-one (5f):**[24] Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and (*E*)-4-(dimethylamino)pent-3-en-2-one **2g** (95 mg, 0.750 mmol) according to the general procedure afforded 24 mg (48 %) of product **5f**, isolated as a white solid: m.p. 57.9–58.7 °C (lit.[24] m.p. 61.3–61.7 °C); IR (neat) $cm^{-1}$: $\tilde{\nu}$ = 3345, 3004, 3065, 2927, 2854, 1683, 1570, 1409, 1360; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.53–7.47 (m, 5H), 2.71 (s, 3H), 2.09 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 193.3, 174.7, 161.9, 130.0, 129.1, 129.0, 128.7, 117.3, 30.6, 13.6; HRMS (APCI-positive ionization): calcd. for $C_{12}H_{12}NO_2$ ($[M + H]^+$): 202.0868, found 202.0879.

**Ethyl 5-methyl-3-phenylisoxazole-4-carboxylate (5g):**[25] Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and ethyl-(*E*)-3-(1-pyrrolindinyl)crotonate **2h** (137 mg, 0.750 mmol) according to the general procedure afforded 34 mg (59 %) of product **5g**, isolated as a white solid: m.p. 46.6–47.6 °C (lit.[25] m.p. 49–50 °C); IR (neat) $cm^{-1}$: $\tilde{\nu}$ = 3413, 3064, 2984, 2934, 2873, 1715, 1604, 1448, 1425, 1150; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.64–7.59 (m, 2H), 7.48–7.39 (m, 3H), 4.23 (q, *J* = 7.0 Hz, 2H), 2.73 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 175.8, 162.6, 162.0, 129.7, 129.4, 128.5, 127.9, 108.5, 60.7, 14.0, 13.6; HRMS (APCI-positive ionization): calcd. for $C_{13}H_{14}NO_3$ ($[M + H]^+$): 232.0974, found 232.0990.

**Ethyl 5-methyl-3-phenylisoxazole-4-carboxylate (5g):** Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and ethyl-(*Z*)-3-(1-pyrrolindinyl)crotonate **2i** (137 mg, 0.750 mmol) according to the general procedure afforded 21 mg (36 %) of product **5g**, isolated as a white solid.

**Large scale reaction for preparation of 1-(3-phenylisoxazol-4-yl)ethan-1-one (4a):** (*E*)-benzaldehyde oxime **1a** (121 mg, 1.0 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (339 mg, 3 mmol) were added to a solution of Koser's reagent (784 mg, 2 mmol) in dichloromethane (9 mL) and the reaction was stirred at room temperature for 3 h. After completion of the reaction, 5 % aqueous $Na_2S_2O_3$ (20 mL) was added, and the mixture was extracted with dichloromethane. The organic phase was dried with anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by column chromatography (hexane/ethyl acetate = 1:1) afforded 159 mg (85 %) of product **4a**.

CCDC 1942937 (for **4a**), CCDC 1942938 (for **4p**) and 1942939 (for **4q**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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[1] a) H. Feuer, (Eds.), *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis; Volume 2*, John Wiley & Sons, Inc. **2008**; b) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366–5412; c) H. Suga, K. Itoh, *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*, John Wiley & Sons, Inc. **2014**, pp. 175–204; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235–3285; e) L. Maiuolo, A. De Nino, *Targets Heterocycl. Syst.* **2015**, *19*, 299–345.

[2] a) F. Hu, M. Szostak, *Adv. Synth. Catal.* **2015**, *357*, 2583–2614; b) A. V. Galenko, A. F. Khlebnikov, M. S. Novikov, V. V. Pakalnis, N. V. Rostovskii, *Russ. Chem. Rev.* **2015**, *84*, 335–377; c) D. Rane, M. Sibi, *Curr. Org. Synth.* **2011**, *8*, 616–627; d) F. M. Cordero, D. Giomi, L. Lascialfari, *Prog. Heterocycl. Chem.* **2016**, *28*, 361–390; e) P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, D. Simoni, *Synthesis* **1987**, 857–869; f) S. Tilvi, K. S. Singh, *Curr. Org. Chem.* **2016**, *20*, 898–929; g) K. Kaur, V. Kumar, A. K. Sharma, G. K. Gupta, *Eur. J. Med. Chem.* **2014**, *77*, 121–133; h) S. Roscales, J. Plumet, *Org. Biomol. Chem.* **2018**, *16*, 8446–8461.

[3] a) V. V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Application of Polyvalent Iodine Compounds*, John Wiley & Sons Ltd, **2014**; b) T. Wirth (Ed.), *Top. Curr. Chem.* **2016**, *373*, 1–310; c) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435; d) G. K. Murphy, L. Racicot, M. S. Carle, *Asian J. Org. Chem.* **2018**, *7*, 837–851; e) D. P. Hari, P. Caramenti, J. Waser, *Acc. Chem. Res.* **2018**, *51*, 3212–3225; f) X. Wang, A. Studer, *Acc. Chem. Res.* **2017**, *50*, 1712–1724; g) A. Maity, D. C. Powers, *Synlett* **2019**, *30*, 257–262; h) A. Yoshimura, A. Saito, V. V. Zhdankin, *Chem. Eur. J.* **2018**, *24*, 15156–15166; i) K. Morimoto, T. Dohi, Y. Kita, *Synlett* **2017**, *28*, 1680–1694; j) T. Dohi, Y. Kita, *Curr. Org. Chem.* **2016**, *20*, 580–615; k) S. V. Kohlhepp, T. Gulder, *Chem. Soc. Rev.* **2016**, *45*, 6270–6288.

[4] a) A. Yoshimura, V. V. Zhdankin, *ARKIVOC* **2017**, *1*, 99–116; b) C. D. Turner, M. A. Ciufolini, *ARKIVOC* **2011**, *1*, 410–428; c) M. A. Ciufolini, *Can. J. Chem.* **2014**, *92*, 186–193; d) A. Kotali, E. Kotali, I. S. Lafazanis, P. A. Harris, *Adv. Org. Synth.* **2013**, *4*, 267–316; e) A. Kotali, E. Kotali, I. S. Lafazanis, P. A. Harris, *Curr. Org. Synth.* **2010**, *7*, 62–77.

[5] a) S. Maiti, P. Samanta, G. Biswas, D. Dhara, *ACS Omega* **2018**, *3*, 562–575; b) B. C. Sanders, F. Friscourt, P. A. Ledin, N. E. Mbua, S. Arumugam, J. Guo, T. J. Boltje, V. V. Popik, G.-J. Boons, *J. Am. Chem. Soc.* **2011**, *133*, 949–957.

[6] a) A. M. Jawalekar, E. Reubsaet, F. P. J. T. Rutjes, F. L. van Delft, *Chem. Commun.* **2011**, *47*, 3198–3200; b) R. Kumar, M. Kumar, O. Prakash, *Heteroat. Chem.* **2016**, *27*, 228–234; c) T. Balalas, C. Peperidou, D. J. Hadjipavlou-Litina, K. E. Litinas, *Synthesis* **2016**, *48*, 281–292; d) M. Kim, Y. S. Hwang, W. Cho, S. B. Park, *ACS Comb. Sci.* **2017**, *19*, 407–413; e) T. von Zons, L. Brokmann, J. Lippke, T. Preusse, M. Huelsmann, A. Schaate, P. Behrens, A. Godt, *Inorg. Chem.* **2018**, *57*, 3348–3359.

[7] a) S. Tanaka, M. Ito, K. Kishikawa, S. Kohmoto, M. Yamamoto, *Nippon Kagaku Kaishi* **2002**, 471–473; b) G. Pal, S. Paul, P. P. Ghosh, A. R. Das, *RSC Adv.* **2014**, *4*, 8300–8307.

[8] A. S. Radhakrishna, K. Sivaprakash, B. B. Singh, *Synth. Commun.* **1991**, *21*, 1625–1629.

[9] a) M. J. Raihan, V. Kavala, C.-W. Kuo, B. R. Raju, C.-F. Yao, *Green Chem.* **2010**, *12*, 1090–1096; b) A. Yoshimura, K. C. Nguyen, G. T. Rohde, P. S. Postnikov, M. S. Yusubov, V. V. Zhdankin, *J. Org. Chem.* **2017**, *82*, 11742–11751.

[10] a) A. Yoshimura, K. C. Nguyen, S. C. Klasen, A. Saito, V. N. Nemykin, V. V. Zhdankin, *Chem. Commun.* **2015**, *51*, 7835–7838; b) A. Yoshimura, K. C. Nguyen, S. C. Klasen, P. S. Postnikov, M. S. Yusubov, A. Saito, V. N. Nemykin, V. V. Zhdankin, *Asian J. Org. Chem.* **2016**, *5*, 1128–1133.

[11] a) 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; b) A. Yoshimura, K. C. Nguyen, G. T. Rohde, A. Saito, M. S. Yusubov, V. V. Zhdankin, *Adv. Synth. Catal.* **2016**, *358*, 2340–2344; c) C. Xiang, T. Li, J. Yan, *Synth. Commun.* **2014**, *44*, 682–688; d) L. Han, B. Zhang, C. Xiang, J. Yan, *Synthesis* **2014**, *46*, 503–509.

[12] a) A. Singhal, S. K. R. Parumala, A. Sharma, R. K. Peddinti, *Tetrahedron Lett.* **2016**, *57*, 719–722; b) B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh, M. A. Ciufolini, *Org. Lett.* **2009**, *11*, 1539–1542.

[13] a) L. Fu, J.-P. Wan, *Asian J. Org. Chem.* **2019**, *8*, 767–776; b) Y. Guo, G. Wang, L. Wei, J.-P. Wan, *J. Org. Chem.* **2019**, *84*, 2984–2990; c) S. Cao, Y. Liu, C. Hu, C. Wen, J.-P. Wan, *ChemCatChem* **2018**, *10*, 5021–5025; d) L. Yang, L. Wei, J.-P. Wan, *Chem. Commun.* **2018**, *54*, 7475–7478; e) A.-Z. A. Elassar, A. A. El-Khair, *Tetrahedron* **2003**, *59*, 8463–8480; f) S. Zhu, S. Shi, S. W. Gerritz, *Tetrahedron Lett.* **2011**, *52*, 4001–4004; g) H. Xu, G.-P. Fan, Z. Liu, G.-W. Wang, *Tetrahedron* **2018**, *74*, 6607–6611.

[14] B. A. Chalyk, A. S. Sosedko, D. M. Volochnyuk, A. A. Tolmachev, K. S. Gavrilenko, O. S. Liashuk, O. O. Grygorenko, *Org. Biomol. Chem.* **2018**, *16*, 9152–9164.

 

[15] a) B. Yu, C.-X. Guo, C.-L. Zhong, Z.-F. Diao, L.-N. He, *Tetrahedron Lett.* **2014**, *55*, 1818–1821; b) M. Xia, Z.-C. Chen, *Synth. Commun.* **1997**, *27*, 1315–1320.

[16] a) A. Nakamura, H. Kanou, J. Tanaka, A. Imamiya, T. Maegawa, Y. Miki, *Org. Biomol. Chem.* **2018**, *16*, 541–544; b) H. Ghosh, B. K. Patel, *Org. Biomol. Chem.* **2010**, *8*, 384–390; c) R. D. Jadhav, H. D. Mistry, H. Motiwala, K. S. Kadam, S. Kandre, A. Gupte, A. K. Gangopadhyay, R. Sharma, *J. Heterocycl. Chem.* **2013**, *50*, 774–780.

[17] R. Oishi, K. Segi, H. Hamamoto, A. Nakamura, T. Maegawa, Y. Miki, *Synlett* **2018**, *29*, 1465–1468.

[18] Q.-f. Jia, P. M. S. Benjamin, J. Huang, Z. Du, X. Zheng, K. Zhang, A. H. Conney, J. Wang, *Synlett* **2013**, *24*, 79–84.

[19] A. Corsaro, U. Chiacchio, G. Perrini, P. Caramella, F. Marinone Albini, *J. Heterocycl. Chem.* **1989**, *26*, 1691–1699.

[20] J. N. Kim, E. K. Ryu, *Heterocycles* **1990**, *31*, 633–670.

[21] G. Adembri, A. Di Tommaso, L. R. Lampariello, M. Scotton, *J. Heterocycl. Chem.* **1988**, *25*, 1621–1625.

[22] J. Kurkowska, I. Zadrozna, *J. Chem. Res. Synop.* **2003**, 254–255.

[23] J. A. Burkhard, B. H. Tchitchanov, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 5379–5382; *Angew. Chem.* **2011**, *50*, 5379–5382.

[24] K. Harada, E. Kaji, S. Zen, *Nippon Kagaku Kaishi* **1981**, 1195–1198.

[25] K. Ohta, J. Iwaoka, Y. Kamijo, M. Okada, Y. Nomura, *Nippon Kagaku Kaishi* **1989**, 1593–1600.

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