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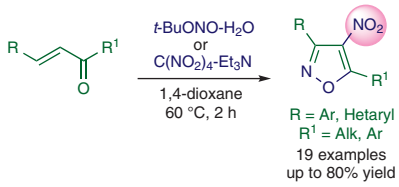
Synthesis of 4-Nitroisoxazoles via NO/NO_2-Mediated Heterocyclization of Aryl-Substituted α,β-Unsaturated Ketones

Dmitry A. Vasilenko[a]
Kirill S. Sadovnikov[a]
Kseniya N. Sedenkova[a,b]
Anastasiya V. Kurova[a]
Yuri K. Grishin[a]
Tamara S. Kuznetsova[a]
Victor B. Rybakov[a]
Yulia A. Volkova[a,c]
Elena B. Averina[*a,b]

[a] Department of Chemistry, Lomonosov Moscow State University, Leninskie Gory 1 bd. 3, Moscow 119991, Russian Federation
elaver@med.chem.msu.ru
[b] Institute of Physiologically Active Compounds, Severny Proezd 1, Chernogolovka, Moscow Region 142432, Russian Federation
[c] N.D. Zelinsky Institute of Organic Chemistry RAS, Leninsky Prospect, 47, Moscow 119991, Russian Federation



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Abstract A straightforward approach for the synthesis of 4-nitroisoxazoles has been developed via heterocyclization of aryl/hetaryl-substituted α,β-unsaturated ketones upon treatment with tetranitromethane-triethylamine (TNM-TEA) complex or *t*-BuONO. This strategy features high efficiency and wide substrate tolerance under simple reaction conditions.

Key words 4-nitroisoxazoles, alkenes, ketones, heterocycles, ring closure, *tert*-butyl nitrite, heterocyclization, tetranitromethane

Isoxazoles possess a variety of applications both as versatile building blocks in organic synthesis[1] and as the compounds with remarkably diverse bioactivity.[2] Isoxazole moiety is present in natural psychoactive molecules such as AMPA, muscimol, and ibotenic acid. Synthetic derivatives of isoxazole are known as marketed antibiotics,[3] anticonvulsants,[4] antipsychotics,[5] antidepressants,[6] anti-inflammatory,[7] and antirheumatic[8] drugs (Figure 1). A variety of bioactive isoxazoles, including regulators of immune functions,[9] cognitive enhancers,[10] antitumor agents,[11] antiviral agents,[12] various glutamate[13] and GABA receptors[14] ligands, inhibitors of apoptosis,[15] and antifungals[16] have been found, making these compounds the object of continued interest for medicinal chemistry.

Among various nitro-substituted isoxazoles the chemistry of 4-nitro regioisomers has attracted a lot of attention of chemists in the past few decades.[17] Particularly, 5-alkyl-

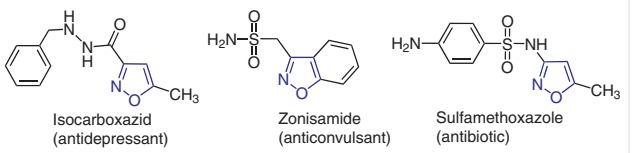

Figure 1 Examples of isoxazole-containing marketed drugs

4-nitroisoxazoles have broad applicability as nucleophiles in enantioselective synthesis of complex isoxazole containing structures.[18] The products of condensation of 5-methyl-4-nitroisoxazoles with carbonyl compounds – 4-nitro-5-styrylisoxazoles – were employed in catalytic asymmetric processes such as Sharpless dihydroxylation,[19] aza-Diels–Alder reaction,[20] 1,3-dipolar cycloaddition,[21] Michael addition,[22] and domino Michael/cyclization reactions.[23]

The synthesis of the 4-nitroisoxazoles can be accomplished via four major approaches.[24] The first one, the direct nitration of isoxazoles, not substituted at position 4, is the best-known method for the synthesis of 4-nitroisoxazoles, though it lacks regioselectivity when an isoxazole contains a (het)aryl moiety. The second method is ring-closure, involving α-nitroketones or their oximes and usually used for the synthesis of 3,5-diaryl-substituted 4-nitroisoxazoles. The 1,3-dipolar cycloaddition of nitrile oxides to nitroalkenes and heterocyclization of acetylene derivatives under the treatment with sodium nitrite have also found their application, though limited by the affordability of starting compounds.

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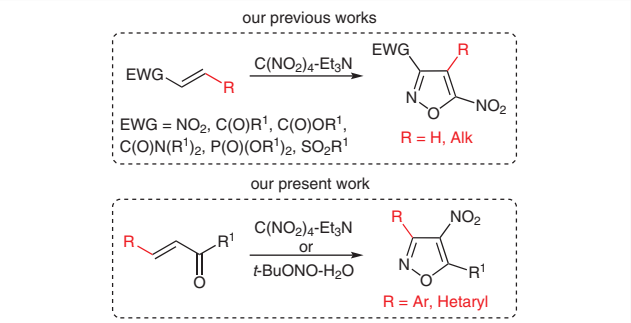
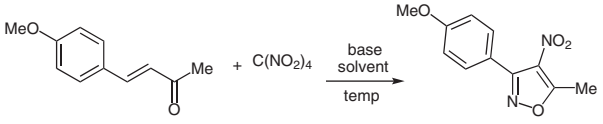
Taking into account the topicality of investigations in chemistry of 4-nitroisoxazoles, the elaboration of novel preparative approaches to these heterocycles starting from available compounds remains highly relevant.

Previously we have elaborated a novel preparative method for the synthesis of functionalized 5-nitroisoxazoles via the reaction of tetranitromethane (TNM) with electrophilic alkenes in the presence of triethylamine (TEA).[25] Now we have found that application of the same reaction conditions to aryl substituted α,β-unsaturated ketones afforded exclusively 4-nitroisoxazoles (Scheme 1). Brief optimization of the heterocyclization of model alkene **1a** upon treatment with TNM-TEA complex showed that previously used conditions (Table 1, entry 3)[25d] were optimal, while the change of the solvent or base reduced the yield of 4-nitroisoxazole **2a** (Table 1).



Scheme 1 Varied reactions of electrophilic alkenes with nitration/nitrosation reagents

Table 1 Optimization of the Conditions for the Reaction of **1a** with TNM[a]



1a **2a**

Entry	Base	Solvent	Temp (°C)	Yield (%)[b]
1	pyridine	1,4-dioxane	80	0
2	Et_3N	1,4-dioxane	80	52
3	**Et_3N**	**1,4-dioxane**	**60**	**76**
4	Et_3N	1,4-dioxane	20	0
5	Et_3N	CH_2Cl_2	40	0

[a] The reaction was carried out using 0.5 mmol of **1a**, 1.25 mmol TNM, and 1 mmol of a base in 2 mL of a solvent under argon atmosphere.
[b] Isolated yields after chromatographic purification.

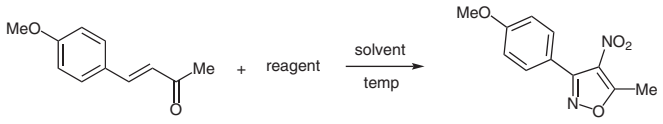
Studying the mechanistic aspects of this reaction we revealed that heterocyclization of model alkene **1a** also proceeded using $NaNO_2$/AcOH system or *t*-BuONO in the presence of water. In this connection, the reaction optimization was carried out for these reagents, by varying their amounts, solvents, and the reaction temperature (Table 2). We initiated our optimization studies by treating alkene **1a** with $NaNO_2$ (10 equiv) in a mixture of AcOH and 1,4-dioxane at 60 °C for 2 hours (Table 2, entry 1). Under these reaction conditions only traces of the isoxazole **2a** were observed. By varying the reaction temperature or the number of $NaNO_2$ equivalents the yield of **2a** was slightly affected (entries 1–5). Only 20% conversion of alkene **1a** to isoxazole **2a** has been achieved using $NaNO_2$/AcOH as a reagent of heterocyclization (entry 2), and after four-fold re-entry of the alkene **1a** in the reaction 80% conversion of the starting material has been achieved. It is likely that low conversion of the unsaturated ketone **1a** is due to the proceeding of the reaction in heterophase conditions.

The use of *t*-BuONO (20 equiv) in the presence of water (3 mL) proved to be more effective compared to $NaNO_2$/AcOH system (Table 2, entry 6). In these conditions, 55% conversion of alkene **1a** into the target heterocycle **2a** took place. To improve the efficiency of heterocyclization different co-solvents, such as EtOH, EtOAc, THF, MeCN, 1,4-dioxane, were tested (entries 7–11,13), and 1,4-dioxane has been found to be the most preferred additional solvent. After screening the reaction temperature, we found that heating at 60 °C is optimal for heterocyclization (entries 13–16). It was found that the number of *t*-BuONO equivalents, its concentration, and the water-1,4-dioxane ratio also affect the efficiency of heterocyclization (entries 17–25).

The complete conversion of **1a** into isoxazole **2a** was achieved using *t*-BuONO (10 equiv) in a solution in 1,3-dioxane-water (0.25 mL/0.75 mL) at 60 °C for 2 hours (Table 2, entry 24). In these conditions, 4-nitroisoxazole **2a** was obtained in 78% isolated yield.

With the optimal conditions of heterocyclization in hand, we investigated the scope of α,β-unsaturated ketones bearing aryl/hetaryl substituents. Starting alkenes **1a–r** were easily available either via condensation of methyl ketones with the corresponding aldehydes or by Wittig reaction. As shown in Scheme 2, both procedures (A and B) permitted to achieve close results. The electronic nature of substituents in aromatic ring had slight effect on the reactivity of α,β-unsaturated ketones **1a–n**, although electron-donating groups in aryl moiety, in principle, were more favorable for the heterocyclization (**1a**,**d–f**) than electron-withdrawing ones, such as CHO (**1i**) or NO_2 (**1j**). When polyaromatic naphthalene and biphenyl substrates were employed, the desired isoxazoles **2k** and **2l** were obtained in 55% and 47% yield, respectively. Heteroaryl-substituted α,β-unsaturated ketones were also investigated giving good isolated yields of isoxazoles **2m**,**n**. However, the influence of steric hindrance was more pronounced. For example, the heterocyclization of ketone **1c** bearing bulky *ortho*-substituted aromatic ring upon the treatment with TNM-Et_3N resulted in complex mixture of oxidation side-products, the major of which was 2-methoxybenzaldehyde. Target isox-

Table 2 Optimization of the Conditions for the Reaction of **1a** with $NaNO_2$ or *t*-BuONO[a]



1a **2a**

Entry	Reagent (equiv)	Solvent	Temp (°C)	Conversion of **1a** (%)[b,c](isolated yield, %)[d]
1	$NaNO_2$ (10)	AcOH/1,4-dioxane (5 mL/5 mL)	60	traces
2	$NaNO_2$ (10)	AcOH/1,4-dioxane (5 mL/5 mL)	80	20 (15)
3	$NaNO_2$ (10)	AcOH/1,4-dioxane (5 mL/5 mL)	100	0
4	$NaNO_2$ (20)	AcOH/1,4-dioxane (5 mL/5 mL)	80	21 (15)
5	$NaNO_2$ (5)	AcOH/1,4-dioxane (5 mL/5 mL)	80	12 (–)
6	*t*-BuONO (20)	H_2O (3 mL)	60	55 (50)
7	*t*-BuONO (20)	EtOH/H_2O (3 mL/3 mL)	60	0
8	*t*-BuONO (20)	EtOAc/H_2O (3 mL/3 mL)	60	32 (25)
9	*t*-BuONO (20)	AcOH/H_2O (3 mL/3 mL)	60	79 (50)
10	*t*-BuONO (20)	THF/H_2O (3 mL/3 mL)	60	53 (45)
11	*t*-BuONO (20)	MeCN/H_2O (3 mL/3 mL)	60	74 (50)
12	*t*-BuONO (20)	1,4-dioxane (3 mL)	60	traces
13	*t*-BuONO (20)	1,4-dioxane/H_2O (3 mL/3 mL)	60	85 (55)
14	*t*-BuONO (20)	1,4-dioxane/H_2O (3 mL/3 mL)	20	30 (2)
15	*t*-BuONO (20)	1,4-dioxane/H_2O (3 mL/3 mL)	40	38 (18)
16	*t*-BuONO (20)	1,4-dioxane/H_2O (3 mL/3 mL)	80	86 (50)
17	*t*-BuONO (20)	1,4-dioxane/H_2O (2 mL/3 mL)	60	84 (54)
18	*t*-BuONO (20)	1,4-dioxane/H_2O (1 mL/3 mL)	60	85 (60)
19	*t*-BuONO (20)	1,4-dioxane/H_2O (0.5 mL/3 mL)	60	84 (62)
20	*t*-BuONO (20)	1,4-dioxane/H_2O (1.5 mL/1.5 mL)	60	95 (66)
21	*t*-BuONO (20)	1,4-dioxane/H_2O (0.5 mL/1.5 mL)	60	100 (70)
22	*t*-BuONO (10)	1,4-dioxane/H_2O (3 mL/3 mL)	60	75 (61)
23	*t*-BuONO (10)	1,4-dioxane/H_2O (0.75 mL/0.75 mL)	60	100 (76)
24	***t*-BuONO (10)**	**1,4-dioxane/H_2O (0.25 mL/0.75 mL)**	**60**	**100 (78)**
25	*t*-BuONO (5)	1,4-dioxane/H_2O (0.25 mL /0.75 mL)	60	76 (60)

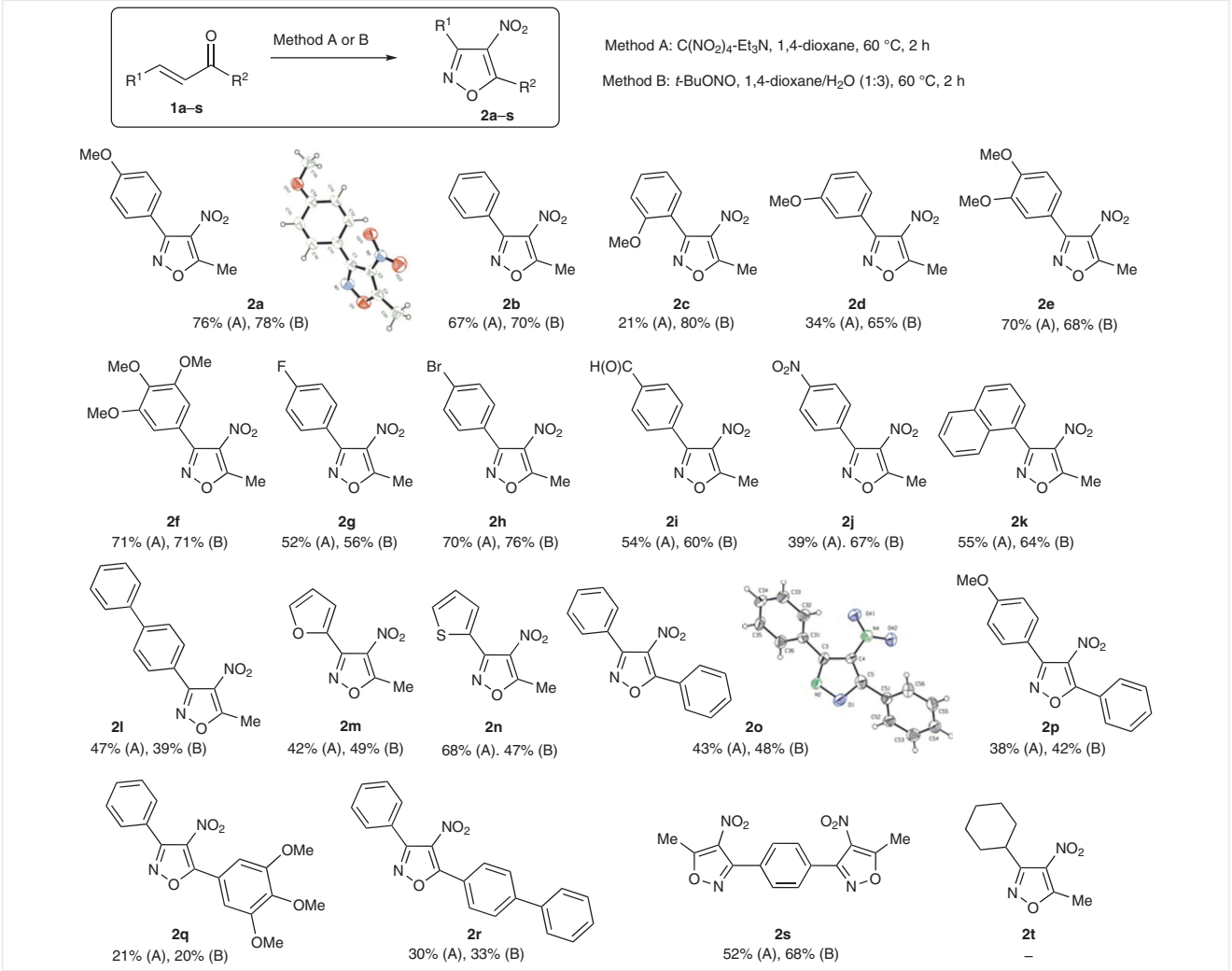
[a] The reaction was carried out using 0.5 mmol of **1a** under argon atmosphere.
[b] Conversion of **1a** into **2a** was estimated via ^1H NMR spectra.
[c] The formation of 10–20% 4-methoxybenzaldehyde as a by-product was observed when using *t*-BuONO as the reagent.
[d] Isolated yields after chromatographic purification.

azole **2c** was isolated from this mixture in poor yield (21%), while the application of *t*-BuONO permitted to avoid the formation of side-products and to isolate **2c** in 80% yield.

To probe the synthetic utility of our approaches to 4-nitroisoxazoles, diaryl-substituted vinyl ketones **1o–r** were used in heterocyclization. As the result, a series of 3,5-diaryl-4-nitroisoxazoles **2o–r** were obtained in moderate yields. Also it was demonstrated that the reaction can be exploited to the synthesis of bis(isoxazole) **2s**, which can be interesting as a precursor of bivalent ligands with increased bioactivities.[26]

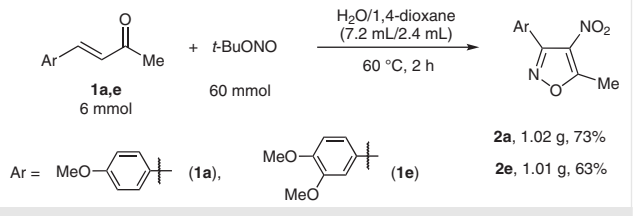
The structures of the obtained 4-nitroisoxazoles were additionally confirmed by X-ray diffraction analysis on the example of compounds **2a** and **2o** (see Supporting Information).

As expected, cyclohexyl-substituted alkene **1t** was not involved in heterocyclization upon treatment with either TNM-TEA or *t*-BuONO-H_2O, that additionally confirms the demand for aryl substituent in β-position of the double bond for this process.



Scheme 2 Synthesis of 4-nitroisoxazoles **2a–s**

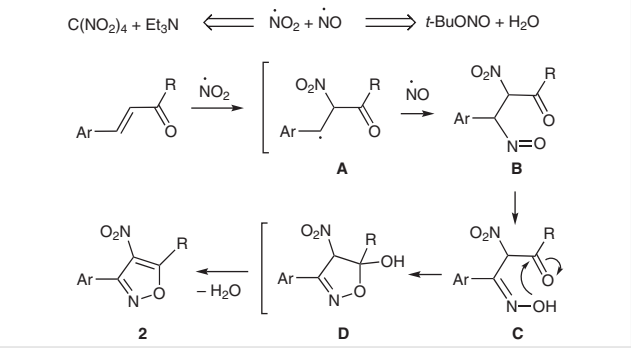
To demonstrate the practical utility of our synthetic method gram-scale synthesis of 4-nitroisoxazoles (6 mmol **1a** or **1e**) was carried out. In standard reaction conditions, heterocycles **2a** and **2e** were obtained in 73% and 64% isolated yield, respectively (Scheme 3).



Scheme 3 Gram-scale preparation of **2a** and **2e**

A putative mechanism is outlined in Scheme 4. We suppose that heterocyclization of α,β-unsaturated ketone in both procedures (A and B) includes a radical pathway with participation of NO/NO_2 radicals. It is described that thermal decomposition of TNM leads to the complex mixture of products containing NO/NO_2 radicals.[27] The possibility of homolytic TNM nitration of aromatic hydrocarbons and nucleophilic double bonds of alkenes is well known and reviewed.[27a,b] Also, there are evidences in the literature that polynitromethanes may produce nitrosation agent(s) in the presence of nucleophiles.[27a,b,28] At the same time, *t*-BuONO can be employed as a source of NO and NO_2 radicals, which are formed in aerobic thermal homolysis or hydrolysis.[29] The heterocyclization of unsaturated ketone is initiated by the attack of NO_2-radical to α-carbon of double bond and generation of the stable benzyl radical **A**. Subsequent nitrogen monoxide trapping leads to the formation of nitroso intermediate **B** followed by tautomerization reaction giving oxime **C**. The intramolecular cyclization of oximino derivative **C** proceeds accompanied by elimination of water from **D** with the formation of 4-nitroisoxazole **2**. The possibility

of the formation of 4-nitroisoxazole from chalcones and dinitrogen trioxide has been demonstrated.[30] In addition, we have found that heterocyclization of alkene **1a** in both conditions (A and B) is suppressed in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 0.5 equiv) that indirectly confirms the radical nature of heterocyclization.



Scheme 4 Plausible pathway accounting for 4-nitroisoxazoles **2**

As follows from the above data and previously published results,[25] the reactivity of electrophilic alkenes towards TNM-TEA complex strongly depends on their structure. As we have shown earlier, β-unsubstituted electrophilic alkenes or alkenes, bearing primary alkyl substituents in β-position, react with TNM-TEA affording 5-nitroisoxazoles. This reaction proceeds through the Michael addition of $^{-}C(NO_2)_3$ to double bond and subsequent intramolecular cyclization. The specific reactivity of β-aryl vinyl ketones towards TNM-TEA is defined by the following reasons: (i) electrophilic alkenes with bulky substituents in β-position do not react with $^{-}C(NO_2)_3$ anion because of steric hindrance,[25] (ii) for these substrates there is a possibility of formation of a stable benzyl radical (type **A**, Scheme 4), and (iii) keto group, present in the molecule, may participate in the intramolecular cyclization allowing 4-nitroisoxazoles.

In summary, a general straightforward and regioselective method for the synthesis of 4-nitroisoxazoles in good to high isolated yields from readily available and inexpensive alkenes has been developed. A wide range of β-aryl/hetaryl-substituted vinyl ketones may be successfully involved in the reactions with TNM-TEA or cheap and practicable *t*-BuONO, including gram-scale protocols. Therefore, the elaborated method provides easy access to 4-nitroisoxazoles, bearing a variety of substituents, that represent valuable precursors in organic and medicinal chemistry.

NMR spectra were recorded on spectrometer Agilent 400-MR (400.0 MHz for ^{1}H; 100.6 MHz for ^{13}C, 376.3 MHz for ^{19}F) at room temperature; chemical shifts (δ) were measured with reference to the solvent $CDCl_3$ for ^{1}H (δ = 7.26), ^{13}C (δ = 77.16) and to $CFCl_3$ as external standard for ^{19}F NMR. Chemical shifts (δ) are given in ppm; *J* values are given in hertz (Hz). When necessary, assignments of signals in NMR spectra were made using 2D techniques. Accurate mass measurements (HRMS) were performed on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The measurements were done in a positive ion mode (interface capillary voltage 4500 V) or in a negative ion mode (3200 V). Analytical TLC was carried out with Silufol aluminum-backed silica gel plates; the detection was done by UV lamp (254 and 365 nm) and chemical staining (5% aq $KMnO_4$). Column chromatography was performed on silica gel (230–400 mesh, Merck).

Compounds **1a**,[31] **1b**,[32] **1c**,[33] **1d**,[34] **1e**,**f**,[35] **1s**[36] were synthesized by the known procedure.[35] Compounds **1g**,**h**,**l**,[37] **1i**,[38] **1j**,[39] **1k**,[33] **1m**,[40] **1n**,[41] **1t**[42] were synthesized by the known procedure.[39] Compounds **1o**,[43] **1p**,[44] **1q**,[45] **1r**[46] were synthesized by the known procedure.[43] All other starting materials were commercially available. All reagents except commercial products of satisfactory quality were purified by literature procedures prior to use.

Compounds 2a–s; General Procedures

Method A: To a solution of $C(NO_2)_4$ (0.28 mL, 590 mg, 2.50 mmol) in 1,4-dioxane (3.0 mL) was added Et_3N (0.28 mL, 202 mg, 2 mmol) dropwise under argon atmosphere at –10 to –5 °C. The resulting mixture was stirred at this temperature for 5 min and then the corresponding alkene **1** (1.0 mmol) in 1,4-dioxane (1.0 mL) was added dropwise. The reaction mixture was stirred at 60 °C for 2 h and then the solvent was evaporated in vacuo. The residue was purified by preparative column chromatography on silica gel.

Method B: To a solution of the corresponding alkene **1** (1.0 mmol) in a mixture of 1,4-dioxane (0.4 mL) and H_2O (1.2 mL) was added *t*-BuONO (1.18 mL, 1.30 g, 10.0 mmol) dropwise under argon atmosphere over 1 h at 60 °C. The resulting mixture was stirred at this temperature for 1 h and then cooled down to rt. The mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried (anhyd $MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by preparative column chromatography on silica gel.

3-(4-Methoxyphenyl)-5-methyl-4-nitroisoxazole (2a)[18b]

White solid; yield: 178 mg (0.76 mmol, 76%) via method A; yield: 183 mg (0.78 mmol, 78%) via method B; mp 127–129 °C; R_f = 0.41 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.85 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3O), 6.96–7.02 (m, 2 H, 2 × CH), 7.55–7.60 (m, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.3 (CH_3), 55.5 (CH_3O), 114.1 (2 × CH), 118.0 (C_{Ar}), 129.7 (CNO_2), 130.9 (2 × CH), 157.4 (C), 161.6 (C_{Ar}), 172.9 (C).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.47; H, 4.44; N, 11.65.

5-Methyl-4-nitro-3-phenylisoxazole (2b)[47]

White solid; yield: 137 mg (0.67 mmol, 67%) via method A; yield: 143 mg (0.70 mmol, 70%) via method B; mp 92–93 °C; R_f = 0.62 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.89 (s, 3 H, CH_3), 7.47–7.56 (m, 3 H, 3 × CH), 7.60–7.63 (m, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 13.9 (CH_3), 125.9 (C, C_6H_5), 128.5 (2 × CH), 129.2 (2 × CH), 129.6 (CNO_2), 130.7 (CH), 157.7 (C), 172.8 (C).

3-(2-Methoxyphenyl)-5-methyl-4-nitroisoxazole (2c)

Light-yellow oil; yield: 49 mg (0.21 mmol, 21%) via method A; yield: 187 mg (0.80 mmol, 80%) via method B; R_f = 0.43 (PE–CH_2Cl_2, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.85 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 7.00 (dd, ^3J = 8.4 Hz, ^4J = 1.0 Hz, 1 H, CH), 7.08 (ddd, ^3J = 7.8 Hz, ^3J = 7.6 Hz, ^4J = 1.0 Hz, 1 H, CH), 7.48 (dd, ^3J = 7.6 Hz, ^4J = 1.8 Hz, 1 H, CH), 7.53 (ddd, ^3J = 8.4 Hz, ^3J = 7.6 Hz, ^4J = 1.8 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 13.6 (CH_3), 55.6 (CH_3O), 111.1 (CH), 115.6 (C_{Ar}), 120.9 (CH), 130.2 (CH), 131.0 (CNO_2), 132.4 (CH), 155.8 (C_{Ar}), 157.6 (C), 170.9 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O_4^+$: 235.0713; found: 235.0710.

3-(3-Methoxyphenyl)-5-methyl-4-nitroisoxazole (2d)

Light-yellow oil; yield: 80 mg (0.34 mmol, 34%) via method A; yield: 152 mg (0.65 mmol, 65%) via method B; R_f = 0.25 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.87 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 7.07 (ddd, ^3J = 8.3 Hz, ^4J = 1.0 Hz, ^4J = 2.6 Hz, 1 H, CH), 7.14 (dd, ^4J = 1.2 Hz, ^4J = 2.6 Hz, 1 H, CH), 7.18 (ddd, ^3J = 7.6 Hz, ^4J = 1.2 Hz, ^4J = 1.0 Hz, 1 H, CH), 7.40 (dd, ^3J = 8.3 Hz, ^3J = 7.6 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.2 (CH_3), 55.5 (CH_3O), 114.6 (CH), 116.8 (CH), 121.7 (CH), 127.1 (C_{Ar}), 129.7 (CH), 129.7 (CNO_2), 157.7 (C_{Ar}), 159.6 (C), 172.8 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O_4^+$: 235.0713; found: 235.0714.

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.42; H, 4.34; N, 11.96.

3-(3,4-Dimethoxyphenyl)-5-methyl-4-nitroisoxazole (2e)

White solid; yield: 185 mg (0.70 mmol, 70%) via method A; yield: 180 mg (0.68 mmol, 68%) via method B; mp 153–155 °C; R_f = 0.33 (PE–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.86 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3O), 3.94 (s, 3 H, CH_3O), 6.96 (d, ^3J = 8.4 Hz, 1 H, CH), 7.15 (d, ^4J = 2.0 Hz, 1 H, CH), 7.23 (dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.3 (CH_3), 56.07 (CH_3O), 56.12 (CH_3O), 110.9 (CH), 112.2 (CH), 118.0 (C_{Ar}), 122.7 (CH), 129.8 (CNO_2), 148.9 (C_{Ar}), 151.2 (C_{Ar}), 157.4 (C), 173.0 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_2O_5^+$: 265.0819; found: 265.0821.

5-Methyl-4-nitro-3-(3,4,5-trimethoxyphenyl)isoxazole (2f)

White solid; yield: 209 mg (0.71 mmol, 71%) via method A; yield: 209 mg (0.71 mmol, 71%) via method B; mp 160–162 °C; R_f = 0.16 PE–EtOAc, 7:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.85 (s, 3 H, CH_3), 3.86 (s, 6 H, 2 × CH_3O), 3.89 (s, 3 H, CH_3O), 6.84 (s, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.2 (CH_3), 56.3 (2 × CH_3O), 61.0 (CH_3O), 106.8 (2 × CH), 120.9 (C_{Ar}), 129.7 (CNO_2), 140.2 (C_{Ar}), 153.2 (2 × C_{Ar}), 157.5 (C), 173.0 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_6^+$: 295.0925; found: 295.0926.

3-(4-Fluorophenyl)-5-methyl-4-nitroisoxazole (2g)

White solid; yield: 115 mg (0.52 mmol, 52%) via method A; yield: 124 mg (0.56 mmol, 56%) via method B; mp 99–102 °C; R_f = 0.63 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.87 (s, 3 H, CH_3), 7.14–7.21 (m, 2 H, 2 × CH), 7.57–7.66 (m, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.2 (CH_3), 115.8 ($^3J_{C,F}$ = 22 Hz, 2 × CH), 122.0 ($^4J_{C,F}$ = 4 Hz, C_{Ar}), 129.7 (CNO_2), 131.6 ($^2J_{C,F}$ = 8.8 Hz, 2 × CH), 157.0 (C), 164.5 ($^1J_{C,F}$ = 251 Hz, C_{Ar}), 173.1 (C).

^{19}F NMR ($CDCl_3$, 376.3 MHz): δ = –109.2 (tt, $^3J_{H,F}$ = 8.5 Hz, $^4J_{H,F}$ = 5.1 Hz).

Anal. Calcd for $C_{10}H_7FN_2O_3$: C, 54.06; H, 3.18; N, 12.61. Found: C, 53.96; H, 3.12; N, 12.51.

3-(4-Bromophenyl)-5-methyl-4-nitroisoxazole (2h)[18b]

White solid; yield: 198 mg (0.70 mmol, 70%) via method A; yield: 215 mg (0.76 mmol, 76%) via method B; mp 121–123 °C; R_f = 0.22 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.88 (s, 3 H, CH_3), 7.52 (d, ^3J = 8.7 Hz, 2 H, 2 × CH), 7.66 (d, ^3J = 8.7 Hz, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.3 (CH_3), 124.9 (C_{Ar}), 125.6 (C_{Ar}), 129.7 (CNO_2), 131.0 (2 × CH), 131.9 (2 × CH), 157.1 (C), 173.2 (C).

Anal. Calcd for $C_{10}H_7BrN_2O_3$: C, 42.43; H, 2.49; N, 9.90. Found: C, 42.36; H, 2.71; N, 9.72.

4-(5-Methyl-4-nitroisoxazol-3-yl)benzaldehyde (2i)

White solid; yield: 125 mg (0.54 mmol, 54%) via method A; yield: 139 mg (0.60 mmol, 60%) via method B; mp 101–102 °C; R_f = 0.16 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.90 (s, 3 H, CH_3), 7.76–7.79 (m, 2 H, 2 × CH), 7.98–7.82 (m, 2 H, 2 × CH), 10.08 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.2 (CH_3), 129.6 (CNO_2), 129.7 (2 × CH), 130.2 (2 × CH), 131.7 (C_{Ar}), 137.7 (C_{Ar}), 157.0 (C), 173.3 (C), 191.6 (CHO).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_8N_2O_4Na^+$: 255.0376; found: 255.0368.

5-Methyl-4-nitro-3-(4-nitrophenyl)isoxazole (2j)[48]

Light-yellow solid; yield: 97 mg (0.39 mmol, 39%) via method A; yield: 167 mg (0.67 mmol, 67%) via method B; mp 152–153 °C; R_f = 0.16 (PE–EtOAc, 7:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.93 (s, 3 H, CH_3), 7.79–7.85 (m, 2 H, 2 × CH), 8.32–8.38 (m, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.3 (CH_3), 123.7 (2 × CH), 129.7 (CNO_2), 130.8 (2 × CH), 132.3 (C_{Ar}), 149.3 ($C_{Ar}NO_2$), 156.3 (C), 173.6 (C).

5-Methyl-3-(naphthalen-1-yl)-4-nitroisoxazole (2k)[18b]

White solid; yield: 140 mg (0.55 mmol, 55%) via method A; yield: 163 mg (0.64 mmol, 64%) via method B; mp 97–98 °C; R_f = 0.12 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.95 (s, 3 H, CH_3), 7.48 (ddd, ^3J = 8.2 Hz, ^3J = 6.9 Hz, ^4J = 1.6 Hz, 1 H, CH), 7.53 (ddd, ^3J = 8.1 Hz, ^3J = 6.7 Hz, ^4J = 1.5 Hz, 1 H, CH), 7.54–7.61 (m, 3 H, 3 × CH), 7.95 (br d, ^3J = 8.2 Hz, 1 H, CH), 8.01–8.08 (m, 1 H, CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.2 (CH_3), 123.6 (C_{Ar}), 124.4 (CH), 125.0 (CH), 126.6 (CH), 127.3 (CH), 128.3 (CH), 128.8 (CH), 130.9 (CNO_2), 131.1 (CH), 131.5 (C_{Ar}), 133.4 (C_{Ar}), 157.3 (C), 172.5 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}N_2O_3^+$: 255.0764; found: 255.0769.

3-Biphenyl-4-yl-5-methyl-4-nitroisoxazole (2l)

Light-yellow solid; yield: 132 mg (0.47 mmol, 47%) via method A; yield: 110 mg (0.39 mmol, 39%) via method B; mp 108–109 °C; R_f = 0.4 (PE–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.88 (s, 3 H, CH_3), 7.38–7.44 (m, 1 H, CH), 7.46–7.51 (m, 2 H, 2 × CH), 7.64–7.68 (m, 1 H, CH), 7.70–7.75 (m, 4 H, 4 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.2 (CH_3), 124.7 (C), 127.2 (2 × CH), 127.3 (2 × CH), 128.0 (CH), 129.0 (2 × CH), 129.6 (CNO_2), 129.8 (2 × CH), 140.1 (C_{Ar}), 143.6 (C_{Ar}), 157.5 (C), 172.9 (C).

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.36; H, 4.36; N, 9.30.

3-(Furan-2-yl)-5-methyl-4-nitroisoxazole (2m)

White solid; yield: 81 mg (0.42 mmol, 42%) via method A; yield: 95 mg (0.49 mmol, 49%) via method B; mp 95–97 °C; R_f = 0.28 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.87 (s, 3 H, CH_3), 6.59 (dd, ^3J = 1.8 Hz, ^3J = 3.6 Hz, 1 H, CH), 7.43 (dd, ^3J = 3.5 Hz, ^4J = 0.7 Hz, 1 H, CH), 7.64 (dd, ^3J = 1.8 Hz, ^4J = 0.7 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.3 (CH_3), 112.1 (CH), 117.2 (CH), 128.8 (CNO_2), 140.2 (C), 145.5 (CH), 148.5 (C), 173.2 (C).

Anal. Calcd for $C_8H_6N_2O_4$: C, 49.58; H, 3.25; N, 14.41. Found: C, 49.49; H, 3.12; N, 14.43.

5-Methyl-4-nitro-3-(thiophen-2-yl)isoxazole (2n)

White solid; yield: 143 mg (0.68 mmol, 68%) via method A; yield: 99 mg (0.47 mmol, 47%) via method B; mp 67–69 °C; R_f = 0.35 (PE–EtOAc, 10:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.87 (s, 3 H, CH_3), 7.18 (dd, ^3J = 3.8 Hz, ^3J = 5.1 Hz, 1 H, CH), 7.56 (dd, ^4J = 1.1 Hz, ^3J = 5.1 Hz, 1 H, CH), 7.88 (dd, ^4J = 1.1 Hz, ^3J = 3.8 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.4 (CH_3), 125.8 (C), 127.9 (CH), 129.3 (CNO_2), 130.1 (CH), 132.0 (CH), 152.0 (C), 173.5 (C).

Anal. Calcd for $C_8H_6N_2O_3S$: C, 45.82; H, 2.85; N, 13.19; S, 15.40. Found: C, 45.71; H, 2.88; N, 13.33; S, 15.25.

4-Nitro-3,5-diphenylisoxazole (2o)[47]

White solid; yield: 114 mg (0.43 mmol, 43%) via method A; yield: 127 mg (0.48 mmol, 48%) via method B; mp 55–57 °C; R_f = 0.41 (PE–EtOAc, 5:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 7.48–7.66 (m, 8 H, 8 × CH), 7.89–7.93 (m, 2 H, 2 × CH).

3-(4-Methoxyphenyl)-4-nitro-5-phenylisoxazole (2p)

White solid; yield: 112 mg (0.38 mmol, 38%) via method A; yield: 124 mg (0.42 mmol, 42%) via method B; mp 121–122 °C; R_f = 0.26 (PE–EtOAc, 8:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 3.88 (s, 3 H, CH_3O), 7.00–7.05 (m, 2 H, 2 × CH), 7.54–7.66 (m, 5 H, 5 × CH), 7.88–7.93 (m, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 55.5 (CH_3O), 114.4 (2 × CH), 118.0 (C_{Ar}), 124.8 (C_{Ar}), 128.9 (2 × CH), 129.0 (CNO_2), 129.1 (2 × CH), 130.5 (2 × CH), 132.7 (CH), 158.1 (C), 161.8 (C_{Ar}), 168.3 (C).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{12}N_2O_4Na^+$: 319.0689; found: 319.0787.

4-Nitro-3-phenyl-5-(3,4,5-trimethoxyphenyl)isoxazole (2q)

White solid; yield: 75 mg (0.21 mmol, 21%) via method A; yield: 71 mg (0.20 mmol, 20%) via method B; mp 100–102 °C; R_f = 0.37 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 3.94 (s, 6 H, 2 × CH_3), 3.97 (s, 3 H, CH_3), 7.24 (s, 2 H, 2 × CH), 7.48–7.60 (m, 3 H, 3 × CH), 7.62–7.67 (m, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 56.5 (2 × CH_3), 61.2 (CH_3), 106.6 (2 × CH), 119.4 (C), 126.1 (C), 128.88 (2 × CH), 128.90 (2 × CH), 129.5 (CNO_2), 131.0 (CH), 142.1 (C), 153.5 (2 C), 158.9 (C), 167.8 (C).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_6^+$: 357.1081; found: 357.1079.

5-([1,1'-Biphenyl]-4-yl)-3-phenyl-4-nitroisoxazole (2r)

Light-yellow solid; yield: 103 mg (0.30 mmol, 30%) via method A; yield: 113 mg (0.33 mmol, 33%) via method B; mp 206–207 °C; R_f = 0.14 (PE–CH_2Cl_2, 2:1).

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 7.41–7.46 (m, 1 H, CH), 7.48–7.58 (m, 5 H, 5 × CH), 7.65–7.69 (m, 4 H, 4 × CH), 7.78–7.82 (m, 2 H, 2 × CH), 8.01–8.05 (m, 2 H, 2 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 123.4 (C_{Ar}), 126.1 (C_{Ar}), 127.4 (2 × CH), 127.7 (2 × CH), 128.6 (CH), 128.9 (2 × CH), 129.0 (2 × CH), 129.2 (2 × CH), 129.2 (CNO_2), 129.5 (2 × CH), 131.0 (CH), 139.6 (C_{Ar}), 145.6 (C_{Ar}), 158.7 (C), 168.2 (C).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_4^+$: 343.1077; found: 343.1066.

1,4-Bis(5-methyl-4-nitroisoxazol-3-yl)benzene (2s)

Light-yellow solid; yield: 172 mg (0.52 mmol, 52%) via method A; yield: 224 mg (0.68 mmol, 68%) via method B; mp 214–216 °C. Compound **2s** crystallized after the addition of MeOH to the reaction mixture and required no additional purification.

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 2.92 (s, 6 H, CH_3), 7.77 (s, 4 H, 4 × CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.3 (2 × CH_3), 128.4 (2 × C_{Ar}), 129.6 (4 × CH), 130.2 (CNO_2), 157.2 (C), 173.2 (C).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{10}N_4O_6^+$: 331.0673; found: 331.0673.

Gram-Scale Synthesis of 2a and 2e

To the solution of alkene **1** (6 mmol) in a mixture of 1,4-dioxane (2.4 mL) and H_2O (7.2 mL) was added *t*-BuONO (7.2 mL, 6.24 g, 60 mmol) dropwise under argon atmosphere over 1 h at 60 °C. The resulting mixture was stirred at this temperature for 1 h and then cooled down to r.t. The mixture was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried (anhyd $MgSO_4$). The solvent was evaporated in vacuo and the crude product was purified by prepared column chromatography.

Compound 2a

White solid; yield: 1.02 g (4.38 mmol, 73%).

Compound 2e

White solid; yield: 1.01 g (3.84 mmol, 64%).

Synthesis of 2a Using $NaNO_2$ and Acetic Acid

To the solution of alkene **1a** (100 mg, 0.57 mmol) in a mixture of 1,4-dioxane (2.5 mL) and AcOH (2.5 mL) was added $NaNO_2$ (393 mg, 5.7 mmol) in one portion under argon atmosphere at 60 °C. The resulting mixture was stirred at this temperature for 2 h and then cooled down to r.t. The mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ and dried (anhyd $MgSO_4$). The solvent was evaporated in vacuo to give 96 mg of the crude product. According the ^1H NMR spectra, the resulting mixture was composed of alkene **1a** (80%) and isoxazole **2a** (20%).

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Supporting Information

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Primary Data

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