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A CONVENIENT SYNTHETIC METHOD OF ISOXAZOLE DERIVATIVES USING COPPER(II) NITRATE

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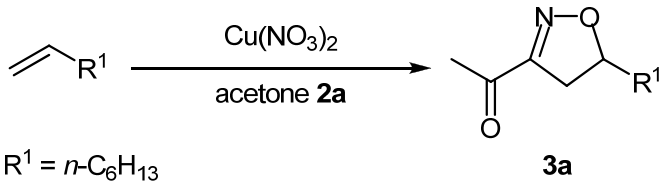
Abstract – 3-Acetylisoxazoles were synthesized by the reaction of alkenes or alkynes in acetone as solvent with copper(II) nitrate and formic acid. In the case of ethyl acetate as solvent, 3-benzoylisoxazoles were yielded by the reaction of alkynes and acetophenone with copper(II) nitrate and nitric acid. This synthetic method provides a convenient production of isoxazole derivatives.

Isoxazole derivatives, five-membered nitrogen-containing heterocycles, are an important class of heterocyclic compounds. They can be converted into a number of useful synthetic units by the reductive ring cleavage, such as β-hydroxy ketones[1] or γ-amino alcohols.[2] Moreover, many compounds bearing the isoxazole moieties show relevant biological activity: very late antigen-4 (VLA-4) antagonist[3] and cyclooxygenase-1 (COX-1) inhibitor.[4] Isoxazole derivatives are synthesized according to an intermolecular [3+2] cycloaddition reaction between alkenes (or alkynes) and nitrile oxides.[5] Nitrile oxides are generally prepared from aldoximes by following two steps: halogenation of aldoxime (into hydroximoyl halide) and dehydrohalogenation using base.[6]

We have recently reported that a newly synthetic method of isoxazole derivatives using ammonium cerium nitrate (CAN)[7] or iron(III) nitrate.[8] 3-Acetyl- and 3-benzoylisoxazoles were synthesized by the

reaction of alkenes (or alkynes) with acetone or acetophenone as solvent in the presence of CAN or iron(III) nitrate involving the nitrile oxide intermediate generated from ketones. Although the reaction using CAN proceeded, the reaction using iron(III) nitrate was inexpensive and non-toxic synthetic method of isoxazole derivatives. The synthetic method using iron(III) nitrate is a simple production of isoxazole derivatives, however, the use of iron(III) nitrate has drawbacks: the resulting brown color of iron salts after the reaction was made difficult to isolate the product from reaction mixture. In addition, since ketone was employed as solvent, it was necessary to remove ketone from the reaction mixture. Here, we wish to report a convenient method for the synthesis of 3-acetyl- and 3-acylisoxazoles using copper(II) nitrate rather than the reaction using CAN or iron(III) nitrate. Copper(II) nitrate is inexpensive and non-toxic reagent compared with CAN, and the resulting dark green color of copper salts after the reaction was easily dissolved by the addition of dilute hydrochloric acid. Moreover, since the quantity of ketone was limited to the amount of substrate by the use of ethyl acetate as solvent, 3-benzoylisoxazoles were obtained from the reaction of alkynes and acetophenone as substrate with copper(II) nitrate and nitric acid in ethyl acetate. The present method is afforded to a simple and efficient synthesis of isoxazole derivatives.

At first, the reaction of 1-octene **1a** (R^1 = *n*-C_6H_{13}) with copper(II) nitrate in acetone **2a** under reflux for 24 h was carried out (Scheme 1 and Table 1).



1a: R^1 = *n*-C_6H_{13} **3a**

Scheme 1

Table 1. The reaction of 1-octene **1a** with copper(II) nitrate in acetone **2a**

Entry[a]	$Cu(NO_3)_2$ (Mol. equiv.)	Yield (%)[b]	
		1a	**3a**
1	0.5	58	18
2	1.0	38	22
3	1.5	14	30
4	2.0	4	28
5	4.0	ND[c]	18

[a]**1a** (0.5 mmol), copper(II) nitrate (0.25-2.0 mmol) and **2a** (5 mL) were employed. [b]Determined by GLC analysis using *n*-dodecane as an internal hydrocarbon standard. [b]Not detected.

3-Acetyl-5-hexyl-4,5-dihydroisxoazole **3a** was obtained in low yield (about 20-30% yields). It seems that the production of isoxazole derivative was inhibited by the formation of copper complex from copper and reaction intermediate. In order to improve the yield of **3a**, we further examined the reactions adding several carboxylic acids (Table 2).

Table 2. The addition of several acids

Entry[a]	$Cu(NO_3)_2$ (Mol. equiv.)	Acid	Mol. equiv.	Yield (%)[b]	
				1a	**3a**
1	1.0	HCO_2H	2.5	ND[c]	53
2	1.0	HCO_2H	5.0	ND	72
3	1.0	HCO_2H	7.5	ND	80
4	1.0	HCO_2H	10.0	ND	80
5	0.5	HCO_2H	10.0	18	62
6	1.5	HCO_2H	10.0	ND	72
7	2.0	HCO_2H	10.0	ND	58
8	1.0	AcOH	5.0	ND	54
9	1.0	AcOH	10.0	ND	55
10	1.0	AcOH	15.0	ND	55
11	1.0	$EtCO_2H$	10.0	ND	51
12	1.0	$PhCO_2H$	10.0	ND	60
13	1.0	$ClCH_2CO_2H$	10.0	ND	62
14	1.0	Cl_3CCO_2H	10.0	ND	65
15	1.0	H_2SO_4	1.0	ND	ND
16	1.0	H_2SO_4	1.5	ND	65
17	1.0	H_2SO_4	2.5	ND	58
18	1.0	H_2SO_4	5.0	ND	25
19	1.0	HCl	1.0	44	23
20	1.0	HCl	2.5	12	24

[a]**1a** (0.5 mmol), copper(II) nitrate (0.25-1.0 mmol), acid (0.5-7.5 mmol) and **2a** (5 mL) were employed under reflux for 24 h. [b]Determined by GLC analysis using *n*-dodecane as an internal hydrocarbon standard. [c]Not detected.

The yields of **3a** increased into about 50-80% yields. In particular, when the reaction adding 7.5 molar equivalent of formic acid was carried out, **3a** was obtained in 80% GLC yield (Table 2, entry 3). Although the reaction using sulfuric acid gave **3a** in about 60% yield (Entries 16 and 17), it was clearly that the formation of **3a** effectively proceeded by the addition of formic acid.

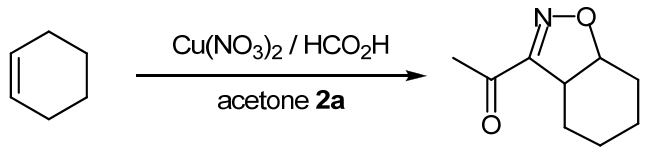
Therefore, the reaction of several alkenes in the presence of copper(II) nitrate and formic acid was performed in acetone under reflux. The results were summarized in Table 3.

Table 3. The reaction of several alkenes **1a**-**1i** with copper(II) nitrate and formic acid in acetone **2a**

Entry	Substrate	R^1	Yield / %[a]
1	**1a**	*n*-C_6H_{13}	**3a** (76)
2	**1b**	*n*-C_8H_{17}	**3b** (82)
3	**1c**	*n*-$C_{10}H_{21}$	**3c** (63)
4	**1d**	*t*-C_4H_9	**3d** (65)
5	**1e**	CN	**3e** (64)
6	**1f**	CH_2OCOMe	**3f** (64)
7	**1g**	*cyclo*-C_6H_{11}	**3g** (82)
8	**1h**	CH_2Cl	**3h** (64)
9	**1i**	CH_2Br	**3i** (46)

[a]Isolated yields.

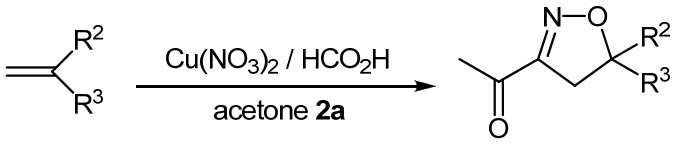
In addition, the reaction of disubstituted alkenes was carried out. In the case of cyclohexene **1j**, the corresponding 4,5-disubstituted isoxazole derivative **3j** was obtained in 19% yield (Scheme 2).



1j **3j**

Scheme 2

The reaction of 2-ethyl-1-butene **1k** and methylenecyclohexane **1l** as 1,1-disubstituted alkenes gave the corresponding 5,5-disubstituted isoxazole derivatives **3k** and **3l** in 13 and 13% yields, respectively (Scheme 3).

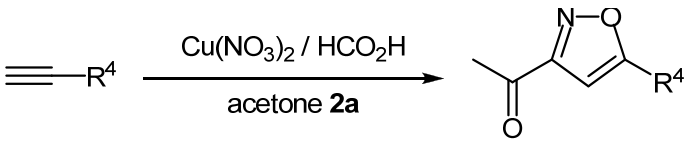


1k: $R^2 = R^3 = Et$
1l: $R^2, R^3 = -(CH_2)_5-$

3k-3l

Scheme 3

The yield of the product from disubstituted alkenes was lowered compared with the reaction of terminal alkenes. We further examined the reaction of several alkynes in the presence of copper(II) nitrate and formic acid in acetone (Scheme 4 and Table 4).



4a-4i **5a-5i**

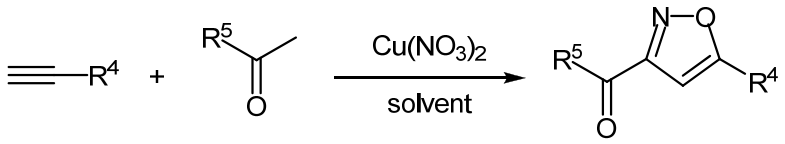
Scheme 4

Table 4. In the case of several alkynes **4a**-**4i**

Entry	Substrate	R^4	Yield / %[a]
1	**4a**	*n*-C_6H_{13}	**5a** (87)
2	**4b**	*n*-C_8H_{17}	**5b** (85)
3	**4c**	Ph	**5c** (39)
4	**4d**	$CO_2C_2H_5$	**5d** (95)
5	**4e**	$SiMe_3$	**5e** (67)
6	**4f**	CH_2Cl	**5f** (83)
7	**4g**	CH_2Br	**5g** (74)
8	**4h**	CMe_2OH	**5h** (91)
9	**4i**	*cyclo*-C_6H_{10}-1-OH	**5i** (92)

[a]Isolated yields.

The present method is a simple and convenient synthesis of 3-acetylisoxazoles, however, since ketone was employed as solvent, it was difficult to apply to the reaction by the use of high boiling ketones. In order to solve the problem, we investigated the reaction using several solvent: chloroform, acetic anhydride, tetrahydrofuran, 1,4-dioxane, ethyl acetate, pyridine, and dimethyl sulfoxide (Scheme 5, Table 5). Among them, it was found that the reaction of 1-octyne **4a** and acetophenone **2b** (R^5 = Ph) in the presence of copper(II) nitrate in ethyl acetate afforded to 3-benzoyl-5-hexylisoxazole **6a** (Table 3, Entry 6).



4 **2b-2e** **6-9**

Scheme 5

Table 5. The reaction of 1-octyne **4a** and acetophenone **2b** with copper(II) nitrate in several solvent

Entry[a]	Solvent	Temp./C°	Yield of **6a**[b]
1	H_2O	80	ND[c]
2	$CHCl_3$	60	ND
3	Ac_2O	80	trace
4	THF	60	trace
5	1,4-dioxane	80	3
6	EtOAc	60	6
7	pyridine	80	ND
8	DMSO	80	ND

[a]**4a** (0.5 mmol), **2b** (0.5 mmol), copper(II) nitrate (0.5 mmol) and solvent (5 mL) were employed for 24 h. [b]Determined by GLC analysis using *n*-dodecane as an internal hydrocarbon standard. [c]Not detected.

In the literature,[7,8] we proposed the reaction mechanism: the corresponding nitrile oxide was transformed from α-nitro ketone via the nitration of ketone. On the basis of our studies, we tried to the reaction adding nitric acid (Table 6).

Table 6. The addition of nitric acid

Entry[a]	**4a** (mol. equiv.)	HNO_3 (mol. equiv.)	Yield of **6a** (%)[b]
1	1	20	24
2	3	20	35
3	5	14	41
4	5	20	45
5	5	25	42
6	5	30	37
7	8	20	35
8	10	20	23

[a]**4a** (0.5-5.0 mmol), **2b** (0.5 mmol), copper(II) nitrate (0.5 mmol), nitric acid (7-15 mmol) and EtOAc (5 mL) were employed at 60 °C for 24 h. [b]Determined by GLC analysis using *n*-dodecane as an internal hydrocarbon standard.

The addition of nitric acid was improved the yield of the product into 24% GLC yield (Table 6, entry 1). Furthermore, it was found that **6a** was obtained in 45% GLC yield under optimum reaction condition (Entry 4).

From the results, we carried out the reaction of alkynes and ketones in the presence of copper(II) nitrate and nitric acid in ethyl acetate (Table 7).

Table 7. Reaction of alkynes and ketones **2b**-**2e** with copper(II) nitrate and nitric acid in ethyl acetate

Run	Alkyne: R^4	Ketone: R^5	Yield / %[a]
1	**4a**: *n*-C_6H_{13}	**2b**: Ph	**6a** (44)
2	**4c**: Ph	**2b**: Ph	**6b** (46)
3	**4i**: *cyclo*-C_6H_{10}-1-OH	**2b**: Ph	**6c** (89)
4	**4j**: CO_2Me	**2b**: Ph	**6d** (83)
5	**4a**: *n*-C_6H_{13}	**2c**: C_6H_4-4-Me	**7a** (39)
6	**4a**: *n*-C_6H_{13}	**2d**: C_6H_4-4-F	**8a** (39)
7	**4a**: *n*-C_6H_{13}	**2e**: 2-thienyl	**9a** (16)

[a]Isolated yields.

In conclusion, we developed a simple and efficient synthesis of 3-acetylisoxazoles by the use of copper(II) nitrate. Moreover, we have succeeded the improvement of the synthesis of 3-benzoylisoxazoles

by the use of ethyl acetate as solvent. These synthetic methods provide a convenient production of isoxazole derivatives.

EXPERIMENTAL

Melting points were determined on a Yanako Micro melting point apparatus. The IR spectra were recorded using a Thermo Electron Nicolet 380 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured using a JEOL JNM-GX400 spectrometer. Tetramethylsilane (δ=0) was used as an internal standard for ^{1}H NMR. Mass analysis was performed on an Agilent G1969LC/MDS TOF. All chemicals were purchased from Tokyo Chemical Industry Co., Ltd, and Wako Pure Chemical Industries, Ltd.

Typical Procedure for the Preparation of 3-Acetylisoxazoles

A mixture of alkenes (or alkynes) (0.5 mmol), copper(II) nitrate trihydrate (0.5 mmol) and formic acid (7.5 mol. equiv.; 3.75 mmol) in acetone (5 mL) was stirred under reflux for 18 h. The reaction mixture was extracted with EtOAc (30 mL) and washed with 1 mol/L HCl (3 mL), aq. $NaHCO_3$ solution (2x3 mL), saturated aq. sodium chloride solution (3 mL) and water (3 mL). The extract was dried over sodium sulfate and was concentrated in vacuo after the filtration. The residue was chromatographed with EtOAc and *n*-hexane on silica gel (Merck silica gel 60: 0.063-0.200 mm).

3-Acetyl-5-octyl-4,5-dihydroisoxazole (3b): a pale yellow oil; IR (neat) 2925, 2855, 1573 cm^{-1}; ^{1}H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.27-1.43 (m, 12H), 1.53-1.59 (m, 1H), 1.70-1.79 (m, 1H), 2.49 (s, 3H), 2.75 (dd, *J* = 8.2, 17.4 Hz, 1H), 3.15 (dd, *J* = 10.9, 17.4 Hz, 1H), 4.78 (m, 1H); ^{13}C NMR δ 14.0, 22.6, 25.1, 26.6, 29.1, 29.2, 29.3, 31.7, 35.1, 36.6, 84.8, 158.2, 193.4; HRMS (TOF-Cl) calcd for $C_{13}H_{24}NO_2$ (MH^+): 226.1807. Found: 226.1817.

3-Acetyl-5-decyl-4,5-dihydroisoxazole (3c): a white solid; mp 34.1-34.3 °C; IR (neat) 2917, 2848, 1691, 1585 cm^{-1}; ^{1}H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.26-1.43 (m, 16H), 1.53-1.59 (m, 1H), 1.70-1.79 (m, 1H), 2.49 (s, 3H), 2.75 (dd, *J* = 8.2, 17.4 Hz, 1H), 3.15 (dd, *J* = 10.9, 17.4 Hz, 1H), 4.78 (m, 1H); ^{13}C NMR δ 14.0, 22.7, 25.1, 26.6, 29.3, 29.4, 29.5, 29.6, 29.6, 31.9, 35.1, 36.7, 84.9, 158.2, 193.4; HRMS (TOF-Cl) calcd for $C_{15}H_{28}NO_2$ (MH^+): 254.2120. Found: 254.2119.

3-Acetyl-5-*t*-butyl-4,5-dihydroisoxazole (3d): a pale yellow oil; IR (neat) 2961, 1689, 1578 cm^{-1}; ^{1}H NMR δ 0.93 (s, 9H), 2.48 (s, 3H), 2.88 (dd, *J* = 9.1, 17.9 Hz, 1H), 2.98 (dd, *J* = 11.5, 17.9 Hz, 1H), 4.50 (dd, *J* = 9.1, 11.5 Hz, 1H); ^{13}C NMR δ 24.7, 26.5, 32.3, 34.1, 92.6, 158.2, 193.4; HRMS (TOF-Cl) calcd for $C_9H_{16}NO_2$ (MH^+): 170.1181. Found: 170.1180.

3-Acetyl-5-cyano-4,5-dihydroisoxazole (3e): a pale brown oil; IR (neat) 3001, 1698, 1592 cm^{-1}; ^{1}H NMR δ 2.55 (s, 3H), 3.55 (d, *J* = 9.2, 2H), 5.37 (t, *J* = 9.2 Hz, 1H); ^{13}C NMR δ 27.0, 38.6, 68.3, 115.9, 157.0, 191.3; HRMS (TOF-Cl) calcd for $C_6H_6N_2O_2$ (MH^+): 138.0429. Found: 138.0426.

3-Acetyl-5-cyclohexyl-4,5-dihydroisoxazole (3g): a yellow oil; IR (neat) 2927, 2854, 1688, 1575 cm^{-1}; ^1H NMR δ 0.99-1.27 (m, 5H), 1.54-1.99 (m, 6H), 2.84 (dd, *J* = 9.2, 17.6 Hz, 1H), 3.05 (dd, *J* = 11.2, 17.6 Hz, 1H), 4.53 (m, 1H); ^{13}C NMR δ 25.5, 25.6, 26.1, 26.5, 28.0, 28.2, 34.1, 42.2, 89.0, 158.2, 193.4; HRMS (TOF-Cl) calcd for $C_{11}H_{18}NO_2$ (MH^+): 196.1337. Found: 196.1345.

3-Acetyl-5-chloromethyl-4,5-dihydroisoxazole (3h): a pale yellow oil; IR (neat) 1693, 1583 cm^{-1}; ^1H NMR δ 2.51 (s, 3H), 3.11 (dd, *J* = 3.2, 18.2 Hz, 1H), 3.27 (dd, *J* = 11.2, 18.2 Hz, 1H), 3.44 (dd, *J* = 6.8, 10.8 Hz, 1H), 3.53 (dd, *J* = 4.0, 10.8 Hz, 1H), 5.05 (m, 1H); ^{13}C NMR δ 26.4, 35.1, 44.5, 82.1, 157.6, 192.4; HRMS (TOF-Cl) calcd for $C_6H_9NO_2Cl$ (MH^+): 162.0321. Found: 162.0319.

3-Acetyl-5-bromomethyl-4,5-dihydroisoxazole (3i): a pale yellow oil; IR (neat) 1692, 1583 cm^{-1}; ^1H NMR δ 2.50 (s, 3H), 3.11 (dd, *J* = 3.2, 18.2 Hz, 1H), 3.27 (dd, *J* = 11.2, 18.2 Hz, 1H), 3.44 (dd, *J* = 6.8, 10.8 Hz, 1H), 3.53 (dd, *J* = 4.0, 10.8 Hz, 1H), 5.05 (m, 1H); ^{13}C NMR δ 26.4, 35.1, 44.5, 82.1, 157.6, 192.4; HRMS (TOF-Cl) calcd for $C_6H_9NO_2Br$ (MH^+): 205.9816. Found: 205.9823.

3-Acetyl-5,5-diethyl-4-hydroisoxazole (3k): a colorless oil; IR (neat) 2925, 1716, 1689, 1577 cm^{-1}; ^1H NMR δ 0.91 (t, *J* = 7.3 Hz, 6H), 1.70 (q, *J* = 7.3 Hz, 4H), 2.48 (s, 3H), 2.84 (s, 2H); ^{13}C NMR δ 7.7, 26.3, 30.6, 38.5, 94.9, 157.9, 193.7; HRMS (TOF-Cl) calcd for $C_9H_{16}NO_2$ (MH^+): 170.1181. Found: 170.1184.

3-Acetyl-5,5-spirohexyl-4-hydroisoxazole (3l): a yellow oil; IR (neat) 2936, 2859, 1688, 1574 cm^{-1}; ^1H NMR δ 1.29-1.50 (m, 4H), 1.60-1.65 (m, 2H), 1.75-1.82 (m, 4H), 2.48 (s, 3H), 2.82 (s, 2H); ^{13}C NMR δ 23.1, 24.7, 26.3, 36.3, 41.6, 91.5, 157.9, 193.8; HRMS (TOF-Cl) calcd for $C_{10}H_{16}NO_2$ (MH^+): 182.1181. Found: 182.1184.

3-Acetyl-5-octylisoxazole (5b): a colorless oil; IR (neat) 2928, 2858, 1707, 1593 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.27-1.36 (m, 10H), 1.70 (quint., *J* = 7.3 Hz, 2H), 2.63 (s, 3H), 2.78 (t, *J* = 7.8 Hz, 2H), 6.35 (s, 1H); ^{13}C NMR δ 14.1, 22.6, 26.6, 27.2, 27.3, 28.9, 29.0, 29.1, 31.7, 99.1, 162.1, 175.6, 192.4; HRMS (TOF-Cl) calcd for $C_{13}H_{22}NO_2$ (MH^+): 224.1650. Found: 224.1660.

3-Acetyl-5-trimethylsilylisoxazole (5e): a yellow oil; IR (neat) 2962, 1705 cm^{-1}; ^1H NMR δ 0.36 (s, 9H), 2.68 (s, 3H), 6.81 (s, 1H); ^{13}C NMR δ -2.0, 27.8, 110.9, 160.6, 180.4, 192.4; HRMS (TOF-Cl) calcd for $C_8H_{14}NO_2Si(MH^+)$: 184.0793. Found:184.0799.

3-Acetyl-5-chloromethylisoxazole (5f): a yellow oil; IR (neat) 3141, 2361, 1707, 1600 cm^{-1}; ^1H NMR δ 2.66 (s, 3H), 4.66 (s, 2H), 6.70 (s, 1H); ^{13}C NMR δ 27.0, 33.8, 102.0, 161.9, 169.0, 191.3; HRMS (TOF-Cl) calcd for $C_6H_7NO_2Cl$ (MH^+): 160.0165. Found: 160.0174.

3-Acetyl-5-bromomethylisoxazole (5g): a yellow oil; IR (neat) 2360, 2341, 1704, 1595 cm^{-1}; ^1H NMR δ 2.65 (s, 3H), 4.50 (s, 2H), 6.68 (s, 1H); ^{13}C NMR δ 17.8, 27.2, 102.1, 162.2, 169.1, 191.5; HRMS (TOF-Cl) calcd for $C_6H_7NO_2Br$ (MH^+): 203.9660. Found: 203.9667.

3-Acetyl-5-(1-hydroxy-1-methylethyl)-isoxazole (5h): a yellow oil; IR (neat) 3440, 2984, 2924, 1705, 1582 cm^{-1}; ^1H NMR δ 1.65 (s, 6H), 2.54 (brs., 1H), 2.64 (s, 3H), 6.53 (s, 1H); ^{13}C NMR δ 27.2, 28.9, 69.0,

97.8, 161.8, 179.6, 192.2; HRMS (TOF-Cl) calcd for $C_8H_{12}NO_3$ (MH^+): 170.0817. Found: 170.0824.

Typical Procedure for the Preparation of 3-benzoylisoxazoles

A mixture of alkynes (2.5 mmol), acetophenone (0.5 mmol), copper(II) nitrate trihydrate (0.5 mmol) and nitric acid (10.0 mmol) in EtOAc (5 mL) was stirred at 60 °C for 24 h. The reaction mixture was extracted with EtOAc (30 mL) and washed with 1 mol/L HCl (3 mL), aq. $NaHCO_3$ solution (2x3 mL), saturated aq. sodium chloride solution (3 mL) and water (3 mL). The extract was dried over sodium sulfate and was concentrated in vacuo after the filtration. The residue was chromatographed with EtOAc and *n*-hexane on silica gel (Merck silica gel 60: 0.063-0.200 mm).

3-Benzoyl-5-methoxycarbonylisoxazole (6d): a pale yellow solid; mp 82.6-83.5 °C; IR (neat) 3144, 1729, 1655, 1596 cm^{-1}; ^1H NMR δ 4.02 (s, 3H), 7.44 (s, 1H), 7.53-7.70 (m, 3H), 8.31-8.33 (m, 2H); ^{13}C NMR δ 53.1, 110.2, 128.7, 130.7, 134.4, 135.1, 156.6, 160.7, 162.1, 184.4; HRMS (TOF-Cl) calcd for $C_{12}H_{10}NO_4$ (MH^+): 232.0604. Found: 232.0609.

3-(4-Methylbenzoyl)-5-hexylisoxazole (7a): a yellow oil; IR (neat) 2954, 2933, 1653, 1606 cm^{-1}; ^1H NMR δ 0.90 (t, J = 7.3 Hz, 3H), 1.30-1.42 (m, 6H), 1.75 (quint., J = 7.3 Hz, 2H), 2.44 (s, 3H), 2.83 (t, J = 7.3 Hz, 2H), 6.50 (s, 1H), 7.31 (d, J = 8.2 Hz, 2H), 8.20 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 14.0, 21.7, 22.4, 26.6, 27.3, 28.6, 31.3, 101.5, 129.2, 130.7, 133.3, 144.9, 161.9, 174.5, 185.7; HRMS (TOF-Cl) calcd for $C_{17}H_{22}NO_2$ (MH^+): 272.1645. Found: 272.1653.

3-(4-Fluorobenzoyl)-5-hexylisoxazole (8a): a yellow oil; IR (neat) 2956, 2931, 1666, 1599 cm^{-1}; ^1H NMR δ 0.90 (t, J = 7.3 Hz, 3H), 1.30-1.42 (m, 6H), 1.75 (quint., J = 7.3 Hz, 2H), 2.84 (t, J = 7.3 Hz, 2H), 6.52 (s, 1H), 7.17-7.21 (m, 2H), 8.37-8.40 (m, 2H); ^{13}C NMR δ 14.0, 22.5, 26.6, 27.4, 28.6, 31.4, 101.6, 115.6, 115.8, 133.4, 133.5, 161.8, 174.9, 184.4; HRMS (TOF-Cl) calcd for $C_{16}H_{19}NO_2F$ (MH^+): 276.1394. Found: 276.1397.

3-(2-Thienylcarbonyl)-5-hexylisoxazole (9a): a yellow oil; IR (neat) 2954, 2929, 1685, 1644, 762, 725, 680, 630 cm^{-1}; ^1H NMR δ 0.89 (t, J = 7.3 Hz, 3H), 1.25-1.43 (m, 6H), 1.74 (quint., J = 7.3 Hz, 2H), 2.83 (t, J = 7.3 Hz, 2H), 6.52 (s, 1H), 7.20-7.22 (m, 1H), 7.78-7.79 (m, 1H), 8.43-8.45 (m, 1H); ^{13}C NMR δ 13.9, 22.4, 26.5, 27.3, 28.6, 31.3, 101.0, 128.4, 135.8, 136.5, 141.6, 161.5, 174.9, 177.3; HRMS (TOF-Cl) calcd for $C_{14}H_{18}NO_2S$ (MH^+): 264.1052. Found: 264.1051.

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