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A CONVENIENT SYNTHESIS OF 3-BENZOYLISOXAZOLES BY 1,3-DIPOLAR CYCLOADDITION

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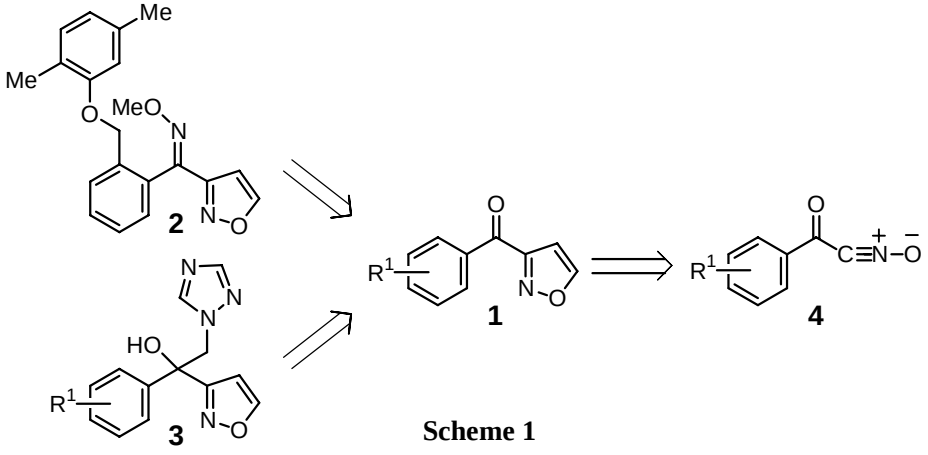
Abstract – A convenient, efficient method for the preparation of 3-benzoylisoxazoles is described. Nitrile oxides generated *in situ* from phenylglyoxylohydroxamyl chlorides and $NaHCO_3$ in isopropyl alcohol smoothly react with dipolarophiles at room temperature to provide the cycloadducts.

INTRODUCTION

Isoxazoles are well known to constitute structural parts of a number of natural products, pharmaceuticals, agrochemicals, polymers and other useful compounds.[1] During the course of our ongoing program on the synthesis of drug candidates, 3-benzoylisoxazoles (**1**) have become interesting key building blocks. For example, 3-[2-(2,5-dimethylphenoxymethyl)-α-methoxyiminobenzyl]isoxazole (**2**) shows a potent fungicidal activity against crop diseases[2] while 2-(1*H*-1,2,4-triazol-1-yl)-1-(3-isoxazolyl)-1-phenylethanols (**3**) show potent oral antifungal activities.[3] Although a few synthetic methods for 4,5-unsubsituted 3-benzoylisoxazoles by means of 1,3-dipolar cycloaddition were reported,[4] those methods comprised rather complicated reaction procedures and the over-all yields were unsatisfactory. Recently, we found a new and convenient method for the construction of 3-benzoylisoxazoles (**1**) by means of 1,3-dipolar cycloaddition between benzoylnitrile oxides (**4**) and dipolarophiles, which is the subject of this paper.

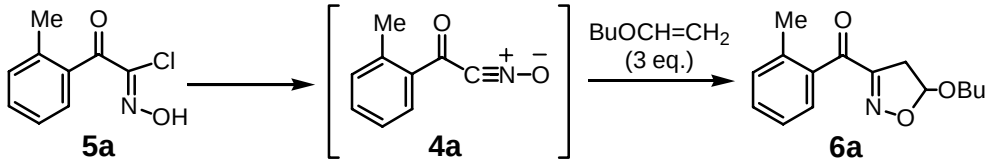


Scheme 1

RESULTS AND DISCUSSION

First, we attempted to develop a method for constructing 3-benzoylisoxazoles by means of 1,3-dipolar cycloaddition between benzoylnitrile oxide and vinyl ether followed by aromatization. For this purpose, 2-methylphenylglyoxylohydroxamyl chloride (**5a**) and butyl vinyl ether was chosen to optimize the reaction conditions, and the results are shown in Table 1. Compound (**5a**) was prepared by chloro-oximation[5] of 2'-methylacetophenone and the product was used for the cycloaddition reaction without further purification. The cycloaddition of **5a** with butyl vinyl ether by the known method[6] resulted in the formation of 5-alkoxy-3-benzoyl-2-isoxazoline (**6a**) in a 64% yield (Entry 1). However, the addition of triethylamine as a base was so exothermic that this reaction condition seemed unsuitable for large scale production. Thermal *in situ* generation[7] of benzoylnitrile oxide (**4a**) by refluxing a mixture of **5a** with excess butyl vinyl ether, provided a cycloaddition product in only 19% yield (Entry 2). Eventually, the cycloaddition reaction of the nitrile oxide, which generated *in situ* through the reaction of **5a** with $NaHCO_3$ in isopropyl alcohol at room temperature,[8] proceeded smoothly and non-exothermically to produce a cycloadduct as a single regioisomer in 79% yield (Entry 3). The $NaHCO_3$ in the reaction was presumed to effect dehydrochlorination for the phenylglyoxylohydroxamyl chloride giving rise to nitrile oxide and NaCl, while preserving the neutral and mild reaction conditions leading to an improved yield.

Table 1 Examination of 1,3-dipolar cycloaddition

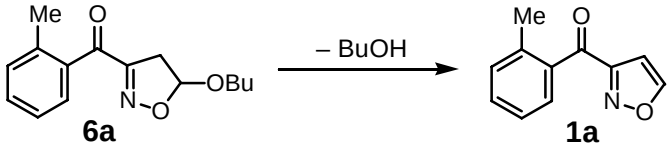


Entry	Base (2 eq.)	Solvent	Conditions	**6a** (%)[a]
1	Et_3N	Ether	rt 15 h	64
2	–	–[b]	reflux 4 h	19
3	$NaHCO_3$	*i*-PrOH	rt 15 h	79

[a] Isolated yields. [b] $BuOCH=CH_2$ (10 eq.)

Next, we examined the aromatization reaction (elimination of alcohol)[9] of **6a** under either basic or acidic conditions (Table 2). Treatment of **6a** with MeONa (0.1 eq.) in methanol at room temperature for 23 h provided a benzoylisoxazole (**1a**) in 48% yield (Entry 1). The desired elimination reaction was completed under refluxing conditions to give **1a** in 87% yield (Entry 2). On the other hand, when **6a** was treated with *p*-TsOH (0.1 eq.) in toluene, elimination reaction did not proceed at room temperature even after 19 h (Entry 3), but the desired product was obtained in high yield after heating (Entries 4 and 5). Among the applied catalysts, H_2SO_4 gave the best result, and the reaction was completed in a shorter time (Entry 6).

Table 2 Examination of aromatization (elimination of alcohol)



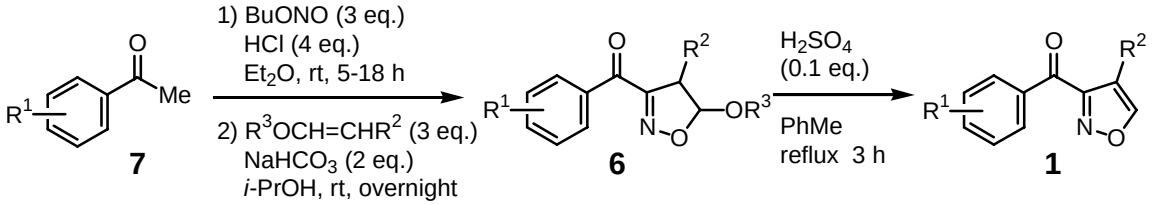
6a **1a**

Entry	Catalyst (0.1 eq.)	Solvent	Conditions	**1a** (%)[a]	**6a** (%)[b]
1	MeONa	MeOH	rt 23 h	48	38
2	MeONa	MeOH	reflux 7 h	87	–
3	*p*-TsOH	Toluene	rt 19 h	0	100
4	*p*-TsOH	Toluene	60°C 19 h	31	62
5	*p*-TsOH	Toluene	reflux 12 h	93	–
6	H_2SO_4	Toluene	reflux 3 h	94	–

[a] Isolated yields. [b] Recovery.

Finally, we applied the optimized reaction conditions (Entry 3 of Table 1 and Entry 6 of Table 2) to the synthesis of various benzoylisoxazoles (**1**) starting from suitable acetophenones (**7**) (Table 3). The 1,3-dipolar cycloaddition was not influenced by either electronic or steric effects of the substituent (R^1), providing isoxazolines (**6a**–**f**) in good yields (Entries 1–8). It is worth to mention that the reaction with ethyl 1-propenyl ether as a dipolarophile proceeded regioselectively to provide 4-methylisoxazolines (**6g**–**h**) (Entries 7 and 8). These results also suggested that an electron-donating group attached to one side of the double bond in dipolarophile controlled the regioselectivity in the reaction.[1, 10] Treatment of **6** with sulfuric acid in toluene under reflux provided benzoylisoxazoles (**1**) in excellent yields.

Table 3 Preparation of 3-benzoylisoxazoles (**1**) from acetophenones (**7**) through cycloaddition followed by aromatization



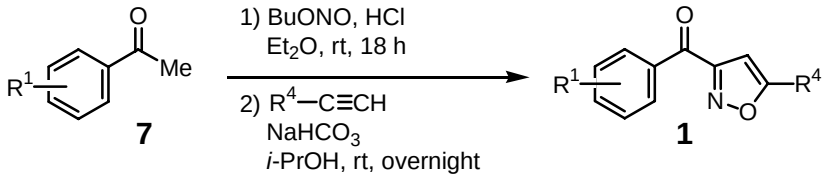
7 **6** **1**

Entry	R^1	R^2	R^3	Isoxazoline	Yield (%)[a]	Isoxazole	Yield (%)[a]
1	2-Me	H	Bu	**6a**	79	**1a**	94
2[b]	H	H	Bu	**6b**	91	**1b**	93
3	4-F	H	Bu	**6c**	73	**1c**	87
4	2-Cl	H	Bu	**6d**	83	**1d**	91
5	4-Cl	H	Bu	**6e**	82	**1e**	99
6	2-(2,5-Me_2-C_6H_3)OCH_2	H	Et	**6f**	80	**1f**	91
7	4-Cl	Me	Et	**6g**	60	**1g**	92
8	3,4-Cl_2	Me	Et	**6h**	50	**1h**	94

[a] Isolated yields. [b] Starting material; $PhCOCH_2Cl$, BuONO (1.5 eq.), HCl (2 eq.).

Although the 1,3-dipolar cycloaddition of nitrile oxides with alkynes is well documented as a useful method especially for preparation of isoxazole derivatives, only a few cycloaddition reactions between nitrile oxides and simple acetylene or 3,3,3-trifluoropropyne were reported.[11] We next attempted to extend this method to 1,3-dipolar cycloaddition with acetylene or trifluoropropyne, and the results are shown in Table 4. The cycloaddition with acetylene produced the corresponding benzoylisoxazoles in good yields (Entries 1 and 2). On the other hand, the reactions with trifluoropropyne gave 5-trifluoromethyl-3-benzoylisoxazoles as a single regioisomer in moderate yields (Entries 3 and 4).

Table 4 Preparation of 3-benzoylisoxazoles (**1**) from acetophenones (**7**) through cycloaddition of alkynes.



Entry	R^1	R^4	Isoxazole	Yield (%)[a]
1	2-Me	H	**1a**	76
2	2-(2,5-Me_2-C_6H_3)OCH_2	H	**1f**	84
3	2-Me	CF_3	**1i**	53
4	4-Cl	CF_3	**1j**	53

[a]Isolated yields.

In conclusion, a convenient method for *in situ* generation of nitrile oxides from chloro-oxime derivatives was developed using $NaHCO_3$ as the base in isopropyl alcohol. By use of this method, a series of 3-benzoylisoxazoles (**1**) were efficiently synthesized in high yield and with high regioselectivity.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a JEOL JNM-GSX 270 spectrometer at 270 MHz using tetramethylsilane (TMS) as an internal standard. The melting points were measured using a Büchi 535 melting point apparatus, and the values are given uncorrected. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer using a potassium bromide disk. Column chromatography (CC) was carried out on Merck silica gel 60 (0.063–0.200 mm).

The general procedure for the synthesis of 5-alkoxy-3-benzoyl-2-isoxazolines (**6a**–**h**).

Butyl nitrite (30.94 g, 0.3 mol) was added dropwise below 10°C over 20 min to a mixture of acetophenones **7** (0.1 mol), 5N hydrogen chloride in dioxane (80 mL, 0.4 mol), and Et_2O (300 mL), then the mixture was stirred

at rt for 5–18 h. The reaction mixture was poured into Et_2O (100 mL) and washed with brine (400 mL × 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give crude phenylglyoxylohydroxamyl chlorides (**5**), which was subjected to cycloaddition reaction without further purification.

$NaHCO_3$ (16.80 g, 0.2 mol) was added to a mixture of crude **5**, butyl vinyl ether (30.05 g, 0.3 mol) and isopropyl alcohol (200 mL) in an ice bath, and the mixture was stirred at rt for 15–24 h. The reaction mixture was concentrated under reduced pressure, poured into ice-cold water (400 mL) and extracted with Et_2O (400 mL). The organic layer was washed with brine (400 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by CC to give the isoxazolines (**6**).

5-Butoxy-3-(2-methylbenzoyl)-2-isoxazoline (6a). From 2'-methylacetophenone (**7a**). CC (AcOEt/ hexane: 1/9 v/v) gave **6a** (79%) as a slightly brownish oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.36 (m, 2H), 1.56 (m, 2H), 2.44 (s, 3H), 3.22 (dd, *J*=18.5, 2.3 Hz, 1H), 3.36 (dd, *J*=18.5, 6.6 Hz, 1H), 3.58 (td, *J*=9.3, 6.6 Hz, 1H), 3.88 (td, *J*=9.3, 6.6 Hz, 1H), 5.73 (dd, *J*=6.6, 2.3 Hz, 1H), 7.22–7.36 (m, 2H), 7.74 (m, 1H), 7.74 (dd, *J*=7.9, 1.3 Hz, 1H). IR (KBr): 2959, 2872, 1660, 1573, 1258, 1188, 1095, 902 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.70; H, 7.33; N, 5.33.

3-Benzoyl-5-butoxy-2-isoxazoline (6b).[12] From 2-chloroacetophenone (**7b**). CC (AcOEt/hexane:1/9 v/v) gave **6b** (90%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.36 (m, 2H), 1.58 (m, 2H), 3.24 (dd, *J*=18.5, 2.3 Hz, 1H), 3.39 (dd, *J*=18.5, 6.6 Hz, 1H), 3.58 (td, *J*=9.3, 6.6 Hz, 1H), 3.89 (td, *J*=9.3, 6.6 Hz, 1H), 5.71 (dd, *J*=6.6, 2.3 Hz, 1H), 7.45–7.51 (m, 2H), 7.61 (m, 1H), 8.20–8.24 (m, 2H). IR (KBr): 2959, 2873, 1655, 1265, 1190, 1097 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.74; H, 6.82; N, 5.47.

5-Butoxy-3-(4-fluorobenzoyl)-2-isoxazoline (6c). From 4'-fluoroacetophenone (**7c**). CC (AcOEt/hexane: 2/8 v/v) gave **6c** (73%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.39 (m, 2H), 1.56 (m, 2H), 3.23 (dd, *J*=18.5, 2.3 Hz, 1H), 3.38 (dd, *J*=18.5, 6.6 Hz, 1H), 3.59 (td, *J*=9.5, 6.6 Hz, 1H), 3.89 (td, *J*=9.5, 6.6 Hz, 1H), 5.72 (dd, *J*=6.6, 2.3 Hz, 1H), 7.15 (m, 2H), 8.30 (m, 2H). IR (KBr): 2960, 2873, 1655, 1599, 1266, 1157, 1098, 902, 849 cm^{-1}. Anal. Calcd for $C_{14}H_{16}NO_3F$: C, 63.39; H, 6.08; N, 5.28; F, 7.16. Found: C, 63.35; H, 6.05; N, 5.19; F, 7.02.

5-Butoxy-3-(2-chlorobenzoyl)-2-isoxazoline (6d). From 2'-chloroacetophenone (**7d**). CC (AcOEt/hexane: 15/85 v/v) gave **6d** (83%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J*=7.3 Hz, 3H), 1.38 (m, 2H), 1.56 (m, 2H), 3.22 (dd, *J*=18.5, 2.3 Hz, 1H), 3.34 (dd, *J*=18.5, 6.6 Hz, 1H), 3.57 (td, *J*=9.2, 6.3 Hz, 1H), 3.86 (td, *J*=9.2, 6.3 Hz, 1H), 5.77 (dd, *J*=6.6, 2.3 Hz, 1H), 7.36 (m, 1H), 7.43–7.48 (m, 2H), 7.55 (m, 1H). IR (KBr): 2959, 2873, 1674, 1573, 1254, 1192, 1099, 917, 833 cm^{-1}. Anal. Calcd for $C_{14}H_{16}NO_3Cl$: C, 59.68; H, 5.72; N,

4.97; Cl, 12.58. Found: C, 59.44; H, 5.58; N, 5.02; Cl, 12.33.

5-Butoxy-3-(4-chlorobenzoyl)-2-isoxazoline (6e). From 4'-chloroacetophenone (**7e**). CC (AcOEt/hexane: 15/85 v/v) gave **6e** (82%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.39 (m, 2H), 1.59 (m, 2H), 3.23 (dd, *J*=18.5, 2.3 Hz, 1H), 3.38 (dd, *J*=18.5, 6.6 Hz, 1H), 3.59 (td, *J*=9.5, 6.6 Hz, 1H), 3.89 (td, *J*=9.5, 6.6 Hz, 1H), 5.71 (dd, *J*=6.6, 2.3 Hz, 1H), 7.46 (m, 2H), 8.20 (m, 2H). IR (KBr): 2959, 2872, 1654, 1587, 1264, 1190, 1093, 913, 840 cm^{-1}. Anal. Calcd for $C_{14}H_{16}NO_3Cl$: C, 59.68; H, 5.72; N, 4.97; Cl, 12.58. Found: C, 60.05; H, 5.84; N, 4.63; Cl, 12.31.

3-[2-(2,5-Dimethylphenoxymethyl)benzoyl]-5-ethoxy-2-isoxazoline (6f). From 2'-(2,5-dimethylphenoxy-methyl)acetophenone (**7f**). CC (AcOEt/hexane: 1/9 v/v) gave **6f** (80%) as a pale yellow solid. Recrystallization (AcOEt/hexane) afforded pale yellow crystals, mp 87–88°C. ^{1}H NMR ($CDCl_3$) δ 1.21 (t, *J*=7.3 Hz, 3H), 2.18 (s, 3H), 2.30 (s, 3H), 3.17 (dd, *J*=18.1, 3.0 Hz, 1H), 3.26 (dd, *J*=18.1, 6.3 Hz, 1H), 3.60 (m, 1H), 3.90 (m, 1H), 5.20 (d, *J*=13.2 Hz, 1H), 5.29 (d, *J*=13.2 Hz, 1H), 5.67 (dd, *J*=6.3, 3.0 Hz, 1H), 6.67 (s, 1H), 6.68 (d, *J*=7.6 Hz, 1H), 7.02 (d, *J*=7.6 Hz, 1H), 7.43 (td, *J*=7.6, 1.3 Hz, 1H), 7.57 (td, *J*=7.6, 1.3 Hz, 1H), 7.70 (d, *J*=7.6 Hz, 1H), 7.91 (dd, *J*=7.6, 1.3 Hz, 1H). IR (KBr): 2978, 2925, 1664, 1577, 1509, 1261, 1129, 897 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.19; H, 6.18; N, 3.97.

3-(4-Chlorobenzoyl)-5-ethoxy-4-methyl-2-isoxazoline (6g). From 4'-chloroacetophenone (**7e**). CC (AcOEt/hexane: 1/9 v/v) gave **6g** (60%, a diastereomeric mixture) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.22–1.34 (m, 6H), 3.48-3.72 (m, 2H), 3.87–4.04 (m, 1H), 5.28 (d, *J*=1.3 Hz, 0.5H), 5.60 (d, *J*=7.3 Hz, 0.5H), 7.42–7.50 (m, 2H), 8.10–8.21 (m, 2H). IR (KBr): 2979, 2936, 1654, 1587, 1255, 1092, 851 cm^{-1}. Anal. Calcd for $C_{13}H_{14}NO_3Cl$: C, 58.32; H, 5.27; N, 5.23; Cl, 13.24. Found: C, 58.25; H, 5.29; N, 5.04; Cl, 13.36.

3-(3,4-Dichlorobenzoyl)-5-ethoxy-4-methyl-2-isoxazoline (6h). From 3',4'-dichloroacetophenone (**7g**). CC (AcOEt/hexane: 1/9 v/v) gave **6h** (50%, a diastereomeric mixture) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.22–1.34 (m, 6H), 3.46–3.72 (m, 2H), 3.87–4.04 (m, 1H), 5.29 (d, *J*=1.7 Hz, 0.5H), 5.62 (d, *J*=7.3 Hz, 0.5H), 7.54–7.58 (m, 1H), 8.01–8.11 (m, 1H), 8.28 (d, *J*=2.0 Hz, 0.5H), 8.34 (d, *J*=2.0, 0.5H). IR (KBr): 3096, 2979, 2936, 1656, 1572, 1390, 1108, 858 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_3Cl_2$: C, 51.68; H, 4.34; N, 4.64; Cl, 23.47. Found: C, 51.65; H, 4.30; N, 4.43; Cl, 23.41.

The general procedure for the synthesis of 3-benzolylisoxazoles (**1a–h**) from 5-alkoxy-3-benzoyl-2-isoxazolines (**6a–h**). A mixture of **6** (0.1 mol) and sulfuric acid (0.98 g, 0.01 mol) in toluene (200 mL) was heated under reflux with stirring for 3 h. The mixture was poured into ice-cold water (400 mL) and extracted with toluene (200 mL). The organic layer was washed with brine (400 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by CC to give 3-benzoylisoxazoles (**1**).

3-(2-Methylbenzoyl)isoxazole (1a). From **6a**. CC (AcOEt/hexane: 1/9 v/v) gave **1a** (94%) as a pale yellow solid, mp 35–37°C. ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 6.91 (d, *J*=1.7 Hz, 1H), 7.29–7.34 (m, 2H), 7.46 (td, *J*=7.6, 1.7 Hz, 1H), 7.82 (dd, *J*=7.6, 1.7 Hz, 1H), 8.55 (d, *J*=1.7 Hz, 1H). IR (KBr): 3129, 3071, 2969, 1672, 1419, 1302, 1193, 885 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.40; H, 4.60; N, 7.45.

3-Benzoylisoxazole (1b).[4] From **6b**. CC (AcOEt/hexane: 1/9 v/v) gave **1b** (93%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.93 (d, *J*=1.7 Hz, 1H), 7.51–7.57 (m, 2H), 7.67 (m, 1H), 8.30–8.34 (m, 2H), 8.56 (d, *J*=1.7 Hz, 1H). IR (KBr): 3160, 3131, 3073, 1662, 1451, 1294, 1199, 1179, 881 cm^{-1}. Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.23; H, 4.09; N, 8.05.

3-(4-Fluorobenzoyl)isoxazole (1c). From **6c**. Recrystallization (AcOEt/hexane) gave **1c** (87%) as slightly brownish prisms, mp 78–79°C. ^{1}H NMR ($CDCl_3$) δ 6.93 (d, *J*=1.7 Hz, 1H), 7.21 (m, 2H), 8.41 (m, 2H), 8.56 (d, *J*=1.7 Hz, 1H). IR (KBr): 3163, 3139, 3062, 1658, 1601, 1421, 1302, 1239, 1166, 893, 858 cm^{-1}. Anal. Calcd for $C_{10}H_6NO_2F$: C, 62.83; H, 3.16; N, 7.33; F, 9.94. Found: C, 62.98; H, 3.05; N, 7.39; F, 9.70.

3-(2-Chlorobenzoyl)isoxazole (1d). From **6d**. CC (AcOEt/hexane: 2/8 v/v) gave **1d** (91%) as a white solid. Recrystallization (AcOEt/hexane) afforded colorless prisms, mp 63.5–64.5°C. ^{1}H NMR ($CDCl_3$) δ 6.94 (d, *J*=1.7 Hz, 1H), 7.37–7.50 (m, 3H), 7.66 (m, 1H), 8.56 (d, *J*=1.7 Hz, 1H). IR (KBr): 3132, 1686, 1591, 1421, 1300, 1199, 1038, 889 cm^{-1}. Anal. Calcd for $C_{10}H_6NO_2Cl$: C, 57.85; H, 2.91; N, 6.75; Cl, 17.08. Found: C, 58.05; H, 2.79; N, 6.79; Cl, 16.76.

3-(4-Chlorobenzoyl)isoxazole (1e). From **6e**. CC (AcOEt/hexane: 2/8 v/v) gave **1e** (99%) as a white solid. Recrystallization (AcOEt/hexane) afforded colorless needles, mp 57–58.5°C. ^{1}H NMR ($CDCl_3$) δ 6.93 (d, *J*=1.7 Hz, 1H), 7.51 (m, 2H), 8.31 (m, 2H), 8.56 (d, *J*=1.7 Hz, 1H). IR (KBr): 3153, 3114, 1670, 1587, 1297, 1199, 1093, 883 cm^{-1}. Anal. Calcd for $C_{10}H_6NO_2Cl$: C, 57.85; H, 2.91; N, 6.75; Cl, 17.08. Found: C, 58.04; H, 2.83; N, 6.76; Cl, 16.76.

3-[2-(2,5-Dimethylphenoxymethyl)benzoyl]isoxazole (1f). From **6f**. CC (AcOEt/hexane: 2/8 v/v) gave **1f** (91%) as a white solid. Recrystallization (AcOEt/hexane) afforded colorless needles, mp 90.5–92°C. ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.29 (s, 3H), 5.32 (2, s), 6.66 (s, 1H), 6.67 (d, *J*=7.6 Hz, 1H), 6.86 (d, *J*=1.6 Hz, 1H), 7.00 (d, *J*=7.6 Hz, 1H), 7.47 (t, *J*=7.6 Hz, 1H), 7.64 (td, *J*=7.6, 1.3 Hz, 1H), 7.81 (d, *J*=7.6 Hz, 1H), 8.02 (dd, *J*=7.6, 1.3 Hz, 1H), 8.51 (d, *J*=1.6 Hz, 1H). IR (KBr): 2923, 1664, 1509, 1415, 1300, 1263, 1130, 1037, 887 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.19; H, 5.28; N, 4.56.

3-(4-Chlorobenzoyl)-4-methylisoxazole (1g). From **6g**. CC (toluene/hexane: 5/95 v/v) gave **1g** (92%) as a white solid. Recrystallization (AcOEt/hexane) afforded colorless needles, mp 93.5–94.5°C. ^{1}H NMR ($CDCl_3$) δ 2.27 (d, *J*=1.0 Hz, 3H), 7.49 (m, 2H), 8.19 (m, 2H), 8.34 (q, *J*=1.0 Hz, 1H). IR (KBr): 3114, 3088,

1664, 1587, 1444, 1282, 1095, 884 cm^{-1}. Anal. Calcd for $C_{11}H_8NO_2Cl$: C, 59.61; H, 3.64; N, 6.32; Cl, 16.00. Found: C, 59.69; H, 3.50; N, 6.37; Cl, 15.65.

3-(3,4-Dichlorobenzoyl)-4-methylisoxazole (1h). From **6h**. CC (AcOEt/hexane: 2/8 v/v) gave **1h** (94%) as a white solid. Recrystallization (AcOEt/hexane) afforded colorless crystals, mp 75–76°C. ^1H NMR ($CDCl_3$) δ 2.28 (d, *J*=1.0 Hz, 3H), 7.60 (d, J=8.6 Hz, 1H), 8.11 (dd, *J*=8.6, 2.0 Hz, 1H), 8.35–8.36 (m, 2H). IR (KBr): 3123, 3092, 1669, 1440, 1282, 1233, 964, 911 cm^{-1}. Anal. Calcd for $C_{11}H_7NO_2Cl_2$: C, 51.59; H, 2.76; N, 5.47; Cl, 27.69. Found: C, 51.55; H, 2.61; N, 5.62; Cl, 27.52.

The general procedure for the synthesis of 3-benzoylisoxazoles (**1a**) and (**1f**) from alkyne.

Acetylene gas (excess) was passed through a solution of crude **5** (0.02 mol) in isopropyl alcohol (60 mL) at rt over 30 min, and $NaHCO_3$ (3.36 g, 0.04 mol) was added to the mixture. Acetylene gas (excess) was passed through the above mixture at rt over 8 h, and the mixture was stirred at rt for 18 h. The reaction mixture was poured into Et_2O (200 mL) and washed with water (200 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by CC to give the isoxazoles.

3-(2-Methylbenzoyl)isoxazole (1a). From 2'-methylacetophenone (**7a**). CC (AcOEt/hexane: 1/9 v/v) gave **1a** (76%) as a pale yellow solid.

3-[2-(2,5-Dimethylphenoxymethyl)benzoyl]isoxazole (1f). From 2'-(2,5-dimethylphenoxymethyl)aceto-phenone (**7f**). CC (AcOEt/hexane: 2/8 v/v) gave **1f** (84%) as a white solid.

The general procedure for the synthesis of 3-benzoyl-5-trifluoromethylisoxazoles (**1i**–**j**).

3,3,3-Trifluoropropyne gas (0.02 mmol) was passed through a solution of crude **5** (0.01 mmol) in isopropyl alcohol (30 mL) below –50°C over 30 min, and $NaHCO_3$ (1.68 g, 0.02 mol) was added to the mixture, and the mixture was stirred at rt for 20 h. The reaction mixture was poured into Et_2O (150 mL) and washed with water (100 mL × 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by CC to give 3-benzoyl-5-trifluoromethylisoxazoles.

3-(2-Methylbenzoyl)-5-trifluoromethylisoxazole (1i). From 2'-methylacetophenone (**7a**). CC (AcOEt/hexane: 1/9 v/v) gave **1i** (53%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H), 7.23 (d, *J*=1.0 Hz, 1H), 7.31-7.37 (m, 2H), 7.51 (td, *J*=7.6, 1.3 Hz, 1H), 7.87 (dd, *J*=7.6, 1.3 Hz 1H). IR (KBr): 3141, 2970, 2932, 1682, 1316, 1243, 1167, 966, 895 cm^{-1}. Anal. Calcd for $C_{12}H_8NO_2F_3$: C, 56.47; H, 3.16; N, 5.49; F, 22.34. Found: C, 56.56; H, 3.33; N, 5.58; F, 22.63.

3-(4-Chlorobenzoyl)-5-trifluoromethylisoxazole (1j). From 4'-chloroacetophenone (**7e**). CC (AcOEt/

hexane: 1/9 v/v) gave **1j** (53%) as a white solid. Recrystallization (AcOEt/hexane) afforded colorless prisms, mp 46–47°C. ^{1}H NMR ($CDCl_3$) δ 7.25 (d, *J*=1.0 Hz, 1H), 7.54 (m, 2H), 8.31 (m, 2H). IR (KBr): 3144, 1663, 1587, 1255, 1202, 1149, 898 cm^{-1}. Anal. Calcd for $C_{11}H_5NO_2ClF_3$: C, 47.94; H, 1.83; N, 5.08; Cl, 12.86; F, 20.68. Found: C, 47.77; H, 1.88; N, 5.57; Cl, 12.51; F, 20.18.

Preparation of 2'-(2,5-dimethylphenoxymethyl)acetophenone (**7f**).

A solution of methylmagnesium bromide in THF (0.92 M, 16.3 mL, 15 mmol) was added dropwise to a solution of *N*-methoxy-*N*-methyl-2-(2,5-dimethylphenoxymethyl)benzamide[13] (2.99 g, 10 mmol) in THF (20 mL) below –45°C over 5 min and the mixture was stirred at –45 to 20°C for 2 h. After completion of the reaction, saturated aqueous ammonium chloride solution (50 mL) and water (50 mL) were added, and the mixture was extracted with Et_2O (100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by CC (AcOEt/hexane: 2/8 v/v) to give 1.69 g (66 %) of **7f** as a white solid. Recrystallization (AcOEt/hexane) afforded colorless plates, mp 86–87°C. ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.31 (s, 3H), 2.66 (s, 3H), 5.40 (s, 2H), 6.70 (d, *J*=7.3 Hz, 1H), 6.76 (s, 1H), 7.05 (d, *J*=7.6 Hz, 1H), 7.42 (t, *J*=7.3 Hz, 1H), 7.59 (td, *J*=7.6, 1.3 Hz, 1H), 7.88 (dd, *J*=7.6, 1.3 Hz, 1H), 7.92 (d, *J*=7.6 Hz, 1H).

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