Synthesis M. R. Reddy et al. Paper

Copper(II) Triflate Catalyzed Synthesis of 2,4-Disubstituted Oxazoles from α-Diazoketones

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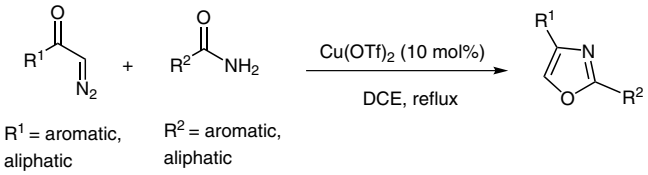

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Abstract A novel method is devised for the synthesis of 2,4-disubstituted oxazole derivatives via the coupling of α-diazoketones with amides using copper(II) triflate as the catalyst. The synthetic versatility of this approach is exemplified in the synthesis of an analogue of balsoxin.

Key words α-diazoketones, amides, copper(II) triflate, oxazoles

The oxazole motif is often found in biologically active natural products (Figure 1), agrochemicals and medicinally important compounds.[1,2] In particular, di- and trisubstituted oxazoles are known to exhibit promising antibacterial,[3a] antimycobacterial,[3b] antiviral,[3c] hypoglycemia[3d] and anticancer activities.[3e] Consequently, numerous methods have been developed for the synthesis of oxazole derivatives, which include intramolecular cyclization of amides,[4] domino reactions of ketones,[5] oxidative cyclization of imines,[6] transition-metal-catalyzed cross-coupling reactions,[7] Fischer oxazole synthesis[8a] and the Robinson–Gabriel synthesis of oxazoles.[8b] Moses et al. have reported the one-step synthesis of oxazoles from α-haloketones, a method which shows broad substrate scope and tolerance to a variety of functional groups.[9a] Recently, Wang et al. reported an oxidative domino reaction for the synthesis of functionalized oxazoles from aryl methyl ketones and benzyl amines.[5c] More recently, Zhang and co-workers reported the synthesis of functionalized oxazoles from α-bromoketones and benzyl amine using the iodine–potassium carbonate (I_2–K_2CO_3) reagent system,[9b] however, this method only worked with aryl ketones. Though numerous procedures have been reported for the synthesis of oxazoles, simple and expedient approaches still remain scarce.

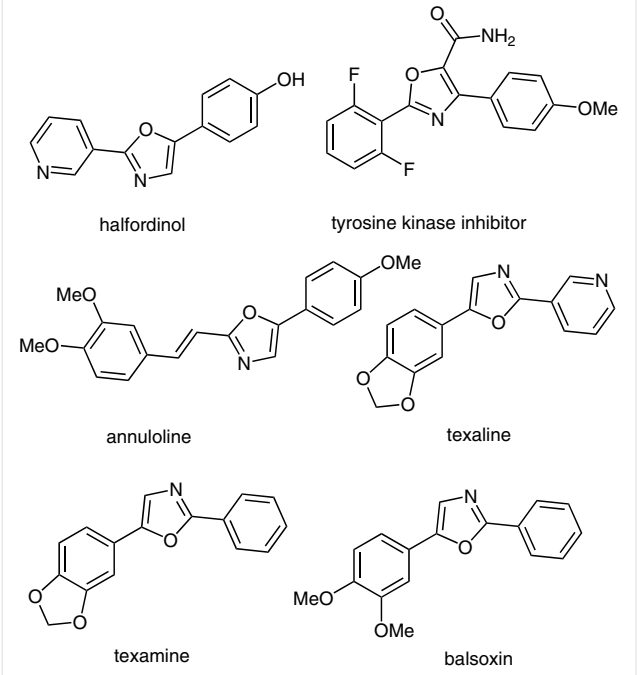
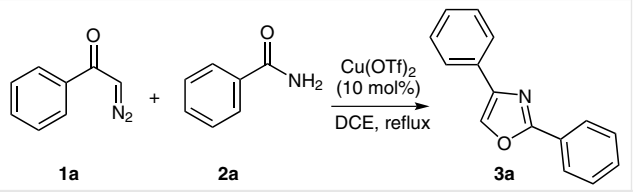


Figure 1 Examples of biologically active natural products containing an oxazole motif

The relative stability and facile decomposition of α-diazocarbonyl compounds under thermal, photochemical and transition-metal-catalysis conditions make them useful intermediates in organic synthesis.[10] Inspired by the synthetic potential of α-diazoketones, we have also explored these compounds for the synthesis of biologically active heterocycles such as imidazo[1,2-*a*]pyridines, 2-aminothiazoles, quinoxalines, and sugar cyclopropanes.[11] Indeed, Moody et al. previously reported the dirhodium tetraacetate [$Rh_2(OAc)_4$] catalyzed reaction of α-diazo-β-ketocarboxyl-

ates and phosphonates with aryl carboxamides to produce 2,4,5-trisubstituted oxazoles by N–H insertion followed by cyclodehydration.[12] However, the scope was limited to the synthesis of oxazoles carrying an additional acceptor group such as carboxylate, phosphonate or sulfone.

In continuation of our interest in the application of α-diazoketones,[13] we herein report a simple and convenient approach for the synthesis of 2,4-disubstituted oxazoles through the coupling of α-diazoketones with amides. As a model reaction, we first attempted the cross-coupling of 2-diazo-1-phenylethanone (**1a**) with benzamide (**2a**) in the presence of copper(II) triflate [$Cu(OTf)_2$] (10 mol%) in 1,2-dichloroethane. The reaction was sluggish at room temperature, however, by increasing the temperature from 25 to 80 °C, the desired product, 2,4-diphenyloxazole (**3a**),[14] was obtained in 87% yield (Scheme 1).



Scheme 1 Synthesis of 2,4-diphenyloxazole (**3a**)

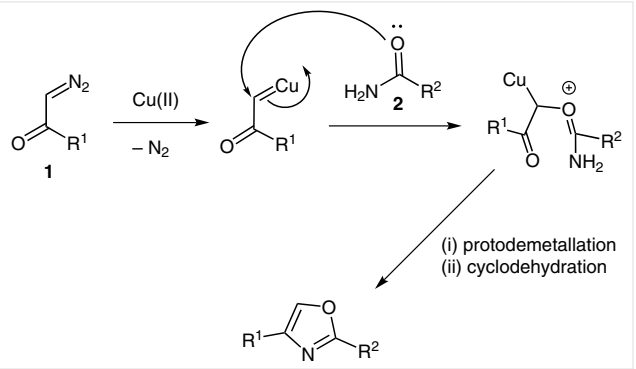
In order to optimize the reaction conditions, several metal catalysts including dirhodium tetraacetate, copper(II) triflate, copper(I) triflate (CuOTf), scandium(III) triflate [$Sc(OTf)_3$], indium(III) triflate [$In(OTf)_3$], bismuth(III) triflate [$Bi(OTf)_3$], copper(II) hexafluoroacetylacetonate [$Cu(hfacac)_2$], copper(II) acetate [$Cu(OAc)_2$], copper(II) acetylacetonate [$Cu(acac)_2$], copper(I) iodide (CuI) and copper(II) sulfate [$CuSO_4$] were screened. Among them, copper(II) triflate (10 mol%) gave the best results in terms of conversion (Table 1, entry 1). In addition, dirhodium tetraacetate (10 mol%) was also effective for this transformation (Table 1, entry 4), however, its use here cannot be recommended as rhodium is significantly more expensive than copper. Furthermore, metal triflates such as scandium(III) triflate, indium(III) triflate, and bismuth(III) triflate were found to be less effective (Table 1, entries 11–13). Solid acids such as clays, heteropolyacids and ion-exchange resins failed to give the desired product. Of the different solvents tested, toluene and tetrahydrofuran were found to be less effective resulting in the formation of product **3a** in lower yields (Table 1, entries 2 and 3).

Next, we extended this method to other aromatic α-diazoketones including 3,4,5-trimethoxyphenyl and 3-methylphenyl derivatives. In most cases, the corresponding oxazole derivatives were obtained in good yields (Table 2, entries 3, 4, 7 and 8). Furthermore, we also examined the reactivity of different aliphatic diazoketones. Interestingly, alkyl α-diazoketones such as 1-diazo-3,3-dimethylbutan-2-one, 1-diazo-3-methylbutan-2-one and 1-diazobutan-2-one afforded the corresponding oxazoles in good yields (Table 2, entries 5, 6 and 10). In addition, this method worked with aliphatic amides. However, the reaction was not successful if both substrates were aliphatic. With aliphatic amides, the corresponding alkyl-substituted oxazoles were obtained in relatively lower yields (Table 2, entries 2, 4 and 8) compared with their aromatic counterparts. In all the cases, the reactions proceeded efficiently in the presence of copper(II) triflate (10 mol%) at 80 °C in 1,2-dichloroethane, and the corresponding products were obtained in good yields. No side products arising from Wolff rearrangements were observed under the present reaction conditions.

Table 1 Screening of Different Catalysts for the Formation of **3a**[a]

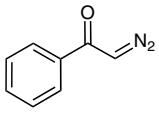
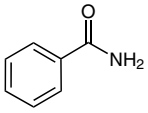
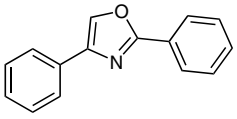
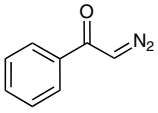
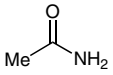
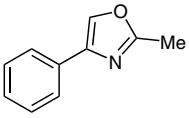
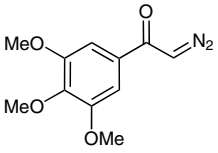
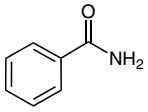
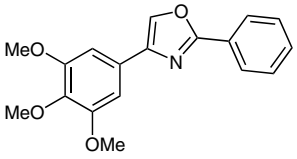
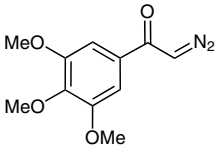
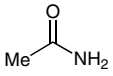
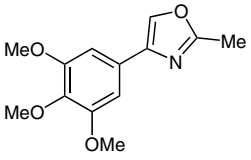
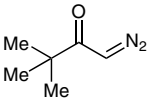
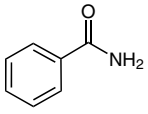
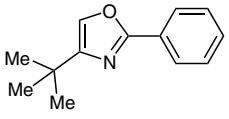
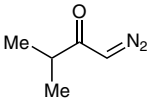
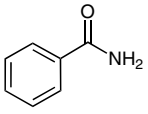
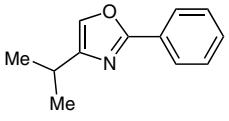
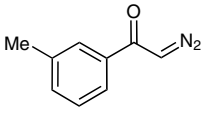
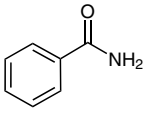
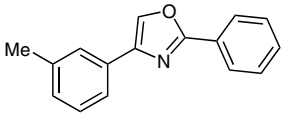
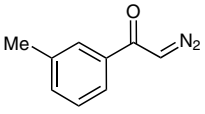
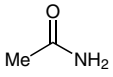
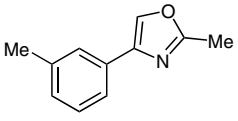
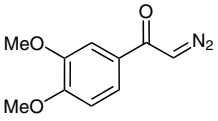
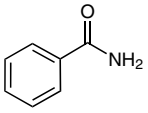
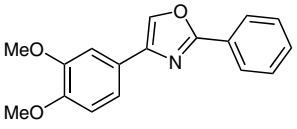
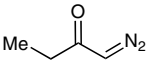
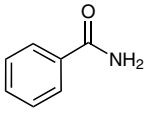
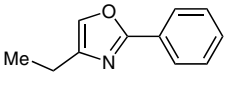
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	$Cu(OTf)_2$	DCE	1	87
2	$Cu(OTf)_2$	THF	2	50
3	$Cu(OTf)_2$	toluene	1	70
4	$Rh_2(OAc)_4$	DCE	1	80
5	$Cu(hfacac)_2$	DCE	2	50
6	$Cu(acac)_2$	DCE	2	50
7	CuOTf	DCE	3	78
8	$Cu(OAc)_2$	DCE	2	65
9	CuI	DCE	3	60
10	$CuSO_4$	DCE	3	65
11	$Sc(OTf)_3$	DCE	5	10
12	$In(OTf)_3$	DCE	4	10
13	$Bi(OTf)_3$	DCE	5	10

[a] Reactions were performed on 0.5 mmol scale with respect to **1a** using 10 mol% of the catalyst.
[b] Yield of isolated pure product after column chromatography.



Scheme 2 A plausible reaction pathway

Table 2 Synthesis of 2,4-Disubstituted Oxazoles[a]

Entry	α-Diazoketone	Amide	Product[a]	Time (h)	Yield (%)[b]
1			3a 	1	87
2			3b 	2	80
3			3c 	1	85
4			3d 	1.5	78
5			3e 	2	75
6			3f 	2	80
7			3g 	2	85
8			3h 	2	75
9			3i 	1	73
10			3j 	2	76

[a] The structures of the products were established from their NMR and IR spectra.
[b] Yield of isolated pure product after column chromatography.

To show the synthetic utility, we applied the present protocol to the synthesis of an analogue of balsoxin. The 2,5-diaryloxazole motif is found in various natural products such as texamine and balsoxin (Figure 1), which were isolated from the roots of *Amyris texana* and *A. plumieri*, respectively.[15] Accordingly, the coupling of commercially available benzamide (**2a**) with 2-diazo-1-(3,4-dimethoxyphenyl)ethanone (**1i**) in the presence of copper(II) triflate (10 mol%) gave the balsoxin analogue **3i** in 73% yield (Table 2, entry 9). This procedure is efficient and practical compared to previous methods.[16]

A plausible mechanism for this reaction is proposed in Scheme 2. In the presence of a catalytic amount of copper(II) triflate in 1,2-dichloroethane, diazoketone **1** decomposes with evolution of nitrogen to form a copper carbenoid species, which reacts rapidly with carboxamide **2**. Subsequent attack of the carbonyl group, in preference to N–H insertion on the copper carbenoid, followed by cyclodehydration gives the desired 2,4-disubstituted oxazole (Scheme 2).

In the case of carboxamides, N–H insertion, with formation of a C–N bond, is generally a favorable reaction pathway.[12b] However, there are a few examples reported involving the formation of a C–O bond in the reaction of a carbene with a carboxamide when an N–H bond is also available for insertion.[17] In the present case, the change in selectivity is presumably electronic in nature, reflecting the changes in the electrophilicity of the carbene.

In conclusion, we have developed a novel protocol for the synthesis of 2,4-disubstituted oxazoles. This method offers several advantages such as good yields, the use of cost-effective reagents, and a low catalyst loading, which should make it an attractive procedure for the synthesis of a wide range of 2,4-disubstituted oxazoles.

The α-diazoketones were prepared using reported conditions.[18] CH_2Cl_2 was distilled from CaH under an N_2 atmosphere. Column chromatography was performed using **??**brand**??** silica gel (**??**mesh size**??**). Melting points were measured on a Triad Scientific Micro melting point apparatus. IR spectra were recorded on a Shimadzu FT-IR spectrometer and absorptions are reported in reciprocal centimeters (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 500 MHz and 300 MHz spectrometers. Tetramethylsilane (TMS) (δ = 0) was used as the internal standard for ^1H NMR spectroscopy, and the values are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets). Coupling constants are reported in Hz. The signal for residual non-deuterated $CDCl_3$ (δ = 77.27) was used as the internal standard for ^{13}C NMR spectroscopy, and spectra were obtained with complete proton decoupling. Low- and high-resolution mass spectra were obtained using a VG AutoSpec triple sector mass spectrometer.

2,4-Disubstituted Oxazoles; General Procedure

A mixture of α-diazoketone (1.2 mmol), amide (1 mmol) and $Cu(OTf)_2$ (0.1 mmol) in DCE (10 mL) was stirred at 80 °C for the appropriate period of time (see Table 2). After completion, as indicated by TLC, the mixture was quenched with H_2O and extracted with EtOAc (2 × 15 mL). Evaporation of the solvent followed by purification over silica gel (**??**–**??**) afforded the pure oxazole **3**.

2,4-Diphenyloxazole (3a)

Yield: 190 mg (87%); white solid; mp 72–74 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.14–8.06 (m, 2 H, Ar-H), 7.92 (s, 1 H, oxaz-CH), 7.80–7.77 (m, 3 H, Ar-H), 7.48–7.36 (m, 4 H, Ar-H), 7.31–7.25 (m, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 141.2, 132.7, 130.4, 129.7, 128.0, 127.4, 126.9, 125.9, 125.0.

MS (ESI): *m*/*z* = 222 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}NO$: 222.0918; found: 222.0951.

2-Methyl-4-phenyloxazole (3b)

Yield: 127 mg (80%); semi-solid.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (s, 1 H, oxaz-CH), 7.64 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.34 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.25–7.21 (m, 1 H, Ar-H), 2.50 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 139.8, 132.4, 128.0, 127.2, 124.7, 14.7.

MS (ESI): *m*/*z* = 160 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{10}NO$: 160.0762; found: 160.0769.

2-Phenyl-4-(3,4,5-trimethoxyphenyl)oxazole (3c)

Yield: 264 mg (85%); semi-solid.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.09 (m, 2 H, Ar-H), 7.86 (s, 1 H, oxaz-CH), 7.47–7.42 (m, 3 H, Ar-H), 6.99 (s, 2 H, Ar-H), 3.94 (s, 6 H, OCH_3), 3.84 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 153.5, 141.8, 133.1, 130.4, 128.7, 127.3, 126.7, 126.4, 106.0, 102.7, 60.9, 56.2, 56.1.

MS (ESI): *m*/*z* = 312 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{17}NO_4Na$: 334.1055; found: 334.1058.

2-Methyl-4-(3,4,5-trimethoxyphenyl)oxazole (3d)

Yield: 194 mg (78%); semi-solid.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.70 (s, 1 H, oxaz-CH), 6.87 (s, 2 H, Ar-H), 3.90 (s, 6 H, OCH_3), 3.82 (s, 3 H, OCH_3), 2.50 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 152.5, 139.7, 137.1, 132.1, 126.1, 102.2, 61.0, 56.3, 14.6.

MS (ESI): *m*/*z* = 272 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{15}NO_4Na$: 272.0898; found: 272.0895.

4-*tert*-Butyl-2-phenyloxazole (3e)

Yield: 150 mg (75%); semi-solid.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.97 (m, 2 H, Ar-H), 7.46–7.31 (m, 3 H, Ar-H), 7.23 (s, 1 H, oxaz-CH), 1.30 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 160.5, 129.7, 128.6, 127.8, 125.9, 120.9, 32.4, 28.6.

MS (ESI): *m*/*z* = 202 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{16}NO$: 202.1231; found: 202.1234.

4-Isopropyl-2-phenyloxazole (3f)

Yield: 149 mg (80%); semi-solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.97 (m, 2 H, Ar-H), 7.42–7.37 (m, 3 H, Ar-H), 7.33 (s, 1 H, oxaz-H), 2.86–2.83 (m, 1 H, CH), 1.29 (d, *J* = 6.8 Hz, 6 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 158.1, 129.7, 128.6, 127.8, 125.9, 121.7, 26.2, 20.6.

MS (ESI): *m*/*z* = 188 $[M + H]^+$.

2-Phenyl-4-(3-tolyl)oxazole (3g)

Yield: 199 mg (85%); brown solid; mp 70–72 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11–8.08 (m, 2 H, Ar-H), 7.89 (s, 1 H, oxaz-H), 7.61–7.54 (m, 2 H, Ar-H), 7.47–7.41 (m, 3 H, Ar-H), 7.26–7.22 (m, 1 H, Ar-H), 7.07 (d, *J* = 7.5 Hz, 1 H, Ar-H), 2.41 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 150.8, 141.1, 129.7, 128.9, 128.7, 128.0, 126.4, 124.9, 124.3, 123.0, 21.8.

MS (ESI): *m*/*z* = 236 $[M + H]^+$.

2-Methyl-4-(3-tolyl)oxazole (3h)

Yield: 129 mg (75%); semi-solid.

IR (KBr): 2937, 1683, 1542, 1384, 1015, 935, 762 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (s, 1 H, oxaz-H), 7.45 (d, *J* = 1.2 Hz, 1 H, Ar-H), 7.40–7.37 (m, 1 H, Ar-H), 7.18–7.13 (m, 1 H, Ar-H), 7.01 (d, *J* = 7.5 Hz, 1 H, Ar-H), 2.44 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 139.9, 137.6, 132.4, 128.0, 127.9, 125.4, 121.8, 22.0, 14.6.

MS (ESI): *m*/*z* = 174 $[M + H]^+$.

4-(3,4-Dimethoxyphenyl)-2-phenyloxazole (3i)

Yield: 205 mg (73%); brown solid; mp 98–100 °C.

IR (KBr): 2983, 1675, 1496, 1378, 1031, 948, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12–8.10 (m, 2 H, Ar-H), 7.53–7.46 (m, 3 H, Ar-H), 7.36 (s, 1 H, oxaz-H), 7.33 (dd, *J* = 1.9, 8.3 Hz, 1 H, Ar-H), 7.22 (d, *J* = 1.9 Hz, 1 H, Ar-H), 6.96 (d, *J* = 8.3 Hz, 1 H, Ar-H), 4.01 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0, 150.7, 148.9, 148.7, 129.7, 128.4, 127.1, 125.7, 121.8, 120.7, 116.9, 111.2, 107.2, 56.1, 56.1.

MS (ESI): *m*/*z* = 282 $[M + H]^+$.

4-Ethyl-2-phenyloxazole (3j)

Yield: 137 mg (80%); semi-solid.

IR (KBr): 2802, 1623, 1525, 1376, 1043, 788 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.96 (m, 2 H, Ar-H,), 7.44–7.35 (m, 4 H, Ar-H, oxaz-H), 2.60 (q, *J* = 7.6 Hz, 2 H, CH_2), 1.28 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 129.7, 128.6, 127.8, 125.9, 122.0, 28.3, 17.2.

MS (ESI): *m*/*z* 174 $[M]^+$.

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Supporting Information

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