One-Pot Synthesis of Isoxazolines from Aldehydes Catalyzed by Iodobenzene

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Abstract: A convenient one-pot, three-step procedure for the synthesis of isoxazolines starting from aldehydes has been developed involving catalytic cycloaddition between nitrile oxides and alkenes, in which iodobenzene is used as the catalyst for the in situ generation of a hypervalent iodine intermediate. In this approach, the aldehydes are first transformed with hydroxylamine sulfate into aldoximes, which are then oxidized to nitrile oxides by the in situ generated hypervalent iodine intermediate; finally, a 1,3-dipolar cycloaddition between the nitrile oxides and alkenes occurs to provide the isoxazolines in moderate to good yields.

Key words: one-pot synthesis, isoxazolines, iodobenzene, hypervalent iodine intermediate, catalytic cycloaddition

Isoxazolines are very important nitrogen-containing heterocycles, which are found in a large number of natural products and biologically active compounds.[1] A variety of synthetic methods have been developed for the preparation of isoxazolines, of which the most convenient and attractive route is probably the 1,3-dipolar cycloaddition of nitrile oxides to alkenes.[2] Nitrile oxides are commonly generated from aldoximes via oxidation using various oxidants, including NBS, NCS, NaOCl, *t*-BuOCl and *t*-BuOI.[3] All of these methods involve two steps and give highly variable yields. With low toxicity, ready availability, easy handling and reactivity similar to that of heavy metal reagents, hypervalent iodine reagents have been used to induce the 1,3-dipolar cycloaddition of nitrile oxides derived from aldoximes to alkenes in a new improvement of the process.[4] However, a stoichiometric amount of the hypervalent iodine reagent is usually needed in this process, a situation which is not perfect from both environmental and economic viewpoints.

In recent years, the catalytic utilization of hypervalent iodine reagents has been increasing in importance, with a growing interest in the development of environmentally benign synthetic transformations.[5] In these catalytic reactions, a catalytic amount of an iodine-containing compound together with a stoichiometric oxidant is used. Very recently, Zhdankin and co-workers have published two papers on the organocatalytic cycloaddition of nitrile oxides to alkenes.[6] Using Oxone® ($2KHSO_5$–$KHSO_4$–K_2SO_4) as the terminal oxidant, they found that the inorganic salt potassium iodide and aryl iodides can improve the cycloaddition when used in various methods as catalysts via the in situ generated hypoiodous acid and hypervalent iodine intermediates. At the same time, we have also developed a similar catalytic cycloaddition between nitrile oxides derived from aldoximes and alkenes using iodobenzene (PhI) as the catalyst and *m*-chloroperoxybenzoic acid (*m*-CPBA) as the terminal oxidant. Based on this, a convenient one-pot, three-step procedure for the synthesis of isoxazolines starting from the easier-to-obtain and mostly commercially available aldehydes is now reported. To our knowledge, such a one-pot synthesis of isoxazolines starting from aldehydes using PhI as the catalyst and *m*-CPBA as the terminal oxidant has not been reported previously.

Initially, benzaldehyde was chosen as the representative aldehyde for reaction with hydroxylamine hydrochloride to form the corresponding aldoxime; however, it was found that the byproduct NaCl can be oxidized by *m*-CPBA into Cl_2, which disturbed the catalytic cycloaddition. To avoid formation of Cl_2, hydroxylamine sulfate was selected for use in the reaction. Then, the one-pot reaction of benzaldehyde (**1a**) with hydroxylamine sulfate (0.6 equiv), styrene (**2a**, 2.0 equiv) and *m*-CPBA (1.4 equiv) in the presence of a catalytic amount of PhI (0.2 equiv) in different solvents was investigated (Table 1). As hydroxylamine sulfate is an ionic compound with poor solubility in organic solvents, we first examined three kinds of high polarity organic solvents, namely methyl alcohol, glycol and 2,2,2-trifluoroethanol (TFE); however, although the reaction in TFE provided a 47% yield of isoxazoline **3a**, the other solvents usually led to rather poor yields (Table 1, entries 1–3). The same experiment was conducted in water, but none of the desired product was found as the oxidant *m*-CPBA is nearly water insoluble (Table 1, entry 4). In order to improve the reaction, a mixed solvent was used to ensure that both organic compounds and ionic salts have good solubility. TFE and water were mixed as the mixed solvent; when the one-pot reaction was carried out in TFE–H_2O (3:1, v/v), a surprising improvement to 70% isolated yield was obtained (Table 1, entry 5). Encouraged by this result, we undertook a series of experiments with different solvent volume ratios; TFE–H_2O (2.6:1, v/v) was found to be the most effective for the one-pot reaction (Table 1, entries 6–12). Other organic–water mixed solvents were also tested, but none of the yields exceeded 36% (Table 1, entries 13–18).

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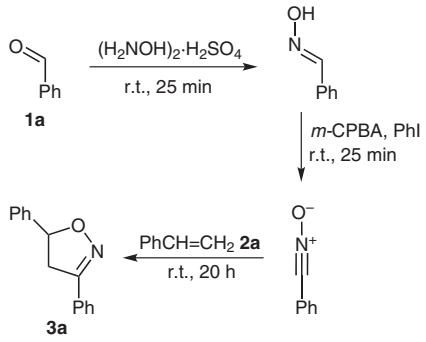
Table 1 Synthesis of Isoxazoline **3a** in Different Solvents



Entry	Solvent	Yield[a] (%)
1	MeOH	22
2	glycol	13
3	TFE	47
4	H_2O	–
5	TFE–H_2O (3:1)	70
6	TFE–H_2O (6:1)	21
7	TFE–H_2O (5:1)	64
8	TFE–H_2O (4:1)	68
9	TFE–H_2O (2.6:1)	75
10	TFE–H_2O (2:1)	72
11	TFE–H_2O (1.5:1)	71
12	TFE–H_2O (1:1)	68
13	MeOH–H_2O (2.6:1)	36
14	EtOH–H_2O (2.6:1)	16
15	MeCN–H_2O (2.6:1)	3
16	THF–H_2O (2.6:1)	9
17	DMF–H_2O (2.6:1)	9
18	glycol–H_2O (2.6:1)	32

[a] Isolated yields.

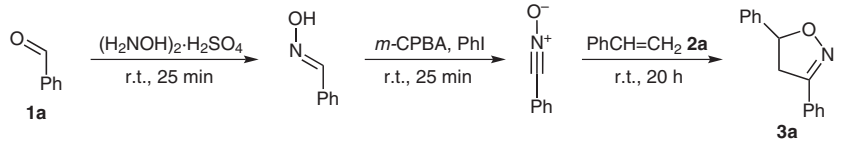
Using the mixture of TFE–H_2O (2.6:1, v/v) as solvent, other reaction conditions were optimized. As shown in Table 2, when 1.0 equivalent of benzaldehyde (**1a**) was treated consecutively with 0.6 equivalents of hydroxylamine sulfate, 1.4 equivalents of *m*-CPBA and 2.0 equivalents of styrene (**2a**) in the absence of PhI at room temperature for several hours, none of the desired product, 3,5-diphenyl-4,5-dihydroisoxazole (**3a**), was observed (Table 2, entry 1). When catalytic amounts of PhI were added under the same reaction conditions, the reaction was improved and the product **3a** was provided in moderate to good yields; use of 0.2 equivalents of PhI to mediate the reaction resulted in the best yield of 82% (Table 2, entries 2–4), which is higher than that obtained by Zhdankin and co-workers.[6b]

The optimal amounts of hydroxylamine sulfate, *m*-CPBA and styrene (**2a**) were also investigated and finally determined: 0.6 equivalents of hydroxylamine sulfate for step one (Table 2; entries 3, 5 and 6), 1.4 equivalents of *m*-CPBA for step two (entries 3, 7 and 8) and 2.0 equivalents of **2a** for the last step (entries 3, 9 and 10) were selected. The suitable reaction times for the three steps are 60 minutes (Table 2; entries 3, 11 and 12), 30 minutes (entries 3, 13 and 14) and 5 hours (entries 3, 15 and 16), respectively.

With the optimal reaction conditions in hand, the one-pot, three-step procedure starting from aldehydes was investigated, and a series of isoxazolines was obtained; the results are summarized in Table 3. When benzaldehyde (**1a**) was used as starting material, the reaction was compatible with the studied alkenes and provided the corresponding isoxazolines in moderate to good yields, except for the reaction with indene (**2f**) (Table 3, entries 1–8). Other aromatic aldehydes, such as 2-naphthaldehyde (**1b**) and substituted benzaldehydes which bear an electron-donating group (**1c**, **1d**) or electron-withdrawing group(s) on the benzene ring (**1e**–**h**), all reacted easily with styrene (**2a**) and afforded the isoxazolines in good to excellent yields (Table 3, entries 9–15). When aliphatic rather than aromatic aldehyde was used, the results were quite different: use of phenylacetaldehyde (**1i**) led to a rather low yield of 36%, while no product was observed with propanal (**1j**) (Table 3, entries 16 and 17). In the same manner, phenylacetylene (**2i**) was used, taking the place of alkene, to explore the possibility of the synthesis of isoxazoles. The yield of the desired isoxazole **3q**, however, was poor (Table 3, entry 18), indicating that this one-pot, three-step procedure is more suitable for the synthesis of isoxazolines.

Based on the remarkable catalytic effect of iodobenzene for the oxidation of aldoxime, a plausible catalytic mechanism is proposed (Scheme 1). Thus, iodobenzene is first oxidized by *m*-CPBA to the hypervalent iodine intermediate, which then transforms the aldoxime, derived from the aldehyde, into the nitrile oxide. Finally, a 1,3-dipolar cycloaddition of the nitrile oxide to the alkene occurs to provide the corresponding isoxazoline. The reduced byproduct, PhI, is reoxidized to the hypervalent iodine reagent by *m*-CPBA in the recycling reaction.

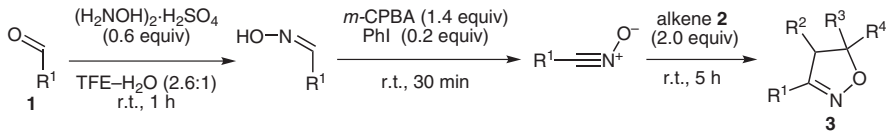
Table 2 Optimization of the Catalytic Cycloaddition for the Synthesis of Isoxazoline **3a** in TFE–H_2O (2.6:1)



Entry	$(H_2NOH)_2{\cdot}H_2SO_4$ (equiv)	Time 1 (min)	*m*-CPBA (equiv)	PhI (equiv)	Time 2 (min)	**2a** (equiv)	Time 3 (h)	Yield[a] (%) of **3a**
1	0.6	60	1.4	0	30	2.0	5	0
2	0.6	60	1.4	0.1	30	2.0	5	51
3	0.6	60	1.4	0.2	30	2.0	5	82
4	0.6	60	1.4	0.3	30	2.0	5	62
5	0.5	60	1.4	0.2	30	2.0	5	71
6	0.7	60	1.4	0.2	30	2.0	5	70
7	0.6	60	1.2	0.2	30	2.0	5	54
8	0.6	60	1.6	0.2	30	2.0	5	67
9	0.6	60	1.4	0.2	30	1.5	5	80
10	0.6	60	1.4	0.2	30	2.5	5	83
11	0.6	40	1.4	0.2	30	2.0	5	77
12	0.6	80	1.4	0.2	30	2.0	5	78
13	0.6	60	1.4	0.2	20	2.0	5	81
14	0.6	60	1.4	0.2	40	2.0	5	70
15	0.6	60	1.4	0.2	30	2.0	3	75
16	0.6	60	1.4	0.2	30	2.0	7	80

[a] Isolated yields.

Table 3 One-Pot Synthesis of Isoxazolines from Aldehydes Catalyzed by Iodobenzene



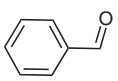
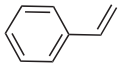
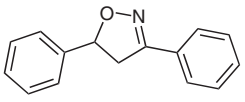
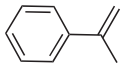
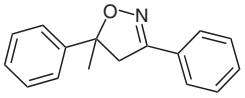
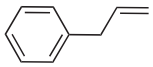
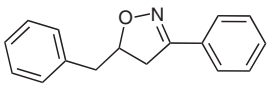
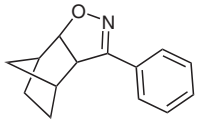
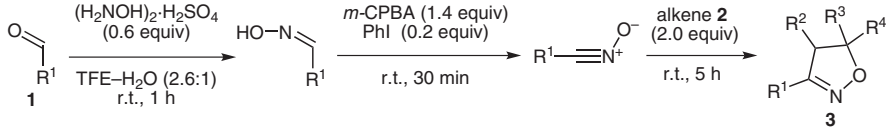
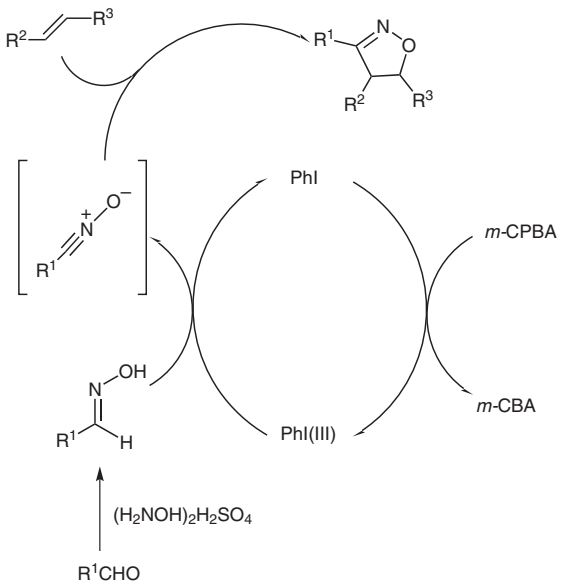
Entry	Aldehyde		Alkene		Product		Yield[a] (%)
1	**1a**		**2a**		**3a**		82
2	**1a**		**2b**		**3b**		62
3	**1a**		**2c**		**3c**		73
4	**1a**		**2d**		**3d**		80

Table 3 One-Pot Synthesis of Isoxazolines from Aldehydes Catalyzed by Iodobenzene (continued)



Entry	Aldehyde	Alkene	Product	Yield[a] (%)
5	**1a**	**2e**	**3e**	63
6	**1a**	**2f**	**3f**	49
7	**1a**	**2g**	**3g**	82
8	**1a**	**2h**	**3h**	67
9[b]	**1b**	**2a**	**3i**	82
10	**1c**	**2a**	**3j**	84
11[c]	**1d**	**2a**	**3k**	78
12[d]	**1e**	**2a**	**3l**	90
13[d]	**1f**	**2a**	**3m**	94
14[d]	**1g**	**2a**	**3n**	71
15[d]	**1h**	**2a**	**3o**	82
16	**1i**	**2a**	**3p**	36
17	**1j**	**2a**	–	–[e]
18	**1a**	**2i**	**3q**	29

[a] Isolated yields.
[b] The time for the oxidation of aldoxime was 50 min.
[c] The time for the oxidation of aldoxime was 45 min.
[d] The time for the oxidation of aldoxime was 1 h.
[e] Not detected.



Scheme 1 Proposed reaction mechanism for the one-pot synthesis of isoxazolines

In conclusion, we have developed a convenient one-pot, three-step procedure for the synthesis of isoxazolines starting from aldehydes. This approach, which was improved by the addition of a catalytic amount of iodobenzene for the in situ generation of a hypervalent iodine intermediate, has advantages such as the use of easily available aldehydes, mild reaction conditions and a simple procedure, and provided a series of isoxazolines in moderate to good yields. Furthermore, the scope of hypervalent iodine reagents in organic synthesis was extended.

Melting points were measured with an XT-4 melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet 6700 instrument, ^{1}H and ^{13}C NMR spectra were measured on a Bruker AVANCE III (500 MHz) spectrometer, and mass spectra were determined on a Thermo ITQ 1100 mass spectrometer. Aldehydes, alkenes, hydroxylamine sulfate, *m*-CPBA, PhI and phenylacetylene were commercially available.

One-Pot Synthesis of Isoxazolines 3; General Procedure

To a mixture of TFE (2.2 mL) and H_2O (0.8 mL), an aldehyde **1** (0.5 mmol) and hydroxylamine sulfate (0.3 mmol) were first added, and the mixture was stirred at r.t. for 1 h. Then, *m*-CPBA (0.7 mmol) and PhI (0.1 mmol) were added and stirring was continued. After 30 min, an alkene **2** (1 mmol) was added to the mixture which was stirred for another 5 h, until the reaction was completed. Then, H_2O (10 mL), sat. aq $Na_2S_2O_3$ (2 mL) and sat. aq Na_2CO_3 (2 mL) were added, and the mixture was stirred for 10 min. The mixture was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by TLC on a silica gel plate (petroleum ether–EtOAc, 3:1) to provide the corresponding pure isoxazoline **3**.

3,5-Diphenyl-4,5-dihydroisoxazole (3a)

Yield: 91 mg (82%); white solid; mp 72–73 °C (Lit.[7] 74–75 °C).

IR (neat): 1448, 1365, 896, 752, 696, 545 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 2 H), 7.45–7.39 (m, 7 H), 7.38–7.33 (m, 1 H), 5.77 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.81 (dd, *J* = 15.0, 10.0 Hz, 1 H), 3.37 (dd, *J* = 15.0, 10.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.09, 140.93, 130.12, 129.47, 128.75, 128.73, 128.21, 126.73, 125.86, 82.56, 43.15.

MS (ESI): *m*/*z* (%) = 224 (100) [M$^+$ + 1].

5-Methyl-3,5-diphenyl-4,5-dihydroisoxazole (3b)

Yield: 73 mg (62%); white solid; mp 75–76 °C (Lit.[7] 72–76 °C).

IR (neat): 1445, 1360, 902, 749, 700, 537 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 2 H), 7.56–7.53 (m, 2 H), 7.42–7.38 (m, 5 H), 7.33–7.30 (m, 1 H), 3.53 (q, *J* = 15.0 Hz, 2 H), 1.85 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.07, 145.41, 129.86, 129.79, 128.57, 128.41, 127.27, 126.45, 124.59, 87.98, 48.58, 28.12.

MS (ESI): *m*/*z* (%) = 238 (100) [M$^+$ + 1].

5-Benzyl-3-phenyl-4,5-dihydroisoxazole (3c)

Yield: 87 mg (73%); white solid; mp 67–69 °C (Lit.[1h] 67.5–68.2 °C).

IR (neat): 1446, 1360, 917, 755, 700, 511 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 2 H), 7.43–7.39 (m, 3 H), 7.38–7.33 (m, 2 H), 7.31–7.26 (m, 3 H), 5.05–4.99 (m, 1 H), 3.34 (dd, *J* = 15.0, 10.0 Hz, 1 H), 3.20 (dd, *J* = 15.0, 5.0 Hz, 1 H), 3.08 (dd, *J* = 15.0, 5.0 Hz, 1 H), 2.92 (dd, *J* = 15.0, 10.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.40, 136.90, 129.95, 129.68, 129.35, 128.90–128.60 (m), 127.07, 126.65 (d, *J* = 16.3 Hz), 81.83, 41.01, 39.35.

MS (ESI): *m*/*z* (%) = 238 (100) [M$^+$ + 1].

3-Phenyl-3a,4,5,6,7,7a-hexahydro-4,7-methano-1,2-benzisoxazole (3d)

Yield: 85 mg (80%); white solid; mp 97–98 °C (Lit.[8] 97–100 °C).

IR (neat): 2969, 1448, 1357, 913, 774, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 2 H), 7.43–7.38 (m, 3 H), 4.64 (d, *J* = 10.0 Hz, 1 H), 3.50 (d, *J* = 10.0 Hz, 1 H), 2.63 (d, *J* = 5.0 Hz, 1 H), 2.53 (s, 1 H), 1.62–1.51 (m, 3 H), 1.38–1.32 (m, 1 H), 1.23–1.15 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.83, 129.63, 129.36, 128.63, 126.78, 87.82, 57.00, 42.95, 39.22, 32.27, 27.37, 22.67.

MS (ESI): *m*/*z* (%) = 214 (100) [M$^+$ + 1].

5-Butyl-3-phenyl-4,5-dihydroisoxazole (3e)

Yield: 64 mg (63%); white solid; mp 39–41 °C (Lit.[9] 40–42 °C).

IR (neat): 2955, 2929, 2858, 1360, 918, 903, 756, 691, 549 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.64 (m, 2 H), 7.44–7.37 (m, 3 H), 4.78–4.71 (m, 1 H), 3.40 (dd, *J* = 15.0, 10.0 Hz, 1 H), 2.98 (dd, *J* = 15.0, 10.0 Hz, 1 H), 1.84–1.77 (m, 1 H), 1.69–1.62 (m, 1 H), 1.54–1.45 (m, 1 H), 1.43–1.36 (m, 3 H), 0.94 (t, *J* = 10.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.32, 129.89, 129.79, 128.58, 126.51, 81.43, 39.87, 34.96, 27.59, 22.49, 13.93.

MS (ESI): *m*/*z* (%) = 204 (65) [M$^+$ + 1], 181 (100).

3-Phenyl-3a,8b-dihydro-4*H*-indeno[2,1-*d*]isoxazole (3f)

Yield: 58 mg (49%); pale yellow solid; mp 125–127 °C (Lit.[10] 134–135 °C).

IR (neat): 1443, 1349, 913, 891, 758, 744, 692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77–7.70 (m, 2 H), 7.62–7.58 (m, 1 H), 7.47–7.40 (m, 3 H), 7.36–7.31 (m, 2 H), 7.24–7.20 (m, 1 H), 6.24 (d, *J* = 10.0 Hz, 1 H), 4.56 (td, *J* = 10.0, 5.0 Hz, 1 H), 3.51 (dd, *J* = 15.0, 10.0 Hz, 1 H), 3.26 (dd, *J* = 15.0, 5.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.50, 140.60 (d, *J* = 12.5 Hz), 129.74, 129.42, 128.69, 127.48, 127.01, 125.70, 124.69, 89.41, 50.25, 36.41.

MS (ESI): *m*/*z* (%) = 236 (100) [M^+ + 1].

5-(4-Bromophenyl)-3-phenyl-4,5-dihydroisoxazole (3g)
Yield: 124 mg (82%); white solid; mp 128–129 °C (Lit.[6a] 129.8–130.3 °C).

IR (neat): 2872, 1487, 1447, 1356, 883, 804, 761, 690 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79–7.62 (m, 2 H), 7.60–7.50 (m, 2 H), 7.47–7.38 (m, 3 H), 7.29 (dd, *J* = 8.8, 2.0 Hz, 2 H), 5.72 (dd, *J* = 11.0, 8.0 Hz, 1 H), 3.81 (dd, *J* = 16.6, 11.0 Hz, 1 H), 3.31 (dd, *J* = 16.6, 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.06, 140.04, 131.90, 130.30, 129.24, 128.80, 127.57, 126.77, 122.15, 81.81, 43.20.

MS (ESI): *m*/*z* (%) = 302 (52) [M^+ + 1], 383 (100).

5-(Hydroxymethyl)-3-phenyl-4,5-dihydroisoxazole (3h)
Yield: 59 mg (67%); white solid; mp 78–79 °C (Lit.[1i] 83–84 °C).

IR (neat): 3393, 1361, 1052, 895, 755, 691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 2 H), 7.45–7.39 (m, 3 H), 4.91–4.86 (m, 1 H), 3.90–3.86 (m, 1 H), 3.72–3.68 (m, 1 H), 3.40 (dd, *J* = 20.0, 10.0 Hz, 1 H), 3.30 (dd, *J* = 15.0, 5.0 Hz, 1 H), 2.24 (dd, *J* = 5.0, 5.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.07, 130.16, 129.30, 128.69, 126.69, 81.26, 63.62, 36.31.

MS (ESI): *m*/*z* (%) = 178 (8) [M^+ + 1], 195 (100).

3-(Naphthalen-2-yl)-5-phenyl-4,5-dihydroisoxazole (3i)[11]
Yield: 112 mg (82%); orange-red solid; mp 125–127 °C.

IR (neat): 3056, 2920, 909, 863, 822, 767, 703, 478 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.92 (d, *J* = 0.5 Hz, 1 H), 7.86 (ddd, *J* = 12.7, 7.7, 5.2 Hz, 3 H), 7.58–7.51 (m, 2 H), 7.48–7.38 (m, 4 H), 7.35 (ddt, *J* = 5.9, 4.5, 2.3 Hz, 1 H), 5.82 (dd, *J* = 11.0, 8.3 Hz, 1 H), 3.92 (dd, *J* = 16.5, 11.0 Hz, 1 H), 3.56–3.45 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.30, 140.97, 134.07, 133.02, 128.82, 128.60, 128.34 (d, *J* = 13.6 Hz), 127.88, 127.28–126.92 (m), 126.73, 125.95, 123.64, 82.79, 43.11.

MS (ESI): *m*/*z* (%) = 274 (100) [M^+ + 1].

3-(4-Methylphenyl)-5-phenyl-4,5-dihydroisoxazole (3j)
Yield: 100 mg (84%); white solid; mp 96–97 °C (Lit.[3i] 97 °C).

IR (neat): 1350, 901, 824, 758, 698, 532 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 5.0 Hz, 2 H), 7.44–7.37 (m, 4 H), 7.36–7.32 (m, 1 H), 7.24 (d, *J* = 5.0 Hz, 2 H), 5.74 (dd, *J* = 10.0, 10.0 Hz, 1 H), 3.79 (dd, *J* = 15.0, 10.0 Hz, 1 H), 3.35 (dd, *J* = 15.0, 5.0 Hz, 1 H), 2.40 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.03, 141.03, 140.34, 129.41, 128.70, 128.14, 126.67, 125.86, 82.38, 43.26, 21.41.

MS (ESI): *m*/*z* (%) = 238 (100) [M^+ + 1].

3-(4-Isopropylphenyl)-5-phenyl-4,5-dihydroisoxazole (3k)
Yield: 103 mg (78%); yellow solid; mp 57–59 °C.

IR (neat): 2957, 1457, 1433, 898, 839, 761, 701, 559 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.62 (m, 2 H), 7.43–7.36 (m, 4 H), 7.36–7.26 (m, 3 H), 5.74 (dd, *J* = 10.9, 8.1 Hz, 1 H), 3.83–3.75 (m, 1 H), 3.35 (dd, *J* = 16.6, 8.1 Hz, 1 H), 2.96 (heptet, *J* = 6.9 Hz, 1 H), 1.28 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.99, 151.25, 141.06, 128.69, 128.13, 127.00, 126.80, 125.84, 82.36, 43.28, 34.04, 23.75.

MS (ESI): *m*/*z* (%) = 266 (75) [M^+ + 1], 167 (100).

HRMS: *m*/*z* [M^+] calcd for $C_{18}H_{19}NO$: 265.1467; found: 265.1468.

3-(2-Chlorophenyl)-5-phenyl-4,5-dihydroisoxazole (3l)[12]
Yield: 116 mg (90%); yellow oil.

IR (neat): 3064, 3032, 1434, 1078, 1038, 900, 756, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76–7.67 (m, 1 H), 7.49–7.29 (m, 8 H), 5.78 (dd, *J* = 10.8, 8.5 Hz, 1 H), 3.94 (dd, *J* = 17.1, 10.8 Hz, 1 H), 3.54 (dd, *J* = 17.1, 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.15, 140.55, 132.87, 130.90, 130.61 (d, *J* = 5.6 Hz), 129.03, 128.78, 128.31, 127.03, 125.97, 83.29, 45.45.

MS (ESI): *m*/*z* (%) = 258 (100) [M^+ + 1].

3-(2-Bromophenyl)-5-phenyl-4,5-dihydroisoxazole (3m)
Yield: 142 mg (94%); yellow oil.

IR (neat): 3063, 3032, 1431, 1341, 1028, 894, 755, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 1 H), 7.62–7.55 (m, 1 H), 7.50–7.33 (m, 6 H), 7.29 (dt, *J* = 7.6, 1.6 Hz, 1 H), 5.79 (dd, *J* = 10.8, 8.5 Hz, 1 H), 3.94 (dd, *J* = 17.1, 10.9 Hz, 1 H), 3.59–3.48 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.08, 140.46, 133.69, 131.09, 130.95, 130.87, 128.71, 128.24, 127.49, 125.93, 121.83, 83.18, 45.49.

MS (ESI): *m*/*z* (%) = 302 (19) [M^+ + 1], 167 (100).

HRMS: *m*/*z* [M^+] calcd for $C_{15}H_{12}BrNO$: 301.0093; found: 301.0102.

3-(4-Fluorophenyl)-5-phenyl-4,5-dihydroisoxazole (3n)[13]
Yield: 86 mg (71%); white solid; mp 91–92 °C.

IR (neat): 3068, 2885, 1349, 1230, 902, 844, 758, 699, 596, 541 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76–7.65 (m, 2 H), 7.46–7.31 (m, 5 H), 7.17–7.05 (m, 2 H), 5.76 (dd, *J* = 11.0, 8.3 Hz, 1 H), 3.84–3.70 (m, 1 H), 3.39–3.28 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.79, 162.80, 155.15, 140.80, 128.88–128.54 (m), 128.30, 125.94–125.65 (m), 115.98, 115.81, 82.69, 43.22.

MS (ESI): *m*/*z* (%) = 242 (100) [M^+ + 1].

3-(2-Bromo-4-chlorophenyl)-5-phenyl-4,5-dihydroisoxazole (3o)
Yield: 137 mg (82%); yellow oil.

IR (neat): 3065, 3032, 1474, 1336, 1103, 901, 861, 822, 757, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 2.1 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 1 H), 7.46–7.39 (m, 4 H), 7.38–7.33 (m, 2 H), 5.79 (dd, *J* = 10.8, 8.6 Hz, 1 H), 3.96–3.87 (m, 1 H), 3.51 (dd, *J* = 17.1, 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.28, 140.29, 136.34, 133.50, 131.67, 129.70, 128.81, 128.39, 127.92, 125.94, 122.21, 83.46, 45.31.

MS (ESI): *m*/*z* (%) = 336 (23) [M^+ + 1], 181 (100).

HRMS: *m*/*z* [M^+] calcd for $C_{15}H_{11}BrClNO$: 334.9713; found: 334.9729.

3-Benzyl-5-phenyl-4,5-dihydroisoxazole (3p)[1h]
Yield: 43 mg (36%); pale yellow oil.

IR (neat): 3062, 3029, 2916, 1494, 1454, 758, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.21 (m, 10 H), 5.55 (dd, *J* = 10.8, 8.4 Hz, 1 H), 3.75 (q, *J* = 14.9 Hz, 2 H), 3.26 (dd, *J* = 17.1, 10.9 Hz, 1 H), 2.82 (dd, *J* = 17.1, 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.43, 141.02, 135.66, 128.94–128.58 (m), 128.05, 127.15, 125.76, 81.86, 44.50, 34.16.

MS (ESI): *m*/*z* (%) = 238 (100) [M^+ + 1].

3,5-Diphenylisoxazole (3q)
Yield: 32 mg (29%); pale yellow solid; mp 130–132 °C (Lit.[4b] 138–140 °C).

IR (neat): 3114, 3048, 2199, 1451, 1402, 950, 917, 821, 764, 693 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93–7.84 (m, 4 H), 7.53–7.44 (m, 6 H), 6.85 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.41, 162.98, 130.21, 130.00, 129.15, 129.00, 128.92, 127.47, 126.81, 125.83, 97.47.

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