Iodoarene-Mediated One-Pot Preparation of 2,4,5-Trisubstituted Oxazoles from Ketones

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Abstract: 2-Methyl-5-aryloxazole and 2-ethyl-5-aryloxazole derivatives were smoothly and efficiently obtained in one-pot manner from alkyl aryl ketones with iodoarene, *m*-chloroperbenzoic acid, and trifluoromethanesulfonic acid in acetonitrile and propionitrile, respectively. In these reactions, iodoarene works as a catalyst.

Key words: 2,4,5-trisubstituted oxazoles, one-pot reaction, MCPBA, iodoarene

The synthetic study of oxazole units is very important because of the potent biological activity of these moeities and their utility as versatile starting materials in organic synthesis.[1] One of the most reliable and direct methods for the construction of oxazole ring is the cyclodehydration of α-acylamino ketones using dehydrating reagents, such as sulfuric acid, phosphorus pentachloride, and polyphosphoric acid.[1] To our knowledge, there are two methods for the direct preparation of oxazoles from ketones with nitriles, which use copper(II) triflate[2] and thallium(III) triflate.[3] As less toxic and efficient methods, the preparation of 2,5-disubstituted oxazoles from aryl methyl ketones using (diacetoxyiodo)benzene with trifluoromethanesulfonic acid (TfOH) in acetonitrile,[4] and the preparation of 2,4,5-trisubstituted oxazoles from carbonyl compounds using [(hydroxy)(2,4-dinitrobenzenesulfonyloxy)iodo]benzene with amides under solvent-free microwave irradiation conditions[5] were reported recently. Especially, the former method is readily available for the direct preparation of 2-methyl-5-aryloxazoles, and a variety of 2,4,5-trisubstituted oxazoles can be obtained using different types of aryl alkyl ketones in acetonitrile and other nitrile solvents. On the other hand, recently, PhI-catalyzed α-acetoxylation of ketones with *m*-chloroperbenzoic acid (MCPBA) in AcOH in the presence of $BF_3{\cdot}OEt_2$ and water was reported to provide the corresponding α-acetoxyketones in moderate yields,[6] and hypervalent iodine(III)-catalyzed oxidative cyclization of β-(4-hydroxyaryl)propanoic acids with MCPBA was reported to give the corresponding spirolactones.[7] We also reported direct one-pot preparation of various [(hydroxy)(sulfonyloxy)iodo]arenes from iodoarenes with MCPBA and sulfonic acids at room temperature,[8] PhI-catalyzed α-tosyloxylation of ketones with MCPBA and *p*-toluenesulfonic acid,[9] and efficient conversion of ketones to α-tosyloxyketones with MCPBA and *p*-toluenesulfonic acid in the presence of a catalytic amount of IL (ionic liquid)-supported PhI in [emim]OTs (1-ethyl-3-methylimidazolium tosylate).[10]

Herein, as part of our study on organic synthesis using PhI-catalyzed system with MCPBA, we report the PhI-mediated direct preparation of 2,5-disubstituted and 2,4,5-trisubstituted oxazoles from alkyl aryl ketones with TfOH in acetonitrile or propionitrile.

The reaction was carried out as follows:[11] To an acetonitrile solution were added iodoarene (1.1 equiv), MCPBA (1.1 equiv), and TfOH (2.0 equiv), and the mixture was stirred for 0.5–2 hours, depending on the substrate, to generate the corresponding arene iodonium species. Then, a solution of alkyl aryl ketone (1.0 equiv) in acetonitrile (2 mL) was added, and the obtained mixture was refluxed for 2–4 hours to provide the corresponding 2-methyl-5-aryloxazole. First, the effect of iodoarenes with MCPBA, acetophenone, and TfOH was studied, using iodobenzene, 4-iodotoluene, 4-chloroiodobenzene, 4-iodoanisole, 1-iodonaphthalene, 4,4′-diiodobiphenyl, 1,4-bis(4′-iodophenyl)benzene, and poly(4-iodostyrene) as shown in Table 1 (entries 2–9). In the absence of iodoarene, 2-methyl-5-phenyloxazole was not formed at all, and acetophenone was recovered in ca. 70% yield (entry 1). However, in the presence of iodoarene, 2-methyl-5-phenyloxazole was formed in moderate yields (54–60%) in a one-pot manner, especially with iodobenzene, 4-iodotoluene, and 4-chloroiodobenzene (entries 2–4). When 4-iodoanisole or 1-iodonaphthalene was used, the reaction provided black tar species, without formation of 2-methyl-5-phenyloxazole, whereas, when 1,4-bis(4′-iodophenyl)benzene or poly(4-iodostyrene) was used, the yield of 2-methyl-5-phenyloxazole was poor due to the low solubility in acetonitrile. Based on these results, 2-methyl-5-(4′-methylphenyl)oxazole (entries 10–12), 2-methyl-5-(4′-chlorophenyl)oxazole (entries 13–15), and 2-methyl-5-(4′-nitrophenyl)oxazole (entries 16–18) were obtained in moderate yields from 4-methylacetophenone, 4-chloroacetophenone, and 4-nitroacetophenone, respectively. When propiophenone and nonanophenone were used under the same conditions, 2,4-dimethyl-5-phenyloxazole (entries 19–21) and 2-methyl-4-heptyl-5-phenyloxazole (entries 22–24) were obtained in moderate yields. Here, iodoarene worked as a catalyst, and in the reaction of 4-chloroiodobenzene, MCPBA, and TfOH with 4-nitroacetophenone in acetonitrile, 4-chloroiodobenzene was

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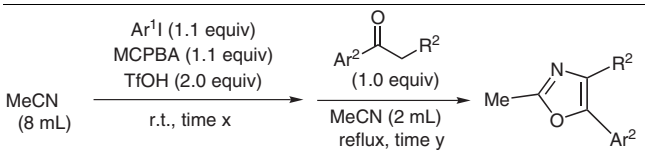
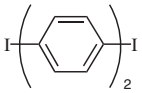
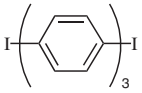
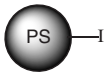
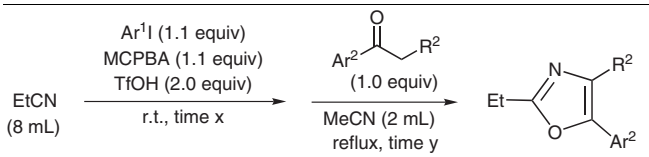
Table 1 Iodoarene-Mediated Preparation of 2-Methyloxazoles with Ketones, MCPBA, and TfOH in MeCN



Entry	Ar^1I	Ar^2	R^2	Time x (h)	Time y (h)	Yield (%)[a]
1	–	Ph	H	0.5	2	0
2	PhI	Ph	H	0.5	2	56
3	4-MeC_6H_4I	Ph	H	2	2	60
4	4-ClC_6H_4I	Ph	H	1	2	54
5	4-$MeOC_6H_4I$	Ph	H	2	2	0
6	$C_{10}H_7I$	Ph	H	2	2	0
7		Ph	H	2	2	17
8		Ph	H	2	2	14
9		Ph	H	2	2	35
10	PhI	4-MeC_6H_4	H	0.5	2	64
11	4-MeC_6H_4I	4-MeC_6H_4	H	2	2	58
12	4-ClC_6H_4I	4-MeC_6H_4	H	1	2	63
13	PhI	4-ClC_6H_4	H	0.5	2	61
14	4-MeC_6H_4I	4-ClC_6H_4	H	2	2	54
15	4-ClC_6H_4I	4-ClC_6H_4	H	1	2	57
16	PhI	4-$O_2NC_6H_4$	H	0.5	2	77
17	4-MeC_6H_4I	4-$O_2NC_6H_4$	H	2	2	47
18	4-ClC_6H_4I	4-$O_2NC_6H_4$	H	1	2	68[b]
19	PhI	Ph	Me	0.5	2	66
20	4-MeC_6H_4I	Ph	Me	2	2	58
21	4-ClC_6H_4I	Ph	Me	1	2	55
22	PhI	Ph	C_7H_{15}	0.5	3	50
23	4-MeC_6H_4I	Ph	C_7H_{15}	2	3	44
24	4-ClC_6H_4I	Ph	C_7H_{15}	1	3	45

[a] Isolated yield.
[b] 4-Chloroiodobenzene was recovered in 100% yield.

Table 2 Iodoarene-Mediated Preparation of 2-Ethyloxazoles with Ketones, MCPBA, and TfOH in EtCN



Entry	Ar^1I	Ar^2	R^2	Time x (h)	Time y (h)	Yield (%)[a]
1	PhI	Ph	H	2	3	51
2	4-MeC_6H_4I	Ph	H	2	3	68
3	4-ClC_6H_4I	Ph	H	2	3	61
4	PhI	4-MeC_6H_4	H	2	3	33
5	4-MeC_6H_4I	4-MeC_6H_4	H	2	3	45
6	4-ClC_6H_4I	4-MeC_6H_4	H	2	3	39
7	PhI	4-ClC_6H_4	H	2	3	48
8	4-MeC_6H_4I	4-ClC_6H_4	H	2	3	42
9	4-ClC_6H_4I	4-ClC_6H_4	H	2	3	63
10	PhI	4-$O_2NC_6H_4$	H	2	3	40
11	4-MeC_6H_4I	4-$O_2NC_6H_4$	H	2	3	55
12	4-ClC_6H_4I	4-$O_2NC_6H_4$	H	2	3	78[b]
13	PhI	Ph	Me	2	3	59
14	4-MeC_6H_4I	Ph	Me	2	3	55
15	4-ClC_6H_4I	Ph	Me	2	3	52
16	PhI	Ph	C_7H_{15}	2	4	22
17	4-MeC_6H_4I	Ph	C_7H_{15}	2	4	36
18	4-ClC_6H_4I	Ph	C_7H_{15}	2	4	30

[a] Isolated yield.
[b] 4-Chloroiodobenzene was recovered in 97% yield.

recovered in 100% yield, together with 2-methyl-5-(4′-nitrophenyl)oxazole (entry 18). Other iodoarenes such as iodobenzene and 4-iodotoluene could also be recovered in high yields. Under the present conditions, dialkyl ketones gave the corresponding oxazoles in poor yields (~10%).

When the same reaction was carried out in propionitrile instead of acetonitrile, 2-ethyl-5-phenyloxazole, 2-ethyl-5-(4′-methylphenyl)oxazole, 2-ethyl-5-(4′-chlorophenyl)oxazole, and 2-ethyl-5-(4′-nitrophenyl)oxazole were obtained in moderate yields from acetophenone, 4-methylacetophenone, 4-chloroacetophenone, and 4-nitroacetophenone, respectively, as shown in Table 2 (entries 1–12). 2-Ethyl-4-methyl-5-phenyloxazole and 2-ethyl-4-heptyl-5-phenyloxazole were obtained in moderate yields, when propiophenone and nonanophenone were used instead of aryl methyl ketones under the same conditions (entries 13–18). In entry 12, 4-chloroiodobenzene was recovered in 97% yield as a catalyst. The proposed reaction pathway is shown in Scheme 1. Iodoarene is oxidized to aryl iodonium species **A** by MCPBA and TfOH, and it reacts with the enolate form of ketone to form the corresponding α-keto iodonium species **B**. Finally, α-keto iodonium species **B** reacts with nitrile to provide the oxazole through the intermediate **C**.

In conclusion, 2-methyl-5-aryloxazole and 2-ethyl-5-aryloxazole derivatives were smoothly and efficiently obtained in one-pot manner from alkyl aryl ketones with iodoarene, MCPBA, and TfOH in acetonitrile and propionitrile, respectively. Here, iodoarene worked as a catalyst.

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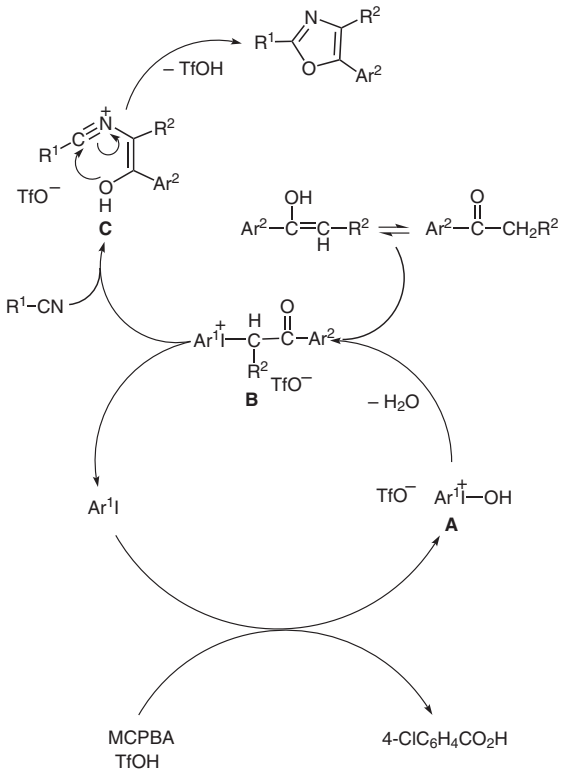

Scheme 1 Reaction pathway

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(11) **Typical Experimental Procedure**: To a mixture of iodobenzene (purity 98%, 1.1 mmol, 228 mg) and MCPBA (purity 65%, 292 mg) in MeCN (8 mL) was added TfOH (2.0 mmol, 0.17 mL). The obtained mixture was stirred for 0.5 h at r.t. under an argon atmosphere. Then, a solution of acetophenone (purity 98.5%, 1.0 mmol, 122 mg) in MeCN (2 mL) was added, and the mixture was stirred for 2 h under refluxing conditions. After the reaction, the reaction mixture was poured into sat. aq $NaHCO_3$ solution and extracted with $CHCl_3$ (3 × 30 mL). The organic layer was dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: hexane–EtOAc, 5:1) to give 2-methyl-5-phenyloxazole in 56% yield.
2-Methyl-5-phenyloxazole: mp 57–58.5 °C (lit.[12] mp 57–58 °C). IR (KBr): 1580, 1560, 1480 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 7.20 (s, 1 H), 7.30 (tt, *J* = 1.5, 7.8 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 2 H), 7.60 (dd, *J* = 1.5, 7.8 Hz, 2 H). MS (FAB): *m/z* = 160 [M + H].
Analytical data for selected oxazoles are as follows:
2-Methyl-5-(4′-chlorophenyl)oxazole: mp 71–72 °C (lit.[13] mp 74–75.5 °C). IR (KBr): 3060, 1580, 1560, 1480, 1090, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, s), 7.20 (s, 1 H), 7.38 (d, *J* = 8.9 Hz, 2 H), 7.54 (d, *J* = 8.9 Hz, 2 H).
2-Methyl-5-(4′-nitrophenyl)oxazole: mp 161–162 °C (lit.[14] mp 167–168 °C). IR (KBr): 3020, 1610, 1560, 1500, 1350, 1330, 1130, 1110, 1060, 940, 850, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.58 (s, 3 H), 7.42 (s, 1 H), 7.76 (d, *J* = 9.0 Hz, 2 H), 8.28 (d, *J* = 9.0 Hz, 2 H). MS (FAB): *m/z* = 205 [M + H].
2-Methyl-5-(4′-methylphenyl)oxazole: mp 54–55 °C (lit.[14] mp 56–57 °C). IR (KBr): 1580, 1560, 1500, 1460, 1380 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 2.52 (s, 3 H), 7.15 (s, 1 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H).
2-Ethyl-5-phenyloxazole: oil. IR (neat): 3060, 2980, 2940, 1580, 1560, 1490, 1450, 760, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.6 Hz, 3 H), 2.86 (q, *J* = 7.6 Hz, 2 H), 7.22 (s, 1 H), 7.30 (tt, *J* = 1.4, 7.6 Hz, 1 H), 7.40 (dd, *J* = 7.6, 8.0 Hz, 2 H), 7.61 (dd, *J* = 1.4, 8.0 Hz, 2 H). HRMS: *m/z* [M + H] calcd for $C_{11}H_{12}NO$: 174.0919; found: 174.0922.
2-Ethyl-5-(4′-nitrophenyl)oxazole: mp 81–82 °C (lit.[12] mp 85–86 °C). IR (KBr): 3120, 2990, 1620, 1560, 1500, 1330, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.6 Hz, 3 H), 2.90 (q, *J* = 7.6 Hz, 2 H), 7.44 (s, 1 H), 7.76 (d, *J* = 9.0 Hz, 2 H), 8.28 (d, *J* = 9.0 Hz, 2 H).

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