A Facile One-Pot Synthesis of 2,5-Disubstituted Oxazoles Using Iodobenzene Diacetate

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A facile one-pot synthesis of oxazoles **1a-h** is described that utilizes readily available aromatic α-methyl ketones and a safe hypervalent iodine reagent, iodobenzene diacetate.

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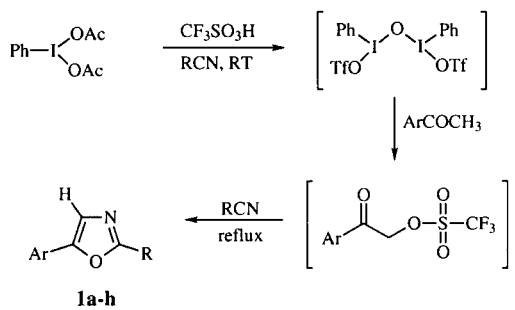
The utility of the hypervalent iodine reagent, iodobenzene diacetate, has been amply demonstrated in organic synthesis [1,2]. We have recently added another dimension to the oxidative utility of iodobenzene diacetate by impregnating it on aluminum oxide support that enables the utilization of this reagent in microwave-assisted rapid reactions under solvent-free conditions [2c,d]. Oxazole derivatives have attracted attention because of their potential biological activity and their use as a versatile starting material in organic synthetic transformations [3]. The majority of the oxazole derivatives, however, are prepared from precursors such as α-halo-ketones [4], α-diazoketones [5], or α-azidoketones [6] in a multi-step synthetic effort. Among the earlier known methods for the synthesis of oxazoles from ketones, there are two expeditious routes available. The first involves the use of copper triflate [7], in a process that fails to deliver the 2,5-disubstituted oxazoles. The second method uses thallium(III) acetate [8], an inherently toxic reagent. In continuation of our ongoing program to develop newer applications of iodobenzene diacetate [2], herein we report a facile and simple method for the conversion of aromatic α–methyl ketones to oxazoles using iodobenzene diacetate in one-pot process.

Scheme



1a-h

Treatment of the aromatic α-methyl ketones with 1.2 equivalent of iodobenzene diacetate in presence of trifluoromethanesulfonic acid and acetonitrile afford oxazole derivatives exclusively. Iodobenzene diacetate on treatment with trifluoromethanesulfonic acid, presumably forms μ-oxobis[trifluoromethanesulphonato(phenyl)-iodine] [9] *in situ* which converts aromatic α-methyl ketones to α-keto triflates. The subsequent nucleophilic addition of nitriles results in the formation of the corresponding oxazole derivatives. In case of alkyl nitriles, oxazole derivatives are obtained in excellent yields whereas moderate to good yields are obtained for arylnitriles. It is quite likely that the reaction proceeds *via* carbocation formation at nitrile carbon, which is more stable in case of benzonitrile and consequently results in comparatively low yield of 2,5-diphenyl oxazole. Attempted reactions with [hydroxy(tosyloxy)iodo]benzene, however, failed to deliver the desired oxazole derivatives and invariably resulted in the formation of α-tosyloxy ketones. Apparently, triflate being a better leaving group is responsible for the efficient cyclization, whereas reaction fails to proceed with the intermediacy of the α-tosyloxy ketones.

Table

Synthesis of 2,5-disubstituted oxazoles

No.	Ar	R	Mp (Lit) [5e] °C	Yield (%) [a]
1a	C_6H_5	CH_3	56-57 (58-59)	94
1b	4-MeC_6H_4	CH_3	56 (56-57)	91
1c	4-ClC_6H_4	CH_3	84-85 (86-87)	90
1d	4-$MeOC_6H_4$	CH_3	106 (107-108)	84
1e	C_6H_5	C_6H_5	69 (74-75)	37
1f	C_6H_5	$C_6H_5CH_2$	88 (91-92)	82
1g	C_6H_5	CH_2OCH_3	oil	64
1h	4-ClC_6H_4	CH_2OCH_3	oil	62

[a] Unoptimized yields of the pure products that exhibit physical and spectral properties in conformity with the assigned structures [5e].

In conclusion, this novel method provides a ready and general entry to the substituted oxazole ring system under milder conditions from easily accessible aromatic α-methyl ketones and relatively inexpensive, non toxic and readily available reagent, iodobenzene diacetate.

EXPERIMENTAL

Melting points were determined on a Mel-Temp II hot stage apparatus using Fluke 51 K/J digital thermometer and are uncor-

rected. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform on Jeol Eclipse 300 (300 MHz for ^1H nmr and 75 MHz for ^{13}C nmr) spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hewlett Packard® 5890 mass spectrometer (70 eV) using a gc/ms coupling or direct inlet system. Iodobenzene diacetate and trifluoromethanesulphonic acid were obtained from Aldrich and Acros Chemical Co., respectively. The synthesis of 2-methyl-5-phenyloxazole (**1a**) is representative of the general procedure employed.

Trifluoromethanesulfonic acid (0.68 g, 4.5 mmoles) was added to a stirred solution of iodobenzene diacetate (0.39 g, 1.2 mmoles) in acetonitrile (10 ml) and stirred at room temperature for 20 minutes. To this reaction mixture acetophenone (0.12 g, 1.0 mmole) was added and contents were refluxed for 2 hours. After completion of the reaction, followed by tlc in ethyl acetate:hexane (1:4, v/v), the excess of acetonitrile was removed and the crude product was extracted into dichloromethane (3 x 10 ml). The combined organic extracts were then washed with a saturated solution of sodium bicarbonate (3 x 10 ml), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was further purified by passing it through a short bed of silica gel using ethyl acetate:hexane (1:9, v/v) as an eluent to afford **1a** as crystalline solid, mp 56-57° (lit 58-59°) [5e], yield 0.150 g (94%); ^1H nmr (deuteriochloroform): δ 2.52 (s, 3H), 7.19-7.61 (m, 6H).

2-Methoxymethyl-5-phenyloxazole (**1g**) [8].

This compound had ^1H nmr (deuteriochloroform): δ 3.47 (s, 3H, OCH_3), 4.56 (s, 2H, OCH_2), 7.30-7.63 (m, 6H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 58.9 (CH_3) 66.5 (CH_2), 122.0 (C-4), 124.4 (C-2' and C-6'), 128.6 (C-1'), 128.7 (C-4') 129.0 (C-3' and C-5') 150.1 (C-5), 160.2 (C-2); ms: m/z 189 (10.52), 159 (73.68), 130 (5.26), 103 (81.05), 77 (67.36), 51 (31.50), 45 (100).

2-Methoxymethyl-5-(4-chlorophenyl)oxazole (**1h**).

This compound had ^1H nmr (deuteriochloroform): δ 3.46 (s, 3H, OCH_3), 4.57 (s, 2H, OCH_2), 7.37-7.57 (m, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 58.9 (CH_3), 66.4 (CH_2), 122.4 (C-4), 125.6 (C-3' and C-5'), 126.3 (C-1') 129.2 (C-2' and C-6') 134.6 (C-4'), 151.4 (C-5), 160.3 (C-2); ms: m/z 225 (7.36), 223 (22.10), 195 (23.15), 193 (72.63), 139 (35.78), 137 (44.21), 111 (34.73), 85 (41.05), 75 (27.36), 45 (100).

Anal. Calcd. for $C_{11}H_{10}NO_2Cl$: C, 59.10; H, 4.50; N, 6.30. Found: C, 58.75; H, 4.12; N, 5.98.

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