

## A Facile One-pot Synthesis of 2,5-Disubstituted Oxazoles Using Poly[styrene(iodosodiacetate)]

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2,5-Disubstituted oxazoles were prepared conveniently by treatment of aromatic  $\alpha$ -methyl ketones and nitriles with poly[styrene(iodosodiacetate)] in a one-pot manner.

**Keywords** poly[styrene(iodosodiacetate)], 2,5-disubstituted oxazole, one-pot synthesis

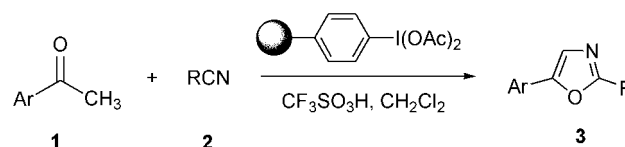
It is well known that polymer-supported reagents have the advantage of allowing the application of a larger excess of the reagent without additional purification steps. The most important point is that regeneration and reuse of the recovered polymer-supported reagents are possible, thus providing an environmentally benign process.<sup>1</sup> Some polymer-supported trivalent iodine reagents have been synthesized and used in organic synthesis in the chemical and pharmaceutical industries.<sup>2</sup> Among them, poly[styrene(iodosodiacetate)] is most widely used as a mild and clean oxidant.

Oxazole derivatives have attracted attention because of their potential biological activity and their use as a versatile starting material in organic synthetic transformations.<sup>3</sup> However, most of syntheses of the oxazole derivatives were realized from precursors such as  $\alpha$ -haloketones,<sup>4</sup>  $\alpha$ -diazoketones,<sup>5</sup>  $\alpha$ -azidoketones<sup>6</sup> in a multi-step procedure. In the presence of copper triflate<sup>7</sup> or thallium(III) acetate,<sup>8</sup> the oxazoles were also prepared from ketones. Compared with these methods, the method using (diacetoxyiodo)benzene has the advantage of simple operation from ketones.<sup>5</sup> But the by-product, *i.e.*, iodobenzene, could not be reused and may contaminate the target product. In this paper, 2,5-disubstituted oxazoles are synthesized by employing immobilized (diacetoxyiodo) benzene.

Poly[styrene(iodosodiacetate)] and trifluoromethanesulfonic acid were stirred in  $\text{CH}_2\text{Cl}_2$  for 1 h. Then the aromatic  $\alpha$ -methyl ketones **1** and nitriles **2** were added and the solution was refluxed for 5 h. After the evaporation of solvent, the ether was added to the resulting mixture to cause precipitation. The resin was removed by filtration, the organic layer was evaporated under reduced pressure, and the crude products **3** were purified by preparative thick layer chromatography us-

ing ethyl acetate and hexane (1 : 4) as eluant (Scheme 1). The results are shown in Table 1.

### Scheme 1



**Table 1** Synthesis of 2,5-disubstituted oxazoles

Entry	Ar	R	Yield <sup>a</sup> /%
1	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> ( <b>3a</b> )	93
2	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>3b</b> )	89
3	4-BrC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>3c</b> )	87
4	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>3d</b> )	90
5	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>3e</b> )	92
6	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub> ( <b>3f</b> )	83
7	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> ( <b>3g</b> )	78
8	C <sub>6</sub> H <sub>5</sub>	ClCH <sub>2</sub> ( <b>3h</b> )	83
9	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> ( <b>3a</b> )	92 <sup>b</sup>

<sup>a</sup> The isolated yields are based on the aromatic  $\alpha$ -methyl ketones.

<sup>b</sup> Using regenerated resin.

After the reaction, poly(iodostyrene), which was collected by simple filtration, was converted to poly[styrene(iodosodiacetate)] using peracetic acid (Scheme 2). The loading of the resin was 2.75 mmol/g by iodometry.<sup>9</sup> This result showed that the resin had almost the same amount of functional group as the one prepared initially. We used the regenerated resin to the synthesis of 2,5-disubstituted oxazoles and obtained

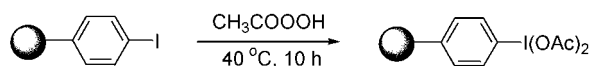
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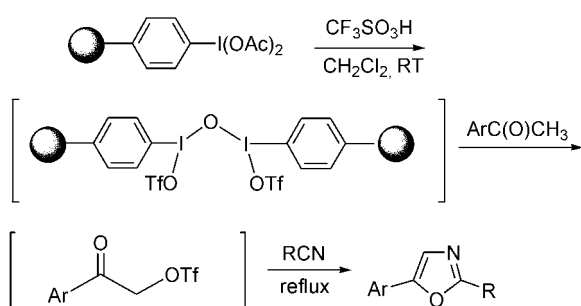
good results.

### Scheme 2



Poly[styrene(iodosodiacetate)] on treatment with trifluoromethanesulfonic acid, presumably forms poly-styrene supported  $\mu$ -oxobis[trifluoromethanesulphonato (phenyl)iodine] *in situ* which converts aromatic  $\alpha$ -methyl ketones to  $\alpha$ -keto triflates. The subsequent nucleophilic addition of nitriles results in the formation of the corresponding oxazole derivatives (Scheme 3).

### Scheme 3



In conclusion, in the presence of trifluoromethanesulfonic acid and poly[styrene(iodosodiacetate)], the aromatic  $\alpha$ -methyl ketones can react readily with nitriles to produce oxazoles in good yields. After the reaction, poly[styrene(iodosodiacetate)] can be recovered by the reaction of poly(iodostyrene) with peracetic acid.

## Experimental

### General

Poly[styrene(iodosodiacetate)] was prepared as described in the literature<sup>9</sup> and its loading in terms of the functional group is 2.80 mmol/g by iodometry. The melting points were uncorrected.  $^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) spectra were recorded on a Bruker Advance 400 spectrometer in  $\text{CDCl}_3$  with TMS as the internal standard, chemical shifts were quoted and  $J$  values were given in Hz. IR spectra were run on a Shimadzu IR-408 spectrometer. EIMS was run on an HP 5989B mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

### Synthesis of 2,5-disubstituted oxazoles (3a—3h)

Trifluoromethanesulfonic acid (4 mmol) was added to a solution of poly[styrene(iodosodiacetate)] (2 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL). The resulting solution was stirred for 1 h. Then, the aromatic  $\alpha$ -methyl ketone **1** (1 mmol) and nitrile **2** (1 mmol) were added and the reaction mixture was refluxed for 5 h. After evaporation, ether was added to cause precipitate and the mixture was filtered to remove the resin. Then the solution was treated with a saturated solution of sodium hydrogen carbonate.

It was extracted with ether ( $3 \times 10$  mL) and dried over  $\text{MgSO}_4$ . Ether was evaporated and the crude product **3** was purified by preparative thick layer chromatography using ethyl acetate and hexane (1 : 4, V : V) as eluant.

**2-Methyl-5-phenyl oxazole (3a)** m.p. 57—58  $^\circ\text{C}$  (lit.<sup>10</sup> 56—57  $^\circ\text{C}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.62—7.30 (m, 5H), 7.19 (s, 1H), 2.51 (s, 3H); IR (KBr)  $\nu$ : 1752, 1706, 1653, 1578, 1560, 1504, 1485, 1451, 1384, 1216, 1132, 1062, 941, 834, 763  $\text{cm}^{-1}$ ; MS (70 eV)  $m/z$  (%): 160  $[(\text{M}+1)^+$ , 50.2], 159 ( $\text{M}^+$ , 12.0), 105 (45.9), 77 (54.9), 51 (38.6), 43 (100).

**2-Methyl-5-(4-chlorophenyl) oxazole (3b)** m.p. 85—86  $^\circ\text{C}$  (lit.<sup>10</sup> 84—85  $^\circ\text{C}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.54 (d,  $J=8.8$  Hz, 2H), 7.38 (d,  $J=8.8$  Hz, 2H), 7.20 (s, 1H), 2.53 (s, 3H); IR (KBr)  $\nu$ : 1654, 1599, 1574, 1560, 1441, 1381, 1216, 1132, 1111, 1059, 941, 812  $\text{cm}^{-1}$ ; MS (70 eV)  $m/z$  (%): 195  $[(\text{M}+1)^+$ , 33.7], 193  $[(\text{M}-1)^+$ , 100], 138 (74.8), 89 (76.1), 75 (70.4), 43 (46.3).

**2-Methyl-5-(4-bromophenyl) oxazole (3c)** m.p. 82—83  $^\circ\text{C}$  (lit.<sup>6a</sup> 83—85  $^\circ\text{C}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.53 (d,  $J=8.4$  Hz, 2H), 7.46 (d,  $J=8.4$  Hz, 2H), 7.21 (s, 1H), 2.52 (s, 3H); IR (KBr)  $\nu$ : 1664, 1574, 1550, 1481, 1360, 1211, 1134, 1077, 950, 817  $\text{cm}^{-1}$ ; MS (70 eV)  $m/z$  (%): 239  $[(\text{M}+1)^+$ , 84.4], 237  $[(\text{M}-1)^+$ , 99.2], 130 (66.2), 103 (62.6), 89 (100), 43 (43.6).

**2-Methyl-5-(4-methylphenyl) oxazole (3d)** m.p. 56—57  $^\circ\text{C}$  (lit.<sup>10</sup> 56  $^\circ\text{C}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.50 (d,  $J=8.0$  Hz, 2H), 7.22 (d,  $J=8.0$  Hz, 2H), 7.16 (s, 1H), 2.53 (s, 3H), 2.38 (s, 3H); IR (KBr)  $\nu$ : 1646, 1597, 1574, 1555, 1485, 1385, 1211, 1131, 1092, 1060, 956, 824, 818  $\text{cm}^{-1}$ ; MS (70 eV)  $m/z$  (%): 173 ( $\text{M}^+$ , 100), 144 (36.1), 117 (56.3), 91 (35.6), 43 (14.7).

**2-Methyl-5-(4-methoxyphenyl) oxazole (3e)** m.p. 106—107  $^\circ\text{C}$  (lit.<sup>10</sup> 106  $^\circ\text{C}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.57 (d,  $J=8.2$  Hz, 2H), 7.45 (d,  $J=8.2$  Hz, 2H), 7.18 (s, 1H), 3.87 (s, 3H), 2.51 (s, 3H); IR (KBr)  $\nu$ : 1664, 1574, 1550, 1481, 1360, 1250, 1135, 1077, 1056, 940, 824  $\text{cm}^{-1}$ ; MS (70 eV)  $m/z$  (%): 189 ( $\text{M}^+$ , 100), 134 (40.7), 77 (40.8), 51 (20.8), 43 (23.3).

**2-Methyl-5-(2,4-dichlorophenyl) oxazole (3f)** m.p. 62—63  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.71 (d,  $J=8.4$  Hz, 1H), 7.63 (s, 1H), 7.48 (s, 1H), 7.33—7.30 (m, 1H), 2.54 (s, 3H);  $^{13}\text{C}$  NMR: 161.6, 147.2, 134.2, 131.3, 130.8, 128.5, 127.8, 127.6, 125.9, 14.4; IR (KBr)  $\nu$ : 1631, 1600, 1585, 1471, 1378, 1149, 1033, 939, 809  $\text{cm}^{-1}$ ; MS (70 eV)  $m/z$  (%): 229  $[(\text{M}+1)^+$ , 67.2], 227  $[(\text{M}-1)^+$ , 100], 172 (52.6), 137 (33.5), 123 (45.3), 54 (35.4), 43 (29.4). Anal. calcd for  $\text{C}_{10}\text{H}_7\text{Cl}_2\text{NO}$ : C 52.63, H 3.07, N 6.14; found C 52.65, H 3.00, N 5.93.

**2-Methoxymethyl-5-phenyl oxazole (3g)** oil (lit.<sup>10</sup> oil);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.63—7.30 (m, 5 H), 7.20 (s, 1H), 4.56 (s, 2H), 3.47 (s, 3H); IR (neat)  $\nu$ : 1637, 1604, 1580, 1473, 1369, 1209, 1149, 1033, 941, 811  $\text{cm}^{-1}$ ; MS (70 eV)  $m/z$  (%): 189 ( $\text{M}^+$ , 73.1), 103 (18.3), 87 (62.2), 51 (18.7), 43 (100).

**2-Chloromethyl-5-phenyl oxazole (3h)** m.p. 72—73  $^\circ\text{C}$  (lit.<sup>5b</sup> 74—75  $^\circ\text{C}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.60—7.30 (m, 5H), 7.22 (s, 1H), 4.65 (s, 2H); IR (KBr)

$\nu$ : 1631, 1600, 1585, 1471, 1378, 1209, 1149, 1033, 939, 809  $\text{cm}^{-1}$ ; MS (70 eV)  $m/z$  (%): 195 [(M+1)<sup>+</sup>, 22.1], 193 [(M-1)<sup>+</sup>, 53.2], 103 (68.2), 51 (23.4), 43 (100).

#### Purification of recovered poly(iodostyrene)

3 g of the recovered poly(iodostyrene) was dissolved in  $\text{CHCl}_3$  (50 mL) at 60 °C and methanol was added to precipitate the poly(iodostyrene) (2.2 g).

#### Regeneration of poly[styrene(iodosodiacetate)]

The purified poly(iodostyrene) (2.2 g) was dissolved in 15 mL of  $\text{CH}_2\text{Cl}_2$  and 9 mL of peracetic acid was added dropwise. The mixture was stirred for 10 h. After addition of ether to the solution, a white polymer was isolated. The loading of the resin is 2.75 mmol/g by iodometry.

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