Aerobic oxidative synthesis of 3,5-disubstituted isoxazoles directly from α,β-unsaturated ketones

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Using an efficient aerobic oxidative method, the synthesis of ten 3,5-disubstituted isoxazoles by treatment of α,β-unsaturated ketones with hydroxylamine and NaOH at room temperature has been achieved.

Keywords: α,β-unsaturated ketone, hydroxylamine, aerobic oxidation, 3,5-disubstituted isoxazole

Isoxazoles have attracted much attention as a result of their diverse biological activities, including antibacterial,[1] antimalarial,[2] antifungal,[3] anticancer[4] and antioxidant[5] behaviours. In fact, the isoxazole framework is a frequent structural motif in natural products. Due to the presence of a comparatively weak N–O bond, isoxazoles can be readily transformed into useful structures such as α-hydroxy-β-diketones and other β-dicarbonyl compounds.[6]

Reported methods that have been employed for the synthesis of isoxazoles, include (i) the oxidation of chalcone oximes,[7] (ii) the reaction of *N*-hydroxy-4-toluenesulfonamide with α,β-unsaturated aldehydes/ketones,[8] (iii) cycloaddition of nitrile oxides to terminal acetylenes,[9,10] (iv) four-component coupling of a terminal alkyne, hydroxylamine, carbon monoxide and an aryl iodide,[11] (v) intramolecular cyclisation of alkynone *O*-methyloximes[12,13] and (vi) the [3 + 2] cycloaddition of aromatic imidoyl chlorides to terminal alkynes.[14]

However, the commonest methods usually involve the use of expensive or commercially unavailable oxidants, such as *o*-iodoxybenzoic acid (IBX),[15] MnO_2,[16] Selectfluor[17] and *t*-butyl hypoiodite (*t*-BuOI),[18] which largely limit the wide applications of this method to the chemical industry.

Here, we report a convenient and simple method for the synthesis of 3,5-disubstituted isoxazoles directly from α,β-unsaturated ketones using air as the oxidant.

Results and discussion

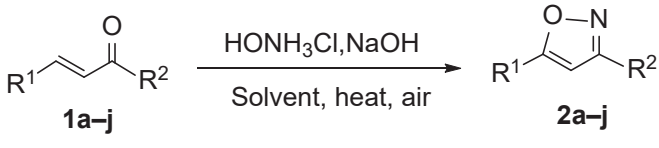
Our plan was to react an α,β-unsaturated ketone with $HONH_2$ in the presence of a base in a suitable solvent in which autoxidation could occur (Scheme 1). We chose chalcone (**1a**, $R^1 = R^2 = Ph$) as a model substrate and it was found that its reaction with $HONH_3Cl$ in the presence of *t*-BuONa using DMSO under air could produce 3,5-diphenylisoxazole (**2a**, $R^1 = R^2 = Ph$) by a one-step procedure in 86% yield (Table 1, entry 2).

Other bases were investigated and of *t*-BuOK, $NaHCO_3$, KOH and NaOH (Table 1, entries 3–6), NaOH was the most suitable base for the reaction (Table 1, entry 6). No reaction was observed in the absence of base (Table 1, entry 1).

The choice of solvent was found to be important. Reaction in EtOH, 1,4-dioxane or PhMe gave no product (Table 1, entries 9–11), but DMSO, DMF and MeCN were effective solvents for the reaction (Table 1, entries 6–8). However, the best yield was obtained by using DMSO as solvent (Table 1, entry 6). Moreover, some transition metal compounds such as CuCl, CuI, AgI and $FeCl_3$ were also examined for catalytic activity, but no obvious improvement to the yield was observed (data not tabulated).

In addition, it is important to mention that keeping the reaction exposed to the air at 100 °C was also an essential condition for the reaction.

Using these optimised conditions, a series of α,β-unsaturated ketones were investigated and the yields of the corresponding 3,5-disubstituted isoxazoles are shown in Table 2. It was found that α,β-unsaturated ketones with either electron-donating



1a–j 2a–j

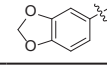
Scheme 1 Aerobic oxidative synthesis of 3,5-disubstituted isoxazoles.

Table 1 The effect of reaction conditions (base, solvent, temperature) on the yield of 3,5-diphenylisoxazole (**2a**, $R^1 = R^2 = Ph$) (Scheme 1)[a]

Entry	Base	Solvent	Temp./°C	Yield/%[b]
1	–	DMSO	100	0
2	*t*-BuONa	DMSO	100	86
3	*t*-BuOK	DMSO	100	82
4	$NaHCO_3$	DMSO	100	65
5	KOH	DMSO	100	85
6	NaOH	DMSO	100	88
7	NaOH	DMF	100	80
8	NaOH	MeCN	80	63
9	NaOH	EtOH	80	0
10	NaOH	1,4-Dioxane	100	0
11	NaOH	PhMe	100	0

[a]Reaction conditions: **1a** (0.5 mmol), $HONH_3Cl$ (1.0 mmol) and base (2.0 mmol) were stirred at the appropriate temperature for 8 h in solvent (5 mL) under air.
[b]Isolated yields.

Table 2 Yields of 3,5-disubstituted isoxazoles **2a–j** prepared by the aerobic oxidative method (Scheme 1)[a]

Compound	R^1	R^2	Yield/%[b]
2a	C_6H5	C_6H_5	88
2b	C_6H_5	4-FC_6H_4	81
2c	C_6H_5	3-BrC_6H_4	83
2d	C_6H_5		80
2e	4-$CH_3OC_6H_4$	C_6H_5	74
2f	4-FC_6H_4	C_6H_5	78
2g	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	83
2h	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	82
2i	4-$CH_3OC_6H_4$	4-ClC_6H_4	77
2j		C_6H_5	76

[a]Reaction conditions: **1** (0.5 mmol), $HONH_3Cl$ (1.0 mmol) and NaOH (2.0 mmol) were stirred at 100 °C for 8 h in DMSO (5 mL) under air.
[b]Isolated yields.

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(CH_3, CH_3O) or electron-withdrawing (F, Cl, Br) groups on either of the aromatic rings could be converted successfully into the corresponding products **2b**, **2c**, and **2e**–**j** in good to high yields. In addition, an α,β-unsaturated ketone bearing a heterocyclic group (thiophen-2-yl) could also be converted into the corresponding product **2d** in a satisfactory yield.

The mechanism for the aerobic oxidative synthesis of 3,5-disubstituted isoxazoles is unknown.

Experimental

^{1}H NMR and ^{13}C NMR spectra were obtained with a Mercury-400BB or Mercury-600BB spectrometer using $CDCl_3$ as solvent and Me_4Si as the internal standard. Elemental analyses were performed on a Vario El Elemental Analysis instrument. Melting points were observed using an Electrothermal melting point apparatus. α,β-Unsaturated ketones were prepared according to a literature procedure.[19]

Preparation of 3,5-disubstituted isoxazoles; general procedure

A mixture of α,β-unsaturated ketone (0.5 mmol), $HONH_3Cl$ (1.0 mmol) and NaOH (2.0 mmol) in DMSO (5 mL) was stirred under air at 100 °C for 8 h. After completion of the reaction, the resulting mixture was cooled to room temperature, diluted with ethyl acetate and washed with saturated sodium carbonate solution. The resulting organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was isolated by column chromatography using petroleum ether (boiling point: 60–90 °C)/ethyl acetate (10:1) as eluent to give the pure product.

3,5-Diphenylisoxazole (**2a**): White solid, m.p. 138–139 °C (lit.[15] 140–142 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 6.5 Hz, 2H, ArH), 7.83 (d, *J* = 7.1 Hz, 2H, ArH), 7.44–7.49 (m, 6H, ArH), 6.82 (s, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.4, 163.0, 130.2, 130.0, 129.1, 129.0, 128.9, 127.5, 126.8, 125.8, 97.4. Anal. calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; found: C, 81.34; H, 4.99; N, 6.35%.

3-(4-Fluorophenyl)-5-phenylisoxazole (**2b**): Grey solid; m.p. 112–114 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83–7.87 (m, 4H, ArH), 7.46–7.51 (m, 3H, ArH), 7.17 (t, *J* = 8.6 Hz, 2H, ArH), 6.79 (s, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.4, 159.5, 157.8, 156.8, 125.1, 123.8, 123.6, 123.5, 120.6, 110.9, 110.8, 92.1. Anal. calcd for $C_{15}H_{10}FNO$: C, 75.30; H, 4.21; N, 5.85; found: C, 75.39; H, 4.20; N, 5.87%.

3-(3-Bromophenyl)-5-phenylisoxazole (**2c**): Grey solid; m.p. 128–130 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (s, 1H, ArH), 7.80–7.84 (m, 3H, ArH), 7.59 (d, *J* = 7.8 Hz, 1H, ArH), 7.47–7.51 (m, 3H, ArH), 7.35 (t, *J* = 7.9 Hz, 1H, ArH), 6.81 (s, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8, 161.7, 132.9, 131.1, 130.5, 130.4, 129.8, 127.2, 125.8, 125.3, 123.0, 97.3. Anal. calcd for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67; found: C, 59.88; H, 3.35; N, 4.65%.

5-Phenyl-3-(thiophen-2-yl)isoxazole (**2d**): Grey solid; m.p. 104–106 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, *J* = 9.4 Hz, 2H, ArH), 7.52 (d, *J* = 5.2 Hz, 1H, ThH), 7.47–7.48 (m, 3H, ArH and ThH), 7.14 (t, *J* = 6.5 Hz, 1H, ThH), 6.75 (s, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 158.1, 130.8, 130.3, 129.0, 127.6, 127.5, 127.3, 127.1, 125.8, 97.4. Anal. calcd for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16; found: C, 68.79; H, 4.00; N, 6.14%.

5-(4-Methoxyphenyl)-3-phenylisoxazole (**2e**): Grey solid; m.p. 132–134 °C (lit.[7] 120–121 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, *J* = 6.5 Hz, 2H, ArH), 7.81 (d, *J* = 8.6 Hz, 2H, ArH), 7.45–7.50 (m, 3H, ArH), 7.02 (d, *J* = 8.6 Hz, 2H, ArH), 6.78 (s, 1H, CH), 3.86 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.1, 162.6, 161.0, 130.1, 129.0, 128.2, 127.6, 125.8, 121.6, 114.3, 97.4, 55.4. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57; found: C, 76.42; H, 5.19; N, 5.56%.

5-(4-Fluorophenyl)-3-phenylisoxazole (**2f**): Grey solid; m.p. 116–118 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.7 Hz, 1H, ArH), 7.86 (d, *J* = 7.7 Hz, 2H, ArH), 7.62–7.66 (m, 2H, ArH), 7.51 (d, *J* = 7.7 Hz, 2H, ArH), 7.18 (t, *J* = 8.1 Hz, 2H, ArH), 6.78 (s, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.4, 164.6, 163.0, 132.8, 130.3, 128.9, 128.6, 128.5, 127.9, 126.8, 116.3, 97.3. Anal. calcd for $C_{15}H_{10}FNO$: C, 75.30; H, 4.21; N, 5.85; found: C, 75.17; H, 4.23; N, 5.84%.

3,5-Bis(4-methoxyphenyl)isoxazole (**2g**): Grey solid; m.p. 134–136 °C (lit.[15] 142–143 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.80 (m, 4H, ArH), 6.98 (d, *J* = 8.4 Hz, 4H, ArH), 6.65 (s, 1H, CH), 3.86 (s, 6H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 162.5, 161.1, 160.9, 128.1, 127.4, 121.8, 120.4, 114.4, 114.3, 95.9, 55.4, 55.3. Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; found: C, 72.51; H, 5.35; N, 5.00%.

*5-(4-Methoxyphenyl)-3-(*p*-tolyl)isoxazole* (**2h**): Grey solid; m.p. 142–144 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.6 Hz, 2H, ArH), 7.71 (d, *J* = 8.0 Hz, 2H, ArH), 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 6.99 (d, *J* = 8.6 Hz, 2H, ArH), 6.71 (s, 1H, CH), 3.85 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 162.5, 161.0, 140.4, 129.6, 128.2, 127.4, 126.7, 125.7, 114.3, 96.7, 55.3, 21.5. Anal. calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28; found: C, 76.88; H, 5.69; N, 5.30%.

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)isoxazole (**2i**): Grey solid; m.p. 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.80 (m, 4H, ArH), 7.44 (d, *J* = 8.4 Hz, 2H, ArH), 6.99 (d, *J* = 8.4 Hz, 2H, ArH), 6.67 (s, 1H, CH), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 161.9, 161.2, 135.9, 129.1, 128.9, 128.0, 127.8, 127.4, 126.8, 120.1, 114.4, 95.9. 55.4. Anal. calcd for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; N, 4.90; found: C, 67.37; H, 4.23; N, 4.88%.

*5-(Benzo[*d*][1,3]dioxol-5-yl)-3-phenylisoxazole* (**2j**): Grey solid; m.p. 128–130 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.9 Hz, 2H, ArH), 7.46 (d, 3H, ArH), 7.37 (d, *J* = 8.0 Hz, 1H, ArH), 7.29 (s, 1H, ArH), 6.90 (d, *J* = 8.0 Hz, 1H, ArH), 6.69 (s, 1H, CH), 6.04 (s, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.1, 162.9, 149.3, 148.2, 130.0, 129.2, 128.9, 126.8, 121.6, 120.5, 108.6, 106.2, 101.6. 96.5. Anal. calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28; found: C, 72.56; H, 4.19; N, 5.30%.

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