Simple Synthesis of Symmetrical 4-Substituted 3,5-Dialkylisoxazoles†

J. Chem. Research (S), 1998, 388–389†

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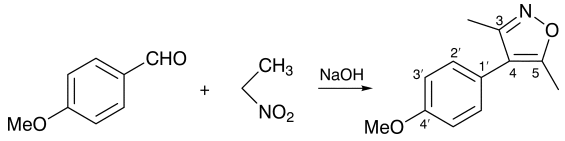
A number of symmetrical 4-substituted 3,5-dialkylisoxazoles have been prepared by treatment of aromatic aldehydes with nitroalkanes and aqueous sodium hydroxide.

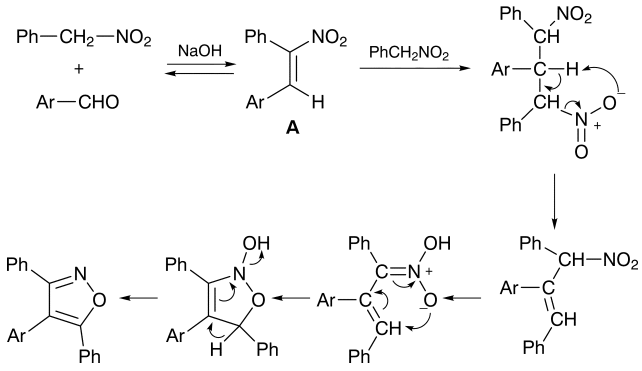
In a project aimed at determining the effects of various bases on the condensation of nitroethane with 4-methoxybenzaldehyde, it was found that using butylamine, triethylamine, DBU or sodium hydroxide differing amounts of 4-(4-methoxyphenyl)-3,5-dimethylisoxazole **1** were produced. Whereas the first three bases yielded only ≈5% of the isoxazole, use of sodium hydroxide resulted in the formation of the compound in 69% isolated yield (Scheme 1). The structure of **1** was determined from its spectral characteristics. Importantly, HMBC techniques showed that the two methyls (δ_C 10.7 and 11.4; δ_H 2.24 and 2.38) on the heterocyclic ring were symmetrically disposed with respect to C4 (δ_C 116.2).



Scheme 1

Treatment of a number of aromatic aldehydes under the same conditions yielded the corresponding 4-aryl 3,5-dimethylisoxazoles in good yields (Table 1). The only exception was *N*,*N*-dimethylaminobenzaldehyde which afforded 12% of the corresponding isoxazole, as determined by GC-MS analysis. A poor yield was also obtained with the alkyl aldehyde 2,2-dimethylpropionaldehyde. As expected, aldehydes with α-protons, *e.g.* butyraldehyde, or with α,β-unsaturation, cinnamaldehyde, did not survive treatment with sodium hydroxide and little or no formation of the corresponding isoxazole could be detected by GC-MS analysis of the recovered products. Reaction of nitropropane with 4-methoxybenzaldehyde afforded the 3,5-diethylisoxazole **9** in 78% yield.

Of the numerous methods available for the synthesis of isoxazoles, one that has been used frequently involves the condensation of doubly activated nitro compounds, nitrophenylmethane and ethyl nitroacetate, with an aromatic aldehyde.[1] Since better yields of the isoxazoles can be obtained simply by treatment of the intermediate β-nitrostyrene (**A**, Scheme 2) with potassium hydroxide, the mechanism must also involve a retroaldol reaction of the β-nitrostyrene. Thus, reaction of 4-methoxy-β-nitrostyrene with potassium hydroxide produced 4-*p*-methoxyphenyl-3,5-diphenylisoxazole.



Scheme 2

Aliphatic nitroalkanes have not been generally used in this type of synthesis of isoxazoles, although the formation of 3,4,5-trimethyl- or 3,4,5-triethyl-isoxazoles on treatment of nitroethane or nitropropane with alkali-metal hydroxides has been known for a long time.[1] To our knowledge, the only other example available refers to the condensation of 6-bromo-3,4-methylenedioxybenzaldehyde with nitroethane, butylamine and sodium carbonate. Instead of the expected β-nitrostyrene, a low yield (3%) of the 4-aryl-3,5-dimethylisoxazole was obtained, the structure of which was determined by ^{13}C NMR methods.[2] Under our conditions, use of sodium hydroxide, 3,4-methylenedioxybenzaldehyde and nitroethane afforded 85% of the isoxazole (Table 1).

Of some interest is the reaction of nitroethane with 4-nitrobenzaldehyde. The unstable isoxazole produced gave

Table 1 Products from the reaction of nitroethane and nitropropane with various aldehydes

Aldehyde	Product	Yield (%)
4-Methoxybenzaldehyde	4-(4-methoxyphenyl)-3,5-dimethylisoxazole (**1**)	69
2-Methoxybenzaldehyde	4-(2-methoxyphenyl)-3,5-dimethylisoxazole (**2**)	70
Benzaldehyde	3,5-dimethyl-4-phenylisoxazole (**3**)	73
3,4-Methylenedioxybenzaldehyde	4-(3,4-methylenedioxyphenyl)-3,5-dimethylisoxazole (**4**)	85
4-Chlorobenzaldehyde	4-(4-chlorophenyl)-3,5-dimethylisoxazole (**5**)	92
4-Nitrobenzaldehyde	3,5-dimethyl-4-(4-nitrophenyl)isoxazole (**6**)	71
Furfuraldehyde	4-(2-furyl)-3,5-dimethylisoxazole (**7**)	96
2,2-Dimethylpropionaldehyde	3,5-dimethyl-4-(1,1-dimethylethyl)isoxazole (**8**)	6
4-Methoxybenzaldehyde	4-(4-methoxyphenyl)-3,5-diethylisoxazole (**9**)	78

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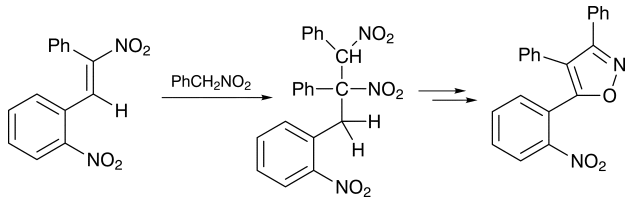
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 2 ^{13}C NMR data of 4-substituted 3,5-dialkylisoxazoles, determined in $CDCl_3$ at 75 MHz

Compound	C3	C4	C5	C3-Alkyl	C5-Alkyl	Others
1	164.8	116.2	158.8	11.3	10.7	122.6 (C1′), 130.2 (C2′, 6′), (C2′, 6′), 114.2 (C3′, 5′); 159.0 (C4′), 55.3 (OMe)
2	165.5	113.0	157.0	11.3	10.4	118.7 (C1′), 159.5 (C2′), 110.8 (C3′), 129.3 (C4′), 120.4 (C5′), 131.2 (C6′), 55.0 (OMe)
3	165.1	116.4	158.7	11.5	10.7	130.4 (C1′), 129.0 (C2′, 6′), 128.7 (C3′, 5′), 127.5 (C4′)
4	164.7	116.3	158.7	11.4	10.7	123.9 (C1′), 109.4 (C2′), 147.0 (C3′), 147.9 (C4′), 122.6 (C5′), 108.6 (C6′), 101.2 (OCH_2O)
5	165.3	115.6	158.4	12.4	11.5	133.5 (C1′), 130.3 (C2′, 6′), 129.0 (C3′, 5′), 128.8 (C4′)
6	166.3	115.1	158.1	11.8	10.9	137.5 (C1′), 124.2 (C2′, 6′), 130.0 (C2′, 5′), 147.1 (C4′)
7	165.4	108.2	157.7	12.4	11.5	145.6 (C2′), 106.6 (C3′), 111.1 (C4′), 141.8 (C5′)
8	163.0	120.6	159.1	14.0	13.6	28.9 (C1′), 29.9 (C1′ methyl carbons)
9	162.8	114.9	159.0	18.9	18.9	122.7 (C1′), 130.5 (C2′, 6′), 114.5 (C3′, 5′), 163.6 (C4′), 12.1, 12.2 (methyl carbons), 55.2 (OMe)

spectroscopic properties consistent with a 4-aryl-3,5-dimethyl substitution. It is interesting that the reaction of nitrophenylmethane with 2-nitrobenzaldehyde has been reported[3] to produce the 5-aryl-3,4-diphenylisoxazole. This could arise from Michael addition at the β-carbon of the styrene directed by the electron-withdrawing nitro group in the aromatic ring (Scheme 3).



Scheme 3

Experimental

^1H and ^{13}C NMR spectra (Table 2) were measured for $CDCl_3$ solutions at either 200 (Varian Gemini 200) or 300 MHz (Brucker AM-300). Melting points were determined with a Kofler block. GC-MS data were obtained with a Hewlett-Packard instrument equipped with an HP1 column (10 m). The GC temperature was programmed from 70 to 310 °C at 20 °C min^{-1}.

General Procedure for the Synthesis of Isoxazoles.—A mixture of nitroethane or nitropropane (9.3 mmol), aldehyde (4.41 mmol) and ethanol (7 ml) was stirred rapidly at room temperature (r.t.). A solution of NaOH (6.4 M, 2 ml) was added dropwise and the mixture heated under reflux for 5 to 18 h. The cooled reaction mixture was extracted with diethyl ether and the ether fraction washed with brine and dried over $MgSO_4$. The residue remaining after evaporation of the ether was purified either by column chromatography (silica) or by distillation. Since nitroethane and nitropropane were used in excess, trimethyl- and triethyl-isoxazole were also produced. These could be removed by column chromatography, or, given their volatility, under vacuum.

4-(4-*Methoxyphenyl*)-3,5-*dimethylisoxazole* **1**.—Crystalline, mp 37–38 °C (lit.,[4] 65.6–67.5 °C); GC 7.52 min (Found: C, 70.8; H, 6.4; N, 7.0. Calc. for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5; N, 6.9%); δ_H 2.24 (2 H, s, C5 methyl), 2.38 (3 H, s, C3 methyl), 3.84 (3 H, s, OCH_3), 6.90–7.20 (4 H, AA′BB′ pattern, aromatic hydrogens); *m*/*z* 203 (M^+) (96), 188 (5), 160 (18), 134 (92), 119 (100), 91 (49), 43 (40%).

4-(2-*Methoxyphenyl*)-3,5-*dimethylisoxazole* **2**.—Oil; bp 106–109 °C (block temp.)/3 Torr; GC 7.39 min (Found: C, 71.0; H, 6.5; N, 7.0. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.5; N, 6.9%); δ_H (200 MHz) 2.17 (3 H, s, C5 methyl), 2.27 (3 H, s, C3 methyl), 3.78 (3 H, s, OCH_3), 6.90–7.20 (4 H, m, aromatic hydrogens); *m*/*z* 203 (M^+) (56), 160 (25), 147 (19), 131 (18), 119 (30), 91 (100), 43 (61%).

3,5-*Dimethyl*-4-*phenylisoxazole* **3**.—Needles; mp 40–42 °C (lit.,[4] oil); GC 6.34 min (Found: C, 76.3; H, 6.4. Calc. for $C_{11}H_{11}NO$: C, 76.3; H, 6.4%); δ_H (200 MHz) 2.27 (3 H, s, C5 methyl), 2.43 (3 H, s, C3 methyl), 7.22–7.48 (5 H, m, aromatic hydrogens); *m*/*z* 173 (M^+) (98), 158 (30), 130 (45), 104 (100), 89 (69), 78 (68), 63 (43), 43 (49%).

4-(3,4-*Methylenedioxyphenyl*)-3,5-*dimethylisoxazole* **4**.—Plates; mp 50–52 °C; GC 8.12 min (Found: C, 66.5; H, 5.3; N, 6.4. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.5%); δ_H (200 MHz) 2.28 (3 H, s, C5 methyl), 2.38 (3 H, s, C3 methyl), 6.04 (2 H, s, methylenedioxy), 6.75–6.92 (3 H, m, aromatic protons); *m*/*z* 217 (M^+) (100), 202 (9), 174 (24), 148 (62), 147 (95), 133 (26), 89 (23), 75 (35), 43 (42%).

4-(4-*Chlorophenyl*)-3,5-*dimethylisoxazole* **5**.—Oil; bp 98–100 °C (block temp.)/0.2 Torr; GC 7.10 min (Found: N, 6.9, $C_{11}H_{10}ClNO$ requires N, 6.8%); δ_H (200 MHz) 2.22 (3 H, s, C5 methyl), 2.36 (3 H, s, C3 methyl), 7.12–7.42 (4 H, m, aromatic protons); *m*/*z* 209/207 (M^+) (70/23), 194 (16), 166 (27), 140 (85), 125 (41), 133 (100), 63 (25), 43 (95%).

3,5-*Dimethyl*-4-(4-*nitrophenyl*)*isoxazole* **6**.—Rosettes, mp 85–87 °C; GC 8.54 min (Found: N, 13.2. $C_{11}H_{10}N_2O_3$ requires: N, 12.8%); δ_H (200 MHz) 2.28 (3 H, s, C5 methyl), 2.45 (3 H, s, C3 methyl), 7.45–8.32 (3 H, AA′BB′, aromatic protons); *m*/*z* 218 (M^+) (29), 203 (10), 130 (12), 103 (22), 91 (15), 77 (32), 63 (16), 51 (13), 43 (100%).

4-(2-*Furyl*)-3,5-*dimethylisoxazole* **7**.—Needles; mp 42–44 °C; GC 4.98 min (Found: C, 66.3; H, 5.6. $C_9H_9NO_2$ requires C, 66.3; H, 5.6%); δ_H 2.38 (3 H, s, C5 methyl), 2.55 (3 H, s, C3 methyl), 6.32 (1 H, dd, *J* 9, 2, H-3′), 6.46 (1 H, dd, *J* 9, 7, H-4′), 7.47 (1 H, dd, *J* 7, 2 Hz, H-5′); *m*/*z* 163 (M^+) (19), 148 (8), 121 (10), 107 (20), 94 (21), 79 (22), 66 (67), 51 (46), 43 (100%).

3,5-*Dimethyl*-4-(1,1-*dimethylethyl*)*isoxazole* **8**.—Oil; GC 4.14 min; δ_H (200 MHz) 1.32 (9 H, s, *tert*-butyl protons), 2.34 (3 H, s, C5 methyl), 2.42 (3 H, s, C3 methyl), 7.45–8.32 (3 H, AA′BB′, aromatic protons); *m*/*z* 153 (M^+, $C_9H_{15}NO$) (17), 139 (12), 138 (100), 96 (61), 80 (61), 80 (10), 53 (11), 43 (88%).

3,5-*Diethyl*-4-(4-*methoxyphenyl*)*isoxazole* **9**.—Oil; GC 8.13 min (Found: N, 6.0. $C_{14}H_{17}NO_2$ requires N, 6.1%); δ_H (200 MHz) 1.18 (3 H, t, *J* 6.4, C5 methylene), 1.23 (3 H, t, *J*, 6.4, C3 methylene), 2.64 (2 H, q, *J* 6.4), 2.72 (2 H, d, *J* 6.4 Hz), 3.88 (3 H, s, OCH_3), 6.88–7.22 (4 H, AA′BB′, aromatic protons); *m*/*z* 232 (M^+) (63), 216 (100), 202 (15), 174 (10), 148 (12), 134 (18), 119 (14), 105 (10), 91 (11%).

Received, 19th February 1998; Accepted, 27th March 1998
Paper E/8/01428K

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