Nitrile Oxides Cycloadditions to Cinnamaldehyde. Facile Dehydrogenation of 4-Formyl-4,5-dihydroisoxazoles

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Nitrile oxides (**1**) react with cinnamaldehyde (**2**) at the ethylenic double bond to give 4-formyl-4,5-dihydroisoxazoles (**3**) as the predominant regioisomers (^{1}H nmr). These primary cycloadducts easily dehydrogenate to the corresponding isoxazoles (**4**). In the presence of an excess of nitrile oxide (**1**), either the aldehydes (**3**) and (**4**) undergo further cycloaddition at the C=O bond yielding the bis-cycloadducts (**5**) and (**6**), respectively.

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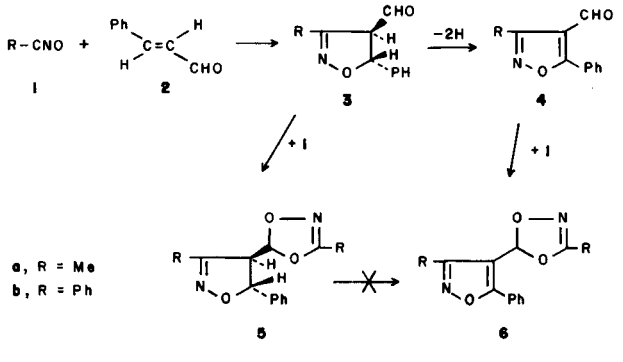
Nitrile oxides cycloaddition to conjugated ketones has been extensively studied [2], but little has been done with conjugated aldehydes: benzonitrile oxide cycloaddition to acrolein has been reported to be regioselective, leading to 5-formyl-4,5-dihydro-3-phenylisoxazole [3]. We found the opposite orientation to be predominant in the reactions of nitrile oxides **1** with *trans*-cinnamaldehyde (**2**) (referred to as cinnamaldehyde, hereinafter): 4-formyl-4,5-dihydroisoxazoles (**3**) were in fact largely predominant in the crude reaction mixtures. A comparison of the two sets of ^{1}H nmr signals exhibited by the cycloadducts **3a** and **3b** indicates that the proton adjacent to CHO, rather than the one adjacent to Ph, is affected by the substituent (R) change and therefore must be closer to R. Furthermore, the structure **3a** is supported by the mass spectrum, in which the base-peak at m/z 105 ($PhCO^+$) rules out the regioisomeric structure (*cf.* the spectra of the regioisomeric acylisoxazolines, [4]). The large observed difference between chemical shifts of the heterocyclic H atoms ($\Delta\delta 4,5$ = 2.4 **3a** and 1.58 **3b**) agrees with the values reported for the analogous regioisomers obtained from nitrile oxides and benzylideneacetones [2]. The coupling constants between the ring H-atoms (**3a**, J 6 Hz; **3b**, J 7.6 Hz) accord with a *trans* structure [2] *i.e.* with a stereospecific cycloaddition.

The formyldihydroisoxazoles **3** are very easily dehydrogenated in the neutral reaction medium to the corresponding formylisoxazoles **4**: the spectra of the aldehydes **3** are modified in a few days according to this reaction, the conversion time being considerably reduced if oxygen is bubbled into the samples. Attempted distillation of the liquid aldehydes **3**, carried out under inert gas, was unsuccessful, due to extended thermal dehydrogenation.

Such a facile dehydrogenation has been previously noticed on some condensed pyrazolino-cycloketones [5] and, by base treatment, on 4-acyl-4,5-dihydroisoxazoles, analogous to the aldehydes **3** [6]. However, neither 5-acyl-4,5-dihydroisoxazoles [5] nor the 5-formyl-4,5-dihydro-3-phenylisoxazole [3] behave similarly. In addition, when the 4-formyl group is protected, as in the bis-cycloadducts **5**, see later, or in the dimethylacetal of the aldehyde **3a**, prepared directly from the cinnamaldehyde acetal, no dehydrogenation occurs spontaneously. This reaction appears therefore to be related to the enhanced mobility of the H atom in position 4 of the 4,5-dihydroisoxazole (or 4,5-dihydropirazole) ring, in the presence of a geminal electron-withdrawing group. In 4,5-dihydro-4-nitroisoxazoles, only thermal elimination of HNO_2 was known [7], until dehydrogenation has been reported recently to occur, depending on the reaction conditions [8].

On treatment with an excess of nitrile oxide **1**, the formyl dihydroisoxazoles **3** undergo further cycloaddition at the C=O bond with production of the bis-cycloadducts **5**. Two (racemic) diastereoisomers **5** are obtained, roughly in 1:1 ratio. The ^{1}H nmr spectra of the **5b** pair show very close chemical shifts and identical coupling constants between isoxazoline H atoms (4.2 Hz), but the coupling constant between the dioxazolyl H atom and the one adjacent on the other ring is 3 Hz in one isomer, 6 in the other. Therefore, both diastereoisomers **5b** have *trans* configuration at the dihydroisoxazole ring (*cis* coupling constant would be much higher, [2]), but opposite configuration at the dioxazole CH. The **5a** diastereoisomers give identical ^{1}H nmr spectra, but can be distinguished by ^{13}C nmr spectroscopy.



1 2 3 4 5 6

The formylisoxazoles **4** also react slowly with nitrile oxides **1** at the C=O bond, to give the bis-cycloadducts **6**. This reaction accords with the known reactivity of conjugate carbonyl groups towards nitrile oxides [9,10]. By contrast, the observed higher reactivity of the unconjugate carbonyl group in the formyldihydroisoxazoles **3** is unex-

pected: the bis-cycloadducts **5** are detected even when the nitrile oxides **1** are not in exccess.

EXPERIMENTAL

Melting points were determined on a RCH Kofler apparatus. Ir spectra were recorded on a Perkin-Elmer 457 spectrophotometer. The nmr spectra (solvent deuteriochloroform) were recorded with Perkin-Elmer R 32 (pmr) and Varian FT-80 (cmr) spectrometers. Mass spectra were obtained at 20 eV by direct inlet, unless otherwise stated, using LKB 2091 (low resolution) and Kratos MS-80 (high resolution) mass spectrometers. A Perkin-Elmer 800 gas chromatograph was used for gc analyses, and a Perkin-Elmer 240 C elemental analyzer for microanalyses. Column chromatographies (silica gel) were carried out under nitrogen pressure, using a Jobin-Yvon Chromatospak Prep-10 apparatus. Liquid products were distilled by a Büchi GKR-50 Kugelrohr distillator.

Nitrile Oxides (**1**).

Known procedures were followed for the synthesis of acetonitrile oxide **1a** [11] and benzonitrile oxide **1b** [12].

Cinnamaldehyde (**2**).

Commercial *trans*-cinnamaldehyde was distilled before use.

4-Formyl-4,5-dihydro-3-methyl-5-phenylisoxazole (**3a**).

A solution of acetonitrile oxide **1a** (1.32 g = 23 mmoles) in chloroform (10 ml) was stored in refrigerator and added in portions (1 ml every 20 minutes) to cinnamaldehyde **2** (8.26 ml = 69 mmoles) at 0° under nitrogen with stirring. After 1 day at 0°, the solvent, some dimethylfuroxan and most cinnamaldehyde were removed *in vacuo* (80° at 0.06 torr) and the adduct **3a** obtained as an oily residue containing about 30% of the bis-cycloadduct **5a**. No significant signals were detected in the CHO region (pmr), in addition to those of compounds **2**, **3a**, and **4a**. Attempted distillation converted in part the product **3a** into the dehydrogenated aldehyde **4a**; pmr (crude **3a** other than the aromatic and methyl protons): δ 3.88 (dd, C*H*-CHO), 5.79 (d, Ph-C*H*, J 6 Hz), 9.72 (d, HC=O, J 2 Hz); ms: 189 (M^+, 7), 188 ($M^+ - H$, 5), 187 ($M^+ - 2H$, 11), 172 ($M^+ - Me$, 6), 161 (4), 160 ($M^+ - CHO$, 25), 148 ($M^+ - MeCN$, 15), 147 (31), 132 ($PhCHCHCHO^+$, 11), 131 (27), 106 (5), 105 ($PhCO^+$, 100), 84 ($M^+ - PhCO$, 20), 83 (11).

4-Formyl-3-methyl-5-phenylisoxazole (**4a**).

The above crude mixture of the adducts **3a** and **5a**, dissolved in chloroform, was stirred for 3 days at room temperature under oxygen, then concentrated and column chromatographed (eluant: light petroleum bp 40-70°, chloroform, methanol, 15:5:1). The aldehyde **4a**, 0.4 g (10% yield with respect to the nitrile oxide), was recrystallized twice from ethanol, mp 90-91°; ir (potassium bromide): 1680 cm^{-1} (C=O); pmr δ 2.48 (s, 3H), 7-8 (m, 5H), 10.05 (s, 1H); cmr (other than aromatic): δ 11.19 (q, Me), 115.3 (s, *C*-CHO), 159.65 (s, C-*C*=N), 175.2 (s, C=*C*-O), 184.3 (d, HC=O, $^1J_{CH}$ 178 Hz); ms (gc introduction): 187 (M^+, 100), 186 (19), 158 ($M^+ - CHO$, 15), 130 (Ph-C≡C-CHO^+, 15), 105 ($PhCO^+$, 78), 91 (6), 81 (11), 77 (15), 42 (11). High resolution exact mass Calcd. for $C_{11}H_9NO_2$: 187.0630. Found: 187.0630.

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.72; H, 4.85; N, 6.98.

4,5-Dihydro-3-methyl-4-(3-methyl-1,4,2-dioxazol-5-yl)-5-phenylisoxazole (**5a**), Two Diastereoisomers.

A chloroform solution (10 ml) of cinnamaldehyde **2** (0.9 ml = 7 mmoles) and acetonitrile oxide **1a** (*ca.* 30 mmoles) was set aside under nitrogen in refrigerator. After 1 day, the pmr spectrum showed that the bis-adduct **5a** was the main product: in addition, the aldehydes **3a**, **4a** and **2** (overall 40% of **5a**) and dimethylfuroxan were detected. The solvent and the furoxan were removed *in vacuo* and the residue column chromatographed (same eluant as for **4a**). Several fractions were collected, containing two diastereoisomers **5a**, separated in part: oil, yield 0.79 g (46% with respect to cinnamaldehyde). The two isomers distilled together at 180° and 0.08 torr; pmr (identical for the two diastereoisomers): δ 1.97 (s, 3H), 2.0 (s, 3H), 3.47 (dd, CH-C*H*-CH, 1H), 5.50 (d, Ph-C*H*, 1H, J 6.5 Hz), 6.05 (d, O-CH-O, 1H, J 5 Hz); cmr (head diastereoisomer **5a**-H, other than aromatic): δ 8.37 and 12.12 (both q), 62.41 (d, CH-*C*H-CH, $^1J_{CH}$ 138 Hz), 81.60 (d, Ph-*C*H, $^1J_{CH}$ 163 Hz), 105.79 (d, O-CH-O, $^1J_{CH}$ 176 Hz), 151.57 and 157.94 (both s, C=N); (tail diastereoisomer **5a**-T, other than aromatic): δ 8.43 and 12.39 (both q), 62.48 (d, CH-*C*H-CH, $^1J_{CH}$ 138 Hz), 81.93 (d, Ph-*C*H, $^1J_{CH}$ 163 Hz), 106.3 (d, O-CH-O, $^1J_{CH}$ 176 Hz), 151.69 and 157.94 (both s, C=N); ms (gc introduction, identical for the two diastereoisomers): 246 (M^+, 0.5), 245 (2), 161 (21), 160 (dihydromethylphenylisoxazolyl$^+$), 131 (9), 120 (51), 119 (40), 105 ($PhCO^+$, 16), 91 (49, $C_7H_7^+$), 86 (methyldioxazolyl$^+$), 58 (17).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.51; H, 5.72; N, 11.26.

3-Methyl-4-(3-methyl-1,4,2-dioxazol-5-yl)-5-phenylisoxazole (**6a**).

A large excess of acetonitrile oxide **1a** (5 g) was added in six portions during two weeks to a solution of the aldehyde **4a** (111 mg) in deuteriochloroform (2 ml). The solution was then concentrated *in vacuo* (60° at 0.07 torr), and the residue column chromatographed (see eluant as for **4a**). After small amounts of dimethylfuroxan and of the starting aldehyde **4a**, the fractions containing the product **6a** were collected to give, on concentration, 100 mg (69%) of oil; pmr (other than aromatic): δ 2.08 (s, 3H), 2.38 (s, 3H), 6.80 (s, 1H); cmr (other than aromatic): δ 8.89 and 10.80 (both q), 102.38 (d, O-CH-O, $^1J_{CH}$ 174 Hz), 108.59 (s, *C*-CH), 158.55 and 159.19 (both s, C=N), 170.07 (s, C-Ph); ms: 244 (M^+, 6), 203 ($M^+ - MeCN$, 13), 202 (18), 201 (17), 187 ($M^+ - MeCNO$, 95), 186 (30), 184 (27), 161 (11), 158 (methylphenylisoxazolyl$^+$, 19), 131 (14), 130 (Ph-C≡C-CHO^+, 15), 118 (10), 105 ($PhCO^+$, 100), 86 (methyldioxazolyl$^+$, 20), 84 (30), 81 (13), 78 (18), 77 (Ph^+, 15), 43 (94), 42 (13), 41 (13). High resolution exact mass Calcd. for $C_{13}H_{12}N_2O_3$: 244.0861. Found: 244.0862.

4-Formyl-4,5-dihydro-3,5-diphenylisoxazole (**3b**).

Benzonitrile oxide **1b** (2.12 g = 17.8 mmoles) in chloroform (20 ml) was treated with cinnamaldehyde **2** (6.3 ml = 53 mmoles) by the same procedure described for the preparation of the adduct **3a**. After removing the solvent and most cinnamaldehyde *in vacuo* (80°, 0.06 torr), the reaction mixture showed by pmr only negligible signals (less than 10%) in the CHO region, in addition to those of compounds **2**, **3b**, and **4b**. By tlc (silica gel Merck F_{254}, 0.25 mm, eluant methylene chloride and light petroleum bp 40-70°, 5:1) the following main components were detected: diphenylfuroxan (R_F 0.57), bis-cycloadduct **5b** (two diastereoisomers, R_F 0.46 and 0.42, ratio 1:1 by pmr), cinnamaldehyde **2** (R_F 0.35), primary adduct **3b** (R_F 0.21). These were separated by column chromatography (eluant: chloroform, light petroleum bp 40-70°, 1:1). The crude adduct **3b** thus obtained was too unstable for further purification; ir (potassium bromide): 1740 cm^{-1} (C=O); pmr: δ 4.45 (dd, C*H*-CHO), 6.0 (d, Ph-C*H*, J 7.6 Hz), 7-8 (m, aromatic, 10 H), 9.72 (d, HC=O, J 2.4 Hz).

4-Formyl-3,5-diphenylisoxazole (**4b**).

The crude mixture of the adducts (**3b**) and (**5b**) with diphenylfuroxan, obtained as above, was dissolved in chloroform (20 ml) and stirred under oxygen at room temperature for 2.5 days. After removal of the solvent, the mixture (in which the products **4b** and **5b** were in molar ratio 5:1) was column chromatographed (eluant as for **3b**) to give 0.65 g of crude aldehyde **4b**, mp 113-114°, recrystallized twice from ethanol; ir (potassium bromide): 1695 cm^{-1} (C=O); pmr: δ 7.0-7.3 (m, 10H), 10.08 (s, 1H); cmr (other than aromatic): δ 114.1 (s, *C*-CHO), 163.0 (s, C-*C*=N), 175.0 (s, C=*C*-O), 183.7 (d, HC=O, $^1J_{CH}$ 180); ms: 249 (M^+, 43), 248 (10), 220 ($M^+ - CHO$, 15), 219 ($M^+ - NO$, 26), 143 ($M^+ - CHO - Ph$, 10), 105 ($PhCO^+$, 100), 103 ($PhCN^+$, 23).

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.03; H, 4.44; N, 5.57.

4,5-Dihydro-3,5-diphenyl-4-(3-phenyl-1,4,2-dioxazol-5-yl)isoxazole (**5b**), Two Diastereoisomers.

A chloroform solution (10 ml) of cinnamaldehyde **2** (1 ml, 7.9 mmoles)

and benzonitrile oxide **1b** (24 mmoles) was set aside under nitrogen in refrigerator. After one day cinnamaldehyde, the adduct **3b** and the *bis*-adducts **5b** were detected by pmr in molar ratios 6:6:14. Addition of more nitrile oxide **1b** (22 mmoles) and further storage in refrigerator for one day caused complete conversion into the *bis*-cycloadducts **5b**. The solvent was then removed *in vacuo* and the residue column chromatographed (eluant as for **3b**) to give diphenylfuroxan and the two diastereoisomers **5b**, separated in part: overall yield 2.28 g (78% with respect to cinnamaldehyde). From ethanol, the head diastereoisomer **5b**-H had mp 105°, the tail diastereoisomer **5b**-T had mp 122°.

Head Diastereoisomer (**5b**-H).

This isomer had pmr: δ 4.18 (dd, CH-C*H*-CH, 1H), 5.92 (d, Ph-C*H*, 1H, J 4.2 Hz), 6.37 (d, O-CH-O, J 3 Hz), 7-8 (m, aromatic, 15 H); cmr (other than aromatic): δ 59.57 (d, CH-*C*H-CH, $^1J_{CH}$ 139 Hz), 82.17 (d, Ph-*C*H, $^1J_{CH}$ 151 Hz), 106.3 (d, O-CH-O, $^1J_{CH}$ 178 Hz), 152.81 (s, CH-*C*=N), 159.00 (s, O-C=N).

Tail Diastereoisomer (**5b**-T).

This isomer had pmr: δ 4.17 (dd), 5.86 (d, J 4.2 Hz), 6.32 (d, J 6 Hz), 7-8 (m); cmr (other than aromatic): δ 59.57 (d, $^1J_{CH}$ 139 Hz), 82.98 (d, $^1J_{CH}$ 151 Hz), 106.38 (d, $^1J_{CH}$ 178), 153.26 (s), 158.55 (s); ms (identical for both diastereoisomers): 370 (M^+, 0.6), 368 (0.6), 267 (M^+ − PhCN, 1), 251 (M^+ − PhCNO, 6), 249 (18), 238 (11), 223 (dihydrodiphenylisoxazolyl$^+$, 22), 222 (55), 178 (66), 148 (phenyldioxazolyl$^+$, 13), 132 (11), 131 (13), 122 (47), 120 (21), 119 (PhCNO$^+$, 67), 106 (21), 105 (PhCO$^+$, 100), 91 (18), 86 (11), 84 (16), 77 (23).

Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.70; H, 4.88; N, 7.33.

3,5-Diphenyl-4-(3-phenyl-1,4,2-dioxazol-5-yl)isoxazole (**6b**).

By the procedure described for the preparation of **6a**, the aldehyde **4b** (182 mg) was treated with benzonitrile oxide (2.9 g) in deuteriochloroform (5 ml). Removal of the precipitated diphenylfuroxan, then of the solvent *in vacuo*, followed by column chromatography (eluant as for **3b**) gave 25 mg of the starting aldehyde and 170 mg (yield 63%) of the product **6b**, mp 133-134° (from ethanol); pmr (other than aromatic): δ 6.84 (s); cmr (other than aromatic): δ 102.9 (d, O-CH-O, $^1J_{CH}$ 175 Hz), 108.1 (s, *C*-CH), 159.6 and 163.1 (both s, C=N), 171.3 (s, C=*C*-O); ms: 368 (M^+, 5), 265 (M^+ − PhCN, 2), 249 (M^+ − PhCNO, 52), 221 (15), 220 (diphenylisoxazolyl$^+$, 20), 193 (11), 144 (10), 121 (10), 119 (PhCNO$^+$, 51), 105 (PhCO$^+$, 100), 103 (PhCN$^+$, 26), 91 (11), 77 (Ph$^+$, 11), 45 (21).

Anal. Calcd. for $C_{23}H_{16}N_2O_3$: C, 74.99: H, 4.38; N, 7.60. Found: C, 75.42; H, 4.55; N, 7.62.

Reaction of Acetonitrile Oxide (**1a**) with Cinnamaldehyde Dimethylacetal.

A solution of the nitrile oxide **1a**, (4 mmoles) and of cinnamaldehyde dimethylacetal (**7**) (1 mmole), in deuteriochloroform (0.5 ml), was set aside at room temperature. After one day, the nitrile oxide in excess was converted into dimethylfuroxan and about half the acetal into the cycloadduct; pmr: δ 5.36 (d, J 7 Hz), 4.46 (d, J 6 Hz); the other signals are covered in part (these two doublets did not change with time); ms (gc introduction): 204 (M^+ − MeO, 0.1), 175 (0.3), 174 (0.5), 147 (PhCH=CH-CH-OMe$^+$, 1), 131 (1), 128 (M^+ − H − PhCHO, 1), 121 (1.5), 115 (2), 105 (PhCO$^+$, 4), 98 (M^+ − MeO − PhCHO, 11), 91 ($C_7H_7^+$, 2), 77 (Ph$^+$, 7), 76 (4), 75 [CH(OMe)$_2^+$, 100], 51 (3), 47 (10).

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