Studies in isoxazole chemistry. IV. Isoxazoles via isoxazolines

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4- or 5-Chloro- or cyanoisoxazoles, 5-chloromethylisoxazoles, and 5-methylisoxazoles were made by the 1,3-dipolar cycloaddition of nitrile oxides to α-halogeno- or α-alkoxyolefins. In the case of *cis*- and *trans*-1,2-dichloroethylene, (**5***a* and *b*) the intermediate *cis*- and *trans*-4,5-dichloroisoxalines (**6***a* and *b*) were isolated. Both **6***a* and *b* were dehydrochlorinated with base to give the 4-chloroisoxazole (**7***a*) exclusively. The *cis*-isomer **6***a* reacted faster than the *trans*-isomer **6***b*. The reactions were found to be specific in every reaction since only one isomer was isolated. The structures of the products were established from n.m.r. spectral analysis.

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In continuation of our work on the preparation of isoxazoles via isoxazolines (1, 2) we decided to study the 1,3-dipolar cycloaddition of nitrile oxides to α-halogeno- and α-alkoxyolefins. Cycloadditions involving bromoethylenes have been reported to produce isoxazoles via unstable isoxazolines (3–7), and Bianchi and Grünanger have recently described a convenient route to isoxazoles by converting 2-isoxazolines to their bromo derivatives followed by dehydrobromination (8). 1,3-Dipolar cycloadditions are stereoselective (9) and the synthesis of isoxazolines by this method usually produces the thermodynamically more stable isomer (10). The reaction of a nitrile oxide with an olefin substituted in the α-position with a suitable leaving group such as halogen, alkoxy, amino, or nitro, is hence a potentially useful method of preparing a variety of specifically substituted isoxazoles (see Scheme 1). By using other dipoles such as nitrile imines, diazoalkanes, and azides, this same approach could lead to similarly substituted pyrazoles (11) and triazoles.

By using appropriately substituted ethylenes it should be possible to obtain either the 3,4-disubstituted isoxazoles **7** or the 3,5-disubstituted compounds **4** from these reactions, as illustrated in Scheme 1.

The n.m.r. spectroscopy is a convenient method of establishing the substitution pattern of these isoxazoles, since the C_4-proton signals in compounds of type **4** are usually found at *ca.* τ 3.2 (see ref. 12), while the C_5-proton signals of compounds **7** are found further downfield at *ca.* τ 1.0. This method is especially useful when both isomers, for example **4***a* and **7***a*, or **4***b* and **7***c* are available.

2,5-Dichlorobenzonitrile oxide (**1**) was chosen as the dipole for this study because it is fairly stable at room temperature (13), can be isolated, and gave high yields of cycloaddition products (1, 2). All the α-halogeno- and α-alkoxyolefins used in this study are commercially available. These reactions were found to be selective (9, 10), and the n.m.r. spectrum of the product from every reaction showed the presence of only one isomer (either **4** or **7**). In most cases the intermediate isoxazoline (**3** or **6**) was not detected, since it was transformed spontaneously into the isoxazole (**4** or **7**). It was only with *cis*- (**5***a*) and *trans*-1,2-dichloroethylene (**5***b*), that the *cis*- (**6***a*) and *trans*-4,5-dichloroisoxazoline (**6***b*) were isolated. In agreement with the findings of Huisgen (9) on similar systems, the *trans*-isomer **5***b* was found to react at least five times as fast as the *cis*-isomer **5***a*.

The 4,5-dichloroisoxazolines **6***a* and *b* could be expected to undergo dehydrochlorination to give either **4***a* or **7***a*. Both **6***a* and *b* reacted readily with sodium hydroxide in methanol to form the 4-chloroisoxazole (**7***a*). No trace of the 5-isomer **4***a* was found in the n.m.r. spectrum of the crude product. A preliminary study showed that although both isomers **6***a* and *b* underwent rapid dehydrochlorination with base, the *cis*-isomer **6***a* reacted faster than the *trans*-isomer **6***b*. Thus an n.m.r. analysis of the reaction product after 10 s at room temperature (25 °C) showed complete dehydrochlorination in the case of the *cis*-isomer **6***a*, but only *ca.* 66% reaction with the *trans*-isomer **6***b*. Triethylamine in ether reacted very slowly with **6***a* and *b*.

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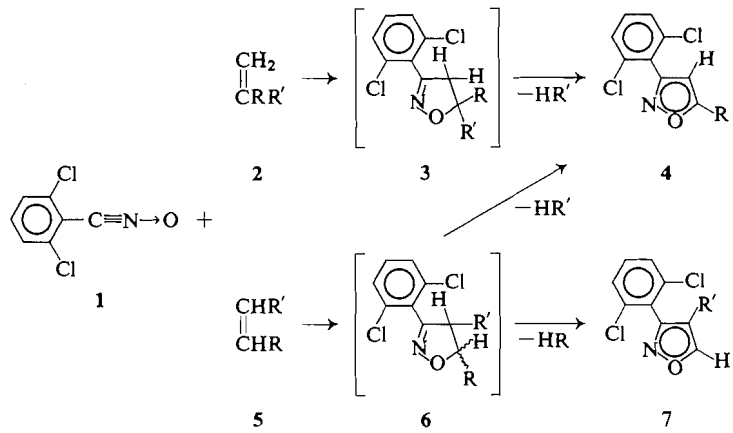

2 and **3**
a R = R′ = Cl
b R = CN, R′ = Cl
c R = CH_3, R′ = Br
d R = CH_2Cl, R′ = Cl

4
a R = Cl
b R = CN
c R = CH_3
d R = CH_2Cl

5 and **6**
a R = R′ = Cl (*cis*)
b R = R′ = Cl (*trans*)
c R = OEt, R′ = CN
d R = CH_3, R′ = Br

7
a R′ = Cl
c R′ = CN

SCHEME 1

In the case of the bromoolefins **2***c* and **5***d*, there was i.r. spectroscopic evidence for the concurrent formation of oximes similar to those recently reported in reactions with acetylenes (14, 15). We have not yet investigated this aspect in detail.

Experimental

The instruments used were those described previously (1). 2,5-Dichlorobenzonitrile oxide **1** was made as described by Grundmann and Dean (13). A sample of 3-ethoxyacrylonitrile **5***c* was obtained from Kay-Fries Chemicals Inc., New York 10017; all other olefins were purchased from commercial sources.

General Procedure

(*a*) 2,6-Dichlorobenzonitrile oxide (5.6 g, 0.03 mole) was added to a stirred solution of the olefin (0.036 mole) in dry THF (10 ml) cooled in an ice-bath. In some cases an exothermic reaction took place. After 1/2 h the solution was left at room temperature until the reaction was complete. The course of the reaction was followed by the disappearance of the nitrile oxide band in the i.r. spectrum of the reaction mixture. When the reaction was complete the mixture was concentrated under reduced pressure and triturated with a small volume of cold dry ether. The solid furoxan was removed by filtration and the ether solution concentrated. The residue, if solid, was crystallized, and if liquid, was distilled under reduced pressure.

(*b*) The reaction was done as described above except that the solvent used was ether (50 ml). Triethylamine (10 ml) was added after 24 h at room temperature. After a further 2 days at ambient temperature the mixture was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure.

3-(2,6-Dichlorophenyl)-5-chloroisoxazole (4a)

1,1-Dichloroethylene (**2***a*) by method *a* gave a 72% yield of **4***a*, b.p. 119°/0.8 mm, m.p. 34–37°; see ref. 2.

3-(2,6-Dichlorophenyl)-trans-4,5-dichloroisoxazoline (6b)

Trans-1,2-dichloroethylene (**5***b*) after 3 days (method *a*) gave a 76% yield of **6***b*, m.p. 109–112° (hexane). The n.m.r. ($CDCl_3$) τ 2.59 (s, 3H), 3.40 (s, 1H), 4.34 (s, 1H). The C-4 and -5 protons in this case gave sharp singlets, which is surprising in view of the fact that other similar *trans*-isoxazolines show $J_{4,5}$ of *ca.* 6 Hz (16). This effect is probably due to hydrogen bonding and steric interactions which compress the dihedral angle of the vicinal hydrogen atoms to about 90° resulting in singlets for these protons (17).

Anal. Calcd. for $C_9H_5Cl_4NO$: C, 37.90; H, 1.76; N, 4.91. Found: C, 38.20; H, 1.81; N, 4.68.

3-(2,6-Dichlorophenyl)-cis-4,5-dichloroisoxazoline (6a)

Cis-1,2-dichloroethylene (**5***a*), required 2 weeks (method *a*) for the reaction to be complete. The product was purified by elution from a silica column using ether:hexane (1:19). Fractions (400 ml) were collected and monitored by the i.r. spectrum and weight of the residue after evaporation. Fractions 4 to 8 were collected and recrystallized from carbon tetrachloride when 1.7 g (20%) of **6***a*, m.p. 98–100° was obtained. The n.m.r. ($CDCl_3$) τ 2.57 (s, 3H), 3.22 (d, 1H), 4.05 (d, 1H), $J_{4,5}$

6.5 Hz. The reported $J_{4,5}$ for similar *cis*-isoxazolines is *ca.* 11 Hz (16).

Anal. Calcd. for $C_9H_5Cl_4NO$: C, 37.90; H, 1.76; N, 4.91. Found: C, 38.20; H, 1.68; N, 5.11.

3-(2,6-Dichlorophenyl)-5-cyanoisoxazole (4b)

2-Chloroacrylonitrile (**2***b*) (method *a*) gave 93% of **4***b*, m.p. 115–117° (CCl_4). The n.m.r. ($CDCl_3$) τ 2.59 (s, 3H), 2.94 (s, 1H).

Anal. Calcd. for $C_{10}H_4Cl_2N_2O$: C, 50.21; H, 1.67; N, 11.72; Cl, 29.71. Found: C, 50.26; H, 1.45; N, 11.76; Cl, 29.41.

3-(2,6-Dichlorophenyl)-4-cyanoisoxazole (7c)

3-Ethoxyacrylonitrile (**5***c*) (method *a*) gave 60% of 7*c*, m.p. 97–98° (hexane). The n.m.r. ($CDCl_3$) τ 0.95 (s, 1H), 2.57 (s, 3H).

Anal. Calcd. for $C_{10}H_4Cl_2N_2O$: C, 50.21; H, 1.67; N, 11.72; Cl, 29.71. Found: C, 50.21; H, 1.90; N, 11.73; Cl, 29.10.

3-(2,6-Dichlorophenyl)-5-methylisoxazole (4c)

Both 1-bromopropene (**5***d*) and 2-bromopropene (**2***c*) by method *b*, gave the same product **4***c* (b.p., i.r., and n.m.r. spectra identical) in yields of 73 and 95% respectively. The compound was a faint yellow oil, b.p. 110°/0.1 mm. The n.m.r. ($CDCl_3$) τ 2.60 (s, 3H), 3.89 (s, 1H), 7.51 (s, 3H). The signals at τ 3.89 and 7.51 although apparent singlets showed considerable broadening due to coupling between the C_4-proton and the C_5-methyl protons.

Anal. Calcd. for $C_{10}H_7Cl_2NO$: C, 52.68; H, 3.07; N, 6.14; Cl, 31.14. Found: C, 52.36; H, 2.97; N, 5.91; Cl, 30.80.

Method *a* in both cases gave a crude product which showed a strong broad i.r. absorption band at *ca.* 3200 cm^{-1}, and no band at 2300 cm^{-1}. Treatment of this reaction product in ether with triethylamine immediately gave a strong sharp band at 2300 cm^{-1}.

3-(2,6-Dichlorophenyl)-5-chloromethylisoxazole (4d)

2,3-Dichloropropene (**2***d*) (method *a*) gave 65% of **4***d*, b.p. 144–146°/0.3 mm. The n.m.r. (CCl_4) τ 2.69 (s, 3H), 3.63 (s, 1H), 5.33 (s, 2H).

Anal. Calcd. for $C_{10}H_6Cl_3NO$: C, 45.72; H, 2.29; N, 5.33. Found: C, 45.78; H, 2.36; N, 5.50.

3-(2,6-Dichlorophenyl)-4-chloroisoxazole (7a)

A 3 *M* solution of sodium hydroxide in methanol (2.7 ml, 0.008 mole) was added slowly to a stirred mixture of **6***a* or *b* (2.28 g, 0.008 mole) in methanol (35 ml). After 15 min the mixture was concentrated, the residue shaken with water (50 ml), and extracted with ethyl acetate (3 × 50 ml). The combined organic layers were dried ($MgSO_4$), filtered, and solvent removed when 1.9 g (100 %) of the 4-chloroisoxazole 7*a* was obtained. Recrystallization from hexane gave 1.6 g (86 %) of crystals m.p. 84–85°. The n.m.r. ($CDCl_3$) τ 1.37 (s, 1H), 2.58 (s, 3H).

Anal. Calcd. for $C_9H_4Cl_3NO$: C, 43.45; H, 1.61; N, 5.63; Cl, 42.86. Found: C, 43.71; H, 1.80; N, 5.38; Cl, 42.39.

Comparison of Rates of Dehydrochlorination of 6a and b

A solution of sodium hydroxide in methanol (1 ml of a 1 *M* solution, 0.001 mole) was added in one lot with shaking to a solution of **6***a* or *b* (280 mg, *ca.* 0.001 mole) in methanol (30 ml) at room temperature. After 10 s the equilibrium was frozen by adding hydrochloric acid (1 ml of a 3 *M* solution, 0.003 mole). The solutions were taken to dryness and an n.m.r. spectrum ($CDCl_3$) run on each residue.

The residue from **6***a* showed two sharp signals at τ 1.40 and 2.56 which is characteristic of 7*a* above.

The residue from **6***b* showed sharp signals at τ 1.40 and 2.56 characteristic of 7*a* and at τ 3.40 and 4.33 characteristic of **6***b*. The integration ratio of the signals at τ 1.40, 3.40, and 4.33 was 2:1:1 showing that there was *ca.* 66% conversion of **6***b* to 7*a*.

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