

The Reactions of 2,4-Dichlorobenzonitrile Oxide with Enolizable Schiff Bases

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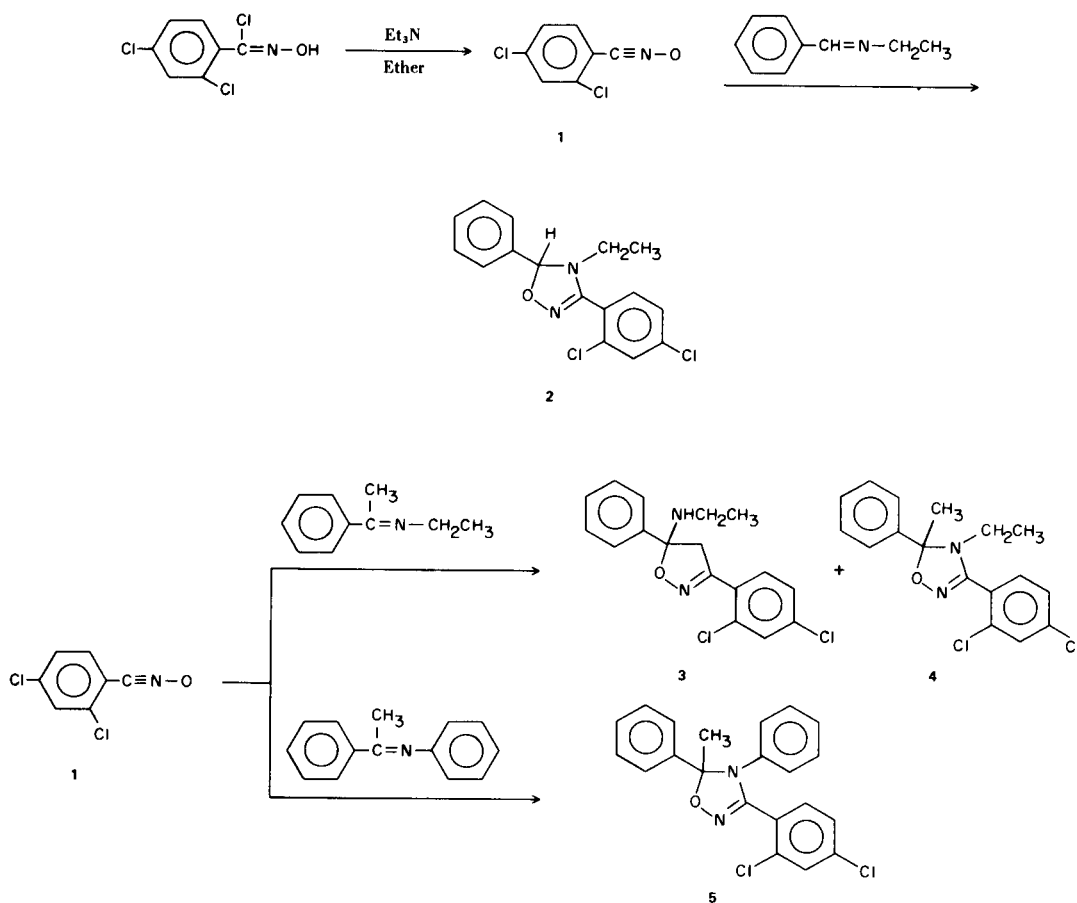
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The 1,3-dipolar cycloaddition reactions of nitrile oxides with Schiff Bases yielding 4,5-dihydro-1,2,4-oxadiazoles, have generally involved the use of aldimines as the dipolarophile (1-4). Hence, the treatment of a refluxing mixture of *N*-benzylidene-ethylamine and triethylamine in ether with an ethereal solution of 2,4-dichlorobenzohydroxamyl chloride furnished 3-(2,4-dichlorophenyl)-4-ethyl-5-phenyl-4,5-dihydro-1,2,4-oxadiazole (2) in 55% yield.

Reactions of nitrile oxides with dipolarophiles capable of exhibiting imine-enamine tautomerization have, in some cases, been reported to yield mixtures of isomeric products, for example, cycloadditions of nitrile oxides with

β -ketoimines or cyanoacetic esters (5). Morocchi, *et al.*, however, found that the reaction of benzonitrile oxide with acetophenone or propiophenone imines furnished a single product, the 4,5-dihydro-1,2,4-oxadiazoles (6).

In the present case, reaction of *N*-(α -methylbenzylidene)-ethylamine, triethylamine, and 2,4-dichlorobenzohydroxamyl chloride in ether furnished a mixture of products which were readily separated by column chromatography. In addition to isolating a small amount of 3,4-di(2,4-dichlorophenyl)furoxan, the dimer arising from the nitrile oxide (7), two cycloaddition products were obtained: 3-(2,4-dichlorophenyl)-5-ethylamino-5-phenyl-4,5-dihydro-



isoxazole (**3**) (13% yield), and 3-(2,4-dichlorophenyl)-4-ethyl-5-methyl-5-phenyl-4,5-dihydro-1,2,4-oxadiazole (**4**) (22% yield). Identification of each isomer was made on the basis of their respective nmr spectra.

Replacement of the Schiff Base, used in the previous reaction, with *N*-(α -methylbenzylidene)aniline resulted in the formation of a single cycloaddition product, the dihydrooxadiazole derivative (**5**) in 28% yield. Nmr examination of the crude reaction mixture failed to provide evidence for the presence of a dihydroisoxazole corresponding to **3**, i.e., an AB quartet in the region of 3.5 δ . The equilibrium between the enamine and imine forms of this Schiff Base, being shifted in favor of the imine by the extended conjugation offered, may account for the formation of a single product in the latter reaction.

EXPERIMENTAL (8)

3-(2,4-Dichlorophenyl)-4-ethyl-5-phenyl-4,5-dihydro-1,2,4-oxadiazole (**2**).

A solution of 2,4-dichlorobenzohydroxamyl chloride (**7**) (6.75 g., 0.03 mole) in anhydrous ether (25 ml.) was added, in dropwise portions, to a refluxing mixture of *N*-benzylideneethylamine (4.0 g., 0.03 mole) and triethylamine (3.0 g., 0.03 mole) in anhydrous ether (100 ml.). The reaction mixture was heated to reflux for an additional three hours, then cooled, filtered, and the ether filtrate evaporated to dryness. The residue obtained was washed with hexane and then recrystallized from aqueous methanol, thereby yielding the product as a colorless solid (5.30 g., 55% yield), m.p. 93.5-95°; nmr (deuteriochloroform): CH₃ (0.90 δ , t); CH₂ (2.93 δ , q); CH (6.40 δ , s); aromatic protons (7.15-7.80 δ , m).

Anal. Calcd. for C₁₆H₁₄Cl₂N₂O: C, 59.82; H, 4.39; N, 8.72. Found: C, 59.90; H, 4.39; N, 8.72.

Reaction of **1** with *N*-(α -Methylbenzylidene)ethylamine.

A refluxing mixture of *N*-(α -methylbenzylidene)ethylamine (**9**) (4.40 g., 0.03 mole) and triethylamine (3.0 g., 0.03 mole) in anhydrous ether (200 ml.) was treated with a solution of 2,4-dichlorobenzohydroxamyl chloride (6.75 g., 0.03 mole) in anhydrous ether (50 ml.) in dropwise amounts. Continued to heat the reaction mixture to reflux for three hours, then cooled and filtered. Evaporation of the ether filtrate left a yellow semi-solid (11.4 g.). This residue was dissolved in benzene (25 ml.) and chromatographed on a column of silica gel (Silicar CC-7; 125 g.) in benzene. The column was continuously eluted with benzene and the eluates (ca. 25 ml. volumes) were examined by tlc. After isolating a small amount (0.15 g.) of 3,4-di(2,4-dichlorophenyl)furoxan, the following cycloaddition products were obtained:

3-(2,4-Dichlorophenyl)-5-ethylamino-5-phenyl-4,5-dihydroisoxazole (**3**).

This compound was obtained in 13% yield (1.35 g.), m.p. 101-103° (ethanol); nmr (deuteriochloroform): CH₃ (1.11 δ , t); NH (2.12 δ , broad s); CH₂N (2.70 δ , m); ring CH₂ (3.55 δ , AB q); aromatic protons (7.20-7.55 δ , m).

Anal. Calcd. for C₁₇H₁₆Cl₂N₂O: C, 60.90; H, 4.81; N, 8.36. Found: C, 60.71; H, 4.90; N, 8.35.

3-(2,4-Dichlorophenyl)-4-ethyl-5-methyl-5-phenyl-4,5-dihydro-1,2,4-oxadiazole (**4**).

This compound was obtained in 22% yield (2.20 g.), b.p. 188-189°/0.4 torr, m.p. 73-77° (methanol-water, 1:1); nmr (deuteriochloroform): CH₃ (0.70 δ , t); CH₃ (1.96 δ , s); CH₂ (2.90 δ , q); aromatic protons (7.25-7.91 δ , m).

Anal. Calcd. for C₁₇H₁₆Cl₂N₂O: C, 60.90; H, 4.81; N, 8.36. Found: C, 60.68; H, 4.70; N, 8.51.

3-(2,4-Dichlorophenyl)-4,5-diphenyl-5-methyl-4,5-dihydro-1,2,4-oxadiazole (**5**).

Using the conditions described above, a similar experiment was carried out using *N*-(α -methylbenzylidene)aniline (5.85 g., 0.03 mole) as the Schiff Base. Evaporation of the filtered reaction mixture furnished a yellow oil (12.75 g.), which was chromatographed on silica gel in benzene. Elution with 1% ethyl acetate-benzene provided the product (**5**) (3.30 g., 28% yield), m.p. 125-127° (petroleum ether 60-70°); nmr (deuteriochloroform): CH₃ (1.91 δ , s); aromatic protons (6.60-7.80 δ , m).

Anal. Calcd. for C₂₁H₁₆Cl₂N₂O: C, 65.81; H, 4.21; N, 7.31. Found: C, 66.11; H, 4.31; N, 7.17.

Further elution with 15% ethyl acetate-benzene failed to provide the isomeric dihydroisoxazole.

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