1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides and Nitrile Imines with 2-Methoxyvinyl Phenyl Ketone

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Nitrile oxides react regioselectively with 2-methoxyvinyl phenyl ketone **1** to give 4-benzoylisoxazoles **4** *via* elimination of methanol from the primary cycloadducts **3**. After heating with an excess of nitrile oxide bis-cycloadducts **5** were also formed. Reactions of nitrile imines with **1** are less regioselective yielding both 4-benzoylpyrazoles **9** and 5-benzoylpyrazoles **10**, whereas no bis-cycloadducts were isolated.

Reactions of nitrile oxides and nitrile imines with several α,β-unsaturated ketones have been extensively studied in order to rationalize the orientation phenomena in 1,3-dipolar cycloaddition reactions [1,2]. It has been shown that the substitution has an important influence on the orientation of the addition. Thus in cases such as vinyl phenyl ketone only the 5-acyl derivatives have been obtained with both classes of 1,3-dipoles. Alkyl or aryl substitution on the β-carbon of the vinyl group has no effect on the regiochemistry of addition with nitrile imines, while with the nitrile oxides both regioisomers, 4- and 5-acyl derivatives, have been isolated, the 5-acyl derivatives being the dominant one. However, as we have previously shown [3], introduction of a substituent with strong directive effect, as methylthio, reverses the regioselectivity of the reactions with nitrile oxides and the 4-acyl derivatives are exclusively formed. In connection with the above work, we examined in this paper the 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrile imines with 2-methoxyvinyl phenyl ketone **1**, bearing in conjugation with the enonic system a methoxy group. The methoxy group is expected to have
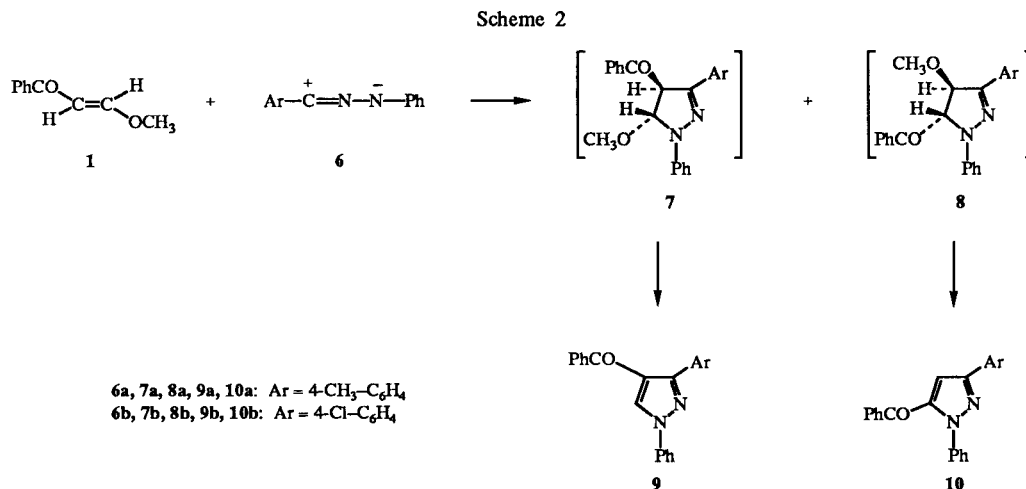
a strong directive effect on the regioselectivity of the reactions analogous to the methylthio group. On the other hand it can be easily removed and the starting cycloadducts can be converted into the corresponding aromatic systems.

At first, the reactions of 2-methoxyvinyl phenyl ketone **1** with nitrile oxides **2** were carried out in chloroform solution at room temperature (48 hours) using the nitrile oxide in excess. After the removal of the solvent the crude reaction mixtures of **1** with the stable nitrile oxides **2b** and **2c** showed in the ^{1}H nmr two doublets, characteristic of the isoxazolines **3**, at δ 5.02 (J = 2 Hz) and 5.83 (J = 2 Hz) for **3b** and at δ 5.40 (J = 2 Hz) and 6.15 (J = 2 Hz) for **3c**. However, isoxazolines **3** were not isolated. Instead the isoxazoles **4** were obtained in 80-90% yield after column chromatography of the reaction mixture. Isoxazoles **4** are obviously formed from isoxazolines **3** *via* elimination of methanol. In the case of the reaction of **1** with the unstable benzonitrile oxide **2a**, prepared *in situ* from benzohydroxamoyl chloride and triethylamine, the crude reaction mixture showed no isoxazoline hydrogens in the ^{1}H

Scheme 1
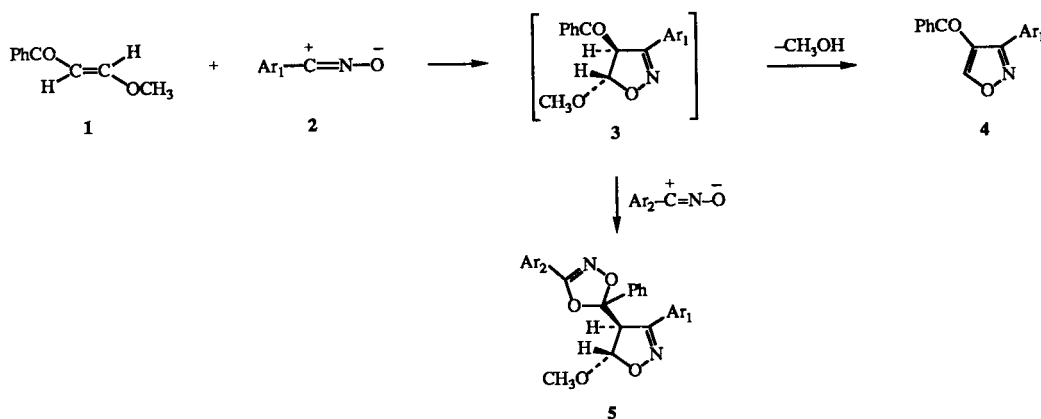
2a, 3a, 4a: $Ar_1 = C_6H_5$
2b, 3b, 4b: $Ar_1 = 2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$
2c, 3c, 4c: $Ar_1 = 2,6\text{-}Cl_2\text{-}C_6H_3$
5b: $Ar_1 = Ar_2 = 2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$
5c: $Ar_1 = Ar_2 = 2,6\text{-}Cl_2\text{-}C_6H_3$
5d: $Ar_1 = 2,6\text{-}Cl_2\text{-}C_6H_3$, $Ar_2 = 2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$

Scheme 2

6a, 7a, 8a, 9a, 10a: Ar = 4-CH$_3$–C$_6$H$_4$
6b, 7b, 8b, 9b, 10b: Ar = 4-Cl–C$_6$H$_4$

nmr. The presence of triethylamine catalyzes probably the elimination of methanol. After reflux (48 hours) of the crude reaction mixtures, containing unreacted nitrile oxide, isoxazolines **3** undergo further cycloaddition to the carbonyl double bond affording the bis-cycloadducts **5**. Also, when in a cross experiment mesitonitrile oxide **2b** was added to the crude reaction mixture of **1** with **2c** and the mixture was refluxed, in addition to the isoxazole **4c**, two bis-cycloadducts **5c** and **5d** were isolated in 10% and 50% yields respectively. The 4-dioxazolylisoxazolines **5** are more stable than the corresponding 4-benzoylisoxazolines **3** and it was possible to isolate them by column chromatography. This increased stability is probably due to the decreased mobility of the 4-C hydrogen of the isoxazoline, when the 4-carbonyl is protected as in the bis-cycloadducts **5**.

Reactions of **1** with nitrile imines **6** are less regioselective and give both regioisomeric pyrazoles **9** and **10** in ratios 50:21 for the reaction with **6a** and 45:16 for the reaction with **6b**. The ^{1}H nmr spectra of the reaction mixtures, before column chromatography, showed no pyrazoline hydrogens. The triethylamine used for the *in situ* preparation of nitrile imines catalyzes probably the elimination of methanol from the intermediate pyrazolines **7**, **8**, as in the case of the reaction with benzonitrile oxide. Also, no bis-cycloadducts analogous to **5** were isolated, although the reactions were carried out by reflux in benzene solution for 48 hours using nitrile imine in excess.

The known compounds **4a**, **4b**, **4c** were identified by comparison of their physical and spectra data with those previously reported [3,4], whereas the new compounds **5b**, **5c**, **5d**, **9a**, **10a**, **9b** and **10b** were characterized by their elemental analysis and their ir, ^{1}H nmr and mass spectra. For the cycloadducts **3** and **5** the stereochemistry follows from the coupling constant of the isoxazoline hydrogens (J = 2 Hz), which is consistent with the *trans* configuration [5]. The proposed regiochemistry comes from the trans-

formation of **3** to the known isoxazoles **4**. Bis-cycloadducts **5** resulted from **3** by cycloaddition to the carbonyl double bond must have the same regiochemistry. In fact, the hydrogen adjacent to the carbonyl group of **3** (the high field shift of the two doublets) has a diamagnetic shift of $\Delta\delta = 0.52$-0.55 in compounds **5**, as it is expected for the proposed structures. The differentiation between the two regioisomers **9** and **10** was mainly based on their ^{1}H nmr spectra, where regioisomers **9** give a singlet at $\delta = 8.23$-8.25 corresponding to a 5-C hydrogen of the pyrazole ring [6,7].

The regiochemistry of the reactions of **1** with nitrile oxides is the same as that observed in the reactions of nitrile oxides with 2-methylthiovinyl phenyl ketone [3] and alkoxybutenones [8], whereas from the reactions of alkoxybutenones with nitrile imines the isolation of only 4-acylpyrazoles is reported [8]. Concerning the formation of the bis-cycloadducts **5**, it should be mentioned that uncatalyzed cycloadditions to the carbonyl bond are usually observed only when activated by electron withdrawing substituents [9]. Thus, benzonitrile oxide is reported to add onto the carbonyl bond of α-azidovinyl ketones but not onto that of β-azidovinyl ketones [10]. The results are explained by the $-I$ effect of the azide function and the isoxazoline nucleus. For the formation of **5** some activation of the carbonyl bond is also probably caused by the isoxazoline nucleus. By contrast the conjugated carbonyl bond of isoxazole **4c** is unreactive towards nitrile oxides and no product was detected by tlc after prolonged heating of **4c** with mesitonitrile oxide **2b**. Analogous higher reactivity of the unconjugated carbonyl group of 4-formylisoxazolines compared with the conjugated carbonyl group of 4-formylisoxazoles was also observed in the cycloadditions of nitrile oxides to cinnamaldeyde [11].

The observed regioselectivity of the reactions can be explained in terms of frontier molecular orbital considerations of the reacting systems. According to Houk's approx-

imations [12] and CNDO/2 calculations carried out on the analogous to **1** (*E*)-methyl 2-methylthiovinyl ketone [3] the larger HOMO coefficient of **1** must be on the carbon atom adjacent to the carbonyl and the larger LUMO coefficient on the carbon atom adjacent to the methoxy group. In the reactions with nitrile oxides union of the atoms with the larger coefficients in both interactions (LUMOdipole-HOMOdipolarophile, HOMOdipole-LUMOdipolarophile) leads to the formation of the 4-benzoyl regioisomer. In the reactions with nitrile imines and for their linear configuration both interactions should also favor the formation of the 4-benzoyl regioisomer. However, if a bent geometry of nitrile imines is assumed [13], HOMOdipole controlled interaction must lead to 5-benzoyl regioisomer. It should be noted that this assumption has been recently invoked to explain the regioselectivity of nitrile imines in many cases [2, 14-16].

In summary, in both the reactions with nitrile oxides and nitrile imines the strong directive effect of the methoxy group dominates the regiochemistry of the reaction resulting in 4-benzoyl heterocycles as the sole or the main products in contrast to the reactions with benzoylalkenes and benzoylalkynes, which give 5-benzoyl heterocycles as main products.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were recorded as nujol mulls on a Perkin-Elmer 297 spectrometer. The ¹H nmr spectra were obtained with a Bruker AW 80 spectrometer in deuteriochloroform with tetramethylsilane as the internal standard. The mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6L spectrometer and elemental microanalyses were performed with a Perkin-Elmer analyzer Model 240B.

Preparation of Starting Materials.

2-Methoxyvinyl phenyl ketone **1** was prepared from the sodium salt of the hydroxymethylene acetophenone [17] by treatment with methyl sulfate [18]. Mesitonitrile oxide **2b** and 2,6-dichlorobenzonitrile oxide **2c** were prepared according to a known procedure [19] from the corresponding aldoximes with *N*-bromosuccinimide and triethylamine. Benzonitrile oxide **2a** and nitrile imines **6a,b** were prepared *in situ* with triethylamine from benzohydroxamoyl chloride [20] and the corresponding *N*-phenylarylhydrazonoyl chloride [21] respectively.

Reaction of **1** with Benzonitrile Oxide **2a**.

A solution of **1** (1 mmole), benzohydroxamoyl chloride (2 mmoles) and triethylamine (2.2 mmoles) in chloroform (5 ml) was allowed to react at room temperature for 2 days. Then the reaction mixture was extracted with water to remove triethylamine hydrochloride and was dried. After evaporation of the solvent the residue was chromatographed on a silica gel column (hexaneethyl acetate 9/1) to give in addition to diphenylfuroxan and unreacted alkene 3-phenyl-4-benzoylisoxazole **4a** in 32% yield, mp 77-81° (lit [4] 82°).

Reaction of **1** with Mesitonitrile Oxide **2b**.

A solution of **1** (2 mmoles) and **2b** (4 mmoles) in chloroform (10 ml) was allowed to stay at room temperature and the reaction was monitored by tlc and ¹H nmr. After 2 days the one half of the reaction mixture was chromotographed on a silica gel column (hexane-ethyl acetate 9/1) to give 3-mesityl-4-benzoylisoxazole **4b** in 90% yield, mp 113-115° (lit [4], 116°). The other half of the reaction mixture was refluxed for two days. After evaporation of the solvent the residue was chromatographed on a silica gel column (hexane-ethyl acetate 9/1) to give in order of elution:

a) *trans*-3-mesityl-4-(3-mesityl-5-phenyl-5*H*-1,4,2-dioxazol-5-yl)-5-methoxy-4,5-dihydroisoxazole **5b** in 44% yield, mp 100-103° (from methanol); ir: ν C=N 1635 cm⁻¹; ¹H nmr: δ 2.12 (s, 12H), 2.23 (s, 6H), 3.52 (s, 3H), 4.50 (d, J = 2 Hz, 1H), 5.70 (d, J = 2 Hz, 1H), 6.57 (br s, 2H), 6.82 (s, 2H), 6.97-7.42 (m, 5H); ms: m/z (%) 323 (M⁺-MesCNO, 4), 291 (1), 266 (2), 263 (3), 187 (1), 161 (24), 105 (100).

Anal. Calcd. for $C_{30}H_{32}N_2O_4$: C, 74.35; H, 6.66; N, 5.78. Found: C, 74.28; H, 6.59; N, 5.70.

b) Isoxazole **4b** was obtained in 41% yield.

Reaction of **1** with 2,6-Dichlorobenzonitrile Oxide **2c**.

The same procedure with the reaction with **2b** was followed. From the reaction at room temperature 3-(2,6-dichlorophenyl)-4-benzoylisoxazole **4c** was isolated in 80% yield, mp 152-155° (lit [3], 154-156°). After reflux for 2 days, besides **4c** in 65% yield, *trans*-3-(2,6-dichlorophenyl-4-[3-(2,6-dichlorophenyl)-5-phenyl-5*H*-1,4,2-dioxazol-5-yl]-5-methoxy-4,5-dihydroisoxazole **5c** was isolated in 9% yield, mp 179-181° (from diethyl ether); ir: ν C=N 1640 cm⁻¹; ¹H nmr: δ 3.63 (s, 3H), 4.92 (d, J = 2 Hz, 1H), 6.10 (d, J = 2 Hz, 1H), 6.85-7.70 (m, 11H); ms: m/z (%) 349 (M⁺-Cl₂C₆H₃CNO, 2), 292 (4), 289 (1), 213 (11), 187 (61), 105 (100).

Anal. Calcd. for $C_{24}H_{16}Cl_4N_2O_4$: C, 53.55; H, 3.00; N, 5.21. Found: C, 53.36; H, 3.00; N, 5.22.

Reaction of **3c** with mesitonitrile Oxide **2b**.

A solution of **1** (1 mmole) and 2,6-dichlorobenzonitrile oxide **2c** (2 mmoles) in chloroform was allowed to stay at room temperature for 2 days. After checking the formation of isoxazoline **3c** by ¹H nmr, mesitonitrile oxide **2b** (2 mmoles) was added and the solution was refluxed for 2 days. Then the solvent was evaporated and the residue was chromatographed on a silica gel column (hexane-chloroform 2/1) to give in order of elution: a) **4c** in 32% yield; b) *trans*-3-(2,6-dichlorophenyl)-4-(3-mesityl-5-phenyl-5*H*-1,4,2-dioxazol-5-yl)-5-methoxy-4,5-dihydroisoxazole **5b** in 50% yield, mp 161-166° (from diethyl ether); ir: ν C=N 1635 cm⁻¹; ¹H nmr: δ 2.32 (s, 9H), 3.64 (s, 3H), 4.95 (d, J = 2 Hz, 1H), 5.95 (d, J = 2 Hz, 1H), 6.83-7.70 (m, 10H); ms: m/z (%) 510 (M⁺, 1), 349 (2), 317 (2), 289 (11), 266 (8), 213 (40), 187 (22), 161 (94), 105 (100).

Anal. Calcd. for $C_{27}H_{24}Cl_2N_2O_4$: C, 63.41; H, 4.74; N, 5.48. Found: C, 63.68; H, 4.92; N, 5.57.

c) compound **5c** was obtained in 10% yield.

Reaction of **1** with C-(4-Methylphenyl)-*N*-phenylnitrile Imine **6a**.

To a stirred solution of **1** (1 mmole) and *C*-(4-methylphenyl)-*N*-phenylhydrazonoyl chloride (2 mmoles) in benzene (10 ml) triethylamine (2.2 mmoles) was added at once. The reaction mixture was refluxed for 48 hours and the precipitated triethylammonium hydrochloride was filtered off. The filtrate was evaporated and the residue was chromatographed on a silica gel column (hexaneethyl acetate 9/1) to give in order of elution: a) 1-phenyl-3-(4-

methylphenyl)-5-benzoylpyrazole **10a** in 21% yield, mp 118-120° (from diethyl ether-hexane); ir: ν C=O 1645 cm^{-1}; ^{1}H nmr: δ 2.40 (s, 3H), 7.06 (s, 1H), 7.13-8.06 (m, 14H); ms: m/z (%) 338 (M$^+$, 100), 309 (10), 261 (13), 105 (44).

Anal. Calcd. for C$_{23}$H$_{18}$N$_2$O: C, 81.62; H, 5.27; N, 8.28. Found: C, 81.49; H, 5.35; N, 8.21.

b) 1-Phenyl-3-(4-methylphenyl)-4-benzoylpyrazole **9a** was obtained in 50% yield, mp 137-140° (from dichloromethane-hexane); ir: ν C=O 1645 cm^{-1}; ^{1}H nmr: δ 2.33 (s, 3H), 7.02-7.97 (m, 14H), 8.23 (s, 1H); ms: m/z (%) 338 (M$^+$, 100), 309 (7), 261 (96), 105 (20).

Anal. Calcd. for C$_{23}$H$_{18}$N$_2$O: C, 81.62; H, 5.27; N, 8.28. Found: C, 81.66; H, 5.32; N, 8.24.

Reaction of 1 with C-(4-Chlorophenyl)-N-phenylnitrile Imine 6b.

The same procedure with the reaction with **6a** was followed. They were isolated: a) 1-phenyl-3-(4-chlorophenyl)-5-benzoylpyrazole **10b** in 16% yield, mp 127-130° (from diethyl ether-hexane); ir: ν C=O 1645 cm^{-1}; ^{1}H nmr: δ 7.02 (s, 1H), 7.09-7.96 (m, 14H); ms: m/z (%) 358 (M$^+$, 100), 329 (13), 281 (11), 105 (44).

Anal. Calcd. for C$_{22}$H$_{15}$ClN$_2$O: C, 73.63; H, 4.22; N, 7.81. Found: C, 73.87; H, 4.10; N, 7.60.

b) 1-phenyl-3-(4-chlorophenyl)-4-benzoylpyrazole **9b** in 45% yield, mp 142-145° (from dichloromethane-hexane); ir: ν C=O 1640 cm^{-1}; ^{1}H nmr: δ 7.05-7.97 (m, 14H), 8.25 (s, 1H); ms: m/z (%) 358 (M$^+$, 28), 329 (2), 281 (25), 105 (12), 77 (100).

Anal. Calcd. for C$_{22}$H$_{15}$ClN$_2$O: C, 73.63; H, 4.22; N, 7.81. Found: C, 73.68; H, 4.35; N, 7.83.

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