1,3-Dipolar Cycloaddition of Nitrile Oxides with 2-Phenyl-4-ethoxymethylene-5(4*H*)-oxazolone

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2-Phenyl-4-ethoxymethylene-5(4*H*)-oxazolone **1** reacts regioselectively with nitrile oxides to give cycloadducts **3**. Reactions of the cycloadducts **3** with nucleophiles lead to 4-aminoisoxazole derivatives.

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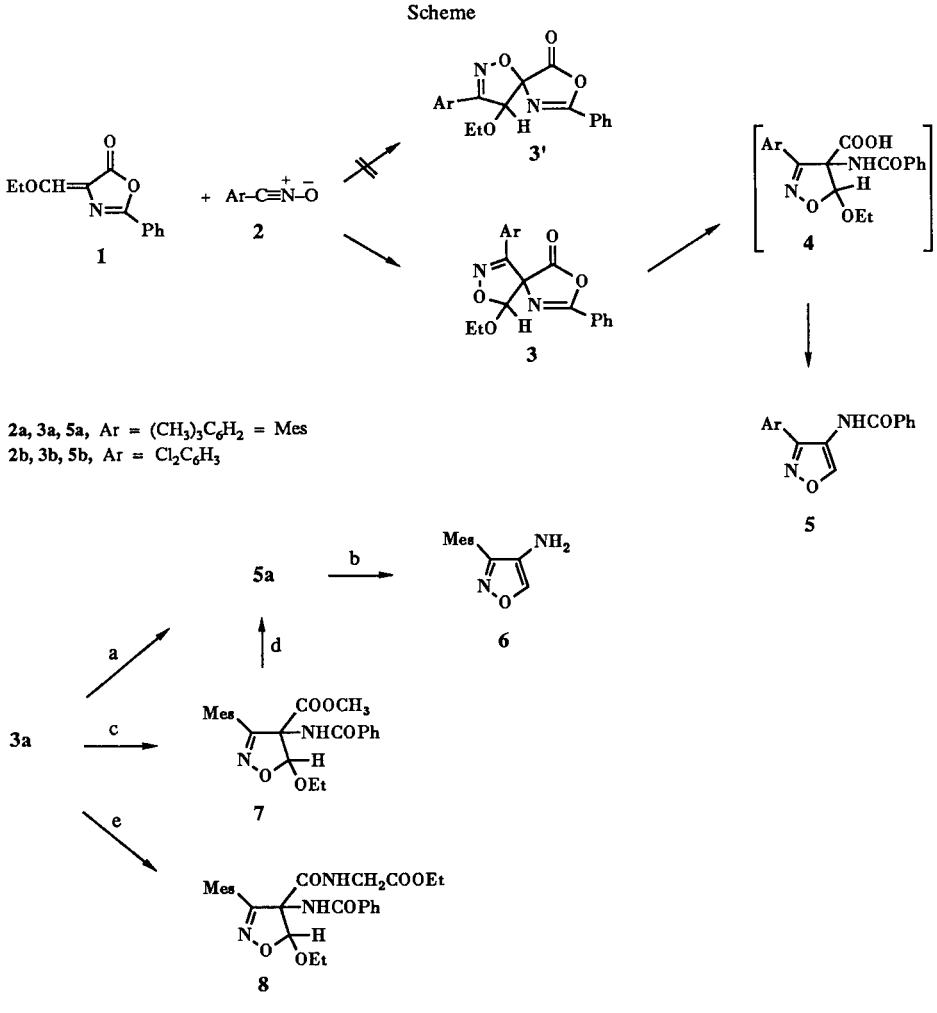
During our studies on 1,3-dipolar cycloaddition reactions to 4-arylidene-5(4*H*)-oxazolones and their thia and aza analogues [1,2,3,4], we have invalidated our first suggestion about the regiochemistry of the reactions [1] and we have proved that in all cases one regioisomer is formed in which the heteroatom of the dipole is bonded to the spiro carbon atom [2]. However in previous reports [5,6] the opposite, incorrect to our opinion regiochemistry, is proposed for the cycloaddition products of 4-arylidene-5(4*H*)-oxazolones with nitrile imines.

In order to have some more information about the regiochemistry of this kind of reactions and for synthetic purposes, in this paper we have studied the 1,3-dipolar cycloaddition reactions of nitrile oxides with 2-phenyl-4-ethoxymethylene-5(4*H*)-oxazolone **1**. Oxazolone **1** is a useful intermediate for the synthesis of diverse products, since

Scheme



[a] H_2O-CH_3COCH_3, [b] hydrocholoric acid-CH_3OH, [c] CH_3OH, [d] aqueous KOH-CH_3OH, [e] NH_2CH_2COOEt

besides the general ring opening reactions of oxazolones shows high electrophilic reactivity at the methylene carbon and gives substitution reactions with several nucleophiles [7,8]. On the other hand the exocyclic carbon-carbon double bond, as a cross conjugated system is expected to show a rather low dipolarophilicity. Thus, attempted cyclopropanation of **1** with diazomethane was unsuccessful [9], although the addition of diazomethane to the carbon-carbon double bond of 4-arylidene-5(4*H*)-oxazolones is a well established procedure for the synthesis of 1-amino-1-cyclopropanecarboxylic acids [7,10].

Reactions of oxazolone **1** with the stable nitrile oxides **2** were carried out by heating at reflux equimolar amounts of the reactants in dichloromethane for 20 days. In both cases only one cycloadduct was formed as it was shown by tlc and ^{1}H nmr of the crude reaction mixtures. Cycloadduct **3a** was obtained in 60% yield and it was isolated from the reaction mixture by fractional crystallization, whereas after treatment of the reaction mixture on a column, **3a** was partially decomposed to the amide **5a**. Cycloadduct **3b** was not isolated in a pure form but only as an intermediate in the crude reaction mixture. Column chromatography gave the amide **5b** in 50% yield. The amides **5** are probably formed from the intermediate hydrolysis products **4** *via* decarboxylation and ethanol abstraction. In fact, hydrolysis of **3a** gave **5a** in 80% yield. Methanolysis of **3a** afforded the ester **7** in 85% yield, whereas glycinolysis gave the dipeptidic derivative **8** in 70% yield. Alkaline hydrolysis of the ester **7** gave also quantitatively the amide **5a**. Further acid hydrolysis of **5a** afforded the amine **6** in 90% yield.

All the isolated new compounds **3a, 5a, 5b, 6, 7, 8** gave satisfactory elemental analyses and spectroscopic data for the proposed structures. Between the two possible regioisomeric structures **3** and **3′**, structure **3** was assigned to the formed cycloadducts mainly on the basis of their transformation products. In the ^{1}H nmr spectra the isoxazoline ring protons of **3a, 3b, 7** and **8** resonate at δ 5.79, 5.89, 6.16 and 6.18 respectively. Although these high frequency values are more compatible with structure **3** than **3′**, they do not suffice to establish structure **3**. However, in addition the isoxazole ring protons of **5a, 5b** and **6** resonate at δ 9.36, 9.39 and 8.08 ppm respectively. These chemical shifts are characteristic of 5-CH isoxazole ring protons [11]. Furthermore in the mass spectra compounds **7** and **8** give peaks at m/z corresponding to fragments M^+–HCOOEt accompanied by metastable peaks. This fragmentation can be rationalized only by 5-ethoxyisoxazole derivatives.

Thus, the well established on the basis of the above data regiochemistry of the reaction of **1** with nitrile oxides, in which the carbon atom of the dipole is bonded to the spiro carbon atom is the opposite one to that observed in the 1,3-dipolar cycloadditions to 4-arylidene-5(4*H*)-oxazolones [2]. This reversal of the regiochemistry is not surprising, since the ethoxy group has a strong directive effect and it usually governs the orientation of the cycloaddition resulting in 5-ethoxy-heterocycles [12]. Considering the reactivity of the cycloadduct **3a** with nucleophiles it gives readily reactions from nucleophilic attact at the carbonyl double bond, whereas the ethoxy group is not substituted. The obtained isoxazoline-4-aminoacid derivatives are easily transformed to 4-aminoisoxazole derivatives offering a new convenient [3+2] route for their synthesis.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. The ir spectra were taken in Nujol with a Perkin-Elmer 297 spectrometer. The ^{1}H nmr spectra were recorded with a Bruker AW 80 (80 MHz) spectrometer (chemical shifts in δ units with tetramethyl silane as internal standard). The mass spectra were measured with a Hitachi-Perkin-Elmer RMU-6L spectrometer with an ionization energy of 70 eV. Elemental analyses were performed with a Perkin-Elmer Model 240B CHN Analyser.

Preparation of Starting Materials.

2-Phenyl-4-ethoxymethylene-5(4*H*)-oxazolone was purchased from Aldrich and used without further purification. Mesitonitrile oxide **2a** and 2,6-dichlorobenzonitrile oxide **2b** were prepared by reaction of the corresponding aldoximes with *N*-bromosuccinimide and triethylamine [13].

Reaction of Oxazolone **1** with Nitrile Oxide **2a**.

A solution of oxazolone **1** (1 mmole) and mesitonitrile oxide **2a** (1 mmole) in dichloromethane (10 ml) was heated to reflux for 20 days. The crude reaction mixture was checked by ^{1}H nmr, in which the chemical shift at δ 5.79 was indicative of isoxazoline **3a**, whereas no peak at δ 9.36 of the compound **5a** was present. After evaporation of the solvent the residue was triturated with dichloromethane/hexane to give 5-ethoxy-3-mesityl-2′-phenylspiro[isoxazole-4(5*H*),4′(5′*H*)-[1,3]oxazole]-5′-one **3a** as a colorless solid. Treatment of the filtrates with column chromatography (silica gel, hexane/ethyl acetate 5:1) gave a second crop of **3a** (total yield 60%) and 3-mesityl-4-benzoylaminoisoxazole **5a** in 20% yield.

Compound **3a** was recrystallized from dichloromethane/hexane, mp 148-150°; ir (Nujol): 1810 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.25 (t, 3H), 2.15 (s, 3H), 2.30 (s, 6H), 3.62-4.20 (m, 2H), 5.79 (s, 1H), 6.77 (s, 2H), 7.32-7.60 (m, 3H), 7.81-8.00 (m, 2H); ms: m/z 378 (7, M^+), 332 (12), 304 (14), 217 (9), 161 (3), 105 (100).

Anal. Calcd. for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40. Found: C, 70.00; H, 5.81; N, 7.32.

Compound **5a** was recrystallized from methanol, mp 131-134°; ir (Nujol): 3400 (NH), 1655 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.10 (s, 6H), 2.32 (s, 3H), 6.70-7.75 (m, 8H), 9.36 (s, 1H); ms: m/z 306 (25, M^+), 277 (2), 201 (3), 185 (7), 105 (100).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.54; H, 5.92; N, 9.10.

Reaction of Oxazolone **1** with Nitrile Oxide **2b**.

The same procedure with the above reaction was followed. In the ^{1}H nmr of the crude reaction mixture there was the chemical

shift at δ 5.89 characteristic of **3b** and no peak at δ 9.39. Fractional crystallization of compound **3b** by trituration of the reactin mixture with several solvents was unsuccessful, whereas treatment with column chromatography gave the 3-(2,6-dichlorophenyl)-4-benzoylaminoisoxazole **5b** in 50% yield, mp 157-159°; ir (Nujol): 3300 (NH), 1650 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.18-7.78 (m, 9H), 9.39 (s, 1H); ms: m/z 336/334/332 (5, M^+), 307/305/303 (2), 175/173/171 (11), 105 (100).

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2O_2$: C, 57.66; H, 3.00; N, 8.41. Found: C, 57.41; H, 3.13; N, 8.33.

Hydrolysis of Compound **3a**.

A solution of **3a** (0.2 mmole) in acetone (4 ml) and water (1 ml) was heated at reflux for 8 hours. After evaporation of the solvents recrystallization of the residue from methanol gave **5a** in 80% yield.

Methanolysis of Compound **3a**.

A solution of **3a** (0.2 mmole) in methanol (5 ml) was heated at reflux for 3 hours. After the evaporation of the methanol recrystallization of the residue from dichloromethane/hexane gave methyl 4,5-dihydro-3-mesityl-4-benzoylamino-5-ethoxy-4-isoxazolecarboxylate **7** in 85% yield, mp 152-154°; ir (Nujol): 3410 (NH), 1740, 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.12 (t, 3H), 2.19 (s, 3H), 2.22 (s, 6H), 3.75-4.10 (m, 5H), 6.16 (s, 1H), 6.43 (br s, 1H), 6.96 (s, 2H), 7.32-7.76 (m, 5H); ms: m/z 410 (7, M^+), 336 (12), 304 (13), 289 (3), 249 (13), 161 (3), 105 (100), $m^* = 336^2/410 = 275.4$.

Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.39; N, 6.83. Found: C, 67.25; H, 6.34; N, 6.68.

Glycinolysis of Compound **3a**.

A solution of **3a** (0.2 mmole) and ethyl glycinate (0.6 mmole) in dichloromethane (5 ml) was allowed to stay at room temperature for 12 hours. Then the solvent was evaporated and the residue was crystallized from methanol/diethyl ether to give ethyl 4,5-dihydro-3-mesityl-4-benzoylamino-5-ethoxy-4-isoxazoylglycinate **8** in 70% yield, mp 135-137°; ir (Nujol): 3440, 3340 (NH), 1730, 1690 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00-1.38 (m, 6H), 2.25 (s, 6H), 2.31 (s, 3H), 3.54-4.38 (m, 6H), 6.18 (s, 1H), 6.30 (br s, 1H), 6.92 (s, 2H), 7.20-7.78 (m, 6H); ms: m/z 481 (2, M^+), 407 (4), 304 (5), 274 (8), 161 (9), 105 (100), $m^* = 407^2/481 = 344.4$.

Anal. Calcd. for $C_{26}H_{31}N_3O_6$: C, 64.85; H, 6.49; N, 8.73. Found: C, 64.70; H, 6.49; N, 8.58.

Alkaline Hydrolysis of Compound **7**.

A solution of **7** (0.2 mmole) in methanol (4 ml) and aqueous potassium hydroxide (1 ml, 10%) was heated at reflux for 1 hour. Then the methanol was evaporated and the residue was diluted with water and extracted with diethyl ether. The organic layer was dried and evaporated to give quantitatively the amide **5a**.

Acid Hydrolysis of Compound **5a**.

A solution of **5a** in methanol containing 40% hydrochloric acid (34%) was heated at reflux for 10 hours. After evaporation of the solvent the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dried, evaporated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate 4:1) to give 3-mesityl-4-aminoisoxazole **6** in 90% yield. Compound **6** was initially isolated as an oil, which was solidified after a long period of staying; mp 66-68°; ir (Nujol): 3410, 3320 (NH_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.09 (s, 6H), 2.30 (s, 3H), 2.70 (br s, 2H), 6.92 (s, 2H), 8.08 (s, 1H); ms: m/z 202 (49, M^+), 173 (32), 146 (100).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.97; N, 13.85. Found: C, 71.19; H, 6.97; N, 13.75.

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