Synthesis of Heterocyclic Compounds XLIX [1a]. An Unexpected Synthesis of Isoxazolamines [1b]

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Reaction of 3-aryl-1-phenyl-2-nitropropenones **1** with potassium cyanide leads to 4-aryl-3-benzoyl-5-isoxazolamines **5** in a one-step process involving the formal reduction of the nitro group followed by nucleophilic attack at the cyano group. Treatment of the isoxazolamine with an aromatic aldehyde yields the corresponding *N*-arylideneisoxazolamine.

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Introduction.

5-Isoxazolamines are usually obtained from hydroxylamine and appropriate nitriles [2-6]. In other types of synthesis the ring is made up of two parts: $-C{\equiv}N^{+}-O^{-}$ from nitrile oxides and two carbon atoms from nitriles with active methylene groups [7-10]. In other cases, the reaction of chlorooxime with cyanide leads to the corresponding 5-isoxazolamine [11,12]. On the other hand, in previous papers on the synthesis of heterocyclic compounds, we have reported on the cyclization of 4-oxonitriles leading to a synthesis of 2-aminofurans [13], some of which had to be isolated in stable form as their Schiff bases [14].

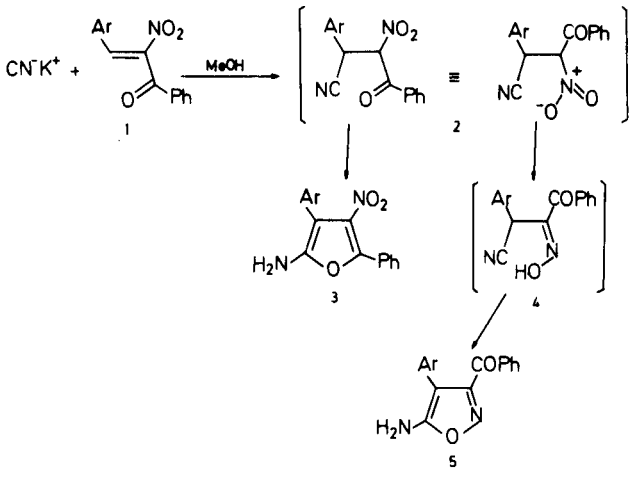
Results and Discussion.

In this paper, we report on the reaction of potassium cyanide with 1,3-diphenyl-2-nitropropenone (**1a**), leading to an intermediate 4-oxonitrile which, upon cyclization, could lead to a nitrofuranamine. The reaction affords a final, stable compound, but its analytical and spectroscopic data does not agree with those expected for the nitrofuranamine, but for a compound with one oxygen missing ($C_{16}H_{12}N_2O_2$). On the other hand, ir and ^{1}H-nmr spectra confirm the presence of an amino group, and the ^{13}C nmr spectrum shows the presence of an aromatic carbonyl group at 188.6 ppm. A structure of 3-benzoyl-4-phenyl-5-isoxazolamine (**5**) is in agreement with these data and with the chemical shifts of the other signals in the ^{13}C-nmr spectrum. C_4 appears at 91.8 ppm and C_3 and C_5 at 159.8 and 167.2 ppm, which agree with reported values for related compounds [15].

Scheme I represents a likely mechanism for the formation of this compound, in a reaction which proved to be general for substituted derivatives of **1**.

The reaction begins with the conjugate addition of hydrogen cyanide to nitropropenones **1**. The intermediate oxonitrile **2** could cyclize by nucleophilic attack of the carbonyl oxygen at the cyano group, leading to furanamines **3**. However, the reaction takes a different course and the nitro group is involved in the cyclization. A formal reduction of the nitro group leads to oxime **4** which cyclizes to isoxazolamines **5** without isolation of any intermediate compound.

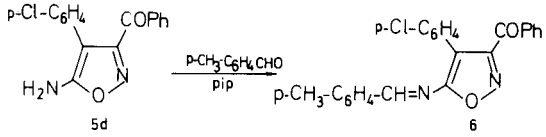
Scheme I



It must be pointed out that formal reductions of a nitro group have been previously reported to occur in α-nitroketones. When they are heated in alcoholic solvents, α-ketooximes are obtained through a radical process [16]. On the other hand, electrochemical reduction of the nitro group in some nitropropanenitriles has recently been reported to lead to a similar reduction and cyclization [17].

Preparation of isoxazolamines **5** is fairly simple and is carried out in one step, in methanol solution at low temperature to avoid polymerization. Only compound **5a** crystallized in the reaction mixture, and compounds **5b-d** had to be isolated by means of column chromatography. Isoxazolamines **5** react with aromatic aldehydes to yield their Schiff bases. Thus, 4-(*p*-chlorophenyl)-3-benzoyl-5-isoxazolamine (**3d**) and *p*-methylbenzaldehyde react in ethanol solution and with piperidine as the catalyst leading to 3-benzoyl-4-(*p*-chlorophenyl)-*N*-(*p*-methylbenzylidene)-5-isoxazolamine (**6**).

Scheme II



In an attempt to extend the synthesis to 3-acetyl substituted isoxazolamines, 4-phenyl-3-nitro-3-buten-2-one (**7**) was treated with potassium cyanide, but the reaction leads to a complex mixture from which no pure compound could be isolated.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were measured with a Perkin-Elmer 257 spectrophotometer in potassium bromide pellets. ^{1}H nmr spectra were obtained at 60 MHz with a Varian T-60 A spectrometer and ^{13}C-nmr spectra with a Varian XL-300 at 75.43 MHz. Chemical shifts are given as δ values referring to TMS as the internal standard in both cases. Mass spectra were recorded with a Varian MAT 711 instrument at 100 eV. Thin-layer chromatography was performed on silica gel plates (Merck) using toluene, ethyl acetate or mixtures of both as the eluent. Column chromatography was carried out on silica gel 60 (Merck) using a mixture of benzene/ethyl acetate 4:1 or toluene/ethyl acetate 4:1. Microanalyses were performed by the "Centro Nacional de Química Orgánica".

3-Aryl-1-phenyl-2-nitropropenones **1**.

These compounds were prepared according to the method described by Dornow [18] for the 1,3-diphenyl-2-nitropropenone, but using butylimines of aromatic aldehydes instead of their methylimines. Their reaction with ω-nitroacetophenone [19] leads to the desired 2-nitropropenones.

The following have not been previously reported in the literature:

3-(*p*-Methylphenyl)-1-phenyl-2-nitropropenone (**1b**).

This compound was obtained in 75% yield, mp 63-65° (from methanol); ^{1}H-nmr (carbon tetrachloride): δ 8.10 (s, 1H, =CH), 6.8-8.0 (m, 9H, arom), 2.26 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.87; N, 5.24. Found: C, 71.77; H, 4.76; N, 5.13.

3-(*p*-Methoxyphenyl)-1-phenyl-2-nitropropenone (**1c**).

This compound was obtained in 70% yield, mp 84-85° (from ethanol).

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59; N, 4.95. Found: C, 67.68; H, 4.62; N, 4.84.

4-Aryl-3-benzoyl-5-isoxazolamines **5**. General Procedure.

To a suspension of 0.01 mole of the corresponding 3-aryl-1-phenyl-2-nitropropenone (**1**) in 20 ml of ethanol at $-10°$ (salt-ice bath) a solution of 0.011 mole of potassium cyanide in the minimal amount of water is added under stirring. After a few hours the corresponding 5-isoxazolamine (**5**) is isolated either by filtration or by column chromatography as pointed out in each case. Then, it is recrystallized from the appropriate solvent.

3-Benzoyl-4-phenyl-5-isoxazolamine (**5a**).

This compound was isolated by filtration after stirring the reaction mixture for three and one half hours in 23% yield, mp 164-166° dec (from methanol); ir (potassium bromide): 3420, 3320, 1630, 1575, 1500, 1470, 1450, 1230, 880, 695 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7-8.3 (m, 10H, arom), 4.7 (br s, 2H, NH_2, disappears on addition of trifluoroacetic acid); ms: m/e 264 (M^+, 5), 106 (9), 105 (100), 77 (47), 51 (13); ^{13}C-nmr (DMSO-d_6): δ 188.6 (*C*OPh), 167.2 (C_5), 159.8 (C_3), 135.8-125.9 (8 signals, arom), 91.8 (C_4).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.89; H, 4.20; N, 10.32.

3-Benzoyl-4-(*p*-methylphenyl)-5-isoxazolamine (**5b**).

After stirring the reaction mixture for 2 hours at $-10°$, it is kept overnight at room temperature. Then, it is subjected to column chromatography using benzene/ethyl acetate 4:1 as the eluent, yield, 26%, mp 158-160° (from ethanol); ir (potassium bromide): 3480, 3320, 1660, 1630, 1520, 1480, 1450, 1430, 1230, 890, 825, 695 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.0-8.2 (m, 9H, arom), 4.7 (br s, 2H, NH_2, disappears on addition of trifluoroacetic acid), 2.3 (s, 3H, CH_3); ms: m/e 278 (M^+, 4), 106 (7), 105 (100), 77 (38), 51 (7).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.25; H, 5.13; N, 10.12.

3-Benzoyl-4-(*p*-methoxyphenyl)-5-isoxazolamine (**5c**).

After stirring for 2 hours, the reaction is subjected to column chromatography using toluene/ethyl acetate 4:1 as the eluent, to give product **5c** in 19% yield, mp 115-117° (from toluene); ir (potassium bromide): 3420, 3300, 1660, 1630, 1590, 1520, 1450, 1245, 1175, 900, 840 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 6.7-8.2 (m, 9H, arom), 4.7 (br s, 2H, NH_2, disappears on addition of trifluoroacetic acid), 3.76 (s, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.79; N, 9.52. Found: C, 69.30; H, 4.85; N, 9.46.

3-Benzoyl-4-(*p*-chlorophenyl)-5-isoxazolamine (**5d**).

The reaction mixture was subjected to column chromatography after two hours under stirring. Toluene/ethyl acetate 4:1 was used as the eluent. The product was obtained in 15% yield, mp 146-147° (from toluene); ir (potassium bromide): 3420, 3320, 1650, 1630, 1590, 1500, 1450, 1220, 1090, 1000, 900, 705 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.0-8.0 (m, 9H, arom), 4.7 (br s, 2H, NH_2, disappears on addition of trifluoroacetic acid).

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.32; H, 3.71; N, 9.38; Cl, 11.87. Found: C, 64.28; H, 3.79; N, 9.40; Cl, 11.58.

3-Benzoyl-4-(*p*-chlorophenyl)-*N*-(*p*-methylbenzylidene)-5-isoxazolamine (**6**).

Twelve mg of 3-benzoyl-4-(*p*-chlorophenyl)-5-isoxazolamine (**5d**) is dissolved in 2 ml of absolute ethanol. Then, 2 drops of *p*-methylbenzaldehyde and 1 drop of piperidine are added to the solution, and the mixture is refluxed for two hours. Then, the reaction is kept at room temperature for 6 days, and the yellow needles are filtered off, and recrystallized from ethanol. Compound **6** is obtained in 56% yield, mp 130-132° (from ethanol); ir (potassium bromide): 1655, 1590, 1560, 1440, 1425, 1300, 1225, 1180, 1165, 1085, 990, 890, 815 cm^{-1}; ms: m/e 402 (M^++2, 0.5), 401 (M^++1, 0.4), 400 (M^+, 1), 223 (1), 151 (1), 149 (3), 106 (8), 105 (100), 77 (27).

Anal. Calcd. for $C_{24}H_{17}ClN_2O_2$: C, 71.90; H, 4.28; N, 6.99. Found: C, 71.89; H, 4.56; N, 7.30.

3-Nitro-4-phenyl-3-buten-2-one (**7**).

This compound was prepared from nitroacetone [20] and the butylimine of benzaldehyde, according to Dornow procedure [21].

Reaction of 3-Nitro-4-phenyl-3-buten-2-one (**7**) with Potassium Cyanide.

To a suspension of 1.0 g of 3-nitro-4-phenyl-3-buten-2-one (**7**) (5.2 mmoles) in 10 ml of ethanol, a solution of 0.35 g of potassium cyanide (5.4 mmoles) in 2 ml of water is added at $-10°$ with stirring. One hour later thin layer chromatography shows a complex mixture of products, from which no pure compound could be isolated, neither by crystallization nor by column chromatography.

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