The Reaction of 2-Nitrosopyridine with Nitrile Oxides: First Synthesis of 1,2,4-Triazolo[1,5-*a*]pyridine 1,3-Di-*N*-oxides

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Reactions of 2-nitrosopyridine with nitrile oxides afford either the novel title compounds or the corresponding 1,2,4-triazolo[1,5-*a*]pyridine 3-oxides.

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We have recently reported [1] that benzofurazan *N*-oxides react with nitrile oxides, as their "*o*-dinitrosobenzene" equivalents, yielding the novel benzo-*as*-triazine tri-*N*-oxides, *via* a bis-nitrosonitrone intermediate. Similarly, the reaction of nitrosobenzene with nitrile oxides [2], affords an unstable nitrosonitrone intermediate isolable at lower temperature, which can further undergo cyclisation to 1-hydroxybenzimidazole 3-oxides or 4*H*-1,2,4-benzoxadiazines, depending upon the reaction conditions and the nature of the substituents.

It is subsequently likely, that the *C*-nitroso-*N*-(2-pyridyl)-nitrones **4**, expected intermediates of the reaction of 2-nitrosopyridine **1** with nitrile oxides, should cyclise to the hitherto unknown [3] 1,2,4-triazolo[1,5-*a*]pyridine 1,3-di-*N*-oxides **5**. The 3-oxides of several 1,2,4-triazolo[1,5-*a*]pyridine derivatives have been prepared by an analogous cyclisation of *C*-nitroso-*N*-(2-pyridyl)imines [4], *in situ* generated from reactions of *S,S*-dimethyl-*N*-(2-pyridyl)sulfimides with nitrile oxides, or by oxidation of 2-pyridylamidoximes. Their isomeric 1-oxides are also known [5], prepared by treatment of 1-amino-2-chloropyridinium mesylate with hydroxylamine and subsequent reaction with carboxylic acids.

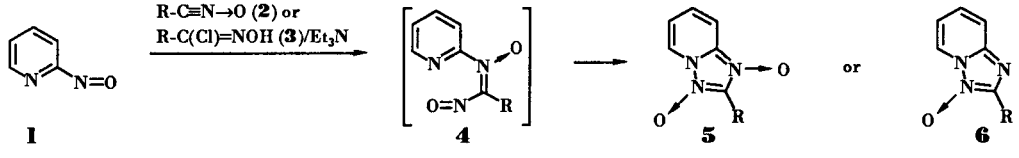
When 2-nitrosopyridine **1** reacted in methylene chloride solution with nitrile oxide **2b**, or with hydroxylamoyl chloride **3f** in the presence of triethylamine, di-*N*-oxides **5b,f** were formed in good yields, evidently by cyclisation of the nitrosonitrone intermediates **4**, and precipitated from the reaction mixture in microcrystallic form. Their ^{1}H nmr spectra are consistent with the proposed structures [3,4], while the mass spectra reveal the presence of two exocyclic oxygen atoms. The parent ion of compounds **5b,f** at 70 eV are of low intensity, whereas the peaks due to the consecutive loss of two oxygen atoms (M^+-16 and M^+-32) are mostly characteristic.

However, no di-*N*-oxide **5** was obtained from the reactions of 2-nitrosopyridine **1** with nitrile oxide **2a** or with the hydroxylamoyl chlorides **3c-e** in the presence of triethylamine in methylene chloride solution. The main products isolated chromatographically along with a variety of byproducts were the 1,2,4-triazolo[1,5-*a*]pyridine 3-oxides **6a,c-e**. These give in their mass spectra at 70 eV significant molecular ions, as well as peaks due to M^+-16 and M^+-30 fragments. Mass spectra at 25 eV or negative ion mass spectra did not show any peak corresponding to the di-*N*-oxides **5** parent ion.

The fact that these products are the 3-oxides **6** and not their isomeric 1-oxides, is easily concluded since product **6d** is identical to an authentic sample prepared according to the literature procedure [4a] from reaction of *S,S*-dimethyl-*N*-(2-pyridyl)sulfimide with **3d** in the presence of triethylamine. Furthermore, compound **6d** was deoxygenated by phosphorus trichloride to the known [4a] 2-(4-tolyl)-1,2,4-triazolo[1,5-*a*]pyridine in 55% yield, confirming thus unequivocally the presence of the 1,2,4-triazolo[1,5-*a*]pyridine fused system.

The difference in the reactions discussed are apparently due to the nature of the substituent R, which could affect

Scheme



1 **4** **5** **6**

a, R = 2,4,6-$CH_6H_2Me_3$
b, R = 2,6-$C_6H_3Cl_2$
c, R = C_6H_5
d, R = 4-C_6H_4Me
e, R = 4-C_6H_4Cl
f, R = 4-$C_6H_4NO_2$

the stability of both the intermediates **4** and the di-*N*-oxides **5**. Although the formation of 3-oxides only and not their isomeric 1-oxides in entries **a,c-e** is an indication of the fact that the oxygen expulsion occurred rather before than after the cyclisation of **4**, the process involving at first cyclisation followed by deoxygenation, could not be excluded.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ^{1}H nmr spectra were obtained at 80 MHz on a Bruker AW80 spectrometer, with tetramethylsilane as the internal standard. Mass spectra were recorded at 70 eV on a VG TS-250 spectrometer and microanalyses were performed on a Perkin-Elmer 240B element analyser.

2-Mesityl-1,2,4-triazolo[1,5-*a*]pyridine 1-Oxide **6a**.

A solution of 2-nitrosopyridine **1** [6] (216 mg, 2 mmoles) and nitrile oxide **2a** (403 mg, 2.5 mmoles) in dry methylene chloride (20 ml) was refluxed for 6 hours. The reaction mixture was then chromatographed on silica gel using ethyl acetate as the eluant. The reaction byproducts were eluted at first, followed by compound **6a** (116 mg, 23%), mp 244-246° (ethanol/water); ^{1}H nmr (deuteriochloroform): δ 2.11 (s, 6H), 2.39 (s, 3H), 7.0 (s, 2H), 7.2 (m, 2H), 8.0 (m, 2H); ms: m/z (%) 253 (M^+, 22), 237 (M^+-16, 90), 236 (83), 222 (19), 146 (64), 78 (33).

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.81; H, 5.86; N, 16.39.

2-(2,6-Dichlorophenyl)-1,2,4-triazolo[1,5-*b*]pyridine 1,3-Di-*N*-oxide **5b**.

A solution of 2-nitrosopyridine **1** [6] (216 mg, 2 mmoles) and nitrile oxide **2b** (470 mg, 2.5 mmoles) in dry methylene chloride (20 ml) was refluxed for 2 hours. Compound **5b** was precipitated and collected with filtration (380 mg, 65%), mp 193-195° (ethanol/water); ^{1}H nmr (deuteriochloroform/trifluoroacetic acid): δ 7.6 (s, 3H), 7.9 (m, 2H), 8.8 (m, 2H); ms: m/z (%) 295/297/299 (M^+, 2/2/1), 279/281/283 (M^+-16, 59/43/8), 263/265/267 (M^+-32, 100/78/17), 173/175/177 (91/64/12), 78 (56).

Anal. Calcd. for $C_{12}H_7Cl_2N_3O_2$: C, 48.67; H, 2.38; N, 14.19. Found: C, 48.43; H, 2.52; N, 14.38.

General Procedure for the Synthesis of **6c-e**.

A solution of 2-nitrosopyridine **1** [6] (216 mg, 2 mmoles), hydroxamoyl chloride **3c-e** (2.5 mmoles) and triethylamine (1 ml) in methylene chloride (20 ml) was allowed to stand at room temperature for 24 hours. The reaction mixture was then chromatographed on silica gel using ethyl acetate as the eluant. The reaction byproducts were eluted at first, followed by the compounds **6c-e**.

2-Phenyl-1,2,4-triazolo[1,5-*a*]pyridine 1-Oxide **6c**.

This compound had mp 186-188° (192 mg, 45%) (ethanol/water); ^{1}H nmr (deuteriochloroform): δ 7.1-7.7 (m, 6H), 8.7 (m, 3H); ms: m/z (%) 211 (M^+, 19), 195 (M^+-16, 29), 181 (M^+-30, 69), 78 (100).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.03; H, 3.99; N, 19.65.

2-(4-Tolyl)-1,2,4-triazolo[1,5-*a*]pyridine 1-Oxide **6d**.

This compound had mp 160-162° (155 mg, 34%) (ethanol/water) (lit [4a] mp 163-164°); ^{1}H nmr (deuteriochloroform): δ 2.44 (s, 3H), 7.0-7.75 (m, 5H), 8.6 (d, J = 9.5 Hz, 2H), 8.7 (d, J = 6.5 Hz, 1H); ms: m/z (%) 225 (M^+, 25), 209 (M^+-16, 25), 195 (M^+-30, 100), 78 (94).

2-(4-Chlorophenyl)-1,2,4-triazolo[1,5-*a*]pyridine 1-Oxide **6e**.

This compound had mp 178-180° (131 mg, 27%) (ethanol/water); ^{1}H nmr (deuteriochloroform): δ 7.1-7.7 (m, 5H), 8.65 (d, J = 9 Hz, 2H), 8.7 (d, J = 6.5 Hz, 1H); ms: m/z (%) 245/247 (M^+, 25/13), 229/231 (M^+-16, 20/9), 215/217 (M^+-30, 77/39), 78 (100).

Anal. Calcd. for $C_{12}H_8ClN_3O$: C, 58.67; H, 3.28; N, 17.10. Found: C, 58.68; H, 3.23; N, 17.15.

2-(4-Nitrophenyl)-1,2,4-triazolo[1,5-*a*]pyridine 1,3-Di-*N*-oxide **5f**.

A solution of 2-nitrosopyridine **1** [6] (216 mg, 2 mmoles), hydroxamoyl chloride **3f** (2.5 mmoles, 501 mg) and triethylamine (1 ml) in methylene chloride (20 ml) was allowed to stand at room temperature for 1 hour. Compound **5f** was precipitated and collected with filtration (310 mg, 57%), mp 203-205° dec (ethanol/water); ^{1}H nmr (deuteriochloroform/trifluoroacetic acid): δ 7.9 (m, 1H), 8.4 (m, 2H), 8.5 (d, J = 9 Hz, 2H), 8.75 (d, J = 9 Hz, 2H), 9.2 (d, J = 6.5 Hz, 1H); ms: m/z (%) 272 (M^+, 4), 256 (M^+-16, 30), 240 (M^+-32, 60), 226 (M^+-46, 43), 78 (100).

Anal. Calcd. for $C_{12}H_8N_4O_4$: C, 52.95; H, 2.96; N, 20.58. Found: C, 52.86; H, 3.08; N, 20.76.

2-(4-Tolyl)-1,2,4-triazolo[1,5-*a*]pyridine.

A solution of **6d** (50 mg, 0.22 mmole) and phosphorus trichloride (1.0 g) in methylene chloride (10 ml) was allowed to stand at room temperature for 24 hours. Then, ice-water was added, the organic layer was dried (magnesium sulfate) and evaporated, and the residue was chromatographed on silica gel with methylene chloride as the eluant, to give 2-(4-tolyl)-1,2,4-triazolo[1,5-*a*]pyridine (22 mg, 55%), mp 167-169° (lit [4a] mp 168-169°); ^{1}H nmr (deuteriochloroform): δ 2.40 (s, 3H), 6.94 (t, J = 6.5 Hz, 1H), 7.5 (m, 4H), 8.18 (d, J = 9.5 Hz, 2H), 8.56 (d, J = 6.5 Hz, 1H); ms: m/z (%) 209 (M^+, 100), 78 (89).

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