Chemistry of *N*-Nitrososulfonamides. Substitution Reaction by the Acetyl Group

Masaaki Iwata* and Hiroyoshi Kuzuhara
Riken (The Institute of Physical and Chemical Research), Wako, Saitama 351-01

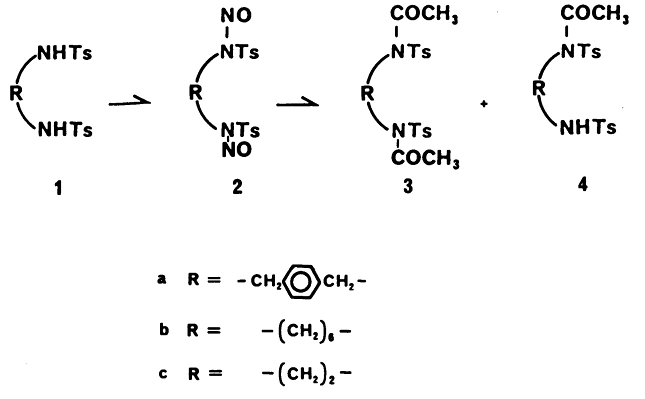
(Received April 1, 1985)

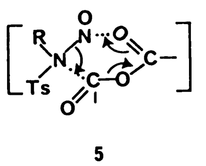
Synopsis. The *N*-nitroso group on *N*-nitrososulfonamides was substituted for the acetyl group in chloroform to give *N*-acetylsulfonamides in moderate yields.

We started the present research in order to understand fundamental chemical properties of sulfonamides. From attempts to survey the reactivity of the sulfonamide group, we found a new substitution reaction of the *N*-nitroso derivatives for an acetyl group without a base.

Nitrosation of sulfonamide was performed in quantitative yield by use of a modified procedure using a sodium nitrite–acetic anhydride–acetic acid mixture.[1–3] Thus, α,ω-bis(*N*-nitrososulfonamide)s, **2a—c**, were prepared from the corresponding sulfonamides **1a—c**. The nitroso group could be removed by either light, protic solvents, radical initiator such as AIBN, or L-ascorbic acid to regenerate the corresponding sulfonamides.

It was predicted that acid anhydride and *N*-nitrososulfonamide can be disposed to take a six-membered cyclic transition state advantageous for the lowered activation energy upon a substitution reaction through an intermediate (**5**). When a suspended mixture of **2a**, acetic anhydride, and chloroform was refluxed, **3a** (diacetyl sulfonamide) and **4a** (monoacetyl sulfonamide) were obtained in 54 and 13% yields, respectively. In the same way, **2b** and **2c** gave the corresponding diacetyl sulfonamides, **3b** and **3c**, in 38 and 29% yields, respectively. Usual acetylation of **1a** employing acetic anhydride and pyridine afforded neither mono- nor diacetyl sulfonamide. In addition, more drastic acetylation using acetyl chloride unsatisfactorily gave **3c** and **4c**. These results indicate that the acetyl substitution reaction of *N*-nitrososulfonamides effectively proceeds through such a transition state **5** as predicted.





5

IR and ¹H-NMR spectral data suggested the stronger electrophilic nature of the acetyl group on *N*-acetylsulfonamides than those in usual acetates and acetamides. When a mixture of **3a** and anhydrous potassium carbonate in a mixed solvent of methanol–water was refluxed,[4] **1a** was obtained in quantitative yield.

The net cycle of introduction-removal of the *N*-acetyl group regarding sulfonamides will become a possible route to utilize the *N*-acetyl group as a protecting group for a variety of synthetic purpose.

Experimental

¹H-NMR spectra were recorded on a JEOL JNM GX-400 (400 MHz) spectrometer with Me_4Si as the internal standard in $CDCl_3$; chemical shifts (δ) and coupling constants (J) are in parts per million and Herz, respectively. Infrared spectra (IR) was obtained on a Shimadzu IR-27G spectrophotometer. Electronic absorption spectra (UV) were recorded on a Hitachi 124 spectrophotometer. Mass spectra (MS; rel. intensity) were recorded with a Hitachi RMU-6MG spectrometer by using an ionizing potential at 20 eV. Merck silica-gel 60 (Art. 7734, 0.063—0.20) was used for column chromatography and Merck precoated silica-gel 60 F_{254} plates (Art. 5715, 20×20) were used for thin-layer chromatography (TLC). The solvent system employed for column chromatography and TLC was benzene–ethyl acetate (10:1 v/v) and R_f values are referred to this solvent system, unless otherwise noted. α,ω-Disulfonamides (**1**) were prepared by the previously described method.[5] Elemental analyses were performed at Riken. The uncorrected melting points were measured with a micro melting-point apparatus (Yanagimoto Seisakusho).

N-Nitrosation of Sulfonamides. Optimal *N*-nitrosation was achieved by the following modified method of that described by de Boer *et al.*[2b] To a suspended mixture of sulfonamide (**1**) (1 g), acetic anhydride (10 ml), and acetic acid (2 ml), was added sodium nitrite (2 mol eq to **1**) portion by portion at *ca.* 10 °C, while rapidly stirred. After stirring for 30 min at room temperature, water (30 ml) was added to quench the reaction. The mixture was stirred for 30 min at *ca.* 10 °C. Crystalline α,ω-bis(*N*-nitrososulfonamide)s (**2**) were collected by filtration and washed well with water. This pale-yellow crystalline solid was pure enough.

2a: (90% yield) mp 131—133 °C. Calcd for $C_{22}H_{22}N_4S_2O_6$: C, 52.58; H, 4.41; N, 11.15; S, 12.76%. Found: C, 52.36; H, 4.40; N, 10.91; S, 12.72%. IR (KBr) 1510(N=O), and 1380 and 1170(SO_2) cm⁻¹. R_f 0.75.

2b: (99% yield) mp 86—88 °C. Calcd for $C_{20}H_{26}N_4S_2O_6$: C, 49.78; H, 5.43; N, 11.61; S, 13.29%. Found: C, 50.26; H, 5.49; N, 10.77; S, 13.33%. IR (KBr) 1510(N=O), and 1375 and 1169(SO_2) cm^{-1}. R_f 0.75.

2c: (99% yield) mp 120 °C (decomp). Calcd for $C_{16}H_{18}N_4S_2O_6$: C, 45.06; H, 4.25; N, 13.14; S, 15.04%. Found: C, 45.34; H, 4.26; N, 12.96; S, 14.88%. IR (KBr) 1516(N=O), and 1384, 1188, 1174, and 1155(SO_2) cm^{-1}. R_f 0.75.

Reaction of N-*Nitrososulfonamides with Acetic Anhydride in Chloroform.* When a suspended mixture of *N*-nitrososulfonamide (**2**) (1 g), acetic anhydride (1 ml) and chloroform (20 ml) was refluxed, the suspension disappeared in 10 min. The reaction was monitored by tlc till no more change was observed (15—30 h). After cooling, the reaction mixture was evaporated and the residue was chromatographed on a silica-gel column. Thus **2a** gave *N,N'*-diacetyl-*N,N'*-ditosyl-*α,α'*-*p*-xylenediamine (**3a**) in 54% yield and *N*-acetyl-*N,N'*-ditosyl-*α,α'*-*p*-xylenediamine (**4a**) in 13% yield.

Recrystallization of **3a** from diethyl ether gave colorless crystals; mp 178—180 °C. Calcd for $C_{26}H_{28}N_2S_2O_6$: C, 59.07; H, 5.34; N, 5.30; S, 12.13%. Found: C, 59.06; H, 5.36; N, 5.10; S, 12.10%. IR (KBr) 1700(C=O), and 1350 and 1160(SO_2) cm^{-1}. ^{1}H-NMR; 2.31 ($COC\underline{H}_3$), 2.43 ($C\underline{H}_3$), and 5.07 ($C\underline{H}_2$). MS; *m/z* 444 (0.4%), 374 (100%), and 332 (38%).

Recrystallization of **4a** from diethyl ether gave colorless crystals; mp 142—143 °C. Calcd for $C_{24}H_{26}N_2S_2O_5$: C, 59.24; H, 5.39; N, 5.76; S, 13.18%. Found: C, 59.27; H, 5.45; N, 5.58; S, 12.96%. IR (KBr) 3280(NH), 1700(C=O), and 1358, 1318, 1163, and 1148(SO_2) cm^{-1}. ^{1}H-NMR; 2.28 ($COC\underline{H}_3$), 2.44 and 2.45 ($C\underline{H}_3$), 4.11 (J=6.11, $C\underline{H}_2$), 4.62 (J=6.11, $N\underline{H}$), and 5.02 ($C\underline{H}_2$). MS; *m/z* 445 (0.9%), 332 (87%), 290 (100%).

N,N'-Diacetyl-*N,N'*-ditosyl-1,6-hexanediamine (**3b**) was obtained from **2b** in 29% yield (R_f 0.5, benzene–ethyl acetate 4:1 v/v), accompanied by two other unidentified products at R_f 0.8 and 0.66. Recrystallization of **3b** from acetone–diethyl ether gave colorless crystals; mp 155—157 °C. Calcd for $C_{24}H_{32}N_2S_2O_6$: C, 56.67; H, 6.34; N, 5.51; S, 12.61%. Found: C, 56.70; H, 6.36; N, 5.33; S, 12.50%. IR (KBr) 1700(C=O), and 1360 and 1158(SO_2) cm^{-1}. ^{1}H-NMR; 1.37 ($C\underline{H}_2$), 1.71 ($C\underline{H}_2$), 2.32 ($COC\underline{H}_3$), 2.45 ($C\underline{H}_3$), 3.76 (J=7.56, $NC\underline{H}_2$). MS; *m/z* 337 (100%), 296 (30%), and 254 (42%).

N,N'-Diacetyl-*N,N'*-ditosyl-1,2-ethanediamine (**3c**) was obtained from **2c** in 38% yield (R_f 0.58, benzene–ethyl acetate 4:1 v/v), accompanied by an unidentified product at R_f 0.77. Recrystallization of **3c** from benzene gave colorless fine needles; mp 215—216 °C. Calcd for $C_{20}H_{24}N_2S_2O_6$: C, 53.08; H, 5.35; N, 6.19; S, 14.17%. Found: C, 53.02; H, 5.33; N, 6.16; S, 14.02%. IR (KBr) 1700(C=O), and 1340 and 1170(SO_2) cm^{-1}. ^{1}H-NMR; 2.43 ($COC\underline{H}_3$), 2.45 ($C\underline{H}_3$), and 4.01 ($NC\underline{H}_2$). MS; *m/z* 240 (27%), 226 (4.2%), and 184 (100%).

Reaction of Sulfonamide (1c) with Acetyl Chloride. To a suspended mixture of 0.5 g of **1c** in 20 ml of chloroform, 1 ml of acetyl chloride was added all at once. To the mixture, 1 ml of triethylamine was added at 0—5 °C. After 15 min, the reaction was found to be almost completed on TLC. After evaporation of solvents, the residue was chromatographed on a silica-gel column eluted with chloroform–acetone (93:7 v/v), to give 49 mg (8% yield) of **3c** and 152 mg (27%) of *N*-acetyl-*N,N'*-ditosyl-1,2-ethanediamine (**4c**). The rest was the unchanged starting **1c**. **4c** was obtained as colorless viscous liquid (spontaneous cryst.). Calcd for $C_{18}H_{22}N_2S_2O_5$: C, 52.66; H, 5.40; N, 6.83; S, 15.62%. Found: C, 52.59; H, 5.39; N, 6.74; S, 15.43%. IR (KBr) 3250(NH), 1700(C=O), and 1360, 1328, and 1158(SO_2) cm^{-1}. ^{1}H-NMR; 2.31 ($COC\underline{H}_3$), 2.44 and 2.46 ($C\underline{H}_3$), 3.24 (J=6.10, $NC\underline{H}_2$), 3.88 (J=6.10, $NC\underline{H}_2$), 4.95 (J=6.10, $N\underline{H}$). MS; *m/z* 255 (18%), 213 (3.2%), 197 (19%), and 184 (100%).

Spontaneous Decomposition of N-*Nitrososulfonamide (2a) in Ethanol.* When an ethanolic solution of **2a** (0.315 mg/20 ml) was allowed to stand on a bench top, the reaction induced by ambient room light was monitored by repetitive measurements of the UV spectra (every day in the range 210—350 nm). The original shoulder band at 250 nm revealed hypochromism and a band at 290 nm, hyperchromism, having an isosbestic point at 271 nm. After 47 d, the decomposition of **2a** became less significant. The eventual UV spectrum was superimposable to that of **1a**.

Removal of the N-*Nitroso Group in* N-*Nitrososulfonamide (2c) with* L-*Ascorbic Acid.* When a mixture of 0.43 g (1 mmol) of **2c** and 0.178 g (1 mmol) of L-ascorbic acid in 20 ml of ethanol was heated at *ca.* 70 °C overnight, **1c** was the only isolable product in quantitative yield. At the lowered temperature, the reactioin was markedly retarded.

Removal of N-*Acetyl Group in* N-*Acetylsulfonamide (3a) with Potassium Carbonate.* When a mixture of 90 mg of **3a** and 0.188 g (8 mmol eq) of anhydrous potassium carbonate in a mixed solvent of methanol–water (20 ml:1 ml) was refluxed for 1 h, **1a** was obtained in quantitative yield (76 mg) after silica-gel chromatography eluted with chloroform–methanol (17:3 v/v).

We are grateful to Dr. Haruo Homma and his staff at Riken for performing elemental analyses and Dr. Jun Uzawa and Mrs. Tamiko Chijimatsu at Riken for recording ^{1}H-NMR spectra.

References

1) a) B. C. Challis and J. A. Challis, "The Chemistry of Amides," ed by Zabicky, J. Interscience Publishers, London, 1970; pp. 780. b) B. C. Challis and S. A. Kryptpoulos, *J. Chem. Soc., Chem. Commun.*, **1976**, 877.

2) a) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955). b) T. J. de Boer and H. J. Backer, *Org. Synth.* Coll. Vol. IV, 225 (1963). c) C. G. Overberger and J.-P. Anselme, *J. Org. Chem.*, **28**, 592 (1963).

3) K. Yoshida and K. Yano, *Bull. Chem. Soc. Jpn.*, **55**, 2200 (1982).

4) J. E. Nordlander, M. J. Payne, M. A. Balk, J. L. Gress, F. D. Harris, J. S. Lane, R. F. Lewe, S. E. Marshall, D. Nagy, and D. J. Rachin, *J. Org. Chem.*, **49**, 133 (1984).

5) M. Iwata and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **55**, 2153 (1982).