

Heterocycles from Substituted Amides, V. (1).
1,2,3,5-Oxathiadiazolin-4-one 2-Oxides from Thionyl Chloride and *N*-Hydroxyureas

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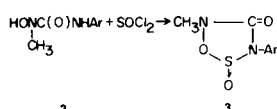
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The reaction of certain *N*-hydroxy-*N*-methyl-*N'*-aryl ureas, **2**, with thionyl chloride are shown to give a new heterocycle, 1,2,3,5-oxathiadiazolin-4-one 2-oxides, **3**, in a synthesis that appears to have more severe structural requirements than the previously reported ring closures from α -hydroxyacylanilides and thionyl chloride. Isolable amounts of **3** are obtained only if the aryl group contains deactivating substituents, and the hydroxy group is attached to the *N*-alkyl nitrogen; otherwise, resin formation or ring chlorination are found to occur. The assigned structure as **3** was verified by a full three dimensional X-ray analysis of a representative example, **3a**, 3-(4-bromophenyl)-5-methyl-1,2,3,5-oxathiadiazolin-4-one.

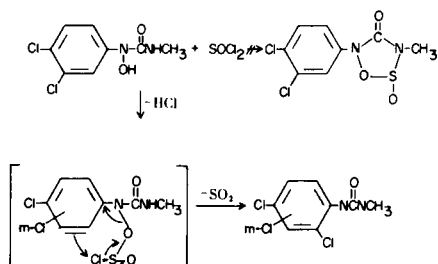
It was recently demonstrated (2) that 1,2,3-oxathiazolidin-4-one 2-oxides, **1**, could be conveniently prepared by the reaction of α -hydroxyacylanilides and thionyl chloride. It now has been shown that certain *N*-hydroxy-*N'*-arylureas, **2** (Table I), are also capable of undergoing cyclization to form 1,2,3,5-oxathiadiazolin-4-one 2-oxides, **3**, (Scheme 1), (Table II).

Scheme 1



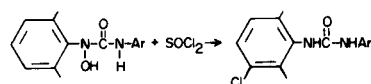
The reaction is accompanied by side reactions, and **3**, as finally purified, is obtained in 33% yield or less. The success of the reaction appears to be quite sensitive to structural features of the starting *N*-hydroxyurea. Thus, attempts to prepare the positional isomer of **3d** from *N*-hydroxy-*N*-(3,4-dichlorophenyl)-*N'*-methylurea, gave instead chlorination of the *ortho* positions (Scheme 2).

Scheme 2



Substitution of alkyl groups in both *ortho* positions either led to resinous materials from *N*-aryl-*N*-hydroxy-*N'*-methylurea, or *meta* chlorination when thionyl chloride was reacted with an *N,N'*-diaryl-*N*-hydroxyurea (Scheme III).

Scheme 3



The heterocycle **3**, can apparently only be prepared successfully *via* Scheme 1, if the aryl group contains deactivating groups in the aromatic ring, such as halogen or trifluoromethyl, and these preferably in the *ortho* position.

As discussed earlier (1,2), for heterocycles **1**, cyclization with thionyl chloride could conceivably form the alternative imino isomer, with both sulfur bonds attached to oxygen. To verify that the latter does not occur, and Scheme 1 does indeed represent the reaction sequence, a representative material, **3a**, was examined in detail using three dimensional X-ray crystallographic techniques. The structure of this 1,2,3,5-oxathiadiazolin-4-one 2-oxide, **3a**, is shown in Figure 1, while Table III lists pertinent bond lengths and angles.

Calculation of the least squares planes through the atoms of the two rings shows a dihedral angle of $52 \pm 3^\circ$. The hetero ring has considerable out-of-plane distortion. The nitrogen atom, N1, shows the largest deviation from the plane, being 0.4 Å below the plane described by the other four ring members. Although the carbonyl oxygen, O3, as

Table I

N'-Aryl-*N*-Hydroxy-*N*-Methylureas (a)

Material	Ar	% Yield	M.p.	C=O (ir)	C	Calcd. H	Analysis			
							N	C	Found H	N
2a	4(Br)C ₆ H ₄	66	157-159		39.20	3.70	11.43	39.27	3.65	11.51
e	4(Cl)-2(CF ₃)C ₆ H ₃	75	125-128	6.02	40.24	3.00	10.43	40.17	3.03	10.45
f	4(Cl)-3(CF ₃)C ₆ H ₃	61	120-122	6.00	40.24	3.00	10.43	40.37	3.02	10.62
g	2(CF ₃)C ₆ H ₄	48	77-80	6.05	46.16	3.87	11.96	46.15	3.78	12.22
h	3(CF ₃)C ₆ H ₄	62	137-140		46.16	3.87	11.96	46.63	4.05	11.96
i	2(F)C ₆ H ₄	81	124-126	6.03	52.17	4.93	15.21	52.40	4.81	15.31
j	3(F)C ₆ H ₄	77	114-115	6.03	52.17	4.93	15.21	52.21	4.90	15.29
k	2,5(F) ₂ C ₆ H ₃	55	107-109	6.00	47.53	3.99	13.86	47.50	4.13	13.91

(a) Materials **2b**, **c**, **d** have been previously described. See Ref. (3).

Table II

1,2,3,5-Oxathiadiazolin-4-one 2-Oxides, **3**, from
Reaction of *N'*-Aryl-*N*-hydroxy-*N*-methylureas and Thionyl Chloride

Material	Ar	Yield	M.p.	C=O (ir)	C	Calcd.				Found			
						H	N	S	C	H	N	S	
3a	4-(Br)C ₆ H ₄ ⁻	15	61-64	5.8	33.00	2.42	9.62	11.01	33.11	2.41	9.57	11.02	
b	3-(Cl)C ₆ H ₄ ⁻	15	60-62	5.8	38.95	2.86	11.36	13.00	38.97	2.89	11.29	13.19	
c	4-(Cl)C ₆ H ₄ ⁻	9	49-53	5.8	38.95	2.86	11.36	13.00	39.22	2.92	11.23	13.07	
d	3,4-(Cl) ₂ C ₆ H ₃ ⁻	26	87-90	5.8	34.18	2.15	9.97	11.41	34.32	2.41	9.98	11.51	
e	4-(Cl)-2-(CF ₃)C ₆ H ₃ ⁻	33	102-105	5.8	34.35	1.92	8.90	10.19	34.48	2.01	8.73	10.27	
f	4-(Cl)-3-(CF ₃)C ₆ H ₃ ⁻	17	56-58	5.8	34.35	1.92	8.90	10.19	34.88	2.00	9.08	10.25	
g	2-(CF ₃)C ₆ H ₄ ⁻		94-96	5.8	38.57	2.52	10.00	11.44	38.47	2.38	10.10	11.32	
h	3-(CF ₃)C ₆ H ₄ ⁻	21	60-65	5.8	38.57	2.52	10.00	11.44	38.84	2.54	10.02	11.40	
i	2-(F)C ₆ H ₄ ⁻	17	72-74	5.8	41.74	3.06	12.17	13.93	41.87	3.17	12.21	13.82	
j	3-(F)C ₆ H ₄ ⁻	18	61-62	5.8	41.74	3.06	12.17	13.93	41.69	3.07	12.25	14.11	
k	2,5-(F) ₂ C ₆ H ₃ ⁻	9	108-113	5.8	38.71	2.44	11.29	12.92	39.14	2.57	11.31	12.89	

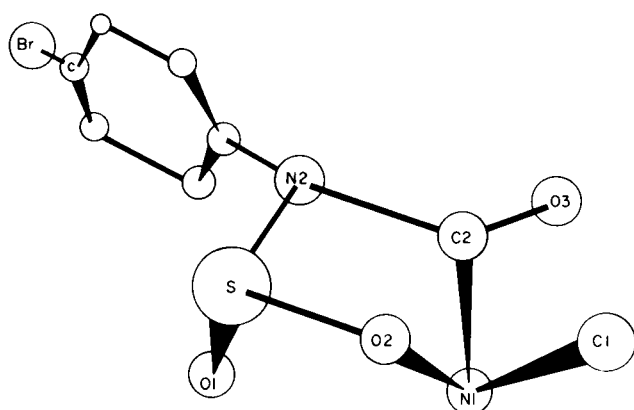


Figure 1. Three dimensional representation of molecule **3a**. See Table III for pertinent bond distance and angles.

Table III

Bond Lengths and Angles for **3a**

Atoms	Length (Å)	Atoms	Angle (°)
S-O1	1.47	O1-S-O2	109
S-O2	1.65	O1-S-N2	109
S-N2	1.61	O2-S-N2	90
N2-C2	1.49	S-N2-C2	123
C2-N1	1.45	N2-C2-N1	97
N1-C1	1.57	C2-N1-O2	115
N1-O2	1.44	N1-O2-S	106
C2-O3	1.10	Cl-N1-O2	112
Br-C	1.92	Cl-N1-C2	109

expected, is in the plane of the hetero ring, the sulfonyl oxygen is 1.5 Å below this plane, while the methyl group is found above. This *trans* relationship of the methyl and

sulfinyl oxygen in the crystal for **3a** is entirely consistent with the dominant spatial configuration previously found for the related 1,2,3-oxathiazolidin-4-one 2-oxides (1).

EXPERIMENTAL

Spectral data were recorded as follows: Nmr determined by a Vairan T-60; ir by a Perkin-Elmer Infracord; and X-ray by General Electric XRD-6 equipped with goniostat and scintillation counter, using Zr filtered MoK α radiation.

The preparation of the 1,2,3,5-oxathiadiazolin-4-one 2-oxides, **3**, involved preparing the intermediate *N*-hydroxyurea from the respective isocyanate and *N*-methylhydroxylamine (3). Purified **2** was then reacted with thionyl chloride to give **3**. Preparation of **3e** is illustrative.

3-(4-Chloro-2-trifluoromethylphenyl)-5-methyl-1,2,3,5-oxathiadiazolin-4-one 2-Oxide, **3e**.

N-methylhydroxylamine hydrochloride (12.4 g.) (0.115 mole) was stirred 24 hours at ambient temperature with 16.6 g. (0.165 mole) of triethylamine in ca. 150 ml. of ether. The mixture was filtered to remove triethylamine hydrochloride, then the ether solution was treated with 22.1 g. (0.1 mole) of 4-chloro-2-(trifluoromethyl)phenyl isocyanate. Infrared monitoring (4.5 μ) of the reaction mixture one-half hour after addition, indicated complete reaction of the isocyanate. The ether was evaporated and the residue induced to crystallize with scratching, followed by recrystallization from methylcyclohexane, to give a 20.0 g. yield, **2e**, m.p. (sealed tube).

The *N*-hydroxyurea, **2e**, (12.0 g., 0.45 mole) was placed in ca. 17 ml. of thionyl chloride, and the mixture heated to reflux and held at that temperature for five minutes. The mixture was quickly cooled, then ether added. The material was vacuum treated to remove volatiles, ether was added to the residue, and vacuum treatment repeated. The residual solid was taken up in boiling hexane, and the insolubles filtered off. The product **3e** crystallized from the filtrate on cooling. A second recrystallization from hexane afforded 5.6 g. of white crystals.

Reaction of Thionyl Chloride with *N*-Hydroxy-*N*-(3,4-dichlorophenyl)-*N'*-methylurea.

To a suitable 500 ml. flask that had been flushed with nitrogen, 12.0 g. of 3,4-dichlorophenylhydroxyl amine (4) was added contained in ca. 50 ml. of dry ether, followed by 3.85 g. of methyl isocyanate. After 5 minutes, and development of a noticeable exotherm, a white precipitate developed. The mixture was refluxed for ca. one-half hour, cooled and filtered. Ether was evaporated from the filtrate, and the residual solid recrystallized from toluene, m.p. 120-121 $^{\circ}$.

The *N*-(3,4-dichlorophenyl)-*N*-hydroxy-*N'*-methylurea (2.3 g.) was mixed with 5 ml. of thionyl chloride, wherein an unusually strong exotherm developed. The material was refluxed for one-half hour, then thionyl chloride removed under vacuum (using ether and benzene for co-distillation). The residue was triturated with ether, then recrystallized from acetonitrile. Two successive recrystallizations from acetonitrile gave 1.0 g. of crystals, m.p. 188-190 $^{\circ}$. The nmr of the product displayed two labile (N-H) protons (determined by deuterium oxide wash); two aromatic protons and the *N*-methyl group as a doublet. Both the nmr and ir spectra, as well as the elemental analyses, were essentially identical with *N*-methyl-*N'*-(2,4,5-trichlorophenyl)urea. A mixture m.p. with authentic material was not depressed, although the pure urea melted higher

(m.p. 219-220 $^{\circ}$), indicating that the product from thionyl chloride probably contained several percent of the other *ortho* isomer [i.e., *N*-methyl-*N'*-(2,3,4-trichlorophenyl)urea].

Reaction of *N*-(2,6-Dimethylphenyl)-*N*-hydroxyureas with Thionyl Chloride.

A mixture of 50 g. of 2-nitro-*m*-xylene (0.33 mole), 50 ml. of ten percent ammonium chloride solution and 250 ml. of ethanol were heated to 60 $^{\circ}$. At this temperature, 86 g. of zinc dust was gradually added at such a rate that the mixture achieved and maintained reflux. After addition, the mixture was refluxed an additional 15 minutes, then filtered into 250 g. of ice. The resulting solid from the filtrate was filtered, washed with hot water, air dried, recrystallized from heptane to give a 26.1 g. yield (58%), of *N*-(2,6-xylyl)hydroxylamine, m.p. 97-100 $^{\circ}$.

Anal. Calcd. for C₈H₁₁NO: C, 70.40; H, 8.08; N, 10.21. Found: C, 70.15; H, 8.11; N, 10.10.

a. Resin Formation.

N-(2,6-Dimethyl)-*N*-hydroxy-*N'*-methylurea [from *N*-(2,6-xylyl)hydroxylamine and methyl isocyanate] was added to excess thionyl chloride, and an extreme exotherm noted. The material immediately turned black. From the resin, obtained upon evaporation of thionyl chloride, no crystalline material could be derived.

b. *meta*-Chlorination.

Scheme 3 was found to be fairly general for *N*-hydroxy-*N*-(2,6-xylyl)-*N'*-arylureas. The reaction of thionyl chloride with *N*-(2,6-xylyl)-*N'*-(4-fluorophenyl)-*N*-hydroxyurea is typical. The hydroxy urea (3.0 g., 0.011 mole) was added portionwise to ca. ten ml. of thionyl chloride. An exotherm was evident on addition. Ether was then added and the precipitate filtered, washed further with ether to give 2.1 g. (65% yield) *N*-(3-chloro-2,6-xylyl)-*N'*-(4-fluorophenyl)urea. An analytical sample was further refined by recrystallization from 2-propanol, m.p. 237-239 $^{\circ}$; nmr (deuteriochloroform-deuteriodimethylsulfoxide): δ 2.20 (s, 3, ArCH₃), 2.24 (s, 3, ArCH₃), 6.8-7.6 (multiplets, 6, ArH), 7.75 (broad s, 1, NH), 8.8 (broad s, 1, NH).

Anal. Calcd. for C₁₅H₁₄ClFN₂O: C, 61.54; H, 4.82; N, 9.57. Found: C, 61.32; H, 4.68; N, 9.48.

These results were compared with the *p*-isomer, prepared from authentic 4-chloro-2,6-dimethylaniline (5) and *p*-fluorophenyl isocyanate. This urea (sublime > 285 $^{\circ}$), unlike the above *meta*-isomer, possess in a variety of solvents only one sharp singlet for the two aromatic-*methyl* groups in its nmr spectra.

X-Ray Crystallography (6).

Compound **3a** crystallizes in space group PT with $a = 13.5 \pm 0.1$, $b = 6.71 \pm 0.05$, $c = 6.46 \pm 0.05$, $\alpha = 90.0 \pm 0.5$, $\beta = 68.8 \pm 0.5$, $\gamma = 100.4 \pm 0.5$, and $z = 2$. Three dimensional intensity data were collected and corrected for Lorentz and polarization factors only. The 879 largest reflections were used to straightforwardly solve the structure using Patterson and heavy atom techniques. The structure refined isotropically to a conventional R-factor of 0.18. The uncertainty obtained by least squares for the positions of the carbon atoms is ± 0.05 Å, with lesser errors for the heavier atoms. The determination gave averages and standard deviations of 1.41 ± 0.06 Å for the C-C distance in the benzene ring and $119.8 \pm 4.5^{\circ}$ for the angle.

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