Synthesis of 1,2,3-Triazine N-Oxides

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N-Oxidation of substituted 1,2,3-triazines afforded the 1- and/or 2-oxides. The molecular structure of 4,5,6-triphenyl-1,2,3-triazine 2-oxide was studied crystallographically.

Keywords——1,2,3-triazine; 1,2,3-triazine 1-oxide; 1,2,3-triazine 2-oxide; heteroaromatic N-oxide; crystallography; X-ray analysis; synthesis

Despite numerous reports on pyridine and diazine N-oxides, relatively little is known on triazine N-oxides, and especially, very little on monocyclic 1,2,3-triazine N-oxides. It would be desirable to determine the properties of 1,2,3-triazine N-oxides in order to compare them with the properties of other azine N-oxides. Neunhoeffer briefly noted[2] the synthesis of 4,5,6-triaryl-1,2,3-triazine 1-oxides in a review, and we have outlined[3] the N-oxidation of a 1,2,3-triazine in a communication. This paper presents further data on the synthesis and properties of 1,2,3-triazine N-oxides.

When 1,2,3-triazines (1b—i) were allowed to react with m-chloroperbenzoic acid (MCPBA) in methylene chloride, they gave the N-oxides as major products, as shown in Table I, and some properties of the N-oxides are listed in Table II.

Dimethyl-, trimethyl-, and phenyl-substituted triazines (1d—i) afforded the N-oxides (2, 2′, and/or 3) in medium to high yields. However, the yields of the monomethyltriazine N-oxides (2 and/or 3b and 3c) were low and we have not succeeded in obtaining the unsubstituted 1,2,3-triazine N-oxides (2a and/or 3a), although the nuclear magnetic resonance (NMR) spectra of the reaction mixture showed the presence of a small amount of 3a in the

TABLE I.   Synthesis of 1,2,3-Triazine N-Oxides

	R^4	R^5	R^6	Yield (%)[a] of 2	Yield (%)[a] of 2′	Yield (%)[a] of 3
a	H	H	H	0	= 2a	Trace
b	Me	H	H	0	15	32
c	H	Me	H	0	= 2c	17
d	Me	H	Me	20	= 2d	48
e	Me	Me	Me	15	= 2e	32
f	Ph	H	H	0	0	63
g	Me	H	Ph	0	29	60
h	Ph	H	Ph	0	= 2h	81
i	Ph	Ph	Ph	0	= 2i	53[b]

a) Isolation yields.   b) Yield 35% from 1i by oxidation with H_2O_2–AcOH.

TABLE II. Melting Points, Elemental Analyses, and Infrared Spectra
of 1,2,3-Triazine N-Oxides

	mp (°C)[a]	Formula	Analysis (%) Calcd (Found)			IR (cm^{-1})[b]		
			C	H	N			
2b'	162	$C_4H_5N_3O$	43.24	4.54	37.83	1602 (s)	1522 (s)	1455 (m)
	Flakes from iso-Pr_2O		(43.55	4.44	37.50)	1416 (m)	1386 (m)	1332 (s)
2d	182	$C_5H_7N_3O$	47.99	5.64	33.58	1610 (m)	1354 (s)	
	Needles from benzene–CCl_4		(48.04	5.59	33.88)			
2e	140	$C_6H_9N_3O$	51.78	6.52	30.20	1590 (m)	1500 (m)	
	Needles from hexane–Et_2O		(52.00	6.88	30.12)	1442 (m)	1402 (m)	1350 (s)
2g'	197	$C_{10}H_9N_3O$	64.16	4.85	22.45	1610 (m)	1486 (m)	
	Needles from ethyl acetate		(64.43	4.79	21.84)	1450 (m)	1362 (s)	
3b	95	$C_4H_5N_3O$	43.24	4.54	37.83	1553 (s)	1410 (s)	
	Needles from iso-Pr_2O		(43.30	4.45	37.83)	1292 (m)		
3c	127	$C_4H_5N_3O$	43.24	4.54	37.83	1600 (m)	1518 (s)	
	Needles from iso-Pr_2O		(43.56	4.50	38.11)	1422 (s)		
3d	88	$C_5H_7N_3O$	47.99	5.64	33.58	1575 (s)	1430 (m)	
	Needles from Et_2O		(48.15	5.59	33.88)	1380 (m)	1338 (s)	
3e	112	$C_6H_9N_3O$	51.78	6.52	30.20	1530 (s)	1440 (s)	
	Needles from hexane–Et_2O		(52.05	6.90	30.00)	1380 (m)	1360 (m)	1350 (m)
3f	125	$C_9H_7N_3O$	62.42	4.07	24.27	1550 (s)	1495 (m)	
	Flakes from $CHCl_3$–Et_2O		(62.50	4.09	24.55)	1425 (s)	1380 (m)	
3g	178	$C_{10}H_9N_3O$	64.16	4.85	22.45	1560 (s)	1442 (s)	
	Needles from benzene		(64.29	4.66	22.32)	1345 (s)		
3h	188	$C_{15}H_{11}N_3O$	72.27	4.45	16.86	1565 (s)	1525 (s)	
	Needles from hexane–iso-Pr_2O		(72.03	4.46	17.11)	1495 (m)	1420 (s)	1345 (s)
3i	300	$C_{21}H_{15}N_3O$	77.52	4.65	12.92	1525 (m)	1505 (m)	
	Prisms from benzene		(77.30	4.56	12.71)	1470 (m)	1425 (s)	1360 (s)

a) Uncorrected. b) KBr disc.
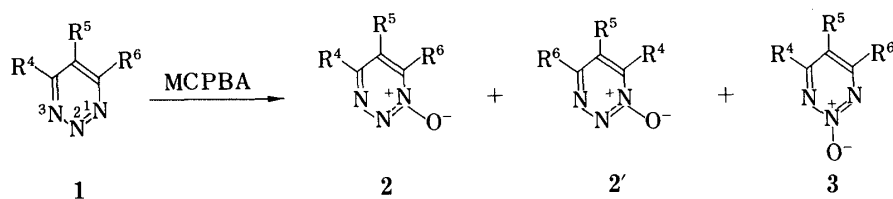
Chart 1

R^4, R^5, R^6 : see Table I.

mixture as discussed later (see Experimental).

As was expected from the nonequivalent nitrogen atoms in the parent base (**1**), the N-oxidation of some triazines afforded the respective 1-oxides (**2**) and 2-oxides (**3**) concurrently, as shown in Table I. The product distributions are generally explicable in terms of substituent effects. First, the comparatively low yields of 6-methyl-1,2,3-triazine 1-oxide (**2b'**) and 5-methyl-1,2,3-triazine 2-oxide (**3c**) and the absence of 4-methyl-1,2,3-triazine 1-oxide (**2b**) mean that electron donation by the methyl groups did not significantly enhance the N-oxidation. Although the oxidation of symmetrically methyl-substituted triazines (**1d** and **1e**) gave the respective 1-oxides (**2d, e**) and 2-oxides (**3d, e**), the reaction of symmetrically phenyl-substituted triazines (**1h** and **1i**) afforded exclusively the 2-oxides (**3h, i**). This phenomenon may be a result of the steric hindrance of the phenyl groups, as the effect likewise operates in

TABLE III.   Mass Spectra of 1,2,3-Triazine N-Oxides$^{a)}$

	M^+	$[M-O]^+$	$[M-N_3O]^+$	$[M-N_2]^+$	$[M-NO]^+$	Other noteworthy peaks
2b′	wk	abs	Base	md	abs	$[M-MeCNO]^+$ md, $[MeCNO]^+$ wk
2d	tr	tr	Base	md	wk	$[M-MeCNO]^+$ md, $[MeCNO]^+$ md
2e	wk	tr	Base	md	wk	$[M-MeCNO]^+$ md, $[MeCNO]^+$ wk
2g′	tr	tr	Base	str	wk	$[M-MeCNO]^+$ md, $[MeCNO]^+$ wk
3b	Base	tr	str	abs	md	$[M-MeCNO]^+$ md
3c	Base	tr	str	abs	tr	
3d	Base	abs	md	abs	str	
3e	Base	abs	md	abs	str	
3f	str	abs	md	abs	md	$[PhC_2H]^+$ base
3g	str	abs	md	abs	str	$[PhC_2H]^+$ base
3h	str	abs	md	abs	md	$[PhC_2H]^+$ base
3i	str	abs	md	abs	md	$[Ph_2C_2]^+$ base

a) Direct ionization/EI at 70 eV.   wk, weak. abs, absent. md, medium. tr, trace. str, strong.

the N-oxidation of 2-phenylpyridine derivatives.[4] The N-oxidation of the 4-methyl-6-phenyl-1,2,3-triazine (1g) gave the 1-oxide (2g′) and the 2-oxide (3g), while the other 1-oxide (2g) was absent, presumably because of the steric effect. The N-oxidation of 4-phenyl-1,2,3-triazine (1f) afforded the 2-oxide (3f) in a reasonable yield and neither 6-phenyltriazine 1-oxide (2f′) nor 4-phenyltriazine 1-oxide (2f) was obtained, although the latter seemed not to be a sterically disadvantageous product.
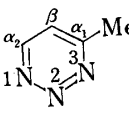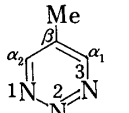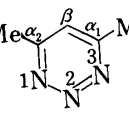
Thus, the 1-oxides (2a—c and 2f) were not formed when the carbon atom (6-C) adjacent to the target nitrogen atom (1-N) was unsubstituted. No definite explanation for this can be offered here. However, it could be proposed that, though the 1-oxides are formed as intermediates in the reaction, they are unstable and decompose into intractable compounds under the oxidizing conditions when their 6-positions are unsubstituted.

Structural elucidation of the N-oxides obtained here has been carried out as follows. Table III shows the principal ion peaks in the mass spectra (MS) of the N-oxides and indicates their characteristic features. As is structurally expected, all the present 1-oxides (2 and 2′) showed an $[M-28(N_2)]^+$ peak of medium or high intensity, while the peak due to the molecular ion was weak or trace. On the other hand, the M^+ peak was prominent (in some cases, the base peak) and the $[M-28]^+$ peak was absent for all the 2-oxides (3). Thus, the structural distinction between the 1-oxides and the 2-oxides is clearly reflected in the MS. Further, the 1-oxides usually showed only a weak or no $[M-30(NO)]^+$ peak, while the corresponding peak of the 2-oxides was medium or strong with the exception of 3c. Moreover, the $[M-57(MeCNO)]^+$ peak, which was accompanied with the m/z 57(MeCNO) peak, was prominent with the 1-oxides in which the 6-position is substituted by a methyl group. Thus, 2b′ was assigned as 6-methyl-1,2,3-triazine 1-oxide (not 4-methyl-1,2,3-triazine 1-oxide). Similarly, the N-oxide (2g′) was decided to be 4-phenyl-6-methyl-1,2,3-triazine 1-oxide because it showed an $[M-57]^+$ peak of medium strength together with a weak m/z 57 peak.

Next, the proton nuclear magnetic resonance (^1H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of the N-oxides (3c—e and 3h) showed symmetrical features, so that the positions of the N-oxide groups can be decided. (For the structure of 3i, see later.) On the other hand, the structures of other (unsymmetrical) N-oxides could not be determined directly from the NMR spectra alone, although the NMR spectra showed characteristic features as stated below.

The NMR spectral data of methyltriazine N-oxides are shown in Table IV. In the ^{13}C-NMR spectra, upfield shifts of signals ascribable to the carbons in the o- and p-positions to

TABLE IV.   NMR Chemical Shifts[a] of Ring Carbons and Ring Protons of 1,2,3-Triazines and Their N-Oxides

	C (α_1)	C (β)	C (α_2)	Other carbons	H (α_1)	H (β)	H (α_2)	Other protons
Parent base (1b)	159.7	117.8	148.8	21.4 (Me)	—	7.33	8.92	2.70 (Me)
1-Oxide (2b'; 3-NO)	146.9	123.5	137.4	17.4 (Me)	—	7.44	8.44	2.52 (Me)
2-Oxide (3b; 2-NO)	168.7	107.9	156.0	21.7 (Me)	—	6.79	8.50	2.53 (Me)
Parent base (1c)	150.8	129.1	150.8	15.9 (Me)	8.93	—	8.93	2.40 (Me)
2-Oxide (3c; 2-NO)	157.8	118.4	157.8	14.7 (Me)	8.48	—	8.48	2.31 (Me)
Parent base (1d)	158.8	117.6	158.8	21.1 (Me)	—	7.11	—	2.68 (Me)
1-Oxide (2d; 1-NO)	146.1	123.9	148.1	17.2 and 20.6 (Me)	—	7.68	—	2.46 and 2.60 (Me)
2-Oxide (3d; 2-NO)	167.2	108.6	167.2	20.9 (Me)	—	6.70	—	2.46 (Me)
4-Phenyl-1,2,3-triazine[b]								
Parent base (1f)					—	7.72	9.05	7.40—7.70 (3H, Ar); 8.17—8.30 (2H, Ar)
2-Oxide (3f; 2-NO)					—	7.29	8.65	7.40—7.75 (3H, Ar); 8.00—8.20 (2H, Ar)

a) δ ppm from TMS in CDCl$_3$.   b) Full assignments of the ^{13}C-NMR signals have not been made for these compounds.

the N-oxide groups, relative to the signals attributed to the corresponding carbons of the parent triazines (1), were regularly observed together with downfield shifts of the m-position carbon signals. The higher shift can be explained by a back-donation of electrons due to resonance, from the oxygen atom to the ring carbons, while on the other hand, the low shift can be rationalized in terms of a decrease of total π-electron density of the triazine ring due to the coordination of the nitrogen atom to the oxygen atom.

The ^{1}H-NMR spectra also exhibited similar shifts of the signals; the observed upfield shifts of the signals of protons in p-positions to the N-oxide groups (4-H of 2b' and 5-H of 3b, d; and 3f) and downfield shifts of protons in m-positions (5-H of 2b' and 2d) might be dependent on the above-mentioned back-donation and decrease of total electron density, respectively. High-field shifts of the signals of protons in m-positions to the (2-)N-oxide groups (4-H of 3b and 3c, as well as 6-H of 3f) are not surprising, as similar shifts are usually observed at 3-H of pyridazine 1-oxides (i.e., m-position protons to the N–O moiety).[5]

Moreover, broadening of the signals (independent of couplings) due to 4- and 6-H were observed in the NMR spectra of the 2-oxides (3b, c, and 3f); this is again not surprising, because similar phenomena are generally observed for 3-H of pyridazine 1-oxides.

N-Oxidation of 4,5,6-triphenyltriazine (1i) with peracetic acid gave a single N-oxide which was identical with 3i, although Neunhoeffer[2] had reported the formation of the 1-oxide (2i) as the major product[6] of the oxidation of 1i with peracetic acid. Hence, we investigated the molecular structure of 4,5,6-triphenyl-1,2,3-triazine N-oxide (3i) by a crystallographic X-ray analysis, and decided the structure to be the 2-oxide. A view of the molecular structure along the c-axis is shown in Fig. 1, and the final non-hydrogen atom positional parameters are given in Table V.

In addition, a fraction obtained from alumina column chromatography of the reaction mixture of the oxidation of 1a showed a characteristic broad doublet at δ 8.55 (2H) and a triplet at δ 6.84 (1H), strongly suggesting the presence of 3a in the fraction.

Finally, reaction of the 1-oxide (2d) with dimethyl sulfate led to the formation of an intractable mixture; however, the reaction of the 2-oxide (3d) afforded a single product, 1,4,6-trimethyl-2-oxo-1,2,3-triazin-2-ium methosulfate, (4d), whose unsymmetrical structure was
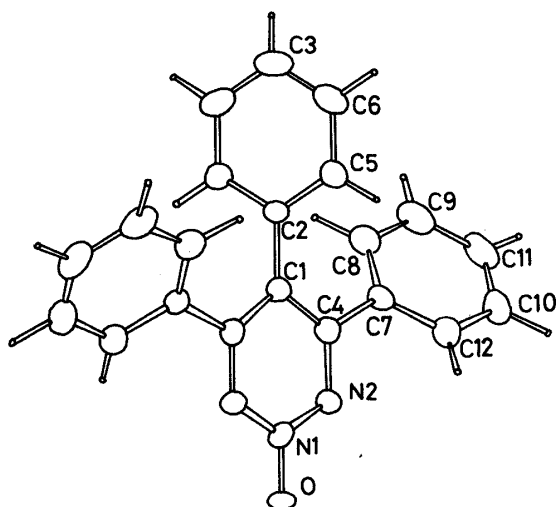
Fig. 1.   Molecular Structure of 4,5,6-Triphenyl-
1,2,3-triazine 2-Oxide

Numbers given for the atoms are independent of
those in the text. The atoms O, N1, C1, C2, and H-C3
are located on the dyad axis in the crystal.

TABLE V.   Final Atom Parameters ($\times 10^4$) and Equivalent Thermal Parameters,
with Estimated Standard Deviation in Parentheses[a]

Atom	x	y	z	$B_{eq.}$ (Å^2)
O	2500 (0)	-861 (3)	0 (0)	3.2 (.08)
N1	2500 (0)	190 (4)	0 (0)	2.2 (.08)
C1	2500 (0)	2453 (5)	0 (0)	1.9 (.07)
C2	2500 (0)	3699 (5)	0 (0)	2.0 (.08)
C3	2500 (0)	6023 (6)	0 (0)	3.9 (.12)
N2	1745 (3)	702 (3)	664 (3)	2.2 (.05)
C4	1754 (3)	1827 (3)	662 (3)	1.9 (.05)
C5	1558 (4)	4280 (4)	-443 (4)	2.7 (.06)
C7	905 (3)	2290 (3)	-441 (5)	3.5 (.08)
C8	1148 (4)	3206 (4)	1444 (4)	2.1 (.05)
C9	349 (5)	3554 (4)	2959 (4)	3.5 (.08)
C10	-684 (5)	2994 (5)	3027 (5)	3.8 (.08)
C11	-933 (4)	2101 (5)	2299 (5)	3.7 (.08)
C12	-139 (4)	1745 (4)	1500 (4)	2.9 (.07)

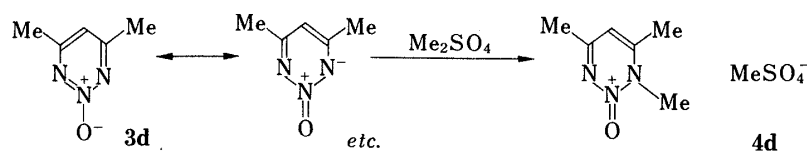a) Atom numbers are given independently of those in the text; they conform to those in Fig. 1.

Chart 2

clear from the ^{13}C- and ^{1}H-NMR spectra (see Experimental).

The formation of the N-methylated salt is relatively unique, because the methylation of
N-oxides of pyridine and diazine derivatives normally resuts in O-methylation, and this
suggests a contribution of resonance forms of the 2-oxides (3) (Chart 2).

Experimental

Infrared (IR) spectra were recorded on a JASCO A102 and NMR spectra were taken on a JEOL FX-100 (δ from
tetramethylsilane (TMS) in CDCl$_3$ unless otherwise noted). MS were run on a JEOL D300 instrument.
N-Oxidation of 1,2,3-Triazines; General Procedure——A solution of 1 mmol of a 1,2,3-triazine (1) and 1.3 mmol

of MCPBA in CH_2Cl_2 (50—100 ml) was allowed to stand at room temperature for 1—3 d. Consumption of **1** was followed by alumina and/or silica-gel thin layer chromatography (TLC) (PhH–CH_2Cl_2). After most of **1** had been consumed, the solution was washed with aqueous $KHCO_3$ to eliminate the acid and the organic layer was dried over $MgSO_4$, followed by evaporation of the solvent under reduced pressure. The residue was chromatographed on a column of aluminum oxide or silica gel, or on a thick layer (PhH–CH_2Cl_2). ^{1}H-NMR spectral data ($CDCl_3$ unless otherwise noted) of **2** and **3** (except for those listed in Table IV) are shown below: **2e**, δ: 2.32 (3H, s, CH_3), 2.46 (3H, s, CH_3), 2.56 (3H, s, CH_3); **3e**, δ: 2.23 (3H, s, 5-CH_3), 2.44 (6H, s, 4- and 6-CH_3); **2g′**, δ: 2.57 (3H, s, CH_3), 7.48—7.67 (3H, m, phenyl-H), 7.81 (1H, s, 5-H), 8.00—8.16 (2H, m, phenyl-H); **3g**, δ: 2.58 (3H, s, CH_3), 7.21 (1H, s, 5-H), 7.48—7.67 (3H, m, phenyl-H), 8.00—8.16 (2H, m, phenyl-H); **3h**, δ: 7.53—7.62 (7H, m, 5-H and phenyl-H), 8.06—8.16 (4H, m, phenyl-H); **3i**, (DMSO-d_6) δ: 6.80—7.45 (m).

N-Oxidation of **1a** with MCPBA——A mixture of 100 mg of the triazine (**1a**) and 335 mg of MCPBA in 30 ml of CH_2Cl_2 was allowed to stand for 3 d at room temperature in a dark place. The mixture was filtered, and the filtrate was evaporated to dryness without neutralization, since washing with aq. $KHCO_3$ resulted in complete decomposition of the materials. The residue was chromatographed over alumina (PhH–CH_2Cl_2). The ^{1}H-NMR spectrum of the fraction (*ca.* 20 mg) eluted with CH_2Cl_2 showed signals at δ 8.55 (2H, br d, $J = 5.5$ Hz) and 6.84 (1H, t, $J = 5.5$ Hz) besides those due to **1** and other contaminants. However, further attempts to crystallize the *N*-oxides (**2a** and/or **3a**) from the mixture were unsuccessful.

N-Oxidation of **1i** with Peracetic Acid——The triazine (**1i**, 300 mg) was suspended in 30 ml of acetic acid. Hydrogen peroxide (30% H_2O_2, 0.2 ml) was added to the mixture at room temperature and the whole was heated at 70 °C. Further portions of 0.2 ml of hydrogen peroxide were added at every 2 h (twice) during the heating. The heating was continued until all of the **1i** was consumed, and the mixture was cooled to room temperature. Precipitated crystals were filtered off and recrystallized from benzene to give 111 mg (35%) of **3i**. The acidic filtrate was evaporated to dryness under reduced pressure and chromatographed over silica gel (PhH–CH_2Cl_2) to give 12 mg (4%) of triphenylisoxazole, which was identical with an authentic sample,[7] besides small amounts of **1i** and **3i**.

Crystallography of 4,5,6-Triphenyl-1,2,3-triazine 2-Oxide (**3i**)——The observed crystal data were as follows: molecular formula $C_{21}H_{15}N_3O$, molecular weight $= 325$, monoclinic, space group $I2/C$, $Z = 4$ (1/2 molecule is included in an asymmetric unit), $a = 11.861$ (6), $b = 11.954$ (6), $c = 11.554$ (6) Å, $\beta = 91.62$ (1) °. The lattice constants and intensity data were obtained on a Philips PW 1100 diffractometer using graphite-monochromated CuK_α radiation by the θ-2θ scan method. The scans were repeated twice when the total counts during the first scan were less than 2000. The background was measured at each end of the scan range for half the total scan time. A total of 1579 reflections were measured within the 2θ angle of 156 °. Intensities were corrected for Lorentz and polarization factors and averaged for symmetry-equivalent reflections, but no absorption correction was applied.

The crystal structure was determined by the direct method using MULTAN[8] and refined by the block-diagonal least-squares method.[9] The final R value was 0.085 including anisotropic and isotropic thermal parameters, respectively, for heavier and hydrogen atoms.

Reaction of 3d with Dimethyl Sulfate——A mixture of 200 mg (0.8 mmol) of **3d** and 1 ml of Me_2SO_4 was heated at 90 °C for 3 h. After cooling, the mixture was washed twice with 5 ml each of Et_2O and then twice with 5 ml each of 1 : 10 MeOH–Et_2O mixture. The residue was dried *in vacuo* and 400 mg ($\sim$quant.) of an oily product (**4d**) was obtained. Perchlorate, mp 152 °C. ^{1}H-NMR (CD_3OD) δ: 2.71 (3H, s, $=C$-CH_3), 2.90 (3H, s, $=C$-CH_3), 4.17 (3H, s, N-CH_3), 7.76 (1H, s, $=CH$). ^{13}C-NMR (CD_3OD) δ: 22.06 ($=C$-$\underline{C}H_3$), 22.26 (C-$\underline{C}H_3$), 40.03 (N-$\underline{C}H_3$), 115.36 ($=\underline{C}H$), 166.32 ($=\underline{C}$-CH_3), 173.02 ($=\underline{C}$-CH_3). IR (KBr): 3350, 3080, 1590, 1565, 1358, 1085 cm^{-1}. *Anal.* Calcd for $C_6H_{10}ClN_3O_5$: C, 30.07; H, 4.21; N, 17.54. Found: C, 30.18; H, 4.14; N, 17.35.

References and Notes

1) In part (X-ray analysis).
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4) For example, E. Ochiai, "Aromatic Amine Oxides," Elsevier, Amsterdam, 1967 and references cited therein.
5) Kawazoe *et al.* explained this higher shift in terms of a decrease of the paramagnetic deshielding effect of the lone-pair electrons on 2-N, caused by a decreased contribution of n–π^* transition of the electrons as a result of (1-)*N*-oxidation; see also reference 4.
6) All attempts to detect **2i** failed, and instead, we obtained a small amount of triphenylisoxazole, mp 208 °C and m/z (M$^+$) 297, which is identical to the m/z of [M $-$ 28]$^+$ of **2i**.
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