SYNTHESIS OF 2-SUBSTITUTED ISOTHIAZOLO[5,4-*b*]PYRIDIN-3(2*H*)-ONE 1,1-DIOXIDES

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Abstract - The Isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxides (**3a-g**) were prepared from the corresponding isothiazolo[5,4-*b*]pyridin-3(2*H*)-ones (**1a-g**) by means of an oxidation with oxone® ($KHSO_5$) and sodium hypochlorite (NaOCl) in two steps. The influence of the substituents (R), in position 2 of this system, on the oxidation process was studied. While the oxidation of **1a-g** with 3-chloroperoxybenzoic acid gave yields of **3a-g** depending greatly on the nature of R, the combined $KHSO_5$/NaOCl method gave good yields of **3a-g** in all of the cases studied.

INTRODUCTION

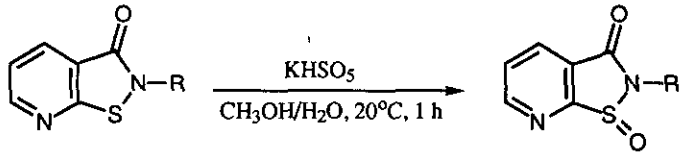
Isothiazol-3(2*H*)-one 1,1-dioxides with fused pyridine rings are valuable precursors of important anti-inflammatory drugs[1] and of some recently discovered inhibitors of the HIV1 reverse transcriptase.[2] Motivated by these applications, we have investigated the preparation of the new sultam derivatives (**3a-g**) starting from the easily accessible isothiazolo[5,4-*b*]pyridin-3(2*H*)-ones (**1a-g**). The oxidation of **1a-g** has scarcely been studied and the published methods (85% *m*-CPBA,[3] $KMnO_4$[4]) gave low yields of the corresponding 1,1-dioxide derivatives. However, we have found that the compounds (**3a-g**) can be prepared in high yields from **1a-g** through a simple and unexpensive modification of known oxidation methods[5] that utilize potassium hydrogen persulfate ($KHSO_5$), commercially available as oxone®, and sodium hypochlorite. In order to establish the generality of the proposed method, we introduced various substituents in the 2 position of the isothiazolo[5,4-*b*]pyridin-3(2*H*)-one system. The selected 2-

substituents (R) modified the steric and electrostatic fields around the sulfur atom during the oxidation.

RESULTS AND DISCUSSION

The starting isothiazolo[5,4-*b*]pyridin-3(2*H*)-ones (**1a-g**) were synthesized in only one step by the reaction of 2-chlorothio-3-pyridinecarbonyl chloride with amines according to our recently published method.[6] The first step in the oxidation of **1a-g** occurred with 1.5 equivalents of $KHSO_5$ in the form of oxone® dissolved in 50% aqueous methanol at 20°C (Scheme 1). The oxone completely oxidized compounds (**1a-g**) to their 1-oxides in 1 h, giving good yields (81-93%) of isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1-oxides (**2a-f**). Under these conditions, formation of the isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxides (**3a-g**) was negligible.

Scheme 1

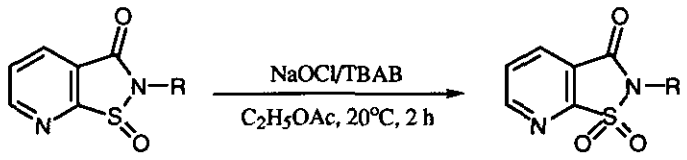


1 **2**

Entry	Precursor	R	Product	Yield (%)
a	**1a**	CH_3	**2a**	87
b	**1b**	$C(CH_3)_3$	**2b**	93
c	**1c**	C_6H_4Br-*p*	**2c**	92
d	**1d**	CH_2CH_3	**2d**	85
e	**1e**	$CH_2C_6H_5$	**2e**	81
f	**1f**	$CH_2CH_2COOC_2H_5$	**2f**	85
g	**1g**	$CH_2COOC_2H_5$	**2g**	85

Although oxone is a good oxidizing agent for converting sulfides into sulfones,[7] the treatment of **1a-g** with 4 equivalents of $KHSO_5$ in aqueous methanol at 20°C for 24 h gave the corresponding 1-oxides (**2a-g**) with only small quantities of the 1,1-dioxides (30% of **3a** and less than 10% of **3b-g** respectively). 1,1-Dioxides (**3a-g**) were synthesized in high yields (81-94%) by treating 1-oxides (**2a-g**) for 2 h at 20°C with 4 fold excess of 5% aqueous NaOCl in ethyl acetate and tetrabutylammonium bromide as a phase-transfer catalyst (Scheme 2).

Scheme 2



2 3

Entry	Precursor	R	Product	Yield (%)
a	**2a**	CH_3	**3a**	85
b	**2b**	$C(CH_3)_3$	**3b**	87
c	**2c**	C_6H_4Br-*p*	**3c**	94
d	**2d**	CH_2CH_3	**3d**	88
e	**2e**	$CH_2C_6H_5$	**3e**	83
f	**2f**	$CH_2CH_2COOC_2H_5$	**3f**	81
g	**2g**	$CH_2COOC_2H_5$	**3g**	87

m-CPBA also is able to oxidize the isothiazolo[5,4-*b*]pyridin-3(2*H*)-one system. However, when **1a-g** reacted with 2.2 equiv. of 95% *m*-CPBA in dichloromethane at 20°C, compounds (**1a-g**) were completely consumed within an hour giving the 1-oxides (**2a-g**), but after 24 h the yields of 1,1-dioxides were 78% for **3a**, 74% for **3b**, 20% for **3c**, 38 % for **3d**, 42% for **3e**, 41% for **3f** and 18% for **3g**; the yields of **2**, which accompany **3**, account for the rest of the material. The results obtained show that the combined oxone®/NaOCl method for the oxidation of **1** offers much better yields of 1,1-dioxides (**3**) than *m*-CPBA for 2-aryl derivatives, such as **3c**, or when substituents in the 2 position interact strongly with the sulfoxide group of the isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1-oxide system, such as occurs in **2g**. This supposition agrees with the spectroscopic data (Table 1), as well as the known electronic interactions of heteroaromatic sulfoxides.[8] Also, the oxone®/NaOCl method has advantages with respect to the oxidation of the isothiazolo[5,4-*b*]pyridin-3(2*H*)-ones by potassium permanganate,[4] since it does not produce potassium sulfonic acid salts from further reaction of the 1,1-dioxides. Additionally, the oxidation of **1a** was also studied with other oxidizing agents. Sodium hypochlorite[9] did not react with **1a**, sodium periodate in aqueous methanol[10] or chlorine in acetic acid[11] oxidized **1a** to **2a** but not to **3a**, and hydrogen peroxide in methanol[12] only gave 21% of **3a** from **1a**.

In summation, our procedure is simple, cheap, and useful for the preparation of isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxides (**3**) since the commercially available sodium hypochlorite and oxone can be directly used.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were obtained in a CHNS Carlo Erba EA1108 analyzer from vacuum-dried samples (over phosphorus pentoxide at 3-4 mm Hg, 6-12 h at 30-70ºC). Infrared spectra were recorded on a Nicolet 510M FT-IR apparatus, using potassium bromide tablets. The ^{1}H nmr spectra were obtained on a Varian Gemini (200 MHz) instrument at 20°C, with tetramethylsilane as an internal standard at a concentration of about 0.1 g/ml and deuterochloroform as solvent; the chemical shifts are reported in ppm from tetramethylsilane and are in δ value. Thin-layer chromatography (tlc) was carried out on silica gel (Schleicher & Schuell F1500/LS 254) with ethyl acetate:cyclohexane (2:1) as solvent and the plates were scanned under 254 and 366 nm ultraviolet light. Column chromatography was carried out on silica gel 60 Merck (70-230 mesh ASTM) with indicated solvents. Solvents were usually removed under vacuum, when stated, in a rotavapory evaporator. Unless otherwise noted materials were obtained from commercial suppliers and used without further purification. The *m*-CPBA of 95% purity was prepared by washing the commercial 50-60% *m*-CPBA with a phosphate buffer of pH 7.5 and drying the residue at reduced pressure.[13] The following starting materials were synthesized by known procedures: 2-chlorothio-3-pyridinecarbonyl chloride,[6] isothiazolo[5,4-*b*]pyridin-3(2*H*)-ones **1a**,[14] **1e**,[15] and **1g**.[6]

2-(1,1-Dimethylethyl)isothiazolo[5,4-*b*]pyridin-3(2*H*)-one (1b)

To a suspension of 2-chlorothio-3-pyridinecarbonyl chloride[6] (3.12 g, 15.0 mmol) in CH_2Cl_2 (20 ml), a solution of *tert*-butylamine (3.28 g, 45.0 mmol) in CH_2Cl_2 (20 ml) was dropwise added with stirring at 0°C. After the addition was completed, stirring was continued at 20°C for further 3 h. Water (60 ml) was added and the organic layer was separated, washed with H_2O (2 x 30 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (EtOAc/cyclohexane 2:1, v/v). The product was recrystallized from EtOH/H_2O to give **1b** (1.90 g, 61%) as white needles (Table 1). Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.66; H, 5.82; N, 13.45; S, 15.39. Found: C, 57.45; H, 5.92; N, 13.51; S, 15.15.

2-(4-Bromophenyl)isothiazolo[5,4-*b*]pyridin-3(2*H*)-one (1c)

To a suspension of 2-chlorothio-3-pyridinecarbonyl chloride[6] (3.12 g, 15.0 mmol) in $CHCl_3$ (20 ml), a solution of *p*-bromoaniline (2.58 g, 15.0 mmol) and triethylamine (3.03 g, 30.0 mmol) in $CHCl_3$ (20 ml) was dropwise added with stirring at 0°C. After the addition was completed, stirring was continued at 20°C for an hour. The resulting solid material was collected and recrystallized from EtOAc to give **1c** (3.31 g, 72%) as white needles (Table 1). Anal. Calcd for $C_{12}H_7N_2OBrS$: C, 46.92; H, 2.30; N, 9.12; S, 10.44.

Found: C, 46.94; H, 2.20; N, 9.13; S, 10.67.

Table 1. Characterization Data of the New Isothiazolo[5,4-*b*]pyridin-3(2*H*)-ones and their *S*-Oxides

Compd	recrystn. solvent[a]	mp (°C)	ir υ (cm^{-1})[b] -SO_x-	-COO-	-CON-	^{1}H nmr δ (ppm), *J* (Hz)[c]
1b	A	61-62			1645	1.69 (9H, s), 7.28 (1H, dd, *J*=4.6, *J*=8.0), 8.17 (1H, dd, *J*=1.8, *J*=8.0), 8.69 (1H, dd, *J*=1.8, *J*=4.6).
1c	B	204-206			1675	7.39 (1H, dd, *J*=4.8, *J*=8.0), 7.58 (4H, s), 8.32 (1H, dd, *J*=1.8, *J*=8.0), 8.80 (1H, dd, *J*=1.8, *J*=4.8).
1d	C	79-81			1650	1.37 (3H, t, *J*=7.2), 3.95 (2H, q, *J*=7.2), 7.32 (1H, dd, *J*=4.8, *J*=7.9), 8.24 (1H, dd, *J*=1.8, *J*=7.9), 8.71 (1H, dd, *J*=1.8, *J*=4.8).
1f	D	103-105		1725	1665	1.25 (3H, t, *J*=7.2), 2.79 (2H, t, *J*=7.4), 4.1-4.2 (4H, m), 7.33 (1H, dd, *J*=4.8, *J*=8.0), 8.25 (1H, dd, *J*=1.6, *J*=8.0), 8.73 (1H, dd, *J*=1.6, *J*=4.8).
2a	C	113-114	1106		1714	3.41 (3H, s), 7.67 (1H, dd, *J*=4.8, *J*=7.8), 8.27 (1H, dd, *J*=1.6, *J*=7.8), 8.92 (1H, dd, *J*=1.6, *J*=4.8).
2b	E	89-91	1105		1701	1.73 (9H, s), 7.62 (1H, dd, *J*=4.8, *J*=8.0), 8.19 (1H, dd, *J*=1.6, *J*=8.0), 8.88 (1H, dd, *J*=1.6, *J*=4.8).
2c	B	203-204	1094		1718	7.41 (2H, d, *J*=8.8), 7.64 (2H, d, *J*=8.8), 7.74 (1H, dd, *J*=4.8, *J*=7.8), 8.38 (1H, dd, *J*=1.6, *J*=7.8), 9.00 (1H, dd, *J*=1.6, *J*=4.8).
2d	B	112-114	1104		1713	1.42 (3H, t, *J*=7.2), AB part of ABX_3 system (δ_A = 3.86, δ_B = 4.04, J_{AX}=J_{BX}=7.2, J_{AB}=14.4), 7.66 (1H, dd, *J*=4.8, *J*=7.8), 8.27 (1H, dd, *J*=1.6, *J*=7.8), 8.91 (1H, dd, *J*=1.6, *J*=4.8).
2e	C	138-140	1111		1715	4.74 (1H, d, *J*=16.0), 5.32 (1H, d, *J*=16.0), 7.3-7.5 (5H, m), 7.67 (1H, dd, *J*=5.0, *J*=8.0), 8.29 (1H, dd, *J*=1.6, *J*=8.0), 8.92 (1H, dd, *J*=1.6, *J*=5.0).
2f	C	52 - 54	1107	1724	1711	1.23 (3H, t, *J*=7.2, $OCH_2C\underline{H}_3$), 2.80 (2H, td, *J*= 4.0, 7.0, $CH_2C\underline{H}_2CO$), 4.08-4.20 (4H, m), 7.66 (1H, dd, *J*=4.8, *J*=7.8), 8.25 (1H, dd, *J*=1.6, *J*=7.8), 8.90 (1H, dd, *J*=1.6, *J*=4.8).
2g	D	70 - 72	1125	1744	1715	1.28 (3H, t, *J*=7.0), 4.23 (2H, q, *J*=7.0), 4.37 (1H, d, *J*=18.2), 4.81 (1H, d, *J*=18.2), 7.70 (1H, dd, *J*=5.0, *J*=8.0), 8.31 (1H, dd, *J*=1.6, *J*=8.0), 8.96 (1H, dd, *J*=1.6, *J*=5.0).
3a	C	140-142	1338 1163		1730	3.29 (3H, s), 7.76 (1H, dd, *J*=4.8, *J*=7.8), 8.37 (1H, dd, *J*=1.6, *J*=7.8), 8.99 (1H, dd, *J*=1.6, *J*=4.8).
3b	E	147-149	1335 1148		1731	1.77 (9H, s), 7.71 (1H, dd, *J*=4.8, *J*=7.8), 8.19 (1H, dd, *J*=1.6, *J*=7.8), 8.88 (1H, dd, *J*=1.6, *J*=4.8).
3c	B	194-196	1343 1170		1742	7.41 (2H, d, *J*=8.6), 7.68 (2H, d, *J*=8.8), 7.82 (1H, dd, *J*=4.9, *J*=7.9), 8.45 (1H, dd, *J*=1.6, *J*=7.9), 9.05 (1H, dd, *J*=1.6, *J*=4.9).
3d	C	90-91	1342 1158		1731	1.45 (3H, t, *J*=7.2), 3.88 (2H, q, *J*=7.2), 7.75 (1H, dd, *J*=4.8, *J*=7.9), 8.35 (1H, dd, *J*=1.6, *J*=7.9), 8.97 (1H, dd, *J*=1.6, *J*=4.8).
3e	F	122-124	1352 1169		1727	4.92 (2H, s), 7.3-7.5 (m, 5H), 7.74 (1H, dd, *J* =4.8, *J*=7.8), 8.32 (1H, dd, *J*=1.6, *J*=7.8), 9.01 (1H, dd, *J*=1.6, *J*=4.8).

3f	C	87 - 89	1325 1170	1744	1732	1.26 (3H, t, *J*=7.2), 2.87 (2H, t, *J*=7.4), 4.1-4.2 (4H, m), 7.76 (1H, dd, *J*=4.8, *J*=7.8), 8.36 (1H, dd, *J*=1.6, *J*=7.8), 8.98 (1H, dd, *J*=1.6, *J*=4.8).
3g	D	94 - 96	1339 1177	1752	1736	1.27 (3H, t, *J*=7.0), 4.24 (2H, q, *J*=7.0), 4.45 (2H, s), 7.78 (1H, dd, *J*=4.8, *J*=7.8), 8.38 (1H, dd, *J*=1.6, *J*=7.8), 8.99 (1H, dd, *J*=1.6, *J*=4.8).

[a]A: EtOH/H_2O, B: EtOAc, C: Isopropanol, D: EtOAc/cyclohexane, E: Cyclohexane, F: Et_2O,
[b]Using KBr tablets.
[c]Spectra were recorded in $CDCl_3$

2-Ethylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (1d)

To a suspension of 2-chlorothio-3-pyridinecarbonyl chloride[6] (3.12 g, 15.0 mmol) in dioxane (30 ml), a solution of ethylamine (2.03 g, 45.0 mmol) in water (60 ml) was dropwise added with stirring at 0°C. After the addition was completed, stirring was continued at room temperature for further 3 h. After the addition of CH_2Cl_2 (150 ml), the organic layer was separated, washed with H_2O (2 x 30 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was recrystallized from 2-propanol to give **1d** (1.73 g, 64%) as pale yellow needles (Table 1). Anal. Calcd for $C_8H_8N_2OS$: C, 53.31; H, 4.47; N, 15.50; S, 17.73. Found: C, 53.42; H, 4.59; N, 15.45; S, 17.66.

2-(1-(Ethoxycarbonyl)ethyl)isothiazolo[5,4-*b*]pyridin-3(2*H*)-one (1f)

To a suspension of 2-chlorothio-3-pyridinecarbonyl chloride[6] (3.12 g, 15.0 mmol) in dioxane (30 ml), a freshly prepared solution of ethyl 3-aminopropionate hydrochloride (9.21 g, 60.0 mmol) and sodium hydroxide (2.40 g, 60 mmol) in H_2O (60 ml) was dropwise added with stirring at 0°C. After the addition was completed, stirring was continued at room temperature for further 3 h. Subsequently, H_2O (200 ml) was added and then the pH was brought to 6 with hydrochloric acid (1 M). The resulting solid material was collected and recrystallized from cyclohexane/EtOAc (3:1) to give **1f** (2.33 g) as white needles. A second crop (0.58 g) was obtained by extraction of the aqueous filtrate with CH_2Cl_2 (3 x 100 ml); total yield 2.91 g (77%) (Table 1). Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 52.36; H, 4.80; N, 11:11; S, 12.71. Found: C, 52.19; H, 4.87; N, 11.03; S, 12.70.

Preparation of 2-substituted isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1-oxides (2a-g). General procedure.

To a stirred mixture of the corresponding isothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**1a-g**) (9.0 mmol) in 50% aqueous MeOH (30 ml) at 20°C, oxone® (0.83 g, 13.5 mmol of $KHSO_5$) was added in small portions. When the reaction had been completed, the reaction mixture was poured into H_2O (100 ml) and extracted with CH_2Cl_2 (3 x 25 ml). Organic layers were dried (Na_2SO_4) and evaporated, and the residue was

recrystallized to give **2a-g** (Table 1). **2a** Anal. Calcd for $C_7H_6N_2O_2S$: C, 46.14; H, 3.33; N, 15.38; S, 17.60. Found: C, 46.31; H, 3.37; N, 15.42; S, 17.89. **2b** Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.54; H, 5.40; N, 12.49; S, 14.29. Found: C, 53.36; H, 5.51; N, 12.57; S, 13.99. **2c** Anal. Calcd for $C_{12}H_7N_2O_2BrS$: C, 44.60; H, 2.19; N, 8.67; S, 9.92. Found: C, 44.59; H, 2.07; N, 8.61; S, 9.62. **2d** Anal. Calcd for $C_8H_8N_2O_2S$: C, 48.96; H, 4.12; N, 14.28; S, 16.34. Found: C, 49.03; H, 4.25; N, 14.13; S, 16.15. **2e** Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.44; H, 3.91; N, 10.85; S, 12.41. Found: C, 60.57; H, 4.06; N, 10.90; S, 12.70. **2f** Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.52; N, 10.44; S, 11.95. Found: C, 49.20; H, 4.68; N, 10.15; S, 11.60. **2g** Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.23; H, 3.97; N, 11.02; S, 12.61. Found: C, 47.35; H, 4.03; N, 11.13; S, 12.87.

Preparation of *2-substituted isothiazolo*[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxides (3a-g). General procedures.

From 2a-g: A mixture of the corresponding isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1-oxide (**2a-g**) (7.5 mmol) and tetrabutylammonium bromide (0.10 g, 0.3 mmol) in EtOAc (50 ml) at 20°C was treated with 5% aqueous NaOCl (44.70 g, 30.0 mmol). The mixture was stirred vigorously and the reaction monitored by tlc. After the sulfoxide was completely consumed, water (100 ml) was added and the organic layer was separated and washed with H_2O (2 x 50 ml). The resulting solution was dried (Na_2SO_4) and concentrated in vacuo, and the crude material was recrystallized to give **3a-g** (Table 1).

From 1a-g: To a suspension of the corresponding isothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**1a-g**) (4.0 mmol) in CH_2Cl_2 (10 ml), a solution of 95% m-CPBA (1.44 g, 8.2 mmol) in CH_2Cl_2 (10 ml) was added dropwise with stirring at 20°C. After the addition was completed, stirring was continued at 20°C for further 24 h. The mixture was washed with phosphate buffer of pH 7.5 (2 x 20 ml) and the organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (EtOAc/cyclohexane 2:1, v/v). After recrystallization, overall yields were 78% for **3a**, 74% for **3b**, 20% for **3c**, 38% for **3d**, 42% for **3e**, 41% for **3f** and 18% for **3g**. **3a** Anal. Calcd for $C_7H_6N_2O_3S$: C, 42.41; H, 3.06; N, 14.14; S, 16.17. Found: C, 42.65; H, 3.13; N, 14.10; S, 16.46. **3b** Anal. Calcd for $C_{10}H_{12}N_2O_3S$: C, 49.98; H, 5.04; N, 11.66; S, 13.34. Found: C, 50.15; H, 5.16; N, 11.62; S, 13.08. **3c** Anal. Calcd for $C_{12}H_7N_2O_3BrS$: C, 42.49; H, 2.08; N, 8.26; S, 9.45. Found: C, 42.58; H, 2.02; N, 8.18; S, 9.64. **3d** Anal. Calcd for $C_8H_8N_2O_3S$: C, 45.27; H, 3.81; N, 13.20; S, 15.11. Found: C, 45.43; H, 3.93; N, 13.19; S, 15.02. **3e** Anal. Calcd for $C_{13}H_{10}N_2O_3S$: C, 56.92; H,

3.68; N, 10.21; S, 11.69. Found: C, 56.90; H, 3.70; N, 10.16; S, 11.31. **3f** Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.26; N, 9.86; S, 11.28. Found: C, 46.20; H, 4.18; N, 9.75; S, 11.01. **3g** Anal. Calcd for $C_{10}H_{10}N_2O_5S$: C, 44.44; H, 3.74; N, 10.37; S, 11.86. Found: C, 44.45; H, 3.68; N, 10.15; S, 11.60.

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10. 2 equiv. of $NaIO_4$, 50 mM of substrate in MeOH/H_2O (v/v, 1:1), 25°C, 72 h.
11. Excess of Cl_2, 70mM of substrate in HOAc/H_2O (v/v, 1:1), -19°C, 3 h.
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