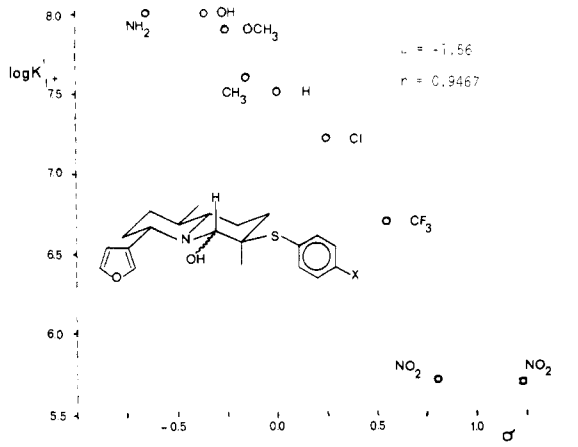

Figure 2. A plot of log K'_{I^+} against σ_p (○) and σ_p^- (□) for para-substituted α-(arylthio) hemiaminal derivatives (**1–9**) in 70% methanol–water solution at 25 °C. Points are designated according to the para substituent (X) of the arylthio group.

tributed to too low a σ_p value, one which fails to account for the protonation of the NH_2 group in acidic solution. The variance of the point for the *p*-NO_2 derivative (**3**) can be attributed to the delocalization of electrons from the sulfur atom toward the nitro group. If σ_p for the *p*-nitro group is replaced by σ_p^-, proposed for reactions in which electron withdrawal of the substituent is greater than that of the usual resonance interaction,[5] and the point for the *p*-NH_2 compound is omitted, a much better linear correlation results for seven points; $\rho = -1.42$ and $r = 0.9976$ are obtained.

Clearly the sign of ρ indicates stabilization of the CT iminium ion resulting from para electron-donating aryl groups attached to the sulfur atom. The magnitude of ρ indicates an involvement of sulfur similar to this element's stabilization of cationic intermediates produced during the solvolysis of various β-chloroethyl sulfides. By way of comparison, ρ values of −1.671,[6] −1.398,[7] and −1.431[7] have been determined from the solvolysis rates of β-chloroethyl, *trans*-2-chlorocyclopentyl, and *trans*-2-chlorocyclohexyl aryl sulfides, respectively. Also instructive is the comparison of the log K'_{I^+} value for the methylthio, **10**, with the log K'_{I^+} values for the arylthio groups (**2**, **5**, **8**, **9**) that are capable of strong electron release by way of resonance. All are nearly the same. A final noteworthy comparison is the larger log K'_{I^+} value for the β-thio diastereomer, **3** (β used in the usual stereochemical sense), compared to its α counterpart, **4**. The result is in agreement with an earlier finding[1] regarding log K'_{I^+} values for **10** and **11**, a finding that was rationalized in terms of greater resistance to solvolysis from the α surface of the iminium ion than the less hindered β surface.

Experimental Section

The pH of a solution of the α-(thioaryl) hemiaminal, 0.10–0.21 mg/mL in 70% methanol–water, was adjusted with solid NaOAc or KOH to its highest level, as determined with a pH meter, and the CD was determined from 250 to 400 nm with a Jasco Model 5 spectropolarimeter. The pH was adjusted downward in increments with HOAc, and the pH and CD were determined after each increment. For each set of CDs, a CT peak was chosen that was furthest removed from the aryl absorptions observed at the highest pH. The [θ] values were calculated for this peak at each pH. Plots of pH vs. [θ] were made, and the value of $pH_{1/2}$ was

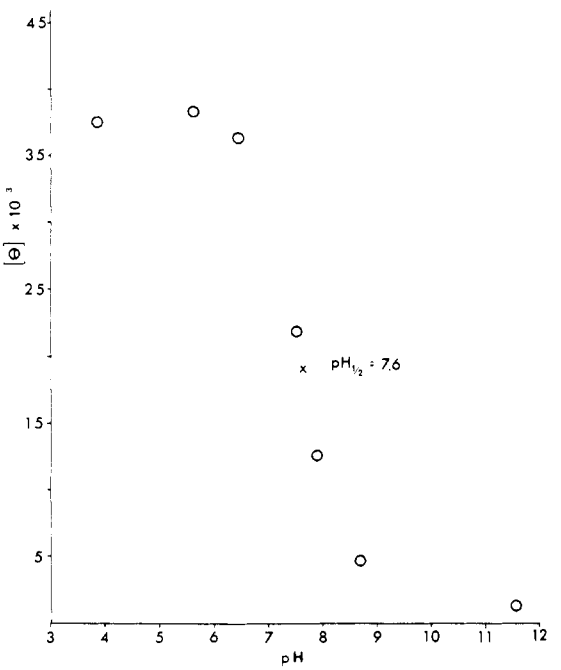

Figure 3. A plot of the charge-transfer molecular ellipticity, [θ], × 10^{-3} in degree/mole for the 300-nm band vs. pH for (*R*)-6-[(4-methylphenyl)thio]deoxynupharidin-6-ol, **2**, in 70% methanol–water solution at 25 °C.

taken from the resulting S-shaped curve as half the difference of the maximum [θ] at the lowest pH and the minimum [θ] at the highest pH. An example of such a plot is shown in Figure 3.

Registry No. 1, 57897-34-4; 1 iminium ion, 57897-40-2; **2**, 59187-39-2; **2** iminium ion, 86994-05-0; **3**, 86994-00-5; **3** iminium ion, 87011-62-9; **4** iminium ion, 87011-63-0; **5**, 86994-01-6; **5** iminium ion, 87011-64-1; **6**, 86994-02-7; **6** iminium ion, 86994-06-1; **7**, 86994-03-8; **7** iminium ion, 86994-07-2; **8**, 87011-61-8; **8** iminium ion, 86994-08-3; **9**, 86994-04-9; **9** iminium ion, 86994-09-4.

(5) Hammett, L. P. "Physical Organic Chemistry", 2nd ed.; McGraw Hill: New York, 1970; p 360.
(6) Jaffe, J. J. *Chem. Rev.* **1953**, *53*, 191.
(7) Goering, H. L.; Howe, K. L. *J. Am. Chem. Soc.* **1957**, *79*, 6542.

2-Mercapto-1,3-benzoxazole: A Useful Reagent for the Preparation of Symmetrical and Unsymmetrical Sulfides

John C. Sih* and David R. Graber

Experimental Science Research, The Upjohn Company, Kalamazoo, Michigan 49001

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One of the most commonly used methods for the preparation of mixed sulfides is the alkylation of thiols.[1] This approach is straightforward if the thiol starting materials are readily available. However, when the thiols must be prepared by synthesis, the procedure becomes less satisfactory, owing to the wide variations in thiol yields and the unpleasant odors accompanying these preparations.

We report a novel, convenient, and odorless procedure for the synthesis of sulfides which takes advantage of the base lability of 2-(alkylthio)-1,3-benzoxazole derivatives (**1**, BoxSR, Scheme I). In the presence of sodium hydroxide and a halide (RX), **1** functions as a sulfur-transferring agent to provide sulfides **2** and **4** in good yields.[2]

(1) Sandler, S. R.; Karo, W. "Organic Functional Group Preparations"; Academic Press: New York, 1968; p 486.

0022-3263/83/1948-3842$01.50/0

Scheme I

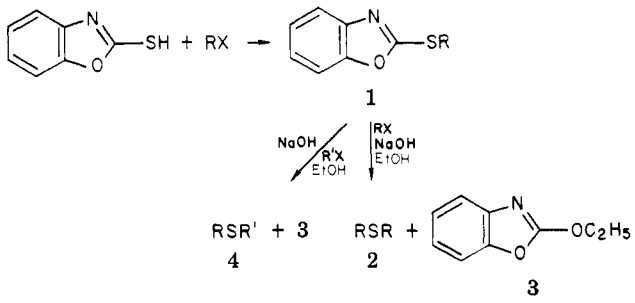
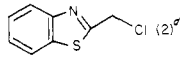
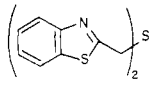
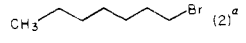
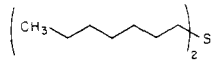
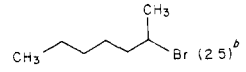
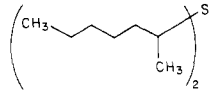
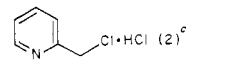
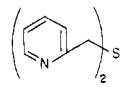


Table I. Preparation of Symmetrical Sulfides

$$\text{BoxSH} + \text{RX} \xrightarrow[95\%\ \text{EtOH}]{\text{NaOH}} \text{RSR}$$
65–70 °C

R-X (equiv)	product	yield, %
$PhCH_2Cl$ (2)[a]	$(PhCH_2)_2S$	75
		62
		62[d]
		43[d]
		53

[a] 3 equiv of NaOH, 1–2 h. [b] 5 equiv of NaOH, 6 h. [c] 4 equiv of NaOH, 2 h. [d] Approximately 5% disulfide isolated from the reaction.

For the preparation of symmetrical sulfides, the method simply involved heating a 95% ethanol solution of 2-mercaptobenzoxazole (0.4 M), an alkyl or aralkyl halide (2 equiv), and 10 N sodium hydroxide (3 equiv) for 1–2 h at 65–70 °C. The pure sulfides **2** (Table I) were obtained by a conventional workup and silica gel chromatography.[3]

The BoxSR (**1**) starting materials used for the synthesis of the unsymmetrical sulfides were readily prepared by alkylation of BoxSH with an appropriate alkyl, aralkyl, or cyclohexyl halide and triethylamine (Table II). The unsymmetrical sulfides **4** were then prepared by heating a solution of **1** (0.2 M) in 95% ethanol with R′X (2 equiv) and 10 N sodium hydroxide (2 equiv) for 1 h at 65–70 °C. The mixed sulfides prepared by this method are summarized in Table III.

Several points regarding the preparation of mixed sulfides are noteworthy. There was no difference in the reactivity of $BoxSCH_2Ar$ (Ar = 3,4,5-trimethoxyphenyl) with allylic, benzylic, primary, and secondary alkyl bromides or chlorides (entries 1–7); these reactions were completed after 10–15 min at 65–70 °C. Reaction of $BoxSCH_2Ar$ with cyclohexyl halides (Br, Cl) and neopentyl chloride failed to yield any sulfide; in one instance, we isolated $ArCH_2SH$ in 52% yield (entry 8). Use of primary and secondary alkyl

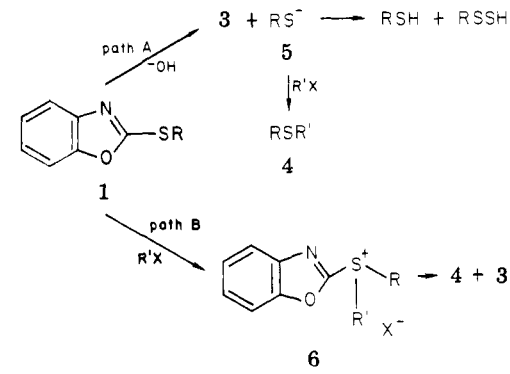
Table II. Preparation of BoxSR Substrates

$$\text{BoxSH} + \text{RX} \xrightarrow{\text{Et}_3\text{N}} \underset{\mathbf{1}}{\text{BoxSR}}$$

R-X (equiv)	solvent	reaction time	temp, °C	yield, %
3,4,5-trimethoxybenzyl bromide[a] (1)	CH_2Cl_2	30 min	45	96[c]
benzyl chloride[a] (1)	CH_2Cl_2	2 h	45	70[c]
sec-heptyl bromide[a] (1.5)	$CHCl_3$	48 h	65	82[d]
n-heptyl bromide[a] (1)	CH_2Cl_2	16 h	45	83[d]
cyclohexyl bromide[b] (1.5)	DMF	22 h	80	45[d]
3-picolyl chloride hydrochloride[a] (1)	CH_2Cl_2	16 h	45	87[c]

[a] 2 equiv of triethylamine. [b] 1 equiv of triethylamine. [c] Crude product used without purification. [d] Purified by silica column chromatography.

Scheme II



and cyclohexyl BoxSR substrates gave sulfides in lower yields (entries 12, 13, 16), and these were accompanied by some disulfide formation.

One possible reaction mechanism (Scheme II) involves initial attack of hydroxide ion at the C-2 position of **1** to generate thiolate anion **5**. Capture of **5** by R′X give sulfides (path A). In the absence of R′X or with sterically hindered less reactive halides, **5** can yield thiol and disulfide products. The formation of disulfides via air oxidation of **5** in alkaline solution is an especially favored process.[4] It is less likely that a sulfonium salt intermediate is involved in the reaction (path B). S-Alkylation of conjugated vinylic or aryl sulfides such as **1** would be difficult because of the reduced nucleophilicity of sulfur due to $p\pi$ delocalization.[5] The use of very reactive alkylating agents, particularly trialkyloxonium salts[6] and fluorosulfonates,[7] is generally required with these substrates. With the alkylating agents employed in this study, we would not expect nor have we ever observed any **6** when heating an ethanolic solution of **1** and R′X.

The present method offers some advantages over current methods for sulfide synthesis.[8] The procedure does not

(2) After completion of this manuscript, the preparation of sulfides by the reaction of **1** with sodium alkoxides has been recently reported. See: Yamato, M.; Takeuchi, Y.; Hattori, K.; Hashigaki, K. *Synthesis* **1982**, 1014.

(3) Primarily on the basis of the reaction scale (0.5–2.0 g), column chromatography was the most efficient method for product isolation. On a larger scale, distillation or direct crystallization of the product may be more expedient.

(4) N.; Kharasch, C. Y., Meyers, Ed. "The Chemistry of Organic Sulfur Compounds"; Pergamon Press: New York, 1966; Vol. 2, p 205.

(5) Boonstra, H. J.; Brandsma, L., unpublished results quoted in: "The Chemistry of the Ether Linkage"; Patai, S., Ed.; Interscience: New York, 1967; p 152.

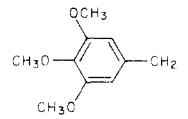
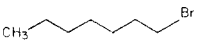
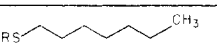
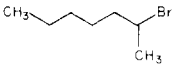
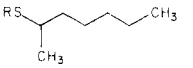
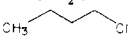
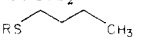
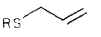
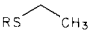
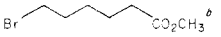
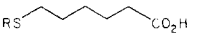
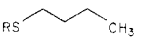
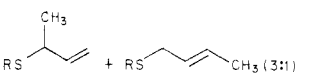
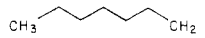
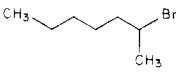
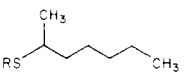
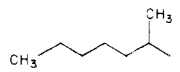
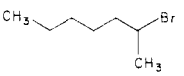
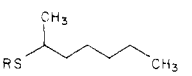
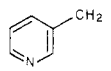
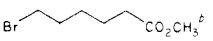
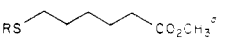
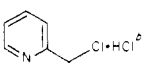
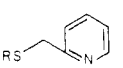
(6) Baldwin, J. E.; Hackles, R. E.; Kelly, D. P. *J. Am. Chem. Soc.* **1968**, *90*, 4758.

(7) Vedejs, E.; Engler, D. A. *Tetrahedron Lett.* **1976**, 3487.

(8) (a) Furukawa, M.; Suda, T.; Hayashi, S. *Synthesis* **1974**, 282. (b) Tamura, Y. Saito, T.; Ishibashi, H.; Ikeda, M. *Ibid.* **1975**, 641. (c) Tanigawa, Y.; Kanamaru, H.; Murahashi, S. *Tetrahedron Lett.* **1975**, 4655. (d) Labuschagne, A. J. B.; Malherbe, J. S.; Meyer, C. J.; Schneider, D. F. *Ibid.* **1976**, 3571.

Table III. Preparation of Unsymmetrical Sulfides

$$\text{BoxSR} + \text{R'X} \xrightarrow[\substack{95\%\ \text{EtOH}\\ 65\text{–}70\ ^\circ\text{C}}]{\text{NaOH}} \text{RSR'}$$

entry	R	R'X[a]	product	yield, %
1	 I			78
2	I			75
3	I	$PhCH_2Cl$	$RSCH_2Ph$	76
4	I			73
5	I	$CH_2{=}CHCH_2Cl$		67
6	I	CH_3CH_2Br		76
7	I	 [b]		67
8	I		RSH	52
9	$PhCH_2$			77
10	$PhCH_2$	$CH_2{=}CHCH(CH_3)Cl$		87
11	 II	$PhCH_2Cl$	$RSCH_2Ph$	74
12	II			62[c]
13				48
14	 III	 [b]	 [d]	66
15	III	 [b]		68
16		$PhCH_2Cl$	$RSCH_2Ph$	57[e]

[a] 2 equiv of halide. [b] 3 equiv of NaOH. [c] 2% disulfide (RSSR) isolated from the reaction. [d] Product obtained after methylation with ethereal diazomethane. [e] 84% yield based on recovered Box-S-R.

require thiol starting materials and utilizes readily available alkyl and aralkyl halides and a relatively cheap, commercial reagent, 2-mercaptobenzoxazole. On the basis of the product yields and the simplicity of the procedure, the present method is superior to the existing methods for the preparation of the mixed sulfides reported in this study.[9] Another feature which makes this process particularly attractive is the fruity, sweet-smelling aroma of the common imino ether byproduct **3**. Its presence masks any thiol odors produced in the reaction.

Experimental Section

General Procedures for the Preparation of Sulfides. Symmetrical Sulfides (Table I). To a magnetically stirred solution of 10 mmol of 2-mercaptobenzoxazole (BoxSH) in 25 mL of 95% ethanol was added 20 mmol of RX and 30 mmol of 10 N sodium hydroxide. The contents were then stirred in a 65–70 °C oil bath for 2 h. After cooling to room temperature, the reaction mixture was diluted with chloroform and washed with water and saturated brine, and the chloroform solution was dried through anhydrous sodium sulfate. Removal of the solvent in vacuo gave the crude product, which was purified by silica gel column chromatography with 0–20% ethyl acetate in hexane as the eluent.

Unsymmetrical Sulfides (Table III). To a magnetically stirred solution of 1 mmol of 1 in 5 mL of 95% ethanol was added 2 mmol of RX and 2 mmol of 10 N sodium hydroxide. The contents were then placed in a 65–70 °C oil bath for 1 h. The reaction mixture was worked up, and the sulfides were purified in the same manner as described above.

Typical Procedure for the Preparation of BoxSR (1). To a magnetically stirred solution of BoxSH (6.39 g, 42.31 mmol) in 125 mL of methylene chloride was added 11.00 g (42.31 mmol) of 3,4,5-trimethoxybenzyl bromide and 8.55 g (84.62 mmol) of triethylamine. The contents were heated at reflux for 30 min, cooled to room temperature, and diluted with methylene chloride. The organic solution was washed with water and saturated brine and dried through anhydrous sodium sulfate. Concentration of the solvent in vacuo gave 13.47 g (96% yield) of 2-[[(3,4,5-trimethoxyphenyl)methyl]thio]benzoxazole, which was sufficiently

(9) For the preparation of the symmetrical sulfides reported in this study, the use of phase-transfer catalysts gives higher yields. See: Landini, D.; Rolla, F. *Synthesis* **1974**, 565. Herriott, A. W.; Picker, D. *Ibid.* **1975**, 447.

pure to be used without purification; mp 83–84 °C (recrystallized from Skellysolve B). Anal. Calcd for $C_{17}H_{17}NO_4S$: c, 61.63; H, 5.17; N, 4.23; S, 9,66. Found: C, 61.80; H, 5.29; N, 4.17; S, 9.56.

Registry No. 1 (R = H), 2382-96-9; 1 (R = 3,4,5-trimethoxybenzyl, 86971-23-5; 1 (R = benzyl), 86971-24-6; 1 (R = *sec*-heptyl), 86971-25-7; 1 (R = *n*-heptyl), 86971-26-8; 1 (R = cyclohexyl), 86971-27-9; 1 (R = 3-picolyl), 86971-28-0; 2 (R = benzyl), 538-74-9; 2 (R = 2-benzothiazolylmethyl), 86971-29-1; 2 (R = *n*-heptyl), 629-65-2; 2 (R = *sec*-heptyl), 45162-42-3; 2 (R = 2-picolyl), 5832-32-6; 4 (R = 3,4,5-trimethoxybenzyl; R^1 = *n*-heptyl), 86971-30-4; 4 (R = 3,4,5-trimethoxybenzyl; R^1 = *sec*-heptyl), 86971-31-5; 4 (R = 3,4,5-trimethoxybenzyl; R^1 = benzyl), 86971-32-6; 4 (R = 3,4,5-trimethoxybenzyl; R^1 = *n*-butyl), 86971-33-7; 4 (R = 3,4,5-trimethoxybenzyl; R^1 = allyl), 86971-34-8; 4 (R = 3,4,5-trimethoxybenzyl; R = ethyl), 86971-35-9; 4 (R = 3,4,5-trimethoxybenzyl; $R^1 = (CH_2)_5CO_2H$), 86971-36-0; 4 (R = 3,4,5-trimethoxybenzyl; R^1 = H), 80192-89-8; 4 (R = benzyl; R^1 = *n*-butyl), 5184-47-4; 4 (R = benzyl; $R^1 = CH(CH_3)CH{=}CH_2$), 75238-62-9; 4 (R = benzyl; $R^1 = CH_2CH{=}CHCH_3$), 31409-96-8; 4 (R = *n*-heptyl; R^1 = benzyl), 58587-21-6; 4 (R = *n*-heptyl; R^1 = *sec*-heptyl), 86971-37-1; 4 (R = 3-picolyl; $R^1 = (CH_2)_5CO_2CH_3$), 86971-38-2; 4 (R = 3-picolyl; R^1 = 2-picolyl), 86971-39-3; 4 (R = cyclohexyl; R^1 = benzyl), 19843-98-2; benzyl chloride, 100-44-7; 2-(chloromethyl)benzothiazole, 37859-43-1; *n*-heptyl bromide, 629-04-9; *sec*-heptyl bromide, 1974-04-5; 2-picolyl chloride hydrochloride, 6959-47-3; 3,4,5-trimethoxybenzyl bromide, 21852-50-6; cyclohexyl bromide, 108-85-0; 3-picolyl chloride hydrochloride, 6959-48-4; *n*-butyl chloride, 109-69-3; allyl chloride, 107-05-1; ethyl bromide, 74-96-4; methyl 6-bromohexanoate, 14273-90-6; 3-chloro-1-butene, 563-52-0.

1,3,4-Dioxazol-2-ones: A Potentially Hazardous Class of Compounds†

William J. Middleton

Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

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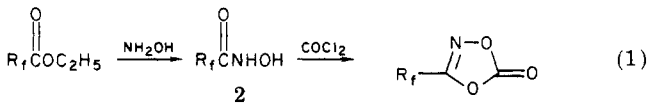
Trifluoromethyl isocyanate and other perfluoroaliphatic isocyanates are usually prepared by the classical Curtius rearrangement.[1] However, the acyl azide precursors are capriciously explosive, and more than one investigator has been injured while trying to prepare trifluoromethyl isocyanate by this method.

In a search to find a safer method of generating perfluoroaliphatic isocyanates, we examined several other precursors that could be used in place of acyl azides. One class of compounds investigated was the cyclic carbonates of perfluoroaliphatic hydroxamic acids (5-(perfluoroalkyl)-1,3,4-dioxazol-2-ones, 1).[2] We found that these compounds are indeed efficient intermediates to isocyanates, but they are surprisingly similar to acyl azides in that they are also dangerously explosive.

The cyclic carbonates (1) were prepared in high yield by the reaction of phosgene with perfluoroaliphatic hydroxamic acids in diglyme solvent (eq 1). No base was

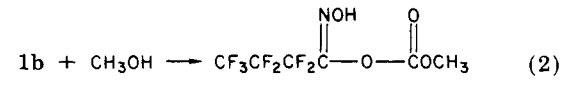


(1)

1a, $R_f = CF_3$
b, $R_f = CF_2CF_2CF_3$
c, $R_f = (CF_2)_6CF_3$

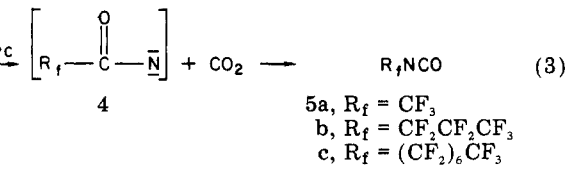
needed to remove the hydrogen chloride. In fact, if a base was added to the reaction mixture, cyclic carbonates were not obtained, probably because of their extreme reactivity toward nucleophiles.

1,3,4-Dioxazol-2-ones can be regarded as mixed anhydrides of carbonic acid and hydroxamic acids, and so it is not surprising that they react vigorously with water, alcohols, and amines. With methanol, 5-(heptafluoropropyl)-1,3,4-dioxazol-2-one (**1b**) gives the adduct ester **3** (eq 2).



(2)

Pyrolysis of the cyclic carbonates **1** at 275 °C and atmospheric pressure (eq 3) results in expulsion of carbon



(3)

5a, $R_f = CF_3$
b, $R_f = CF_2CF_2CF_3$
c, $R_f = (CF_2)_6CF_3$

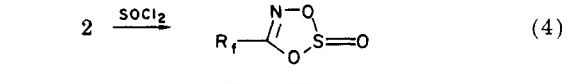
dioxide, and the resulting acylnitrenes (**4**) rearrange to give a nearly quantitative yield of perfluoroalkyl isocyanates. Trifluoromethyl, heptafluoropropyl, and perfluoroheptyl isocyanates (**5a–c**) were prepared by this method. Pyrolysis at lower tempertures gave incomplete conversions.

Our first attempts to prepare **5a** by the pyrolysis of **1a** were highly successful, but a later attempt resulted in a forceful explosion when the remaining (ca. 20 g) unpyrolyzed **1a** contained in a glass dropping funnel (25 °C) detonated. Subsequently, we found that an electrically heated wire will cause an unconfined sample of **1a** to detonate. A sample of **1a** contained in a sealed stainless steel tube also detonated when heated rapidly to 220 °C, but it was not sensitive to mechanical shock.

1,3,4-Dioxazol-2-ones that contain larger perfluoroalkyl substituents apparently are safer to handle. A hot wire failed to initiate a propagating decomposition (detonation) of **1b**. Nonetheless, **1b** cannot be considered safe, for in a subsequent preparation, it detonated while being distilled at atmospheric pressure.

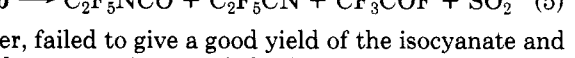
Our conclusions are that cyclic carbonates of hydroxamic acids (1,3,4-dioxazol-2-ones) can be pyrolyzed under certain conditions to give high yields of isocyanates, but the process is hazardous and offers no advantage over the pyrolysis of acyl azides.

In related work, several cyclic sulfites **6** were prepared by the reaction of perfluoroaliphatic hydroxamic acids with thionyl chloride (eq 4). Pyrolysis of sulfite **6b** (eq 5),



(4)

6a, $R_f = CF_3$
b, $R_f = C_2F_5$
c, $R_f = CF_2CF_2CF_3$



(5)

however, failed to give a good yield of the isocyanate and instead gave a mixture of the isocyanate, pentafluoropropionitrile, and trifluoroacetyl fluoride.

A bicyclic phosphorane (**7**) was also prepared from trifluoroacetohydroxamic acid and phosphorous penta-

† Contribution No. 3237.

(1) Barr, D. A.; Haszeldine, R. N. *J. Chem. Soc.* **1956**, 3428. Sprenger, G. H.; Wright, K. J.; Shreeve, J. M. *Inorg. Chem.* **1973**, *12*, 2890.
(2) Eibler, E.; Sauer, J. *Tetrahedron Lett.* **1974**, 2565. These authors report low yields of arylisocyanates by the pyrolysis of 5-aryl-1,3,4-dioxazol-2-ones in dimethyl sulfoxide.

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