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Synthesis and Reactions of Some New Sulfur Transfer Reagents[1]

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Abstract: Six new azole sulfur transfer reagents have been prepared from their trimethylsilyl derivatives and S_xCl_2 (x = 1, 2) The reactions of these reagents are different from those of SCl_2 or the corresponding phthalimide reagent with thiols, amines, and alcohols. A possible mechanism is discussed. Of particular interest is the facile, high-yield formation of sultines **21** and **22** with the monosulfur azole reagent, *N,N'*-thiobisbenzimidazole (**6a**).

Introduction

Sulfur di- and monochloride (**1a,b**) have been known since the late 1800s[2] and employed as valuable synthetic reagents

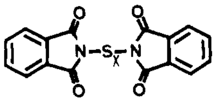
SCl_2 S_2Cl_2

1a 1b

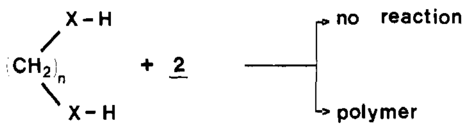
for a wide range of purposes. Possessing two leaving groups, they allow the formation of both ring and special polymer chains under the appropriate conditions. However, several features considerably limit the utility and effectiveness of these reagents: they are both liquids of a disagreeable odor and are unstable due to disproportionation.[3] Even a minimal procedure involves one or more distillations prior to use.[4]

$$SCl_2 \rightleftharpoons S_2Cl_2 \rightleftharpoons S_3Cl_2 \rightleftharpoons S_nCl_2 + S_8 + Cl_2$$

The crystalline, phthalimide-blocked sulfur-transfer analogues (**2a,b**) have been investigated in our[5] and other laboratories.[6] While they possess several improved features compared with the sulfur halides, we have observed that a number of bifunctional reagents **3**, when treated with **2**, either formed intractable polymers or simply did not react. It appears that in the case of the phthalimide group a price in reactivity is paid for the increased shelf stability over sulfur halides **1**.



2a, x = 1
2b, x = 2



3, n = 2,3,4
X = S, NH, NR, O

The importance of this type of reagent in synthesis has led to the present work of trying to find a workable compromise between these two properties. We report here the synthesis and some properties of a series of new sulfur-transfer reagents with nitrogen heterocycles as a leaving group.

Results

The initial approach taken to synthesize compounds **4–8** was

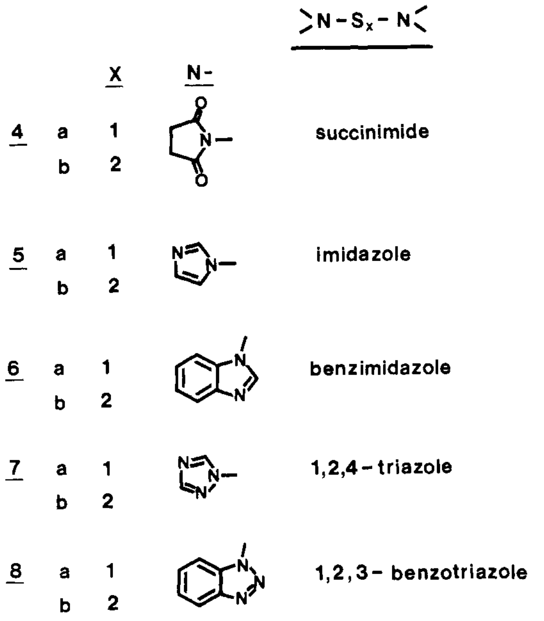


Table I. Silylated Derivatives of Azoles[a]

$(CH_3)_3Si$-	Reaction time, h	% yield	Bp, °C (mm)	Lit.[8a] bp, °C (mm)
Imidazole	16	68	92-95 (12)	91 (12)
1,2,4-Triazole	16	76	72-75 (12)	74 (12)
1,2,3-Benzotriazole[b]	16	86	136-137 (6)	

[a] These materials are highly hygroscopic. [b] Exact mass calcd ($C_9H_{13}N_3Si$), 191.0879; found, 191.0862.

essentially the same as that reported by Kalnins[7] for the preparation of the phthalimide reagents **2.** This involved treating phthalimide or its potassium salt with the sulfur halides. However, in a variety of combinations and solvents no sulfur transfer agents were isolated; only unidentifiable mixtures were formed.

A different, completely general route for the preparation of **4-8** has been worked out in detail. It involves the reaction of the trimethylsilyl derivatives of nitrogen heterocycles with either **1a** or **1b.** The silylated precursors (Table I) were synthesized by reaction of the imide or azole with hexamethyldisilazane (HMDS).[8a]

$$(CH_3)_3SiNHSi(CH_3)_3 + HN{<} \rightarrow$$

$$(CH_3)_3SiN{<} \xrightarrow[x=1,2]{S_xCl_2} {>}NS_xN{<} + (CH_3)_3SiCl$$

The synthesis of **4-8** via the silylated intermediate and sulfur halides **1** has the advantage not only of high yields of clean products, but also of easy monitoring by ^1H NMR spectroscopy by disappearance of the singlet due to the *N*-trimethylsilyl group, in favor of the singlet of chlorotrimethylsilane. In addition, this product is a liquid of low boiling point (58 °C) and is easily removed from the reaction. The products **4-8** may be used as isolated from the reaction mixture and do not require further purification.

Evidence of this derives from the reaction of **2** and **4-8** with benzyl mercaptan to give the tri- or tetrasulfide derivative. The imide compounds **2** and **4** give mixtures of polysulfides when treated with 2 mol of benzyl mercaptan. However, in sharp contrast, the azole agents **5-8** provide analytically pure samples of the corresponding tri- or tetrasulfide in near-quantitative yield (92-100%, Tables II, III).

$$2\ RSH + {>}N{-}S_x{-}N{<} \longrightarrow R{-}S{-}S_x{-}S{-}R + 2\ H{-}N{<}$$

x = 1, 2 **9** x = 1

10 x = 2

Recently, the utility of *N,N'*-thiobisphthalimide (**2a**) was demonstrated in the small-scale synthesis of dimethyl-d_6 trisulfide.[5a] The isolated yield based on the sulfur transfer reagent was 21%; however, a 3-equiv excess of the expensive precursor to the deuterated mercaptan was found to be necessary, so that the effective yield was only 7%. Repetition of the procedure using stoichiometric amounts of the deuterated precursor and *N,N'*-thiobisbenzimidazole (**6a**) as the sulfur transfer reagent, without imidazole as catalyst, resulted in a significantly higher isolated yield (40 vs. 7%).[10]

Preliminary results in several reactions of the azole sulfur-transfer reagents further attest to their unique features in contrast with halides **1** and the imide derivatives **2** and **4.**[11]

Table II

$$2C_6H_5CH_2SH + {>}N{-}S{-}N{<} \xrightarrow{C_6H_6} C_6H_5CH_2S_3CH_2C_6H_5 + 2\,{>}NH$$

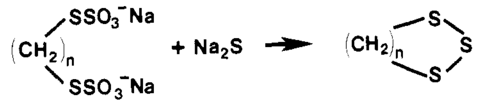
>N-S-N<	Reaction time, h	Temp, °C	% yield	% excess reagent
Phthalimide (**2a**)	1.8	Reflux	27	Nil
Succinimide (**4a**)	2.5	50	84	10
1,2,3-Benzotriazole (**8a**)	1.3	25	86	10
Benzimidazole (**6a**)	0.5	25	~100	5
1,2,4-Triazole (**7a**)	0.1	25	~100	Nil

Table III

$$2C_6H_5CH_2SH + {>}N{-}S{-}S{-}N{<} \xrightarrow{C_6H_6} C_6H_5CH_2S_4CH_2C_6H_5 + 2\,{>}NH$$

Reagent	Temp, °C	Time, h	% yield	% excess reagent
Phthalimide (**2b**)	Reflux	2	*a*	Nil
	25	16	*a*	Nil
Succinimide (**4b**)	50	2.5	*a*	10
1,2,3-Benzotriazole (**8b**)	25	1.0	92[b]	10
Benzimidazole (**6b**)	25	0.75	~100[b]	5

[a] Product was an oil and NMR spectra showed it to be a mixture of mono-, di-, tri-, and tetrasulfide with tetrasulfide being the major component. This oil had a strong smell of H_2S and could not be induced to crystallize. Chromatographic separation of the sulfides was not possible because of the similar mobilities of the polysulfides in a variety of solvents tried. [b] This product was also isolated as an oil but was easily induced to crystallize from absolute ethanol/hexanes to give the reported yields, with no trace of H_2S (smell) evident. Yellow-white crystals, mp 52-53 °C (lit.[28] 52.5-53 °C). Exact mass calcd ($C_{14}H_{14}S_4$), 309.9978; found, 309.9952.



11 **12**

One of the most common methods of synthesizing cyclic polysulfides is that developed by Swan and co-workers.[12] They treated Bunte salts of the form **11** with Na_2S to obtain the cyclic derivatives **12.** This approach has rather limited synthetic value owing to the difficulty of forming the Bunte salts and of obtaining pure Na_2S; the latter compound is highly hygroscopic[13] and often contaminated with polysulfides of the form Na_2S_x. Swan[12a] attempted to synthesize sulfides **13-15**

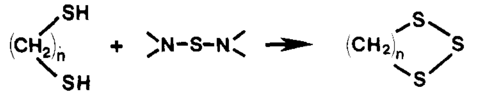
13

14

15

and reported only limited success with **14.** In our hands, attempts directed toward the synthesis of these small cyclic trisulfides have not been successful.[14-16]

Treatment of the dithiol precursors **16, 17,** and **18** with



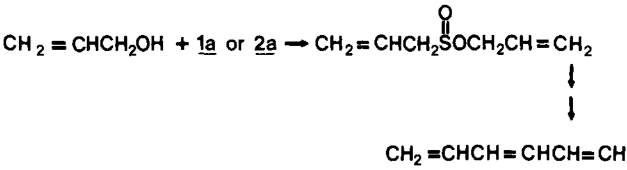
16 n = 2 **13** n = 2

17 n = 3 **14** n = 3

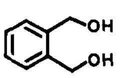
18 n = 4 **15** n = 4

N,N'-thiobisimidazole (**5a**) or *N,N'*-thiobis-1,2,4-triazole (**7a**) yielded the following results. Polymer was formed from **16**, a mixture of polymer and monomer from **17**; and, unlike Swan's results, vacuum sublimation of crude **14** gave a decomposed brownish-black tar. A white, crystalline solid was obtained for **15**, whose ^{1}H NMR spectrum compared favorably with that reported;[15b] however, vapor pressure osmometric molecular weight determinations indicate it to be a low molecular weight polymer.[16]

Some allylic alcohols have recently been shown to react with the phthalimide reagent **2a** as well as with SCl_2 (**1a**) to give sulfinate esters via allylic rearrangement.[6] This reaction forms the basis for a useful olefin synthesis. We felt that benzylic alcohols, and in particular diols **19** and **20**, might be induced to rearrange to sultines **21** and **22**,[17] respectively, when similarly treated.



$$CH_2{=}CHCH_2OH + \mathbf{1a}\text{ or }\mathbf{2a} \rightarrow CH_2{=}CHCH_2\overset{O}{\overset{\|}{S}}OCH_2CH{=}CH_2 \downarrow CH_2{=}CHCH{=}CHCH{=}CH_2$$



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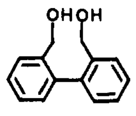

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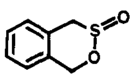

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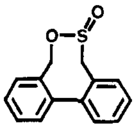


22

In each case there was no reaction with phthalimide reagent **2a**, and while a reaction took place between both **19** and **20** and SCl_2 (**1a**), no trace of sultine **21** or **22** could be isolated or detected spectroscopically. Reaction of **19** with **1a** gave considerable quantities of elemental sulfur; the major product isolated was 2-chloromethyl benzyl alcohol.

In sharp contrast to these results, near-quantitative yields of sultines **21** and **22** were obtained when **19** and **20** were treated with either azole reagents **5a** or **6a**. Sultine **21** had previously been synthesized by Durst[18] by an elegant, completely different procedure requiring several steps. A variety of alcohols react with *N,N'*-thiobisbenzimidazole (**6a**) to yield sulfinate esters and sultines; this reaction will be discussed in a separate article.

Discussion

Order of Reactivity of the Sulfur Transfer Reagents. The reagents were assessed for reactivity toward nucleophiles by following the consumption of starting material on TLC for similar reactions with certain nucleophiles. A qualitative order of reactivity toward nucleophiles is summarized as follows.

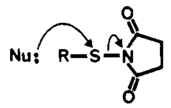
	imidazole		1,2,4-triazole		benzimidazole		1,2,3-benzotriazole		succinimide		phthalimide
		≥		>		≥		>		>	
pK_a	6.95		2.27		5.53		1.6		9.5		8.3[19]
pK_b	14.52		10.26		12.78		8.64				
	5a,b		**7a,b**		**6a,b**		**8a,b**		**4a,b**		**2a,b**

In each case the dithio reagent was more reactive than the thio analogue. However, the shelf stability of the reagents follows the reverse order. For example, although the imidazole reagents are very reactive, they are also highly hygroscopic and have a shelf life of only a few weeks, even in a desiccator. The triazole reagents can be stored this way with very little decomposition. In the absence of excessive humidity, the benzimidazole reagents are very stable and also have been found to be sufficiently reactive toward nucleophiles to make them the reagents of choice.

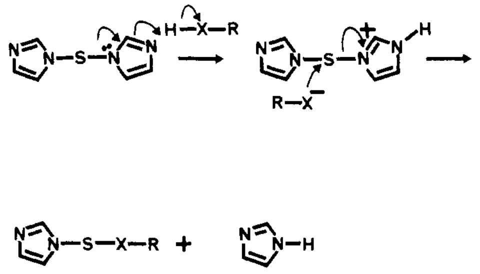
However, the very fact that these reagents are highly reactive precludes their use for unsymmetrical substitution (vide supra). Thus *N,N'*-thiobisphthalimide is still a very useful reagent for this purpose.[5c]

Originally it was thought that the phthalimide reagents should be the most reactive because of the leaving ability of the phthalimide group (i.e., its capacity to support a negative charge). These reagents, in fact, have been found to be the least reactive in various nucleophilic reactions, perhaps because the first step in a transfer reaction is not a nucleophilic displacement as initially postulated[5] (eq 1), but rather a protonation (eq 2). In this situation the leaving group is a neutral species.

Eq. 1



Eq. 2



The order of reactivity would roughly follow the order of the pK_a of the *conjugate acids* of the azoles **5a–8a.** Thus, imidazole would be the best neutral leaving group and 1,2,3-benzotriazole the worst. Although the pK_as of the conjugate acid of benzimidazole and triazole are inconsistent with the reactivity order, it is possible to rationalize[20] this anomaly and the actual order of reactivity can be qualitatively accounted for.

All of the sulfur-transfer reagents described (**2–8**) are reactive toward functional groups of the type R-X-H where X is O, S, NR, or NH. The same synthetic approach (trimethylsilyl intermediate) has also been used successfully to synthesize the corresponding -SO-, $-SO_2-$, P, P=O, -CO-, and -CS- analogues, and their synthetic utility is currently being investigated.

Experimental Section

Chemical reagents were of commercial grade and were used without prior purification unless otherwise stated. Hexamethyldisilazane was obtained from Silar Laboratories Inc., Scotia, N.Y. Melting points were obtained on a Gallenkamp block apparatus and are uncorrected; similarly, all boiling points recorded are uncorrected.

Thin layer chromatography (TLC) was performed on Eastman chromogram sheets containing a fluorescent indicator and the solvent system used is specified. All infrared spectra were recorded on a Perkin-Elmer Model 257 grating spectrophotometer calibrated on the 1602-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance spectra were obtained through the use of a Varian T-60 instrument. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane used as an internal standard. Abbreviations used to indicate the type of splitting are as follows: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet.

High- or low-resolution mass spectra were recorded on a Model AEI-MS-902 spectrometer using a direct insertion probe with an ionization potential of 70 eV. Use of high-resolution mass spectrometry for elemental composition was carried out with the aid of a computer according to the best fits of the measured masses. Where the mass spectrum is given, only the eight most intense peaks are listed, with the relative intensity in brackets. In some, only the M^+ and base peaks are identified.

Organic microanalysis was performed by Dr. C. Daesslé of Montréal.

Purification of Sulfur Dichloride (1a) and Sulfur Monochloride (1b). Sulfur dichloride (SCl_2, **1a**) was distilled over phosphorus pentachloride (PCl_5) (0.1% by weight of SCl_2) and the fraction boiling between 55 and 70 °C (760 mm) was collected. This was then redistilled in the same manner, isolating the fraction boiling at 58–60 °C (760 mm) (lit.[4] 59 °C (760 mm)). To this, 0.01% PCl_5 by weight was added for stabilization and the dark red liquid (SCl_2) was stored in the freezer.

Sulfur monochloride (S_2Cl_2, **1b**) was purified by the method described by Fieser.[4] This red-yellow liquid was also stored in the freezer.

Preparation of *N,N'*-Thio- and *N,N'*-Dithiobisphthalimide (2a,b). *N,N'*-Thio- and -dithiobisphthalimide (**2a,b**) were prepared as described by Kalnins[7] with minor modifications. Crystallization of these two products was found to be facilitated by the addition of methanol, which increased their solubility in chloroform. If potassium phthalimide is used in the preparation, distilled water can be used to remove the salts, since the reagents are water stable and insoluble. Preparation of **2a** in DMF with S_2Cl_2 requires the special precaution of the *complete* removal of DMF by vacuum drying prior to recrystallization of the crude material. Yields averaged to about 80% for both reagents to give **2a**, mp 315–318 °C, and **2b**, mp 226–229 °C (lit.[7] **2a**, mp 315–317 °C, and **2b**, mp 228–230 °C).

Attempted Preparation of *N,N'*-Thio- and -Dithiobissuccinimide (4a,b) by Variations of the Procedure Used for the Phthalimide Reagents. The attempted preparation of **4a** and **4b** by treating the imide or its sodium or potassium salt with sulfur dichloride or sulfur monochloride in either petroleum ether, benzene, or chloroform, with or without triethylamine as an acid scavenger in the case of the imide, at room or reflux temperature, failed to give the target compounds. Also, treatment of the imide or its salt in dimethylformamide (DMF) with sulfur monochloride did not give **4a**.

In all cases the predominant product obtained was succinimide, identified by infrared and mixture melting point. Various side products were also formed, none of which had the expected properties of the sulfur transfer reagents.

Preparation of the Trimethylsilyl Precursors. *N*-Trimethylsilylsuccinimide. A 1000-mL three-necked flask equipped with a mechanical stirrer was charged with 198 g (2.0 mol) of succinimide, 242 g (1.5 mol) of hexamethyldisilazane, and 1–2% (2.0–3.0 g) of imidazole (based on grams of succinimide). The mixture was gently refluxed for 12 h using a condenser equipped with a mercury seal. A gentle stream of dry nitrogen gas bubbled through the reaction mixture helped to expel the ammonia produced and maintained the system under anhydrous conditions.

The reaction mixture was filtered to remove any residual solid, and distilled; the fraction boiling at 97–98 °C (4 mm) or 112–114 °C (12 mm) (265 g, 77%) was collected and stored under dry nitrogen (lit.[8b] bp 120 °C (18 mm)). Omission of imidazole in the reaction mixture lowered the average yield to about 32%. NMR (neat) δ 0.35 (s, 9 H), 2.59 (s, 4 H); MS *m/e* 171 (M^+), 156 (base peak); IR (film) 1765, 1695 (s) (C=O), 1330 (s), 1255 (s), 1170 (s), 855 cm^{-1} (s).

***N*-Trimethylsilylphthalimide.** In a manner similar to the previous reaction, 36.8 g (0.25 mol) of phthalimide, 81 g (0.5 mol) of hexamethyldisilazane (HMDS), and 2.0 g of imidazole were refluxed for 2 days. Volatile material was then evaporated under reduced pressure and the residue recrystallized in benzene to give 46.8 g (85%) of a white, crystalline solid which was highly hygroscopic, mp 68–70 °C (lit.[9] 65–67 °C). Silylation did not occur without imidazole. Exact mass measurement: calcd ($C_{11}H_{13}NO_2Si$) 219.0715; found, 219.0702.

The remaining silylated precursors to the sulfur transfer reagents were prepared as described by Birkofer and Richter.[8a] Therefore, only the procedure for benzimidazole is reproduced here and the others are summarized in Table I. 1-Trimethylsilyl-1,2,3-benzotriazole was not found in the literature, but nevertheless was silylated in the same fashion. Care must be taken in its distillation because the parent compound has been known to explode during vacuum distillation.[23a]

1-Trimethylsilylbenzimidazole. To a 1000-mL three-necked flask, 118 g (1.0 mol) of benzimidazole and 121 g (0.75 mol) of HMDS were added and the mixture was refluxed while stirring. This was continued until the solid dissolved (about 10 h) and followed by an additional 2 h. Excess HMDS was removed by vacuum distillation at room temperature, leaving behind a white solid which was vacuum distilled using a warmed condenser to yield 139 g (73%) of a liquid with bp 155 °C (4 mm) (lit.[8a] 112 °C (0.3 mm)). Upon standing the liquid crystallized to a white solid with mp 60–65 °C (lit.[8a] 66–67 °C). This solid was crushed to a fine, white powder in a dry nitrogen bag and stored under dry nitrogen. Exact mass measurement: calcd ($C_{10}H_{14}N_2Si$), 190.0926; found, 190.0912.

Preparation of the Sulfur Transfer Reagents via the Silylated Precursor. Although the reagents are all prepared similarly, small changes in the procedure for each one makes the difference between an almost analytically pure compound in quantitative yield and an impure product in lower yield. Obtaining nearly pure "crude" reagents in this way is highly desirable because their reactivity and/or hygroscopicity appear to contribute to extensive decomposition upon recrystallization.

Preparation of *N,N'*-Thio- and -Dithiobissuccinimide (4a,b). A 1000-mL three-necked flask equipped with an efficient stirrer (preferably mechanical), a reflux condenser with a drying tube, and a pressure-equilibrated dropping funnel was charged with 85.5 g (0.5 mol) of the silylated imide in 200 mL of benzene or carbon tetrachloride under a dry nitrogen atmosphere. To this, 26 g (0.25 mol) of SCl_2 or 34 g (0.25 mol) of S_2Cl_2 in 200 mL of the same solvent was added dropwise over a period of 4 h. After the addition of the chlorosulfane, the reaction was gently heated on an oil bath set at 60–65 °C (55–60 °C reaction temperature). This temperature is critical for the preparation of **4b**. The reaction was followed by NMR until no more starting material (silylated imide) remained (about 24 h for **4a** and 36 h for **4b**). Following this, the precipitate was filtered off and restirred in 200 mL of fresh benzene. This step was repeated once more and the solid filtered and dried to yield 55 g (96%) of **4a**, mp 195–205 °C, a light yellow solid, or 64 g (100%) of **4b**, mp 140–160 °C, also as a light yellow solid. Recrystallization of **4a** or **4b** in CH_2Cl_2/hexanes led to extensive decomposition; however, it was possible to obtain a white, crystalline solid for **4a**, mp 205–207 °C, and the same for **4b**, mp 190–193 °C (lit.[11] 189–190 °C). IR (KBr) of **4a** (identical with that of crude **4a**) 1730 (s), 1305 (s), 1267 (s), 1240 (s), 1228 (s), 1210 (s), and 1120 cm^{-1} (s); MS *m/e* (rel intensity) 228 (29, M^+), 100 (27), 99 (53), 98 (12), 70 (15), 64 (24), 56 (56), 55 (100). IR (KBr) of **4b** (identical with that of crude **4b**)[11] 1720 (s), 1295 (s), 1280 (s), 1235 (s), 1145 (s), and 1132 cm^{-1} (s); MS *m/e* (rel intensity) 260 (9, M^+), 100 (90), 70 (17), 64 (70), 56 (100), 55 (43), 44 (17), 43 (17), 42 (17). Anal. ($C_8H_8N_2O_4S$) C, H, N, S. ($C_8H_8N_2O_4S_2$) C, H, N, S.

Preparation of 1,1'-Thio- and -Dithiobis(imidazole/1,2,4-triazole) (5a/5b and 7a/7b). Note: These reagents are highly hygroscopic and must therefore be kept under strictly anhydrous conditions at all times.

A 1000-mL three-necked flask, equipped with a pressure-equilibrated dropping funnel, was charged with 70 g (0.5 mol) of *N*-trimethylsilylimidazole or 70.5 g (0.5 mol) of *N*-trimethylsilyl-1,2,4-triazole in 200 mL of carbon tetrachloride. To this, 26 g (0.25 mol) of SCl_2 or 34 g (0.25 mol) of S_2Cl_2 in 200 mL of the same solvent were added dropwise with good stirring over a period of 3 h. Within 0.5 h a white precipitate began to form. Upon complete addition of the chlorosulfane the reaction was allowed to continue with stirring for an additional 2 h. At this point, if the reaction mixture appears clean (colorless supernate and white precipitate) the solvent need only be evaporated under N_2 followed by high vacuum to remove the last traces. If, however, the reagent appears to be discolored, it is best to filter and wash the precipitate with hexanes under anhydrous conditions, followed by vacuum drying. The reagents decompose within a few minutes upon exposure to the atmosphere, particularly **5a** and **5b**, so that purification by crystallization is not practical, nor was it found to be necessary (vide supra) for these or any of the other reagents except the phthalimide derivatives. The reaction can also be carried out in benzene at a slight sacrifice in yield and quality of reagent. Yield based on crude material was virtually quantitative. Without further purification the following results were obtained: **5a**, mp 112–118 °C dec (sealed tube) (lit.[8a] 110–111 °C). Exact mass calcd ($C_6H_6N_4S$), 166.0313; found, 166.0316. **5b**, mp 81–86 °C dec (sealed tube) (lit.[24] 91–92 °C). These compounds decompose even in a desiccator within a few weeks. **7a**, mp 146–150 °C. Exact mass calcd ($C_4H_4N_6S$), 168.0218; found, 168.0232.[25] **7b**, mp 125–128 °C dec (sealed tube). Exact mass calcd ($C_{H_4}N_6S_2$), 199.9939; found, 199.9952.

Preparation of 1,1'-Thio- and -Dithiobisbenzimidazole/1,2,3-Benzotriazole (6a/6b and 8a/8b). Note: The silylated azoles are highly hygroscopic, so appropriate precautions should be taken.

A 1000-mL three-necked flask equipped with a dropping funnel and a mechanical stirrer was charged with 95 g (0.5 mol) of trimethylsilylbenzimidazole or 95.5 g (0.5 mol) of trimethylsilylbenzotriazole in 300 mL of CCl_4 under a dry nitrogen atmosphere. To this, 26 g (0.25 mol) of SCl_2 or 34 g (0.25 mol) of S_2Cl_2 in 200 mL of

CCl_4 were added dropwise over 5 h with vigorous stirring. Immediate reaction was shown by the disappearance of the colored chlorosulfane as it was added. For the benzimidazole reagents a snow-white precipitate formed within a few minutes. In the case of benzotriazole the reagent precipitates as a white solid within 0.5 h. Slow addition of the chlorosulfane is critical for the final purity of these reagents. Upon complete addition, the reaction mixture was stirred for 0.5 h, followed by addition of 200 mL of hexanes and stirring for an additional 1 h. The reaction mixture was then filtered quickly under suction, but not to dryness. The "solvent wet" reagent was then washed by stirring in 500 mL of fresh hexanes under N_2 for 0.3 h. The washing procedure was repeated twice more; then the reagent was finally dried in a desiccator at 60 °C (5 mmHg). In each case the yield was essentially quantitative: **6a** crude mp 180–185 dec, 184–186 dec, 187–190 °C dec (depending on purity of the starting material) recrystallized from CH_2Cl_2/hexanes 187–190 °C dec; **6b** crude mp 138–145, 147–152 °C dec, recrystallized (CH_2Cl_2/hexanes) 168–172 °C dec; **8a** crude mp 210–213 °C dec, recrystallized (CH_2Cl_2/hexanes) 215–216 °C dec; and **8b,** a white solid which readily yellowed when exposed to a moist atmosphere and would not lend itself to recrystallization, mp 150–155 °C dec. IR (KBr) **6a** 1492 (s), 1473 (s), 1438 (s), 1248 (s), 1155 (s), 1125 (s), 750 (s); **6b** 1485 (s), 1471 (s), 1439 (s), 1255 (s), 1192 (s), 1185 (s), 1165 (s), 1138 (s), 778 (s), 766 (s), 751 (s); **8a** 782 (s), 760 (s); **8b** 1305 (s), 1272 (s), 958 (s), 942 (s), 788 (s), 749 cm^{-1} (s). MS *m/e* (rel intensity) **6a** 266 (23, M^+), 160 (9), 149 (66), 119 (43), 118 (100), 117 (17), 91 (77), 90 (45); **6b** 298 (30, M^+), 119 (65), 118 (75), 91 (60), 90 (60), 64 (100), 63 (65), 45 (60), 39 (60); **8a** 268 (M^+), (base peak) 119; **8b** 300 (M^+), (base peak) 64.

It is recommended that no further purification of the reagents be attempted owing to excessive losses of the compound. The reagents (0–5% excess) can be used as isolated and afford derivatives in very high yields (vide supra). Because of decomposition during recrystallization, organic analysis was performed on the reagent as isolated from the reaction mixture. Anal. Calcd for $C_{14}H_{10}N_4S$ (**6a**): C, 63.16; H, 3.76; N, 21.05; S, 12.04. Found: C, 62.05; H, 3.88; N, 20.70; S, 12.10.[25] Calcd for $C_{14}H_{10}N_4S_2$ (**6b**): S, 21.50. Found: S, 20.47.[25] Calcd for $C_{12}H_8N_6S$ (**8a**): S, 11.95. Found: S, 12.42.[25] Exact mass calcd for $C_{12}H_8N_6S_2$ (**8b**), 300.0252; found, 300.0249.[25]

Note: The reagents were synthesized in several solvents such as hexanes, CCl_4, C_6H_6, and $CHCl_3$. While the reaction proceeded fastest in hexane, and indeed exothermically in contrast to the CCl_4-solvated reaction, the reagent so obtained was of poor quality and tended to decompose more easily.

Attempts to treat benzimidazole with SCl_2 or S_2Cl_2 did not provide the respective reagents.

This set of four reagents has been found to be very good for overall reactivity and stability; the benzimidazole series is preferable. Another advantage of these reagents lies in the difference in solubility properties of benzimidazole and benzotriazole. If the desired product is very soluble in the common organic solvents, the benzimidazole product is sometimes simply filtered off. If the product is fairly insoluble, the benzotriazole reagents would offer the reverse effect.

Reactions with the Reagents. Reaction of a 1:1 Mole Ratio of Benzyl Mercaptan with the Reagent. The same procedure was followed for all the thio reagents, so that only the reaction of benzyl mercaptan with *N,N'*-thiobisphthalimide (**2b**) is described.

Preparation of *N*-(Benzyldithio)phthalimide. To a slurry of 6.5 g (0.02 mol) of **2a** in 100 mL of benzene, 2.5 g (0.02 mol) of benzyl mercaptan was added dropwise (0.5 h) with stirring. The reaction was then heated to 50 °C (oil bath) and followed by TLC (hexanes) until no more starting thiol was evident (ca. 3 h). The reaction mixture was then allowed to cool to room temperature and insoluble material was filtered and washed with benzene to give 3.0 g (100%) of a white solid identified by mp 232–236 °C (lit.[23b] 238 °C) and infrared spectrum as phthalimide. The filtrate was then evaporated to give a yellow solid, 5.7 g (mp 110–120 °C). Recrystallization of this in absolute ethanol gave 4.5 g of first crop and 1.0 g of second crop for a total of 5.5 g (92%) yield of the white, crystalline product, mp 133–135 °C (lit.[26] 133.5–135 °C). Anal. ($C_{15}H_{11}NO_2S_2$) C, H, N, S.

A 1:1 mole ratio of benzyl mercaptan and the reagents *N,N'*-thiobissuccinimide (**4a**), 1,1'-thiobisbenzimidazole (**6a**), and 1,1'-thiobisbenzotriazole (**8a**) proceeded to give only dibenzyl trisulfide (observed by TLC, NMR, and IR) as an oil. Inducing crystallization of this oil from ethanol/hexanes was very difficult owing to the presence of unreacted and decomposed sulfur transfer reagent. Thus, the reactions were repeated using a 2:1 mole ratio of mercaptan to crude reagent. Excess reagent (0–10%, depending on the purity of the crude reagent) was used to ensure complete consumption of the thiol. Table II summarizes the results. Anal. ($C_{14}H_{14}S_3$) C, H, S.

Similar treatment of a 1:1 mole ratio of benzyl mercaptan and the dithio reagents **2b, 4b, 6b,** and **8b** presented similar problems in product isolation; thus a 2:1 mole ratio of mercaptan and reagent was employed. All the dithio reagents proceeded to disubstitution, regardless of the mole ratio of mercaptan/reagent used. Table III summarizes the results.

Preparation of Dimethyl-d_6 Trisulfide ($CD_3S_3CD_3$). The procedure followed was essentially the same as that reported in the literature,[5a] except that imidazole was not used as catalyst and reagent **6a** was employed instead of **2a.** Thus 3.6 g (10.3 mmol) of methyl isothiourea sulfate-*S*-d_6, treated with 2.7 g (10.3 mmol) of **6a,** yielded 1.1 g of crude trisulfide which was distilled to give 530 mg (40%) of the pure dimethyl-d_6 trisulfide. Analyses (Raman, TLC) of the crude and distilled trisulfide were identical and showed no di- or polysulfides. In addition, a quantitative yield (2.5 g) of benzimidazole was recovered, indicating complete consumption of the sulfur transfer reagent.

Reaction of 1,4-Butanedithiol with 1,1'-Thiobis-1,2,4-triazole (7a). To a suspension of 3.36 g (0.02 mol) of reagent **7a** in 60 mL of benzene under a nitrogen atmosphere, a solution of 2.44 g (0.02 mol) of the dithiol in 40 mL of benzene was added dropwise over a period of 3 h with stirring. Upon complete addition, the mixture was stirred for an additional 3 h, then filtered to remove precipitated triazole (2.7 g). The filtrate was concentrated to yield 3.5 g of a light-green, unpleasant-smelling, slightly viscous oil. To this, 10 mL of CH_2Cl_2 was added and the solution placed in the freezer (−15 °C) overnight. Filtration of the resulting granular crystals and washing with cold hexane afforded 2.75 g (90%) of a compound having mp 48–50 °C; ^1H NMR ($CDCl_3$) δ 1.95 (t, unsym, 4 H), 3.0 (t, unsym, 4 H); 100-MHz ^1H NMR showed the spectrum to actually be two multiplets. ^{13}C NMR (^1H decoupled) showed two sharp peaks of equal intensity at 27.53 and 38.23 ppm from Me_4Si. IR (KBr) 2930 (s), 2910 (s), 2890 (s), 1442 (s), 1439 (s), 1429 (s), 1405 (s), 1295 (s), and 1275 cm^{-1} (s). Exact mass calcd ($C_4H_8S_3$), 151.9788; found, 151.9772. Anal. ($C_4H_8S_3$) C, H, S. Molecular weight (osmometric) required 304; found 1390.

Similar results were obtained by substituting *N,N'*-thiobisbenzimidazole as the sulfur transfer reagent. The compound obtained in both instances had an R_f of 0.7 (C_6H_6) and 0.3 (hexane). However, attempted chromatographic purification over silica resulted in H_2S being liberated (smell, $Pb(OAc)_2$) without any observed mobility. Recovery was accomplished by emptying the column, extracting with warm $CHCl_3$, and filtering to remove the silica. Removal of the solvent under vacuum yielded a yellow rubber whose ^1H and ^{13}C NMR (complex multiplets, ^1H NMR and several peaks, ^{13}C NMR) indicated extensive polymerization. Thus, the low molecular weight polymer having mp 48–50 °C could only be obtained through crystallization as described above. For this reason reagent **7a** proved to be the better choice.

Reaction of 1,2-Ethanedithiol with 1,1'-Thiobisimidazole (5a). To 3.2 g (0.02 mol) of the reagent in 300 mL of CCl_4, 1.88 g (0.02 mol) of the dithiol (**11,** n = 2) in 100 mL of CCl_4 was added dropwise over 3 h with stirring. A white precipitate began to form within a few minutes and the reaction was allowed to continue with stirring for a total of 12 h. Evaporation of the solvent and trituration of the residue with hot chloroform yielded only imidazole (melting point and IR identification). The remainder (1.8 g) was insoluble in any of the usual organic solvents, including CS_2, indicating the formation of a polymer (MS analysis). No further work was done on this residue.

Reaction of 1,3-Propanedithiol (11, n = 3) with 5a. To 3.2 g (0.02 mol) of the reagent **5a** in 200 mL of CCl_4, 2.16 g (0.02 mol) of the dithiol **11** (m = 3) in 100 mL of CCl_4 was added dropwise with stirring over 3 h. After an additional 1 h the reaction mixture was filtered and the solid washed with hot $CHCl_3$. The filtrate and washings were combined and flash evaporated until no more volatile material was present. This left a greenish-yellow liquid which rapidly solidified to a white solid. The solid dissolved in hot $CHCl_3$ but would quickly precipitate to give a white solid of 2.2 g (80%), mp 66–68 °C (lit.[12a] for the trisulfide 44 °C). Mass spectrometry indicated a strong peak at *m/e* 106 and a molecular ion at *m/e* 138. The infrared spectrum did not show the presence of imidazole. Attempts to crystallize the material would only yield the same product (IR) and an increase and broadening of the melting range, suggesting a higher degree of polymerization. Attempts to purify by vacuum sublimation following Swan's method[12a] only led to a decomposed product. Satisfactory combustion analysis could not be obtained.

Attempted Preparation of 1,4-Epidithiopiperazine (24). This reaction was attempted in benzene and chloroform, at room temperature or reflux temperature, with imidazole but no characterizable products were obtained. Similar results were obtained with S_2Cl_2/Et_3N and with *N,N'*-dithiobissuccinimide (**4b**).

Reaction of Piperazine with 1,1'-Dithiobisimidazole (5b). This reaction was carried out in the same way as with *N,N'*-dithiobissuccinimide (**4b**), except that **5b**, being highly hygroscopic and quick to decompose, was used in 20% excess. Workup in a similar fashion gave a near-quantitative yield (based on piperazine) of a compound with mp 211-212 °C dec which was completely insoluble in all the common organic solvents; an attempt to take its Raman spectrum led to rapid decomposition in the beam. IR (KBr) 1440 (s), 1349 (s), 1252 (s), 943 (s), and 695 cm^{-1} (s). Anal. ($C_4H_8N_2S_2$) C, H, N, S.

Synthesis of Sultine 21. To a suspension of 8.0 g (0.03 mol) of **6a** in 100 mL of CCl_4, 4.14 g (0.03 mol) of benzenedimethanol (**19**) was added and the mixture stirred. The reaction was monitored by the formation of a singlet at δ 5.42 in the NMR (presumably due to the benzylic protons of the sulfoxylate intermediate). After 34 h the two AB quartets of the sultine appeared at the expense of the singlet at δ 5.42. Total conversion was found to take about 10 days (only the sulfoxylate and the sultine are soluble in CCl_4). Upon complete conversion, the benzimidazole (8.5 g, quantitative) was collected and the filtrate flash evaporated at 25 °C to leave 5.4 g of a light yellow oil. This was subjected to high vacuum (0.1 mm at 25 °C) to leave 5.0 g (in quantitative yield, pure by NMR and IR). NMR ($CDCl_3$) δ 7.0-7.4 (m, 4 H), 4.80, 5.10 (AB, 2 H, J_{AB} = 14 Hz), 3.34, 4.16 (AB, 2 H, J_{AB} = 16 Hz). IR (film) (S=O), 1120 cm^{-1} (s). Carbon tetrachloride was found to be the best solvent for this reaction. An attempt to synthesize this sultine or sultine **22** using reagent **2a** at room temperature or at reflux led to complete recovery of the starting material.

Attempted Synthesis of 21 Using Sulfur Dichloride (1a). To a suspension of 2.76 g (0.02 mol) of the diol **19** in 50 mL of CCl_4 under dry N_2 at −15 °C (NaCl/ice bath), 2.06 g (0.02 mol) of freshly distilled **1a** in 50 mL of CCl_4 was added dropwise over 2.5 h. The only products detected were 2-chloromethyl benzyl alcohol and α,α'-dichloro-*o*-xylene.

Preparation of 2,2-Bis(hydroxymethyl)biphenyl (20). The diol was prepared as described by Rieche and co-workers,[27] except that diphenic acid was used instead of the anhydride, yield 80%, mp 110-113 °C (lit.[27] 112 °C).

Reaction of 20 with Sulfur Dichloride (1a). To a solution of 2.14 g (0.01 mol) of diol **20** in 75 mL of CH_2Cl_2, 1.24 g (0.012 mol) of SCl_2 in 75 mL of CH_2Cl_2 was added dropwise over 4 h. The reaction, which began immediately, was allowed to continue for 14 h; however, no change in composition was evident (TLC, benzene) after the addition of SCl_2. The solvent and volatile material were flash evaporated, leaving 2.5 g of a yellow oil whose ^1H NMR ($CDCl_3$ δ 5.8, s, aliphatic signal) and infrared spectrum were strong support for the formation of the sulfoxylate precursor. Attempts to persuade this material to rearrange to **22** by heating, stirring over silica in CH_2Cl_2 or ether, or addition of imidazole failed (no change in the ^1H NMR or IR spectra in favor of the sultine was observed).

Preparation of 5*H*,8*H*-Dibenzo[*d,f*]-1,2-oxathiocin 1-Oxide (22). A mixture of 12.9 g (0.06 mol) of diol **20** and 19.0 g (0.07 mol) of reagent **6a** was stirred at room temperature in 350 mL of CCl_4. After 24 h the NMR spectrum of the reaction mixture showed only sultine **22**; but the reaction mixture was allowed to stir for another 24 h to consume completely the remaining 5-10% of the diol (as detected by infrared analysis). The solid was collected to give 18.0 g (crude benzimidazole by infrared) and the filtrate was concentrated to about 50 mL under vacuum at 25 °C. Ether was added dropwise until sultine **22** began to crystallize as white needles; the mixture was cooled to 0 °C and filtered. The process was repeated by reducing the mother liquor to 25 mL to yield a total of 13.4 g (91%) of the sultine: mp 135-137 °C; MS *m/e* (rel intensity) 244 (0.06, M^+), 181 (16), 180 (100), 179 (75), 178 (36), 165 (56), 152 (14), 87 (23), 76 (15); IR (KBr) 1115 (s) (S=O), 910 (s), 905 (s), 771 (s), 765 (s), and 742 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.65, 3.88 (AB, 2 H, J_{AB} = 14 Hz), 4.45, 4.95 (AB, 2 H, J_{AB} = 13 Hz), 7.2-7.6 (m, 8 H). Anal. ($C_{14}H_{12}O_2S$) C, H, S.

Relative Reactivity of Monothio Reagents. The *N,N'*-thiobisimidazole (**5a**) and *N,N'*-1,2,4-thiobistriazole (**7a**) when treated with dithiols or benzyl mercaptan reacted almost instantaneously whereas the benzimidazole **6a** and benzotriazole **8a** reagents did so within a few minutes. The imide reagents were considerably less reactive, particularly in the case of *N,N'*-thiobisphthalimide (**2a**), which was found to be the only reagent which could be stopped at the monosubstitution stage.[5c]

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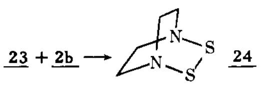
(10) The actual yield was probably even higher in that analysis (Raman, TLC) of the crude trisulfide was identical with that of product isolated after short-path distillation.

(11) J. Suzuki (private communication) has found that *N,N'*-dithiobissuccinimide **4b** reacted with many amines with which reagent **2b** would not. We attempted to prepare the bicyclic bridged disulfide by treating piperazine or its lithium salt **10** with *N,N'*-dithiobisphthalimide **2b**, only to obtain a polymer and mostly starting material. A reinvestigation of this reaction with both **2b** and **4b** was undertaken using a variety of reaction conditions and solvents. With reagent **2b** the starting material was largely recovered, with various polymeric substances as major products in addition to phthalimide. When reagent **4b** reacted totally, the products formed were insoluble and polymeric. Similarly, treatment of piperazine with sulfur monochloride led to uncharacterizable products. In contrast, when piperazine was treated with the azole reagent **5b**, two sulfur atoms were quantitatively transferred and a precipitate of a pale-yellow solid was obtained with a sharp melting point (211-212 °C), sharp infrared bands, and a combustion analysis supporting an empirical formula for **24**. This material is completely insoluble in all common organic solvents; its mass spectrum showed a strong signal for monomer and a smaller one for dimer.



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(16) More recent but preliminary results in the attempted synthesis of higher homologues (*n* = 5, 6, 8) of the series suggest that the compound is, in fact, more likely to be at least a dimer. This is clear where *n* = 6 or 8. These two crystalline compounds have sharp melting points, correct combustion analysis, and consistent IR and Raman spectra for alkyl trisulfides, as well as clean ^{13}C NMR (three peaks for *n* = 6, four for *n* = 8) ^1H NMR and mass spectra. Molecular weight determination using benzophenone or camphor resulted in monomeric molecular weights; however, the more reliable vapor pressure osmometric molecular weight determinations yielded molecular weights of 4241 and 4793, respectively (required for monomer 180 and

208, respectively). A completely independent route to the synthesis of this class of compounds was recently reported: D. N. Harpp and A. Granata, *Tetrahedron Lett.*, 3001 (1976). The cyclic trisulfide ($n = 6$) originally reported as monomeric has been shown by vapor pressure osmometric molecular weight determination to be a dimer.

(17) ^{1}H NMR and infrared evidence indicate that a cyclic sulfoxylate ester (OSO) is precursor to the sultines. Sultine **22** is a missing member of a series of bridged biphenyl molecules of current conformational interest; see N. L. Allinger, M. J. Hickey, and J. Kao, *J. Am. Chem. Soc.*, **98**, 2741 (1976); G. H. Wahl Jr., J. Bordner, D. N. Harpp, and J. G. Gleason, *Acta Crystallogr., Sect. B*, **28**, 2272 (1973); *J. Chem. Soc., Chem. Commun.*, 985 (1972).

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(20) Triazole is a smaller molecule than benzimidazole; thus solvation of the charged species by a nonpolar solvent is preferable to that of a larger one.[21a] In addition, 1,2,4-triazole is more soluble in the common organic solvents[22] making it more available to participate as a base or catalyst in the reaction. Finally, it has been pointed out[19,21] that pK_as observed in aqueous media are unlikely to be the same in other solvents, especially those with a much lower dielectric constant. The trend, however, should remain approximately the same.

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General Acid Catalyzed Breakdown of Ketone Bisulfites[1]

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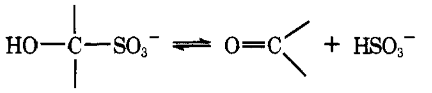
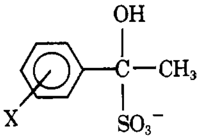
Abstract: The cleavage of 1-methoxy-1-arylethanesulfonic acids, $MeOC(Me)(Ar)SO_3^-$, at 25 °C is catalyzed by the proton and by general acids with $\alpha = 0.6$ (Ar = $MeOC_6H_4$), $k_{H^+}/k_{D^+} = 0.56$, $k_{H_2O}/k_{D_2O} = 2.2$ for catalysis by citric acid buffers, and $\rho = -2.0$ ($\rho^r = -1.0$) for catalysis by the proton. The acid catalyzed cleavage of acetophenone bisulfites, $HOC(Me)(Ar)SO_3^-$, shows similar properties with $\alpha = 0.54$ (Ar = $MeOC_6H_4$) $k_{H^+}/k_{D^+} = 0.81$, and $\rho = -1.6$ ($\rho^r = -1.0$). These similarities and the fact that the absolute rate constants for the two reaction series generally differ by less than an order of magnitude indicate that part, and probably all, of the observed reaction with the acetophenone series occurs by the same mechanism as with the *O*-methyl series, which is kinetically unambiguous. This class n mechanism involves proton donation to the leaving sulfite ion and, in the reverse direction, proton removal from bisulfite as it attacks the oxocarbonium ion $>C{=}OR^+$ (R = Me or H). It is argued that buffer catalysis is enforced in the *O*-methyl series by the diffusion-controlled reaction of SO_3^{2-}, but not water or HSO_3^-, with the oxocarbonium ion. An observed decrease in α with electron-withdrawing substituents on the acetophenone ($\alpha = 0.31$ for *p*-nitroacetophenone bisulfite) can be explained if the proton is in a potential well and motion along the reaction coordinate involves only C–S cleavage in the transition state.

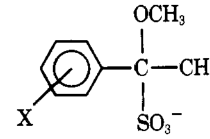
The predominant mechanism (eq 1) for the breakdown of bisulfite addition compounds of carbonyl compounds involves base catalysis with a large Brønsted β value; in the reverse direction this corresponds to the addition of sulfite dianion with modest general acid catalysis.[2] However, at low pH values this reaction pathway is slow and the breakdown of the bisulfite addition compounds of benzaldehyde[3] and *p*-methoxyacetophenone[2] has been reported to proceed through an acid catalyzed pathway. In the reverse direction this corresponds to acid catalysis of the addition of bisulfite ion to the carbonyl compound. Bisulfite ion is a very weak base and, to the best of our knowledge, there is no example of a reaction in aqueous solution involving bisulfite ion as a nucleophile. We were interested, therefore, in investigating the mechanism of acid catalysis of the addition of this weak nucleophile and of the breakdown of the addition compound. To resolve kinetically ambiguous mechanisms for general acid-base catalysis it is useful to use compounds containing a CH_3O– group as models for reactions of compounds containing an HO– group in which there is no removal of the proton from the oxygen atom in the transition state. To this end, we have studied the general acid catalyzed breakdown of substituted acetophenone bisulfites, **1**, and of the analogous 1-methoxy-1-arylethanesulfonic acids, **2**, in aqueous solution.



$$HO{-}\overset{|}{\underset{|}{C}}{-}SO_3^- \rightleftharpoons O{=}C\!\!< + HSO_3^- \qquad (1)$$



1 a, X = *p*-OCH$_3$
b, X = -H
c, X = *p*-Cl
d, X = *p*-NO$_2$



2 a, X = *p*-OCH$_3$
b, X = *p*-CH$_3$
c, X = -H
d, X = *p*-Cl
e, X = *m*-Br

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Organic acids (with the exception of reagent grade formic and acetic acids) were purified by recrystallization or distillation. Substituted acetophenones and acetophenone dimethyl ketals[4] were purified by distillation under reduced pressure or by recrystallization.

Stock solutions of the carbonyl bisulfites were prepared by dissolving a sufficient amount of the carbonyl compound in 1-4 M potassium bisulfite solution to give a final concentration of ~0.01 M and were stored at 4 °C under a nitrogen or argon atmosphere.[2] Aliquots (10-20 μL) were diluted into thermostated spectrophotometer cells containing 3.0 mL of the desired buffer solution and sufficient hydrogen peroxide (10 μL of a 31% solution) to oxidize the excess sulfite to sulfate, thereby driving the reaction to completion. Addition of excess hydrogen peroxide (or its total elimination in the case of *p*-methoxyacetophenone) gave no detectable change in the observed rate constant. The oxidation of sulfite under the conditions used was much faster than the breakdown of the ketone bisulfites, being complete in

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