(s, 2 H); IR ($CHCl_3$) 1740 (C=O), 1600 cm^{-1}; MS m/z 222 (M^+), 178 (M – CO_2). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.01; H, 6.30.

6,7-(Methylenedioxy)isochroman-3-one (22a): white needles (EtOH); mp 131–133 (lit.[2b] mp 130.5–132 °C).

4-Methyl-6,7-(methylenedioxy)isochroman-3-one (22b): white needles (EtOAc); mp 158–160 °C; ^1H NMR ($CDCl_3$) δ 1.55 (d, J = 7.0 Hz, 3 H), 3.52 (q, J = 7.0 Hz, 1 H), 5.11 (d, J = 12.0 Hz, 1 H), 5.19 (d, J = 12.0 Hz, 1 H), 5.96 (s, 2 H), 6.69 (s, 1 H), 6.74 (s, 1 H); IR ($CHCl_3$) 1740 (C=O), 1605 cm^{-1}; MS m/z 206 (M^+), 162 (M – CO_2). Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.94. Found: C, 63.98; H, 5.00.

4-(3′,4′-Dimethoxyphenyl)-6,7-(methylenedioxy)isochroman-3-one (22e): white needles (EtOAc/hexane); mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 3.85 (s, 6 H), 4.88 (s, 1 H), 5.07 (d, J = 12.0 Hz, 1 H), 5.15 (d, J = 12.0 Hz, 1 H), 5.98 (s, 2 H), 6.56 (s, 2 H), 6.72 (s, 1 H), 6.75 (s, 1 H), 6.80 (s, 1 H), 6.81 (s, 1 H); ^{13}C δ 51.02, 55.91 (2 MeO), 69.21, 101.50, 105.43, 108.41, 111.26, 111.53, 120.14, 125.40, 126.63, 127.70, 147.32, 148.27, 148.86, 149.44, 171.09; IR ($CHCl_3$) 1740 (C=O), 1605 cm^{-1}; MS m/z 328 (M^+), 284 (M – CO_2). Anal. Calcd for $C_{18}H_{16}O_6$; C, 65.85; H, 4.91. Found: C, 65.80; H, 5.01.

4-(4′-Fluorophenyl)-6,7-(methylenedioxy)isochroman-3-one (22g): white needles (EtOH); mp 119–121 °C; ^1H NMR ($CDCl_3$) δ 4.80 (s, 1 H), 5.07 (s, 2 H), 5.93 (s, 2 H), 6.46 (s, 1 H), 6.69 (s, 1 H), 7.05 (d, J = 8.0 Hz, 2 H), 7.11 (d, J = 8.0 2 H); IR ($CHCl_3$) 1730 (C=O), 1600, 1500 cm^{-1}; MS m/z 286 (M^+), 242 (M – CO_2). Anal. Calcd for $C_{16}H_{11}O_4F$; C, 67.13; H, 3.87. Found: C, 67.11; H, 3.89.

4-(3′-Fluorophenyl)-6,7-(methylenedioxy)isochroman-3-one (22h): white needles (EtOH); mp 81–82 °C; ^1H NMR ($CDCl_3$) δ 4.96 (s, 1 H), 5.24 (d, J = 12.0 Hz, 1 H), 5.32 (d, J = 12.0 Hz, 1 H), 5.91 (s, 2 H), 6.27 (s, 1 H), 6.71 (s, 1 H), 7.17–7.35 (m, 4 H); IR ($CHCl_3$) 1730 (C=O), 1600, 1590, 1490 cm^{-1}; MS m/z 286 (M^+), 242 (M – CO_2). Anal. Calcd for $C_{16}H_{11}O_4F$; C 67.13; H, 3.87. Found: C, 67.22; H, 3.92.

4-(2′-Fluorophenyl)-6,7-(methylenedioxy)isochroman-3-one (22i): white needles (EtOH); mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 4.91 (s, 1 H), 5.22 (d, J = 12.0 Hz, 1 H), 5.33 (d, J = 12.0 Hz, 1 H), 5.92 (s, 2 H), 6.33 (s, 1 H), 6.59 (s, 1 H), 7.15–7.36 (m, 4 H); IR ($CHCl_3$) 1730 (C=O), 1600, 1590, 1490 cm^{-1}; MS m/z 286 (M^+), 242 (M – CO_2). Anal. Calcd for $C_{16}H_{11}O_4F$; C, 67.13; H, 3.87. Found: C, 67.25; H, 3.97.

Acknowledgment. This work was supported in part by the Welch Foundation, Houston, TX, and by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No. 1, 22002-45-5; **3**, 111210-24-3; **4**, 120-14-9; **5**, 120-57-0; **6a**, 54370-00-2; **6b**, 6642-34-8; **7**, 124618-99-1; **8**, 34679-09-9; **10a**, 124619-00-7; **10b**, 124619-01-8; **10c**, 124619-02-9; **10d**, 124619-03-0; **10e**, 124619-04-1; **10f**, 124619-05-2; **10g**, 124619-06-3; **10h**, 124619-07-4; **11a**, 124619-08-5; **11b**, 124619-09-6; **11c**, 124619-10-9; **11d**, 124619-11-0; **11e**, 124619-12-1; **11f**, 124619-13-2; **11g**, 124619-14-3; **11h**, 124619-15-4; **12**, 124619-44-9; **13b**, 124619-45-0; **13c**, 124619-46-1; **14a**, 124619-16-5; **14b**, 124619-17-6; **15b** (R″ = Me), 124619-47-2; **15b** (R″ = Et), 124619-48-3; **15c** (R″ = Me), 124619-49-4; **15c** (R″ = Et), 124650-72-2; **16a**, 124619-18-7; **16b**, 124619-19-8; **16c**, 124619-20-1; **16d**, 124619-21-2; **16e**, 124619-22-3; **16f**, 124619-23-4; **16g**, 124619-24-5; **16h**, 124619-25-6; **16i**, 124619-26-7; **16j**, 124650-71-1; **17b**, 3840-28-6; **17c**, 86633-25-2; **20a**, 43088-72-8; **20b**, 124619-27-8; **20c**, 124619-28-9; **20d**, 124619-29-0; **20e**, 124619-30-3; **20f**, 124619-31-4; **20g**, 124619-32-5; **20h**, 124619-33-6; **21a**, 16135-41-4; **21b**, 124619-34-7; **22a**, 34140-20-0; **22b**, 124619-35-8; **22c**, 124619-36-9; **22d**, 124619-37-0; **22e**, 124619-38-1; **22f**, 124619-39-2; **22g**, 124619-40-5; **22h**, 124619-41-6; **22i**, 124619-42-7; **22j**, 124619-43-8; CH_3CH_2CN, 107-12-0; $CH_3(CH_2)_2CN$, 109-74-0; $C_6H_5CH_2CN$, 140-29-4; 3-$MeOC_6H_4CH_2CN$, 19924-43-7; 4-$MeOC_6H_4CH_2CN$, 104-47-2; 3,4-$(MeO)_2C_6H_3CH_2CN$, 93-17-4; 3,4,5-$(MeO)_3C_6H_2CH_2CN$, 13338-63-1; 4-$FC_6H_4CH_2CN$, 459-22-3; 3-$FC_6H_4CH_2CN$, 501-00-8; 2-$FC_6H_4CH_2CN$, 326-62-5; 3,4-(methylenedioxy)$C_6H_3CH_2CN$, 4439-02-5; 6-bromopiperonal, 15930-53-7.

Supplementary Material Available: Full characterization data for **10a–f,h**, **14a,b**, **16a–e,g–i**, **20c–f,h**, **22c,d,f,j** (7 pages). Ordering information is given on any current masthead page.

Synthesis and Characterization of (Methoxy(thiocarbonyl))sulfenyl Chloride

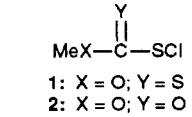
Alayne L. Schroll,[1] Steven J. Eastep, and George Barany*

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received January 11, 1989

(Methoxy(thiocarbonyl))sulfenyl chloride (**1**), a previously elusive compound, has now been generated by cleavage of methoxy(thiocarbonyl) *N*-methyl-*N*-phenylamino sulfide (**7**) with gaseous hydrogen chloride. The sulfenyl chloride **1** had limited stability and was characterized by trapping with *O,O′*-dimethyl thiocarbonate or with methanethiol to yield (methoxycarbonyl)(methoxy(thiocarbonyl))disulfane (**8**) or (methoxy(thiocarbonyl))-methyldisulfane (**9**), respectively. Chlorination of acetyl methoxy(thiocarbonyl) sulfide (**6**) could be arrested at 1 plus acetyl chloride, and further chlorination of 1 provided (methoxydichloromethyl)disulfanyl chloride (**5**).

(Methoxy(thiocarbonyl))sulfenyl chloride (**1**) is the thio analogue of the valuable reagent (methoxycarbonyl)-sulfenyl chloride (**2**),[2,3] a distillable compound (bp 31–32 °C/12 mm) which is indefinitely stable upon storage at −20 °C, and it is the isomer of our recently reported ((methylthio)carbonyl)sulfenyl chloride (**3**),[4] which was shown to rearrange cleanly ($t_{1/2} \approx 75$ min at 25 °C) to (methyldithio)carbonyl chloride, MeSS(C=O)Cl. This paper describes two routes to the preparation of **1**, which has



1: X = O; Y = S
2: X = O; Y = O
3: X = S; Y = O

(1) (a) Taken in part from the Ph.D. Thesis of A. L. Schroll, University of Minnesota, 1986. (b) Present address: Department of Chemistry, St. Michael's College, Winooski Park, Colchester, VT 05404.

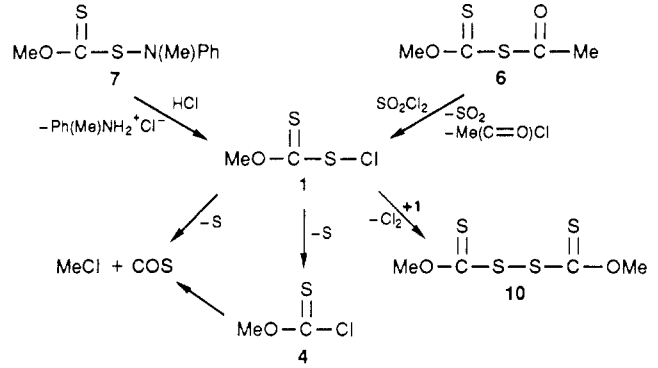
(2) Review: Zumach, G.; Kühle, E. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 54–63.

(3) Barany, G.; Schroll, A. L.; Mott, A. W.; Halsrud, D. A. *J. Org. Chem.* **1983**, *48*, 4750–4761 and references cited therein.

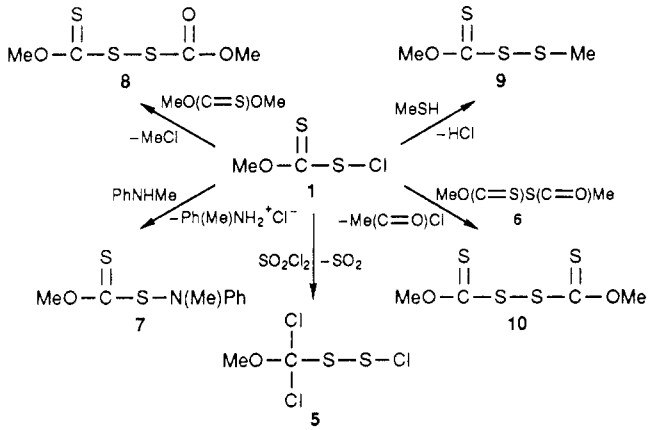
(4) Mott, A. W.; Barany, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2615–2621. In this paper, sulfenyl chloride **3** is reported by HCl treatment of the corresponding *N*-methylanilide.

0022-3263/90/1955-1475$02.50/0

Scheme I



Scheme II



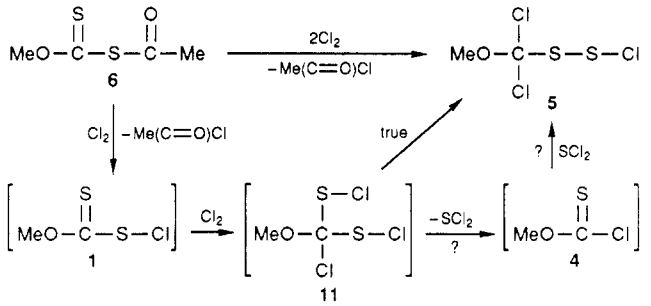
limited stability and decomposes to methoxy(thiocarbonyl) chloride (**4**) plus elemental sulfur ($t_{1/2} \approx$ 3–10 h at 25 °C) (Scheme I). We characterize **1** by several transformations, and thereby explain an unusual method due to Böhme, Brinkman, and Steudel for the synthesis of (methoxydichloromethyl)disulfanyl chloride (**5**) by the chlorination of acetyl methoxy(thiocarbonyl) sulfide (**6**).[5]

Results and Discussion

Preparation and Trapping of (Methoxy(thiocarbonyl))sulfenyl Chloride (1). Parallel studies provided crystalline methoxy(thiocarbonyl) *N*-methyl-*N*-phenylamino sulfide (**7**).[6] Following our earlier precedent for the synthesis of **3**,[4] treatment of *N*-methylanilide **7** with gaseous hydrogen chloride at 25 °C smoothly provided **1** (Scheme I). Alternatively, following the cue of Böhme et al.,[5] treatment of **6** at 25 °C with 1 equiv of sulfuryl chloride[7] gave acetyl chloride plus **1** in equimolar amounts. ^{1}H and ^{13}C NMR data were consistent with the structure of **1**.

Sulfenyl chloride **1**, freshly generated by either method, was trapped (Scheme II) with *O,O'*-dimethyl thiocarbonate[3] to yield (methoxycarbonyl)(methoxy(thiocarbonyl))disulfane (**8**), a new compound confirmed by an alternative route from potassium methyl xanthate plus (methoxycarbonyl)sulfenyl chloride (**2**).[8] Similarly, **1** could be quenched with excess methanethiol to provide the new (methoxy(thiocarbonyl))methyldisulfane (**9**). Compound **9** was also prepared by the reaction of methanesulfenyl chloride with potassium methyl xanthate. Finally, when solutions containing **1** were treated with *N*-methylaniline, derivative **7** was obtained.

Scheme III



Stability of (Methoxy(thiocarbonyl))sulfenyl Chloride (1). The methods for generation of **1** (Scheme I) were best carried out in relatively dilute solutions (e.g., 0.1 M in $CDCl_3$). The stability of **1** was monitored by ^{1}H NMR; methoxy(thiocarbonyl) chloride (**4**) plus elemental sulfur were the main decomposition products formed over a day or so at 25 °C (Scheme I). Under the reaction conditions, **4** could undergo further acid-catalyzed decomposition to methyl chloride plus carbonyl sulfide (Scheme I); the observed methyl chloride may also have been derived directly from **1**. It was difficult to deduce exact rates for the decomposition of **1**, because the process became significantly autocatalytic after about 50% decomposition. Solutions of **1** were appreciably more stable when purged with nitrogen to remove hydrogen chloride or when washed with water to remove acids and *N*-methylaniline hydrochloride.

When **1** was generated from higher concentrations of **6** or **7**, or when pure solutions of **1** were concentrated, decomposition was more pronounced. Desulfurization to **4** occurred more quickly, and much bis(methoxy(thiocarbonyl))disulfane (**10**) was observed (Scheme I). The time course for the appearance of **10** suggests that this compound arises by dimerization of **1** with concomitant formation of molecular chlorine.

Addition Reactions of the (Methoxy(thiocarbonyl))sulfenyl Function. Our earlier work has elucidated a rapid and specific intramolecular rearrangement which occurs in the chlorination of (methoxy(thiocarbonyl))sulfenyl functions.[6,7c,d,9] Although chlorine initially adds across the thiocarbonyl, the products which are isolated contain both chlorines on the carbon while the two sulfurs become linearly connected. In agreement with this understanding, we now find that **1** is rapidly chlorinated *directly* to (methoxydichloromethyl)disulfanyl chloride (**5**) (Scheme II). The presumed intermediate, $MeOC(SCl)_2Cl$ (**11**), was evidently too short-lived to be

(5) Böhme, H.; Brinkman, M.; Steudel, H. P. *Justus Liebigs Ann. Chem.* **1981**, 1244–1251. The chemistry reported in the referenced paper is shown on the top line of Scheme III, see later in this paper. The speculation of Böhme et al. that structure **1** is an intermediate in their process is supported by the experiments described in the present paper; other aspects of their proposed mechanism appear to be incorrect.

(6) Schroll, A. L.; Barany, G. *J. Org. Chem.* **1986**, *51*, 1866–1881.

(7) Böhme et al. (ref 5) recommended use of gaseous chlorine at −35 °C, but findings from our laboratory and others suggest that sulfuryl chloride at 25 °C provides greater control. See: (a) Reference 3. (b) Yen, K. Y.; Cava, M. P. *J. Org. Chem.* **1983**, *48*, 1449–1451. (c) Barany, G. *Tetrahedron Lett.* **1983**, *24*, 5683–5686. (d) Mott, A. W.; Barany, G. *Sulfur Lett.* **1984**, *2*, 241–248. (e) Review: Hansen, H. C.; Senning, A. *Org. Prep. Proced. Int.* **1985**, *17*, 275–315.

(8) The trapping reaction appears to be catalyzed by HCl. When a solution of freshly generated **1** was washed with water (see later in text) prior to adding *O,O'*-dimethyl thiocarbonate, desired **8** was not formed. When a solution of **1** was first purged with nitrogen, the yield of **8** was appreciably lower, and substantial unreacted **1** was noted by ^{1}H NMR. Also, under all conditions, a portion of starting thiocarbonate was transformed to the corresponding *O,O'*-dimethyl carbonate, MeO(C=O)OMe.

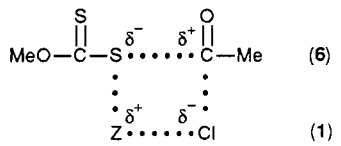
(9) Barany, G.; Mott, A. W. *J. Org. Chem.* **1984**, *49*, 1043–1051.

observed by ^1H NMR spectroscopy. In addition, we have shown that when acetyl methoxy(thiocarbonyl) sulfide (**6**) is chlorinated in a 1:2 ratio,[5] sulfenyl chloride **1** forms and is the *only* intermediate in the reaction pathway to product **5** (Scheme III, top line).

Reaction of **6** with sulfuryl chloride in a ratio of 2:1 occurred smoothly to give bis(methoxy(thiocarbonyl))disulfane (**10**) plus acetyl chloride (2 equiv). Sulfenyl chloride **1** was a clear intermediate (established by ^1H NMR), and the second step (**1** plus **6**; Scheme II, lower right) was estimated to proceed at about half the rate of the first step (**6** plus SO_2Cl_2; Scheme I, upper right). These rates suggest that this chemistry is unrelated to the pathway (Scheme I, lower right) by which **10** forms in the decomposition/dimerization of **1**.

Mechanism of the Böhme Reaction: Chlorination of Acetyl Methoxy(thiocarbonyl) Sulfide (6) Provides (Methoxydichloromethyl)disulfanyl Chloride (5). Based on our findings on the chemistry of (methoxy(thiocarbonyl))sulfenyl chloride (**1**), and on direct spectroscopic examination of the chlorination mixtures at all stages of the reaction, it is possible to reevaluate a mechanism proposed earlier for the preparation of **5** by chlorination of **6** (Scheme III).[5] We confirm the postulate that **1** is an intermediate, but find no evidence for the involvement of methoxy(thiocarbonyl) chloride (**4**). This is in spite of the known rapid reaction of **4** with sulfur dichloride to provide **5**.[5,9] The formation of **5** during the chlorination of **6** is due *exclusively* to an addition/rearrangement process involving intermediate (thiocarbonyl)sulfenyl chloride **1**, and any **11** that presumably forms cannot be detected spectroscopically.

The formation of **1** plus acetyl chloride upon chlorination of **6** (Scheme I), established experimentally in this work, resembles closely the chlorination of acetyl methoxycarbonyl sulfide, which gives acetyl chloride plus (methoxycarbonyl)sulfenyl chloride (**2**).[10] To the best of our knowledge, formation of **1** in this way represents the first example where chlorolytic cleavage of a carbon–sulfur single bond takes precedence over addition of chlorine across a carbon–sulfur double bond. These results and those in the literature[10,11] are best rationalized in terms of polarization of the acetyl–sulfur bond in **6** or related compounds, with the positive charge supported at the carbonyl and the negative charge on the sulfur. The observed products, with molecular chlorine or with the electrophilic sulfenyl chloride of **1**, respectively, follow naturally from such a description.



(6)

(1)

Z = Cl (text route to **1**; **6**:Cl_2 = 1:1)
Z = MeO(C=S)S (Scheme II, lower right; **6**:Cl_2 = 2:1)

Experimental Section

General Methods. ^1H NMR spectra were recorded in $CDCl_3$ at 80 MHz on a Varian HFT-80 spectrometer or at 200 MHz on an IBM NR 200 AF instrument. ^{13}C NMR spectra were recorded on the IBM machine at 50 MHz or on a Nicolet NT-300 spectrometer at 75 MHz (chemical shifts normalized to $CDCl_3$ at δ = 77.0). Electron ionization mass spectra were obtained on a Kratos/AEI MS-30 operated at 70 eV, source 200 °C, gas probe 25 °C. Solvents and chemicals were reagent grade and used without further purification. Acetyl methoxy(thiocarbonyl) sulfide (**6**) [bp 57–60 °C (0.15 mm) [lit.[5] bp 51 °C (0.4 mm)]; ^1H NMR δ 4.24 (s, 3 H, MeO), 2.41 [s, 3 H, Me(C=O)]; ^{13}C NMR δ 204.2, 188.6, 60.5, 30.7] was made on a 0.75-mol scale in 80% yield from freshly prepared potassium methyl xanthate plus acetyl chloride reacted in CCl_4 as described by Böhme et al.[5] Most of the other methods, instrumentation, and materials, as well as detailed spectral parameters, were as described in our earlier publications.[3,4,6,7c,d,9]

(Methoxy(thiocarbonyl))sulfenyl Chloride (1). A. Over a 1-min period, gaseous HCl was bubbled slowly into a 0.1 M solution of methoxy(thiocarbonyl) *N*-methyl-*N*-phenylamino sulfide (**7**)[6] in $CDCl_3$ at 25 °C. The resulting bright yellow solution was shown by ^1H NMR to be free of starting **7** and to contain *N*-methylaniline hydrochloride [δ 7.6 (m, 2 H), 7.4 (m, 3 H), 3.03 (br s, 3 H)] plus a singlet [δ 4.32] assigned to **1**. The ^1H NMR integrations suggested that this reaction was quantitative; quenching experiments gave yields ≥ 70%; see the Experimental Section for **8** (part A) and **9** (part A).

To obtain ^{13}C NMR data, a solution of **1** was concentrated about 8-fold over a 5-min period with a stream of nitrogen, and then the necessary transients were accumulated over 30 min. Signals assigned to **1** [δ 60.6 and 208.1] were readily distinguished from those due to methoxy(thiocarbonyl) chloride (**4**) [δ 63.1 and 187.3] and bis(methoxy(thiocarbonyl))disulfane (**10**) [δ 61.5 and 207.8]. At the higher concentration required for ^{13}C NMR, **1** represented only 30–50% of the total *O*-methyl groups, the remainder being mainly **4** and **10**. The spectrum also showed peaks [δ 136.8 (small), 129.9, 129.2, 122.3, and 37.7] matching a standard of *N*-methylaniline hydrochloride.

The sulfenyl chloride **1** had some stability at 25 °C ($t_{1/2} \approx$ 3–10 h by ^1H NMR, depending on the concentrations of HCl and substrate **7**). When **1** was generated from substrate **7** (0.1 M in $CDCl_3$), with excess HCl purged by nitrogen, the primary decomposition product was methoxy(thiocarbonyl) chloride (**4**) [δ 4.18], resulting from desulfurization. After 24 h, treatment with *N*-methylaniline[3] gave principally *O*-methyl *N*-methyl-*N*-phenylthiocarbamate, MeO(C=S)N(Me)Ph[3] (83% based on **7**) [δ 7.1–7.4 (m, 5 H), 3.97 (s, 3 H, MeO), 3.59 (s, 3 H, MeN)], together with some disulfane **10** [δ 4.24]. The lifetime of **1** could also be enhanced by washing the HCl-treated solution of **7** with water (2×); *N*-methylaniline hydrochloride was removed and after 7 h, **1** remained as the major species present (>90%). Compound **1** represented 65% of the total *O*-methyl groups at 15 h; although **1** was still present at 24–48 h, decomposition products such as **4** and **10** predominated at these later times.

The alternative pathway for decomposition of **1** gave elemental sulfur together with gaseous carbonyl sulfide plus methyl chloride [δ 3.01]. This process was always observed, but more so in samples where HCl had not been removed (acid-catalyzed decomposition of **4** also gives COS plus MeCl).[3]

B. The sulfenyl chloride **1** also formed by careful chlorination[7] of acetyl methoxy(thiocarbonyl) sulfide (**6**). Experimental details are provided in procedures which follow for compounds **5** (part A), **7**, and **9** (parts B and C). ^1H NMR of the chlorination mixtures clearly showed the major formation of **1** (δ 4.32) plus acetyl chloride (δ 2.66), and, depending on reaction time and concentration, also disulfane **10** (δ 4.24). In $CDCl_3$ at 25 °C with both **6** and SO_2Cl_2 being 0.1 M, **1** formed with $t_{1/2} \approx$ 20 min. Kinetics at other concentrations of **6** and SO_2Cl_2 gave rates consistent with a second-order process. The presence of **1** was further supported by formation of **7** or **9** upon quenching respectively with *N*-methylaniline or methanethiol (see Scheme II; these reagents did not react with **10**, which was the most common contaminant in some of the chlorination mixtures). Little disulfane **10** was noted at early times, but **10** eventually accounted for as much as 35% of the total methoxy(thiocarbonyl) groups. Later the level of **10** decreased as further decomposition took place. Solutions of **1** (0.1–0.2 M), generated from **6** plus SO_2Cl_2 in $CDCl_3$, usually decomposed within a day at 25 °C. The principal decomposition products were methyl chloride (≈30–60%) and **4** (≈20–50%), but disulfane **10** and assorted methoxydichloromethyl species were also noted.[12] The decomposition rate was mitigated substantially

(10) Böhme, H.; Steudel, H. P. *Justus Liebigs Ann. Chem.* **1969**, *730*, 121–132.
(11) Chlorination of bis(acetyl)disulfane has long been known to provide acetyl chloride plus acetyldisulfanyl chloride: Böhme, H.; Clement, M. *Justus Liebigs Ann. Chem.* **1952**, *576*, 61–69.

by washing with water as described earlier.

To obtain a solution sufficiently concentrated for ^{13}C NMR, a 1 M solution of **6** in $CDCl_3$ was treated with SO_2Cl_2 (1 equiv) and examined within 30 min. Signals were assigned to **1** [δ 60.6 and 208.2], **10** [δ 61.4 and 207.9], unresolved methoxydichloromethanesulfenyl derivatives[12] [δ 57.0], and acetyl chloride [δ 170.0 and 33.4]. As noted earlier, **1** is very unstable at these high concentrations. At 5 min, the ^1H NMR integration of acetyl chloride equaled that of the total methoxy(thiocarbonyl) groups, of which **1** and **10** represented 44% and 38%, respectively. At 20 min, **1** was only 20% of the total methoxy(thiocarbonyl) groups. Interestingly, when these more concentrated, rapidly decomposing mixtures were diluted in $CDCl_3$, the relative amounts of species (e.g. **1**, **10**, $MeOCCl_2S$) did not change further for several hours.

(Methoxydichloromethyl)disulfanyl Chloride (5). A (Preparative). In a manner similar to that of Böhme et al.,[5] but at half the concentration, a solution of **6** (17.1 g, 114 mmol) in CCl_4 (75 mL) was chilled to −35 °C, and chlorine gas was bubbled in. Progress of the reaction was monitored by ^1H NMR and weight uptake. When less than 1 equiv of Cl_2 had been added, ^1H NMR showed that **1** and acetyl chloride formed in equal amounts, and that the amount of unreacted **6** was as expected from a 1:1 stoichiometry for reaction of **6** with Cl_2. As further Cl_2 was taken up (17 g, 2.0 equiv with respect to **6**), intermediate **1** was replaced by **5**. At this point, the reaction mixture was yellowish-orange, not red as would be expected if sulfur dichloride were present as predicted in the literature mechanism (Scheme III, bottom line).[5] The mixture was brought to 25 °C, concentrated, and then distilled. A forerun (3.2 g) containing methoxydichloromethanesulfenyl chloride, $MeOCCl_2SCl$, was discarded, and the title product (**5**) (17.6 g, 72%) was obtained at bp 47–53 °C (0.15 mm) [lit.[5] bp 29 °C (0.09 mm); lit.[9] bp 49–52 °C (0.15 mm)]; ^1H NMR δ 3.81; ^{13}C NMR δ 117.5, 57.1.

B. A 0.1 M solution of **1** in $CDCl_3$, generated from **7** plus HCl, was washed with water (2×) and treated with SO_2Cl_2 (1 equiv). Formation of **5** was quantitative in 30 min ($t_{1/2} \approx 6.3$ min, with no intermediates noted by ^1H NMR). Treatment of the reaction mixture with *N*-methylaniline provided quantitatively *O*-methyl *N*-methyl-*N*-phenylthiocarbamate, MeO(C=S)N(Me)Ph, (>85% purity), as expected for reaction of **5** plus *N*-methylaniline.[3]

Methoxy(thiocarbonyl) *N*-Methyl-*N*-phenylamino Sulfide (7). The title compound was made in 39% yield by the method reported earlier.[6] Alternatively, SO_2Cl_2 (1.2 mL, 15 mmol) was added quickly at 0 °C to a solution of acetyl methoxy(thiocarbonyl) sulfide (**6**) (1.5 g, 10 mmol) in $CHCl_3$ (10 mL), and after 30 s this mixture was added at 5 °C to *N*-methylaniline in $CHCl_3$ (45 mL, 2 M, 0.09 mol). The usual workup[3] gave a product (3.4 g) which consisted of desired **7** (7.8 mmol), disulfane **10** (0.8 mmol), and *N*-acetyl-*N*-methylaniline (10 mmol) [δ 7.1–7.5 (m, 3 H), 3.27 (s, 3 H, MeN), 1.88 (s, 3 H, Ac)]. Chromatography (silica gel, 100 g, hexane–$CHCl_3$, 4:1 v/v) gave a gold oil (1.4 g), which was crystallized from hot methanol to provide large clear prisms of **7** (730 mg, 34%); mp 67–69 °C [lit.[6] mp 68–69 °C]; ^1H NMR δ 7.1–7.3 (m, 5 H), 4.14 (s, 3 H, MeO), 3.45 (s, 3 H, MeN); ^{13}C NMR δ 219.0, 128.8, 120.4, 115.3, 59.6, and 44.0.

(Methoxycarbonyl)(methoxy(thiocarbonyl))disulfane (8). A. Sulfenyl chloride **1** was generated from HCl plus **7** (154 mg, 0.7 mmol) in $CDCl_3$ (7.0 mL), as described earlier,[8] and then trapped at 25 °C by adding to a solution of *O,O'*-dimethyl thiocarbonate[3] (155 mg, 1.5 mmol) in $CDCl_3$ (1.5 mL). Within 2 min, all of **1** was consumed, and a portion (≈8%) of the *O,O'*-dimethyl thiocarbonate (δ 4.05) was converted to the desulfurized analogue *O,O'*-dimethyl carbonate (δ 3.78). After 10 min, the reaction mixture was extracted with 1 N aqueous HCl, dried ($MgSO_4$), and evaporated to provide **8** (101 mg, 71%), >90% pure by HPLC and ^1H NMR. Unidentified minor signals (δ 4.30 and 3.94) may indicate disproportionated material.

B. A reaction mixture of **6** plus SO_2Cl_2, 0.1 M each in $CDCl_3$, was maintained for 2 h at 25 °C, and then *O,O'*-dimethyl thiocarbonate (1.1 equiv) was added. ^1H NMR revealed that all of the sulfenyl chloride **1** generated in situ reacted with ≈70% of the *O,O'*-dimethyl thiocarbonate ($t_{1/2} \approx 10$ min) to provide a mixture of desired disulfane **8** and disproportionated disulfane **10** in a 4:1 ratio. Also observed were *O,O'*-dimethyl carbonate (≈10% based on the thiocarbonate) and bis(methoxycarbonyl)disulfane[9] (half the amount of **10**). Disproportionation was noted at all stages of the reaction.

C. (Methoxycarbonyl)sulfenyl chloride (**2**)[2,3] (4.2 g, 33 mmol) was added at −50 °C to a suspension of potassium methyl xanthate (4.8 g, 33 mmol) in ethyl ether (60 mL). The reaction mixture was stirred for 1 h at 25 °C, filtered, and concentrated to provide 6.5 g (89%) of ^1H NMR pure **8**. Short-path distillation, bp 63–65 °C (0.2 mm) [lit.[2] for corresponding ethoxythiocarbonyl compound, bp 95 °C (0.3 mm)] provided **8** (3.3 g, 50%): ρ = 1.38 g/mL; ^1H NMR δ 4.25 [s, 3 H, MeO(C=S)], 3.92 [s, 3 H, MeO(C=O)]; ^{13}C NMR δ 208.1, 166.3, 61.5, 55.8; mass spectrum (70 eV) *m/z* 198 ($M^{\bullet+}$, 4), 166 ($M^{\bullet+}$ − S, 2), 138 ($M^{\bullet+}$ − COS, 10), 122 (6), 107 (7), 94 (12), 79 (13), 76 (56), 75 ($MeOCS^+$, 100), 61 (28), 60 (48), 59 (37). Some bis(methoxy(thiocarbonyl))di- and trisulfanes formed during the distillation and came over in later fractions or remained in the residue.

Anal. Calcd for $C_4H_6O_3S_3$ (mol. wt. 198.27): C, 24.23; H, 3.05; S, 48.51. Found: C, 24.48; H, 3.19; S, 48.36.

Freshly distilled **8** had excellent purity (>98%) by HPLC and ^1H NMR. After prolonged storage (several years) at 25 °C, about 70% of the oil remained as the unsymmetrical disulfane **8** with the remainder being the symmetrical disproportioned disulfanes bis(methoxy(thiocarbonyl))disulfane (**10**) and bis(methoxycarbonyl)disulfane, MeO(C=O)SS(C=O)OMe.[9]

(Methoxy(thiocarbonyl))methyldisulfane (9). A. The reaction mixture after generation of **1** from HCl plus **7** (43 mg, 0.2 mmol) in $CDCl_3$ (2 mL) was quenched 2 min later at 0 °C with excess methanethiol in $CDCl_3$ (2 M, 1 mL, 2 mmol). This was washed with 0.1 N aqueous HCl, dried ($MgSO_4$), and concentrated to provide a ^1H NMR pure (>99%) yellow oil (23 mg, 73%), identified as **9**.

B. A solution of **6** (0.75 g, 5 mmol) in $CDCl_3$ (5 mL) was chilled to 0 °C, and SO_2Cl_2 (0.4 mL, 5 mmol) was quickly added. Progress of the reaction was monitored by taking aliquots for 20-fold dilution in $CDCl_3$ and ^1H NMR examination. Through 1 half-life ($t_{1/2} \approx 4$ min), no **10** was formed, but after 20 min the *O*-methyl groups were distributed about evenly between **1** and **10**. The bulk of the reaction mixture was added at 15 min to an excess of a cold solution of methanethiol in $CDCl_3$ (2 M, 25 mL, 50 mmol). This was concentrated in vacuo 10 min later to give a yellow oil (0.77 g) comprising **9**, disulfane **10**, and dimethyl disulfide in a molar ratio of 12:7:9. More prolonged evaporation removed dimethyl disulfide, while the ratio of **9** and **10** in the final product mixture (0.62 g, accounting for 96% of the methoxy groups in **6**) remained the same.

C. A solution of **6** (187 mg, 1.25 mmol) in $CDCl_3$ (12.5 mL) was treated at 25 °C with SO_2Cl_2 (0.1 mL, 1.25 mmol). After 4 h, the reaction mixture was added to a cold solution of methanethiol in $CDCl_3$ (2 M, 3.8 mL, 7.5 mmol), and workup gave an oil (0.19 g, quantitative) which was **9** and disulfane **10** in a molar ratio of 4.3:1. This result accounts for all methoxy groups in **6**, reflects the relative amounts of **1** and **10** prior to the methanethiol quench, and represents a 75% yield of **9** based on **6**.

D. Dimethyl disulfide (2.5 mL, 28 mmol) and SO_2Cl_2 (2.2 mL, 56 mmol) at −78 °C gave methanesulfenyl chloride,[3] which was warmed to 0 °C, diluted with ether (25 mL), and added to a cooled and well-stirred suspension of potassium methyl xanthate (9.0 g, 62 mmol) in ether (100 mL). After 1 h at 25 °C, the reaction mixture was filtered and concentrated to provide a colored oil (7.0 g), which was distilled, bp 48 °C (0.1 mm), to give **9** as a pale yellow oil: ^1H NMR δ 4.28 (s, 3 H, MeO), 2.53 (s, 3 H, MeS); ^{13}C NMR δ 213.3, 61.1, 22.7.

Anal. Calcd for $C_3H_6OS_3$ (mol. wt. 154.27): C, 23.36; H, 3.92; S, 62.35. Found: C, 23.50; H, 3.72; S, 62.25.

After 1 month storage at −20 °C, about 20% of **9** had lost sulfur to form *O*-methyl *S*-methyl dithiocarbonate, MeO(C=S)SMe: ^1H NMR δ 4.19 (s, 3 H, MeO), 2.57 (s, 3 H, MeS); ^{13}C NMR δ 216.3, 60.0, 19.0.

Acknowledgment. We thank David A. Halsrud, Lori J. Enloe, Darci L. Knowlton, and Robert L. Walsky for dedicated technical help. Financial support was from the National Institutes of Health (Grants GM 28934 and CA

(12) As indicated in our earlier publications (refs 6, 7c, 7d, 9), methoxydichloromethanesulfenyl groups, $MeOCCl_2S$–, arise by further chlorination of methoxy(thiocarbonyl) functions.

43285), the Chicago Community Trust (Searle Scholars Program), the American Cancer Society Institutional Research Grant (IN-13-Y-15), and the University of Minnesota (Office of Alcohol and Other Drug Abuse Programming).

Registry No. 1, 124513-37-7; 2, 26555-40-8; 4, 2812-72-8; 5, 79598-17-7; 6, 79598-16-6; 7, 89264-59-5; 8, 124535-50-8; 9, 5813-75-2; 10, 1468-37-7; CH_3Cl, 74-87-3; CH_3SH, 74-93-1; MeOC(=S)SH, 2667-20-1; MeOC(=S)OMe, 1115-13-5; MeOC(=S)N(Me)Ph, 87463-11-4; PhNHMe, 100-61-8; $MeOCCl_2SCl$, 87463-08-9; PhN(Me)Ac, 579-10-2; MeOCOOMe, 616-38-6; $MeOCOS_2CO_2Me$, 26555-41-9; CH_3SCl, 5813-48-9; MeOC(=S)SMe, 19708-81-7.

Decyanation of Tertiary Nitriles by Alkyllithium Reagents Observed during the Synthesis of Imidazoles Pendant to a Quaternary Carbon Center

George B. Gregory, Alexander L. Johnson,* and William C. Ripka

E. I. duPont deNemours & Co., Inc., Medical Products Department, Experimental Station, E353/304, Wilmington, Delaware 19880-0353

Received June 16, 1989

We have devised a five-step synthesis of the new chemical entities **7a–d** from 5-methoxytetralone, **1**, via unsaturated nitrile **3**, the reductive alkylation products **4a–d**, and ketones **5a–d** and **6a–d**. Structures **7a–d** are distinguished by the presence of a 4-imidazolyl moiety pendant to a quaternary center of the 1,2,3,4-tetrahydronaphthalene nucleus. The tertiary nitriles **4a–d** can produce either the desired ketones **5a–d**, **10a,b**, or **11** in reactions in benzene or diethyl ether, or the decyanation products **12a,b,d** and **13a**, in reactions in THF. Apparently fragmentation in 4-centered transition state **9b** to the decyanation products is favored as the Lewis base strength of the solvent increases. Synthetically, it is preferable to use CH_3MgBr in benzene in the conversion of **4a–d** to **5a–d**.

Introduction

In the design of nonpeptide antagonists of the angiotensin II receptor,[1,2] we concluded from computer modeling studies that O-alkylation products derived from structures **7a–d** would be interesting molecules for biological evaluation. Naphthalenoid systems bearing a pendant carbon-linked imidazole substituent are not readily accessible by substitution reactions. Therefore, we selected 5-methoxy-1-tetralone (**1**) as a readily available starting material and are pleased to report that we have devised a five-step synthesis to construct compounds **7a–d**.

Synthesis

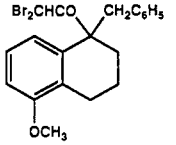
Treatment of **1** with TMSCN and ZnI_2 in benzene solution[3,4] at 25 °C for 3 h gave a quantitative yield of the O-TMS cyanohydrin (**2**) (Scheme I). Conversion of **2** to α,β-unsaturated nitrile **3** can be done stepwise by deprotection to the cyanohydrin with dilute acid[3] followed by dehydration with $POCl_3$–pyridine.[5] However, we found Oda's modification[4] to be most convenient in this synthesis: upon completion of formation of **2** (TLC), it is converted in situ into key intermediate **3** by the addition of $POCl_3$ and pyridine to the reaction vessel followed by heating the mixture at reflux for 5 h.

Nitrile **3** is the key structure in our synthesis because the cyano group serves as the stub from which the imidazole ring is constructed, and provides direction for the α-introduction of the aralkyl group by an extension of the enoate reductive alkylation reaction.[6] Concomitant treatment of nitrile **3** with L-Selectride (Aldrich) and the appropriate aralkyl bromide at −78 °C in THF, followed by warming to room temperature, gave the respective reductive alkylation products **4a–d**.

The imidazole ring attached to the 1-position of the 1,2,3,4-tetrahydrophthalene nucleus was now elaborated from the nitrile group in structures **4a–d** through the methyl ketones **5a–d** and bromomethyl ketones **6a–d** to the desired products **7a–d**.

The respective methyl ketones **5a–d** were prepared by Grignard reaction of **4a–d** with CH_3MgBr at reflux in benzene, followed by an acidic workup. The yields of these ketones were high, as judged by TLC, IR, and ^1H NMR data, but their purification on a multigram scale was not easy. When the organometallic reagent is CH_3Li, both ketone and decyanation products are obtained from **4a–d**; this is discussed in detail below.

The α-bromination reaction of **5a–d** with Br_2 in CH_2Cl_2/ether used to form **6a–d** is not especially clean. The major products, monobromides **6a–d**, are accompanied by small amounts of starting ketones and dibromination products such as **8**. Modification of the bromination conditions, such as lowering the reaction temperature,



8

* Please address correspondence in care of A. L. Johnson, Medical Products Department, E. I. du Pont de Nemours & Co., Inc. Experimental Station, 353 Building, Wilmington, DE 19880-0353. Contribution No. 86-P27/28.

(1) Presented in preliminar form: Johnson, A. L.; Gregory, G. B.; Ripka, W. C. 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 7–12, 1986, Paper No. ORGN-186.

(2) (a) Duncia, J. V.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Wells, G. J.; Chiu, A. T.; Price, W. A.; Timmermans, P. B.; Wong, P. C. *J. Med. Chem.*, in press. (b) Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. *J. Med. Chem.*, in press.

(3) Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, *29*, 3773–3776.

(4) Oda, M.; Yamamuro, A.; Watabe, T. *Chem. Lett.* **1979**, 1427–1430.

(5) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; p 878.

(6) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194–2200.

0022-3263/90/1955-1479$02.50/0