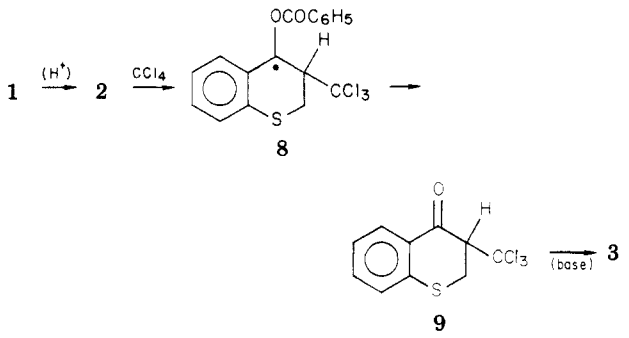
Scheme I



tri-*n*-butyltin hydride under quite forcing conditions all failed, although some evidence of reduction to the monochloro analogue of **3** was found. Likewise, attempts to synthesize **7** starting from 4-thiochromanone and paraformaldehyde, using a recent literature procedure,[6] were also without success.

The question of the mechanism of this unusual reaction is not finally resolved, but certain possibilities can be excluded. The intervention of dichlorocarbene is ruled out here, since no reaction was observed between 4-thiochromanone and dichlorocarbene generated from the thermal decomposition of sodium trichloroacetate.

When **1** was refluxed in carbon tetrachloride in the presence of benzoyl peroxide (radical catalyst), but in the absence of strong acid, no trace of **3** was found. Likewise, when the original experiment was repeated entirely in the dark, none of the dichloro compound was produced. When benzoic anhydride was omitted from the otherwise identical reaction conditions, again none of compound **3** was formed. The cumulative evidence suggests to us the following mechanistic scheme (Scheme I). Strong acid catalysis produces a sufficient concentration of the enol form of **1** or, more likely, the enol benzoate **2**, which then undergoes a free-radical addition with the solvent to form the intermediate **8**. Free-radical additions of both chloroform and carbon tetrachloride with various olefins have been studied mechanistically[7] and the addition of carbon tetrachloride has also been successfully applied recently in a synthesis of chrysanthemic acid derivatives.[8] Loss of a benzoyl radical would be expected to give **9**. Finally, **9** would undergo loss of HCl, perhaps during the workup, to produce compound **3**. Unfortunately, the original target molecule, the enol benzoate **2**, could not be isolated in sufficiently pure form to verify its intermediacy in the reaction with carbon tetrachloride.

This transformation affords an interesting demonstration of the reactivity of even a relatively inert organic solvent under conditions which appear almost tailored to ensure nonparticipation by solvent molecules.

Experimental Section

The IR spectra were recorded on a Perkin-Elmer 298 grating spectrophotometer, UV spectra on a Unicam SP-800 instrument, and ^{1}H NMR spectra on a Varian EM-360 spectrometer. Natural abundance, proton-decoupled ^{13}C NMR spectra were obtained on the Bruker WH-400 instrument at the Southwestern Ontario NMR Centre in Guelph. Routine mass spectral data were obtained on a Bell and Howell 21-490 instrument and the accurate mass measurements on the AEI MS-902. Elemental analyses were performed by Microanalysis Laboratories Ltd., Markham, Ontario L3R 3R6.

Isolation of 3',3'-Dichloro-3-methylene-4-thiochromanone (3). 4-Thiochromanone (3.28 g., 20 mmol) and benzoic anhydride (19.30 g, 85 mmol) were refluxed in carbon tetrachloride (70 mL) containing 2 drops of 60% perchloric acid for 7 days. After cooling, the reaction mixture was poured into cold 10% sodium hydrogen carbonate solution, the organic layer was separated, and the aqueous phase was reextracted several times with ether. The combined organic layer was washed several times with 10% sodium hydrogen carbonate (until no more benzoic acid precipitated on acidification with HCl) and finally with water and dried (Na_2SO_4). Evaporation gave a crude mixture[9] (14.62 g), which was chromatographed on silica gel. Elution with carbon tetrachloride gave a yellow oil (0.55 g, 22%), after correction for recovered **1** (1.62 g, 49%). The oil was purified by short-path distillation: bp 180–185 °C (bath temperature) (10 mm); IR (liquid film) ν 1670 (C=O), 1595 cm^{-1}; UV (MeOH) λ_{max} 249 nm (ϵ 12900), 279 (12600); ^{1}H NMR ($CDCl_3$) δ 4.06 (2, s), 7.20 (3, m), 8.15 (1, m); ^{13}C NMR ($CDCl_3$) δ 182.5, 141.0, 133.4, 131.3, 130.4, 129.8, 128.3, 127.5, 125.6, 32.45; mass spectrum, *m/z* (relative intensity) 246 (42), 244 (57), 209 (45), 181 (57), 136 (100), 108 (52); mass measurement calcd for $C_{10}H_6Cl_2OS$ 243.9516, found 243.9499. Anal. Calcd for $C_{10}H_6Cl_2OS$: C, 48.98; H, 2.45; Cl, 28.95; S, 13.08. Found: C, 49.82; H, 2.96; Cl, 28.63; S, 14.11.

The expected enol benzoate **2** (27%, estimated by NMR) proved to be unstable to the chromatographic conditions employed. however, the original mixture contains a product which, from the spectral characteristics noted below, appears to be **2**. IR ($CHCl_3$) ν 1758 (ester C=O); ^{1}H NMR δ ($CDCl_3$) 3.58 (2, d, J = 5.7 Hz, -CH_2-), 5.79 (1, t, J = 5.7 Hz, =CH-), 6.9–7.7 (7, m, *arom*), 8.0–8.3 (2, m, *ortho* to C=O).

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. The ^{13}C NMR spectrum was obtained at the Southwestern Ontario NMR Centre funded by a Major Installation Grant from NSERC.

Registry No. 1, 3528-17-4; 2, 79971-39-4; 3, 79971-40-7; benzoic anhydride, 93-97-0; carbon tetrachloride, 56-23-5.

(6) Paquette, L. A.; Han, Y.-K. *J. Am. Chem .Soc.* **1981**, 103, 1831.
(7) Asscher, M.; Vofsi, D. *J. Chem. Soc.* **1963**, 1887, 3921.
(8) Nakada, Y.; Endo, R.; Muramatsu, S.; Ide, J.; Yura, Y. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1511.
(9) This mixture contained substantial amounts of unreacted benzoic anhydride.

Regio- and Stereospecific Synthesis of Acetylenic Thio Enol Ethers Occurring in the Genus *Anthemis*

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It has been shown by Bohlmann et al.[1a] that plants of the genus *Anthemis* contain a variety of compounds with the thio enyne fragment **1**. It is well established that this

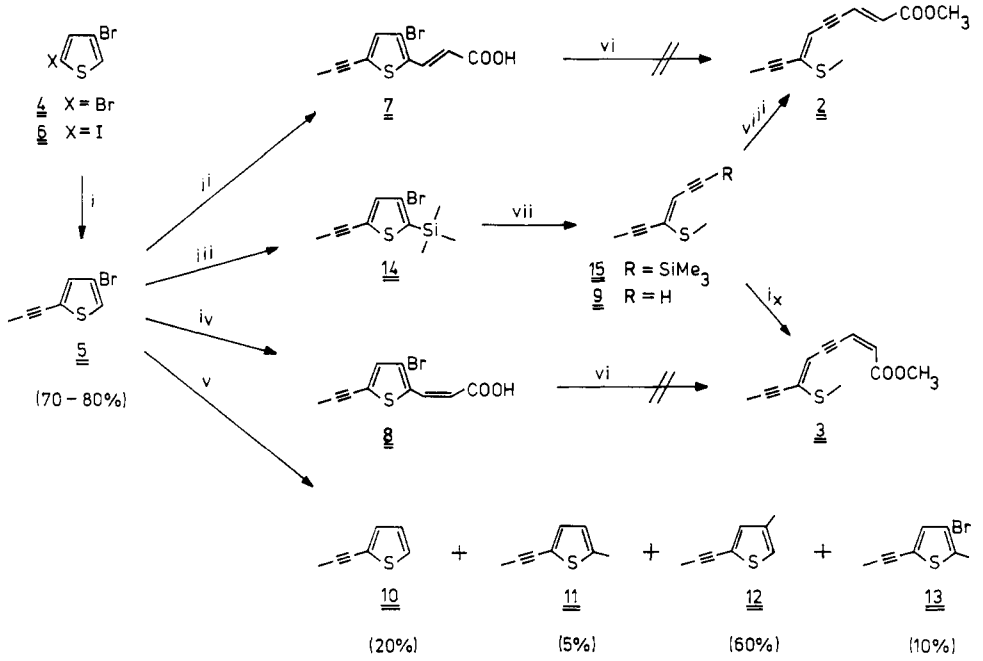
1

structural element with cis geometry around the double bond is formed exclusively in the ring-opening of 3-thienyllithium derivatives.[2] This suggested to us that the

(1) (a) Bohlmann, F.; Burkhardt, T.; Zdero, C. "Naturally Occurring Acetylenes"; Academic Press: New York 1973; p 381. (b) *Ibid.*, p 506.
(2) Frejd, T.; Karlsson, O.; Gronowitz, S. *J. Org. Chem.* **1981**, *46*, 3132. Gronowitz, S.; Frejd, T. *J. Heterocycl. Compd. (Engl. Transl.)* **1978**, 353 and references cited therein.

0022-3263/82/1947-0374$01.25/0

Scheme I[a]



[a] (i) $H_3CC{\equiv}CZnCl$, $Pd(OAc)_2$, PPh_3; (ii) LDA, $ZnCl_2$, then (*E*)-$BrCH{=}CHCO_2CH_3$ and $Pd(PPh_3)_4$, and finally Li/pyridine, reflux; (iii) LDA, Me_3SiCl; (iv) LDA, $ZnCl_2$, then (*Z*)-$BrCH{=}CHCO_2CH_3$ and $Pd(PPh_3)_4$, and finally NaOH/MeOH-H_2O; (v) BuLi/hexane, ether, 20 °C, 1 h, then 5 equiv of MeI; (vi) NaH, THF, then BuLi/hexane, 5 equiv of MeI, and finally esterification; (vii) BuLi/hexane, ether, 20 °C, 30 min gives **15**, and subsequently $KF{\cdot}2H_2O$, DMF gives **9**; (viii) (*E*)-$BrCH{=}CHCO_2CH_3$, $Pd(OAc)_2$, PPh_3, NEt_3; (ix) (*Z*)-$BrCH{=}CHCO_2CH_3$, $Pd(OAc)_2$, PPh_3, NEt_3.

ring-opening reaction could be used as an efficient regio- and stereospecific route to natural products such as **2** and **3** occuring in a number of *Anthemis* species.[1a] It has been found that some of the known natural acetylenes show powerful biological activity such as antifungal and antinematodic effects.[1b] However, only a very limited number of these compounds have been investigated since they are available in scarce amounts only. In this report we present an efficient five-step procedure for the synthesis of the methyl esters **2** and **3** starting from easily available chemicals.

Propynylzinc chloride, prepared from commercially available propynyllithium and dry zinc chloride, was coupled with 2,4-dibromothiophene (**4**) by the use of catalytic amounts of palladium acetate and triphenylphosphine[3] to give 4-bromo-2-(1-propynyl)thiophene (**5**) in 70% yield. By the use of 4-bromo-2-iodothiophene (**6**) it was possible to raise the yield of **5** to 80% (see Scheme I). However, **6** has to be prepared in an extra step from **4**.[4]

An attractive route to **2** and **3** would be the ring-opening of the thiopheneacrylic acids **7** and **8** followed by esterification. Thus the sodium salts of **7** and **8**, prepared by the addition of sodium hydride to the corresponding acids in THF, were treated with butyllithium in hexane. The choice of THF was dictated by the insolubility of the sodium salts of **7** and **8** in ether. As judged by IR and NMR spectroscopy, no ring opening had occurred. Not even had the halogen–metal exchange taken place since in both cases most of the starting materials were recovered.

Ring opening of **5** with butyllithium in hexane/ether would lead to the acetylenic thio enol ether **9** after S-methylation with methyl iodide. The treatment with butyllithium gave no detectable ring-opening products; instead, the reaction mixture, after 1 h at room temperature, contained the compounds shown in Scheme I as evidenced by GC/MS. The formation of the main product **12** clearly indicates that 2-(1-propynyl)-4-thienyllithium was formed but was stable toward ring opening. It should also be noted that we could find no trace of 2-(1-butynyl)thiophenes, which indicates that the propargylic position was not metalated to give a thermodynamically stable lithium derivative under the reaction conditions.[5]

In a recent paper, we have shown that a trimethylsilyl group in the 2-position increased the ring-opening tendency of 3-thienyllithium derivatives.[6] We therefore prepared the trimethylsilyl derivative **14** by metalating **5** with lithium diisopropylamide followed by trimethylsilyl chloride. Subsequent treatment of **14** with butyllithium at room temperature followed by methyl iodide smoothly gave the thio enol ether **15**, which was desilylated with potassium fluoride in dimethylformamide,[7] to give the terminal acetylene **9**. This compound was stereospecifically coupled with (*E*)- and (*Z*)-methyl bromoacrylate according to Heck et al.[8] to give **2** (44%) and **3** (45%), respectively (17% total yield calculated on the basis of **4**). The spectroscopic data for **2** and **3** were in full agreement with those reported by Bohlmann et al.[9]

The use of 0.1 equiv of the palladium catalyst resulted in extensive isomerization of the acrylate moiety, and, consequently, a minimum amount of the catalyst is recommended (we used 0.02 equiv in the best experiment as recommended by Heck et al.[8]).

Compounds **2** and **3** have previously been prepared by Bohlmann and Skuballa in a multistep nonstereospecific

(3) King, A. O.; Negishi, E. *J. Org. Chem.* **1978**, *43*, 358.
(4) Gronowitz, S.; Håkansson, R. *Ark. Kemi* **1960**, *16*, 309.
(5) It is conceivable that a rapid metalation at the propargylic position of **5** could take place, followed by a rapid trans metalation with another molecule of **5** to give **5** and 3-bromo-5-(1-propynyl)-2-thienyllithium, which would give **13** upon reaction with methyl iodide.
(6) Gronowitz, S.; Frejd, T.; Karlsson, J. O.; Lawitz, K.; Pedaja, P.; Pettersson, K. *Chem. Scr.* **1981**, *18*, 192.
(7) Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.* **1973**, 1495.
(8) Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926.
(9) Bohlmann, F.; Skuballa, W. *Chem. Ber.* **1970**, *103*, 1886.

synthesis in very low total yields (0.7% of **2** and 0.1% of **3**).[9] Thus, the present work clearly shows the synthetic utility of the ring opening of suitably substituted 3-thienyllithium derivatives in combination with modern carbon–carbon bond-forming reactions.

Compounds **2** and **3** have been submitted to biological testing.

Experimental Section

GLC analyses were performed on a Perkin-Elmer 900 gas chromatograph, and NMR spectra were recorded with a JEOL MH 100 NMR spectrometer, IR spectra with a Perkin-elmer 298 infrared spectrometer, and mass spectra with a Finnigan mass spectrometer.

All reactions with organometallic reagents were performed in ether or THF freshly distilled over sodium wire under a nitrogen atmosphere.

4-Bromo-2-(1-propynyl)thiophene (5) was prepared according to ref 3 from 50 g (0.21 mol) of 2,4-dibromothiophene[10] and propynyl zinc chloride, prepared from 14 g (0.31 mol) of propynyllithium (Alfa Corp.) and 40 g (0.30 mol) of dry zinc chloride[11] in 400 mL of THF: yield 70%; bp 108–111 °C (10 mm); IR (film) 2240 cm^{-1} (C≡C); NMR ($CDCl_3$) δ 2.05 (brs, 3 H, CH_3), 6.97 (m, 1 H, 3-H), 7.01 (d, 1 H, 5-H, $J_{3\text{-H,5-H}}$ = 1.3 Hz).

Anal. Calcd for C_7H_5BrS: C, 41.8; H, 2.51; S, 15.9. Found: C, 41.8; H, 2.48; S, 15.8.

Preparation of **5** from 4-bromo-2-iodothiophene[4] (**6**) increased the yield to 80%.

Attempted Ring Opening of 5. A solution of 1.0 g (5.0 mmol) of **5** in 10 mL of dry ether was treated with 3.6 mL (5.6 mmol) of BuLi (1.55 M in hexane) under a nitrogen atmosphere. After 1 h 1.0 mL (16 mmol) of methyl iodide was added, and the reaction was left for another hour. An aqueous workup yielded a mixture of products as indicated by GC. GC/MS together with coinjection with authentic material proved the main peak to be 4-methyl-2-(1-propynyl)thiophene (**12**). The other compounds (see Scheme I) were identified by GC/MS.

4-Methyl-2-(1-propynyl)thiophene (12). A solution of 3.1 g (15 mmol) of **5** in 50 mL of dry ether at −70 °C was treated with 12 mL (19 mmol) of BuLi (1.55 M in hexane) under a nitrogen atmosphere. After 15 min, 1.8 mL (19 mmol) of dimethyl sulfate was added. The cooling bath was removed 2 h later. When the reaction mixture had reached room temperature, it was treated with aqueous ammonium hydroxide. The ethereal solution was washed with water, dried ($MgSO_4$), and evaporated: crude yield 1.8 g (90%); NMR ($CDCl_3$) δ 2.01 (brs, 3 H, propargylic), 2.16 (m, 3 H, 4-CH_3), 6.69 (m, 1 H, 5-H), 6.87 (m, 1 H, 3-H, $J_{5\text{-H,4-CH}_3}$ = 1.0 Hz).

Anal. Calcd for C_8H_8S: C, 70.5; H, 5.92. Found: C, 70.4; H, 5.92.

General Method for the Synthesis of 7 and 8. The thiophene derivative **5** (3.0 g, 15 mmol) was metalated in the 5-position with lithium diisopropylamide (16 mmol) as described in the preparation of **14** and treated with dry zinc chloride[11] in THF to yield the corresponding thienylzinc chloride. Coupling with (*E*)- and (*Z*)-methyl 3-bromoacrylate according to ref 3 gave the methyl esters of **7** and **8**, respectively, after an aqueous workup. The crude esters were hydrolyzed with lithium iodide/pyridine (refluxing overnight)[12] and methanolic sodium hydroxide, respectively. The cis acid **8** isomerized to a great extent in the refluxing pyridine. In both cases the mixtures were diluted with water and extracted with ether. The alkaline aqueous phases were made acidic and extracted with ether. The ethereal phase was washed with water, dried ($MgSO_4$ plus carbon black), and evaporated. The crude products were recrystallized from ethanol to give **7** and **8**.

(*E*)-3-[3-Bromo-5-(1-propynyl)-2-thienyl]acrylic acid (7): yield 0.60 g (15%); mp 224–225 °C;[13] IR (KBr) typical carboxylic acid peaks and 1680, 1610, and 960 (trans α,β-unsaturated COOH), 2230 cm^{-1} (C≡C); NMR ($(CD_3)_2SO$) δ 2.16 (s, 3 H, CH_3), 6.24 (d, 1 H, vinylic), 7.24 (s, 1 H, thienylic), 7.55 (d, 1 H, vinylic, $J_{2\text{-H,3-H}}$ = 15.6 Hz).

Anal. Calcd for $C_{10}H_7BrO_2S$: C, 44.3; H, 2.60. Found: C, 44.2; H, 2.56.

(*Z*)-3-[3-Bromo-5-(1-propynyl)-2-thienyl]acrylic acid (8): yield 0.40 g (10%); mp 224–225 °C;[13] IR (KBr) typical carboxylic acid peaks and 1690 and 1595 cm^{-1} (α,β-unsaturated COOH), 2220 cm^{-1} (C≡C); NMR ($(CD_3)_2SO$) δ 2.13 (s, 3 H, CH_3), 5.95 (d, 1 H, vinylic), 7.13 (d, 1 H, vinylic), 7.27 (s, 1 H, thienylic, $J_{2\text{-H,3-H}}$ = 12.3 Hz).

Anal. Calcd for $C_{10}H_7BrO_2S$: C, 44.3; H, 2.60. Found: C, 44.3; H, 2.67.

Attempted Ring Opening of the Thienylacrylic Acids 7 and 8. To a solution of 0.20 g (0.74 mmol) of the respective acid in 20 mL of anhydrous THF under a nitrogen atmosphere was added 19 mg (0.80 mmol) of sodium hydride. The sodium salt of **7** precipitated from the solution. After 15 min, 0.52 mL (0.81 mmol) of BuLi in hexane (1.55 M) was added, and the reaction mixture was allowed to stand for 45 min. Methyl iodide (0.47 mL, 7.4 mmol) was then added in an attempt to esterify the ring-opened acid. Two hours later the reaction mixture was poured onto water and made alkaline. The aqueous phase was extracted with ether. The ethereal phase was evaporated in the hope of finding esters, but only traces were found. The alkaline aqueous phase was made acidic and extracted with ether. The ethereal phase was washed with water, dried ($MgSO_4$), and evaporated. IR (KBr) showed no sign of a second acetylenic bond, which would be present in a ring-opened product. The ^1H NMR spectra ($(CD_3)_2SO$) were very similar to those of the starting materials. Apparently the halogen–metal exchange had not occurred to any great extent.

3-Bromo-5-(1-propynyl)-2-(trimethylsilyl)thiophene (14). To a solution of lithium diisopropylamide prepared from 12 g (0.12 mol) of diisopropylamine in 200 mL of dry ether under a nitrogen atmosphere and 77 mL (0.12 mol) of BuLi (1.55 M in hexane) was added 22 g (0.11 mol) of **5** dropwise. After 30 min, 20 mL (0.15 mol) of trimethylsilyl chloride was added. Two hours later the reaction was poured onto ice–water and worked up. Distillation afforded 19 g (65%) of the title compound: bp 95–97 °C (0.6 mmHg); IR (film) 2250 cm^{-1} (C≡C); NMR ($CDCl_3$) δ 0.41 (s, 9 H, $(Si(CH_3)_3)$, 2.09 (brs, 3 H, propargylic), 7.43 (brs, 1 H, 4-H).

Anal. Calcd for $C_{10}H_{13}BrSSi$: C, 44.0; H, 4.79; S, 11.7. Found: C, 43.8; H, 4.81; S, 11.6.

(*Z*)-4-(Methylthio)-1-(trimethylsilyl)hept-3-ene-1,5-diyne (15). To a solution of 9.0 g (33 mmol) of **14** in 150 mL of dry ether under a nitrogen atmosphere was added 23 mL (36 mmol) of BuLi (1.55 M in hexane) dropwise. After 30 min, 10 mL (0.16 mol) of methyl iodide was added, and the reaction mixture was allowed to stand for 2 h. An aqueous workup yielded a crude product, which was used without further purification in the next reaction step: IR (film) 2220, 2110 cm^{-1} (C≡C); NMR ($CDCl_3$) δ 0.20 (s, 9 H, $Si(CH_3)_3$), 2.07 (d, 3 H, 7-CH_3), 2.42 (s, 3 H, SCH_3), 5.78 (d, 1 H, 3-H, $J_{3\text{-H,7-CH}_3}$ = 0.4 Hz).

(*Z*)-4-(Methylthio)-hept-3-ene-1,5-diyne (9). The crude product **15** was treated overnight with 5 g of potassium fluoride dihydrate in 100 mL of dimethylformamide according to ref 7. The mixture was poured onto ice–water and extracted with methylene chloride. The organic phase was washed with water, dried ($MgSO_4$ plus carbon black), and evaporated to give 2.5 g of the title compound (84% overall yield from **14**). The crude product was used in the next reaction step without further purification due to its instability: IR 3290 cm^{-1} (C≡CH), 2240 (C≡C). NMR ($CDCl_3$) δ 2.08 (brs, 3 H, 7-CH_3), 2.42 (s, 3 H, SCH_3), 3.64 (d, 1 H, 1-H), 5.74 (brd, 1 H, 3-H, $J_{1\text{-H,3-H}}$ = 2.2 Hz).

Methyl (1*E*,5*Z*)-6-(Methylthio)-1,5-nonadiene-3,7-diyne Carboxylate (2). A solution of 0.80 g (5.0 mmol) of **9**, 0.75 g (5.0 mmol) of (*Z*)-methyl 3-bromoacrylate,[8] 11 mg (0.050 mmol) of palladium acetate, and 26 mg (0.10 mmol) of triphenylphosphine in 5 mL of triethylamine was stirred for 24 h under a nitrogen atmosphere. An aqueous workup and chromatography on silica

(10) Lawesson, S.-O. *Ark. Kemi* **1957**, *11*, 317.
(11) The zinc chloride was dried with thionyl chloride according to: Pray, A. R. *Inorg. Synth.* **1957**, *5*, 154.
(12) Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1960**, *43*, 113.
(13) The identical melting point of **7** and **8** is probably due to thermal equilibration to the same structure.

gel with hexane–ethyl acetate (85/15) gave a product which was further recrystallized from ligroin: yield 0.48 g (44%); mp 76–77 °C (lit.[9] mp 84 °C). Spectral data were in good agreement with literature data: IR (KBr) 2220, 2160 (C≡C), 1715 (CO_2R), 1605, 1515 (C=C) cm^{-1}; NMR (CCl_4) δ 2.09 (brs, 3 H, 9-CH_3), 2.43 (s, 3 H, SCH_3), 3.79 (s, 3 H, CO_2CH_3), 5.96 (brd, 1 H, 5-H), 6.14 (d, 1 H, 1-H), 7.00 (q, 1 H, 2-H, $J_{1\text{-H,2-H}}$ = 15.6 Hz, $J_{2\text{-H,5-H}}$ = 2.8 Hz).

Methyl (1*Z*,5*Z*)-6-(methylthio)-1,5-nonadiene-3,7-diyne carboxylate (3) was prepared in the same way as **2** from (*E*)-methyl 3-bromoacrylate by using the same amounts of starting materials. Purification was carried out by chromatography on silica gel with hexane–ethyl acetate (85/15); yield 0.49 g (45%). Spectral data were in good agreement with those reported in the literature: IR (film) 2220, 2160 (C≡C), 1715 (CO_2R), 1605, 1525 (C=C) cm^{-1}; NMR (CCl_4) δ 2.09 (d, 3 H, 9-CH_3), 2.39 (s, 3 H, SCH_3), 3.69 (s, 3 H, CO_2CH_3), 5.92 (brd, 1 H, 5-H), 5.95 (d, 1 H, 2-H), 6.26 (q, 1 H, 2-H, $J_{1\text{-H,2-H}}$ = 11 Hz, $J_{2\text{-H,5-H}}$ = 2.8 Hz, $J_{5\text{-H,9-CH3}}$ = 0.6 Hz).

Acknowledgment. Grants from the Swedish Natural Science Research Council to T.F. and S.G. are gratefully acknowledged.

Registry No. 2, 3102-40-7; **3**, 2739-61-9; **4**, 3140-92-9; **5**, 79916-95-3; **6**, 73882-40-3; **7**, 79916-96-4; **7** methyl ester, 79916-97-5; **8**, 79916-98-6; **8** methyl ester, 79916-99-7; **9**, 79917-00-3; **10**, 23229-66-5; **11**, 79917-01-4; **12**, 79917-02-5; **13**, 79917-03-6; **14**, 79917-04-7; **15**, 79917-05-8; methyl (*E*)-3-bromoacrylate, 6213-87-2; methyl (*Z*)-3-bromoacrylate, 6214-22-8.

A Convenient Synthesis of Hexafluoroacetone

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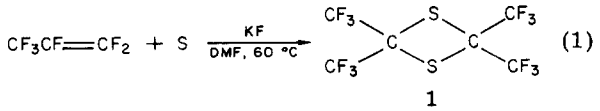
Hexafluoroacetone (HFA) is a powerful electrophile and, as such, has been used as an efficient trapping agent and useful synthetic reagent. Of the many methods which have been reported for the preparation of HFA,[1] several are based on hexafluoropropene (HFP) as the raw material due to its commercial availability, although the first industrial-scale preparation involved the fluorination of hexachloroacetone. Among the former methods is the nitric oxide oxidation of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (1) or hexafluorothioacetone dimer (HFTA dimer) at 600 °C.[2] We have discovered that HFTA dimer can readily be converted by NO and other oxidants to HFA at much lower temperatures, and have also developed a simple and convenient synthesis of HFTA dimer.[3]

HFTA Dimer

When HFP was bubbled into dry DMF containing KF and sulfur at 40 °C, an exothermic reaction occurred, and HFTA dimer was produced in 72–83% yields after workup (eq 1). HFP could be added at a rate such that a reaction temperature of 50–60 °C was maintained without external heating and HFP was consumed as rapidly as it was added.



(1)

1

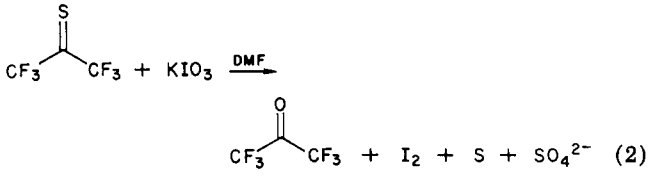
When KF, S, and DMF are mixed, a bluish hue is imparted to the solution. The color rapidly disappears upon the addition of HFP or HFTA dimer. The blue color did not appear if the DMF was wet (0.05% H_2O) although the reaction to produce HFTA dimer still occurred. The reaction takes place under similar conditions in dimethyl sulfoxide, dimethylacetamide, and *N*-methylpyrrolidinone, but little or no reaction took place in sulfolane, acetone, or HFTA dimer. When CsF was substituted for the less soluble KF, the reaction took place in CH_3CN but with considerable byproduct formation.

HFTA dimer is appreciably soluble in DMF at room temperature. Under the conditions of our experiments, the mixture was homogeneous (except for undissolved KF) at the end of the reaction. Cooling the solution to about −20 °C precipitates nearly all of the dimer (mp 23 °C), which can then be filtered, washed with water, and distilled (bp 110 °C). The recovered DMF can be reused.

Hexafluoroacetone

In the presence of fluoride ion, HFTA dimer is in equilibrium with its monomer in DMF solution. Since HFTA is much more reactive than HFTA dimer, we felt that oxidation of the monomer, generated in situ from the dimer, would provide a convenient method for the preparation of HFA, since the ketone (bp −28 °C) would distill out of the reaction mixture. Of the several metallic and nonmetallic reagents used for the oxidation, nearly all reacted. However, most gave a mixture of HFA and CF_3COF (Ag_2O, PbO, SnO, PbO_2, Fe_2O_3) or of HFA and $(CF_3)_3CH$[4] (P_2O_5, Cu_2O, CuO). These same products were also formed in low yield when no oxidant was present. The oxidants alter the product ratios from about 6:2:1 (HFA/CF_3COF/$(CF_3)_3CH$) with DMF, HFTA dimer, and KF alone to nearly all CF_3COF in the presence of PbO_2 and to nearly all HFA in the presence of KIO_3, $NaIO_4$, NO_2, or HgO. These oxidants substantially increased the amount of volatile products.

A convenient reagent for the conversion of HFTA to HFA was KIO_3. Thus, when **1** was added to a mixture of KF and KIO_3 in DMF and the solution heated to reflux, HFA distilled out of the flask (eq 2). Yields were 74–89%.



(2)

Interestingly, SO_2 was not a reaction product. However, sulfur was recovered from the product mixture, in addition to I_2 and K_2SO_4. Elemental sulfur was a substantial byproduct in the oxidation of HFTA with NO_2 also, permitting its recycle in the synthesis of **1**.

The two reactions (HFTA dimer synthesis and conversion to HFA) could be combined in a one-pot procedure in which **1** was not isolated. After preparation of the dimer from HFP, KIO_3 was added and the mixture heated to reflux as before during a period of 0.5–1 h during which HFA distilled out of the reaction mixture. We found that the purity of HFA was reduced in this procedure, being contaminated with $(CF_3)_3CH$ (bp 11–12[5]). For most purposes, this is not likely to adversely effect reactions intended with HFA.

(1) For a review, see Krespan, C. G.; Middleton, W. J. *Fluorine Chem. Rev.* **1967**, *1*, 145.
(2) Middleton, W. J.; Sharkey, W. H. *J. Org. Chem.* **1965**, *30*, 1384.
(3) During the course of our work, England reported the synthesis of HFTA dimer under similar conditions. England, D. C. *J. Org. Chem.* **1981**, *46*, 147.
(4) Identified by IR, ^1H NMR, and ^{19}F NMR.
(5) Brice, T. J.; Lazerte, J. D.; Pearlson, W. H. *J. Am. Chem. Soc.* **1953**, *75*, 2698.

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