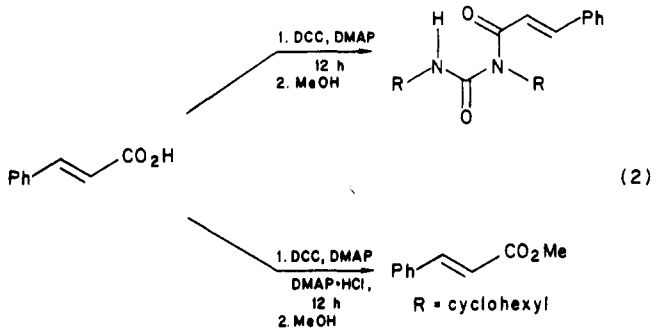
methylamino)pyridine (DMAP) under conditions of high dilution (1 mg/12 mL) for 12 h results in essentially quantitative formation of *N*-acylurea, and addition of large excesses of methanol after 12 h does not result in the formation of detectable quantities of methyl cinnamate. However, in the presence of 4-(dimethylamino)pyridine hydrochloride (DMAP·HCl) *N*-acylurea is produced in only minor amounts, and methyl cinnamate is now the major product. We therefore expect that this simple protocol will prove useful for bimolecular esterifications which must, of necessity, be conducted at rather high dilutions, such as those involving radiolabelled compounds or small amounts of biologically derived materials (eq 2).



(2)

Although the generality of this method for macrolactonization using complex substrates has yet to be demonstrated, *isolated* yields obtained with the usual collection of simple ω-hydroxy acids of various chain lengths (Table I) suggest that this simple procedure may prove competitive with more elaborate methods as an approach to macrolactonization, particularly for the ring sizes commonly encountered in natural products. In this context, we note that all reagents are commercially available except for DMAP·HCl, which is trivially prepared from DMAP and anhydrous HCl in THF. Additionally, the procedure detailed below (which affords a *95%* isolated yield of hexadecanolide on a 200-mg scale) uses only 30 mL of solvent, and the only expensive apparatus employed is a Sage syringe pump, an item common to most laboratories where macrolactonization reactions are performed. Finally, this method has been employed in one reasonably complex example in a synthetic approach to (−)-colletodiol,[10] a system where lactonization has proven quite difficult.[11]

Experimental Section

General Methods. 12-Hydroxydodecanoic acid, cyclododecanone, cyclotridecanone, cyclopentadecanone, and 16-hydroxyhexadecanoic acid were purchased from Aldrich Chemical Company. Oxidation of cyclododecanone, cyclotridecanone, and cyclopentadecanone, using MCPBA in methylene chloride as previously described,[1a] furnished authentic samples of tridecanolide, tetradecanolide, and hexadecanolide, respectively. Hydrolysis with KOH in methanol afforded 12-hydroxydodecanoic acid, 13-hydroxytridecanoic acid, and 15-hydroxyhexadecanoic acid, respectively. Structures assigned to lactonization products from these acids rest on spectral and chromatographic comparisons with authentic samples obtained as described above; the structure of the lactone obtained from 16-hydroxyhexadecanoic acid was assigned from spectral (NMR, IR, MS) data alone.

All lactonizations were performed by using the same general procedure detailed below for the preparation of hexadecanolide.

Hexadecanolide from 15-Hydroxypentadecanoic Acid. A flame-dried 50-mL round-bottomed flask, equipped with stirring bar, reflux condenser with serum cap, argon inlet (through serum cap), and syringe pump inlet (vide infra, through serum cap), was charged with 25 mL of ethanol-free[12] chloroform, 0.343 g (1.66 mmol) of DCC, 0.305 g (2.50 mmol) of 4-(dimethylamino)pyridine, and 0.263 g (1.66 mmol) of 4-(dimethylamino)pyridine hydrochloride. The resulting solution was brought to reflux, and a solution of 0.215 g (0.832 mmol) of 15-hydroxypentadecanoic acid in 5.0 mL of THF[13] was infused via syringe pump over 16 h. (A Glenco gas tight syringe with a Teflon seal and Teflon tubing was utilized, and the inlet of the Teflon tubing was positioned in the condensate formed at the tip of the reflux condenser.) After addition was completed, the syringe apparatus was removed and the reaction mixture was cooled to room temperature. The residual contents of the syringe and Teflon tubing were rinsed into a tared flask and concentrated to afford 11.5 mg of starting hydroxy acid. Methanol (1.0 mL) and acetic acid (0.19 mL, 4.0 equiv) were added to the reaction flask and stirring was continued for 30 min, at which time no DCC was detected by TLC analysis (10% EtOAc–hexanes). Further TLC analysis in two solvent systems revealed the formation of the desired lactone (R_f 0.34 in 10% EtOAc–hexanes), *N*-acylurea (independently prepared, R_f 0.32 in 35% THF–hexanes) was not detected. The mixture was concentrated to 5 mL, diluted with 25 mL of ether, filtered, and concentrated. The residue was taken up in a minimal amount of chloroform and applied to a 24 × 1.5 cm column of silica gel (Davisil 60–200 mesh) slurry packed in hexanes. Elution was with 20 mL of hexanes and then with 3% THF–hexanes; 6-mL fractions were collected. Concentration of fractions 11–13 gave 0.180 g (95%, based on hydroxy acid delivered to the reaction vessel) of hexadecanolide, identical in all respects with an authentic sample.

Acknowledgment. Support of this research by the National Institutes of Health (through Grant No. GM-28961) and the Alfred P. Sloan Foundation is gratefully acknowledged.

Registry No. $HO(CH_2)_{11}CO_2H$, 505-95-3; $HO(CH_2)_{12}CO_2H$, 7735-38-8; $HO(CH_2)_{14}CO_2H$, 4617-33-8; $HO(CH_2)_{15}CO_2H$, 506-13-8; tridecanolide, 1725-04-8; tetradecanolide, 3537-83-5; hexadecanolide, 109-29-5; heptadecanolide, 5637-97-8.

(10) Our efforts in this area will be reported separately.
(11) Schnurrenberger, P.; Hungerbühler, E.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 2209–2212.
(12) Chloroform utilized in this procedure was purified as described in "Purification of Laboratory Chemicals." Perrin, D. D., Armarego, W. L.; F., Perrin, D. R., Eds.; Permagon Press: Oxford, 1966. Without such purification, significant amounts of ethyl esters are formed in small-scale experiments.
(13) Tetrahydrofuran (THF) was utilized only due to the low solubility of this particular hydroxy acid in chloroform; chloroform is preferable as solvent (if possible) since the use of THF as the sole solvent affords very low yields of lactones. The major products formed in THF are *N*-acylureas, most probably because DMAP·HCl is very insoluble in THF, even at reflux temperature.

Isolation and Purification of Benzene-1,2,4,5-tetrathiol

C. W. Dirk, S. D. Cox, D. E. Wellman, and F. Wudl*

Institute for Polymers and Organic Solids, Department of Physics, University of California, Santa Barbara, California 93106

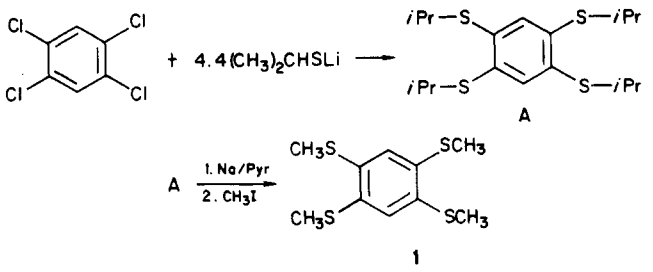
Received December 17, 1984

The title compound has been reported in the literature in the past.[1] Yields were reported to be good to very good but we have had difficulty obtaining these results with reliable frequency. We needed to be able to prepare large amounts of the tetrathiol in a straightforward fashion since we wanted to use it, among other projects,[2] as a monomer.[3]

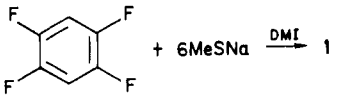
(1) (a) Maiolo, F.; Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Org. Chem.* **1981**, *46*, 3070. (b) Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1980**, *45*, 4376. (c) Reifschneider, W. *Chem. Abstr.* **1968**, *69*, 106244.
(2) Cox, S. D.; Dirk, C. W.; Wellman, D. E.; Wudl, F. *J. Am. Chem. Soc.* **1984**, *106*, 7131.

0022-3263/85/1950-2395$01.50/0

Scheme I



Scheme II



The most recent publication on the preparation of the desired tetrathiol[1a] is clearly the most elegant. However, the main problem that we encountered with the method of Maiolo was isolation of the extremely atmosphere–sensitive product in the presence of HMPA,[4] a solvent that is soluble both in water and hexane. These authors have routinely removed residues of HMPA by short-path chromatography on silica gel but did not give a specific workup of the title compound, and in our hands this procedure fails for attempted isolation of large quantities of tetrathiol.

Previous workers in the field may have been misled by the deceptively small changes that occur when the title tetrathiol is exposed to the atmosphere. It should come as no surprise that such a relatively electron-rich molecule is, in fact, very sensitive to exposure to the atmosphere (particularly in solution); samples of solid which have been left in stoppered vials on a laboratory bench barely changed in appearance (sometimes they would become slightly yellow) but attempts to redissolve them completely in solvents in which **2** is normally soluble (e.g., ether, benzene) failed to give clear solutions. These observations would explain the large discrepancy in melting point observed by us (mp 145–147 °C) on carefully protected samples and by others (mp 139–141 °C,[1c] mp 138–141 °C[1a]).

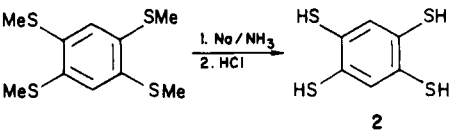
Results and Discussion

In the schemes below we show two excellent procedures for the reproducible preparation and isolation of benzene-1,2,4,5-tetrathiol.

Scheme I involves only a slight (but important for a large-scale experiment) modification of the Testaferri procedure,[1b] i.e., the use of only slightly more than 4 (instead of 8) equiv of mercaptide in HMPA, the use of lithium salt, and the use of pyridine[5] for the reduction solvent. We have found that the tetrathioether **1** is a very convenient protected form of the tetrathiol for storage.

Testaferri had already shown that **1** could not be prepared directly from tetrachlorobenzene because the conditions required for aromatic nucleophilic substitution of chloride by mercaptide are vigorous enough to cause demethylation of some of the initial substitution intermediates.[4] However, since it is known that fluoride is a vastly superior leaving group in certain aromatic nucleophilic substitutions,[6] we expected to circumvent the problems encountered by Testaferri et al. with the use of tetrafluorobenzene.

Scheme III



Scheme II constitutes a vast improvement on the previous scheme, provided expense is no object. The reaction is carried out at room temperature in *N,N'*-dimethylimidazolidinone (DMI)[7] and is very efficient (isolated yield of 94%). The reaction can also be carried out in HMPA, but the yield of pure product is lower and separation of contaminants is difficult (requires HPLC or multiple crystallizations).

The deprotection described in Scheme III is most efficient if carried out at the boiling point of ammonia in as high as possible a dilution, otherwise the only side product (1-(methylthio)-2,4,5-benzenetrithiol) is produced in unacceptable (≃10%) yield. The yield of this side product can be reduced to zero with the use of propylamine,[8] but in our hands the purification of this solvent to reproducibly generate blue electride solutions proved capricious. In this regard, **A** can be reduced directly to the tetrathiol in propylamine; however, conditions to reproducibly obtain product free of contamination with the monoisopropyl derivative proved difficult to establish.

Compound **2** is a white, crystalline solid which is very soluble in most organic solvents. It sublimes readily at temperatures above 80 °C and oil pump vacuum. As formed from the reduction in liquid ammonia, it is usually contaminated with trace amounts of monomethyl thioether as determined by NMR ($CDCl_3$, δ 2.42 relative to Me_4Si); sublimation does not improve the purification considerably. Pure product can be obtained by recrystallization from a minimum amount of benzene. The sensitivity toward atmospheric oxidation can be enhanced dramatically by the presence of any weak base.

The title compound is an excellent bidentate ligand for transition metals[3] and also serves as starting material for a large number of derivatives on the basis of the alkylation,[2] thiolation,[9] and azolation[10] of its mercaptan functional groups.

Experimental Section

All experiments were carried out under a dry nitrogen atmosphere. HMPA was stored over molecular sieves (4A) and DMI was distilled from barium oxide and stored under argon.

1,2,4,5-Tetrakis(isopropylthio)benzene (A). In a 3-L, three-necked flask equiped with a thermometer, magnetic stirring bar, nitrogen inlet, and rubber septum with a needle connected through tubing to a mineral oil bubbler were placed (through the septum) 500 mL of HMPA and 165 mL (1.78 mol) of isopropyl mercaptan. The content of the flask was then degassed by bubbling argon through the liquid for ≃15 min and the whole was cooled to 10 °C (internal) with stirring. At this point, 159

(3) Dirk, C. W.; Wudl, F. *Macromolecules*, submitted for publication.
(4) A referee pointed out that the Italian group has also apparently found HMPA unsatisfactory and has recently developed procedures for thiolations of chlorobenzenes in DMF (Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* **1983**, 751). No preparation of the title compound is given in this article.
(5) Adams, R.; Ferretti, A. *J. Am. Chem. Soc.* **1959**, *81*, 4939.
(6) Chambers, R. D. "Fluorine in Organic Chemistry"; Wiley-Interscience: New York, 1973.
(7) (MacNicol, D. D.; Mallinson, P. R.; Murphy, A.; Sym, G. J. *Tetrahedron Lett.* **1982**, *23*, 4131) have described the advantage of this solvent for just this kind of substitution reaction.
(8) For the recommended use of propylamine for this kind of reduction, see: Odorisio, P. A.; Pastor, S. D.; Spivack, J. D.; Radebaugh, R. K. *Phosphorus Sulfur* **1982**, *13*, 309.
(9) Cox, S. D., unpublished results.
(10) Williams, K. A., unpublished results.

mL of 10.2 molar *n*-butyllithium (1.62 mol) was added. The reason for the excess isopropyl mercaptan over the lithium reagent was to ensure that no excess *n*-butyllithium remained before the aromatic halide was added and to make up for some loss due to quick evolution of butane in the next step. The addition of this highly concentrated lithium reagent should be done very slowly to allow as much of the butane gas to evolve as possible. The addition was done via a gas-tight syringe with a 15-gauge (or larger diameter) needle since the reagent is very viscous. The addition reaction is very exothermic, requiring repeated renewal of the ice in the cooling bath. Since butane is surprisingly soluble in HMPA, one must ensure before proceeding that all the butane is eliminated; this is done by heating the reaction mixture while stirring slowly to ≃60 °C and holding it at that temperature until butane evolution subsides. The reaction mixture is then cooled to 10 °C and 80 g (0.37 mol) of 1,2,4,5-tetrachlorobenzene is added. This reaction is exothermic (temperature rises to between 55 °C and 80 °C). When addition was complete, the mixture was heated to 100 °C for ≃$^1/_2$ h and monitored by TLC (25:75 chloroform:hexane). Only one spot was observed; when more spots were observed, heating was prolonged.

To the clear, orange-yellow reaction mixture was added slowly with stirring an excess of saturated aqueous sodium chloride solution until the product separated as a white solid. This was vacuum-filtered and washed copiously with water and dried. Sometimes this was not enough to remove all the HMPA and NaCl, the product was then dissolved in ether and extracted several times with water. The ether layer was dried and evaporated to yield 125 g (90% based on tetrachlorobenzene), mp 77–79 °C (lit.[1b] mp 78–80 °C). When the yield was much higher, it was found to be due to entrained HMPA which could be removed by washing with cold (0 to −10 °C) methanol.

1,2,4,5-Tetrakis(methylthio)benzene (1). In a three-neck 1-L flask was placed a solution of 25 g (66.72 mmol.) of A in 300 mL of pyridine (previously dried over molecular sieves). The flask was equipped with a thermometer, magnetic stirring bar, and gas inlet and outlet tubes. The mixture was heated rapidly to 105–110 °C and 8.29 g of Na pellets (360 mmol.) were added rapidly against a nitrogen flow. As the sodium metal reacted the reaction mixture turned red. The reaction mixture was maintained below reflux but above 100 °C until all of the sodium had reacted (≃1 h). The mixture was then cooled to 10 °C and methyl iodide (24 mL) was added slowly via syringe, and the resulting mixture (now brown in color) was allowed to stir for 40 min and quenched with 350 mL of saturated aqueous sodium chloride. The quenching had to be done carefully since sometimes some unreacted sodium was found in the reaction mixture prior to quenching. Water was then added until the mixture became a dilute suspension; the latter was filtered under suction and washed copiously with water to yield a yellow, crystalline solid which was washed with up to 150 mL of −10 °C methanol to yield 10.7–11.5 g (61.2–66%) of product; mp 127–129 °C (lit.[1a] mp 128–130 °C).

Direct Preparation of 1. In a three-necked flask equipped with a magnetic stirring bar, septum cap, and gas inlet tube was placed 10.5 g (0.15 mol) of sodium methyl mercaptide (previously prepared from the mercaptan and sodium ethoxide in absolute ethanol followed by complete removal of ethanol under high vacuum for 24 h) and 100 mL of dry DMI. To this suspension was added with stirring 3.75 g (2.79 mL, 0.025 mol) of 1,2,4,5-tetrafluorobenzene via syringe through the septum cap. The addition was at a relatively fast rate, resulting in a mildly exothermic reaction. After 16 h at room temperature, *TLC* (silica gel, 3:1 hexane/ether) showed only one spot. At this point the reaction mixture was added to 500 mL of water, and the white precipitate was filtered and washed copiously with water and sparingly with cold methanol to yield 6.17 g (94% yield) of white powder; mp 128–130 °C.

Benzene-1,2,4,5-tetrathiol (2). The above tetra(methyl thioether) 1 (8 g, 30.5 mmol.) was weighed into a 1-L, three-necked flask equipped with a dry-ice cold finger condenser, magnetic stirring bar, and gas inlet and outlet tubes. A suspension was obtained when ammonia (500–600 mL) was distilled into the flask. To this suspension was added 5.6 g (244 mmol.) of 2–4-mm sodium spheres, the cooling bath was removed, and the ammonia was allowed to reflux for 4–8 h. It is important that the ammonia not be allowed to cool itself below its boiling point; this is accomplished by periodically removing the "snow" condensate or by external "heating" (placing in an ethylene glycol bath). After this period of time the reaction mixture had usually lost its blue color; at this point it was cooled to −78 °C (external), treated with an excess of ammonium chloride, and allowed to evaporate (overnight) under a positive pressure of nitrogen. Next, thoroughly degassed, 5% aqueous HCl (400 mL) was added via canula, and after the inorganic solids dissolved, 500 mL of degassed methylene chloride was added via canula to the light grey suspension. The mixture was stirred until the aqueous layer became clearer (some grey-black particles were always found in the organic layer) and filtered through a Schlenk filter into a 1-L Schlenk flask containing degassed anhydrous sodium sulfate. The dry methylene chloride solution was then Schlenk-filtered into another 1-L Schlenk (or two-necked) flask and the solvent was removed in vacuo. The white (sometimes greyish) solid residue was transferred in a glovebag into a sublimer and sublimed at 80–120 °C and 0.025–0.1 torr to yield a white, crystalline product (4–5.1 g, 64–81% yield); mp 145–147 °C (lit.[1a] mp 138–141 °C; lit.[1c] mp 139–141 °C; UV–vis [CH_2Cl_2, λ_{max} (ϵ)] 248 (31 000), 270 sh, 320 (1900); IR (KBr) 2510 (s), 1425 (s), 1305 (s), 1245 (m), 1120 (s) 1063, (s), 915 (m), 825 (s), 605 (w), 420 (s); NMR ($CDCl_3$, δ relative to Me_4Si) 3.68 s, 2 H (S–H); 7.38 s, 1 H (lit.[1a] ($CDCl_3$?) δ 3.6, 2 H; 7.25, 1 H. This compound is not surprisingly (vide supra) very atmosphere sensitive but can be stored in the solid state in a refrigerator within a drybox for months. Further purification to remove traces of monomethyl thioether (up to 5%) can be accomplished by 2–3 recrystallizations in a glovebag from degassed benzene (4–5 g/20–25 mL).

Acknowledgment. We thank Joan Brennan for technical assistance. This work was supported by the National Science Foundation through Grant DMR 8217924 and by W.R. Grace & Co.

Registry No. 1, 1846-35-1; 2, 20133-21-5; A, 74542-69-1; 1,2,4,5-$Cl_4C_6H_2$, 95-94-3; $(CH_3)_2CHSH$, 75-33-2; 1,2,4,5-$F_4C_6H_2$, 327-54-8; MeSNa, 5188-07-8.