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SULFINIC ACIDS AND RELATED COMPOUNDS. 21. PREPARATION OF CRYSTALLINE SULFINIC ESTERS^{1,2}

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In a search for means of preparing stable crystalline esters of sulfinic acids, yields from *p*-toluenesulfinic acid as a model were 53-92% with 1,1'-carbonyldiimidazole (CDI, **2**) as a coupling reagent for a variety of alcohols. The best coupling reagents were CDI and chlorotrimethylsilane (**16**). The agent **16** could be used with sulfinate salts, as could CDI with *in situ* acidification. The best alcohols were 1-adamantanol and *p*-nitrobenzyl alcohol. Among alkanesulfinic esters, methanesulfonates were unstable oils obtainable only in low yields, but 1-butanedisulfonates were obtained in 52-56% yield (although still as oils). As a stable disulfinic acid, 1,4-butanedisulfinic acid gave a nicely crystalline di-1-adamantyl ester (mp 123-125°C), but another alkanedisulfinate salt or acid that contained a disulfide moiety gave no diester by use either of **2** or **16**.

Key words: 1,1'-Carbonyldiimidazole, chlorotrimethylsilane, sulfinic acids, sulfinic acid esters, sulfinic acid salts, *p*-toluenesulfinic acid.

INTRODUCTION

In connection with our interest in sensitive sulfinic acids and their derivatives, esters afford a number of advantages over the salts.^{3a} We have previously prepared methyl and ethyl esters from sulfinate salts by acidification with methanolic HCl followed by treatment with diazomethane,^{4,5} by reaction with trialkyloxonium fluoroborates^{3a,5,6} and by reaction with alcohols containing BF₃ etherate.^{3a} In addition to considering (but avoiding) other methods for preparing sulfinic esters,³ we also have used the conventional reaction of a sulfinyl chloride with methanol.⁷ In order to capitalize on the advantages of esters,³ recently we have sought particularly mild methods for preparing crystalline sulfinic esters that would be particularly stable and especially amenable to purification. This paper reports the results.

RESULTS AND DISCUSSION

Our first goal was to ascertain the alcohol(s) that seemed most likely to give esters with the desirable properties mentioned. *p*-Toluenesulfinic acid (**1**) was

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TABLE I
p-Toluenesulfonates prepared from *p*-toluenesulfonic acid (1) with CDI (2) as a coupling agent

Ester no.	Alcohol	Mmol of 2 used ^b	Chromatographic purification ^c		Yield, % ^d	Mp, °C (lit. mp)	¹ H NMR (CDCl ₃), [¹³ C NMR (CDCl ₃)]; δ in ppm
			Eluant	TLC R _f used for identif'n			
4	1-adamantanol	8.6	1:1 C-H	0.43	78	79–81 (80–82) ⁹	¹ H spectrum identical with the report of Reference 9 [144.09, 141.82, 129.50, 124.97, 81.79, 43.90, 35.88, 31.22, 21.34]
5	<i>p</i> -nitrobenzyl	7.7	1:1 C-H	0.43	57	69–71	8.15–8.04 (d, 2H, <i>J</i> = 8 Hz), 7.60–7.22(m, 6H), 5.14–4.45 (dd, 2H, <i>J</i> = 42 and 12 Hz), 2.42 (s, 3H)
6	9-fluorene-methanol	12.2	1:1 C-H	0.50	70	78–80	7.76–7.22 (m, 12H), 4.45–4.07 (m, 2H), 4.07–3.72 (m, 1H), 2.37 (s, 3H) [143.63, 143.42, 142.74, 141.31, 129.68, 127.76, 127.03, 125.24, 125.11, 119.91, 65.79, 47.77, 21.93]
7	cholesterol	10.0	1:4 H-C	0.63	56 ^f	136–137 (132–135) ⁹	7.65–7.24(dd, 4H, <i>J</i> = 30 and 8 Hz), 5.43–5.29 (dd, b, 1H, <i>J</i> = 12 and 4 Hz), 4.40–4.00 (m, 1H), 2.40(s, 3H), 2.42–0.66(m, 43H)
8	<i>p</i> -bromobenzyl	6.3	C	0.90	69 ^g	20–22	7.65–7.04 (m, 8H), 4.98–4.36 (dd, 2H, <i>J</i> = 50 and 12 Hz), 2.42(s, 3H)
9	1-adamantane-methanol	8.3	1:4 H-M	0.76	92	46–47	7.60–7.22 (dd, 4H, <i>J</i> = 24 and 8 Hz), 3.62–3.02 (dd, 2H, <i>J</i> =

							50 and 8 Hz), 2.42(s, 3H), 1.98(s, b, 3H), 1.63(s, b, 6H), 1.56 (s, b, 6H)
10	2-adamantanol	8.3	1:4 H-M	0.90	81 ^f	95–96	7.67–7.27 (dd, 4H, <i>J</i> = 28 and 8 Hz), 4.52 (s, b, 1H), 2.42 (s, 3H), 2.16–1.51 (m, 14H)
11	3-hydroxy-4-methoxybenzyl	8.3	3:7 E-M	0.83	69	63–65	7.60–7.20 (dd, 4H, <i>J</i> = 28 and 8 Hz), 6.76–6.50 (m, 4H), 4.92–4.36 (dd, 2H, <i>J</i> = 50 and 10 Hz), 3.84 (s, 3H), 2.42 (s, 3H)
12	2,3,5,6-tetramethyl- <i>p</i> -xylene- α, α' -diol	16.7	1:1:8 C-E-H	0.50	53	175–176	7.64–7.24 (dd, 8H, <i>J</i> = 30 and 8 Hz), 5.20–4.48 (dd, 4H, <i>J</i> = 62 and 10 Hz), 2.44 (s, 6H), 2.20 (s, 12H)
13	1-acenaphthenol	7.8	1:9 E-H	0.58	61 ^f	70–72	7.80–7.04 (m, 10H), 6.35–6.10 (m, b, 1H), 3.85–3.25 (m, 2H), 2.38 (s, 3H)
14	dibenzosuberanol	8.5	h	0.46 (C-H, 3:2)	92	204 dec	7.36–7.00 (m, 12H), 6.52 (s, 2H), 5.36 (s, 1H), 2.36 (s, 3H)
15	N-(hydroxymethyl)phthalimide-	7.8	3:7 E-H	0.43	58	106–108	7.96–7.20 (m, 8H), 5.68–5.44 (m, 2H), 2.36 (s, 3H)

^a All compounds had elemental analyses for C, H, and S(C, H only for **5** and **8**) within $\pm 0.35\%$ of calcd, except Found 75.85%).

^b Mmol used for other reagents are given in the Experimental section.

^c C, CHCl₃; E, EtOAc; H, hexane; M, CH₂Cl₂.

^d Yield of product used for analysis, having the mp stated.

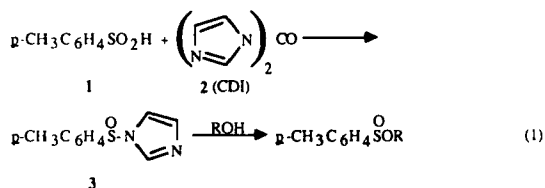
^e In KBr pellets unless otherwise specified.

^f Presumably as a mixture of diastereomers owing to the chiral sulfur atom.

^g Use also of 3.2 mmol of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with **8** gave 69%, but since much elimination was abandoned.

^h See the Experimental section.

used as a model acid and 1,1'-carbonyldiimidazole (**2**, CDI) as a model coupling agent (Equation 1). The general procedure was to allow the acid (**1**) to react with



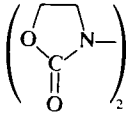
CDI (**2**) for a few minutes to give the presumed intermediate **3** (**3** is a sulfinic-acid counterpart of the carboxylic imidazolides that are intermediates in the reaction of CDI with carboxylic acids).⁸ After addition of the alcohol, the reaction proceeded smoothly and, after 1–2 h at room temperature, it led to the results reported in Table I. So far as we know, CDI has not been used for preparing sulfinic esters previously, although it is effective for preparing derivatives of sulfonic acids.⁸ Except for the ester **14** which crystallized directly, the products were chromatographed and, after being rubbed with solvent or recrystallized, were obtained in analytical purity in the yields shown in Table I (only the *p*-toluenesulfonates **4** and **7** appear to have been reported previously).⁹ All things considered, the most attractive alcohols seemed to be 1-adamantanol and *p*-nitrobenzyl alcohol, which gave the *p*-toluenesulfonates **4** and **5** respectively. Of these, the 1-adamantyl group is preferred, because not only is the yield higher (78% vs. 57%; Table I), but the stability is much better (two years at 0° for **4** vs. four months for **5**). Both the adamantyl (**4**) and *p*-nitrobenzyl esters (**5**) were much easier to crystallize than were **6–15**.

Attempted use of the general procedure for the reaction of phenol with the acid **1** and CDI (**2**) led only to virtually quantitative recovery of phenol, and addition of a base (DBU) or use of phenoxide ion gave the same result. Efforts with aryl esters were abandoned when there seemed little likelihood that any would meet the desiderata mentioned above. For example, attempts by others to synthesize the phenyl ester of **1** led to an unstable product,¹⁰ with *p*-toluenesulfinic acid only *p*-tolyl *p*-toluenethiosulfonate was obtained in low yield,¹¹ and *p*-tolyl benzenesulfinate decomposes at –20°C overnight.¹² Aryl thiosulfonates seemed equally unpromising as derivatives for our purposes. Thus, when the general procedure with **1** and CDI was applied to thiophenol or *p*-thiocresol, complete reaction occurred within five minutes, but the thiosulfonates (isolated in 25–40% yields) were quite unstable and were accompanied by impracticably large amounts of disulfides and thiosulfonates; in a similar vein, although phenyl *p*-toluenethiosulfinate has been obtained from **1** in yields of 34–40% by three other means, in these instances also byproduct formation apparently presented problems.¹³

Although CDI (**2**) was used as the model coupling reagent in the choice of the most promising alcohol(s) (Table I), determination was made of whether another coupling reagent might be superior. Dicyclohexylcarbodiimide has been useful for syntheses of sulfonates (cf. ref 9), but in our hands it was quickly dropped because it produced a strong allergic reaction. Of numerous agents others have tried,^{11,13} all except phenyl dichlorophosphate (**17**, Table II) for our purposes seemed likely

TABLE II

Yields and properties of 1-adamantyl *p*-toluenesulfinate (**4**) prepared with different coupling reagents^a

Coupling reagent	Yield from <i>p</i> -toluenesulfinic acid (1), %	Yield from sodium <i>p</i> -toluenesulfinate (19), %
CDI (2)	78	82 ^b
Me ₃ SiCl (16)	69	66
PhOP(O)Cl ₂ (17)	58	Trace ^c
 P(O)Cl (18)	Trace ^c	—

^a Melting points, TLC *R_f* values, and NMR spectra of the products were identical with those of **4** prepared from **1** and **2** (all mp's were in the range of 79–81°C).

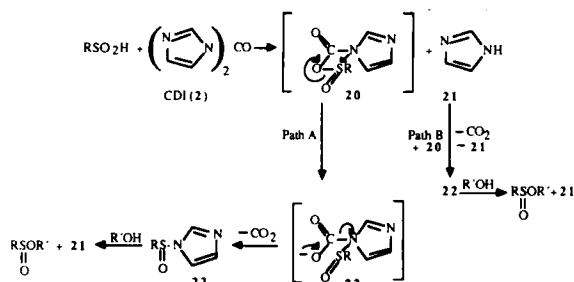
^b The salt in THF was converted to the acid (**1**) in situ by means of HCl in THF before reaction with CDI.

^c Not isolated; indicated by TLC of the product.

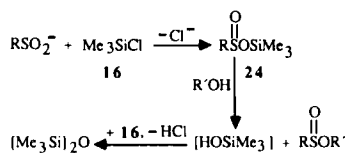
to result in difficult separable byproducts, in lower yields than **2**, and/or in times of reaction that might be suitable for the relatively stable **1** as a model but seemed likely to lead to serious side reactions with the much less stable alkanesulfinic acids. The phosphate **17**,¹³ which also has been used for esterification of carboxylic acids,¹⁴ and two other agents useful with carboxylic acids were compared with CDI (**2**). So far as we know, the latter two agents have not been tried previously with sulfinic acids, viz. chlorotrimethylsilane (**16**, Table II),¹⁵ and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (**18**, Table II).¹⁶ As Table II shows, CDI (**2**) gave the best result, but **16** and **17** also were promising with the acid **1**.

Since salts of sulfinic acids are well known to be much more stable than the acids, the agents listed in Table II also were tried with sodium *p*-toluenesulfinate (**19**) as a model salt. As Table II shows, CDI (**2**) again was the most effective, although it had the disadvantage that the salt (**19**) had to be converted first in THF to the acid (**1**) in situ (referred to henceforth as the HCl–THF/CDI route). The next most promising reagent, the chlorosilane **16**, reacts directly with the salt (**19**), a property that could be quite advantageous in obviating work with unstable alkanesulfinic acids per se.

Scheme 1 outlines possible courses of reaction for CDI on the presumption that



SCHEME 1



SCHEME 2

CDI reacts with sulfinic acids essentially as Staab proposed for its reaction with carboxylic acids (when moist pH-test paper was exposed above the mixture, the expected acidic reaction from CO_2 developed).⁸ Similarly, on the presumption that the chlorosilane **16** reacts with sulfinate ions in the same way as with carboxylate ions, Scheme 2 shows an adaptation of the course of reaction proposed by Brook and Chan for carboxylates to rationalize the reaction with sulfonates; on the basis of evidence presented,^{15b} initial reaction of the sulfinate with **16** seems more likely that of the alcohol with **16** (cf. Reference 15a).

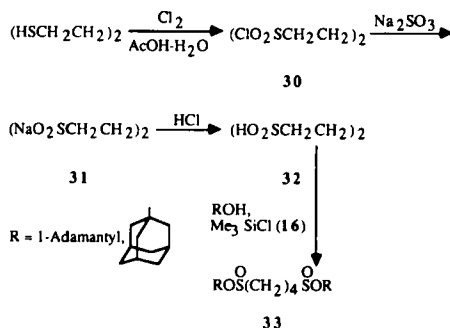
For the change from arenesulfonates to alkanesulfonates, our initial model was sodium methanesulfinate, MeS(O)ONa (**25**).¹⁷ The HCl –THF/CDI route, which had succeeded with the toluenesulfinate **19**, failed with **25** and 1-adamantanol because of near insolubility of the **25** in THF. Use of HCl –MeOH overcame this solubility problem but also failed, presumably because of instability of methanesulfinic acid (which decomposes at 25°C in 48 hrs).¹⁸ Omission of 1-adamantanol and use instead of a large excess of MeOH appeared to give methyl methanesulfinate in 10–15% yield (NMR), but even then the ester could not be purified.²

When the methanesulfinate salt (**25**) was used in the method with the chlorosilane (**16**), *p*-nitrobenzyl alcohol in THF for 48 hrs (instead of the usual 1–2 hrs) gave an oil that had IR and NMR spectra consistent with *p*-nitrobenzyl methanesulfinate, but the yield was only 10%; similarly, presumed 1-adamantyl methanesulfinate was obtained by the same procedure as an oil with consistent NMR and IR spectra but only in 8% yield.² Since both the 1-adamantyl and *p*-nitrobenzyl esters were unstable and developed extra TLC spots at ca. 25°C overnight, we turned from methanesulfinic acid to 1-butan sulfinic acid since it seemed likely to be a more representative alkanesulfinic acid.

The coupling of 1-butan sulfinic acid (**26**) with *p*-nitrobenzyl alcohol essentially by our usual method with CDI (**2**) led to the *p*-nitrobenzyl ester (**27**) in 52% yield. In marked contrast, use of sodium 1-butan sulfinic acid (**28**) in the HCl –MeOH/CDI method gave the ester **27** in only 16% yield (sparing solubility precluded the use of HCl –THF).

In order to test the applicability of the chlorosilane (**16**) method with sodium 1-butan sulfinic acid (**28**), 1-adamantanol was used with **16** and **28**. The 1-adamantyl ester (**29**) was obtained in 56% yield. Other silyl compounds were less effective; dichlorodimethylsilane gave **29** in 37% yield, and dimethylhexylsilyl triflate gave no **29** at all (i.e., $\text{Me}_2\text{CHCMe}_2\text{SiMe}_2\text{OSO}_2\text{CF}_3$). Unfortunately, both the *p*-nitrobenzyl and 1-adamantyl esters, **27** and **29** respectively, could not be crystallized.

Use of the butanesulfinate salt **28** in the HCl –MeOH/CDI route, again with 1-adamantanol as a model, led to a result much like that mentioned with *p*-nitrobenzyl alcohol; the yield of the adamantyl ester (**29**) in a mixture appeared to be only ca. 20%. One can conclude therefore that if a sulfinate salt is so



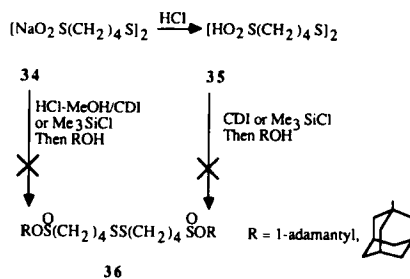
SCHEME 3

sparingly soluble in THF that a change from the HCl–THF/CDI method to the HCl–MeOH/CDI method seems mandated, this change is unlikely to succeed unless the sulfinic acid is stable enough to resist decomposition when the MeOH is evaporated (a necessity to preclude reaction of the MeOH with CDI).

A test of the esterification methods with alkanedisulfinic acids also was made. Use of 1,4-butanedisulfinic acid (**32**) was particularly attractive because of its quite atypical stability (unlike other disulfinic acids, the mp of **32** reportedly does not change during seven months at ca. 25°C).¹⁹

For the preparation of **32** (Scheme 3), readily available 1,4-butanedithiol was used for oxidation to the disulfonyl chloride (**30**) instead of use of the dithiuronium salt,¹⁹ which not only is less readily available but also carries a hazard of explosion (probably owing to NCl₃ generated).²⁰ Reduction of **30**, then acidification, gave the diacid **32**.¹⁹ Our experience more than confirms the extraordinary stability reported for **32**;¹⁹ for example, 80% remained unchanged even after 10 days at 90°C in deoxygenated D₂O (by NMR). The diacid **32** was converted to the di(1-adamantyl) ester (**33**) in 34% yield by use of the silyl chloride route with 1-adamantanol. The use of CDI (**2**) was unsatisfactory because of the sparing solubility of the diacid **32** in THF.

A further extension to α,ω -disulfinic esters was tried, where a central disulfide moiety was present, i.e. with **34** and **35**; 1-adamantanol was used as a model alcohol. The advantages pointed out of stable esters were of special interest with compounds such as **34** because **34** affords significant protection against ionizing radiation.²¹ With the salt **34**, and 1-adamantanol as the alcohol, both the methods with HCl–MeOH/CDI and Me₃SiCl gave a complex mixture (TLC), and NMR spectra showed no indication of sulfinate esters (Scheme 4). Since the disulfinic



SCHEME 4

acid **35** can be isolated from **34**,²² it was subjected to CDI in THF (in which it dissolves) but, again, both this method and that with the silane led only to complex mixtures and no indication by NMR of the ester **36**. Use of 1-adamantanemethanol (as a 1° rather than a 3° alcohol) or of *p*-nitrobenzyl alcohol were no more encouraging.² The difficulty with **34** and **35** evidently stems from attack on the disulfide moiety, but it is puzzling because the trisulfide disulfinate could be esterified by use of HCl–MeOH/diazomethane, trialkyloxonium fluoroborates, or alcohols containing BF₃.^{3a}

Conclusions from the foregoing for synthesis of stable crystalline sulfinic esters can be summarized as follows: (1) The most promising alcohols were 1-adamantanol (best) and *p*-nitrobenzyl alcohol. Aryl or thiol esters were unpromising. (2) The best coupling agents were CDI (**2**) and Me₃SiCl (**16**). Either worked well with relatively stable sulfinic acids. The silane **16** also can be used directly with salts, but with CDI salts must be converted to the acids in situ, either with HCl–THF or HCl–MeOH (the HCl–MeOH procedure for sparingly soluble salts is likely to be satisfactory only with relatively stable sulfinic acids). Conditions with both agents are mild (25°C or below), and reactions generally are clean; times are short with CDI (2 h or less), but longer with Me₃SiCl (24 h). (3) Of the chlorosilanes tried, Me₃SiCl was best. (4) Esters of methanesulfinic acid were obtained only in low yield as unstable oils. (5) With 1-butan sulfinic acid as a more representative alkanesulfinic acid, the two best routes were CDI with the acid (**26**) or Me₃SiCl with the salt (**28**); yields were 52–56%. However, neither 1-adamantyl nor *p*-nitrobenzyl 1-butan sulfinate could be crystallized. (6) The 1-adamantyl ester of 1,4-butanedisulfinic acid had a melting point of 123–125°C, but an ester of an alkanedisulfinate containing a disulfide moiety could not be prepared by the CDI or silane method.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover stirred-liquid apparatus and are corrected. Moist extracts were dried over MgSO₄, and solvent then was removed with a rotary-flask evaporator at aspirator pressure. ¹H NMR spectra, reported in parts per million (ppm, δ), were recorded with JEOL Model JNM-MH-100, JEOL FX-90Q or IBM NR/300 spectrometers (100, 90 and 300 MHz, respectively), with Me₄Si (TMS) as an internal standard, except with Me₃Si(CH₂)₃SO₃Na (DSS) in D₂O; ¹³C NMR spectra were obtained at 22.5 MHz with the JEOL-FX-90Q spectrometer. IR spectra were obtained with KBr pellets unless otherwise specified with a Perkin-Elmer Model 727 spectrometer; bands other than the 4–5 strongest (s) were medium or weak; b = broad. TLC usually was performed on Eastman Chromagram silica gel plates (cat. no. 13181) or Whatman K5F silica gel plates with visualization by UV unless I₂ vapor is specified. Flash chromatography was performed with a 5 × 16-cm column prepared from Baker 7024 silica gel (40 μm). Elemental analysis was by Galbraith Laboratories, Knoxville, TN. Disodium 4,4'-dithiobis(butan sulfinate) (**34**) was prepared as reported.²³ All other materials were commercial products unless otherwise specified; "sodium *p*-toluenesulfinate·XH₂O" was dried for 24 h at 100° at 2 torr.

General Procedure for the Reaction of 1,1'-Carbonyldiimidazole (CDI, **2), *p*-Toluenesulfinic Acid (**1**), and Alcohols (Table I).** The amount of the diimidazole **2** specified in Table I was dissolved in 20–40 mL of CH₂Cl₂ and added to a solution of 6.40 mmol of the sulfinic acid **1** (12.8 for **12** and 7.2 for **14**) in 20–40 mL of CH₂Cl₂. The solution was stirred for 15 min (30 for **6**) at ca. 25°C to allow formation of *N*-*p*-tolylsulfinylimidazole (**3**). A solution then was added of 6.0 mmol (6.3 for **8**, 6.4 for **6**, 5.9 for **4**, and 4.8 for **14**) of the alcohol stated in Table I in enough CH₂Cl₂ to effect solution (20–100 mL); Et₂O·CH₂Cl₂ was used 1:1 for **11**. The resulting solution was stirred for 1–2 h until TLC showed loss of the alcohol and then was washed with ca. 30 mL of 10% aqueous HCl, 20 mL of

cold 10% aqueous NaHCO_3 , and 100 mL of H_2O . The organic layer was dried, solvent was removed, and the product was purified by flash column chromatography with the solvent specified in Table I. The major fraction was identified by the TLC R_f reported in Table I (the solvents shown as eluants usually were used also for TLC), after which solvent was removed. The product then either crystallized in analytical purity (**5**), or when rubbed with pentane at 0°C (**4**, **7**, **9**, **10**, **12**), or when recrystallized (**6**, 1:19 MeOH-pentane; **8**, 1:9 CHCl_3 -pentane; **11**, EtOAc; **13**, hexane; **15**, 1:5 EtOAc-hexane); **14** needed only to be washed with 1:9 CHCl_3 -petroleum ether.

*Reaction of Other Coupling Agents with *p*-Toluenesulfinic Acid (**1**) and 1-Adamantanol (**a**) Chlorotrimethylsilane (**16**).* The silane **16** (Me_3SiCl ; 1.20 g, 11.0 mmol) was added to **1** (1.00 g, 6.4 mmol) in 40 mL of CH_2Cl_2 , and the solution was stirred for 15 min. A solution of 1-adamantanol (0.77 g, 5.06 mmol) in CH_2Cl_2 (20 mL) was added, and stirring was continued for 2 h. The solution then was washed with H_2O (2×100 mL) and dried. CH_2Cl_2 was removed, and the residue was chromatographed with 3:7 CHCl_3 -hexane. Removal of solvent from the fraction indicated by TLC R_f to contain the sulfinic acid **4** (cf. Table I) gave 1.01 g (69%) of **4**: mp $79\text{--}81^\circ\text{C}$; the TLC R_f value and NMR spectrum were identical with those of authentic **4** (Table I).

(b) *Phenyl Dichlorophosphate (**17**).* Addition of 1.26 g (5.97 mmol) of the phosphate **17** to 0.47 g (6.4 mmol) of DMF at 0°C in an ice bath gave a white paste, which was dissolved by adding 20 mL of CH_2Cl_2 . A solution of 1.00 g (6.4 mmol) of the acid **1** in 40 mL of CH_2Cl_2 was added, the ice bath was removed, and the mixture was stirred for 30 min. A solution of 0.91 g (5.98 mmol) of 1-adamantanol in 20 mL of CH_2Cl_2 then was added, the mixture was stirred for 15 min, and 0.50 g of pyridine (6.3 mmol) in 20 mL of CH_2Cl_2 was added. The resulting solution was stirred for 4 h more and then was washed with 10% aqueous HCl (100 mL), saturated NaHCO_3 (50 mL), and H_2O (2×100 mL). The solution was dried, solvent was removed, and the residue (1.7 g) was purified by chromatography as in (a) with 2:3 CHCl_3 -hexane; yield, 1.00 g (58%) of the sulfinic acid **4**: mp $79\text{--}81^\circ\text{C}$; R_f and NMR spectrum identical with those of authentic **4** (Table I).

(c) *Bis(2-oxo-3-oxazolidinyl)phosphinic Chloride (**18**).* Reaction of 6.4 mmol of **1**, 6.01 mmol of BOP-Cl (**18**), and 5.94 mmol of pyridine in CH_2Cl_2 , then 4.99 mmol of 1-adamantanol, after 24 h of stirring gave only a trace of product.

*Reaction of Coupling Agents with Sodium *p*-Toluenesulfinate (**19**) and 1-Adamantanol.* (a) *1,1'-Carbonyldiimidazole (CDI, **2**).* A 0.94 N solution of dry HCl in THF (10 mL, 9.4 mmol) was added to a suspension of 1.00 g (5.6 mmol) of the finely ground salt **19** in 40 mL of THF. After 10 min of stirring, solutions of 0.77 g (5.06 mmol) of 1-adamantanol and of 1.36 g (8.4 mmol) of CDI, each in 40 mL of CH_2Cl_2 , were added separately but simultaneously with stirring. The mixture was stirred for 1 h, solid was removed by filtration, and the filtrate was washed with aqueous 10% HCl (20 mL), NaHCO_3 (10 mL) and H_2O . The solution was dried and concentrated. TLC showed a major spot for **4** and two other spots. Chromatography (3:7 CHCl_3 -hexane) afforded 1.20 g (82%) of **4**, mp $79\text{--}81^\circ\text{C}$; the R_f value and NMR spectrum were identical with those of authentic **4** (Table I).

(b) *Chlorotrimethylsilane (**16**).* A suspension of 1.00 g (5.60 mmol) of finely ground **19** in 40 mL of CH_2Cl_2 was treated with **16** (1.20 g, 11.0 mmol), and the mixture was stirred for 15 min. A solution of 1-adamantanol (0.80 g, 5.25 mmol) in 40 mL of CH_2Cl_2 was added and stirring was continued for 2 h. The mixture then was washed with H_2O , and the crude **4** was purified as in (a); yield 1.00 g (66%); mp $79\text{--}81^\circ\text{C}$; TLC R_f and NMR identical with those of authentic **4** (Table I).

(c) *Phenyl dichlorophosphate (**17**).* To the dichlorophosphate (**17**) (1.18 mmol) and 1.4 mmol of DMF at 0°C , **19** (1.12 mmol) in THF was added. The mixture was stirred, 1-adamantanol (1.31 mmol) in THF was added, and stirring was continued for 24 h. TLC showed only a trace of **4**.

*Reactions of 1-Butanesulfinic Acid (**26**) and Sodium 1-Butanesulfinate (**28**).* (a) **p*-Nitrobenzyl 1-Butanesulfinate (**27**).* 1-Butanesulfinic acid (**26**) was prepared as reported from 2.00 g (22.2 mmol) of 1-butanethiol.²⁴ After removal of *m*-chlorobenzoic acid by (one) filtration at ca. -75°C ,²⁴ 3.50 g of CDI (**2**, 21.6 mmol) in 20 mL of CH_2Cl_2 was added. The mixture was allowed to warm to 25°C and then was stirred for 5 min. *p*-Nitrobenzyl alcohol (2.50 g, 16.3 mmol) in 40 mL of CH_2Cl_2 was added, and the mixture was stirred for 1 h more. The solution then was washed with 10% aqueous HCl (2×40 mL), H_2O (2×100 mL), and was dried (CaCl_2). Removal of solvent left semisolid, which was flash chromatographed (1:9 EtOAc- CH_2Cl_2). The first of three fractions (TLC R_f 0.85), a yellow

liquid, was the desired ester (**27**); yield 2.17 g (52%): IR (neat) 2950, 1600, 1520, 1340 (s), 1130 (s), 1000, 850, 740 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.26–8.23 (d, 2H, $J = 8$ Hz), 7.56–7.53 (d, 2H, $J = 8$ Hz), 5.19–5.09 (dd, 2H, $J = 20$ Hz, 12 Hz); 2.94–2.76 (m, 2H), 1.77–1.67 (quintet, 2H), 1.53–1.41 (sextet, 2H), 0.96 (t, 3H); ^{13}C NMR (CDCl_3) δ 143.29, 128.56, 127.09, 123.90, 68.31, 57.26, 23.30, 22.00, 13.65.

Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_4\text{S}$: C, 51.34; H, 5.88; S, 12.46. Found: C, 51.10; H, 5.62; S, 12.46.

The second fraction (R_f 0.42) was 1.20 g (44%) of bis-*p*-nitrobenzyl carbonate, mp 165–166°C; the elemental analysis, IR spectrum, and NMR spectra (^1H , ^{13}C) were consistent.² The third fraction (R_f 0.38; 10 mg), mp 150°C dec, had IR and NMR (^1H , ^{13}C) spectra consistent with *p*-nitrobenzyl imidazole-*N*-carboxylate and in confirmation gave bis-*p*-nitrobenzyl carbonate and imidazole with *p*-nitrobenzyl alcohol.²

For evaluation of the route with HCl–MeOH/CDI and the salt, sodium 1-butanedisulfinate (**28**) was prepared much as for the methanesulfinate (**25**):¹⁷ A solution of Na_2SO_3 (128 mmol) and NaHCO_3 (129 mmol) in H_2O (100 mL) was added during ca. 10–15 min to 1-butanedisulfonyl chloride (63.8 mmol) in H_2O (30 mL) with stirring. After 15 min, the mixture was heated at 70–80°C for 2 h, washed with CH_2Cl_2 (40 mL), and freeze dried. The residue was partially dissolved in 100 mL of MeOH, inorganic salt was removed by filtration, and the filtrate was concentrated to 50 mL. Addition of Et_2O gave 8.0 g (87%) of the sulfinate **28**: R_f 0.45 (3:7 MeOH–acetone); ^1H NMR (D_2O) δ 2.32 (t, 2H), 1.54–1.44 (quintet, 2H), 1.41–1.29 (sextet, 2H), 0.86 (t, 3H); ^{13}C NMR (D_2O) 63.28, 26.80, 24.40, 15.70. A solution of 0.20 g (1.39 mmol) of the salt **28** in 4 mL of MeOH was treated with 0.6 mL (1.60 mmol) of 2.66 N HCl in MeOH. After 5 min of stirring, MeOH was removed at 6 torr and CDI (0.34 g, 2.10 mmol) in 20 mL of CH_2Cl_2 was added. After 10 min of stirring, *p*-nitrobenzyl alcohol (0.19 g, 1.24 mmol) in 20 mL of CH_2Cl_2 was added. The mixture was stirred for 1 h more, washed with aqueous HCl and H_2O , and dried. Removal of solvent and preparative TLC with 1:9 EtOAc– CH_2Cl_2 gave three fractions: Fraction I was 50 mg of **27** (16% yield); R_f = 0.84, NMR identical with that of **27** described above. Fraction II (100 mg) had a R_f value (0.40) and NMR spectrum of *p*-nitrobenzyl alcohol. Fraction III (10 mg) had a R_f value and NMR spectrum consistent with *p*-nitrobenzyl imidazole-*N*-carboxylate.

(*b*) 1-Adamantyl 1-Butanesulfinate (**29**). Me_3SiCl (**16**; 1.81 g, 16.7 mmol) was added to 0.50 g (3.47 mmol) of the sulfinate salt **28**, and the mixture was stirred for 1 h. 1-Adamantanol (0.32 g, 2.10 mmol) in THF (3 mL) then was added, and the mixture was stirred for 24 h. Removal of the THF left oil, which was extracted with 50 mL of CH_2Cl_2 . The extract was washed with brine (3 \times 50 mL), dried, and concentrated. The residue (0.43 g) was chromatographed (1:9 EtOAc– CH_2Cl_2) and gave 0.30 g (56%) of 1-adamantyl 1-butanedisulfinate (**29**) as colorless liquid; TLC R_f 0.74 (1:9 EtOAc– CH_2Cl_2 , developed with I_2 vapor): IR (neat) 2950, 2850, 1445, 1350, 1125 (s), 1100, 1045 (s), 960, 900 (s), 810, 780, 750, 700 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.72–2.62 (m, 2H), 2.19 (s, b, 3H), 1.96 (s, b, 6H), 1.63–1.56 (m, 8H), 1.49–1.36 (sext., 2H), 0.92 (t, 3H); ^{13}C NMR (CDCl_3) δ 80.88, 57.75, 43.72, 35.94, 31.12, 23.84, 22.02, 13.71.

Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2\text{S}$: C, 65.58; H, 9.43; S, 12.50. Found: C, 65.40; H, 9.27; S, 12.96.

In the HCl–MeOH/CDI route, 1.5 mL of 2.66 N HCl in MeOH (3.99 mmol) was added to a solution of 0.50 g (3.47 mmol) of the salt **28** in 15 mL of MeOH. After 5 min of stirring at 0°C, the MeOH was removed at 0.5 torr, and a solution of 0.85 g (5.24 mmol) of CDI in 40 mL of CH_2Cl_2 was added. The mixture was stirred for 15 min at 25°C, 1-adamantanol (0.48 g, 3.15 mmol) was added in 20 mL of CH_2Cl_2 , and the mixture was stirred for 2 h. The solution was washed with 10% aqueous HCl (20 mL), water (2 \times 50 mL), and dried. Chromatography of the 0.53 g of residue (1:9 EtOAc– CH_2Cl_2) gave 0.22 g of oil, which (NMR) consisted of ca. 75% of the adamantyl ester **29** and ca. 25% of methyl 1-butanedisulfinate; hence the yield of **29** was ca. 20%. These two esters could not be separated by TLC.

Di(1-adamantyl) 1,4-Butanedisulfinate (**33**). 1,4-Butanedisulfonyl chloride (**30**) was prepared by bubbling Cl_2 gas into a solution of 1,4-butanedithiol (5.0 g, 40.9 mmol) in 6 mL of H_2O and 25 mL of AcOH during ca. 15 min with stirring below 30°C. Gummy material was removed, dissolved in hot AcOH, and Cl_2 was passed until a yellow color resulted. The two solutions were combined, solvent was removed, and the white solid obtained was dissolved in warm CHCl_3 . After the solution had been washed with H_2O (50 mL) and dried, removal of the CHCl_3 left 7.0 g (67%) of the chloride **30** as white powder: mp 82–83°C (lit.²⁵ mp 82.5°C; prepared from the disulfonate salt): IR 1460, 1370 (s), 1330, 1320, 1260, 1220, 1160 (s), 1040, 880, 760, 730 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.81–3.67 (m, 4H), 2.34–2.21 (m, 4H); ^{13}C NMR ($\text{Me}_2\text{CO}-d_6$) δ 63.71, 23.11.

Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{Cl}_2\text{O}_4\text{S}_2$: C, 18.83; H, 3.16. Found: C, 18.69; H, 3.21.

Essentially as reported,^{2,19} the dichloride **30** was reduced to disodium 1,4-butanedisulfinate (**31**), which was acidified to give 1,4-butanedisulfonic acid (**32**): mp 122–124°C (lit.¹⁹ mp 124–125°C): IR as

reported;¹⁹ ^1H NMR (D_2O) δ 2.67–2.58 (m, 4H), 1.67–1.55 (m, 4H); ^{13}C NMR (D_2O) δ 59.32, 22.59. The diacid **32** was virtually insoluble in CH_2Cl_2 , CHCl_3 , DMF, THF, or HMPA but was soluble in N-methyl-2-pyrrolidone, MeOH, EtOH, and H_2O . NMR showed that although **32** was oxidized entirely to the disulfonic acid after 48 h in ordinary D_2O at 90°C , in deoxygenated D_2O at 90°C , decomposition began only after 6 h, was only ca. 20% complete after 10 days, and was 100% complete only after ca. 1 month.

For the conversion of the disulfenic acid (**32**) to the diester (**33**), 0.30 g (1.62 mmol) was suspended in 5 mL of THF, 2.82 g (26.0 mmol) of Me_3SiCl was added, and the mixture was stirred for 1 h. 1-Adamantanol (0.49 g, 3.22 mmol) in 5 mL of THF was added, the mixture was stirred for 24 h, and THF then was removed at aspirator pressure. The residue was dissolved in 50 mL of CH_2Cl_2 , which was washed with H_2O (2×50 mL), dried, and evaporated to give 0.6 g of liquid. Chromatography (1:4 hexane-EtOAc) gave 0.25 g (34%) of **33** as colorless liquid (R_f 0.54), which crystallized when rubbed with cold pentane: mp 123–125°C dec; IR (neat) 2925, 2875, 1460, 1360, 1300, 1120 (s), 1060 (s), 970, 910 (s), 820, 790, 760 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.75–2.65 (m, 4H), 2.26 (s, b, 6H), 1.96 (s, b, 12H), 1.82–1.78 (m, 4H), 1.63 (s, b, 12H).

Anal. Calcd for $\text{C}_{24}\text{H}_{38}\text{O}_4\text{S}_2$: C, 63.40; H, 8.42; S, 14.10. Found: C, 63.10; H, 8.70; S, 13.85.

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