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Use of (Thio)Acetal Esters as Reagents for the Protection of Alcohols. Synthesis of 2-Tetrahydrothienyl Ethers[1]

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Primary and secondary alcohols can be converted in high yields into their 2-tetrahydrothienyl (THT) ethers by an acid-catalyzed exchange reaction with 2-tetrahydrothienyl diphenylacetate. The characteristics of the THT group as a protecting group for alcohols are discussed. Conditions for quantitative removal under neutral conditions are described. This acetal exchange reaction also provides an excellent method for the preparation of other mixed acetals, in particular THP and THF ethers.

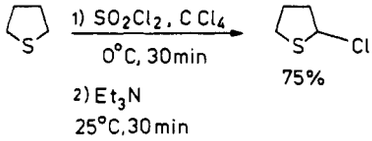
The protection of hydroxyl groups, often as mixed acetals, is an extensively used technique in the synthesis of polyfunctional compounds.[2] Recently, several new protecting groups have been introduced, which can be removed with a highly specific reagent.[3]

The methylthiomethyl (MTM) group has been recommended in this respect because of its stability toward both basic and mildly acidic conditions and its easy cleavage under neutral conditions with certain metal ions.[3b,4,5] In the acetal series, protecting groups with a cyclic structure, in particular 2-tetrahydropyranyl (THP) ethers, have been employed frequently. We have focused our attention on the synthesis of 2-tetrahydrothienyl (THT) ethers. Previously, two THT ethers have been prepared in moderate yield by reaction of alcohols with 2,3-dihydrothiophene,[5] but this procedure is not suitable for the introduction of a THT protecting group. In this study we describe an efficient method for the protection of primary and secondary alcohols with a THT group. This method appears to be also very suitable for the introduction of THP and THF groups. The possibility of selective cleavage of THT ethers in the presence of THF ethers and vice versa is discussed.

Results and Discussion

Synthesis of 2-Chlorotetrahydrothiophene (2-Cl-THT). In view of the favorable results obtained with the reaction of 2-chlorotetrahydrofuran with alcohols,[3d] our initial objective was to use 2-Cl-THT as a reagent for introducing the THT group. Various reports in the literature deal with the chlorination of THT.[6,7] 2-Cl-THT has not been isolated in a pure state because of its lack of stability.[6b]

Conversion of THT into 2-Cl-THT could be accomplished in apolar solvents [*N*-chlorosuccinimide in benzene at 25 °C (50% conversion)[6b] or chlorine in carbon tetrachloride at 40 °C (80% conversion)[6c]]. By contrast, sulfuryl chloride in refluxing pentane was reported to cause extensive polymerization.[6a] Because of the successful application of sulfuryl chloride to the chlorination of tetrahydrofuran[3d] and 1,3-dithiane,[8] we have reexamined its reaction with THT. It appeared that THT could be converted into 2-Cl-THT in 75% yield by a simple and fast procedure.[9]



Polymerization was effectively retarded by addition of triethylamine. In more polar solvents, mixtures of 2-Cl-THT and 2,3-diCl-THT were formed and the yield of chlorinated products decreased (see Table I). The reaction exhibits the same characteristics as the reaction with chlorine which was studied by Wilson and Albert.[7]

It is generally accepted[10] that upon reaction of sulfides with chlorinating agents, sulfonium salts are formed in the first step. In general, two structures are possible.[11] To our knowledge no spectroscopic data are available on sulfonium salts formed with chlorine or sulfuryl chloride.[12] Upon addition of sulfuryl chloride to a solution of THT in $CDCl_3$, the signals of the original NMR spectrum shifted downfield appreciably (α protons, 1.4 ppm; β protons, 0.8 ppm).[13] Interestingly, exactly the same spectrum was obtained when *thionyl chloride* (1.0 equiv) was added at −65 °C to a $CDCl_3$ solution of *THT sulfoxide*.[10e] When $CDCl_3$ solutions of THT and chlorine (1.0 equiv each) were mixed at −75 °C, the NMR spectrum revealed the presence of both THT and the chlorosulfonium chloride **2** (δ 4.2 and 2.7) in about equal quantities. Comparison with data obtained for the 1:1 adduct of THT and bromine (**2a**) (α and β protons shifted 0.8 and 0.3 ppm)[12] leads to the conclusion that the charge separation in the adduct with chlorine is more pronounced, and therefore structure **2** seems most likely. Also, these data indicate that chlorosulfonium salts **1** and **2** have the same cation since their spectra are identical and a different anion. Only **2** is in equilibrium with its components because of the better nucleophilicity of chloride ion.

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Table I. Product Composition from Reactions of THT with Sulfuryl Chloride in Various Solvents[a]

Molar ratio THT/SO_2Cl_2	Solvent	Molar ratio 2-Cl-THT/ 2,3-diCl-THT	Yield (%) of methoxylated derivatives
5:1	CH_2Cl_2	3:2	35
5:1	THF	9:1	35
5:1	Benzene	20:1	60
1:1	Benzene	20:1	35
1:1	CCl_4	20:1	75

[a] See Experimental Section.

Table II. Protection of Primary and Secondary Alcohols as THT Ethers via THT Diphenylacetate

Substrate	Method[a]	Yield, %	δ (2'-H)	$n^{23}D$
1-Hexanol	a	99	5.19	1.4728
2-Phenylethanol	a	95	5.18	1.5496
Benzyl alcohol	a	98	5.21	1.5582
Geraniol	a	99	5.22	1.5123
2-Pentanol	b	85	5.36	1.4711
Cyclohexanol	b	90	5.39	1.5104

[a] Method a: room temperature, 5 h. Method b: 40–50 °C, 16 h.

Reaction of 2-Cl-THT with Alcohols. A solution of 2-Cl-THT in carbon tetrachloride, prepared as depicted above, reacted only sluggishly with alcohols. The best conversions were obtained by reaction with 2 equiv of the THT–sulfuryl chloride reaction mixture in carbon tetrachloride–acetonitrile (1:1) at 25 °C in the presence of triethylamine.[14] However, use of 2-Cl-THT has no advantage over dihydrothiophene.[5] Both suffer from (i) a lack of quantitative conversion of the alcohol and (ii) contamination of the crude product with 4-(2-tetrahydrothienyl)-2,3-dihydrothiophene (**3**), which could only be removed by extensive chromatography (Scheme I). A possible explanation for this deviation from the results obtained with 2-Cl-THF, which reacts rapidly with alcohols at room temperature,[3d] becomes clear by inspection of Scheme I.

Compared with the THF series,[15] the equilibrium between **4** and **5** is shifted toward **4** and the side reaction leading to 2,3-dihydrothiophene and subsequently to **3** becomes important.

Synthesis of THT Ethers by Reaction with THT Diphenylacetate. An excellent preparation of THT ethers could be realized by a (thio)acetal exchange reaction. The reagent

Scheme I

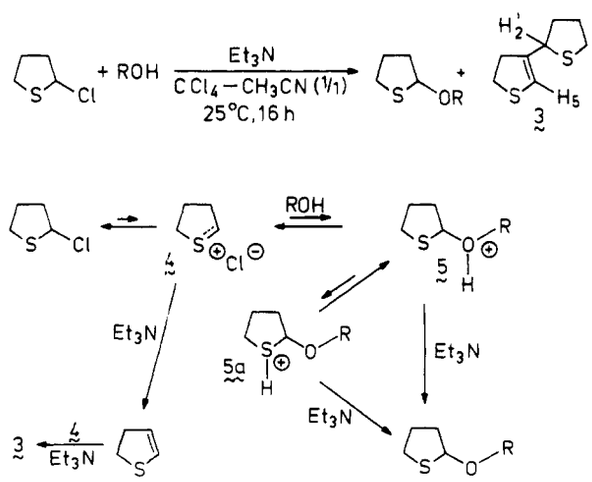
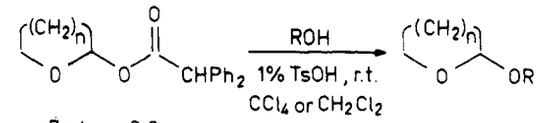


Table III. Synthesis of THF and THP Ethers by Acetal Exchange Reactions

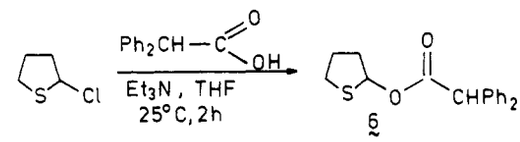


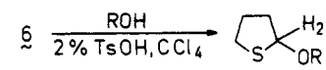
7a,b; n = 2,3

Substrate	Yield (%) of THF ether (n = 2)[a]	Yield (%) of THP ether (n = 3)[b]
1-Hexanol	99	96
2-Phenylethanol	99	94
2-Pentanol	90	85, 96[a]
Cyclohexanol	91	90, 96[a]

[a] CCl_4, 30 min. [b] CH_2Cl_2, 5 min.

2-tetrahydrothienyl diphenylacetate (**6**) is a stable crystalline solid, easily obtainable in 60–65% yield by reaction of diphenylacetic acid with 2-Cl-THT. The procedure for the reaction of (thio)acetal ester **6** with primary alcohols is ex-





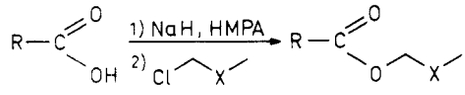
ceedingly simple. Stirring in carbon tetrachloride with a catalytic amount of *p*-toluenesulfonic acid at room temperature for 5 h results in quantitative precipitation of diphenylacetic acid. After addition of some sodium carbonate, the mixture is filtered and concentrated, affording THT ethers of better than 95% purity in the yields indicated in Table II. Optimum yields for THT ethers of secondary alcohols were obtained by reaction at 40–50 °C for 16 h.

By contrast, reaction of **6** with tertiary alcohols and phenols produced mixtures of the expected THT ethers and dimer **3**. This was also observed when the reactions with primary alcohols were conducted in the presence of more than 5% of *p*-toluenesulfonic acid or when more polar solvents were employed.[16] Protection of a primary alcohol in the presence of a tertiary alcohol proceeds with better than 90% selectivity. Comparing tertiary with primary alcohols, the concentration of thiacarbenium ion intermediate **4** will be increased, both because of the lower reaction rate of **4** with tertiary alcohols and because of the faster protonation of THT ethers from tertiary alcohols to give **5**.[17] The use of more polar solvents will also lead to a higher concentration of **4**.[18] As a consequence, the irreversible formation of dimer **3** is favored.

Introduction of Other Protecting Groups by (Thio)-Acetal Exchange Reactions. The appropriate reagents for the protection of alcohols as THF and THP ethers (**7a,b**; see Table III) could be synthesized conveniently by reaction of diphenylacetic acid with 2-Cl-THF and 2,3-dihydropyran in yields of 82 and 64%, respectively. The acid-catalyzed reaction of alcohols with these acetal esters proceeded even faster than with (thio)acetal ester **6**. Applying the same conditions (carbon tetrachloride, 2% *p*-toluenesulfonic acid, and room temperature), quantitative formation of 1-hexanol THF and THT ethers required 10 min and 5 h, respectively.

Thus, by using reagents **7a,b** nearly quantitative conversion of primary and secondary alcohols into THF and THP ethers under mild conditions (carbon tetrachloride, 1% *p*-toluene-

Table IV. Synthesis of MTM and MM Esters



8a-e

	R	X	Yield, %[a]	Mp, °C
8a	Ph_2CH	S	90	31–32
8b	4-NO_2Ph	S	95	55–56
8c	2,4-diNO_2Ph	S	99	25
8d	4-NO_2Ph	O	90	74–75
8e	2,4-diNO_2Ph	O	85	60–61.5

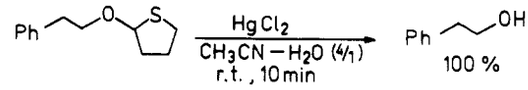
[a] Yields are based on products of better than 95% purity (NMR).

sulfonic acid, and room temperature for 30 min) could be achieved.[19] In more polar solvents, these reactions were still faster but an equilibrium resulted which contained 5–15% of the alcohol. The results are summarized in Table III.

THF- and THP-protected tertiary alcohols were only formed in moderate yields (40 and 75%, respectively) due to their sensitivity to acid. In view of the pronounced advantages of these acetal exchange reactions, we recommend compounds **7a,b** as standard reagents for the protection of alcohols with THF and THP groups.[19]

The suitability of (thio)acetal esters for the introduction of MTM and methoxymethyl (MM) groups was also studied (Table IV).[20] The requisite esters could be synthesized in excellent yields using the conditions described for the formation of phenolic MTM ethers.[21,22] It appeared that the transfer of MTM groups from methylthiomethyl diphenylacetate (**8a**) to 1-hexanol required rather drastic conditions (carbon tetrachloride, 5% *p*-toluenesulfonic acid, and reflux for 2 h). Under these conditions the MTM ether engaged in a disproportionation reaction to form acetal **10** and (dithio)acetal **11a**.[23a] Attempts to circumvent this problem by using (thio)acetal esters **8b–e**, containing better leaving groups, were not successful (see Table V). The MM ether of 1-hexanol was formed in reasonable yields by reaction with **8d,e**, but the formation of disproportionation products **10** and **11b** could not be retarded satisfactorily (see Table V).[23b] It can be concluded that the (thio)acetal exchange reaction is only successful for the protection of alcohols when an appreciable difference in acid sensitivity exists between the (thio)acetal ester and the corresponding ether.

Cleavage of the THT Ethers. The THT group can be removed by a fast reaction under mild conditions. When 2-phenylethanol THT ether was treated with mercuric chloride (1.5 equiv) in acetonitrile–water (4:1; 10 mL per mmol) at 25 °C for 10 min, 2-phenylethanol could be isolated quantitatively. Using standard conditions,[3b] the THT group was removed appreciably faster than the MTM group (see Experimental Section), clearly indicating the possibility of selective removal. Likewise, THT ethers are more sensitive toward acid-catalyzed hydrolysis than MTM ethers, which are fairly resistant to the conditions employed for the removal of THP groups.[3b] In acetic acid–water–THF (3:1:1) at 25 °C, the THT group was 90% cleaved in 3h, a rate comparable to that of the THP group but appreciably slower than that of the THF group.



Also, conditions were elaborated for the selective cleavage of THT ethers in the presence of the highly acid-sensitive THF ethers.[24] These consisted of treatment with (i) mercuric chloride (1.5 equiv) buffered with calcium carbonate (3.0 equiv) in acetonitrile–water (4:1) at 25 °C for 10 min (MTM ethers are unaffected under these conditions[3b]) or with (ii) silver nitrate (2.0 equiv) buffered with 2,6-lutidine (2.0 equiv) in THF–water (4:1) at 25 °C for 90 min. THP, MEM, and $TBMe_2Si$ groups are also unaffected under these conditions. Conversely, THF and THP groups could be removed selectively in the presence of a THT group by reaction with methanol at reflux temperature during 1 h.[3d] Under these conditions, THT ethers are unaffected, while cleavage is rapid in the presence of 5% *p*-toluenesulfonic acid. These results are schematically represented in Table VI.

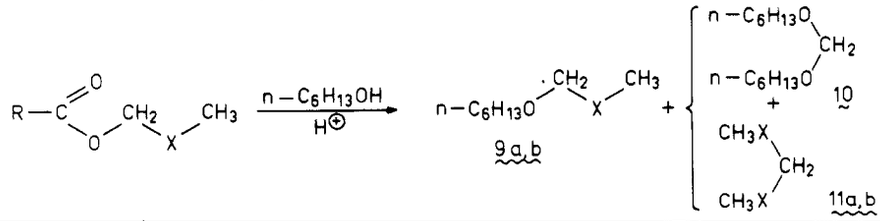
Further work concerning the reactions of 2-Cl-THT and acetal ester **6** with nucleophiles is in progress.

Experimental Section

General. All melting points are uncorrected. IR spectra were recorded on a Unicam SP-100 spectrophotometer. NMR spectra (δ expressed in parts per million) were taken on a Jeol PS-100 instrument. Elemental analyses of the crystalline products were performed by Mr. W. J. Buys, TNO Laboratory of Organic Chemistry, Utrecht, Neth. For analytical and preparative GC analyses, a 2 m, 3% SE-30 on Chromosorb W (80–100 mesh) column and a 6 m, 20% SE-30 on Chromosorb W (60–80 mesh) column were employed, respectively. Column chromatography was performed with silica gel (MN, 70–270 mesh).

Materials. Commercial tetrahydrothiophene (Aldrich) was distilled and stored over calcium chloride. Solvents were purified and dried according to standard procedures. Sulfuryl chloride was distilled in a nitrogen atmosphere before use. Commercial chloromethyl methyl ether was freshly distilled from sodium carbonate. Chloromethyl methyl sulfide[24] and tetrahydrothiophene sulfoxide[25] were prepared

Table V. Acid-Catalyzed Reaction of 1-Hexanol with MTM and MM Esters



No.	(Thio)acetal ester R	X	Conditions for 95% conversion of 1-hexanol	Product distribution[a]
8a	Ph_2CH	S	CCl_4–5% TsOH; reflux (2 h)	**9a** (30%); **10** + **11a** (70%)
8b	4-NO_2Ph	S	Benzene–5% MsOH; 45 °C (6 h)	**9a** (50%); **10** + **11a** (50%)
8c	2,4-diNO_2Ph	S	Benzene–10% MsOH; 20 °C (7 h)	**9a** (25%); **10** + **11a** (75%)
8d	4-NO_2Ph	O	Ether–10% MsOH; 20 °C (16 h)	**9b** (80%); **10** + **11b** (20%)
8e	2,4-diNO_2Ph	O	Benzene–5% MsOH; 20 °C (1.5 h)	**9b** (75%); **10** + **11b** (25%)

[a] GC analysis.

Table VI. Removal of Some (Thio)Acetal Protecting Groups by Selected Reagents

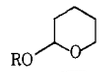
Protecting group	$HgCl_2$	$HgCl_2$–$CaCO_3$	AcOH–H_2O–THF	MeOH
	+	–	–	–
	++	+	+	–
	–	–	+	+
	–	–	++	++

Table VII. Product Composition from Reactions of THT with Sulfuryl Chloride in Chloroform

Volume % THT	Molar ratio THT/SO_2Cl_2	Molar ratio 2-Cl-THT/ 2,3-diCl-THT
7	1:1	3:5
15	2:1	1:1
35	5:1	2:1
20	5:1	3:1
40	10:1	2:1

by known procedures. All reagents were used as high grade commercial products.

2-Chlorotetrahydrothiophene (2-Cl-THT). A solution of sulfuryl chloride (6.75 g, 50 mmol) in carbon tetrachloride (25 mL) was added dropwise with efficient stirring to a chilled solution of THT (4.4 g, 50 mmol) in carbon tetrachloride (100 mL) in an atmosphere of dry nitrogen. A fluffy white precipitate was formed. The ice bath was removed after stirring at 0 °C for 30 min. Upon warming to room temperature, the precipitate dissolved and evolution of hydrogen chloride was observed. Triethylamine (4.0 g, 40 mmol) was added over a 2-min period, and a white precipitate formed. Stirring was continued at room temperature for 30 min. The resulting reaction mixture was cooled to −16 °C to attain complete precipitation of triethylammonium chloride, which was removed by filtration in a nitrogen atmosphere. A slightly yellow colored solution of 2-Cl-THT was obtained which was used directly for subsequent reactions either as such or after evaporation of the solvent to a volume of ca. 25 mL.

Chlorination of THT with Sulfuryl Chloride in Various Solvents (Table I). The chlorinations were carried out under nitrogen by addition of sulfuryl chloride (10 mmol) to well-stirred solutions of THT (30 mL of solvent) at 0 °C. Triethylamine (10 mmol) was added and stirring was continued at 0 °C for 30 min and at room temperature for 1 h. Relative amounts of 2-Cl-THT and 2,3-diCl-THT were determined by NMR spectroscopy after filtration and evaporation of the solvent [($CDCl_3$) 2-H at δ 5.77 (m) and 5.63 (s), respectively]. The yield of chlorinated products was determined by reaction with methanol (20 mmol) in the presence of pyridine (10 mmol), as described by Wilson and Albert.[6c,7] In polar solvents like chloroform, the molar ratio of 2-Cl-THT and 2,3-diCl-THT was dependent upon both the concentration of THT and the molar ratio of the reactants (see Table VII).[7]

Reactions of 2-Cl-THT with Alcohols (Scheme I). To a stirred solution of the alcohol (10 mmol) and triethylamine (15 mmol) in acetonitrile (40 mL) was added at room temperature in two portions a solution of 2-Cl-THT (2 equiv based on THT) in carbon tetrachloride (40 mL). Stirring at room temperature was continued for 16 h. The precipitate was filtered off, and ether was added to the filtrate. The resulting solution was washed with water and brine and dried ($MgSO_4$). After evaporation of the volatile components, the crude product was purified by column chromatography (20 g; 3:1 benzene–hexane). The pure THT ethers were obtained in yields of 60 and 55% for 1-hexanol and cyclohexanol, respectively. In another experiment, a partially evaporated solution of 2-Cl-THT (5 equiv) in carbon tetrachloride (20 mL) was mixed with acetonitrile (50 mL), and the resulting solution was added dropwise to a stirred solution of 1-hexanol (10 mmol) and triethylamine (15 mmol) in acetonitrile (50 mL). After stirring for 16 h and workup as described above, a mixture was obtained of about equal amounts of 1-hexanol THT ether (60% yield) and dimer **3** [NMR ($CDCl_3$) δ 5.9 (s, 1 H, 5-H) and 4.1 (t, 1 H, 2′-H)].

2-Tetrahydrothienyl Diphenylacetate (6). A solution of 2-Cl-THT in carbon tetrachloride (from a 0.1-mol scale chlorination) was concentrated to a volume of ca. 30 mL and diluted with THF (50 mL). This mixture was added to a stirred solution of diphenylacetic acid (10.6 g, 0.05 mol) and triethylamine (10.1 g, 0.10 mol) in THF (100 mL). Precipitation of triethylammonium chloride started almost immediately. The suspension was stirred at room temperature for 2 h. The reaction mixture was kept at −16 °C for 1 h, filtered, diluted with ether (150 mL), and washed with sodium carbonate solution, water, and brine. After drying with a mixture of $MgSO_4$ and MgO (to remove the last traces of triethylammonium chloride) and evaporation of the solvents, an oil was obtained which was dissolved in a minimal amount of dry ether (ca. 20 mL). Upon cooling to −16 °C, **6** crystallized as white needles which were collected by filtration, yield 60–65% (9–10 g). An analytical sample was obtained by crystallization from benzene–hexane: mp 82–83 °C; IR 3050 and 2950 (C–H), 1730 (C–O), 1180, 1145, and 1110 (C–O), and 750 and 700 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.24 (s, 10 H, phenyl), 6.20 (m, 1 H, 2-H), 4.97 (s, 1 H, Ph_2C–H), and two broad multiplets at δ 2.6–2.9 (2 H, 5-H) and 1.7–2.2 (4 H, 3- and 4-H).

Anal. Calcd for $C_{18}H_{18}O_2S$: C, 72.46; H, 6.08; S, 10.72. Found: C, 72.41; H, 6.11; S, 10.89.

General Procedure for the Protection of Alcohols with a THT Group (Table II). For primary alcohols, a solution of the alcohol (5 mmol), (thio)acetal ester **6** (5 mmol, 1.5 g), and *p*-toluenesulfonic acid (0.02 equiv, 19 mg) in carbon tetrachloride (25 mL) was stirred for a minimum of 5 h at room temperature. For secondary alcohols, 1.3 equiv of **6** was employed and the reaction temperature was maintained at 40–50 °C for 16 h. In both cases diphenylacetic acid separated quantitatively. Sodium carbonate (1.0 g) was added, and stirring was continued for 30 min. The reaction mixture was filtered and the solvent evaporated. The residue was treated with hexane (10 mL), and the THT ether could be isolated after filtration and evaporation. Alternatively, aqueous workup was possible by filtering, diluting with ether, washing with sodium carbonate solution and brine, drying ($MgSO_4$), and evaporating the solvents. The yields are given in Table II. THT ethers isolated in this way were of better than 95% purity. The last traces of impurities could be removed by chromatography. The THT ethers are colorless oils which are stable for months when stored at −16 °C with some MgO. Distillation is only convenient with the lower boiling compounds because THT ethers slowly decompose when heated above 100 °C. Also, GC analyses of solutions of THT ethers (temperatures up to 170 °C) could be performed, but purification by preparative GC was not successful. IR spectra of all THT ethers exhibited an absorption at ca. 710 cm^{-1} with medium intensity. In the NMR spectra the signal for the 2′-H is characteristic. It was found at δ 5.2 for protected primary alcohols and at δ 5.35–5.4 for secondary alcohols. Two broad multiplets are found at δ 2.7–2.9 (5′-H) and δ 1.8–2.2 (3′- and 4′-H).

1-Hexanol THT Ether: bp 52 °C (0.025 mm); n^{23}_D 1.4728; IR 2980 and 2900 (C–H), 1075 (C–O), and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.19 (m, 1 H, 2′-H, ΣJ = 6 Hz), 3.56 and 3.22 (t of AB, 2 H, 1-H, J_{AB} = 9 Hz and $J_{1\text{-H},2\text{-H}}$ = 6.5 Hz), 1.5 (m, 2 H, 2-H), 1.25 (m, 6 H, CH_2), and 0.86 (t, 3 H, CH_3).

2-Phenylethanol THT Ether: n^{23}_D 1.5496; IR 3080, 2980, and 2900 (C–H), 1075 (C–O), 750 and 695 (phenyl), and 710 cm^{-1}; NMR ($CDCl_3$) δ 7.16 (s, 5 H, phenyl), 5.18 (m, 1 H, 2′-H, ΣJ = 6 Hz), 3.80 and 3.40 (t of AB, 2 H, 1-H, J_{AB} = 9 Hz and $J_{1\text{-H},2\text{-H}}$ = 7 Hz), and 2.82 (t, 2 H, 2-H, J = 7 Hz).

Benzyl Alcohol THT Ether: n^{23}_D 1.5582; IR 3100, 2980, and 2900 (C–H), 1055 (C–O), 740 and 690 (phenyl), and 710 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 5 H, phenyl), 5.21 (m, 1 H, 2′-H, ΣJ = 6 Hz), and 4.63 and 4.26 (AB, 2 H, 1-H, J_{AB} = 11.5 Hz).

Geraniol THT Ether: n^{23}_D 1.5123; IR 2950 and 2900 (C–H), 1660 (C=C), 1050 (C=O), and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.30 and 5.08 (m, 2 H, =CH), 5.22 (m, 1 H, 2′-H, ΣJ = 6 Hz), 4.08 and 3.85 (d of AB, 2 H, 1-H, J_{AB} = 11.5 Hz and $J_{1\text{-H},2\text{-H}}$ = 7 Hz), 2.02 (m, 4 H, CH_2), 1.63 (s, 6 H, CH_3), and 1.57 (s, 3 H, CH_3).

Pentanol-2 THT Ether: bp 39 °C (0.025 mm); n^{23}_D 1.4711; IR 2980 and 2900 (C–H), 1050 (C–O), and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.36 (m, 1 H, 2′-H), 3.57 (p, 1 H, 1-H, J = 6 Hz), 1.3–1.4 (m, 4 H, CH_2), 1.13 and 1.06 (d, 3 H, CH_3, J = 6 Hz), and 0.88 (m, 3 H, CH_3).

Cyclohexanol THT Ether: bp 70 °C (0.015 mm); n^{23}_D 1.5104; IR 2980 and 2920 (C–H), 1065 (C–O), and 715 cm^{-1}; NMR ($CDCl_3$) δ 5.39 (m, 1 H, 2′-H, ΣJ = 6 Hz), 3.4 (m, 1 H, 1-H), and 1.2–1.8 (m, 10 H, CH_2).

2-Tetrahydrofuranyl Diphenylacetate (7a). This compound was obtained by reaction of diphenylacetic acid and triethylamine with 2-Cl-THF in 82% yield as described in ref 1.

2-Tetrahydropyranyl Diphenylacetate (7b). A solution of diphenylacetic acid (20 mmol, 4.24 g) and 2,3-dihydropyran (18 mmol,

1.50 g) in benzene (25 mL) was refluxed for 16 h. The reaction mixture was washed twice with sodium carbonate solution and with brine. Acetal ester **7b** was isolated after drying ($MgSO_4$), evaporation, and crystallization of the oily residue from hexane as white crystals: 3.4 g (64%); mp 59–60 °C; IR 3050, 2950, and 2900 (C–H), 1740 (C=O), 1200, 1160, 1110, and 1025 (C–O), and 745 and 695 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.24 (s, 10 H, phenyl), 6.06 (m, 1 H, 2-H), 5.04 (s, 1 H, Ph_2C–H), 3.55 (m, 2 H, 6-H), and 1.3–1.7 (m, 6 H, 3-, 4-, and 5-H).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.82; H, 6.93.

General Procedure for the Protection of Alcohols with THF and THP Groups (Table III). To a stirred solution of the alcohol (2 mmol) and *p*-toluenesulfonic acid (0.01 equiv, 4 mg) in carbon tetrachloride (10 mL) was added acetal ester **7** (primary alcohols, 2.1 mmol, and secondary alcohols, 2.2 mmol). Within 5 min precipitation of diphenylacetic acid started. Stirring was continued at room temperature for 30 min, and the reaction mixture was then diluted and washed twice with sodium carbonate solution and with brine. After drying ($MgSO_4$) and evaporation, THF and THP ethers were obtained as products of better than 95% purity. Spectra (GC, IR, and NMR) and refractive indexes were identical with those of products synthesized by literature procedures.[3d,20]

General Procedure for the Preparation of MTM and MM Esters (8a–e) (Table IV). Under an atmosphere of dry nitrogen, sodium hydride (55% dispersion in oil; 2.32 g, 55 mmol) was washed twice with dry pentane (10 mL) and HMPA (5 mL) was added. To this stirred suspension was added dropwise, while cooling with a water bath, a solution of the acid (50 mmol) in HMPA (50 mL). When the addition was completed (ca. 30 min) and hydrogen evolution had ceased, the water bath was removed and the clear solution was stirred for another 30 min. Addition of chloromethyl methyl (thio)ether in one portion caused a slightly exothermic reaction. After stirring for 3 h at room temperature, the mixture was poured into a saturated sodium hydrogen carbonate solution (250 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL) and brine. After drying ($MgSO_4$) and evaporation of the solvent, (thio)acetal esters **8a–e** were isolated in the yields indicated in Table IV. Compounds **8a,c,e** crystallized only with difficulty.

Methylthiomethyl Diphenylacetate (8a): white (hexane); mp 31–32 °C; IR 3150 and 2920 (C–H), 1730 (C=O), 1120 (C–O), 960 (S–C–O), and 740 and 690 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.25 (s, 10 H, phenyl), 5.07 (s, 2 H, S–CH_2–O), 5.02 (s, 1 H, Ph_2C–H), and 1.95 (s, 3 H, CH_3).

Methylthiomethyl 4-Nitrobenzoate (8b): white needles (1:1 ether–pentane); mp 55–56 °C; IR 3080 and 2900 (C–H), 1720 (C=O), 1520 and 1330 (NO_2), and 1240 and 1080 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 8.28 (s, 4 H, phenyl), 5.44 (s, 2 H, S–CH_2–O), and 2.31 (s, 3 H, CH_3).

Anal. Calcd for $C_9H_9NO_4S$: C, 47.58; H, 3.99; N, 6.17; S, 14.09. Found: C, 47.70; H, 4.12; N, 6.15; S, 14.12.

Methylthiomethyl 2,4-Dinitrobenzoate (8c): solidifies slowly at −16 °C; mp 25 °C; IR 3080 and 2900 (C–H), 1740 (C=O), 1530 and 1330 (NO_2), and 1250 and 1080 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 8.76 (d, 1 H, 3-H, J = 2.0 Hz), 8.57 (d of d, 1 H, 5-H, J = 2.0 and 8.0 Hz), 8.01 (d, 1 H, 6-H, J = 8.0 Hz), 5.42 (s, 2 H, S–CH_2–O), and 2.30 (s, 3 H, CH_3).

Methoxymethyl 4-Nitrobenzoate (8d): white needles (1:5 benzene–hexane); mp 74–75 °C; IR 3080 and 2940 (C–H), 1720 (C=O), 1520 and 1340 (NO_2), and 1280, 1160, and 1080 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 8.26 (s, 4 H, phenyl), 5.54 (s, 2 H, O–CH_2–O), and 3.58 (s, 3 H, CH_3).

Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.22; H, 4.27; N, 6.64.

Methoxymethyl 2,4-Dinitrobenzoate (8e): pale yellow (1:1 benzene–hexane); mp 60–61.5 °C; IR 3080 and 2940 (C–H), 1740 (C=O), 1530 and 1330 (NO_2), and 1270, 1167, and 1040 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 8.79 (d, 1 H, 3-H, J = 2.0 Hz), 8.59 (d of d, 1 H, 5-H, J = 2.0 and 8.0 Hz), 8.02 (d, 1 H, 6-H, J = 8.0 Hz), 5.51 (s, 2 H, O–CH_2–O), and 3.57 (s, 3 H, CH_3).

Reactions of 8a–e with 1-Hexanol (Table V). Applying the conditions depicted in Table V, reactions were carried out with equimolar amounts of 1-hexanol and esters **8a–e** (ca. 30 mL of solvent per 10 mmol). The disappearance of **8a–e** and the conversion of 1-hexanol were followed by TLC and GC (120 °C), respectively. Esters **8b–e** were insoluble in carbon tetrachloride. In general, the best conversions were obtained with methanesulfonic acid as a catalyst. The reactions were worked up following the precedure described above for THT, THF, and THP ethers. Products **9a,b, 10,** and **11a** were isolated as pure compounds by preparative GC (190 °C).

1-Hexanol MTM Ether (9a): n^{22}_D 1.4524; IR 2940 and 2880 (C–H), 1070 (C–O), 725, and 675 cm^{-1}; NMR ($CDCl_3$) δ 4.56 (s, 2 H, O–CH_2–S), 3.48 (t, 2 H, O–CH_2, J = 6.5 Hz), 2.04 (s, 3 H, S–CH_3), 1.55 and 1.25 (m, 8 H, CH_2), and 0.87 (t, 3 H, CH_3).

1-Hexanol MM Ether (9b): n^{20}_D 1.4043 (lit.[26] n^{20}_D 1.4045); IR 2960 and 2900 (C–H), and 1140, 1100, and 1040 (O–C–O) cm^{-1}; NMR ($CDCl_3$) δ 4.58 (s, 2 H, O–CH_2–O), 3.50 (t, 2 H, O–CH_2, J = 6.5 Hz), 3.30 (s, 3 H, OCH_3), 1.55 and 1.25 (m, 8 H, CH_2), and 0.89 (t, 3 H, CH_3).

Di-1-hexyloxymethane (10): n^{22}_D 1.4264; IR 2940 and 2880 (C–H), and 1100, 1060, and 1030 (O–C–O) cm^{-1}; NMR ($CDCl_3$) δ 4.59 (s, 2 H, O–CH_2–O), 3.46 (t, 4 H, O–CH_2, J = 6.5 Hz), 1.55 and 1.25 (m, 16 H, CH_2), and 0.88 (t, 6 H, CH_3).

Dimethylthiomethane (11a): NMR ($CDCl_3$) δ 3.56 (s, 2 H, CH_2) and 2.07 (s, 6 H, CH_3) [lit.[27] (CCl_4) δ 3.45 and 2.05].

Cleavage of THT Ethers. General. Mercuric chloride (812 mg, 3 mmol) was added to a stirred solution of 2-phenylethanol THT ether (416 mg, 2 mmol) in a mixture of acetonitrile and water (4:1; 20 mL). After 10 min the reaction mixture was filtered through Celite, which was eluted with ether (2 × 10 mL). The resulting mixture was washed with a 10% ammonium acetate solution, water, and brine and dried with magnesium sulfate. Evaporation of the solvents gave a colorless oil, 248 mg (100%), with spectra identical with an analytical sample of 2-phenylethanol.

Selectivity. The experiments concerning selective cleavage of the THT group were carried out with 1-hexanol THT ether (1 mmol per 25 mL of solvent). The reactions were followed by GC (150 °C) with naphthalene as an internal standard. Disappearance of the THT ether occurred simultaneously with the formation of 1-hexanol; other products were not detected.

Standard conditions for the cleavage of MTM ethers are the following:[3b] (i) mercuric chloride (1.5 equiv) in acetonitrile–water (4:1) at 25 °C for 4 h (THT ether: 0 °C, 5 min) and (ii) silver nitrate (5 equiv) and 2,6-lutidine (3 equiv) in THF–water (4:1) at 25 °C for 45 min (THT ether: 5 min). However, by employing methyl iodide (3 equiv) and sodium hydrogen carbonate (3 equiv) in moist acetone at 25 °C,[3b] the THT ether hydrolyzed at a comparable rate (90% conversion in 6 days).

Registry No.—**3,** 13042-82-5; **7b,** 66675-13-6; **8a,** 31280-16-7; **8b,** 5388-04-5; **8c,** 66675-02-3; **8d,** 66675-03-4; **8e,** 66675-04-5; **9a,** 66675-05-6; **9b,** 66675-06-7; **10,** 54815-12-2; **11a,** 1618-26-4; THT, 110-01-0; sulfuryl chloride, 7791-25-5; 2-Cl-THT, 22432-03-6; THT diphenylacetate, 66675-01-2; 1-hexanol, 111-27-0; 2-phenylethanol, 60-12-8; benzyl alcohol, 100-51-6; geraniol, 106-24-1; 2-pentanol, 6032-29-7; cyclohexanol, 108-93-0; 1-hexanol THT ether, 66675-07-8; 2-phenylethanol THT ether, 66675-08-9; benzylalcohol THT ether, 66675-09-0; geraniol THT ether, 66675-10-3; 2-pentanol THT ether, 66675-11-4; cyclohexanol THT ether, 66675-12-5; 2,3-dihydropyran, 110-87-2.

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(13) When a similar experiment was done with THF and sulfuryl chloride, no change in the spectrum was observed. The enhanced reactivity of THT toward sulfuryl chloride is also apparent from Table I, where THF is used as a solvent for the chlorination of THT.
(14) Yields were not improved by the addition of 2 equiv of sodium iodide or by reaction at 50 °C.
(15) For a discussion of the mechanism of the reaction of 2-Cl-THF with alcohols, see ref 3d.
(16) Some data for 1-hexanol: in acetonitrile the product contains 35% of dimer 3, and the yield of THT ether is 35%; in benzene these values are 5 and 75%, respectively; and in carbon tetrachloride no dimer is detectable with GC and NMR spectroscopy.
(17) A discussion of the relative reaction rates of tertiary and primary alcohols with 2-Cl-THF can be found in ref 3d.
(18) Thiacarbenium ion 4 is also an intermediate in the chlorination of THT (ref 7). In apolar solvents it reacts immediately with chloride ion, but in polar solvents this reaction is reversible and the formation of 2,3-dihydrothiophene, which reacts with chloride to form 2,3-dichloro-THT, is favored.
(19) The introduction of THP groups with 2,3-dihydropyran, which is a standard technique, requires considerably less subtile conditions; see, for instance, ref 2, p 105.
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Reaction of Isocyanides with Divalent Sulfur-Containing Heterocycles[1]

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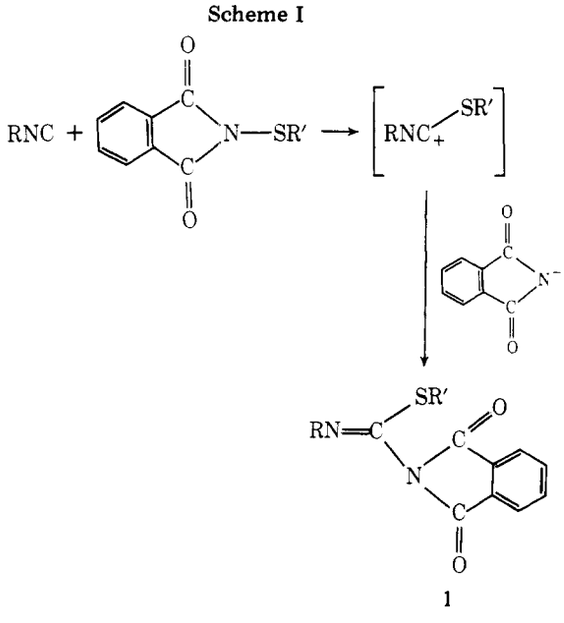
Reaction of *N*-(substituted thio)phthalimides with organic isocyanides results in sulfur–nitrogen bond cleavage and formation of new α adducts **1**. In addition to **1**, 2-alkylthio-5-aminooxazoles (**2**) were prepared for the first time by this method from 2-isocyanoacetamides. Likewise, when sulfur transfer reagents such as 2-alkyldithiobenzimidazoles and benzothiazoles are reacted with isocyanides, sulfur–sulfur fission results in the formation of α adducts possessing attachment of the heterocycle through nitrogen (**4, 6**) or sulfur (**5**) to the isocyanide carbon. Product structure, isomer distribution, and reaction scope are discussed. Reactions of the parent heterocycles with isocyanides are also found to give α adducts **7, 8, 9,** and **10** formed by nitrogen–hydrogen heterolysis.

Reaction of sulfenamides with organic isocyanides (Scheme I) has been found to give α adducts **1** (Table I). The reaction is visualized as proceeding through a polar intermediate, much in keeping with the generally accepted mechanism encountered with a number of other well-known α additions to isocyanides,[2] including certain sulfur compounds.[3–5]

Moreover, sulfenamides have been shown to serve as effective sulfur transfer agents,[6–8] with the products therefrom indicative of sulfur transfer via a positive sulfenium intermediate.

Scheme I



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The reaction appears fairly general, although with certain isocyanides possessing an active methylene group, an alternative reaction is also possible (Scheme II). Although the corresponding α adduct can be isolated, significant amounts of the novel 2-alkylthio-5-aminooxazoles **2** are also formed. Since oxazole formation has been postulated in certain instances to proceed through a nitrile ylid,[9] especially during the Cornforth rearrangement, its intermediacy is suggested here. Curiously, present evidence indicates that the α adduct in Scheme II cannot be transformed to the substituted oxazole, but rather the two products are formed simultaneously and apparently independently regardless of whether the reaction is carried out at room temperature or in refluxing acetonitrile.

To further define the reaction scope, other types of divalent sulfur compounds were reacted with organic isocyanides, with the results diagrammed in Scheme III.

From the examples given in Schemes I–III it becomes apparent that the α additions depicted require facile cleavage of the sulfenamides or mixed disulfides to give relatively stable sulfenium cation and mercaptide or amine anions. A case in point is disulfides derived from benzothiazoline-2-thione which behave analogously to *N*-alkylthiophthalimides, except that while the sulfenamides derived from imides and amines cleave to give a nitrogen anion and sulfenium cation, the mixed disulfides give the latter ion and resonance stabilized mercaptide anion as addends.

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