Experimental Section

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R 24B spectrometer and Varian EM 390 spectrometer equipped with a Varian EM 3940 variable-temperature controller. Me_4Si was used as internal standard (δ = 0 ppm). In liquid ammonia the solvent peak was used as the standard (δ = 0.95 ppm). The ^{13}C NMR spectra were recorded at 75.46 MHz on a Bruker CXP-300 spectrometer equipped with a B-VT 1000 variable-temperature controller. For measurements in anhydrous liquid ammonia, thick-wall 5- and 10-mm o.d. tubes were used for ^{1}H and ^{13}C NMR spectroscopy, respectively. The latter contained an internal 3-mm capillary with acetone-d_6. This was used both for the lock signal and as internal standard (δ = 29.8 ppm). Spectral parameters: 15000-Hz spectral width, 0.27 s acquisition time, 1.2 s pulse delay. IR spectra were recorded on a Hitachi EPG-3 spectrometer.

Starting Materials. 5-Nitropyrimidine,[13] 2-methyl-5-nitropyrimidine,[14] 2-(methylthio)-5-nitropyrimidine,[15] 2-phenyl-5-nitropyrimidine,[12] 2-(methylsulfonyl)-5-nitropyrimidine,[15] and 4-methoxy-5-nitropyrimidine[16] were synthesized as described in the literature.

2-Amino-5-nitropyrimidine (4). Potassium permanganate (440 mg, 1.05 redox equiv) was dissolved in liquid ammonia (ca. 20 mL), and 5-nitropyrimidine (**1a**) (500 mg, 4 mmol) was added to this solution in one portion with stirring. After 15 min, methanol (25 mL) was slowly added through a dry ice/acetone condenser, and the reaction mixture was allowed to stand at room temperature for 1 h. Purification by column chromatography on silica gel using ethanol as eluent gave crystals (250 mg, 45%): mp 234–236 °C (lit.[12] 236 °C) ^{1}H NMR (Me_2SO-d_6) δ 9.06 (s, 2 H), 8.20 (br s, 2 H).

Aminopyrimidines 5a–c and 6 were obtained analogously to the procedure described above. Analytically pure compounds were isolated by TLC on silica gel plates with chloroform/ethyl acetate (20:1) followed by recrystallization from ethanol. All data of **5a–c** and **6** are collected in Table III.

Reaction of 4-Methoxy-5-nitropyrimidine (1h) with Ammonia. A. Without $KMnO_4$. 4-Methoxy-5-nitropyrimidine (310 mg, 2 mmol) was dissolved in 5 mL of liquid ammonia, and the reaction mixture was allowed to stand at room temperature for 10 min (sealed tube was used). After cooling, ammonia was evaporated slowly and the residue recrystallized from ethanol, yielding 210 mg (65%) of **7**: mp 210–212 °C (lit.[16] 212–214 °C) (Table III).

B. In the Presence of $KMnO_4$. 4-Methoxy-5-nitropyrimidine (310 mg, 2 mmol) was added in small portions to a solution of potassium permanganate (220 mg, 1.05 redox equiv) in 20 mL of ammonia at −60 to −70 °C with stirring. The reaction mixture was kept for 15–20 min at −60 °C, and then methanol (20 mL) was added through a dry ice/acetone condenser. 2-Amino-4-methoxy-5-nitropyrimidine (170 mg, 50%) was isolated by column chromatography on silica gel with ethanol: mp 225–227 °C; ^{13}C NMR ($(CD_3)_2SO$) δ 163.8, 162.7 (C-2 and C-4), 158.2 (C-6, $^1J_{C\text{-}H}$ = 189.1 Hz), 123.0 (C-5). For comparison, $^1J_{C\text{-}H}$ values of 5-nitropyrimidine are 207 Hz for C-2 and 192 Hz for C-4(6).

Acknowledgment. We are indebted to Dr. M. A. Posthumus for providing mass spectra and to Mr. H. Jongejan for microanalyses.

Registry No. **1a**, 14080-32-1; **1b**, 84928-77-8; **1c**, 14080-34-3; **1d**, 14001-70-8; **1e**, 68906-00-3; **1f**, 65735-65-1; **1g**, 15846-14-7; **1h**, 15579-58-5; **2a**, 84928-78-9; **2b**, 84928-79-0; **2h**, 84944-06-9; **3a**, 84928-80-3; **3b**, 84944-07-0; **3c**, 84928-81-4; **3d**, 84928-82-5; **3e**, 84928-83-6; **3f**, 84928-84-7; **4**, 3073-77-6; **5a**, 15579-59-6; **5b**, 84928-85-8; **5c**, 84928-86-9; **6**, 84928-87-0; **7**, 15568-46-4; **8**, 84928-88-1; NH_3, 7664-41-7.

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[13] van der Plas, H. C.; Jongejan, H.; Koudijs, A. *J. Heterocycl. Chem.* **1978**, *15*, 485.

[14] Biffin, M. E. C.; Brown, D. J.; Lee, T. C. *J. Chem. Soc. A* **1967**, 573.

[15] Hurst, D. T.; Christophides, J. *Heterocycles* **1977**, *6*, 1999.

[16] Biffin, M. E. C.; Brown, D. J.; Lee, T. C. *Aust. J. Chem.* **1967**, *20*, 1041.

Direct Synthesis of Thioethers from Thiols and Alcohols

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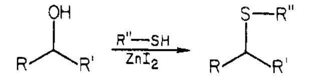
Herein we report a very simple and convenient synthesis of a wide range of thioethers. It is based on the finding that thiols in the presence of zinc iodide react smoothly with activated alcohols to give the corresponding thioethers in excellent yields, according to the following scheme:



R = aryl, alkenyl; R′ = H, alkyl, aryl; R″ = alkyl, aryl

This work grew out of our research into methods for the synthesis of the leukotrienes,[1] related analogues,[2] and potential antagonists or biosynthetic inhibitors, in which it was necessary to develop mild procedures for the formation of a variety of substituted thioethers. In this regard we have developed approaches based on the sulfenyllactonization reaction[2] and the reaction of thiosilane reagents with epoxides.[3]

The present reaction, involving the use of zinc iodide and alcohols, is attractive for its simplicity, effectiveness, and the very mild conditions employed. These advantages were demonstrated dramatically in the synthesis of [1-(phenylthio)pentyl]benzene. Thus reaction of the phenyl thiolate anion with (1-chloropentyl)benzene (Williamson's ether synthesis conditions[4]) lead mainly to elimination of HCl from the alkylating agent, while attempts to prepare the tosylate of 1-phenyl-1-pentanol yielded the ether of the starting alcohol as the principal product. These experiments underline the sensitivity of such systems (benzylic or allylic alkylating agents) to either base or nucleophile, which renders the "classical" approach difficult.

In sharp contrast, with use of the new conditions herein described, thiophenol reacted with 1-phenyl-1-pentanol to yield the desired thioether in 88% yield (Table I, entry 3). In this same context, it is worth pointing out that even a tertiary benzylic alcohol gives a high yield (81%) of thioether, without significant olefin formation (Table I, entry 6).

Although acid-catalyzed displacement of alcohols by thiols has found some isolated examples in the literature,[5] no effort has been made to develop this methodology into a sound and efficient approach to sulfides (thioethers) and to determine its scope and limitations.

Results and Discussion

The choice of Lewis acid was based on the following observations: the alcohols and thiols used are stable to zinc

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[1] (a) Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J. G.; Larue, M.; Young, R. N.; Masson, P.; Home, G. *Tetrahedron Lett.* **1980**, *21*, 1485. (b) Rokach, J.; Zamboni, R.; Lau, C. K.; Guindon, Y. *Ibid.* **1981**, *22*, 2759.

[2] Young, R. N.; Coombs, W.; Guindon, Y.; Rokach, J.; Ethier, D.; Hall, R. *Tetrahedron Lett.* **1981**, *22*, 4933.

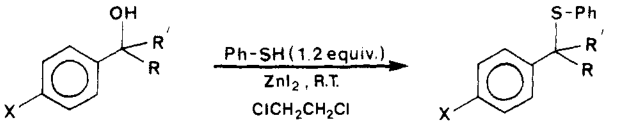
[3] Guindon, Y.; Young, R. N.; Frenette, R. *Synthet. Commun.* **1981**, *11*, 391.

[4] March, J. "Advanced Organic Chemistry"; McGraw-Hill: New York, 1968; p 316.

[5] Some examples involving the syntheses of *S*-diphenylmethyl and *S*-triphenylmethyl thioethers using the following procedures have been reported: (a) Boron trifluoride etherate in trifluoroacetic acid (Hiskey, R. G.; Adams J. B, Jr. *J. Org. Chem.* **1965**, *30*, 1340). (b) Trifluoroacetic acid (Photaki, I.; Papadimitriou, J. T.; Sakarellos, C.; Mazaiakis, P.; Zervas, L. *J. Chem. Soc. C* **1970**, 2683.

0022-3263/83/1948-1357$01.50/0

Table I



Entry	X	R	R'	ZnI_2 (equiv.)	Time[a]	Yield (Isolated Product)[b]
1	H	H	H	0.5	24 h	90%
2	H	H	H	0.5	90 min[c]	90%
3	H	Butyl	H	0.2	12 h	88%
4	H	Butyl	H	0.5	40 min	91%
5	H	Me	H	0.5	40 min	89%
6	H	Me	Me	0.5	5 min	81%
7	OMe	H	H	0.5	50 min	83%
8	OMe	Butyl	H	0.5	5 min	99%
9	CO_2Me	Me	H	0.5	48 h	80%
10	CO_2Me	Me	H	0.5	45 min[c]	92%

[a] Time required for the disappearance of starting material. [b] The products were characterized by NMR, mass spectra, and chemical analysis and melting points (when available). [c] The reaction was performed in refluxing dichloroethane.

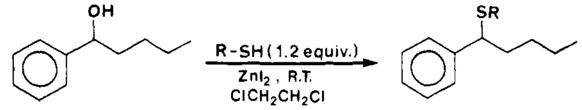
iodide; the reaction is not altered by the order of addition of the reagents involved;[6] the Lewis acid is easy to handle.

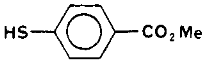
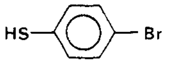
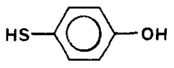
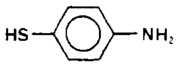
Dichloromethane and 1,2-dichloroethane are the preferred solvents for optimum yields and reproducibility. Other solvents such as CH_3CN, Et_2O, DMF, THF, or EtOAc are unsatisfactory since they contain a site of coordination for zinc iodide. Results of our studies are summarized in Tables I, II, and III.

As can be seen in Table I, the rate of displacement of the hydroxyl group α to the phenyl moiety increases as the level of substitution at this center increases (entries 1, 4, 6) and as the amount of zinc iodide used increases (entries 3, 4). The presence of electron-donating substituents (entries 7, 8) on the phenyl ring increases the rate of the reaction, whereas the presence of electron-withdrawing groups decreases it (entries 9, 10). It is interesting to note that the use of *p*-methoxybenzyl alcohol (entry 7, Table I) gives rise, in 50 min, to the corresponding sulfide when reacted with benzenethiol. This suggests therefore that one can use this methodology advantageously to protect[7] a thiol function by preparing the corresponding *p*-methoxybenzyl thioether.

The reaction can be performed with thiols of different nature as shown in Table II. Here again, substituents on the thiophenol influence the rate of the reaction. Although electronic considerations may account for this phenomenon, one has to consider, as well, certain of these substituents as potential competitive coordination sites (entries 6 and 8) for zinc iodide. This might interfere in the overall process and decrease the reaction rate.

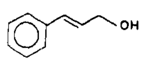
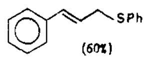
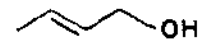
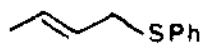
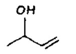
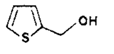
Table II



Entry	R-SH	ZnI_2 (equiv.)	Time[a]	Yield (isolated product)[b]
1	$HS-(CH_2)_3-CH_3$	0.5	8 h	90%
2	$HS-(CH_2)_2-CO_2Me$	0.5	3.5 h	71%
3	$HS-(CH_2)_2-CONH_2$	0.5	12 h	30%
4	$HS-(CH_2)_2-CONH_2$	1.0	8 h	90%
5	HS-Ph	0.5	40 min	91%
6		0.5	3 h	86%
7		0.5	20 min	86%
8		0.5	4 h	94%
9		0.5	-	No reaction[c]

[a] Time required for the disappearance of starting material. [b] The products were characterized by NMR, mass spectra, and chemical analysis and melting points (when available). [c] Formation of insoluble material.

Table III

Entry	Substrate	R-SH	ZnI_2 (equiv.)	Δt	Reaction Time[a]	Product (Yield)[b]
1		Ph-SH	0.5	R.T.	15 min	 (60%)
2		Ph-SH	0.5	R.T.	20 h	 (86%)
3		Ph-SH	0.5	R.T.	20 h	 (75%)
4		Ph-SH	0.5	R.T.	15 min	 (89%)
5	$CH_3-(CH_2)_{14}-OH$	Ph-SH	0.5	R.T.	2 days	No reaction

[a] Time required for the disappearance of starting material. [b] Yield based on isolated material.

Basic substituents such as amides and amines present certain difficulties. In the case of amides, the reaction could be carried to completion by increasing the amount of zinc iodide used (entries 3, 4). However, when a free amine was present, no sulfide was obtained (entry 9).

The zinc iodide catalyzed displacement of (*S*)-α-phenethyl alcohol was also performed to give the α-methylbenzyl phenyl sulfide (entry 5, Table I), which has an $[\alpha]_D$ +12.5° (lit.[8] (*R*)-α-methylbenzyl phenyl sulfide $[\alpha]_D$ +167°). The low optical yield ($\approx$7%) indicates that the displacement is essentially an S_N1 type process. The in-

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[6] In some cases the reaction can be performed with $AlCl_3$ when it is added slowly to a reaction mixture containing the alcohol and the thiol involved. If the alcohol is mixed with either $AlCl_3$, $SnCl_4$, or BF_3 etherate before the addition of thiols, major decomposition occurs. No reaction occurred, at room temperature, when trifluoroacetic acid was used.

[7] (a) Nishimura, O.; Kitada, C.; Fuyino, M. *Chem. Pharm. Bull.* **1978**, *26*, 1576. (b) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, Chichester, Brisbane, and Toronto, 1981.

[8] Jung, F.; *J.* Durst, T. *J. Chem. Soc., Chem. Commun.* **1973**, *1*, 4.

J. Org. Chem. **1983**, *48*, 1359–1360 **1359**

crease in rate of the reaction in cases where there is an electron-donating substituent on the phenyl ring or an alkyl substituent α to the hydroxyl group, as described earlier, also suggests a carbocation character.

The formation of sulfides using this procedure is not restricted to the use of alcohols α to a phenyl ring. As can be seen in Table III, allylic alcohols reacted just as well, leading to the corresponding sulfides. As one can see (entries 2 and 3, Table III), the reaction proceeds smoothly, in high yields, but the rate of reaction is significantly lower than in the cases of alcohols activated by an aromatic group.

It is interesting to note that the regioselectivity of the displacement involved when 1-buten-3-ol is treated with thiophenol (entry 3, Table III) to give [(2-butenyl)thio]benzene involves formally a S$_N$2′ process in that case. No reaction was noted when aliphatic alcohol was used (entry 5).

In conclusion, the reaction of thiols with activated alcohols in the presence of zinc iodide represents a general, simple, efficient, and useful approach to the synthesis of thioethers, particularly when sensitive substrates preclude the use of bases or basic anions.

Experimental Section

In a typical procedure, dried zinc iodide (0.5 mmol) was added to a solution of 1-phenyl-1-pentanol (1 mmol) in dry 1,2-dichloroethane (2 mL). To the obtained suspension was added thiophenol (1.2 mmol), and the mixture was stirred at room temperature for 40 min during which the reaction was completed. The reaction was quenched with water (10 mL), and the reaction products worked up by extraction with dichloromethane (2 × 10 mL). The combined organic extracts were washed with brine and dried over Na$_2$SO$_4$ from which solvent was evaporated at reduced pressure. The residue was chromatographed in a column of silica gel (70–230 mesh), eluting with 1:100 ethyl acetate–hexane to afford [1-(phenylthio)pentyl]benzene (91%).

Excess thiol can be washed out during the workup by treatment with 1 N NaOH if desired.

Acknowledgment. We thank Drs. J. G. Atkinson, C. K. Lau, and R. N. Young for helpful discussions during the preparation of this manuscript.

Registry No. Benzyl alcohol, 100-51-6; 1-phenyl-1-pentanol, 583-03-9; (*S*)-α-phenethyl alcohol, 1445-91-6; 2-phenyl-2-propanol, 617-94-7; *p*-methoxybenzyl alcohol, 105-13-5; 1-(*p*-methoxyphenyl)-1-pentanol, 19523-03-6; methyl *p*-(1-hydroxyethyl)benzoate, 84851-56-9; 1-butanethiol, 109-79-5; methyl 3-mercaptopropionate, 2935-90-2; 3-mercaptopropanamide, 763-35-9; thiophenol, 108-98-5; methyl *p*-mercaptobenzoate, 6302-65-4; *p*-bromothiophenol, 106-53-6; *p*-mercaptophenol, 637-89-8; *p*-thiophenol, 1193-02-8; 3-phenylallyl alcohol, 104-54-1; crotyl alcohol, 6117-91-5; 1-buten-3-ol, 598-32-3; 2-thiophenemethanol, 636-72-6; 1-pentadecanol, 629-76-5; benzyl phenyl sulfide, 831-91-4; [(1-phenylpentyl)thio]benzene, 68602-14-2; (*R*)-α-methylbenzyl phenyl sulfide, 40390-78-1; α,α-dimethylbenzyl phenyl sulfide, 4148-93-0; 1-methoxy-4-[(phenylthio)methyl]benzene, 5023-67-6; 1-methoxy-4-[1-(phenylthio)pentyl]benzene, 60702-18-3; methyl 4-[1-(phenylthio)ethyl]benzoate, 84851-57-0; [(1-phenylpentyl)thio]butane, 84851-58-1; methyl 3-[(1-phenylpentyl)thio]propionate, 84851-59-2; 3-[(phenylpentyl)thio]propanamide, 84851-60-5; methyl 4-[(1-phenylpentyl)thio]benzoate, 84851-61-6; 1-bromo-4-[(1-phenylpentyl)thio]benzene, 84851-62-7; 1-hydroxy-4-[(1-phenylpentyl)thio]benzene, 84851-63-8; 1-phenyl-3-(phenylthio)-1-propene, 10276-14-9; 2-butenyl phenyl sulfide, 702-04-5; 2-[(phenylthio)methyl]thiophene, 69639-48-1; zinc iodide, 10139-47-6.

Supplementary Material Available: Full NMR data, chemical analyses, and melting points for compounds listed in Tables I–III are available (4 pages). Ordering information is given on any current masthead page.

Absolute Rate Constants for the Reactions of Some Arylchlorocarbenes with Acetic Acid[1a]

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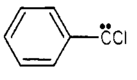
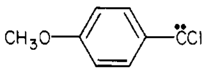
Carbene chemistry has traditionally been investigated by using product studies,[2] which have frequently been combined with assumptions about the multiplicity of the reacting carbene.[3] Consequently, the vast majority of kinetic measurements have yielded only relative rate constants.

Absolute rate constants have been measured for a few reactions of carbenes by using flash photolysis techniques.[4–12] These studies have so far centered on the reactions of carbenes with aromatic substituents, which facilitate optical detection, i.e., diphenylcarbene,[4,5] fluorenylidene,[6–11] phenylchlorocarbene,[12] and 1-naphthylcarbene.[13] The substrates of these studies have been mostly olefins, alcohols, or ketones. No absolute rate constants have been reported for the reactions of any carbenes with acids. In this paper we report the first measurements of this type. In particular, we have examined the reaction of singlet phenylchlorocarbene (Ia) and *p*-anysilchlorocarbene (Ib) with acetic acid.



Ia



Ib

The carbenes were generated by laser excitation of solutions of the corresponding diazirines[14,15] (which in contrast with diazo compounds are not acid sensitive) by using the pulses (337.1 nm, ~8 ns, up to 10 mJ) from a nitrogen laser. The resulting transient absorptions were monitored by using an instrument which has been described elsewhere.[16] All experiments were carried out in deaerated solutions at 300 K.

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[1] (a) Issued as NRCC 20697. (b) Address: Department of Chemistry, University of Prince Edward Island, Charlottetown, P. E. I., Canada C1A 4P3.

[2] Kirmse, W. "Carbene Chemistry", 2nd ed.; Academic Press: New York, 1971; Chapters 7–9.

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[13] Hadel, L. M.; Platz, M. S.; Scaiano, J. C., submitted for publication in *Chem. Phys. Lett.*

[14] The diazirines[15] were purified by chromatography on silica gel before use. Caution: a cold sample of Ib decomposed violently on warming to room temperature.

[15] Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396. Liu, M. T. H.; Toriyama, K. *Can. J. Chem.* **1972**, *50*, 3009.

[16] Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7747–7753.

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