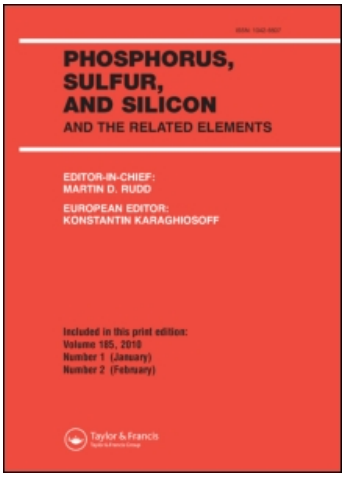

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ALIPHATIC THIOETHERS BY *S*-ALKYLATION OF THIOLS VIA TRIALKYL BORATES

Deniz Gunes[a]; Okan Sirkecioglu[a]; Niyazi Bicak[a]
[a] Istanbul Technical University, Department of Chemistry, Maslak, Istanbul, Turkey

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ALIPHATIC THIOETHERS BY *S*-ALKYLATION OF THIOLS VIA TRIALKYL BORATES

Deniz Gunes, Okan Sirkecioglu, and Niyazi Bicak
Istanbul Technical University, Department of Chemistry, Maslak, Istanbul, Turkey

A simple and convenient one-pot procedure is described for the synthesis of thioethers via boron esters. This procedure involves in-situ generation of alkyl sulfates by reaction of trialkyl borates with concentrated sulfuric acid and subsequent reaction with thiols in the presence of pyridine. The reactions with boron esters of primary or secondary alcohols proceed cleanly at 100°C and afford aliphatic thioethers in reasonable yields (59–93%) within 24 h. Interestingly, the ^{1}H NMR spectra of the products showed no sign of positional isomerisms. The method fails however with thiophenol and does not yield aromatic thioethers, due to electrophilic substitution at the phenyl ring.

Keywords Alkyl sulfates; thioethers; trialkyl borates

INTRODUCTION

Thioethers are valuable key intermediates in various organic syntheses.[1] They are precursors[2–4] for sulfoxides and sulfones. Chiral sulfoxides are useful auxiliaries in asymmetric syntheses. The sulfur ylides derived from thioethers have found extensive use in the syntheses of epoxides[5] and cyclopropanes.[6] The formation of sulfonium salts by reaction of alkyl halides with thioethers is a reversible process.[7] The sulfonium salts with weak nucleophilic anions act as initiating species in thermal- or photo-induced cationic polymerization of oxiranes[8] and vinyl ethers.[9–11]

Numerous methods for the synthesis of thioethers have appeared. *S*-Alkylation of thiols with alkyl halides,[12] *anti*-markovnikov addition of alkanethiols to alkenes,[13] and addition of thiols to carbonyl compounds with subsequent reduction of the generated thionium ions[14] are the most common ways to synthesize them. Other less common routes, such as metal-mediated cross-coupling[15] or metal-catalyzed hydrothiolation of alkynes[16] and Friedel–Crafts reaction of *N*-phenyl thiophthalimide with benzenes[17] have been employed for the synthesis of thioethers. Recently, Saxena et al. described an interesting procedure in which thioethers are generated by oxidative coupling of thiols with alcohols in the presence of nickel nanoparticles as catalyst.[18]

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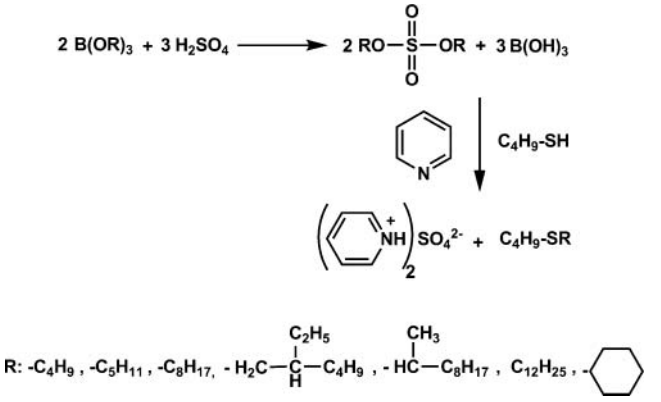
Address correspondence to Niyazi Bicak, Istanbul Technical University, Department of Chemistry, Maslak 34469, Istanbul, Turkey. E-mail: bicak@itu.edu.tr

RESULTS AND DISCUSSION

In this article, we report an alternative procedure for the alkylation of thiols to give thioethers in good to excellent yields (see Table I). In this procedure, trialkyl borates are employed as alkyl precursors. The preparation of boron esters of higher alcohols boiling over 100°C is a relatively simple task that can be achieved by azeotropic removal of water from alcohol–boric acid mixtures at 115–130°C, using toluene or benzene.[19]



Scheme 1

Removal of the toluene gives trialkyl borates as colorless liquids. The yields are generally higher than 90% in proper conditions, and the products are pure enough (>98%) for use in the follow-up reactions, without further purification. The resulting trialkyl borates are converted into alkyl sulfates by reaction with equivalent amounts of sulfuric acid at room temperature. Addition of a pyridine-thiol mixture to the reaction medium and subsequent heating at 100°C for 24 h gives thioethers in reasonable yields. The overall process consists of alkylation of thiols via boron esters in a one-pot procedure as depicted in Scheme 1. Direct heating of a mixture of tributyl borate with butanethiol and pyridine in the absence of sulfuric acid, however, did not yield any thioether product. The ^{1}H NMR spectrum of the reaction mixture showed no trace of thioether, even after a reaction period of 48 h. This

Table I Synthesis of thioethers R—S—Bu via trialkyl borates $B(OR)_3$

R	Reaction time (h)	R—S—Bu	Yield (%)[a]
n-Butyl	6	C_4H_9—S—C_4H_9	64.0
	24		88.0[b]
	30		93.0
n-Pentyl	24	C_5H_{11}—S—C_4H_9	81.2[c]
Cyclohexyl	24	*cyclo*-C_6H_{11}—S—C_4H_9	78.8
n-Octyl	24	C_8H_{17}—S—C_4H_9	68.4
2-Etylhexyl	24	C_4H_9—CH(C_2H_5)—CH_2—S—C_4H_9	71.0
2-Decyl	24	C_8H_{17}—CH(CH_3)—S—C_4H_9	58.7
n-Dodecyl	24	$C_{12}H_{23}$—S—C_4H_9	65.0

[a]Conversion yields assigned by ^{1}H NMR spectroscopy of the reaction mixture.
[b]Isolated yield 64.2%.
[c]Isolated yield 67.2%.

implies that the acidity of the thiol group is not sufficient to protonate the oxygen atom of the boron ester. In other words, trialkyl borates themselves cannot react as alkylating agents but must be converted into alkyl sulfates for the successful alkylation of thiols. The use of alkyl sulfates as alkylating agents for phenols and amines has been well documented in the literature.[20] Dimethyl sulfate is the most common ester of sulfuric acid, having extensive use as a methylating reagent in organic chemistry.[21] In recent years, this compound has been replaced with methyl iodide in methylation reactions due to its potent carcinogenic effects.[22]

The use of alkyl sulfates for the alkylation of thiols could be considered a more direct way to synthesize thioether. However, most of the dialkyl sulfates are not commercially available, and the classical method of their preparation involves sulfatation of alcohols either with chlorosulfonic acid[23,24] or with sulfur trioxide. Besides difficulties in handling of these reagents, a number of side reactions such as dehydration, isomerization, and etherification occur to some extent, depending on the reaction conditions.[3] The direct sulfatation with sulfuric acid, on the other hand, does not give satisfactory yields with higher alcohols and exhibits the disadvantages of side reactions.[4]

Tertiary amine–sulfur trioxide complex salts, e.g., pyridine-SO_3 and triethylamine-SO_3, have been demonstrated to be versatile and safe reagents for the sulfatation of primary and secondary alcohols.[5,6] However, the yields reported were in the range of only 30–60% for C8–C16 alcohols.

Considering the difficulties in the common procedures, the *in-situ* generation of alkyl sulfate intermediates by sulfuric acid according to the present procedure represents an attractive alternative. In order to inspect the extent of the sulfate ester formation, an aliquot of tributyl borate–sulfuric acid mixture (2/3 mol/mol) was digested in ether (10 mL per gram) and filtered. Removal of the ether yielded a clear liquid residue. The ^{1}H NMR spectrum of this product (in $CDCl_3$) indicated pure di-*n*-butyl sulfate (with 98% practical yield), but no other isomers. This reveals that the alkylation of thiols under these condition proceeds via dialkyl sulfate intermediates.

The reactions conducted at 100°C for 24 h gave thioethers in good to excellent yields (59–93%) as listed in Table I. Since thioethers are water-immiscible, they were isolated simply by washing the reaction mixtures with aqueous sodium hydroxide solution and subsequent distillation of the organic phases.

The reaction with butyl mercaptane and tributyl borate at room temperature gave only 32–34% of conversion yields within 48 h. The lower yields at room temperature must be due to the less pronounced reactivity of the second alkyl group of dialkyl sulfates in the alkylation process. Therefore 100°C was chosen as the reaction temperature.

The ^{1}H NMR spectra of the products prior to distillation of the organic phases showed CH_2 proton signals associated with the methylol groups of the alcohol, which is formed by hydrolysis of the boron esters. Integral ratios of those peaks appearing around 3.5 ppm were employed to estimate the conversion rates. In the ^{1}H NMR spectrum of dibutyl sulfide, a sharp triplet of *S*-CH_2 protons is observed at 2.38 ppm. In addition, the terminal methyl protons exhibit a triplet at 0.82 ppm and the methylene protons of the butyl group give two multiplets centered at 1.45 and 1.35 ppm. The integral ratio of those protons is 2:3:2:2, respectively. No other signals at around 2.5 ppm are observed, which implies the absence of positional isomers in the thioether product. A similar ^{1}H NMR pattern is observed in the case of butyl isodecyl sulfide in which the *S*-CH_2-protons of the butyl group and an *S*-CH-proton of the isodecyl group show a complex signal with an integral for three protons as expected.

For the synthesis of aromatic thioethers by this procedure, thiophenol was utilized as a thiol component. However, the reaction did not yield the expected phenyl alkyl sulfide. Instead, the product was 2-butylthiophenol, indicating that the electrophilic substitution at the phenyl ring is favored compared with the *S*-alkylation. Since alkyl phenols are beyond the scope of the present work, this reaction was not studied any further. It is important to note that we were not able to prepare benzyl butyl sulfide starting from tribenzyl borate, because the addition of the sulfuric acid resulted in a violent explosion to give a yellow solid. The solid product formed was identified as poly(1,4-phenylene-methylene) instead of dibenzyl sulfate. Thus, the synthesis of benzyl thioethers by this procedure is not possible. We have also attempted to synthesize symmetrical thioethers by reaction of the dialkyl sulfates with sodium sulfide. Since sodium sulfide is insoluble in organic media, the reaction of dibutyl sulfate was carried out with aqueous sodium sulfide solution at ambient temperatures or at 100°C. However, the ^{1}H NMR spectra of the reaction mixtures revealed a conversion of only 16–28% for the same period of reaction time, due to the rapid hydrolysis of the dialkyl sulfates in water. To avoid hydrolysis of the alkyl sulfate, the reaction was performed under heterogeneous conditions using anhydrous sodium sulfide powder without additional solvent. The yield in this case was even lower (5–7%) owing to insolubility of the sodium sulfide.

In conclusion, the alkylation of thiols with dialkyl sulfates generated in-situ from trialkyl borates and sulfuric acid gave the corresponding thioethers in the presence of pyridine. The reaction can be performed in one step and allows the preparation of aliphatic thioethers in satisfactory yields. This procedure is, however, not applicable to alcohols and thiols with aromatic moieties.

EXPERIMENTAL

Boric acid, thiophenol, 1-butanethiol, alcohols (1-butanol, 1-pentanol, cyclohexanol, 2-ethylhexanol, isodecanol, and 1-dodecanol), and all other chemicals were analytical grade commercial products (Aldrich or E. Merck). They were used as supplied, unless otherwise stated. Products were characterized by comparison with authentic samples, based on FT-IR spectra (which were taken by a Perkin Elmer FT-IR Spectrum One B spectrometer) and ^{1}H NMR spectra (recorded in $CDCl_3$ as solvent, using a Bruker 250 MHz NMR spectrometer), boiling points, and TLC. The boron esters were prepared according to the general procedure given in the literature.[19] The boron esters derived from higher alcohols (isodecanol, 1-dodecanol) were used without distillation.

Preparation of Thioethers

Concentrated H_2SO_4 (8.4 mL, 0.15 mol) was added dropwise to the trialkyl borate (0.1 mol) in a 250 mL flask at 0°C while stirring. Stirring was continued for 30 min. A mixture of butanethiol (27 mL, 0.30 mol) and pyridine (26 mL, 0.30 mol) was then added portionwise within 10 min, and the resulting mixture was heated at 100°C for 24 h. After cooling, NaOH solution (2 M, 200 mL) was added to the mixture. The oily phase was washed with saturated NaCl solution (2 × 150 mL), dried with Na_2SO_4, and distilled under vacuum. Purities of the products were checked by ^{1}H NMR spectroscopy. If necessary, the thioethers were redistilled.

^{1}H NMR spectra (δ, ppm in $CDCl_3$) of the Thioethers

Dibutyl sulfide. (distilled product) 2.38 (t, 4 H, SCH_2), 1.45 (m, 4 H, SCH_2CH_2), 1.12–1.35 (m, 4 H, CH_2), 0.82 (t, 6 H, CH_3). Butanol formed by hydrolysis of unreacted tributyl borate shows a weak triplet at 3.43 ppm associated with its CH_2OH group. This peak disappears after distillation under reduced pressure.

Butyl pentyl sulfide. 2.38 (t, 4 H, SCH_2), 1.43 (m, 4 H, SCH_2CH_2), 1.22–1.35 (m, 6 H, CH_2) 0.80 (t, 6 H, CH_3). Pentanol present in the reaction mixture prior to distillation shows a weak triplet at 3.43 ppm associated with its CH_2OH group. This peak disappears after distillation under reduced pressure.

Butyl cyclohexyl sulfide. 2.47 (bs, H, SCH), 2.32 (t, 2 H, SCH_2), 1.30–1.90 (m, 12 H, CH_2), 1.18 (m, 2 H, 4-CH_2), 0.80 (t, 3 H, CH_3).

Butyl octyl sulfide. 2.33 (t, 4 H, SCH_2), 1.40 (m, 4 H, SCH_2CH_2R), 1.15 (m, 12 H, CH_2), 0.80 (t, 6 H, CH_3). Protons of the CH_2OH groups of octanol show a weak triplet at 3.41 ppm.

Butyl 2-ethylhexyl sulfide. 2.49 (t, 2 H, SCH_2), 2.33 (bs, 2 H, SCH_2) 1.70 (m, 1 H, SCH_2CHR), 1.20–1.60 (m, 12 H, CH_2), 0.82 (m, 9 H, CH_3). Residual 2-ethylhexanol in the crude product shows proton signals (CH_2OH) at 3.52 ppm as a weak triplet.

Butyl 2-decyl sulfide. 2.47 (bs, 2 H, SCH), 2.38 (m, 1 H, SCH_2CH_2R), 1.10–1.40 (m, 18 H, CH_2), 1.00 (m, 3 H, CH_3-CHS), 0.74 (t, 6 H, CH_3). Residual decane-2-ol in the crude product shows proton signals (CH_2OH) at 3.45 ppm as a weak triplet.

Butyl dodecyl sulfide. 2.55 (m, 4 H, SCH_2), 1.43 (m, 4 H, SCH_2CH_2R), 1.20 (m, 20 H, CH_2), 0.80 (s, 6 H, CH_3). Residual dodeanol in the crude product shows proton signals (CH_2OH) at 3.55.

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