Chemistry of Natural Compounds, Vol. 44, No. 4, 2008

BRIEF COMMUNICATIONS

REACTION OF NATURAL-OCCURRING PHENOLIC DERIVATIVES WITH BIS(TRIMETHYLSILYL) SULFATE

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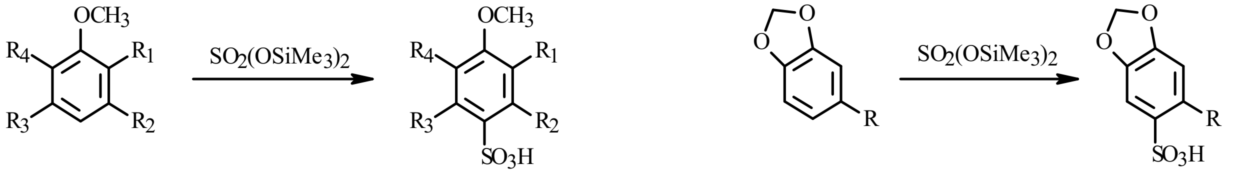
UDC 547.92

Aromatic sulfonic acids and their derivatives are important in chemical industries [1]. They have found applications in the dying industry and in sulfa drugs as antibiotics [2]. Aromatic substrates can be sulfonated with concentrated sulfuric acid, sulfur trioxide-dioxane complex, trifluoroacetic acid-sulfuric acid, or sulfur trioxide in dichloromethane [3]. Bourgeois and Duffaut [4] have shown that bis(trimethylsilyl)sulfate allows the sulfonation of anisole under mild conditions. It is thermally stable and soluble in most organic solvents. Continuing their works, we studied the sulfonation of six natural phenolic derivatives from thymol, carvacrol, 2,5-xylenol, eugenol methyl ether, safrole, and sesamol, which have biological properties but are limited by their solubility in aqueous solvents.

Prior to use, thymol, carvacrol, 2,5-xylenol, and sesamol were *O*-methylated with dimethylsulfate in alkali media [5]. Allylic double bonds of eugenol methyl ether and safrole were hydrogenated by H_2/chloroplatinic acid in absolute ethanol. The *O*-methylation and the hydrogenation avoided the attack of bis(trimethylsilyl) sulfate respectively on the phenolic group and the allylic double bond.

During the sulfonation reaction, water resulting from the spontaneous trimethylsilanol dehydration was eliminated by azeotropic distillation with methylcyclohexane. The resulting trimethylsilyl sulfonates (oily substances) were isolated by distillation under low pressure. Their structures were assigned by ^{1}H NMR: the NMR spectrum of each sulfonate indicated modifications of the aromatic signals and the -SO_3SiMe_3 group at 0.3–0.4 ppm. The sulfonates were hydrolyzed to give the corresponding sulfonic acids. They were characterized by ^{1}H NMR, melting point, and as *S*-benzylthiouronium salts and /or sulfonamide (data not shown). Sulfonamides are widely used in the pharmaceutical industry [6].

Electron-withdrawing groups (nitro, sulfonyl, carbonyl, etc.) are *meta*-directing and make sulfonation difficult, while electron-donating groups (alkyl, alkoxy, hydroxy, etc.) render sulfonation easy and are *ortho-para* directing. In this work, the *para*-trimethylsilyl sulfonate is isolated as a single product, as shown by the analysis of the ^{1}H NMR spectra: two singlets for the aromatic protons (Table 1). *ortho*-Oriented sulfonation did not occur, probably because of steric hindrances.



1a - d **2a - d** **1e - f** **2e - f**

a: R_1 = *i*Pr, $R_2 = R_4$ = H, $R_3 = CH_3$
b: $R_1 = R_3$ = H, R_2 = *i*Pr, $R_4 = CH_3$
c: $R_1 = R_3 = CH_3$, $R_2 = R_4$ = H
d: $R_1 = R_3$ = H, $R_2 = C_3H_7$, $R_4 = OCH_3$
e: R = C_3H_7; **f:** R = OCH_3

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0009-3130/08/4404-0506 ©2008 Springer Science+Business Media, Inc.

TABLE 1. Yields and Chemical Data for Sulfonic Acids **2a-2f**

Sulfonic acids	Yields, %	Chemical shift (300 MHz, C_3D_6O, δ, ppm)	Melting points, °C	Melting points of the *S*-benzylthiouronium salts, °C
2a	70	7.74 (s, 1H); 6.95 (s, 1H), 3.91 (s, 3H); 3.26 (m, 1H), 2.61 (s, 3H), 1.19 (d, 6H)	103	226-228
2b	74	7.90 (s, 1H), 6.73 (s, 1H), 3.86 (s, 3H), 3.62 (m, 1H), 2.23 (s, 3H), 0.92 (d, 6H)*	72	170-172
2c	40	7.63 (s, 1H), 6.86 (s, 1H), 3.86 (s, 3H), 2.58 (s, 3H), 2.13 (s, 3H)	90	174
2d	77	7.43 (s, 1H), 7.00 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.95 (m, 2H), 1.70 (m, 2H), 0.98 (t, 3H)	100	184-186
2e	67	7.33 (s, 1H), 6.74 (s, 1H), 5.96 (s, 2H), 2.92 (m, 2H), 1.63 (m, 2H), 0.93 (t, 3H)	-	175
2f	52	7.25 (s, 1H), 6.87 (s, 1H), 6.09 (s, 2H), 3.89 (s, 3H)	104	174

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*Chemical shifts in $CDCl_3$.

The regiospecificity of the bis(trimethylsilyl) sulfate reagent is noteworthy. The drastic conditions used with other sulfonating reagents can give the so-called abnormally oriented isomers as major products from some *ortho-para* directing as well as *meta*-directing groups [7].

The regiochemistry of the sulfonation of alkoxyphenyl ethers with SO_3 is linked to experimental conditions that lead to a mixture of the *ortho-para* isomers [8]. In addition, depending on chemical factors (temperature, solvent, etc.) side-reactions can also occur, such as formation of diaryl sulfones or arylpyrosulfonic acids [9]. Our results show that these problems are overcome when using bis(trimethylsilyl) sulfate and are in good agreement with results previously obtained by Bourgeois and Duffaut [3].

In an appropriate round-bottom flask fitted with a Dean and Stark apparatus, a mixture of the phenolic derivative (0.02 mol) and bis(trimethylsilyl) sulfate (0.02 mol) in methylcyclohexane (30 mL) were refluxed for 10 h until the expected volume of water calculated from the global sulfonation equation (described in [4]) was obtained. Sulfonates were hydrolyzed by the literature method [4]. *S*-Benzylthiouronium salts and sulfonamides were obtained by literature methods, respectively [4] and [5].

Yields, chemical shifts of ^1H NMR spectra, melting points of the synthesized sulfonic acids, and the corresponding *S*-benzylthiouronium salts are given in Table 1.

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