A new method for thiomethylation of phenols

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Alkyl diethylaminomethyl sulfides are convenient and efficient reagents for introduction of alkylthiomethyl groups into phenols.

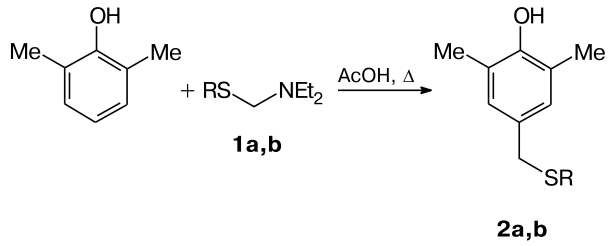
Key words: thiomethylation, phenols, aminothioacetals, aromatic electrophilic substitution.

Alkylthiomethylphenols are promising as antioxidants[1] and bioantioxidants.[2] Current approaches to their synthesis most often involve intermediate products already containing a methylene fragment in a phenol molecule. Mannich bases are the most accessible compounds of this type; however, replacement of the amino group occurs slowly and only under harsh conditions.[3] Alkylthiomethylphenols can also be obtained by condensation of thiols with formaldehyde and phenols.[4]

It is known that aminomethyl sulfides react with C-nucleophiles such as phenylmagnesium bromide[5] and dithiocarboxylic acid esters[6] to mostly give Mannich bases. Aminothioacetals have been used[7] as thiomethylating agents: hydrochlorides of aminomethyl thioacetates and aminomethyl thiobenzoates form thiomethyl derivatives with 1,3-dicarbonyl compounds and phenylacetaldehyde, while phenol and phloroglucinol are inert under similar conditions.

We found that a reaction of diethylaminomethyl dodecyl sulfide (**1a**) with 2,6-dimethylphenol in boiling acetic acid gives 4-(dodecylthiomethyl)-2,6-dimethylphenol (**2a**) in high yield (Scheme 1). According to GLC data, the 98% conversion of the starting compounds was achieved in 1 h and the final mixture contained only the starting compounds and product **2a**.

Scheme 1

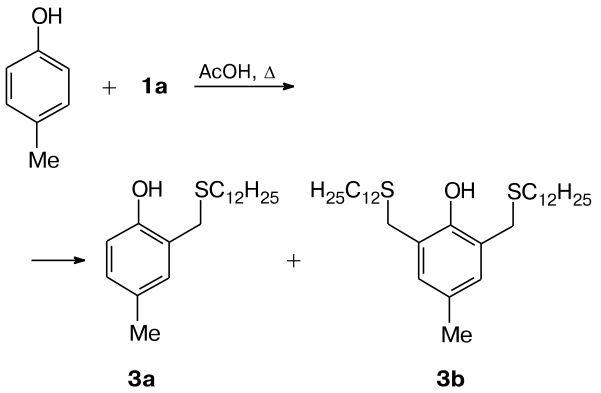


R = $C_{12}H_{25}$ (**a**); $C_{18}H_{37}$ (**b**)

Thiomethylation of 2,6-dimethylphenol with diethylaminomethyl octadecyl sulfide (**1b**) also occurred smoothly.

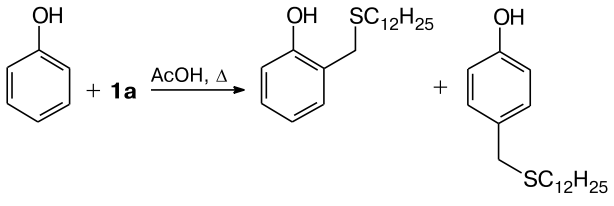
A reaction between equimolar amounts of aminomethyl sulfide **1a** and *p*-cresol gave the expected mono- and disubstitution products in a ratio of 2 : 1 (Scheme 2). The yield of product **3a** was 42%. The yield of product **3b** was 21.5% with respect to *p*-cresol and 43% with respect to reactant **1a**.

Scheme 2



Using unsubstituted phenol in a threefold excess, we attained selective monoalkylation (Scheme 3).

Scheme 3



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HPLC-analysis revealed no polyalkylated phenols in the reaction mixture. The reaction products are 2- and 4-(dodecylthiomethyl)phenols **4a** and **4b** in a ratio of 7 : 1. Therefore, *ortho*-substitution is more favorable under these conditions.

The method we proposed for thiomethylation of phenols is simple and efficient; the reagent used is promising for testing with other nucleophiles.

Experimental

^{1}H NMR spectra were recorded on a Bruker AV-600 instrument in $CDCl_3$. Melting points were determined on a PTP instrument. Elemental analysis was performed at the checking and analysis laboratory of the Research Institute of Antioxidant Chemistry (Novosibirsk State Pedagogical University). Gas chromatography was carried out on an LKhM-80 instrument; HPLC data were obtained on a Milikhrom-4 instrument.

***N,N*-Diethylaminomethyl dodecyl sulfide (1a).** Diethylamine (87.8 g, 1.20 mol) was added to a suspension of paraformaldehyde (36.0 g, 1.20 mol) in ethanol (150 mL). The mixture was stirred to homogenization for 0.5 h, whereupon dodecanethiol (202.4 g, 1.00 mol) was added. After 0.5 h, the reaction mixture was transferred to a separatory funnel, washed with warm water, and dried over Na_2SO_4. The yield of compound **1a** was 284.9 g (99%), colorless liquid, n_D^{20} 1.4689. Found (%): C, 71.22; H, 12.99; N, 4.86; S, 11.19. $C_{17}H_{37}NS$. Calculated (%): C, 71.01; H, 12.97; N, 4.87; S, 11.15. ^{1}H NMR, δ: 0.87 (t, 3 H, C$\underline{H}_3$(CH$_2$)$_{11}$, J = 6.9 Hz); 1.03 (t, 6 H, N(CH$_2$C$\underline{H}_3$)$_2$, J = 7.2 Hz); 1.24—1.34 (m, 18 H, (CH$_2$)$_9$); 1.53 (m, 2 H, C$\underline{H}_2$CH$_2$S); 2.47 (t, 2 H, CH$_2$C$\underline{H}_2$S, J = 7.2 Hz); 2.54 (q, 4 H, N(C$\underline{H}_2$CH$_3$)$_2$, J = 7.2 Hz); 3.99 (s, 2 H, SCH$_2$N).

***N,N*-Diethylaminomethyl octadecyl sulfide (1b).** A mixture of paraformaldehyde (0.75 g, 25 mmol) and diethylamine (1.83 g, 25 mmol) in ethanol (5 mL) was heated with stirring on a water bath (60 °C) for 0.5 h. Then premelted octadecanethiol (5.73 g, 20 mmol) was added and the reaction mixture was stirred for an additional 0.5 h and washed with water. The yield of compound **1b** was 7.32 g (98%), a colorless liquid solidifying at 16—17 °C, n_D^{20} 1.4702. Found (%): C, 74.41; H, 13.30; N, 3.76; S, 8.65. $C_{23}H_{49}NS$. Calculated (%): C, 74.32; H, 13.29; N, 3.77; S, 8.63. ^{1}H NMR, δ: 0.85 (t, 3 H, C$\underline{H}_3$(CH$_2$)$_{17}$, J = 7.2 Hz); 1.01 (t, 6 H, N(CH$_2$C$\underline{H}_3$)$_2$, J = 7.2 Hz); 1.24—1.34 (m, 30 H, (CH$_2$)$_{15}$); 1.51 (m, 2 H, C$\underline{H}_2$CH$_2$S); 2.45 (t, 2 H, CH$_2$C$\underline{H}_2$S, J = 7.5 Hz); 2.52 (q, 4 H, N(C$\underline{H}_2$CH$_3$)$_2$, J = 7.2 Hz); 3.96 (s, 2 H, SCH$_2$N).

4-(Dodecylthiomethyl)-2,6-dimethylphenol (2a). A mixture of 2,6-dimethylphenol (12.22 g, 0.10 mol) and compound **1a** (28.75 g, 0.10 mol) was refluxed in glacial acetic acid (24 mL) for 1 h. On cooling to ~20 °C, the reaction mixture was diluted with water, which resulted in crystallization of the organic layer. The product was recrystallized from aqueous ethanol. The yield of compound **2a** was 32.06 g (95%), white crystals, m.p. 57—58 °C (*cf.* Ref. 2: m.p. 57—58 °C). ^{1}H NMR, δ: 0.88 (t, 3 H, C$\underline{H}_3$(CH$_2$)$_{11}$, J = 6.9 Hz); 1.25 (m, 18 H, (CH$_2$)$_9$); 1.52 (m, 2 H, C$\underline{H}_2$CH$_2$S); 2.20 (s, 6 H, ArCH$_3$); 2.33 (t, 2 H, CH$_2$C$\underline{H}_2$S, J = 7.2 Hz); 3.51 (s, 2 H, SCH$_2$Ar); 4.43 (s, 1 H, OH); 6.83 (s, 2 H, ArH).

2,6-Dimethyl-4-(octadecylthiomethyl)phenol (2b). A mixture of 2,6-dimethylphenol (1.22 g, 10 mmol) and compound **1b** (3.72 g, 10 mmol) was refluxed in glacial acetic acid (4 mL) for 1 h and then cooled to ~20 °C. The precipitate that formed was washed with water, recrystallized twice from ethanol, and washed with ethanol. The yield of compound **2b** was 3.38 g (80%), light cream crystals, m.p. 71 °C. Found (%): C, 77.12; H, 11.52; S, 7.66. $C_{27}H_{48}OS$. Calculated (%): C, 77.08; H, 11.50; S, 7.62. ^{1}H NMR, δ: 0.88 (t, 3 H, C$\underline{H}_3$(CH$_2$)$_{17}$, J = 6.9 Hz); 1.24—1.28 (m, 30 H, (CH$_2$)$_{15}$); 1.51 (m, 2 H, C$\underline{H}_2$CH$_2$S); 2.20 (s, 6 H, ArCH$_3$); 2.32 (t, 2 H, CH$_2$C$\underline{H}_2$S, J = 7.2 Hz); 3.50 (s, 2 H, SCH$_2$Ar); 4.40 (s, 1 H, OH); 6.83 (s, 2 H, ArH).

2-(Dodecylthiomethyl)-4-methylphenol (3a) and 2,6-bis(dodecylthiomethyl)-4-methylphenol (3b) were obtained from *p*-cresol (10.81 g, 0.10 mol) as described for compound **2a**. The organic layer was washed in a separatory funnel with hot water until the odor of *p*-cresol disappeared, dissolved in ethanol, and cooled to 0 °C. Compound **3b** precipitated as a white crystalline solid. The yield was 11.57 g (43% with respect to **1a**), m.p. 43—44 °C. Found (%): C, 73.87; H, 11.27; S, 11.97. $C_{33}H_{60}OS_2$. Calculated (%): C, 73.81; H, 11.26; S, 11.94. ^{1}H NMR, δ: 0.88 (t, 6 H, C$\underline{H}_3$(CH$_2$)$_{11}$, J = 6.9 Hz); 1.24—1.29 (m, 36 H, (CH$_2$)$_9$); 1.53 (m, 4 H, C$\underline{H}_2$CH$_2$S); 2.23 (s, 3 H, ArCH$_3$); 2.36 (t, 4 H, CH$_2$C$\underline{H}_2$S, J = 7.2 Hz); 3.69 (s, 4 H, SCH$_2$Ar); 6.82 (s, 2 H, ArH); 6.83 (br.s, 1 H, OH). Concentration of the mother liquor gave compound **3a** (13.51 g, 42%) as a yellow oil. Found (%): C, 74.50; H, 10.66; S, 9.95. $C_{20}H_{34}OS$. Calculated (%): C, 74.47; H, 10.62; S, 9.94. ^{1}H NMR, δ: 0.89 (t, 3 H, C$\underline{H}_3$(CH$_2$)$_{11}$, J = 6.9 Hz); 1.24—1.31 (m, 18 H, (CH$_2$)$_9$); 1.53 (m, 2 H, C$\underline{H}_2$CH$_2$S); 2.24 (s, 3 H, ArCH$_3$); 2.35 (t, 2 H, CH$_2$C$\underline{H}_2$S, J = 7.2 Hz); 3.69 (s, 2 H, SCH$_2$Ar); 6.72 (d, 1 H, ArH, J = 8.4 Hz); 6.80 (d, 1 H, ArH, J = 1.8 Hz); 6.82 (br.s, 1 H, OH); 6.90 (dd, 1 H, ArH, J = 8.4 Hz, J = 1.8 Hz).

2-(Dodecylthiomethyl)phenol (4a) and 4-(dodecylthiomethyl)-phenol (4b) were obtained from phenol (28.23 g, 0.30 mol) as described for compound **2a**. The organic layer was washed in a separatory funnel with hot water until the odor of phenol disappeared. The product was dissolved in light petroleum and cooled to −15 °C. Compound **4b** precipitated as a white crystalline solid. The yield was 3.66 g (12%), m.p. 71—72 °C. Found (%): C, 74.07; H, 10.50; S, 10.39. $C_{19}H_{32}OS$. Calculated (%): C, 73.97; H, 10.45; S, 10.39. ^{1}H NMR, δ: 0.88 (t, 3 H, C$\underline{H}_3$(CH$_2$)$_{11}$, J = 6.9 Hz); 1.24 (m, 18 H, (CH$_2$)$_9$); 1.51 (m, 2 H, C$\underline{H}_2$CH$_2$S); 2.32 (t, 2 H, CH$_2$C$\underline{H}_2$S, J = 7.2 Hz); 3.57 (s, 2 H, SCH$_2$Ar); 4.95 (br.s, 1 H, OH); 6.68 (d, 2 H, ArH, J = 8.4 Hz); 7.11 (d, 2 H, ArH, J = 8.4 Hz). Concentration of the mother liquor gave compound **4a** (26.85 g, 87%) as a yellow oil. Found (%): C, 74.05; H, 10.54; S, 10.36. $C_{19}H_{32}OS$. Calculated (%): C, 73.97; H, 10.45; S, 10.39. ^{1}H NMR, δ: 0.89 (t, 3 H, C$\underline{H}_3$(CH$_2$)$_{11}$, J = 7.2 Hz); 1.24—1.30 (m, 18 H, (CH$_2$)$_9$); 1.53 (m, 2 H, C$\underline{H}_2$CH$_2$S); 2.35 (t, 2 H, CH$_2$C$\underline{H}_2$S, J = 7.2 Hz); 3.76 (s, 2 H, SCH$_2$Ar); 6.66 (br.s, 1 H, OH); 6.78 (td, 1 H, ArH, J = 7.2 Hz, J = 1.0 Hz); 6.84 (dd, 1 H, ArH, J = 7.5 Hz, J = 1.0 Hz); 7.00 (dd, 1 H, ArH, J = 7.2 Hz, J = 1.0 Hz); 7.13 (td, 1 H, ArH, J = 7.5 Hz, J = 1.0 Hz).

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