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Synthesis of 5-(ω-sulfhydrylalkyl)salicylaldehydes as precursors for the preparation of alkanethiol-modified metal salens

Chang Ji and Dennis G. Peters*

Department of Chemistry, Indiana University, Bloomington, IN 47405, USA

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Abstract—Using multistep syntheses, we obtained two alkanethiol-modified salicylaldehydes, namely 5-(2-sulfhydrylethyl)-salicylaldehyde and 5-(6-sulfhydrylhexyl)salicylaldehyde. These compounds are precursors for the preparation of alkanethiol-substituted metal salens, which can potentially be used to form surface-modified gold electrodes.

For both fundamental and practical reasons, the behavior of surface-modified electrodes has been of considerable interest.[1] Among the many methods used to prepare surface-modified electrodes, the gold–alkanethiol self-assembly method is particularly attractive.[2] Recently, our group has investigated the catalytic reduction of halogenated organic compounds by electrogenerated low-valent metal salens.[3–8] We thought it would be interesting to synthesize alkanethiol-substituted metal salens so that we can use these compounds to prepare and study surface-modified gold electrodes.

A general procedure to synthesize metal salens involves reacting salicylaldehyde with ethylenediamine to give the salen ligand, which is subsequently treated with a metal acetate to form the metal salen. To prepare an alkanethiol-modified metal salen, one must begin with an ω-sulfhydrylalkyl-substituted salicylaldehyde. In this paper, we describe procedures for the high-yield synthesis of salicylaldehydes with alkanethiol side chains of various lengths, and these approaches have been used to obtain two previously unreported compounds—namely, 5-(2-sulfhydrylethyl)salicylaldehyde and 5-(6-sulfhydrylhexyl)salicylaldehyde.

Synthesis of 5-(2-sulfhydrylethyl)salicylaldehyde (**5**) was carried out by the method outlined in Scheme 1. We prepared 4-(2-iodoethyl)phenol (**2**) by refluxing a mixture of 4-methoxyphenethyl alcohol (**1**, Aldrich, 99%) and 47% hydriodic acid.[9] Then 5-(2-iodoethyl)-salicylaldehyde (**4**) was formed via the use of Grignard reagent, paraformaldehyde, and triethylamine;[10] the product was purified by silica-gel column chromatography (5% ethyl acetate–95% hexanes) and was recrystallized from ethanol. Finally, **4** was converted to **5** in high yield through the use of thiourea to afford the isothiuronium salt, followed by treatment with base.[11] All key compounds were characterized by means of GC–MS and NMR spectrometry.[12]

Scheme 2 shows the synthetic route to 5-(6-sulfhydrylhexyl)salicylaldehyde (**10**). We prepared 4-(6-bromohexyl)phenol (**8**) via Friedel–Crafts acylation of anisole with 6-bromohexanoyl chloride (Aldrich, 97%), followed by reduction of the carbonyl group[2] and conversion of the anisole to the phenol.[13] Subsequent synthetic steps are similar to those for 5-(2-sulfhydrylethyl)-salicylaldehyde. GC–MS and NMR data were collected for compounds **6**–**10**.[14] Since ω-haloalkanoyl halides are commercially available, one can obtain 5-(ω-sulfhydrylalkyl)salicylaldehydes with up to eight methylene groups.

In conclusion, we have synthesized 5-(2-sulfhydrylethyl)salicylaldehyde and 5-(6-sulfhydrylhexyl)-salicylaldehyde as precursors for the preparation of alkanethiol-modified metal salens (which can be potentially used to modify the surfaces of gold electrodes), and we have demonstrated the feasibility of an approach consisting of simple steps to afford the desired products in relatively high yields. It should be convenient for one to obtain other 5-(ω-sulfhydrylalkyl)salicylaldehydes by choosing suitable ω-haloalkanoyl halides with various numbers of methylene groups as the starting compounds.

Keywords: 5-(ω-sulfhydrylalkyl)salicylaldehydes; alkanethiol-modified metal salens; surface-modified electrodes.

* Corresponding author. Tel.: +1-812-8559671; fax: +1-812-8558300; e-mail: peters@indiana.edu

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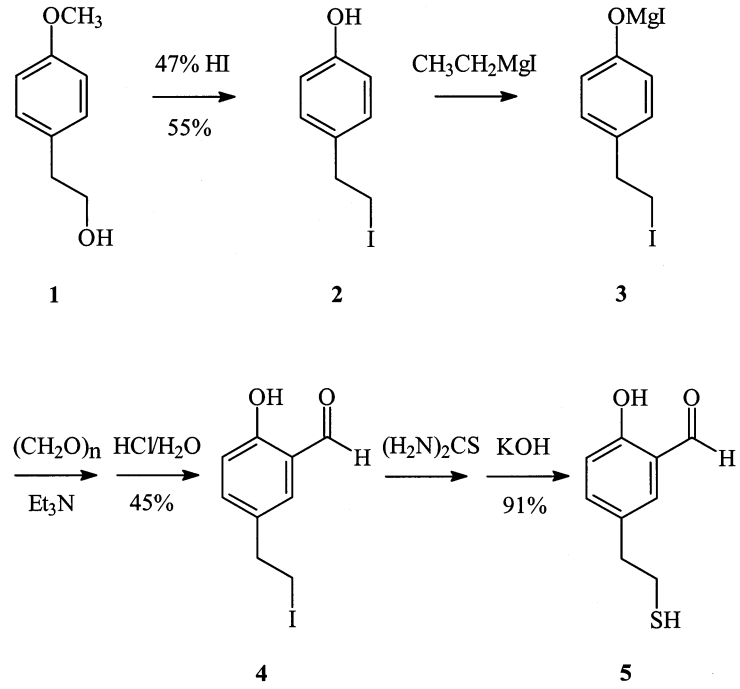
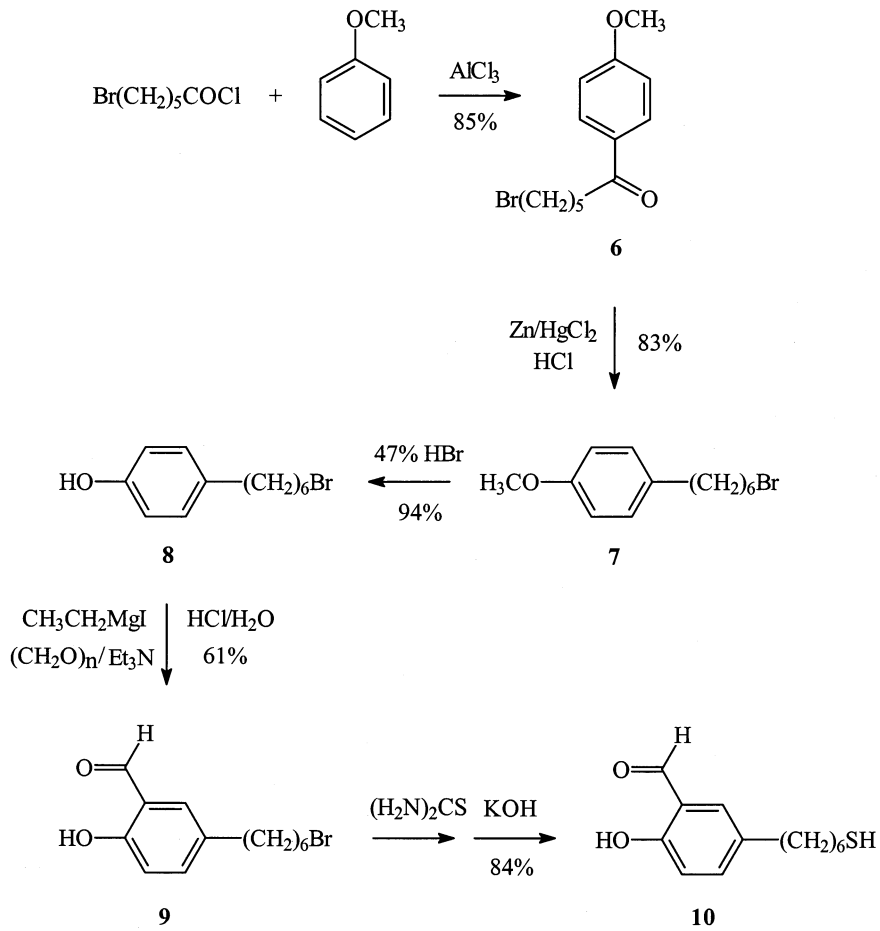


Scheme 1.



Scheme 2.

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12. Product **2**: mp 111–112°C; GC–MS (70 eV) m/z 248, M^+ (9%); 121, $[M-I]^+$ (100%); 107, $[M-CH_2I]^+$ (19%); ^1H NMR ($CDCl_3$): δ 7.06 and 6.78 (2 d, 2H each, Ar**H**), 4.76 (s, 1H, O**H**), 3.31 (t, 2H, C$\mathbf{H}_2$I), 3.10 (t, 2H, ArC$\mathbf{H}_2$). Product **4**: mp 78–79°C; GC–MS (70 eV) m/z 276, M^+ (15%); 149, $[M-I]^+$ (100%); 135, $[M-CH_2I]^+$ (14%); 121, $[M-CH_2CH_2I]^+$ (7%); ^1H NMR ($CDCl_3$): δ 10.96 (s, 1H, ArO**H**), 9.89 (s, 1H, C**H**O), 7.38–7.36 and 6.96 (s and 2 d, 1H each, Ar**H**), 3.35 (t, 2H, C$\mathbf{H}_2$I), 3.16 (t, 2H, ArC$\mathbf{H}_2$). Product **5**: GC–MS (70 eV) m/z 182, M^+ (24%); 164, $[M-H_2O]^+$ (17%); 135, $[M-CH_2SH]^+$ (100%); ^1H NMR ($CDCl_3$): δ 10.91 (s, 1H, ArO**H**), 9.89 (s, 1H, C**H**O), 7.38–7.37 and 6.96 (dd and 2 d, 1H each, Ar**H**), 2.92 (t, 2H, ArC$\mathbf{H}_2$), 2.79 (q, 2H, C$\mathbf{H}_2$SH), 1.36 (t, 1H, CH_2S**H**).
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14. Product **6**: GC–MS (70 eV) m/z 286, M^+ (0.3%); 284, M^+ (0.3%); 205, $[M-Br]^+$ (2%); 163, $[M-(CH_2)_3Br]^+$ (2%); 150, $[M-CH_2{=}CH(CH_2)_2Br]^+$ (68%); 135, $[M-(CH_2)_5Br]^+$ (100%); 107, $[M-CO(CH_2)_5Br]^+$ (6%); 92, $[M-CO(CH_2)_5Br-CH_3]^+$ (9%); ^1H NMR ($CDCl_3$): δ 7.94 and 6.94 (2 d, 2H each, Ar**H**), 3.87 (s, 3H, OC$\mathbf{H}_3$), 3.43 (t, 2H, C$\mathbf{H}_2$Br), 2.94 (t, 2H, COC$\mathbf{H}_2$), 1.92 (q, 2H, C$\mathbf{H}_2$CH$_2$Br), 1.76 (q, 2H, C$\mathbf{H}_2$CH$_2$CH$_2$Br), 1.53 (q, 2H, COCH$_2$C$\mathbf{H}_2$). Product **7**: GC–MS (70 eV) m/z 272, M^+ (8%); 270, M^+ (8%); 121, $[M-(CH_2)_5Br]^+$ (100%); ^1H NMR ($CDCl_3$): δ 7.08 and 6.82 (2 d, 2H each, Ar**H**), 3.78 (s, 3H, OC$\mathbf{H}_3$), 3.39 (t, 2H, C$\mathbf{H}_2$Br), 2.55 (t, 2H, ArC$\mathbf{H}_2$), 1.84 (q, 2H, C$\mathbf{H}_2$CH$_2$Br), 1.59 (q, 2H, ArCH$_2$C$\mathbf{H}_2$), 1.45 (q, 2H, C$\mathbf{H}_2$CH$_2$CH$_2$Br), 1.34 (q, 2H, ArCH$_2$CH$_2$C$\mathbf{H}_2$). Product **8**: GC–MS (70 eV) m/z 258, M^+ (7%); 256, M^+ (7%); 107, $[M-(CH_2)_5Br]^+$ (100%); ^1H NMR ($CDCl_3$): δ 7.03 and 6.75 (2 d, 2H each, Ar**H**), 3.39 (t, 2H, C$\mathbf{H}_2$Br), 2.53 (t, 2H, ArC$\mathbf{H}_2$), 2.06 (s, 1H, O**H**), 1.84 (q, 2H, C$\mathbf{H}_2$CH$_2$Br), 1.58 (q, 2H, ArCH$_2$C$\mathbf{H}_2$), 1.45 (q, 2H, C$\mathbf{H}_2$CH$_2$CH$_2$Br), 1.33 (q, 2H, ArCH$_2$CH$_2$C$\mathbf{H}_2$). Product **9**: GC–MS (70 eV) m/z 286, M^+ (9%); 284, M^+ (9%); 135, $[M-(CH_2)_5Br]^+$ (100%); ^1H NMR ($CDCl_3$): δ 10.86 (s, 1H, ArO**H**), 9.87 (s, 1H, C**H**O), 7.36–7.34 and 6.92 (m and d, 2H and 1H, respectively, Ar**H**), 3.41 (t, 2H, C$\mathbf{H}_2$Br), 2.60 (t, 2H, ArC$\mathbf{H}_2$), 1.86 (q, 2H, C$\mathbf{H}_2$CH$_2$Br), 1.63 (q, 2H, ArCH$_2$C$\mathbf{H}_2$), 1.48 (q, 2H, C$\mathbf{H}_2$CH$_2$CH$_2$Br), 1.35 (q, 2H, ArCH$_2$CH$_2$C$\mathbf{H}_2$). Product **10**: GC–MS (70 eV) m/z 238, M^+ (12%); 187, $[M-H_2O-SH]^+$ (5%); 173, $[M-H_2O-CH_2SH]^+$ (5%); 135, $[M-(CH_2)_5SH]^+$ (100%); ^1H NMR ($CDCl_3$): δ 10.86 (s, 1H, ArO**H**), 9.87 (s, 1H, C**H**O), 7.36–7.33 and 6.91 (m and d, 2H and 1H, respectively, Ar**H**), 2.60 (t, 2H, ArC$\mathbf{H}_2$), 2.52 (q, 2H, C$\mathbf{H}_2$SH), 1.61 (q, 4H, ArCH$_2$C$\mathbf{H}_2$ and C$\mathbf{H}_2$CH$_2$SH), 1.46–1.30 (2 m, 2H and 3H, respectively, ArCH$_2$CH$_2$C$\mathbf{H}_2$, C$\mathbf{H}_2$CH$_2$CH$_2$SH, and S**H**).