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Highly Regioselective One-Pot Synthesis of 7-Hydroxy-6-methylphthalide from 3-Hydroxy-4-methylbenzylalcohol

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Abstract: 7-Hydroxy-6-methylphthalide **2** was synthesized with high regioselectivity and moderate yield using a novel one-pot synthesis that employed 3-hydroxy-4-methylbenzylalcohol **1** and formaldehyde in the presence of tin(IV) chloride as catalyst and triethylamine as base. The proposed mechanism of the formation of **2** involves *ortho*-formylation followed by hemiacetal formation and oxidation.

Keywords: 3-Hydroxy-4-methylbenzylalcohol, 7-hydroxy-6-methylphthalide, one-pot synthesis, regioselective

INTRODUCTION

The 7-hydroxyphthalides are medicinal components of some natural products.[1] Recent agricultural,[2] pharmaceutical,[3] and other potential applications motivate for the development of facile synthetic routes. The preparation of 7-hydroxy-6-methylphthalide **2** was previously reported using a complex flash-vacuum pyrolysis of *ortho*-allyl salicylic methyl ester, which was derived in three steps from 3-methylsalicylic acid.[4] A method for the preparation of 7-hydroxyphthalides from the furanones has been reported[5] but the procedure requires harsh reaction conditions. As shown in Scheme 1a, during the synthesis of the natural product espicufolin, attempts

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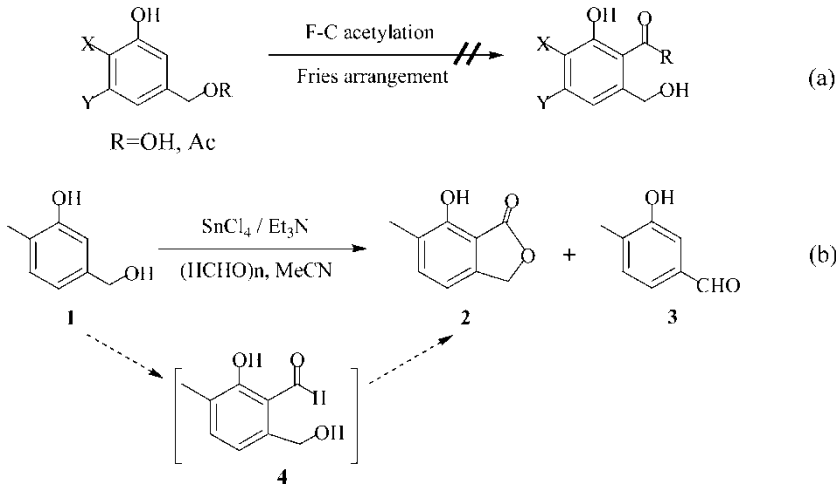


Scheme 1.

at introducing an acetyl group into the starting material, naphthol, by Friedel–Crafts acylation and Fries arrangement failed.[6] No similar *ortho*-formylation of sterically hindered phenols has been reported. Herein, we describe such a reaction in the synthesis of product **2** through a highly regioselective one-pot approach from the diol 3-methyl-4-hydroxybenzylalcohol **1** (Scheme 1b). The latter is readily obtained by borane reduction of commercially available 3-hydroxy-4-methylbenzoic acid.[7] As show in Scheme 1, the diol **1** and formaldehyde (7 eq) were refluxed in acetonitrile in the presence of excess tin(IV) chloride (1.5 eq) as catalyst and triethylamine (4 eq) as base. The product **2** was isolated in high purity and moderate yield. An oxidation product of **1**, 3-hydroxy-4-methylbenzaldehyde **3**, also was detected.

RESULTS AND DISCUSSION

The one-pot synthesis of **2** from **1** was discovered in the course of the synthesis of 2-hydroxy-6-hydroxymethyl-3-methyl-benzaldehyde **4**, an analogue of pyridoxine. Our initial procedure employed magnesium chloride and triethyl amine as base, formaldehyde as formylating/oxidizing agent, and reflux in acetonitrile–benzene mixed solvent. Interestingly, instead of the *ortho*-formylation product **4**, an unexpected colorless product **2** was detected and isolated in 18% yield. Under reaction conditions that were otherwise identical but in which dry solvent was employed, neither **2** nor **4** was obtained using a literature procedure for unhindered phenols.[8]

The structure of the product **2** was not easy to distinguish from the expected *ortho*-formylation product **4** because of the similar molecular

structures. The proton NMR of the colorless solid showed a sharp peak around 7.85 ppm, similar to that for the expected aldehydic proton but sharper than that reported.[4] When the NMR sample was exchanged with D_2O, the peak intensity decreased, suggesting that it corresponds to the phenolic proton. An IR absorption at 1736 cm^{-1} is close to 1737 cm^{-1} of 7-hydroxy-4,6-dimethylphthalide[9a] and different from 1654 cm^{-1} for 3-methyl-5-decylsalicylic aldehyde[9b] and 1716 cm^{-1} for 3-hydroxybenzene-1,2- dicarbaldehyde.[10] These results as well as other analytical data confirm the structure of **2** as the product.

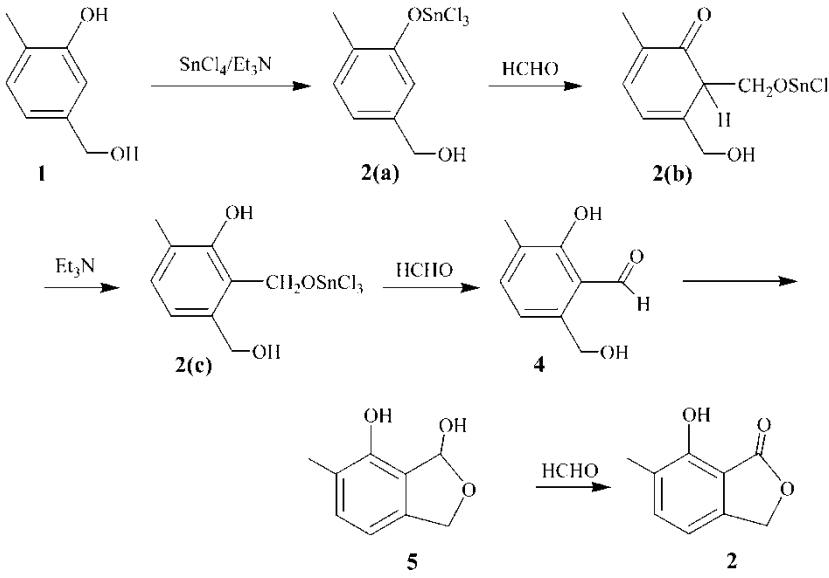
Because the one-pot reaction from **1** to **2** is base dependent, the influence of catalyst, base, and solvent were investigated. The results are given in Table 1. Tin(IV) chloride is the best catalyst tried here (30% yield), and magnesium chloride was also effective. Other Lewis acid catalysts such as Fe, Li, and B halides were also tested, but no product was detected. Benzene as solvent gave results similar to acetonitrile. Reactions with various bases showed strong and sterically hindered ones to be effective in this reaction.

The mechanism shown in Scheme 2, based on that reported by Casiraghi et al.[11] and Hofslokken and Skattebol,[8] is proposed for the production of **2**. The phenolic oxygen of diol **1** initially reacts with tin (IV) chloride to give the phenoxide salt **2(a)**. The intermediate **2(b)** is formed by reaction of **2(a)** with formaldehyde through a coordination complex. Enolization affords **2(c)**, which is then oxidized to the aldehyde intermediate **4** by a second molecule of formaldehyde. The aldehyde undergoes facile internal hemiacetal formation to give **5**, which is oxidized by a third molecule of formaldehyde to give the major product **2**. The intermediates **4**/**5** have not been detected by proton NMR analysis in our experiments. This suggests that steps from **4**

Table 1. Yields for the one-pot synthesis of 2

Entry	Catalyst	Base	Solvents	Reaction time (h)	Isolated yield of **2** (%)
1	$SnCl_4$	Et_3N	Acetonitrile	17	33
2	$MgCl_2$	Et_3N	Acetonitrile	25	9
3	$AlCl_3$	Et_3N	Acetonitrile	20	Trace
4	$SnCl_2$	Et_3N	Acetonitrile	24	—
5	$SnCl_4$	Et_3N	THF	22	12
6	$SnCl_4$	Et_3N	Benzene	23	30
7	$SnCl_4$	2,6-lutidine	Acetonitrile	17	12
8	$SnCl_4$	Me_3N	Acetonitrile: benzene (1:2)	17	6
9	$SnCl_4$	DMAP	Acetonitrile	19	—
10	$MgCl_2$	Et_3N	Acetonitrile: benzene (1:2)	42	18

Reaction condition: Diol **1** (1.0 eq), formaldehyde (7.0 eq), catalyst (1.0–1.5 eq) and base (4.0 eq), reflux.



Scheme 2.

to product **2** should be fast. The observation of **3** as a secondary product would result from direct oxidation of the benzylic alcohol of **1** by formaldehyde.

The formation of 7-hydroxy-6-methylphthalide **2** is the first example of a Friedel–Crafts acylation achieved by a highly regioselective one-pot synthesis from a sterically hindered diol such as **1**. The one-pot reaction provides a simple and mild approach to the synthesis of 7-hydroxyphthalides. An advantage of the current procedure is the simple experimental setup (i.e., open reaction vessel and undried solvent), which could allow the procedure to become a convenient and practical operation for laboratory and industrial use. To this end, the development of a higher-yield procedure for this reaction is in progress.

EXPERIMENTAL

All commercially available reagents and solvents were employed without further purification. NMR spectra were recorded on Varian INOVA-400 spectrometer (^{1}H: 400 MHz and ^{13}C: 101 MHz). Chemical shifts are reported in Δ ppm from CD_3Cl as internal standard. Mass spectra were performed on a Virian Saturn GC-MS spectrometer. Elemental analysis was performed at the Midwest Microlab, Indianapolis. Melting points are uncorrected. Infrared spectra were obtained on a Galaxy series FT-IR 3000 spectrometer.

3-Hydroxy-4-methylbenzyl alcohol (1). Into a solution of 3-hydroxy-4-methylbenzoic acid (2.28 g, 15.0 mmol) in dry THF (30 ml) at 0°C under Ar atmosphere, 1.0 M BH_3-THF solution (25.5 ml, 25.5 mmol) was added dropwise over 1 h. Hydrogen gas evolved and a white solid precipitated. The resulting mixture was stirred at rt overnight. The mixture was treated with aqueous 3.0 M sodium hydroxide (30 ml). The basic aqueous phase was neutralized with 3.0 N hydrochloric acid solution (pH $<$ 7.0) at 0°C and extracted with ether (5 $\times$ 50 ml). The extract was dried over magnesium sulfate and concentrated in vacuo. The residue was purified on silica gel (1 : 1 ether/hexane) to afford product **1** (1.93 g) in 93% yield as a colorless solid. Analytical data: mp 98–100°C (lit.[12] 102–103°C); ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H), 4.61 (s, 2H), 6.82 (s, 1H), 6.82 (d, $J = 6.4$ Hz, 1H), 7.08 (d, $J = 8.0$ Hz, 1H) ppm; GC-MS (m/z): M^+ 138, M^+-OH 121.

7-Hydroxy-6-methylphthalide (2). Triethylamine (1.045 ml, 7.5 mmol) and tin(IV) chloride (0.351 ml, 3.0 mmol) were added dropwise under Ar atmosphere to a colorless solution of diol **1** (0.276 g, 2.0 mmol) in acetonitrile (20 ml), the mixture was stirred for 20 min, and formaldehyde (0.426 g, 13.5 mmol) was added. The yellowish mixture was refluxed for 17 h. The color changed gradually to brown. The progress of the reaction was checked with TLC (dichloromethane). After cooling, the dark brown mixture was filtered and extracted with ether (3 $\times$ 15 ml). The ether extracts were dried over sodium sulfate and concentrated in vacuo. The orange-red oily residue was purified on a silica-gel column with hexane/dichloromethane (4 : 1) as eluent. This gave product **2** (0.11 g) as a colorless solid (lit.[4] brown solid) in 33% yield. Pale yellow plate crystals were recrystallized from a hexane/ether mother liquor. Analytical data: mp 135–136°C (lit.[4] 127–129 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 5.28 (s, 2H), 6.87 (d, $J = 7.6$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 154.5, 143.9, 138.0, 124.7, 112.7, 110.3, 70.3, 14.4; IR(KBr, cm^{-1}): 3440 (OH), 1736 (C=O); GC-MS m/z (%): M^+ 164 (100), 135 (78). Anal. calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.81; H, 4.90.

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