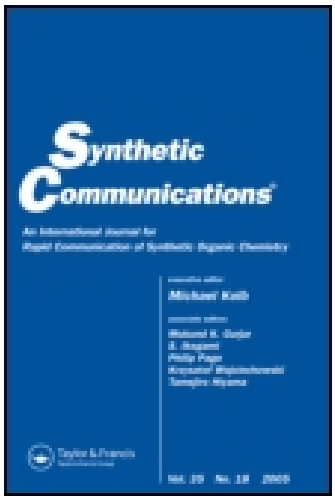

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

O-BENZYLATION OF POLYPHENOLICS. PREPARATION OF 1,2,4-TRIBENZYLOXYBENZENE

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Published online: 09 Nov 2006.

To cite this article: Uffe Anthoni , Carsten Christophersen & Per Halfdan Nielsen (2001) O-BENZYLATION OF POLYPHENOLICS. PREPARATION OF 1,2,4-TRIBENZYLOXYBENZENE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:14, 2223-2229, DOI: 10.1081/SCC-100104477

To link to this article: http://dx.doi.org/10.1081/SCC-100104477

SYNTHETIC COMMUNICATIONS, 31(14), 2223–2229 (2001)

O-BENZYLATION OF POLYPHENOLICS. PREPARATION OF 1,2,4-TRIBENZYLOXYBENZENE

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ABSTRACT

The main phenolic by-products in the *O*-benzylation of 1,2,4-trihydroxy- or 1,2,4-triacetoxybenzene to 1,2,4-tribenzyloxybenzene have been identified as due to incomplete *O*-benzylation and *C*-benzylation. In addition, dibenzyldimethylammonium chloride is formed from DMF and benzyl chloride. The main factors controlling these reactions paths are discussed. An efficient procedure for preparing 1,2,4-tribenzyloxybenzene using NaH in DMF is reported.

1,2,4-Tribenzyloxybenzene (**4A**), by virtue of the protected hydroxy groups, is a convenient starting material for preparation of compounds containing the 1,2,4-trihydroxyphenyl group. Examples include metabolites of dopamine[1,2] and models for topaquinone, the cofactor of mammalian copper amine oxidases.[3] The reported method involves benzylation of 1,2,4-triacetoxybenzene (**1b**) with benzyl chloride and potassium carbonate in

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aqueous acetone.[1,2] However, only a fair yield (around 35%) of pure isomer-free **4A** was obtained. From analysis of the array of by-products it seemed feasible to minimize the occurrence of side reactions and devise an improved method for preparation of **4A**. The preparation was therefore repeated and the products separated by column chromatography. In addition to **4A**, by-products were found to arise both from incomplete *O*-benzylation and from *C*-benzylation.

Conventional theory predicts that the use of the triacetate **1b** instead of 1,2,4-trihydroxybenzene (**1a**) minimizes oxidative loss of phenol. Moreover, the formation of dianions (with increased tendency for *C*-benzylation[4]) is hindered. Finally, the acetyl group decreases the electron density of the benzene ring and accordingly the tendency for *C*-benzylation.[5] The 2-OAc group derived from the most acidic hydroxy group ($pK_A = 9.1$ and 11.6 for 2- and 4-OH, respectively, $pK_A < 11.6$ for 1-OH.[6]) has the highest reactivity while steric approach control favours formation of the 4-OBn group. Since acetate hydrolysis appears to be slow with potassium carbonate in aqueous acetone, a stronger base (*e.g.* NaH in DMF) is essential for rapid formation of **4A**. The amount of the *C*-benzylation is expected to decrease if the phenolate anion is unsolvated (''naked anion'') but the cation strongly solvated. Aqueous acetone is a poor choice because water form strong hydrogen bonds to the phenolate anion.[7] In contrast, the high dielectricity constant and preference for cation solvatisation makes DMF an attractive alternative.[8]

Similar problems have been reported for the benzylation of phloroglucinol to 1,3,5-tribenzyloxybenzene.[9–12] However, dropwise addition of water to a mixture of 1,3,5-triacetoxybenzene, benzyl chloride and NaH in DMF is reported to yield 97% of a product devoid of *C*-benzylated isomers.[5] Under these reaction conditions the OAc-groups are hydrolyzed stepwise followed by a fast *O*-benzylation of the naked anions. Unfortunately, this procedure applied to **1b** furnished only a 45% yield of pure **4A**. Seven phenolic products were identified in the mother liquor as arising from sequential benzylation of 1,2,4-triacetoxybenzene as shown in the scheme. Mono- and di-*O*-benzylation proceeds with steric approach control via (the acetylated) **2A** to **3A** and **3B**. The observation of a series of products arising from incomplete *O*-benzylation indicates that hydrolysis of 1,2,4-triacetoxybenzene is the rate determining step even when NaH in DMF is used. Introduction of further benzyl groups in the *O*-benzylated **4A**, as expected, affords only small amounts of the *C*-benzylated **4B** and 5.

A substantial amount of dibenzyldimethylammonium chloride (**6**) was observed in the aqueous phase after quenching the reaction mixture with water. Since this may act both as a phase transfer reagent and as a detergent, clean extraction of **4A** with EtOAc was not possible. ^{1}H NMR indicated

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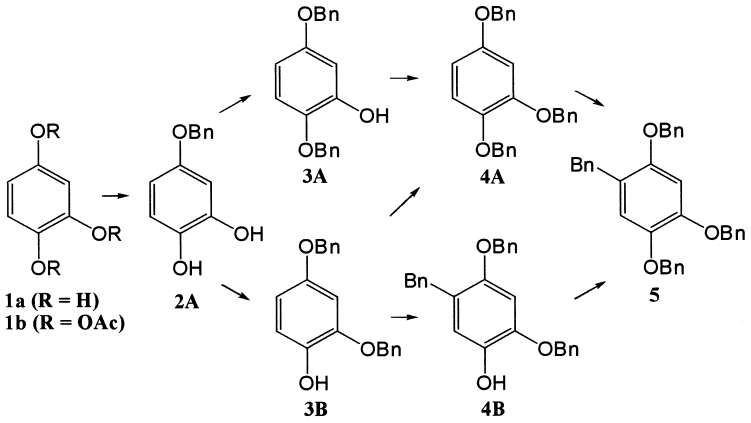

mixtures of DMF-d_7 with benzyl chloride and NaH to be stable for at least 5 h at room temperature although benzyl chloride and DMF when heated for 6 h at 150°C gives rise to a mixture of benzylmethylammonium chlorides.[13] In our experiment, **1b**, benzyl chloride and NaH were allowed to react for only 2.5 h in DMF at room temperature. Accordingly, **6** is probably formed during the reaction by C–N fission of the tetrahedral DMF-phenolate addition product assisted by concomitant *N*-attack of benzyl chloride.

Based upon these observations an improved method for preparation of **4A** was developed. The reaction rate is increased by substituting the free phenol **1a** for **1b**. A 10% excess of NaH, vigorous stirring , and a prolonged reaction time secures complete conversion of **1a** to phenolate in the heterogeneous reaction. Addition of NaH in small portions prevents formation of polyphenolate anions. A 10% excess of benzyl chloride compensates for the competing formation of **6**. This method furnished an excellent yield of a mixture (88:12) of the tribenzylated **4A** and **4B** which can be separated by recrystallization or column chromatography.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian UNITY 400 spectrometer. The position of the OH proton signals were established by exchange with D_2O when necessary. Melting points are uncorrected. Mass spectra were obtained on a JEOL JMS-HX/HX110A spectrometer. The IR spectra originate from a Perkin Elmer FT-IR 1760x instrument. The DMF

was dried for one week with activated molecular sieves. Benzyl chloride was freshly distilled before use.

1,2,4-Tribenzyloxybenzene (4A) from 1,2,4-triacetoxybenzene (1b) and benzyl chloride. The reported procedure[1,2] using K_2CO_3 in aqueous acetone was followed, however, recrystallization and/or purification by VLC only afforded pure **4A** in low yield. The remanence was separated by LC (Si-60 column, EtOAc/heptane 15:85) and shown (NMR, TLC) to contain mainly 2,4-dibenzyloxy-5-benzylphenol (**4B**) together with smaller amounts of mono- and di-*O*-benzyl derivatives of 1,2,4-trihydroxybenzene.

An improved yield was obtained using NaH in DMF. A solution of benzyl chloride (18.4 g, 146 mmol), **1b** (10.4 g, 40 mmol) and NaH (60% in mineral oil, 12.2 g, 304 mmol) in dry DMF (200 ml) was flushed with nitrogen for a few minutes. With efficient stirring, water (2.2 ml, 120 mmol) was added via a syringe over a period of ca. 0.5 h. The reaction, monitored by formation of hydrogen, was complete in a further 2 h. When the almost colourless mixture was quenched with water (200 ml) a dark brown colour developed. Extraction with EtOAc (2×300 ml), washing the extract with water, drying with $MgSO_4$ and evaporation to dryness left the crude, dark brown product (10 g). Recrystallization from hexane/toluene (95/5) furnished pure **4A** (7 g, 45% yield). Mass spectrometry indicated that small amounts of a tetrabenzylic compound, probably **5**, was removed by this procedure.

The aqueous phase contained a considerable amount (ca 1g) of **6**. The mother liquor from recrystallization of **4A** was purified by VLC (EtOH/H_2O) and, when necessary, further purified by LC. The first three fractions contained **2A** in addition to smaller amounts of other *O*- and *C*-monobenzylated products. The following fraction consisted of a mixture of almost equal amounts of the dibenzylated **3A** and **3B**. The final fractions contained **4A** with small amounts of **4B**.

1,2,4-Tribenzyloxybenzene (4A) from 1,2,4-trihydroxybenzene (1a), benzyl chloride and NaH in DMF. A solution of benzyl chloride (16.6 g, 132 mmol) and **1a** (5.0 g, 40 mmol) in dry DMF (100 ml) was carefully flushed with nitrogen at room temperature. 60% NaH in mineral oil (5.3 g, corresponding to 3.2 g pure NaH, 132 mmol) is added in small portions with vigorous stirring over a period of 3.5 h. The slightly exothermic reaction monitored by evolution of hydrogen was complete in a further 1.5 h leaving a dark brown reaction mixture. After dilution with water (250 ml) extraction with EtOAc (250 ml, then 100 ml) was feasible. The EtOAc extracts were combined, filtered, and washed with water (2×100 ml) to remove the dark brown water-soluble by-products. Drying with $MgSO_4$ and evaporation to dryness followed by freeze-drying (to remove DMF) left a light brown solid (13.9 g) shown by ^1H NMR to consist solely of

4A (88%) and **4B** (12%). On extraction of the combined aqueous washings with 100 ml EtOAc further material (1.4 g) with similar composition was secured.

Boiling the combined raw materials (15.3 g) with heptane/EtOAc (95/5) left a dark insoluble material (0.4 g) and gave a light tan solution. Evaporating the solvent and removing the mineral oil (ca. 1 g) left a crystalline residue (12.2 g, 77% yield). Recrystallization once from hexane/toluene (95/5) using active carbon furnished almost colourless **4A** (10.8 g, 69% yield, mp 79–80°C). Alternatively, **4A** and **4B** could be separated by column chromatography (SiO_2, EtOAc/heptane 1/6).

1,2,4-Tribenzyloxybenzene (4A). Mp 81–82°C (lit [1]81–82°C, [14]80–81°C, [2]82°C). TLC (SiO_2, EtOAc/heptane 3:7) $R_f = 0.50$. EIMS *m/z* (relative %): 396 [M^+](24), 305 [M^+-benzyl](14), 181 (11), 91 [benzyl$^+$](100). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 4.96, 5.09, and 5.12 (CH_2, s), 6.46 (H5, dd, J = 8.7, 2.9 Hz), 6.66 (H3, d, J = 2.9 Hz), 6.86 (H6, d, J = 8.7 Hz), 7.2–7.5 (15 Ar-H, m), ^{1}H NMR(DMSO-d_6, 400 MHz, δ): 5.01, 5.03, and 5.13 (CH_2, s), 6.51 (H5, dd, J = 8.7, 2.7 Hz), 6.79 (H3, d, J = 2.8 Hz), 6.94 (H6, d, J = 8.8 Hz), 7.3–7.5 (15 Ar-H, m). ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 70.4, 71.0, and 72.5 (CH_2), 103.7 (C3), 105.6 (C5), 116.9 (C6), 127.2–128.4 (16C), 136.9, 137.5, 143.1, 150.1, 154.0. IR (KBr, cm^{-1}): 1609 m, 1594 m, and 1514 vs (aryl), 1227 vs (aryl-O), 1007 s (O-CH_2). Anal. Calc. for $C_{27}H_{24}O_3$: C 81.79; H 6.10. Found: C 81.60; H 6.03.

2,4-Dibenzyloxy-5-benzylphenol (4B). Mp 107–108°C. TLC (SiO_2, EtOAc/heptane 3:7) $R_f = 0.44$. EIMS *m/z* (relative %): 396 [M^+](9), 305 [M^+-benzyl](4), 181 (8), 91 [benzyl$^+$](100). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 4.71 and 5.04 (O-CH_2, s), 4.93 (C-CH_2, s), 6.57 (H3, s), 6.86 (H6, s), 7.10–7.42 (15 Ar-H, m), 7.4 (OH). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 5.16 (O-CH_2, s), 4.95 and 4.93 (CH_2, s), 6.92 and 6.94 (H3 and H6, s), 7.20–7.47 (15 Ar-H and OH, m) ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 71.6, 71.7, and 72.2 (CH_2), 103.8 (C3), 119.5 (C6), 120.8, 127.0–128.4 (15C), 137.2, 137.4, 137.5, 143.0, 148.6, 150.8. IR (KBr, cm^{-1}): 1601 m and 1507 s (aryl), 1215 vs (aryl-O), 1024 s (O-CH_2). Anal. Calc. for $C_{27}H_{24}O_3$: C 81.79; H 6.10. Found C 82.23; H 6.12. H3 and H6 in $CDCl_3$ were assigned by comparison with **3B** and **4A**. The regiochemistry could now be inferred from cross peaks in the ROESY spectrum ($CDCl_3$, mixing time 200 ms) between H3 and the O-benzylic methylene protons (assigned to positions 2 and 4) in combination with a cross peak between H6 and the C-benzylic methylene protons known to be located at position 5.

2,5-Dibenzyloxyphenol (3A). TLC (SiO_2, EtOAc/heptane 3:7) $R_f = 0.38$. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 4.96 and 5.00 (CH_2, s), 6.34 (H4, dd, J = 8.7, 3.0 Hz), 6.50 (H6, d, J = 3.0 Hz), 6.85 (H3, d, J = 8.9 Hz), 7.25–7.50 (Ar-H, m), 9.12 (OH, s). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3–5 (OH, very

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broad), 5.00 and 5.05 (CH_2, s), 6.44 (H4, dd, J = 8.7, 3.0 Hz), 6.65 (H6, d, J = 3.0 Hz), 6.83 (H3, d, J = 8.8 Hz), 7.3–7.5 (10 Ar-H, m). ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 69.5 and 70.9 (CH_2), 103.8 (C6), 104.2 (C4), 115.9 (C3), 127.6–128.4 (10C), 137.4, 137.7, 141.0 (C2), 148.1 (C1), 153.5 (C5). The regiochemistry was established (HSQCR, HMQCR optimized for J = 7 Hz) by long-range coupling from the OH proton to C1, C2, and C6 in DMSO-d_6. The compound has been reported previously, however, without any NMR data.[15]

2,4-Dibenzyloxyphenol (3B). TLC (SiO_2, EtOAc/heptane 3:7) $R_f = 0.38$. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 4.97 and 5.09 (CH_2, s), 6.43 (H5, dd, J = 8.6, 3.0 Hz), 6.69 (H6, d, J = 8.4 Hz), 6.69 (H3, d, J = 3.0 Hz), 7.25–7.50 (Ar-H, m), 8.51 (OH, s). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3–5 (OH, very broad), 4.99 and 5.06 (CH_2, s), 6.50 (H5, dd, J = 8.6, 2.7 Hz), 6.65 (H3, d, J = 2.8 Hz), 6.85 (H6, d, J = 8.6 Hz), 7.3–7.5 (10Ar-H, m). ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 69.8 and 69.9 (CH_2), 103.1 (C3), 106.1 (C5), 115.7 (C6), 127.6–128.4 (10C), 137.4, 137.5, 141.1 (C1), 147.1 (C2), 151.5 (C4). The regiochemistry was established (HSQCR, HMQCR optimized for J = 7 Hz) by long-range coupling from the OH proton to C1, C2, and C6 in DMSO-d_6. The ^{1}H NMR data in $CDCl_3$ concur with those previously published.[16]

4-Benzyloxycatechol (2A). TLC (SiO_2, EtOAc/heptane 3:7) $R_f = 0.12$. EIMS *m/z* (relative%): 216 [M^+](30), 91 [benzyl$^+$](100). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 4.94 (CH_2, s), 6.07 (H5, dd, J = 8.6, 2.8 Hz), 6.33 (H3, d, J = 2.8 Hz), 6.71 (H6, d, J = 8.6 Hz), 7.4–7.6 (15 Ar-H, m). ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 71.3 (CH_2), 103.9 (C3), 105.0 (C5), 116.8 (C6), 127.5–129.0 (6C), 139.4 (C1), 148.2 (C2), 152.4 (C4). The regiochemistry was established (HSQCR, HMQCR optimized for J = 7 Hz) by long-range coupling from the CH_2 protons to C4.

Dibenzyldimethylammonium chloride (6). An authentic sample was prepared according to the directions given by Kantor and Hauser.[17] Mp 94–95°C (lit^P 94–95°C). FABMS (relative %): *m/z* 226 [M]$^+$(100), 488 + 490 [MCl + M]$^+$(25). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 2.90 ($2CH_3$, s), 4.75 ($2CH_2$, s), 7.50–7.54 (6Ar-H, m), 7.61–7.65 (4Ar-H, m). ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 48.0 (CH_3), 66.8 (CH_2), 128.1, 128.8, 130.2, 133.1. IR (KBr, cm^{-1}): 1621 m, 1598 m, 1584 m and 1494 s (phenyl), 1479 vs and 1455 vs (CH_2N^+/CH_3N^+). Elemental analysis indicated a monohydrate: Calc. for $C_{16}H_{22}NOCl$: C 68.68; H 7.92; N 5.01. Found: C 68.54; H 7.87; N 4.85.

In order to clarify the origin of **6** observed in the reaction mixture from **1b**, benzyl chloride and NaH in DMF, ^{1}H NMR spectra were recorded of a solution of benzyl chloride (70 µl) in DMF-d_7 (650 µl) at room temperature. Since the spectrum was unchanged for 48 h, NaH in mineral oil (30 mg) was added. During the first 5 h no changes were detected in the ^{1}H NMR

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spectrum, but after a further 72 h complete conversion had occurred to a complicated mixture containing *ca* 25% **6**.

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Received in the UK August 14, 2000

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