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Oxidative Acetylation of Tetramethyl Bisphenol-F

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Abstract: Oxidative acetylation of tetramethyl bisphenol-F (**2**) using two different reagents is described. The reaction of (**2**) with $NaIO_4$ in acetic anhydride furnished a novel triacetate (**3**) and its reaction with lead tetraacetate (LTA) in dry benzene resulted in the formation of a novel bis-cyclohexadienone (**4**).

Keywords: Bis(3,5-dimethyl-4-hydroxyphenyl)methane, bis(3,5-dimethyl-3-acetoxy-4-oxocyclohexa-1,5-dienyl)methane, cyclohexa-2,4-dienones, oxidative acetylation

Cyclohexa-2,4-dienones are useful intermediates for preparing a variety of complex natural products.[1–4] We have recently reported a one-pot synthesis of acetoxy-2,4-cyclohexadienones by treatment of substituted phenols with sodium metaperiodate in acetic anhydride.[5] Our continued efforts in this area prompted us to synthesize tetramethyl bisphenol-F (**2**) and investigate its reaction with LTA[6] as well as with sodium metaperiodate in acetic anhydride.[5]

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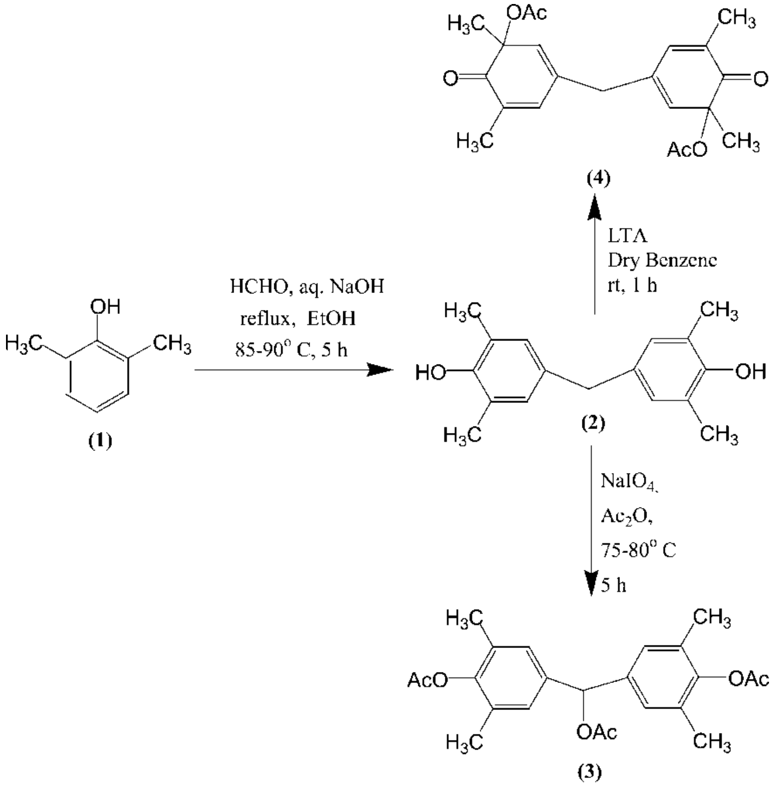
The bisphenol-F (**2**) was prepared from 2,6-dimethylphenol (**1**) by modifying the procedure of Kharasch et al. reported for the preparation of 3,3′,5,5′-tetra-*tert*-butyl-4,4′-dihydroxy diphenyl methane.[7] Thus, treatment of 2,6-dimethylphenol (**1**) with formaldehyde solution (37% w/v) in the presence of aqueous sodium hydroxide at 85°C for 5 h resulted in the formation of tetramethyl bisphenol-F (**2**) in 52% yield (Scheme 1) The structure of (**2**) was readily established through its spectral and analytical data. Its ^{1}H NMR spectra exhibited a singlet at δ_H 3.7 for two protons and a broad singlet at 2.2 for twelve protons on methyl groups along with a singlet at 4.5 for two exchangeable protons, indicating the presence of two phenolic OH groups. The ^{13}C NMR of (**2**) displayed diagnostic signals at δ_C 16.49 for four methyl carbons and a signal at 40.16 for the methylene carbon, among other characteristic signals for aromatic carbons. Its mass spectrum was also consistent with the structure that showed the molecular ion peak at 258 and a base peak at 135 (M-121).

Treatment of (**2**) with sodium metaperiodate in acetic anhydride at 75–80°C for 5 h resulted in the formation of a novel triacetate (**3**) whose



Scheme 1.

structure was fully established through its spectral and analytical data. It showed a characteristic band at 1749 cm^{-1} for the carbonyl absorption in its IR spectrum. It also displayed singlets for methyl groups at δ_H 2.14 (12H) along with 2.15 (3H) and 2.26 (6H). Its ^{13}C NMR spectrum showed signals at δ_C 170.1 and 168.9 for acetate carbonyls along with 21.6 and 20.7 for acetate methyls. The mass spectrum of (**3**) showed a molecular ion peak at 398 and a base peak at 339 (loss of acetic acid) in addition to other diagnostic signals. It was evident that acetylation of the two phenolic OH groups and at the benzylic position led to the formation of the triacetate (**3**).

The compound (**2**) was then treated with LTA in dry benzene for 1 h at room temperature (~27°C). Usual workup and chromatography over silica gel furnished the novel bis(3,5-dimethyl-3-acetoxy-4-oxocyclohexa-1,5-dienyl)methane (**4**) in 45% yield. The structure of the compound (**4**) was confirmed through its spectral and analytical characteristics. The bis-cyclohexadienone (**4**) showed a characteristic band at 1669 cm^{-1} in its IR spectrum for cyclohexadienones.[8] Its ^1H NMR spectrum displayed signals at δ_H 1.37, 1.92, and 2.06 each for 6H along with singlets at 3.05 (2H) and 5.86 (2H) for methylene and olefinic protons respectively. The ^{13}C NMR spectrum of (**4**) was also consistent with the proposed structure and exhibited resonances at δ_C 15.90, 21.07, and 24.63 for methyl carbons and a signal at 40.51 for the methylene carbon in addition to other characteristic signals. Its mass spectrum showed a molecular ion peak at 372 and a base peak at 313 (M-59) indicating loss of acetate ion and was correctly analyzed for $C_{21}H_{24}O_6$. It was interesting to observe that both the aromatic rings participated in the oxidation leading to the novel bis-cyclohexadienone (**4**). It is also noteworthy that although the oxidative acetylation of tetramethyl bisphenol-F could lead in principle to the formation of several addition products through inter- and intramolecular modes of cycloaddition, the reaction only furnished a single product (**4**). To study its possible intra- as well as intermolecular cycloaddition reactions, the bis-dienone (**4**) was also heated under reflux in o-xylene for 5 h with stirring. We observed that the bis-dienone (**4**) is stable under the reaction conditions and remained unchanged.[9] It is also worthwhile to mention here that the tetramethyl bisphenol-F (**2**) was found to be stable toward oxidation with $NaIO_4$ in water even at 80°C and did not yield any cyclohexadienone.[9,10]

Further investigation on the reactivities of the novel acetates (**3**) and (**4**) is currently under way.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer PC-16 FTIR spectrophotometer. NMR spectra were recorded on either a Bruker-200 FT-NMR or Bruker-300 FT-NMR spectrophotometer. Mass spectra were obtained on a Shimadzu QP-5050A mass spectrophotometer with quadrupole detector. Microanalyses were performed on a Perkin–Elmer 2400 CHN/S Analyzer instrument. Column chromatography was performed using Acme's silica gel (60–120 mesh size) and spots on TLC were visualized in iodine vapor.

Tetramethyl Bisphenol-F [Bis(3,5-dimethyl-4-hydroxyphenyl)methane] (2)

An aqueous solution of sodium hydroxide (22 mL, 23% w/v, 0.126 mol) was added to a stirred mixture of 2,6-dimethyl phenol (**1**) (10.0 gm, 0.082 mol) in ethyl alcohol (30 mL) and formaldehyde (15 mL, 37% w/v, 0.185 mol) over a period of 15 min. The reaction mixture was heated at 85–90°C for 5 h under continuous stirring. The reaction mixture was then allowed to cool down to room temperature and was diluted ten times its volume with water and stirred for 15 min. The solid thus obtained was filtered and washed thoroughly with water and dried at 85–90°C under vacuum. The solid mass thus obtained was dissolved in ethyl acetate (100 mL), and the solution was dried over anhydrous sodium sulphate. Column chromatography of the residue over silica gel and elution (light petroleum/ethyl acetate, 95 : 5) furnished (**2**) as a white crystalline solid (52%). Mp 180–182°C, ν_{max} (neat) 3463, 3007, 2915, 2847, 1629, 1608, 1484, 1304, 1227, 1186, 1145, 1013, 882, 774, 730, and 5765 cm^{-1}. δ_H (200 MHZ, $CDCl_3$); 2.2 (s, 12H, methyl), 3.7 (s, 2H, methylenes), 4.5 (s, 2H, exchangeable, phenolic OH), 6.8 (s, 4H, aromatic H). δ_C (50 MHZ, $CDCl_3$): 16.49, 40.16, 124.02, 128.37, 132.62, 151.02. M/z: 256 (M^+), 135 (M-121) (base peak: loss of 2,6-dimethyl phenol). Elemental analysis found: C, 79.80%; H, 7.94%; requires C, 79.69%; H, 7.81% for $C_{17}H_{20}O_2$.

Bis(4-acetoxy-3,5-dimethylphenyl)methyl Acetate (3)

Sodium metaperiodate (1.5 gm, 0.007 mol, excess) was added to a stirred solution of bis(3,5-dimethyl-4-hydroxyphenyl)methane (**2**) (0.50 gm, 0.00195 mol) in acetic anhydride (15 mL) in portions over a period of 1 h. Stirring was continued for 5 h while maintaining the reaction temperature between 75 and 80°C. The reaction mixture was allowed to cool down to room temperature and then poured into a vigorously stirred saturated solution of sodium bicarbonate (125 mL) to neutralize excess acid. The aqueous layer was then extracted with ethyl acetate (3 × 25 mL) and combined organic extracts were successively washed with saturated sodium bicarbonate solution (20 mL), water (20 mL), and brine solution (20 mL). Drying over anhydrous sodium sulphate followed by removal of solvent under reduced pressure furnished a dark brown residue, which was chromatographed using a mixture of light petroleum and ethyl acetate (95 : 5) to furnish the acetylated product (**3**) as a white crystalline solid (0.414 gm, 51.28%). Mp 139°C, (λ_{max}): 250 nm; ν_{max} (neat) 3469, 3016, 2929, 1749, 1607, 1370, 1144 cm^{-1}. δ_H (300 MHZ,

$CDCl_3$); 2.14 (sharp s, 12H, $-C\underline{H}_3$ on aromatic rings), 2.15 (s, 3H, $-OCOC\underline{H}_3$ on the central tetra-substituted carbon), 2.26 (sharp s, 6H, acetate methyl protons), 6.75 (s, 1H, methane proton), 7.02 (s, 4H, aromatic Hs). δ_C (75 MHZ, $CDCl_3$): 170.1, 168.9, 148.0, 137.6, 130.5, 127.5, 76.1, 21.6, 20.7, 16.6. M/z: 398 (M^+), 339 (base peak, M-60, loss of acetic acid), 297 (loss of CH_3CO), 255 (loss of another CH_3CO). Elemental analysis found: C, 68.93%; H, 6.43%; requires C, 69.34%; H, 6.53% for $C_{23}H_{26}O_6$.

Bis(3,5-dimethyl-3-acetoxy-4-oxocyclohexa-1,5-dienyl)methane (4)

LTA (2.66 gm, 0.006 mol) was added to a solution of bis(3,5-dimethyl-4-hydroxyphenyl)methane (**2**) (0.5 gm, 0.002 mol) in dry benzene (30 mL) in portions with constant stirring. The reaction mixture was stirred for 1 h at room temperature (~27°C) after which it was diluted with ethyl acetate (150 mL) and stirred further for 15 min. Removal of the residue by filtration and concentration of the filtrate furnished a pale yellow liquid, which was chromatographed over a column of silica gel. Elution of the column (light petroleum/ethyl acetate 95 : 5) gave (**4**) as a light yellow crystalline solid (45%). Mp 183–184°C, ν_{max} (neat): 2994, 2919, 1734, 1669, 1437, 1371, 1253, 1225, 1060, 859, and 762 cm^{-1}. δ_H (200 MHZ, $CDCl_3$); 1.37 (s, 6H, methyl protons), 1.92 (s, 6H, olefinic methyl protons), 2.06 (s, 6H, acetate methyl protons), 3.05 (s, 2H, methylene protons), 5.86 (s, 2H, olefinic H), 6.59 (s, 2H, olefinic H). δ_C (50 MHZ, $CDCl_3$): 15.90, 21.07, 24.63, 40.51, 78.93, 131.26, 134.61, 137.03, 139.85, 169.91, 199.31. M/z: 372.0 (M^+), 313 (M-59) (loss of acetate ion, base peak), (M-119) (loss of two acetate ions). Elemental analysis found: C, 67.71%; H, 6.44%; requires C, 67.74%; H, 6.45% for $C_{21}H_{24}O_6$.

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