ANTIOXIDANT BUILDING BLOCKS I. THE UNEXPECTED *C*-ACETYLATION OF 2,6-DI-*tert*-BUTYLPHENOL WITH ISOPROPENYL ACETATE

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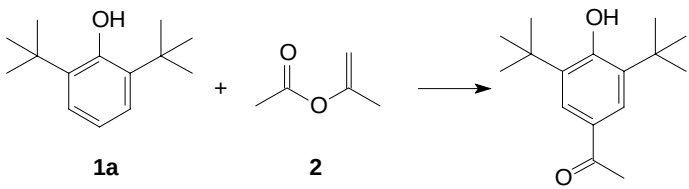
While the reaction of some 2-substituted and 2,6-disubstituted phenols with isopropenyl acetate resulted in the corresponding phenol acetates, in the reaction of 2,6-di-*tert*-butylphenol, a useful starting material of antioxidant building blocks, under the same conditions 4-acetyl-2,6-di-*tert*-butylphenol was the only product.

Key words: 2,6-Di-*tert*-butylphenol acylation; Isopropenyl acetate reaction.

Looking for pharmacophores responsible for antioxidant effect we selected 2,6-di-*tert*-butylphenol (**1a**) as an antioxidant building block for the synthesis of potential neuroprotective pharmacons. When we attempted to protect the phenolic hydroxyl of **1a** with isopropenyl acetate (**2**) prior to further functionalization of the molecule only 4-acetyl-2,6-di-*tert*-butylphenol (**3**) was obtained in good yield (Scheme 1).

Previously we reported some synthetic applications of **2**, among others *C*-acetylation reactions on the pyrrole nucleus[1,2]. Nevertheless we found the formation of **3** rather surprising so we decided to study the reaction in detail.

According to the literature the preparation of **3** was first performed under Friedel–Crafts conditions, using acetyl chloride both as the acetylating agent and the solvent and $AlCl_3$ as Lewis-acid catalyst[3]. Later other methods were reported for the acetylation of **1a** at position 4, like with acetic anhydride using $HClO_4$ as catalyst[4] or with acetic acid in trifluoroacetic anhydride[5].



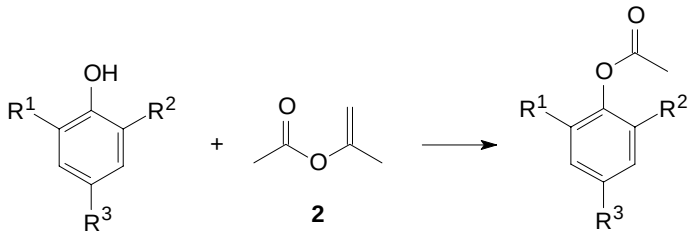
1a **2** **3**

SCHEME 1

We assumed that the steric hindrance around the phenolic OH should play a role in this reaction, so we reacted different 2-substituted, 2,6-disubstituted and 2,4,6-trisubstituted phenols with **2** under identical conditions (Scheme 2).

The results are summarized in Table I. In the case of 2-substituted phenols (**1b**, **1c**) and 2,6-disubstituted phenols (**1d–1f**) the corresponding phenol acetates **4b–4f** were obtained in good yield. Contrary to the results of Nehoroshev et al.[4], who used acetic anhydride with $HClO_4$ successfully for the *O*-acetylation of 4-substituted-2,6-di-*tert*-butylphenols, the isopropenyl acetate/methanesulfonic acid system turned out to be less reactive, and was not able to produce 2,6-di-*tert*-butylphenol acetates, starting from **1g** or **3**.

Meanwhile we achieved our original goal and were able to prepare (2,6-di-*tert*-butylphenyl)acetate[11] applying a phase-transfer method[12]. We attempted to acetylate it with



1b-1g, 3 **4b-4f**

For R^1, R^2, R^3 see Table I

SCHEME 2

TABLE I
Reaction of substituted phenols **1b–1g**, **3** with isopropenyl acetate (**2**)

Compound	R^1	R^2	R^3	Product	Yield, %	b.p. or m.p., °C
1b	CH_3	H	H	**4b**	90	210 (101 kPa)[a]
1c	$C(CH_3)_3$	H	H	**4c**	92	118–120 (0.026 kPa)[b]
1d	CH_3	CH_3	H	**4d**	93	70–73 (0.026 kPa)[c]
1e	$CH(CH_3)_2$	$CH(CH_3)_2$	H	**4e**	90	135–140 (0.026 kPa)[d]
1f	Br	Br	H	**4f**	93	42–44[e]
1g	$C(CH_3)_3$	$C(CH_3)_3$	CH_3	no reaction		
3	$C(CH_3)_3$	$C(CH_3)_3$	$COCH_3$	no reaction		

In accordance with literature data: [a] Ref.[6]; [b] ref.[7]; [c] ref.[8]; [d] ref.[9]; [e] ref.[10].

isopropenyl acetate but the starting material did not change, the 1-acetoxy group prevented the *C*-acetylation in position 4.

From these observations one can conclude that in the proton-catalyzed reaction of phenols with isopropenyl acetate the corresponding phenol acetates are the normal products unless the bulk of substituents in positions 2 and 6 reaches the size of the *tert*-butyl group. When position 4 is blocked in 2,6-di-*tert*-butylphenol derivatives no reaction occurs. The lack of reaction in the case of (2,6-di-*tert*-butylphenyl)acetate suggests that the formation of **3** is not a Fries-type reaction starting with the corresponding *O*-acetate.

Summarising, there are two prerequisites for the *C*-acylation of phenol derivatives. First, the prevention of *O*-acylation as exemplified by the steric hindrance exerted by the 2,6-di-*tert*-butyl substitution. Second, the activation of the C-4 atom as the effect of the conjugation between the lone pair of the O-atom and the electrons of the ring. This conjugation requires an essentially sp^2 O-atom and thus a planar arrangement of the connecting atoms. These conclusions were supported by the results of the calculations performed with the semiempirical AM1 Hamiltonian[13].

EXPERIMENTAL

Proton NMR spectra were recorded in $CDCl_3$ solution on a Varian VXR-300 (300 MHz) instrument and proton chemical shifts are reported in ppm downfield from TMS as internal reference. Infrared spectra were recorded using KBr pellets on a Nikolet 20 DXC FT-IR spectrophotometer. Melting point was determined on a Büchi 510 apparatus.

General Procedure for the *O*-Acetylation of Phenols **1b**–**1f**

A solution of the phenol (0.05 mol), isopropenyl acetate (6.0 ml, 0.055 mol) and methanesulfonic acid (0.5 ml) in 1,2-dichloroethane (50 ml) was refluxed for 30 min. After cooling the reaction mixture was washed with 5% aqueous sodium bicarbonate solution (30 ml), then with water (30 ml). The organic layer was dried and evaporated under reduced pressure. The oily residue was purified by distillation (yield and b.p. or m.p. in Table I).

4-Acetyl-2,6-di-*tert*-butylphenol (**3**)

To a solution of 2,6-di-*tert*-butylphenol (**1a**; 10.3 g, 0.05 mol) in 1,2-dichloroethane (150 ml) methanesulfonic acid (0.5 ml) and isopropenyl acetate (6.0 ml, 0.055 mol) was added. The reaction mixture was refluxed for 1 h and after cooling it was washed with 5% aqueous sodium bicarbonate solution (30 ml), then with water (30 ml). The organic layer was dried and evaporated under reduced pressure. The residue was crystallized from diisopropyl ether to yield **3** (9.92 g, 80%) as white crystalls, m.p. 144–146 °C, identical with a sample prepared by a known procedure[3].

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