O-Acetylation: synthesis of acetylated phenols from aryl-methyl ethers over boron alkoxides

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A new acetylation procedure has been applied to 13 aryl-methyl ethers using boron chemistry. In this procedure, demethylation of aryl-methyl ethers and acetylation of the resulting phenols were combined into one procedure in order to shorten the number of stages and to achieve easy purification. Eleven known with/without bromine and two new [bis(3,4-diacetoxyphenyl)methanone and 5,5′-methylenebis(1,2-diacetoxy-3,4-dibromobenzene) (a natural bromophenol's acetylated derivative)] acetylated arene compounds were synthesised from their methoxy derivatives by this method. The effectiveness of the method was illustrated by producing an acetylated natural bromophenol from its methyl ether. The phenol form was obtained by hydrolysing the acetylated natural bromophenol. Thus, the advantage of this method in the natural product chemistry of phenolic compounds was confirmed.

Keywords: natural bromophenols, acetylation, aryl ether, boron chemistry

Demethylation of aryl methyl ethers with BBr_3 in CH_2Cl_2 at or below room temperature[1,2] is preferred to high temperature procedures[3] (*e.g.* hydrogen bromide in acetic acid at reflux). Thus, aromatic ethers can be cleaved by means of BBr_3 under mild conditions. The cleavage of aryl methyl ethers is commonly used as the last step in the synthesis of phenolic natural compounds,[4–15] which are mostly isolated from marine organisms.

In previous studies, we have observed that synthesised natural phenolic compounds generally need purification, because the final reactions or extractions contain some impurities.[10,13–16]. These impurities are seen in the spectrum and cannot be removed easily. Removal of the impurities by chromatography is difficult because, on the TLC plate, synthesised natural phenols have long tails starting from the baseline. By contrast, acetylated phenols have a spot without a tail (on a TLC alumina plate) and so acetylated products can be more easily purified than the phenols. In addition, the mildness of the temperature in this method, performed using acetic acid, is an advantage. For these reasons, derivatisation during demethylation is important.

In the literature, there is only one example of acetylation during demethylation with addition of Ac_2O and NaOAc on a heated water-bath.[2] In another study, a halogenated methoxy compound was acetylated to achieve good purification.[2] Previously, we synthesised a biologically active, naturally occuring benzyl methyl ether type natural bromophenol by regioselective *O*-demethylation of aryl-methyl ethers. In the study, reactions were completed by addition of MeOH and heating for 3; H, after demethylation.[17]

Results and discussion

The purpose of this study was to combine the demethylation of aryl-methyl ethers with acetylation of the resulting phenols into one reaction procedure in order to shorten the number of stages and to achieve easier purification. We observed that the methoxy benzene compounds could be converted into their acetylated derivatives over boronate esters (79–98%) by addition of AcOH at the end of the BBr_3 demethylation (after 1 day from the reaction starting time) at 0 °C to room temperature (Scheme 1).

This method is an efficient, simple and especially mild procedure. When this procedure was performed on various Methoxy-substituted compounds (Table 1), it was seen that all the $-OCH_3$ groups of the compounds were demethylated and acylated under the reaction conditions (Scheme 2).

The ^{1}H NMR spectrum of the new compound **20** were analysed and it was seen that the ^{1}H NMR spectra of **20** includes two methyl group proton peaks belonging to acetates (2.29 and 2.30 ppm) and there were no methyl peaks related to methoxy derivative **12** (methoxy peaks: 3.92 and 3.94 ppm for **12**).[18] The ^{13}C NMR spectrum of compound **20** also includes resonances in agreement with the proposed structure.

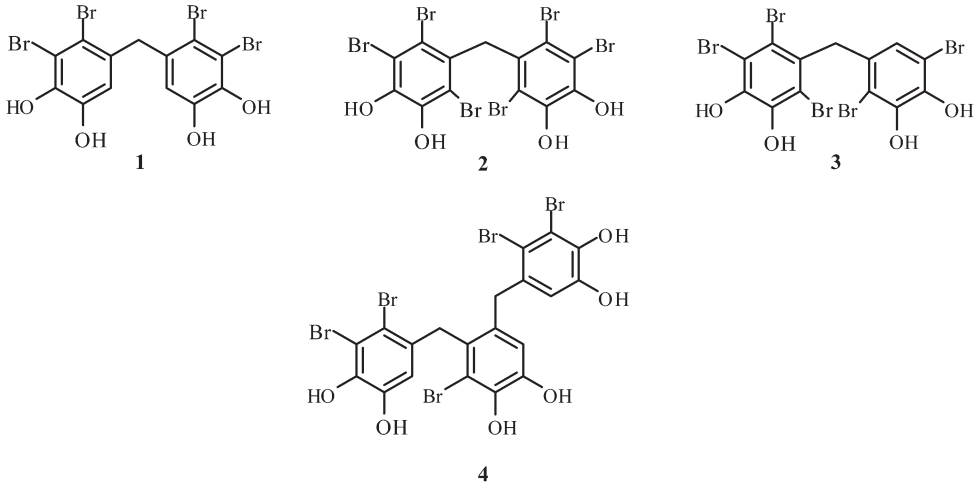

Fig. 1 Examples of natural phenolic natural compounds.

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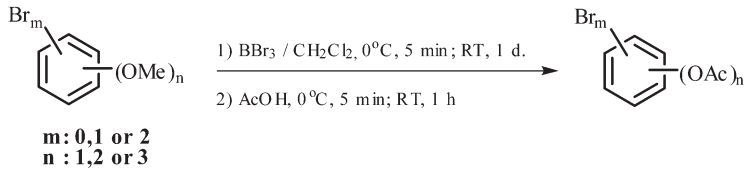
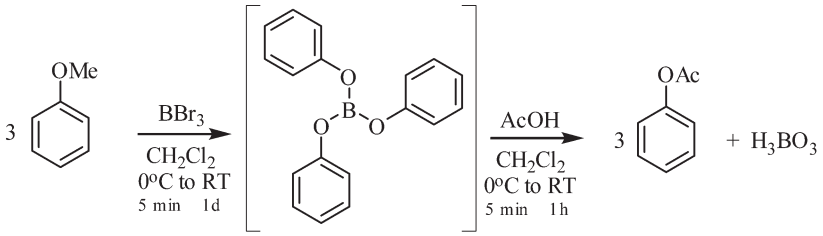
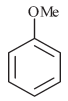
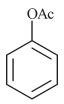
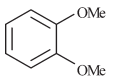
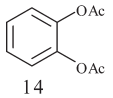
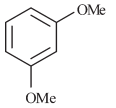
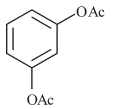
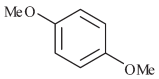
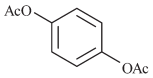
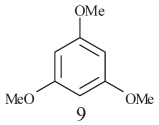
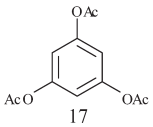
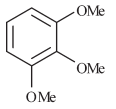
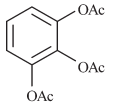
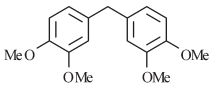
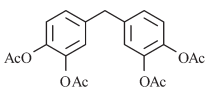
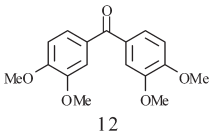
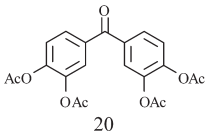


Scheme 1



Scheme 2

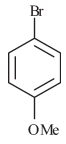
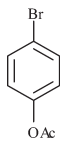
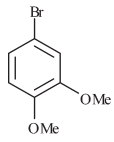
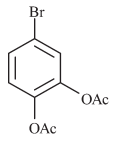
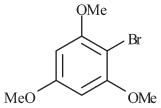
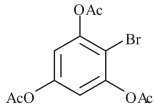
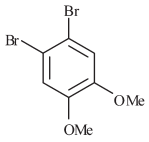
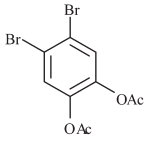
Table 1 Acetylated products of mono to tetra-methoxyarenes and their yields

Entry	Methoxy compounds	Products	Yield/%	R_f[b]
1	 5	 13	88%	0.79[a]
2	 6	 14	95%	0.56[a]
3	 7	 15	82%	0.62[a]
4	 8	 16	96%	0.56[a]
5	 9	 17	79%	0.36[a]
6	 10	 18	98%	0.26[a]
7	 11	 19	91%	0.54[a]
8	 12	 20	90%	0.77[a]

[a]Isolated yield. [b]EtOAc/hexane (3/7) as mobile phase.

Some brominated aryl ethers were also treated with BBr_3 and then with acetic acid to provide the corresponding acetylation products (Table 2). Disappearance of the methoxy group peaks and the presence of acetate resonances in their ^1H NMR spectra supported complete demethylation and complete acetylation.

Table 2 Acetylated products of mono and dibromo substituted methoxyarenes and their yields

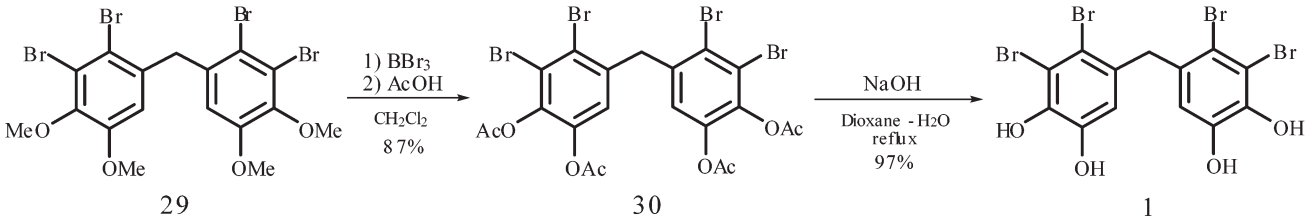
Entry	Methoxy compounds	Products	Yield/%	R_f[b]
1	 21	 25	95%	0.82
2	 22	 26	97%	0.64
3	 23	 27	84%	0.40
4	 24	 28	97%	0.67

[a]Isolated yield. [b]EtOAc/hexane (3/7) as mobile phase.

The known molecules' ^1H NMR data and/or melting points were crosschecked with the literature[19–23] (see Electronic Supplementary Information). The retardation factors (R_f) of all the synthesised molecules were calculated and are shown in Tables 1 and 2.

We believed that some diphenyl methane type natural compounds (Fig. 1) could be synthesised by this method. In order to test our hypothesis, the methoxy derivative of **1** (**29**) was synthesised by a coupling reaction in polyphosphoric acid (PPA) from its brominated benzene monomers (from (2,3-dibromo-4,5-dimethoxyphenyl)methanol and 1,2-dibromo-3,4-dimethoxybenzene). Compound **29** was reacted with BBr_3 and then AcOH was added. Compound **30**, the acetylated derivative of natural bromophenol **1**, was synthesised effectively (Scheme 3).

The ^1H NMR spectrum of **30** was analysed and revealed two methyl resonances belonging to acetyls (2.26 and 2.35 ppm), and no methyl peaks related to methoxy derivative **29** (methoxy peaks: δ_H 3.74 and 3.85 ppm for **29**).[10] The ^{13}C NMR spectrum of **29** also supports the structure of **30**. Finally, compound **30**



29 30 1

Scheme 3

was hydrolysed by reflux with 0.16M NaOH solution (in dioxane–water:1:1 V/V) and was converted (97%) into the natural bromophenol **1** as the sole product to prove this method's effectiveness (Scheme 3).

Conclusion

This report includes a concise strategy for the direct synthesis of acetylated phenols from aryl-methyl ethers. The procedure combines the BBr_3 demethylation of ethers with acetylation of OH groups. After BBr_3 demethylation, acetylated compounds were produced by the addition of acetic acid instead of water, methanol or another additional reagent. Thus, an efficient method was developed to achieve easier purification of natural phenolic compounds, useful in synthesis, by the functional group changing, from OMe to OAc in organic solvents under mild conditions and in a single step.

Experimental

All chemicals and solvents were commercially available. Column chromatography was performed on silica gel (SiO_2, 60 mesh; Merck). TLC was performed on E. Merck Silica Gel 60 F_{254} plate (0.2 mm). Melting points were determined on a Buchi 530 capillary melting apparatus and were uncorrected. IR Spectra were obtained from solutions in 0.1-mm cells on Perkin Elmer Spectrum One FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on 400 (100)-MHz Bruker Avance III and Varian Mercury spectrometers and are reported in δ units with Me_4Si as internal standard. Elemental analyses were carried out on a Leco CHNS-932 analyser (see Electronic Supplementary Information).

Acetylation of aryl methyl ethers: general procedure

A solution of bis(3,4-dimethoxyphenyl)methanone (**12**, 1.00 g, 3.31 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C and then a solution of BBr_3 (2.1 mL, 21.8 mmol) in CH_2Cl_2 (22.3 mL) was added dropwise under N_2 over 5 minutes. After the cold bath was removed, the mixture was stirred at RT and under N_2 for 1 day. After one day mixing and monitoring with TLC, the mixture was cooled to 0 °C and glacial acetic acid (3.65 g) was added drop by drop over 5 min. After stirring for an additional 1 h, the mixture was extracted with a cooled Na_2CO_3 aqueous solution (5%) and washed with 0–5 °C water. Then the organic phase was dried over Na_2SO_4 and solvent was evaporated. bis(3,4-dia cetoxyphenyl)methanone (**20**) was obtained as a white solid (1.23 g, 90%).

Bis(3,4-diacetoxyphenyl)methanone (**20**): M.p. 192–193 °C. Found: C, 60.49; H, 4.25. $C_{21}H_{18}O_9$ requires: C, 60.87; H, 4.38%; IR (KBr) 2398, 2073, 1777, 1729, 1663, 1606, 1585, 1501, 1463, 1421, 1372, 1294, 1262, 1200 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.71 (dd, 2H, A part of AB - system, J = 1.8, 8.4 Hz, aromatic), 7.66 (s, 2H, aromatic), 7.32 (dd, 2H, B part of AB - system, J = 0.7, 8.4 Hz, aromatic), 2.30 (s, 6H, CH_3), 2.29 (s, 6H, CH_3); δ_C (100 MHz, $CDCl_3$) 192.5 (CO), 168.2 (CO, acetate), 168.0 (CO, acetate), 146.0 (C), 142.3 (C), 135.5 (C), 128.7 (C), 125.7 (CH), 123.8 (CH), 20.9 (CH_3), 20.8 (CH_3).

5,5'-Methylenebis(1,2-diacetoxy-3,4-dibromobenzene) (**30**): (Crystallised from CH_2Cl_2/hexane ratio of 2/1 and the product was obtained as yellow crystals.) M.p. 213–215 °C. Found: C, 34.86; H, 2.26. $C_{21}H_{16}Br_4O_8$ requires: C, 35.23; H, 2.25%; IR (KBr) 1781, 1725, 1634, 1586, 1448, 1429, 1371, 1276, 1199, 1140 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.85 (s, 2H, aromatic), 4.30 (s, 2H, CH_2), 2.35 (s, 6H, CH_3), 2.26 (s, 6H, CH_3); δ_C (100 MHz, $CDCl_3$) 167.9 (CO, acetate), 167.2 (CO, acetate), 142.8 (C), 140.9 (C), 138.1 (C), 125.1 (C), 124.1 (CH), 122.6 (C), 45.4 (CH_2) 20.8 (CH_3), 20.6 (CH_3).

Hydrolysis of **30**: To a solution of **30** (0.220 g, 0.31 mmol) in dioxane (20 mL) was added a solution of NaOH (0.25 g, 6.25 mmol) in water (20 mL). After the mixture was stirred at reflux for 5 h it was cooled and neutralised with a solution of HCl (1%). Then, the mixture was extracted with EtOAc and washed twice with water. After drying over Na_2SO_4, the solvent was removed under reduced pressure. The natural bromophenol **1** was the sole product obtained as a pale orange solid (0.164 g, 97%), m.p. 202–205 °C (lit.,[24] 199.0–199.8 °C). ^1H NMR (200 MHz, CD_3COCD_3): δ 8.95 (s, OH, 2H); 8.34 (s, OH, 2H); 6.57 (s, 2H); 4.05 (s, CH_2, 2H).[25,26]

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Electronic Supplementary Information

Found and literature data on melting points and NMR spectra of the known products together with observed spectra for **20** and **30** have been deposited in the ESI available through stl. publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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