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Controlled dealkylation by BBr_3: efficient synthesis of *para*-alkoxy-phenols

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ABSTRACT

Controlled dealkylation of dialkyl-aryl-ethers by substoichiometric BBr_3 has been developed as a general tool for the differentiation of the oxygen functions in hydroquinone derivatives. The reaction proceeds smoothly at rt either on linear or branched alkyl-ethers and provides the corresponding *p*-alkoxy-phenols RO-Ar-OH in high yields. With respect to the conventional alkylation path of $Ar(OH)_2$, this process represents a tunable and convenient route to key intermediates for conjugated materials with differentiated side chains.

A key aspect of synthetic chemistry is the need for proper molecular design to be empowered by versatile synthetic routes. These are precious tools in the pursuit of desired continuous improvement in the properties of target compounds, whether pharmaceuticals[1] or organic functional materials.[2] In particular, the differentiation of the oxygen functions in hydroquinone derivatives is a synthetic challenge which regards the synthesis of aryl-ethers with antioxidant and antitumor activities,[3] as well as the full exploitation of functional complexity in π-conjugated polymers.[4]

In detail, bis-alkoxy compounds **I**, provided with iodine atoms, are widely employed as precursors of π-conjugated materials of various types.[5] Structures of type **I** bear R groups which are mostly alkyl chains but can also be crown ethers, sugars, or peptides, inferring solubility, processability, and functional properties. In perspective, the access to compounds of type **II** endowed with differentiated oxygen substituents is highly desirable, according to the most recent developments in the field (See Fig. 1). In fact, such structures would ensure functional diversity and hence molecular architectures suitable for tuning properties and complex functions in the polymers. The straightforward route to such structures involves the *p*-alkoxy-phenol derivatives **III** whose hydroxyl group can be subsequently transformed (Fig. 2). Efforts to prepare intermediates **III** by controlled alkylation at one of the two hydroxyl groups of hydroquinone have been carried out to some extent,[6] in most cases resulting in low yields, so that a few examples of complex polymeric architectures have been obtained in this way.[7] As a consequence, nowadays an alternative strategy toward functional diversity in polymers consists in the copolymerization of two distinct monomers each endowed with one of the desired side groups.[8] Such an approach suffers from clear limitations, the most evident being different solubilities and reactivities of the two partners during the polymerization process.

In general, despite the recent advances in currently available synthetic procedures,[9] full control over the two oxygen positions of hydroquinone remains an open task.

Herein we propose the controlled dealkylation of 1,4-$Ar(RO)_2$ with Ar = 2,5-diiodobenzene and R ≠ Me (**1**) by boron tribromide (BBr_3) as a convenient and simple strategy to manipulate at pleasure the hydroquinone core and obtain *p*-alkoxy-phenols RO-Ar-OH (**2**). The alkyl chains in **1** and **2**, either linear or branched, are those most commonly found in π-conjugated polymers.[10]

Preliminary experiments were devoted to verify the effective limits and potentials of the alkylation strategy and were performed by treating 1,4-dihydroxy-2,5-diiodo-benzene (**3**) with octylbromide as the alkylating reagent (Scheme 1). The corresponding monoalkylated product, 2,5-diiodo-4-octyloxy-phenol (**2a**), was isolated in poor yields (14–28%),[11] in agreement with the synthesis of this compound already reported in the literature.[7c] The product distribution of a reactive process between a difunctional substrate and a monofunctional reactant is predictable by means of statistics, in the hypothesis that the transformation of one function does not affect reactivity at the second site.[12]

By applying such a simple statistical treatment to the investigated process, a first serious limitation to the usage of the controlled alkylation strategy is the maximum yield of monoalkylated product being fixed at 50% for alkylations performed in a 1:1 molar ratio between the hydroquinone substrate and the alkylbromide (see Fig. S1 in the Supplementary data).

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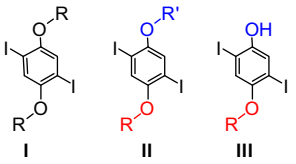


Figure 1. Bis-alkoxy precursors of π-conjugated polymers.

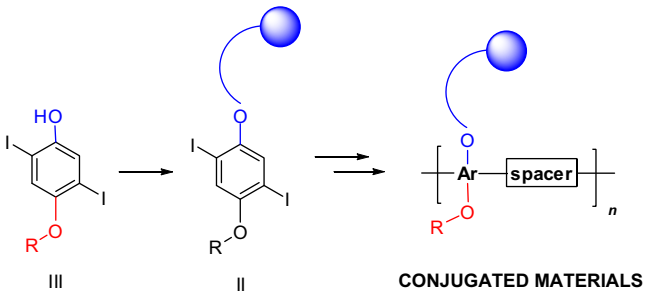


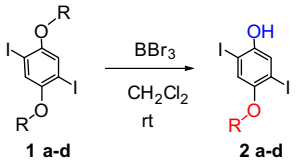
Figure 2. Route to complex π-conjugated polymers with differentiated oxygen substituents.

Moreover, comparing the isolated yields of our experiments with the calculated values, we observed a negative deviation from the statistical distribution, suggesting that the alkylation process is not suitable for the efficient preparation of the monoalkylated product, feasibly because this species can rapidly react a second time evolving to the bisalkylated compound.[13] Alternatively, the low efficiency of the process could also be due to the increase, at lower alkylating agent concentrations, of degradation, disproportion, or side reactions of the iodinated hydroquinone substrate in the alkaline medium.[14] These observations, along with the poor results reported in the literature for the process, confirm the need for an efficient route to access *p*-alkoxy-phenols from hydroquinone derivatives.

Inspired by the work of Bunz and co-workers who used boron tribromide to remove only one of the ethereal bonds of 2,5-diiodo-1,4-dimethoxy-benzene (**4**),[10] we envisioned BBr_3 as an eligible candidate for convenient manipulation of the hydroquinone core. Due to its well-known efficiency in ethereal bond removal, BBr_3 is widely employed for methoxy- and ethoxy-arylethers exhaustive cleavage, on either mono- or di-functional substrates.[15,16] In addition, with respect to other dealkylating reagents and conditions (e.g. $AlBr_3$ or HBr/AcOH), it is compatible with the presence of iodine atoms in the substrates.[17] No examples are available to date of controlled cleavage reactions performed at only one ethereal function of dialkyl-aryl-ethers with R ≠ Me, in spite of the potential relevance in organic synthesis.

As a first experiment we performed the reaction of compound **1a** (R = C_8H_{17}) with BBr_3 at r.t. in dichloromethane, under the conditions described for the controlled dealkylation of **4**[10] (**1a** 0.4 M in dry dichloromethane, **1a**:BBr_3 = 1:1 mol/mol, 24 h, Table 1, entry 1). Unfortunately, the isolated yield in the corresponding monodealkylated species **2a** was very low (7%),[18] the main product of

Table 1
Controlled dealkylation for the synthesis of *p*-alkoxy-phenols **2a-d** by BBr_3



a, OR =
b, OR =
c, OR =
d, OR =

Entry	**1**:BBr_3 (mol/mol)	Time (h)	Product	Yield[a] (%)
1	**1a**:1	24	**2a**	7
2	**1a**:0.5	24	**2a**	58
3	**1a**:0.7	4	**2a**	81
4	**1b**: 0.7	4	**2b**	75
5	**1c**: 0.7	4	**2c**	80
6	**1d**: 0.7	4	**2d**	10
7	**1d**: 0.7	1.5	**2d**	75

[a] Isolated yields.

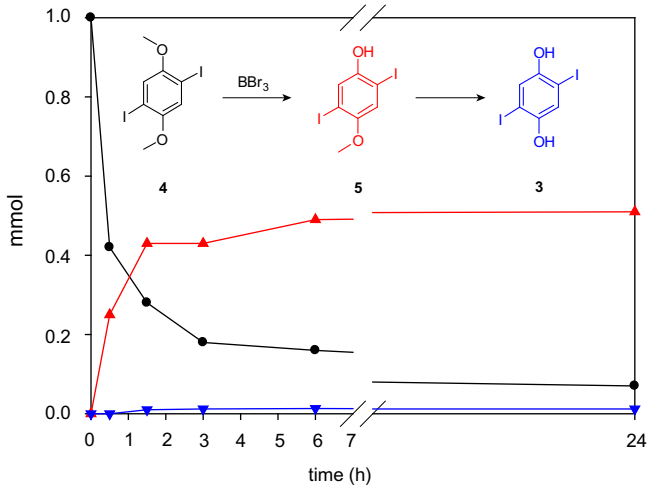
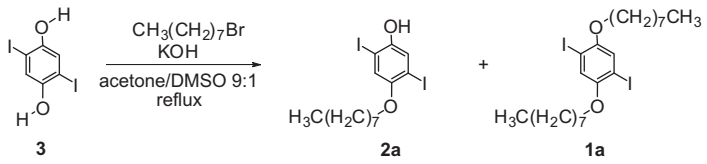
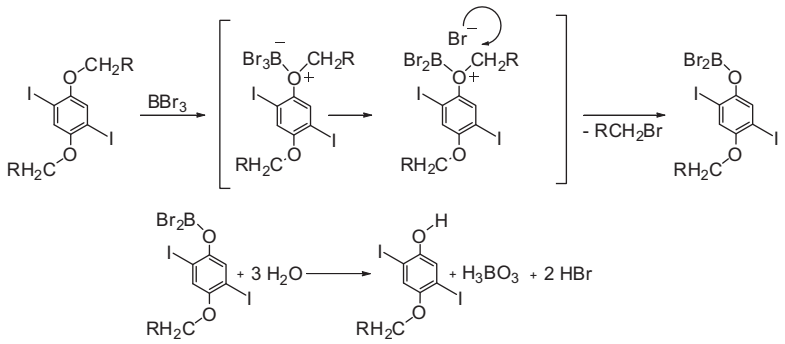


Figure 3. Controlled dealkylation of **4** with BBr_3 (0.5 equiv).

this reaction being fully demethylated 1,4-dihydroxy-2,5-diiodo-benzene (**3**). When compared to the isolated yield of 68% reported for 2,5-diiodo-4-methoxy-phenol, this result points out to a higher reactivity of the octyl substrate. The possibility of working in substoichiometric ratios of BBr_3 versus the dialkyl-aryl-ethers was therefore investigated by carrying out a model reaction on **4** (**4**:BBr_3 = 1:0.5 mol/mol). The reaction progress was followed by GCMS analysis (Fig. 3). At 6 h reaction time, the amount of



Scheme 1. Alkylation of 1,4-dihydroxy-2,5-diiodo-benzene (**3**) with octylbromide.



Scheme 2. Accepted mechanism of dealkylation by BBr_3 applied to substrates **1a**–**d**.

monodemethylated product **5** is around 50%, already far beyond the calculated value (38%). Moreover, the reaction did not evolve further with time, as the mixture at 24 h did not show a higher amount of product **3**. This picture suggests a fortunate accumulation of the desired *p*-methoxy-phenol. This is to be attributed to the fact that the reactivity of the second site in the dealkylation process is indeed lower than that of the first one.[19] As a consequence, the dealkylation process under substoichiometric amounts of BBr_3 seemed a viable synthetic tool for our purposes.

The reaction performed on compound **1a** (**1a**:BBr_3 = 1:0.5 mol/mol, 24 h, Table 1, entry 2) allowed the isolation of product **2a** in 58% yield, which represents a notable improvement with respect to the 1:1 conditions and the previously discussed alkylation procedures. Encouraged by this result and taking into account that 17% of unreacted octyl-aryl-ether **1a** was recovered from the reaction mixture, we explored the use of a slightly higher [BBr_3] while carefully choosing the reaction time. The treatment of **1a** with BBr_3 for 4 h (**1a**:BBr_3 = 1:0.7 mol/mol, Table 1, entry 3) gave an optimal yield of 81% in **2a**.

In order to evaluate the potential of the BBr_3 controlled dealkylation as a general methodology, the study was extended to the substrates **1b**–**d** featuring different alkyl chains. Compound **1b**, endowed with a hexadecyl group, was chosen to test the effect of chain length on the process.[20] Substrates with branched alkyl chains were also considered, as they might result critical due to increased steric hindrance near the reaction center. Reactions were performed on **1b**–**d** (Table 1, entries 4–6) under the conditions which were previously optimized for the octyl substrate (**1**:BBr_3 = 1:0.7 mol/mol, 4 h). Excellent yields were obtained for **2b** and **2c**, which show that the dealkylation process is not affected by either chain length or substitution. By contrast, the isolated yield for compound **2d** (R = 2-ethylhexyl) was only 10%, the main product for this reaction being fully dealkylated **3**. This result suggested that compound **1d** is extremely reactive. Therefore, a more detailed investigation was performed by using various substoichiometric **1d**:BBr_3 molar ratios and following the reaction over time (see Table S2 in the Supplementary data). We found that simple shortening of the reaction time from 4 to 1.5 h resulted in the isolation of compound **2d** in 75% yield (**1d**:BBr_3 = 1:0.7 mol/mol, 1.5 h, Table 1, entry 7).

The whole of our experimental data highlights that various alkyl substituted substrates can be successfully reacted via controlled cleavage with BBr_3 by careful tuning of stoichiometric ratios (>0.5 and <1 equiv) and reaction times. In particular, dealkylation of alkyl-ethers (**1**) with 0.7 equiv of BBr_3 and reaction times ranging from 1½ up to 4 h proved to give the corresponding *p*-alkoxy-phenols (**2**) in high yields.

Our results can be explained by taking into account the accepted mechanism for the BBr_3 cleavage of the ethereal bond, which is depicted in Scheme 2.

A Lewis acid-base interaction leads to an ylide adduct, which bears a negative charge on the boron atom and a positive charge on the oxygen; this is followed by bromide transfer to the alkyl chain, namely to the carbon (C_α) next to the positively charged oxygen atom.[15] As a result, an alkyl-bromide and an aryloxy-boron derivative are obtained. The hydrolysis of such aryloxy-boron species in the workup yields the dealkylated product. Currently, there is no information on the nature of the bromide transfer, whether it proceeds according to S_N2- or S_N1-type mechanism. Reasonably, branched substrates could be poorly reactive, if the bromide transfer is S_N2-like and hence impaired by steric hindrance, or highly reactive, if the transfer is of S_N1 type, favored by the formation of a more stable carbocation. The observed reactivities of the two branched substrates **1c** and **1d**, which differ in the position of the substitution, on the C_γ and C_β carbons respectively, shed light on this aspect. In particular, the remarkable reaction rate of **1d** may be due to the possibility of the primary carbocation from the ylide adduct to transpose to a tertiary one thanks to the stabilizing effect of the ethyl group in the β position. The observation that the reaction rate is dependent on the nature of the alkyl chain suggests that the C–O bond breaking is in the rate determining step of the BBr_3-assisted ether cleavage and points out to its S_N1 character.

In conclusion, we have reported on a novel protocol for the differentiation of the hydroxyl groups of hydroquinone substrates based on the controlled dealkylation of dialkyl-aryl-ethers by BBr_3. It represents a convenient alternative to the monoalkylation path of bis-hydroxy substrates to the corresponding *p*-alkoxy-phenols. The proposed synthetic procedure is efficient and versatile under mild conditions (r.t.). It can be applied to iodoarene substrates with different alkyl chains by tuning stoichiometric ratios and reaction time parameters, with isolated yields above 75% in each case. In all cases, no side products from transhalogenation or dehalogenation reactions were observed. We believe that many fields of application employing functionalized hydroquinone cores will benefit the disclosure of sophisticated molecular architectures from such a protocol, including pharmaceuticals, functional organic polymers or liquid crystals to name a few.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.132.

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5. These halogenated substrates are conveniently prepared by exhaustive alkylation of hydroquinone followed by iodination (see Supporting Information). They can be used directly as monomers in the polymerization process (e.g.: PPs and PPVs), or they can be further functionalized with triple bonds (e.g.: PPEs, and PPEVs).
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11. Yields are here percentages of conversion of 3.
12. If one mole of a difunctional species (AA) reacts with n moles of a monofunctional one (B), in the hypothesis of a fully statistic behavior, the reaction mixture will be composed by $(n/2)^2$% of bis-reacted product, $[1-(n/2)]^2$% of starting reagent (AA) and $2[n/2(1-n/2)]$% of mono-reacted product.
13. An easy rationale for this route can be given by the different extent of activation offered to the phenoxide nucleophile by the –OH (lower effect) and the–OR (higher effect) group, respectively, in the first and second nucleophilic event.
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17. Under electrophilic conditions the iodo moiety can be lost because of protodeiodination reactions, resulting in transhalogenation or dehalogenation side processes Waldvogel, S. R. *Sci. Syn., Knowledge Updates* **2010**, *1*, 487–498. However, we did not observe the formation of products other than the monodealkylated and the fully dealkylated hydroquinone.
18. Dealkylation yields are given as percentages of conversion of 1.
19. Higher stabilization offered to the ylide adduct (Scheme 2) by –OR (electron-donor) in the first cleavage event, with respect to –OBBr2 (electron-withdrawing), in the second cleavage event, might explain this evidence.
20. Conjugated polymers featuring hexadecyl side chains exhibit peculiar surfactant properties (Li, S.; Qin, Y.; Shi, J.; Guo, Z.-X.; Li, Y.; Zhu, D. *Chem. Mater.* **2005**, *17*, 130–135. and behaviour in the solid state (Ref. 6a).