How Attractive is Bromine as a Protecting Group in Aromatic Chemistry?

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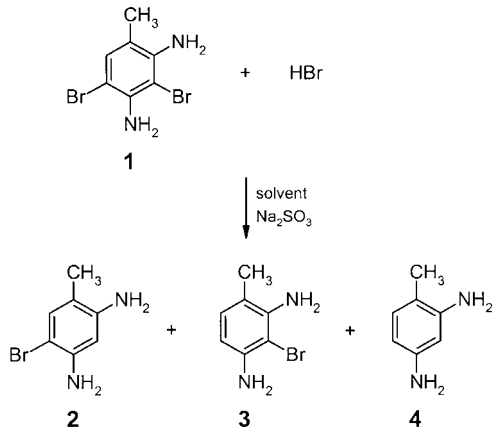
The bromination of aromatic systems belongs to the best investigated reactions in organic chemistry. Kekulé had already concluded from the bromination of bromobenzene, which yielded only three and not four isomeric dibromobenzenes, that fast fluctuating double bonds were present in benzene rings. The bromination of aromatic compounds in both the laboratory and industry is straightforward: the bromoarenes expected from substitution rules can be readily obtained in good yields under common bromination conditions. Hence bromination is regarded as being irreversible. Similar investigations that previously confirmed that alkylation and sulfonation are reversible have attracted little attention up to now regarding the reversibility of the halogenation[1] and acylation[2] of aromatic compounds.

In a recent publication[3] Choi and Chi reported on interesting synthetic applications based on the reversibility of arene bromination. The authors describe in particular two aspects of the reversibility in an application: first, the possibility of a selective protodebromination in the presence of a "scavenger" of bromine, for example, sodium sulfite (Scheme 1), and second, the utilization of bromine as a protecting group in reactions of aromatic compounds (Scheme 2).

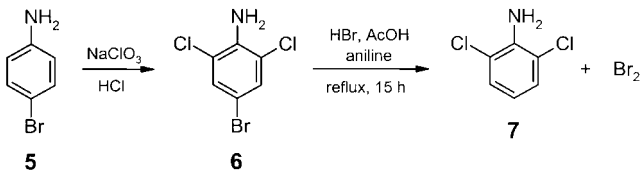


Scheme 1. Protodebromination of aromatic systems using HBr in the presence of Na_2SO_3 as a scavenger of bromine.

The protodebromination of **1**, for example, which proceeds with total yields of greater than 90%, gives the completely dehalogenated compound **4** at longer reaction times. Of the primarily formed monobrominated products **2** and **3** which are obtained at shorter reaction times, **3** reacts more rapidly than **2** to give **4**. Thus, compound **2**, as well as the already formed **4**, is selectively accessible.

The stabilities of the intermediate σ complexes are decisive in the rates of bromine elimination in these protodebrominations, which represent the back reaction of the electrophilic aromatic bromination; that is, the known rules of electrophilic aromatic substitution are also valid for the selectivity of bromine elimination. Thus, as expected, 2,3,4,6-tetrabromoaniline was protodebrominated exclusively to yield 3-bromoaniline as a stable end product.[3]

A prerequisite for the application of bromine as a protecting group in arene reactions as proposed by Choi and Chi[3] is the removal of cationic bromine from the primarily formed σ complexes. An example of bromine being used as a protecting group is given by the preparation of 2,6-dichloroaniline (Scheme 2),[3] which is generally synthesized from



Scheme 2. Utilization of bromine as a protecting group in the selective preparation of substituted aromatic compounds.

4-aminobenzoic acid by dichlorination followed by decarboxylation.[4] It would be particularly advantageous for the application of bromine as a protecting group if the eliminated bromine could be transferred to the scavenger to reform the starting compound, for example, **5**. This possibility is not mentioned by the authors.

The use of bromine as a protecting group in arene chemistry instead of SO_3H, NO_2, COOH, or *tert*-butyl is an interesting alternative for the selective preparation of specially substituted aromatic compounds. The advantages of bromine as a protecting group are:

- One or more bromo substituents can be introduced in aromatic compounds without problems.

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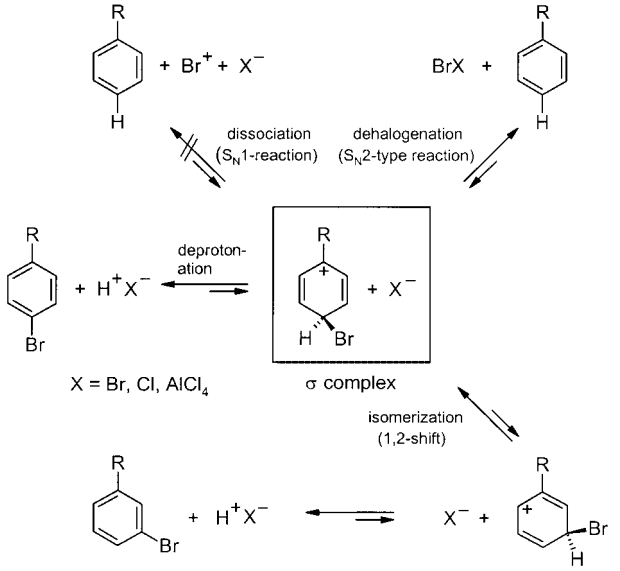
- The lower deactivating effect of bromine in contrast to other typically used protecting groups (SO_3H, NO_2, COOH) enables the more facile electrophilic introduction of additional substituents.
- Debromination occurs under typical electrophilic conditions, and hence it is also applicable in the presence of acceptor groups, which is not the case in the commonly applied reductive debrominations.

The reversibility of electrophilic arene bromination has been reported in earlier publications,[5, 6] however, the application of bromine as a protecting group was not indicated in these papers. In the following text, all the important experimental results[3, 5, 6] obtained using bromine as a protecting group in aromatic chemistry are interpreted mechanistically (Scheme 3).



Scheme 3. Possible follow-up reactions of aromatic bromo–σ complexes.

In the examples described so far, reversibility was only observed in the bromination of activated aromatic compounds such as phenols (R = OH) or aminobenzenes (R = NH_2). Hence, the bromoarene must be as electron-rich as these compounds since protonation of the σ complex occurs to a sufficient extent. Consequently, bromine is removed selectively in the position *ortho* or *para*, respectively, to the electron-donating groups OH or NH_2, whereas bromine in a *meta* position is unaffected (see the preparation of 3-bromoaniline from tetrabromoaniline).[3]

While the influence of the substituent R on the protonation step is generally known, this is not the case for the decisive influence the anion X^- has on follow-up reactions of the bromo–σ complexes. Besides deprotonation, an aromatic σ complex can in principle react by 1) dissociation by a S_N1 reaction, 2) nucleophilic removal of the introduced electrophile by anion attack ("S_N2-type"), and 3) isomerization (Scheme 3).

Whereas a dissociation (S_N1-type) can be excluded for bromo–σ complexes because of the instability of bromo cations, the elimination of isopropyl, *tert*-butyl, or sulfonic acid protecting groups follows this mechanism. An elimination of bromine by nucleophiles (S_N2-type reaction) strongly depends on the nucleophilicity of the anion X^- ($Br^- > Cl^- \gg AlCl_4^-$). Therefore, removal of bromine is either not observed[3] or markedly suppressed[5, 6] by replacing HBr by HCl. Bromine is not removed at all with extremely weak nucleophiles (for example, $AlCl_4^-$), but an intramolecular 1,2-shift (isomerization) occurs. Although isomerization of halogenated aromatic and heteroaromatic compounds, via cationic σ complexes could be of great synthetic potential, very little is known about this reaction. On the contrary, the isomerization of methyl–σ complexes is not only well-known but is also applied in a technical process. Thus, the methylation of toluene with $AlCl_3$ as a catalyst ($X^- = AlCl_4^-$) at lower temperature affords mainly *ortho*- and *para*-xylene, at higher temperature the kinetically more stable *meta*-xylene is formed exclusively.

The potential of bromine as a versatile protecting group in aromatic chemistry can impressively be demonstrated, for example, in the preparation of 3-bromothiophene, an important building block for many pharmaceuticals. The synthesis of 3-bromothiophene is almost exclusively described by reductive dehalogenation of 2,3,5-tribromothiophene. A very efficient alternative route to 3-bromothiophene described recently is by an isomerization (Scheme 3) of the readily available 2-bromothiophene by means of Fe^{III}-covered zeolites.[7] The protodebromination developed by Choi and Chi should prove to be an interesting alternative to the reductive dehalogenation.

This short overview on the fundamentals of the reversibility of electrophilic aromatic bromination achieves its objective if it motivates researchers to apply this very useful method to a greater extent in preparative aromatic chemistry.

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