A Facile Debromination Reaction: Can Bromide Now Be Used as a Protective Group in Aromatic Systems?

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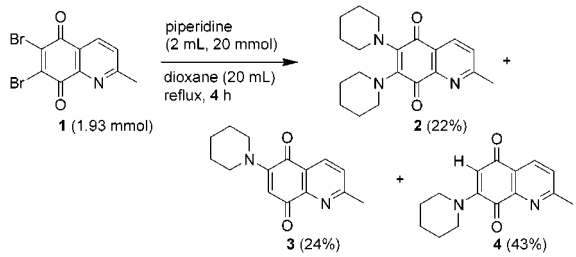
Bromine as an aromatic substituent is very useful as a site for further substitution, using palladium-catalyzed and other aromatic substitution strategies. However, because the replacement of an aromatic bromine by hydrogen generally requires rather harsh ionic, catalytic, or radical reduction conditions, this group is generally not considered useful as a protecting group. During a recent study of quinoline-5,8-dione chemistry,[1,2] we have encountered a facile debromination reaction of an olefinic bromide (shown in Scheme 1), that led to the investigations described herein, through which we have developed useful methods by which bromine can be used as a protective group in aromatic systems.

In our first experience with this debromination process (Scheme 1), we thought that the HBr, produced during the amination of dibromoquinaldine-5,8-dione, might be playing an important role in the debromination process. In fact, when the debromination of 6-bromo-7-piperidinoquinaldine-5,8-dione was tested in the presence of concentrated HBr in dioxane (Scheme 2), we were able to obtain the debrominated product in 85% yield, under optimized conditions. When we tested the debromination reaction of 2,4-dibromoaniline with concentrated HBr in refluxing acetic acid for 4 h, disproportionation products (2,4,6-tribromoaniline, 15.2%; 2,4,6-tribromoacetanilide, 0.6%; 2,4-dibromoaniline, 59.6%; 2,4-dibromoacetanilide, 1.5%; 2,6-dibromoaniline, 0.6%; 4-bromoaniline, 17.9%; 2-bromoaniline, 2.2%) were isolated.

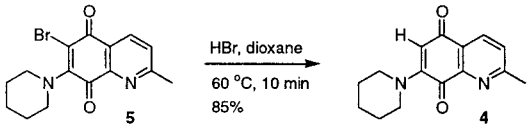
We have found only a few reports on these kinds of isomerizations and disproportionations of bromophenol,[3,4] anisol,[4] aniline,[4] and pyrrole[5] systems in the literature. The process of arene bromination and debromination is reversible, but typically, bromination predominates over debromination to a very great extent (Scheme 3). Questions that are key in assessing the potential utility of reversing this bromination−debromination equilibrium are: (1) is it possible to shift the equilibrium toward debromination by using a scavenger of bromine? and (2) if this reversal can be achieved, can bromide then be used as a protecting group in aromatic systems?

To investigate the first issue, we tested the debromination of the much more activated 2,4-diamino-3,5-dibromotoluene, using either sodium sulfite, aniline, or phenol as a scavenger of bromine (Table 1). Under optimized conditions, one of the bromines was removed within 10 min and the other bromine within 4 h (entry 6). Debromination proceeded more rapidly with higher boiling and more strongly acidic solvents, but debromination was slower with anhydrous HBr than with concentrated HBr (entries 1−5). The debromination reaction did not proceed at all in concentrated HCl (entry 8) or under a neutral condition (entry 10), and only side products were obtained in concentrated HI (entry 9). As a result of these investigations, we selected concentrated HBr/AcOH as a solvent and sodium sulfite as a scavenger for reducing bromine to bromide.

Scheme 1



Scheme 2



Scheme 3

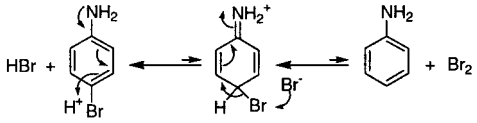
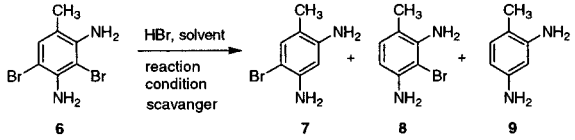


Table 1. Debrominations of 2,4-Diamino-3,5-dibromotoluene in Various Reaction Conditions



entry	solvent	reagent[a]	time[b]	scavenger[c] (equiv)	yield (%)[e] 6[d]	7	8	9	total
1	MeOH	HBr	50 min	A (11)	0	54	40	0	94
2	EtOH	HBr	50 min	A (11)	0	55	27	16	98
3	AcOH	HBr	50 min	A (11)	0	47	0	48	95
4	HBr	HBr	50 min	A (11)	0	22	0	76	98
5	AcOH	HBr	50 min	A (11)	62	22	10	3	97
6	AcOH	HBr	4 h	A (11)	0	0	0	95	95
7	AcOH	HBr	10 min	A (11)	0	59	0	28	87
8	AcOH	HCl	10 min	A (11)	100	0	0	0	100
9	AcOH	HI	10 min	A (11)	0	0	0	0	0
10	EtOH	NaBr	30 min	A (11)	100	0	0	0	100
11	AcOH	HBr	4 h	B (11)	0	0	0	70	70

[a] Concentrated acid used except in entries 5 (dry HBr) and 10. [b] At reflux. [c] A = Na_2SO_3, B = aniline. [d] Recovered. [e] Isolated yield.

Regarding the potential of using aromatic bromine as a protecting group, it is worth noting that generally aromatic bromide is converted back to hydrogen by various reducing agents such as metal hydride[6−8] or catalytic hydrogenation[9] etc., and that these reductions have the following selectivities: (1) no selectivity between bromide and NO_2, COOH, and other halogen,[7a,b,8a,9a−c] (2) I > Br > Cl,[7b−e,8b−d,9a,d,e,10a,b] (3) X in EWG-arenes > EDG-arenes,[7b,c,f,10a,b] (4) *o*-X > *p*-X.[7b,c,f,10a,b]

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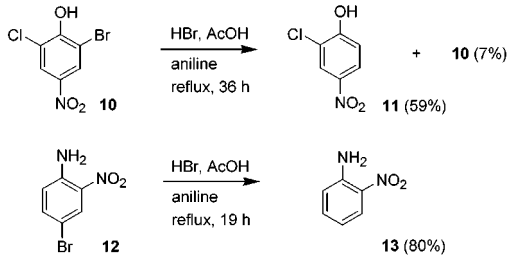
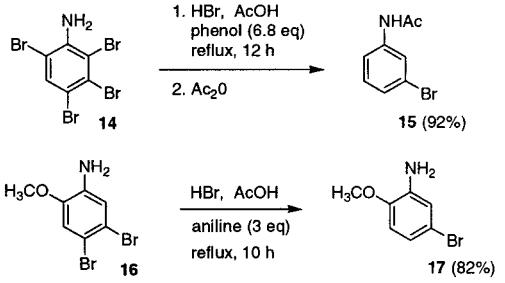
Scheme 4



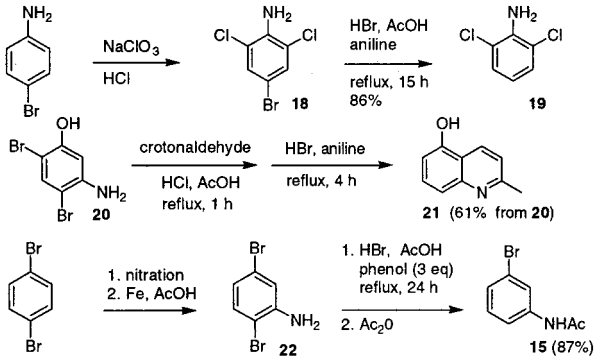
Scheme 5



We investigated the substituent selectivities of debromination in some compounds, and the results, shown in Scheme 4, illustrate one of the most attractive aspects of HBr as a reducing agent: by our method, we can remove bromine without affecting other reducible groups, such as the nitro group or chloride. To the best of our knowledge, this has not been reported before.

Scheme 5 shows another attractive aspect of HBr as a reducing agent: in a highly brominated aniline, only the *o*,*p*-bromines were selectively reduced; the bromine that was meta with respect to the electron-donating group was unaffected. To our knowledge, such a regioselective debromination has not been achieved. The selective processes for the preparation of ortho- or para-substituted aromatic compounds are of great interest in organic chemistry. However, there is always a chance of getting an isomeric mixture of ortho- or para-substituted products. To avoid this intrinsic problem, protective groups such as sulfonic acid and carboxylic acid are typically used, thus allowing a substituted compound in the desired position to be obtained after desulfonylation or decarboxylation.[11]

Scheme 6



We tried to apply our bromine protecting−reductive debromination deprotecting approach to the synthesis of some compounds which are normally considered difficult to prepare. As shown in Scheme 6, we found that 2,6-dichloroaniline, which is generally prepared from an aminocarboxylic acid by dichlorination followed by decarboxylation,[10] could be readily prepared by substituent-selective debromination. In a second example, 5-hydroxyquinaldine was prepared from protected dibromohydroxyaniline with bromine using a Skraup reaction, followed by deprotection of bromine with HBr. Since the Skraup reaction of 3-hydroxyaniline with crotonaldehyde produces 7-hydroxyquinaldine as the major product along with 5-hydroxyquinaldine as the minor one, it has not been easy to prepare 5-hydroxyquinaldine. In the last example, 3-bromoaniline, which cannot be prepared directly from aniline, was prepared by regioselective debromination from *p*-dibromobenzene.

In conclusion, although this acid-catalyzed, bromine-scavenging debromination requires a high temperature and a stability of compounds toward HBr, it should prove to be very useful. The method is inexpensive, easy to handle, selective against another reducible groups, and regioselective (with *o*,*p*-debromination proceeding in preference to *m*-bromination with electron-donating systems). It is hoped that this work, which demonstrates that the bromination−debromination equilibrium can be shifted toward debromination using a scavenger of bromine, will lead to the greater use of bromine as a protecting group in aromatic systems and will facilitate the preparation of many aromatic systems.

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Supporting Information Available: Experimental procedures including characterization of all compounds (PDF). This material is available free of charge via a Internet at http://pubs.acs.org.

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