Radical Reactions

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Radical Hydrodehalogenation of Aryl Bromides and Chlorides with Sodium Hydride and 1,4-Dioxane

*Tobias Hokamp, Abhishek Dewanji, Maximilian Lübbesmeyer, Christian Mück-Lichtenfeld, Ernst-Ulrich Würthwein, and Armido Studer**

Abstract: *A practical method for radical chain reduction of various aryl bromides and chlorides is introduced. The thermal process uses NaH and 1,4-dioxane as reagents and 1,10-phenanthroline as an initiator. Hydrodehalogenation can be combined with typical cyclization reactions, proving the nature of the radical mechanism. These chain reactions proceed by electron catalysis. DFT calculations and mechanistic studies support the suggested mechanism.*

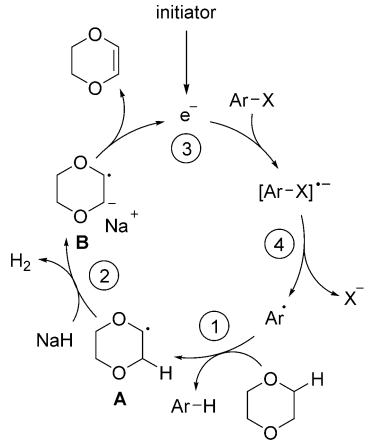
An important task for chemists is the development of simple and cost-efficient processes. Therefore, discovering new reactivity for established and cheap textbook reagents is of great interest. Sodium hydride (NaH) is a versatile and cheap reagent that has been heavily used.[1] It is readily stored and commonly used as a Brønsted base.[1] NaH has also found application as a reducing reagent, albeit less frequently. Hence, non-enolizable carbonyl compounds,[2] disulfides,[3] aryl iodides,[4] benzylic halides,[5] and *gem*-dihalocyclopropanes[6] can be reduced by NaH.

Recently, the Chiba group extended the application frame to the reduction of nitriles, amides, and imines.[7] They also applied NaH to the ionic hydrodebromination of aryl bromides,[8a] and to amide-directed C–H sodiation.[8b] This unprecedented NaH reactivity is induced by the addition of LiI or NaI in a stoichiometric or super-stoichiometric amount.

Radical hydrodehalogenation has been studied intensively since it occurs under mild conditions and shows higher functional group compatibility than metal–halogen exchange processes[9] and other metal-mediated transformations.[10] The radical approach allows the hydrodehalogenation to be combined with a C–C bond-forming step. Radical chain reducing reagents developed include tin hydrides,[11] silanes,[12] silylated cyclohexadienes,[13] N-heterocyclic carbene–borane complexes,[14] sodium alcoholates,[15] and catechols[16] among others. However, these compounds are either toxic or hazardous, or are not commercially available and hence must be generated prior to use.

Herein we present radical hydrodehalogenation using 1,4-dioxane as a solvent in combination with cheap NaH as a base. We show that these reductions proceed via radical chain processes under electron catalysis.[17]

Our design was based on the following facts: a) a C–H bond is acidified by an adjacent C radical center by up to 25 p*K*a units;[18] b) 1,4-dioxane is an efficient H-atom donor for reactive aryl radicals; and c) aryl radicals are readily generated from aryl halides by single-electron reduction. These facts led us to propose the working model depicted in Scheme 1. An aryl radical (Ar•) generated upon single-electron-transfer (SET) reduction in the initiation step is reduced by 1,4-dioxane to give the target Ar–H along with the dioxanyl radical **A** (step 1). **A** might be deprotonated by NaH to give radical anion **B** (step 2), which should further react as a very strong reducing agent with 1,4-dioxene with formal liberation of an electron.[17a] The reduction potential of 1,4-dioxene was measured to be below −2.7 V vs. ferrocene (see the Supporting Information) documenting the reductive strength of its radical anion. Note that deprotonation could also be achieved by other bases and NaH was chosen because it is readily available and cheap. SET reduction of the substrate aryl halide (step 3) proceeds to provide the corresponding aryl halide radical anion, which upon halide fragmentation leads to the aryl radical (Ar•) completing the cycle (step 4).[19]



Scheme 1. Working model.

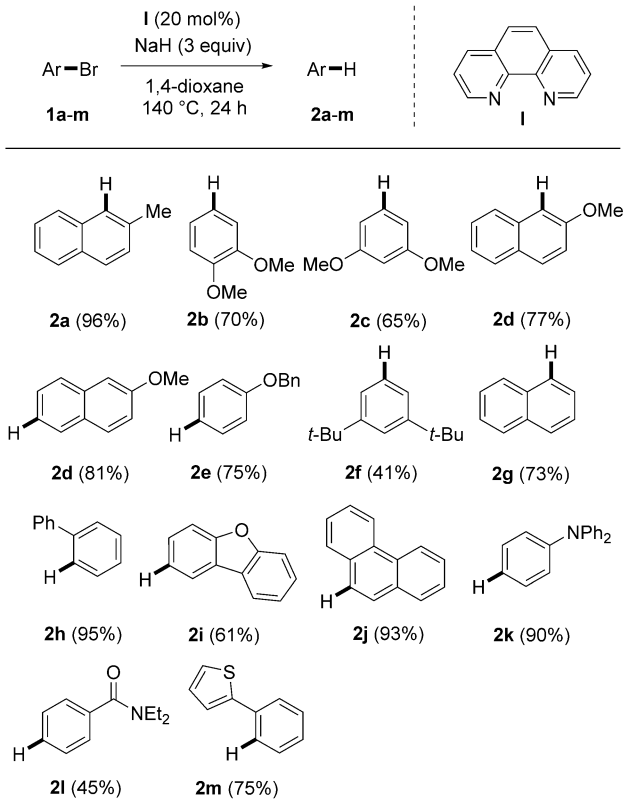
[*] T. Hokamp, Dr. A. Dewanji, M. Lübbesmeyer, Dr. C. Mück-Lichtenfeld, Prof. Dr. E.-U. Würthwein, Prof. Dr. A. Studer
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität
Corrensstraße 40, 48149 Münster (Germany)
E-mail: studer@uni-muenster.de
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201706534.

We first addressed the proposed electron transfer cycle, including the key deprotonation step from **A** to **B,** with DFT calculations for Ar = Ph including solvent effects implicitly (B2PLYP-D3/def2-TZVP(PCM-1,4-dioxane), see the Supporting Information for details). 1,4-Dioxane acts as a strong hydrogen atom donor to the aryl radical, generating **A** and the product arene (for step 1, $\Delta G = -17.7$ kcal mol^{-1}). The deprotonation of **A** by hydride anion (step 2) is exothermic ($\Delta G = -8.7$ kcal mol^{-1}), as is the electron transfer to the aryl halide (step 3, -45.3 kcal mol^{-1} for PhBr, -36.6 kcal mol^{-1} for PhCl, -13.7 kcal mol^{-1} for PhF). The radical anions $ArX^{\bullet-}$ (X = Cl, Br) resemble complexes of the aryl radical with the respective halide ions and are in equilibrium with the free radical (step 4, $\Delta G_{diss} = -5.0$ kcal mol^{-1} for PhBr, -4.8 kcal mol^{-1} for PhCl), whereas the structure of the radical anion $PhF^{\bullet-}$ is similar to that of PhF with $\Delta G_{diss} = 9.4$ kcal mol^{-1}. The total free energy change along the complete cycle ($-76.6/-67.8/-36.2$ kcal mol^{-1} for PhBr/PhCl/PhF, respectively) indicates the strong driving force of the reaction, especially for the bromide species, which compensates other contributions not covered here, for example, the lattice energies of NaH vs. NaX.

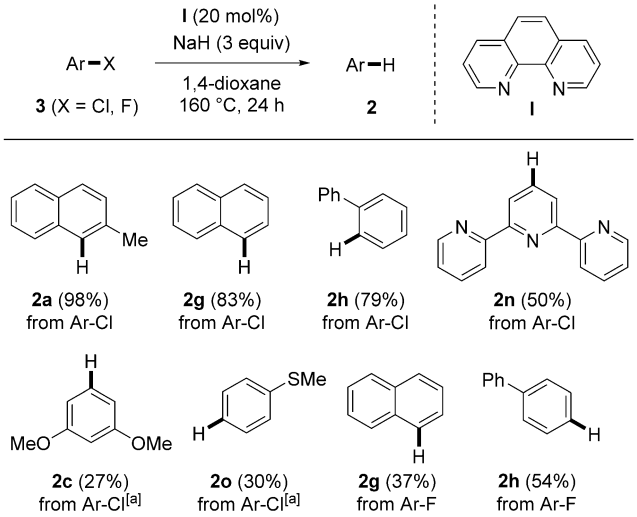
Motivated by the theoretical results, we chose 1-bromo-2-methylnaphthalene (**1a**) as a test substrate and 1,10-phenanthroline as an initiator.[20] The best result was achieved by treatment of **1a** with 1,10-phenanthroline (20 mol%) and NaH (3 equiv) in 1,4-dioxane at 140 °C for 24 hours, and 2-methylnaphthalene (**2a**) was obtained in 96% yield (Scheme 2). Other initiators and ethers tested provided worse results (see the Supporting Information). Attempted reduction in the absence of the radical initiator did not provide **2a**, indicating that the process is likely radical in nature. The reaction also proceeds smoothly, albeit less efficiently, when KO*t*Bu is used as a base, confirming the hydride's main role as a base.

The reaction scope was explored next: Electron-rich dimethoxy-substituted bromobenzenes provided the arenes **2b** (70%) and **2c** (65%) in good yields. Methoxy-substituted bromonaphthalenes reacted with similar efficiency to give **2d** (77% and 81%). Switching from methyl to benzyl ethers did not affect the outcome (**2e**, 75%). However, a significantly lower yield was achieved for the reduction of 1-bromo-3,5-di-*tert*-butylbenzene to **2f**. Product **2g** was isolated in 73% yield from 1-bromonaphthalene, and 2-bromobiphenyl was reduced to **2h** (95%). Compound **2i** was obtained in good yield (61%) from 2-bromodibenzofuran (**1i**) and 9-bromophenanthrene (**1j**) yielded phenanthrene (**2j**, 93%). 4-Bromo-*N*,*N*-diphenylaniline **1k** furnished triphenyl amine (**2k**, 90%), but the reaction of the electron-poorer 4-bromobenzamide (**1l**) was significantly lower yielding (**2l**, 45%). This is likely because the Br fragmentation is less efficient due to the increased stability of the intermediate aryl radical anion.[21] Our method was also applicable to the heteroarene **1m** to give 2-phenylthiophene (**2m**, 75%).[22]

Due to the stronger C–Cl bond, reduction of chloroarenes is more challenging and only few reports have appeared.[23] Pleasingly, at 160 °C hydrodechlorination occurred smoothly and **2a** was isolated in 98% yield (Scheme 3). High yields were achieved for the reduction of **3g** (83%) and **3h** (79%),



Scheme 2. Substrate scope of the hydrodebromination. Reactions were carried out under argon atmosphere with 0.3 mmol of **1**, 0.9 mmol of NaH, and 0.06 mmol of **I** in 1,4-dioxane (3.0 mL). Yield of isolated product given.

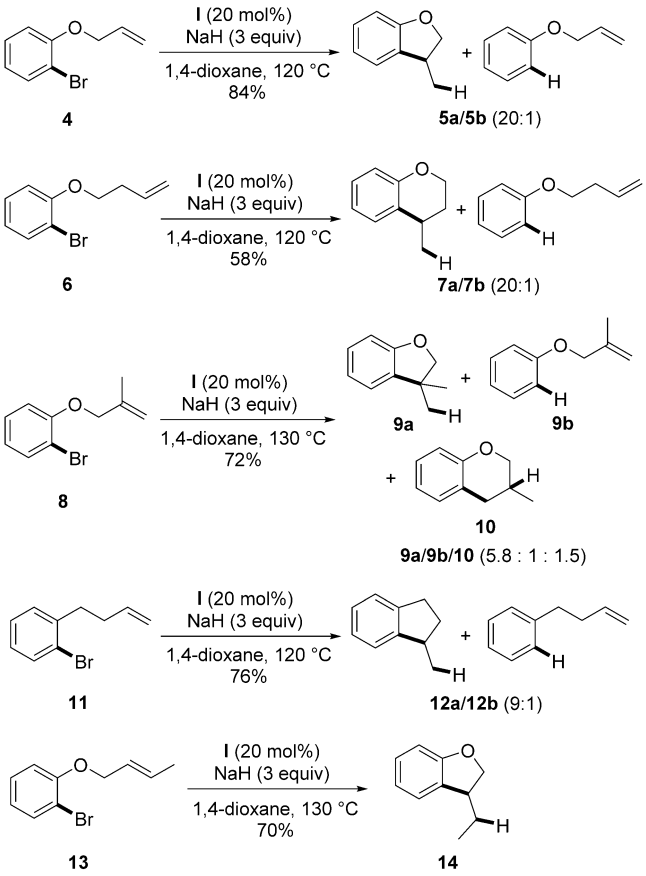


Scheme 3. Hydrodechlorination and hydrodefluorination (20 mol% of **I** for chlorides and 40 mol% **I** for fluorides). Yield of isolated product given. [a] 20 mol% of additional **I** added after 6 h.

and reduction of **3n** afforded terpyridine (**2n**, 50%). However, the more electron-rich chloroarenes did not show good reactivity, and products **2c** and **2o** were isolated in moderate yields. Although the hydrodechlorination was not as efficient

and general as the hydrodebromination, we were encouraged to tackle fluoroarenes. For two selected examples we managed the highly challenging C–F bond cleavage: 1-fluoronaphthalene and 4-fluorobiphenyl afforded the corresponding products **2g** and **2h** in 37% and 54% yield.

One advantage of the radical hydrodehalogenation over the ionic NaH reduction[8a] is that the radical chain process can be combined with a cyclization reaction, and therefore we studied the reductive cyclization of bromide **4** to **5a** (Scheme 4). At 140°C we found that a NaH-promoted

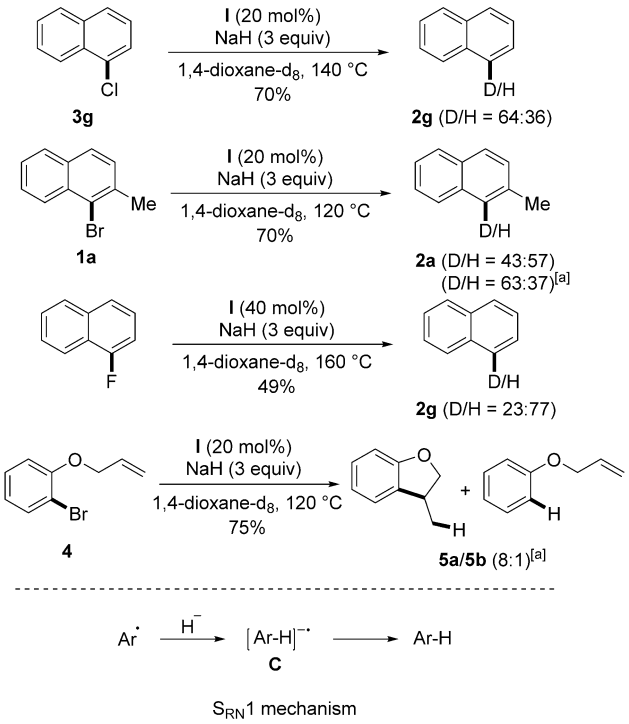


Scheme 4. Reductive radical cyclizations.

isomerization of the double bond in **4** occurred prior to the hydrodebromination, and phenyl prop-1-en-1-yl ether was formed (*E*/*Z* mixture). However, at 120°C, double-bond isomerization was suppressed and **5a** was isolated in 84% yield as mixture with the direct reduction product **5b**.

In analogy, **6** was converted to dihydrobenzopyran **7a** which was formed along with the direct reduction product **7b**. Allyloxybenzene **8** reacted at 130°C via reductive 5-*exo*-cyclization to **9a**. The 6-*endo*-product **10** and the noncyclized product **9b** were formed in significant amounts. Reaction of bromide **11** provided cyclization product **12a** and its noncyclized isomer **12b** (76%). Finally, substrate **13** containing an internal alkene furnished exclusively the *exo*-cyclization product **14** (70%). Reductive cyclizations with chloroarenes were lower yielding: **11**-Cl provided the cyclization products **12a**,**b** in 41% yield along with unreacted starting material.

To verify the source of the H atom, we reacted 1-chloronaphthalene (**3g**), 1-bromo-2-methylnaphthalene (**1a**), and 1-fluoronaphthalene with NaH in 1,4-dioxane-d_8. In all cases, deuteration of products **2g** and **2a** was not complete (Scheme 5). On the one hand, these experiments show that



Scheme 5. Deuterodehalogenation in perdeuterated dioxane. [a] NaH was washed with hexane to remove mineral oil.

intermediate aryl radicals are partially reduced via D-atom abstraction from the solvent, in agreement with the suggested mechanism (Scheme 1). On the other hand, these experiments also indicate that other H sources have to be considered such as NaH. We therefore replaced NaH with KO*t*Bu and found for the deuterodehalogenation of **1a** a D/H-ratio of 87:13 in **2a** (see the Supporting Information). We ascribe the hydrogen content to residual hydrogen in the perdeuterated dioxane (approx. 1%) considering isotope effects. Additional H incorporation might derive from the mineral oil in which the NaH is dispersed. When **1a** is reacted with prewashed NaH, the amount of D incorporation increases slightly, indicating that the mineral oil is a minor H source. Therefore, we assume that the hydride may act as a H source likely via an $S_{RN}1$-type process[24] where the hydride in an unprecedented way acts as a nucleophile to trap the C radical to form the corresponding radical anion **C**, which upon oxidation leads to the isolated hydrodehalogenation product (Scheme 5, bottom). This is further supported by the reductive cyclization of **4** in 1,4-dioxane-d_8 where no D incorporation was observed. For reduction of fluoronaphthalene, which had to be conducted at much higher temperature, an aromatic nucleophilic substitution by the hydride cannot

be ruled out. 1,4-Dioxene suggested as a byproduct could not be traced due to its instability under the applied conditions.

In summary, a method for radical chain reduction of various aryl bromides was introduced. NaH and 1,4-dioxane act as a reagent couple for the hydrodehalogenation. Both reagents are cheap and commercially available. The method is also applicable to the more challenging reduction of aryl chlorides, and even selected aryl fluorides can be reduced. Harnessing the potential of radical chemistry, it was also shown that reductive cyclization can be achieved with this novel approach.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: hydrodehalogenation · radical anions · sodium hydride · $S_{RN}1$ reactions

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