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Research Article

Radical Reduction of Alkyl and Aryl Halides under Mechanochemical Conditions

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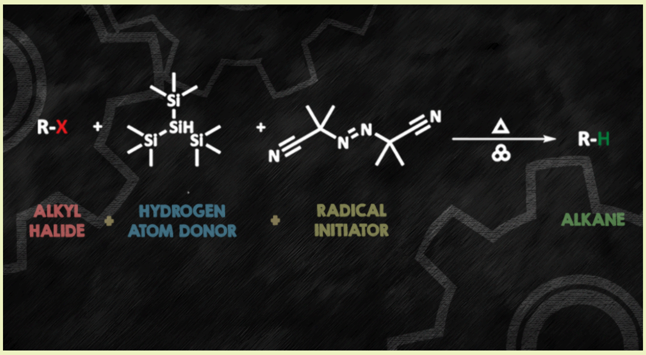
ABSTRACT: Herein, we report a novel method for solvent-free reduction of alkyl and aryl halides under mechanochemical conditions. Reduction reactions were performed by using various alkyl and aryl halides in the presence of different radical initiators and hydrogen atom donors at elevated temperatures. Although we think the mechanism for the reaction under mechanochemical conditions is similar to that observed in solution, we observed a few differences. We found that tris(trimethylsilyl)silane-mediated reductions using AIBN as an initiator gave the highest yields. To the best of our knowledge, this reports the first use of mechanochemistry as a benign tool to perform reduction reactions of alkyl and aryl halides.



KEYWORDS: *green chemistry, solvent-free, organosilanes, mechanochemistry, radical reduction*

INTRODUCTION

There are numerous free-radical reactions in chemistry; however, the reduction of alkyl and aryl halides is one of the most common synthetic transformations which are widely applicable in various synthetic processes.[1,2] For several decades, one of the most commonly used hydrogen atom donors is organotin hydrides (Scheme 1). Of them, tributyltin hydride is highly used in large-scale industries because of its high efficiency. However, these classes of molecules are acutely toxic to living organisms and are known environmental toxins.[3−5] Also, the reduction products are frequently contaminated with organotin complexes, which prohibits them to be used in pharmaceutical synthesis.[6] In addition to the environmental concerns with hydrogen atom donors, the solvents with which many of these reactions are conducted are problematic as well. Because the solvent needs to be inert to radical chemistry, solvents used to conduct these reactions are limited.[7−10] One solvent that has been widely used in radical chemistry is benzene. Benzene is known to cause various health complications, both short term such as eye, skin, and respiratory tract irritation and long term such as reduced number of red blood cells and various complications in blood in humans.[11,12] Therefore, when it is possible, alternative methods should be used to limit or eliminate the usage of these solvents in synthetic transformations.

Scheme 1. Reduction of Alkyl Halides Using Organotin Hydrides

$$\text{R-X} + \text{R'-Sn-H} \longrightarrow \text{R-H} + \text{R'-Sn-X} \quad \text{where R'-Sn-H} = \left[CH_3(CH_2)_3\right]_3\text{SnH} \qquad (1)$$

Mechanochemistry has been shown to be a simple and solvent-free alternative for reactions that are problematic in solution.[13−16] Therefore, the ability to conduct radical reactions under mechanochemical conditions may solve many of these environmental concerns. Furthermore, it was thought that, given the high concentration of the process, we may observe more radical coupling products than those typically observed in solution. We present a solvent-free environmentally benign method to perform the reduction of alkyl and arylhalides under mechanochemical conditions (Scheme 6).

RESULTS AND DISCUSSION

We started our studies with the radical reduction of *p*-bromobenzyl bromide, using 2,2′-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (VA-044) as the radical initiator and sodium hypophosphite monohydrate as the hydrogen atom donor (Scheme 2a).[17−19] We thought that using a low-temperature water-soluble initiator and a water-soluble hydrogen atom donor would allow the ability to develop isolation conditions where we could isolate our potential products via a water wash. Upon milling for extended periods of time at 45 °C

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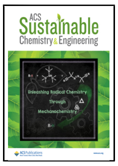

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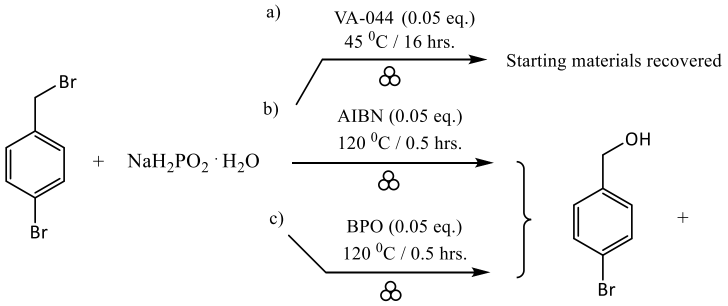
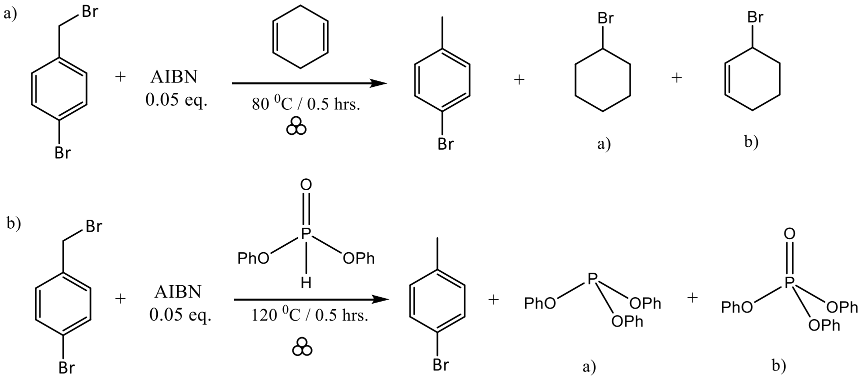
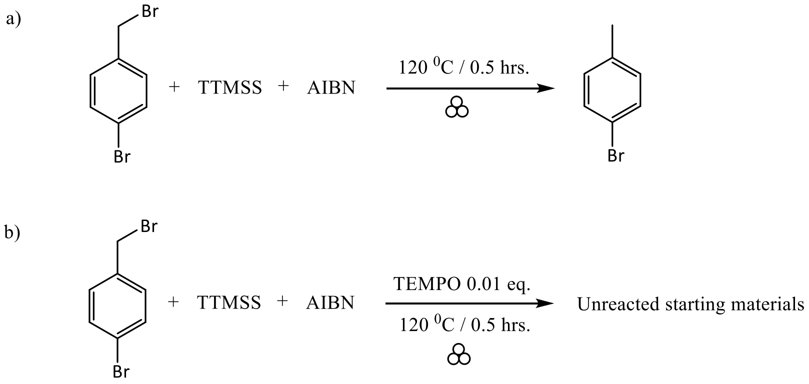
Scheme 2. Reaction between *p*-Bromobenzyl Bromide with Sodium Hypophosphite Monohydrate Using (a) 2,2′-Azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride, (b) Azobisisobutyronitrile, and (c) Benzoyl Peroxide as Radical Initiators under Mechanochemical Conditions



Scheme 3. Reaction between *p*-Bromobenzyl Bromide with (a) 1,4-Cyclohexadiene and (b) Diphenyl Phosphite as Hydrogen Atom Donors in the Presence of Azobisisobutyronitrile as a Radical Initiator under Mechanochemical Conditions



Scheme 4. (a) Reduction of *p*-Bromobenzyl Bromide Using Azobisisobutyronitrile (0.05 equiv) as the Radical Initiator and Tris(trimethylsilyl)silane as the Hydrogen Atom Donor at 120 °C for 30 min. (b) Reaction between *p*-Bromobenzyl Bromide Using Azobisisobutyronitrile as the Radical Initiator and Tris(trimethylsilyl)silane as the Hydrogen Atom Donor at 120 °C for 30 min in the Presence of 0.01 equiv of Radical Inhibitor (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl

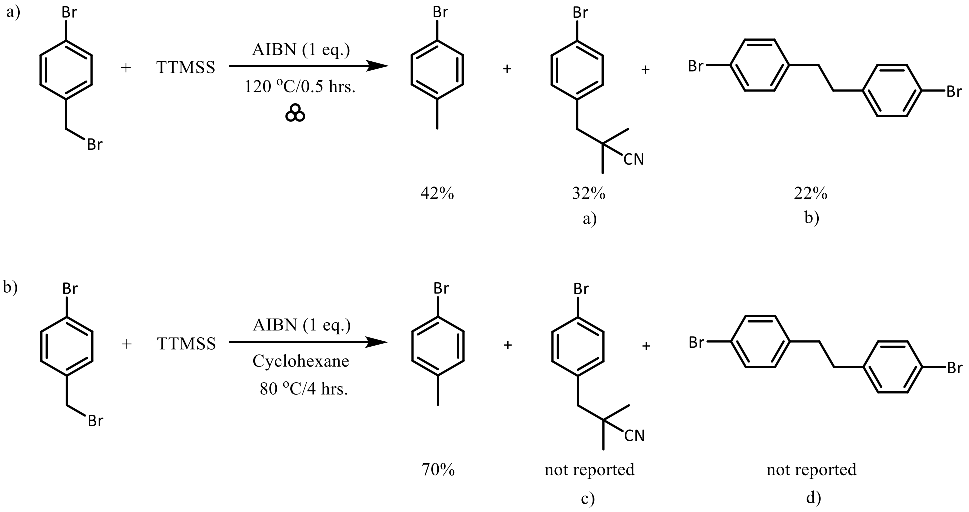


in the presence of our water-soluble initiator, we observed only unreacted starting materials. Even at increased temperatures, in the presence of azobisisobutyronitrile (AIBN) (Scheme 2b) or benzoyl peroxide (BPO) (Scheme 2c), the reduction does not occur with sodium hypophosphite monohydrate. We determined that instead of the reduced product, substrates are oxidized to the corresponding alcohol and/or aldehyde by sodium hypophosphite monohydrate.

This led us to examine other alternative hydrogen atom donors, such as 1,4-cyclohexadiene and diphenyl phosphite. Unfortunately, neither of these hydrogen atom donors provided high yields of reduced products. 1,4-cyclohexadiene participated in the reaction generating side products such as bromocyclohexane (Scheme 3a-a) and 3-bromo-cyclohexene (Scheme 3a-b), and diphenyl phosphite generated side products such as triphenyl phosphite (Scheme 3b-a) and triphenyl phosphate (Scheme 3b-b).

We next moved to organosilanes which have been demonstrated to be excellent hydrogen atom donors in solution; therefore, we wanted to determine how well they would perform under solvent-free conditions. Our initial attempt was with tris(trimethylsilyl)silane (TTMSS), which has been used in the literature as a strong hydrogen atom donor.[20] Our initial attempt in the reduction of *p*-bromobenzyl bromide was carried out using azobis(isobutyronitrile) as the radical initiator and tris(trimethylsilyl)silane as the hydrogen atom donor at 120

Scheme 5. (a) Based on ^{1}H NMR Conversions under Mechanochemical Conditions in the Presence of 1 equiv of Radical Initiator, Radical Coupling between Alkyl Radicals and 2-Cyanoisopropyl Radicals is more Prominent; (b) Based on ^{1}H NMR Conversions in Solution, Radical Coupling between Alkyl Radicals and 2-Cyanoisopropyl Radicals is Not Reported



°C for 30 min. In this mechanism, initiation occurs by generating two radicals from the initiator by thermal decomposition. These radicals abstract a hydrogen atom from organosilane to generate an organosilane radical, which propagates by abstracting a halogen radical from the alkyl/aryl halide and generating an alkyl/aryl radical. Formation of an alkane occurs when this alkyl/aryl radical abstracts a hydrogen atom from the organosilane and generates an organosilane radical. This organosilane radical can act as a radical generator to form new alkyl radicals in the propagation step. Termination occurs by radical−radical combination between two alkyl/aryl radicals, between two organosilane radicals, or between an alkyl/aryl radical and an organosilane radical.

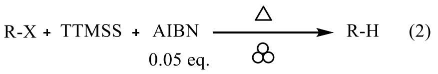
Based on the GC yield, we observed 57% of *p*-bromotoluene as the reduction product (Scheme 4a). Under the same conditions, when benzoyl peroxide was used as the radical initiator, a similar yield was obtained. However, due to its short half-life and high thermal decomposition temperature, benzoyl peroxide would not be compatible with substrates such as benzyl chloride and benzyl bromide that yield a low boiling point reduction product such as toluene. Therefore, we decided that it would be best to use azobis(isobutyronitrile) as the initiator moving forward.

After a successful conversion into *p*-bromotoluene, our objective was to understand whether the mechanism was radical in nature. Typically, these reactions follow a free-radical chain mechanism in solution.[21] To determine whether this is indeed a radical process, we conducted the same reaction in the presence of a radical inhibitor to see if this would prevent the reduction. When we conducted the reaction in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), we did not observe the expected reduction product, suggesting that the mechanism is radical in nature (Scheme 4b). We also conducted the reaction using different organosilanes such as triethylsilane. However, even though these organosilanes are cheaper alternatives, it was not a comprehensive hydrogen atom donor enough with a diverse set of alkyl halides. Therefore, we continued to use tris(trimethylsilyl)silane (TTMSS) as ahydrogen atom donor to develop our optimized conditions.

Now that we have identified the most suitable hydrogen atom donor, we wanted to determine the optimal amount of radical initiator to use in the reaction. When 1 equiv of AIBN was present, a high concentration of radicals is formed, producing products stemming from radical coupling between the alkyl radicals (Scheme 5A-a with 22%) and the 2-cyanoisopropyl radical (Scheme 5A-b with 32%) with 42% *p*-bromotoluene as the reduction product. This is compared to only seeing the reduction product in solution.

However, in some cases, we observed that in the absence of a radical initiator, we were able to reduce the alkyl halide to the corresponding alkane. This could be due to the varying stabilities of the substrate radical and the reaction temperature. However, most alkyl halides need a radical initiator under these conditions; therefore, we concluded that it was best to conduct our reactions with a radical initiator which would provide better yields. We discovered that the optimum amount of initiator for reduction was 0.05 equiv. After optimizing the reaction conditions for the reduction of alkyl halides, different substrates were subjected to reduction conditions. Reduction of alkyl halides with tris(trimethylsilyl)silane occurs, with yields ranging from 22 to 74% at 90 and 120 °C under mechanochemical conditions in the presence of 0.05 equiv of AIBN (Scheme 6).

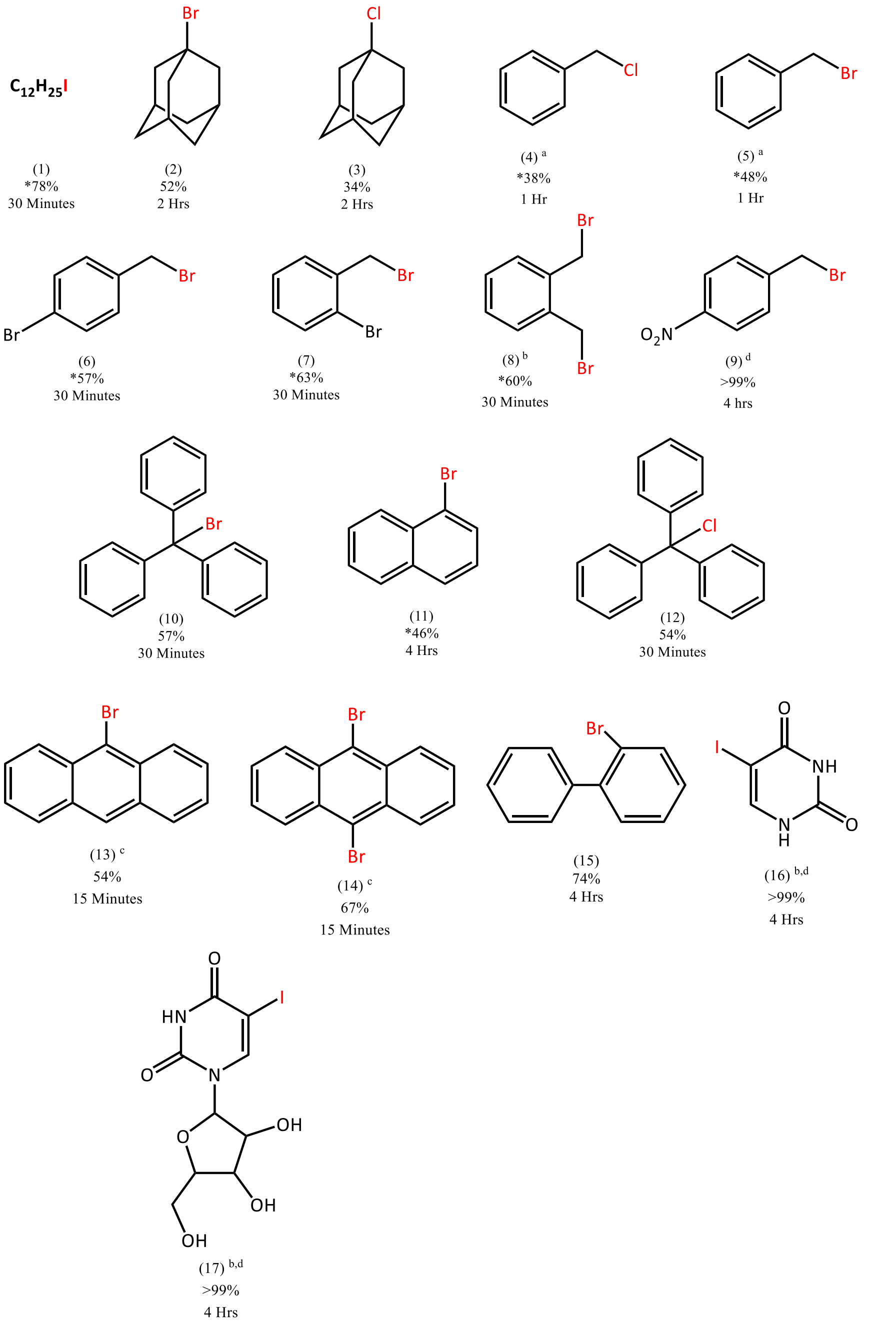
Scheme 6. Reduction of Alkyl Halides under Mechanochemical Conditions Using Tris(trimethylsilyl)silane as the Hydrogen Atom Donor in the Presence of AIBN (0.05 equiv)



$$\text{R-X} + \text{TTMSS} + \underset{0.05\ \text{eq.}}{\text{AIBN}} \xrightarrow{\triangle} \text{R-H} \qquad (2)$$

Primary alkyl halides such as dodecyl iodide (Scheme 7, entry 1) reacted within 30 min to dodecane (GC yield = 78%), and products of tertiary alkyl halides such as 1-bromoadamantane and 1-chloroadamantane (Scheme 7, entries 2 and 3) could be isolated (52 and 34% respectively) after 2 h by recrystallization. However, substrates like benzyl chloride (Scheme 7, entry 4) and benzyl bromide (Scheme 7, entry 5) undergo reduction at 90 °C within 1 h to yield toluene (GC yield = 38 and 48%, respectively). As toluene has a relatively low boiling point, in order to identify the reduction product, these substrates cannot be reduced at temperatures higher than 90 °C. A comparison is

Scheme 7. Percent Yields for the Reduction of Alkyl and Aryl Halides under Mechanochemical Conditions Using 1/8" Stainless Steel Ball and a Stainless Steel Vial



[*]GC yield for the reduction of alkyl halides. [a]Reaction was performed at 90 °C. [b]Reaction was performed in the presence of 2 equiv of TTMSS. [c]Reaction was performed in the presence of 3 equiv of TTMSS. [d]Conversion in percentage, as measured by ^{1}H NMR spectroscopy.

made between the reduction of benzyl bromide and substituted analogues to their respective reduction products. *p*-Bromobenzyl bromide, *o*-bromobenzyl bromide, and *α*,*α*'-dibromo-*o*-xylene (Scheme 7, entries 6–8) have shown that reduction occurs in 30 min with 57, 63, and 60% GC yield, respectively. At the end of the reaction, *p*-nitrobenzyl bromide (Scheme 7, entry 9) shows >99% conversion to *p*-nitrotoluene, as measured by ^{1}H NMR spectroscopy. Aromatic tertiary alkyl halides such as trityl chloride and trityl bromide (Scheme 7, entries 10 and 12) provide isolated yields of 54 and 57%, respectively. We also ran scale-up reactive extrusion using a twin-screw extruder for triphenyl bromide.[22] Since recrystallization often traps materials in the mother liquor, yields are often lower on small scale. To alleviate this problem, we decided to conduct these reactions on a twin-screw extruder on 10 g scale. As an example, triphenylmethane which was isolated in 54% (Scheme 7, entry 12) under milling conditions was isolated at 75% with an increased scale. If the material that is typically left in the barrel is accounted for, the adjusted yield is above 90%. This gram-scale reaction gave a 75% isolated yield.

Under mechanochemical conditions, substrates like 9-bromoanthracene and 9,10-dibromoanthracene in the presence of excess amounts of TTMSS have shown isolated yields of 54 and 67% within only 15 min. With 1-bromonaphthalene, 9-

bromoanthracene, and 9,10-dibromoanthracene (Scheme 7, entries 11, 13, and 14), we observed relatively small amounts of 1,1′-binaphthalene and 9,9′-bianthracene most likely through homocoupling.[23,24] We could isolate 74% of the product from the reduction of 2-bromobiphenyl (Scheme 7, entry 15) after 4 h. This is largely due to the stability of the generated radical under mechanochemical conditions. We extended our substrate scope by also subjecting 5-iodouracil and 5-iodouridine (Scheme 7, entries 16 and 17) to reduction under mechanochemical conditions. At the end of the reaction, both these substrates show >99% conversion to uracil and uridine, as measured by ^{1}H NMR spectroscopy.

Finally, in order to assess the environmental impact, sustainability, and effectiveness of the developed method, we calculated the ecoscale factors for two representative substrates reacting with tris(trimethylsilyl)silane (Table 1). The evaluation supported the advantages of the solvent-free reduction of alkyl halides under mechanochemical conditions over traditional solution chemistry.

Table 1. Ecoscale Comparison of Solution and Mechanochemical Reduction of Alkyl Halide Protocols for Two Representative Substrates

	ecoscale	
entry	solution	mechanochemistry
1	68	79
6	66	76

CONCLUSIONS

In conclusion, we have shown, to the best of our knowledge, the first reduction of alkyl halides under mechanochemical conditions with a broad substrate scope. This is a very important transformation, which typically requires harmful solvents and toxic reagents such as *n*-butyltin hydride and benzene. After testing several possible hydrogen atom donors, we were able to replace organotin halides with a benign hydrogen atom donor tris(trimethylsilyl)silane. Under these conditions, chloro, bromo, and iodo substrates have shown reduction. In the absence of a radical initiator, certain substrates have shown conversion, though majority of the substrates require 0.05 equiv or less amount of initiator under the tested conditions. This work demonstrates a novel method for the environmentally benign reduction of alkyl halides in the absence of solvents under mechanochemical conditions.

General Procedure for the Reduction of Alkyl and Aryl Halides. A 3 mL stainless steel vial was charged with a choice of alkyl and aryl halide, hydrogen atom donor, and azobis-(isobutyronitrile) (0.05 equiv), together with a 1/8 inch stainless steel ball. The vial was sealed with a Teflon gasket and fixed in a modified Spex (Metuchen, NJ, USA) 8000 M mixer/mill and milled for varying periods of time at elevated temperatures.[25] Quantification of the products was done by GC, ^{1}H NMR and isolation was done by simple recrystallization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.3c01544.

Additional experimental details, materials, methods, ^{1}H and ^{13}C NMR spectra for selected compounds, and ecoscale comparison for selected reactions (PDF)

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Notes

The authors declare no competing financial interest.

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