Iron-catalyzed protodehalogenation of alkyl and aryl halides using hydrosilanes†

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A simple and efficient iron-catalyzed protodehalogenation of alkyl and aryl halides using phenylhydrosilane is disclosed. The reaction utilizes FeCl₃ without the requirement of ligands. Unactivated alkyl and aryl halides were successfully reduced in good yields; sterically hindered tertiary halides were also reduced including the less reactive chlorides. The scalability of this methodology was demonstrated by a gram-scale synthesis with a catalyst loading as low as 0.5 mol%. Notably, disproportionation of phenylsilane leads to diphenylsilane that further reduces the halides. Preliminary mechanistic studies revealed a non-radical pathway and the source of hydrogen is PhSiH₃ via deuterium labeling studies. Our methodology represents simplicity and provides a good alternative to typical tin, aluminum and boron hydride reagents.

Introduction

Protodehalogenation is being utilized in various fields including organic synthesis, biochemistry and environmental protection.¹ In organic synthesis, bromo-cyclization followed by protodehalogenation to cyclic molecules² and the reduction of carbonyl compounds to an alkane via alkyl halides are routinely utilized.³ A most common method for protodehalogenation is the tributyltin hydride mediated free radical transformation. However, the toxic nature of tin reagents makes them less attractive in the pharmaceutical industries due to the fact that they are hard to be removed from the desired product. There have been numerous efforts to circumvent the issue including the immobilization of tin reagents,⁴ the use of photocatalysis (limited to iodides and activated halides),⁵ and metal hydrides.⁶–⁹

The robustness of metal hydrides attracted several research groups. Baba et al. reported that indium hydride (10 mol%) generated from NaBH₄/InCl₃ efficiently reduces alkyl iodides and bromides via a radical intermediate; however the chloride was ineffective.10 Recently, Fensterbank, Ollivier, Jutand et al. have reported the reductive cyclization of alkyl halides at elevated temperature that proceeds via a radical intermediate (10 mol% of FeCl₂ and NaBH₄) (Scheme 1b).11,12,13 The above-mentioned methods are expected to undergo metal–halogen exchange followed by a reductive protodehalogenation. Though the majority of these reactions are reported to proceed through a radical intermediate, Brookhart et al. reported a cationic Ir(III)hydride–phosphine complex that does not follow a radical pathway and it can reduce a broad range of alkyl halides including chlorides (Scheme 1a).⁸ Other transition metal complexes including palladium,¹²,¹³ ruthenium,¹₄ and iron/Grignard¹¹ are reported to be effective for protodehalogenation.

In our ongoing studies, in the field of iron mediated cross-coupling reactions, we found that 1-(3-bromobutyl)-4-methoxy-

![Scheme 1](image-url)
benzene 1a was efficiently reduced (protodehalogenated) to alkane. In this context, we became interested in exploring the iron mediated protodehalogenation since it is economical, environmentally benign, and naturally abundant, and the use of iron catalysis in the reduction of alkyl halides is very limited. Moreover, hydrosilanes are not much explored in iron catalysis. Hydrosilanes, being less toxic, can be an attractive alternative to tin-hydrides; however, the activation towards the reduction of alkyl halides is challenging. In(OAc)₃/PhSiH₃ in combination with Et₃B and oxygen is reported to reduce the alkyl halides. The reduction of halides is challenging, In(OAc)₃/PhSiH₃ in combination with Et₃B and oxygen is reported to reduce the alkyl halides that proceed through a radical intermediate. AlCl₃, PdCl₂, and Ir(III)phosphine complexes have also been used instead of NaOMe (3 eq.). Hydrosilanes other than PhSiH₃ were ineffective (entries 3 and 4). Having an excess of PhSiH₃ and NaOMe (3 eq.) was useful in driving the reaction to completion in a shorter time, although stoichiometric reagents proved to be sufficient to obtain a similar yield provided that the reaction was allowed to run for a longer time (10 h, Scheme 2, 1d). While THF offered a quantitative yield, the reaction was sluggish in Et₂O (see the ESI† for more details). The major challenge was to avoid the formation of 2b that is inseparable from the product and also to find a suitable hydrogen donor to improve the yield of 2a.

We found that PhSiH₃ was very effective and observed no detectable amount of the eliminated product. FeCl₃ proved to be a better catalyst over FeCl₂ and Fe(acac)₃ (Table 1, entries 5 and 6). The inorganic bases and sodium methoxide offered a quantitative yield (99%, entry 1) in 5 h whereas phosphate, carbonate (see the ESI†), fluorides (entry 11) and an organic base (entry 13) were poor yielding. While NaOMe as a base offered a quantitative yield, KOMe gave traces of the product (entry 12).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from the standard conditions</th>
<th>Time (h)</th>
<th>Yield 2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>5</td>
<td>99 (92)</td>
</tr>
<tr>
<td>2</td>
<td>iBuOH instead of PhSiH₃</td>
<td>32</td>
<td>ND</td>
</tr>
<tr>
<td>3b</td>
<td>Me₂PhSiH or Et₃SiH</td>
<td>15</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>Ph₂SiH</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>10 mol% FeCl₃</td>
<td>15</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>10 mol% Fe(acac)₃</td>
<td>15</td>
<td>62</td>
</tr>
<tr>
<td>7a,d</td>
<td>1.8 eq. Na₂Bu</td>
<td>32</td>
<td>82</td>
</tr>
<tr>
<td>8b,10</td>
<td>1.8 eq. KO'Bu</td>
<td>32</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>2 eq. PhSiH₃</td>
<td>15</td>
<td>83 (78)</td>
</tr>
<tr>
<td>10e</td>
<td>0.3 eq. NaOMe</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>11d</td>
<td>1.8 eq. CsF</td>
<td>32</td>
<td>&lt;5</td>
</tr>
<tr>
<td>12f</td>
<td>1.8 eq. KOMe</td>
<td>15</td>
<td>&lt;5</td>
</tr>
<tr>
<td>13</td>
<td>Lutidine</td>
<td>12</td>
<td>ND</td>
</tr>
<tr>
<td>14</td>
<td>Without FeCl₃</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>Without NaOMe</td>
<td>12</td>
<td>ND</td>
</tr>
<tr>
<td>16</td>
<td>Without PhSiH₂</td>
<td>12</td>
<td>ND</td>
</tr>
<tr>
<td>17b</td>
<td>CH₃CN</td>
<td>15</td>
<td>31</td>
</tr>
</tbody>
</table>

General reaction conditions: 0.36 mmol of 1a, 2 mL of THF, 5 mol% FeCl₃, 1.08 mmol of PhSiH₃, and NaOMe. **b** Determined by GC analysis using dodecane as an internal standard; values in parentheses are the isolated yields. **e** Elimination to 2b was observed. **f** Instead of NaOMe (3 eq.). **g** 10 mol% of FeCl₃. ND: not detectable.

With the optimized reaction conditions in hand, we explored the scope of the substrates. As expected, the secondary alkyl iodide 1e took only 30 minutes for the complete con-
While the primary alkyl bromides overnight for the complete conversion with 63% isolated yield. While the primary alkyl bromides, 1d, 1h, and 1j were also reduced efficiently at room temperature in 90%, 94% and 80% isolated yield (Scheme 2), the corresponding chlorides exhibited reduced reactivity and required elevated temperature. Chloride 1e took 19 h to offer the reduced product in 40% yield at 75 °C and chloride 1k took 17 h at 100 °C for the complete conversion with 62% yield (Scheme 2). A double protodehalogenation of substrate 1i was also effected with 61% yield.

Sterically crowded and challenging tertiary alkyl bromides 1f and 1l were successfully reduced with 78% and 54% yields respectively; even 1-chloroadamantane 1g was reduced with 89% yield. Cholesteryl iodide 1m offered the protodeiodinated cholest-5-ene in 86% yield. Competitive experiments were conducted to determine the order of reactivity, chlorocedecane 1j, bromide 1k and iodide were subjected to the standard reaction conditions in a single pot, the complete consumption of iodide was observed within 20 minutes, bromide 1k took 24 h to get completely consumed; however, the chloride 1j was intact even after 48 h (see the ESI† for more details). We carried out a gram-scale synthesis to demonstrate the practicability of this iron mediated protodehalogenation; it is worth noting that 0.5 mol% of FeCl₃ oxidized poor yields (Scheme 2; see the ESI† for more details). We conducted to determine the order of reactivity, chlorocedecane 1j, bromide 1k and iodide were subjected to the standard reaction conditions in a single pot, the complete consumption of iodide was observed within 20 minutes, bromide 1k took 24 h to get completely consumed; however, the chloride 1j was intact even after 48 h (see the ESI† for more details). We carried out a gram-scale synthesis to demonstrate the practicability of this iron mediated protodehalogenation; it is worth noting that 0.5 mol% of FeCl₃ oxidized poor yields (Scheme 2; see the ESI† for more details). We carried out a gram-scale synthesis to demonstrate the practicability of this iron mediated protodehalogenation; it is worth noting that 0.5 mol% of FeCl₃ oxidized poor yields (Scheme 2; see the ESI† for more details).

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Notably, the reported metal hydrides (FeCl₃/NaBH₄, In(OAc)/PhSiH₃, and InCl₃/Et₃SiH) for the reduction of alkyl halides are also applicable for the reduction of aryl halides. The methodology and the results obtained are comparable to that of tin, aluminum and boron hydride reagents. Interestingly, the above optimized reaction conditions for alkyl halides are also applicable for the reduction of aryl halides. Notably, the reported metal hydrides (FeCl₃/NaBH₄, In(OAc)/PhSiH₃ and InCl₃/Et₃SiH) for the reduction of alkyl halides are known to follow a radical pathway that does not reduce aryl halides and it was usually carried out with PdCl₂,12 [RuCl₂(η₅-C₅Me₅)]₁₄ (PNN)RuHCl(CO),₃,₇ and Fe(acac)₃/RMgX.¹¹ 1-Bromonaphthalene 4a was reduced with 40% yield in 30 minutes and 1-chloronaphthalene 4b took 12 h to complete the reaction with 71% isolated yield (Scheme 2). While 1-bromo-4-(tert-butyl)benzene 4c offered 74% yield in 1 h, 1-chloro-4-methylbenzene 4e and 5-bromoiodo 4d required elevated temperature and gave 74% and 40% yields respectively (Scheme 2). 5-Bromo-1,2,3-trimethoxybenzene 4f and 4-chloro, bromo and iodo anisole 4g-i offered 61%, 78%, 66% and 46% yields respectively; 1-chloro-4-iodobenzene 4k was also reduced in 50% yield. The functional groups that are susceptible to reductions (ketone 4j and ester 1p) were also reduced (Scheme 2). Both the alkyl and aryl fluorides were intact under the reaction conditions.

Despite the successful reduction of aryl halides, certain substrates offered poor yields (Scheme 2; see the ESI†) and this can be attributed to the formation of a silyl-coupled side product. When 5-bromo-N,N-dimethylpyridin-2-amine 6 was subjected to the optimized reaction conditions, we observed the formation of silane coupled product 7 in 24% isolated yield along with the expected reduced product 8 in 20% yield (Scheme 3). A similar coupled product was also observed with 1-bromonaphthalene 4a. Our efforts to suppress the formation of the silylated product were not successful.

Deuterium labeled experiments were conducted in order to find the source of the hydrogen atom. When PhSiD₃ (>99% D, synthesized from PhSiCl₃ and LiAlD₄) was used, we observed 72% of deuterium incorporation in the product; however when the reaction was conducted in THF-d₈, we observed no incorporation of deuterium in the product (Scheme 4). These results clearly indicate that the source of the hydrogen atom is PhSiH₄. Based on the earlier studies, our initial expectation was the formation of a radical intermediate and the subsequent reduction to the product; however, our mechanistic studies revealed a non-radical pathway. When we introduced either a TEMPO or galvinoxyl radical inhibitor in the reaction medium, the reaction was not inhibited and we obtained the reduced product (1a to 2a) in 72% and 92% yields respectively. Moreover, the alkene substrate 9a is expected to undergo cyclization if the reaction proceeds through a radical intermediate; however, we observed the formation of uncyclized reduced product 10b (Scheme 5).

When the reaction was carried out in CH₃CN (a favorable solvent for the radical reaction) instead of THF (no reaction in
DMF), the reaction was sluggish and produced a mixture of cyclized 10a and uncyclized 10b products (based on crude NMR and GC-MS); further efforts to improve the selective formation of the cyclized product in CH₃CN were not successful. Similarly, an un-cyclized product was observed with substrate 11 and a carbonyl trap experiment also led to the uncyclized product.10 These experiments clearly demonstrate a non-radical mechanistic pathway under the established conditions.

The exposure of phenylsilane to NaOMe in THF resulted in the formation of diphenylsilane 12 via disproportionation (Scheme 6).19 The isolated diphenylsilane 12 was subjected to protodehalogenation that offered 2a in 93% yield. Based on our observation, a mechanistic hypothesis is represented in Scheme 7. A rapid disproportionation of phenylsilane leads to the formation of diphenylsilane that reduces FeCl₃ (in the presence of NaOMe) to HFeLₙ, subsequent oxidative addition of halides followed by reductive elimination could lead to the protodehalogenated product. Additional investigation is necessary to completely elucidate the mechanism.

Conclusions

In summary, we have demonstrated a simple catalytic system based on FeCl₃ that can efficiently reduce both the alkyl and aryl halides. The loading of FeCl₃ can be reduced to as low as 0.5 mol%. The moderate yield obtained for aryl halides can be attributed to the formation of silylated side products; furthermore, mechanistic studies revealed that the reaction does not proceed through a radical intermediate.

Conflicts of interest

There are no conflicts to declare.

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Notes and references