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Ph_3P/ICH_2CH_2I-promoted reductive deoxygenation of alcohols†

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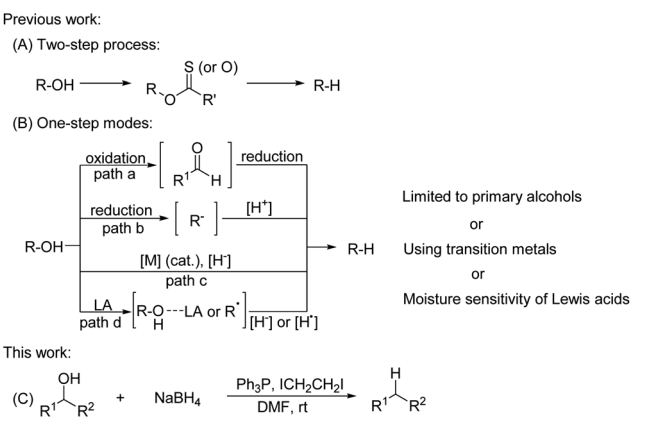
Owing to the ubiquity of the hydroxyl group, reductive deoxygenation of alcohols has become an active research area. The classic Barton–McCombie reaction suffers from a tedious two-step procedure. New efficient methods have been developed, but they have some limitations, such as a narrow substrate scope and the use of moisture-sensitive Lewis acids. In this work, we describe the Ph_3P/ICH_2CH_2I-promoted reductive deoxygenation of alcohols with $NaBH_4$. The process is applicable to benzyl, allyl and propargyl alcohols, and also to primary and secondary alcohols, demonstrating a wide substrate scope and a good level of functional group tolerance. This protocol features convenient operation and low cost of all reagents.

Introduction

The hydroxyl unit is one of the most accessible functional groups since alcohols are not only abundant feedstock but also commonly found in a wide range of naturally occurring products and synthetic intermediates. Owing to the ubiquity of the hydroxyl group, reductive deoxygenation of alcohols has become a useful synthetic tool in organic chemistry.[1] The Barton–McCombie reaction has proved to be a valuable deoxygenation protocol, which relies on stoichiometric toxic trialkyl tin hydride and a two-step process, involving the conversion of hydroxyl into thionoester/ester as a good leaving group (Scheme 1A).[1a–g] Although trialkyl tin reagents can be used in a catalytic amount[2] or even be eliminated,[1f,3] the tedious synthesis of thionoesters or esters from alcohols is still necessary. Apparently, direct reductive deoxygenation is an attractive strategy due to the convenient one-step operation. However, direct deoxygenation of alcohols is challenging because of the high C–O bond dissociation energy and the poor leaving ability of the hydroxyl group. Some one-step modes have been developed by the *in situ* activation of the hydroxyl group (Scheme 1B). The combination of dehydrogenative oxidation and the Wolff–Kishner reduction, first developed by the Li group[4] and modified by the Milstein group,[5] requires the use of a transition-metal complex as a catalyst and can only be applied to primary alcohols (Scheme 1B, path a). Alcohols can also be reduced to alkyl anions by reducing reagents[6] or under electrochemical conditions,[7] and the subsequent protonation would readily provide alkanes (Scheme 1B, path b). Transition metal catalysis, which usually involves the activation of alcohols by oxi-



Scheme 1 Reductive deoxygenation of alcohols.

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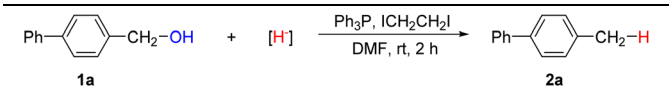
dative addition to transition metals or a heterolytic cleavage of the C–OH bond under acidic conditions to form carbocations, can be applied to primary, secondary and tertiary alcohols (Scheme 1B, path c).[8] This strategy has demonstrated a wide substrate scope and good functional group compatibility, but the use of an expensive transition metal complex is usually necessary. Alcohols can be first activated by a Lewis acid (LA) and would then readily undergo reduction with a hydrogen source (Scheme 1B, path d).[9] Although efficient, this approach may suffer from the high moisture sensitivity of the used Lewis acid.

Previously, we have shown that a Ph_3P/ICH_2CH_2I system can effectively activate the hydroxyl group in DMF, allowing for a wide range of dehydroxylative functionalizations,[10] such as halogenation,[10a] fluorination,[10d] and sulfonylation.[10f] In particular, the halogenation protocol was successfully applied to dehydroxylative chlorination in the total synthesis of Clionastatins A and B reported by the Zhang group, an important step that cannot be achieved by commonly used chlorination methods probably due to the complexity of the molecule.[11] We speculated that this system should be able to promote reductive deoxygenation of alcohols with a suitable hydride ion source. Apparently, the compatibility of reagents may be an issue. The reaction of Ph_3P with ICH_2CH_2I in DMF would generate a key intermediate for the activation of alcohols. The key intermediate, ICH_2CH_2I, and DMF are all electrophilic species, which may be easily attacked by the hydride ion and thus hinder the nucleophilic attack of the hydride ion on alcohols. However, if the processes for both the activation of alcohols and the nucleophilic attack of the hydride on the C–OH bond are rapid enough, the side reactions may be suppressed. Herein we describe the Ph_3P/ICH_2CH_2I-promoted reductive deoxygenation of alcohols with sodium borohydride ($NaBH_4$) in DMF (Scheme 1C). All reagents are cheap and widely available. A wide substrate scope and a good level of functional group tolerance were observed.

Results and discussion

Various hydrogen sources were first screened for the Ph_3P/ICH_2CH_2I-promoted reductive deoxygenation of benzyl alcohol **1a** in DMF (Table 1, entries 1–9). Si–H reagents were not found to be effective at all (entries 1–4). NaH and $LiAlH_4$ are both strong hydride sources, but neither of them was reactive toward this process (entries 7 and 8). To our delight, the desired product was detected albeit in a low yield (11%) with the use of $NaBH_4$, which is a cheap and mild reagent, as a nucleophilic hydride (entry 9). The yield was significantly increased by increasing the loading of $NaBH_4$ (entries 10–13). The loadings of both Ph_3P and ICH_2CH_2I played an important role in this deoxygenation reaction. Their use in slight excess (1.2 equiv.) could give the desired product in almost quantitative yields (entries 12 and 13). However, decreasing their loading slightly led to a dramatic decrease in the yield (entry 14) or completely suppressed the expected conversion (entry 15). We have previously demonstrated that the Ph_3P/ICH_2CH_2I-promoted nucleophilic substitution can occur in DMF[10b,c,f] or CH_3CN.[10a,d] But no desired product was produced in CH_3CN (entry 16).

Table 1 The optimization of the reaction conditions



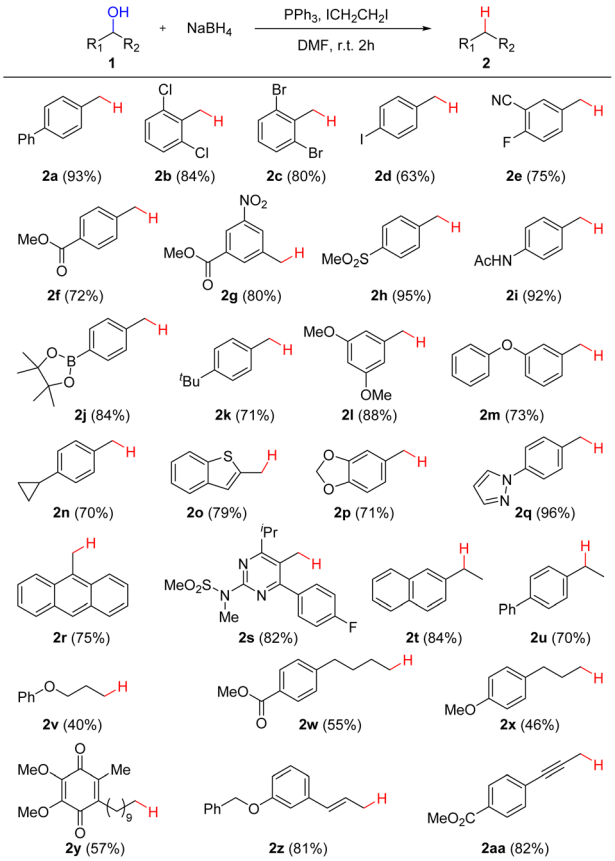
1a **2a**

Entry	Molar ratio[a]	[H⁻]	Yield[b] (%)
1	1 : 1.2 : 1.2 : 1.5	Et_3SiH	N.D.
2	1 : 1.2 : 1.2 : 1.5	Ph_2CH_3SiH	N.D.
3	1 : 1.2 : 1.2 : 1.5	Ph_3SiH	N.D.
4	1 : 1.2 : 1.2 : 1.5	Cl_3SiH	N.D.
5	1 : 1.2 : 1.2 : 1.5	NH_4OAc	N.D.
6	1 : 1.2 : 1.2 : 1.5	Hantzsch ester	N.D.
7	1 : 1.2 : 1.2 : 1.5	NaH	N.D.
8	1 : 1.2 : 1.2 : 1.5	$LiAlH_4$	Trace
9	1 : 1.2 : 1.2 : 1	$NaBH_4$	11
10	1 : 1.2 : 1.2 : 1.5	$NaBH_4$	54
11	1 : 1.2 : 1.2 : 2	$NaBH_4$	58
12	1 : 1.2 : 1.2 : 2.5	$NaBH_4$	98
13	1 : 1.2 : 1.2 : 3	$NaBH_4$	99
14	1 : 1 : 1.2 : 2.5	$NaBH_4$	11
15	1 : 1 : 1 : 2.5	$NaBH_4$	N.D.
16[c]	1 : 1.2 : 1.2 : 2.5	$NaBH_4$	N.D.

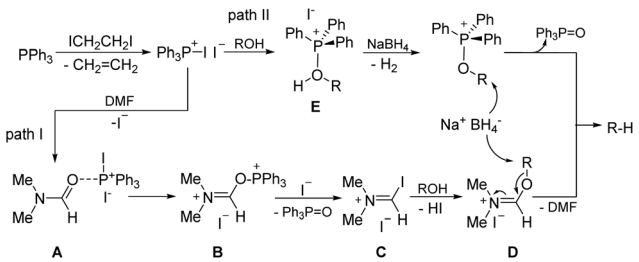
Reaction conditions: Substrate **1a** (0.2 mmol), PPh_3, and ICH_2CH_2I in DMF (2 mL) at room temperature under a N_2 atmosphere for 2 h. [a] Molar ratio of **1a** : Ph_3P : ICH_2CH_2I : $NaBH_4$. [b] The yields were determined by ^1H NMR spectroscopy with CH_2Br_2 as the internal standard. [c] CH_3CN was used as the reaction solvent instead of DMF.

With the optimal conditions in hand (Table 1, entry 12), we then investigated the substrate scope of the Ph_3P/ICH_2CH_2I-promoted reductive deoxygenation of alcohols. As shown in Scheme 2, the deoxygenation process could be extended to a wide range of alcohols, demonstrating a wide substrate scope. Various functional groups were tolerated, especially the widely used boronic ester group (**2j**) and the highly electron-deficient groups such as cyano, nitro, ester and sulfonyl groups. Besides primary alcohols, secondary alcohols (**2t and 2u**) were also reactive under these conditions and good yields were obtained. Alkyl alcohols showed lower reactivity and the desired products were produced in moderate yields (**2v–2y**). Allylic and propargyl alcohols could also be converted smoothly to afford the expected products (**2z and 2aa**).

On the basis of the above results and our previous mechanism studies,[10] we propose a plausible reaction mechanism, as shown in Scheme 3. The *in situ* generated $Ph_3P^+I\ I^-$ from the Ph_3P/ICH_2CH_2I system may directly coordinate with DMF to produce intermediate **A**. The strong P–O bond would then weaken the C–O bond to provide intermediate **B**, which is then easily transformed into a Vilsmeier–Haack-type intermediate (**C**). The Vilsmeier–Haack-type intermediate can readily activate alcohols by forming intermediate **D**, the subsequent nucleophilic attack on which affords the final product. On the other hand, $Ph_3P^+I\ I^-$ can also directly activate alcohols *via* the formation of intermediate **E**, allowing the following nucleophilic attack of a hydride on alcohols.



Scheme 2 The substrate scope of the Ph_3P/ICH_2CH_2I-promoted reductive deoxygenation of alcohols. Isolated yields are shown. Reaction conditions: substrate **1** (0.5 mmol), PPh_3 (0.6 mmol), ICH_2CH_2I (0.6 mmol) and $NaBH_4$ (1.25 mmol) in DMF (5 mL) at room temperature under a N_2 atmosphere for 2 h.



Scheme 3 The plausible reaction mechanism.

Conclusions

In summary, we have described the Ph_3P/ICH_2CH_2I-promoted reductive deoxygenation of alcohols to provide alkanes. This protocol features convenient operation, the use of ubiquitous hydroxyl groups, and low cost of all reagents. This process is applicable to benzyl, allyl and propargyl alcohols, and also to primary and secondary alcohols, demonstrating a wide substrate scope and a good level of functional group tolerance.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

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