New reductive deiodination reaction by hydrogen atom transfer from cyclohexane

Jean Boivin,[a] Béatrice Quiclet-Sire,[b] Laure Ramos[a] and Samir Z. Zard*[a,b]

[a] *Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, 91128 Palaiseau, France*
[b] *Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-Sur-Yvette, France*

Secondary iodides flanked by one or more inductive electron-withdrawing groups can be reduced *via* a radical chain reaction involving a hydrogen atom transfer from cyclohexane, the process being triggered by a small amount of an initiator such as dilauroyl peroxide.

Although organoiodine compounds are seldom found in nature and are therefore rarely synthetic targets themselves, they are nevertheless very useful intermediates in organic synthesis in general.[1] Iodides are not only starting materials in a wide variety of organometallic transformations: the introduction of an iodine atom is often an integral part of the creation of another bond, as in the iodo-lactonisation reaction and other related processes.[2] When introduced in this way, and after its task has been accomplished, the iodine atom must then often be reductively removed. The most generally employed reagent for this purpose is tributylstannane, used either in stoichiometric amounts or, when possible, regenerated *in situ* by an auxiliary reducing agent such as sodium borohydride or cyanoborohydride.[3,4] Other procedures include catalytic hydrogenation, reduction with dissolving metals or low valent metal salts and, in some cases, with complex hydrides.[4] Apart perhaps from catalytic hydrogenation, most of these methods are not generally applicable to iodides derived from iodo-lactonisation since they usually cause either reductive opening of the lactone ring or reduce the lactone itself. We now report a new radical chain process where reduction is achieved by an unusual hydrogen atom transfer from cyclohexane.

The reaction of iodides with radicals is a fast and reversible process, the equilibrium lying normally to the side of the most stable radical. This important property is the basis of the Kharasch-type atom transfer reactions, which have been elegantly exploited in organic synthesis in recent years.[5] It seemed that if an *unstabilised* secondary radical generated from the corresponding iodide and rendered electrophilic by one or more inductively electron-withdrawing groups (represented by a β-acetoxy group in **1**) present in the vicinity, then it should be possible to establish the chain process outlined in Scheme 1. The key, and rate determining, step is the hydrogen abstraction from cyclohexane.[6] This process is not normally efficient with ordinary aliphatic radicals, allowing cyclohexane to be used for example as solvent in replacement of the more toxic benzene.[6] However, when the radical has electrophilic character then the hydrogen abstraction rate is promoted by favourable polar factors.[7] The requirement for secondary radicals that are not stabilised by resonance comes from a need to make the process nearly thermoneutral (and preferably slightly exothermic) rather than strongly endothermic. With primary iodides, the hydrogen abstraction step (step B) would be even more favoured, but the subsequent iodine transfer equilibrium (step A) would shift to the wrong side.

This conjecture was reduced to practice as shown by the examples (and yields) compiled in Fig. 1. The reaction is performed in the following way: a solution of the iodide in cyclohexane (0.1 M) is heated to reflux under an inert atmosphere for 20–30 min and dilauroyl peroxide (typically 17

mol% with respect to the iodide, but this amount can be decreased or increased depending on the scale and purity of the iodide) is added in one portion to the deoxygenated reaction mixture. After heating for 2–3 h (TLC monitoring), the solution is concentrated under partial vacuum and the residue purified by column chromatography. The concomitant formation of cyclohexyl iodide was confirmed by GC–MS analysis of the reaction mixture. Carbohydrate-derived iodides are ideal substrates since the presence of several carbon–oxygen bonds around the radical centre make them especially electrophilic. It is worth
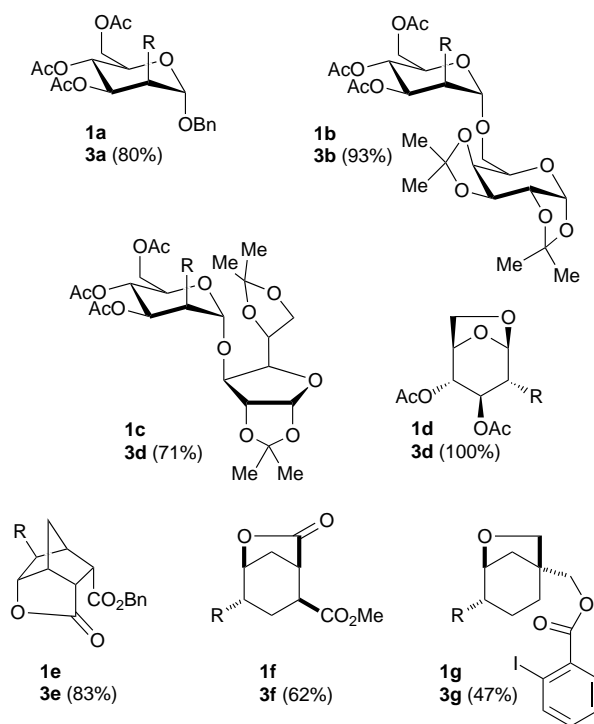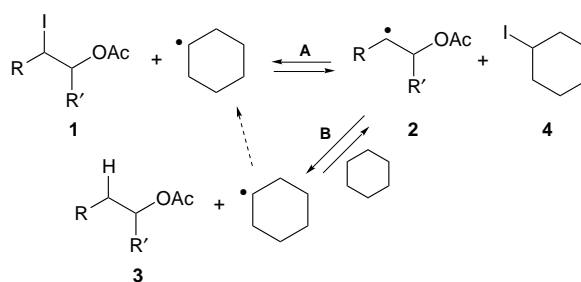

Scheme 1

Fig. 1 Reduction of iodides **1a–g** (R = I) into **3a–g** (R = H)

pointing out that all the substrates were constructed using either an iodo-etherification or an iodo-lactonisation reaction,[2,8] both powerful processes that introduce at the same time the iodide and an electron-withdrawing group. For example, **1b** and **1c** were made by reacting tri-*O*-acetyl-d-glucal with a 1,2:3,4-di-*O*-isopropylidene-d-galactopyranose or diacetone-d-glucose in the presence of iodosuccinimide.[8]

The importance of the electron-withdrawing group is shown by the behaviour of iodo lactones **1e** and **1f** and iodo ether **1g**. These compounds contain only one electron-attracting group next to the incipient radical centre, in contrast to the carbohydrate examples; consequently, the reaction required more dilauroyl peroxide (up to 37%). In the case of the cyclic iodo ether **1g** the yield was modest, reflecting the poorer electron-withdrawing ability of the ether linkage. Moreover, when a *mixture* of both **1f** and **1g** was subjected to the reaction conditions, lactone **1f** reacted much faster (about 5 times), as ascertained by GC–MS monitoring of the reaction. It is interesting to note that the aromatic iodide in **1g** remains largely unaffected. In fact, this competition experiment reveals aspects of selectivity that could be exploited in synthesis, and work aimed at exploring such possibilities is under way.

The present process represents a convenient and inexpensive method for reducing an important class of iodides. A number of useful and commonly encountered functional groups are tolerated. From a more fundamental point of view, it strengthens the notion that it is polar[7] and not steric effects[9] that play a predominant role in the so-called β-C–O bond effect discovered Barton and his collaborators[10] several years ago. It was noted at the time that xanthates derived from carbohydrates underwent deoxygenation more smoothly and sometimes at a lower temperature than simpler derivatives when exposed to tributyltin hydride.

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