Tetrahedron 72 (2016) 7727–7737

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Iron(II) catalyzed reductive radical cyclization reactions of bromoacetals in the presence of $NaBH_4$: optimization studies and mechanistic insights

Sara H. Kyne [a], [†], Christophe Lévêque [a], Shiwen Zheng [a], Louis Fensterbank [a], [*], Anny Jutand [b], [*], Cyril Ollivier [a], [*]

[a] Institut Parisien de Chimie Moléculaire, UMR CNRS 8232, Sorbonne Universités, UPMC Univ Paris 06, 4 Place Jussieu, CC 229, F-75005 Paris, France
[b] Ecole Normale Supérieure – PSL Research University, Département de Chimie, Sorbonne Universités, UPMC Univ Paris 06, CNRS UMR 8640 PASTEUR, 24 Rue Lhomond, F-75231 Paris, Cedex 05, France

ARTICLE INFO

Article history:
Received 14 April 2016
Received in revised form 4 August 2016
Accepted 12 August 2016
Available online 13 August 2016

Keywords:
Iron
Radical cyclization
Homogenous catalysis
Reduction
Electrochemistry
NMR spectroscopy

ABSTRACT

5-*Exo*-trig radical reductive cyclization reactions of bromoacetals are catalyzed by iron in the presence of the reducing agent $NaBH_4$. Both iron(II) and iron(III) were found to effectively mediate these reactions. As shown by cyclic voltammetry, iron(III) can be reduced to an iron(II) precatalyst before passing through an identical reaction mechanism in which monoelectronic activation of the substrate would occur by an anionic hydridoiron(I) complex. Further studies have established that both the substrate (iodo- vs bromo-derivative) and the precatalytic mixture are decisive in determining the reaction outcome.

1. Introduction

Free radical processes are established as powerful and versatile tools for organic synthesis.[1] The notoriety of tin hydrides as reliable radical chain carriers and good hydrogen donors is well documented.[2] However, providing efficient alternatives that are less toxic and easier to remove at the end of the reaction is highly desirable for modern synthetic chemistry.[3]

In this context, intensive research has been conducted on the development of tin-free mediators, mainly focused on hydrides of main-group elements including silicon,[4] germanium,[5] boron[6] and phosphorus[7] derivatives. Besides these examples, interesting alternatives have been discovered with hydrides of gallium,[8] indium[8] and transition metal complexes including titanium,[9] zirconium[10] and chromium.[11] However most of these reactions require stoichiometric or substoichiometric amount of reagents, and challenges remain to develop catalytic alternatives.

A solution to this problem was the design of new metal/hydride systems that used a catalytic amount of metal complex. The story began with the work of Kuivila,[12] Corey[13] and Stork[14] who used catalytic amounts of tin hydride with a stoichiometric hydride source ($LiAlH_4$, $NaBH_4$, $NaBH_3CN$) for the simple reduction of halides. But to avoid the use of tin, other metal complexes based on gallium,[8] indium,[15] titanium,[9c,16] zirconium,[10] chromium,[17] cobalt[18] and nickel[19] associated with a reducing agent such as Red-Al or sodium borohydride have proven to be effective for such reductive transformations. Frequently, it has been proposed that under reducing conditions transition metal hydride species are formed, acting as the mediator for reductive radical reactions. However, the in situ formation of the hydrido transition metal species, and the subsequent reaction mechanism have both remained largely unexplored.

Of particular interest was the reactivity of iron for mediating reductive radical reactions since iron is abundant, cheap and has a low toxicity. Intermolecular radical reactions mediated by iron have been established.[20] However interestingly, there are considerably fewer examples of related iron-mediated reductive intramolecular radical reactions. The first example by Meunier reported the radical cyclization of 5-hexenyl bromide involving a single electron transfer process with a stoichiometric amount of an iron

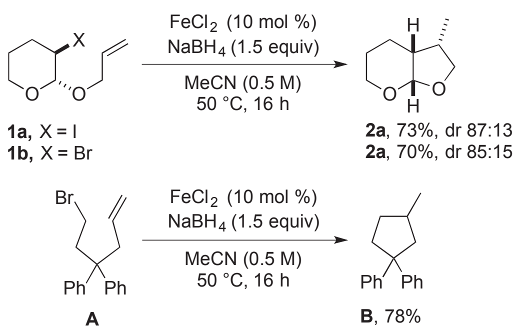
---

[*] Corresponding authors. E-mail addresses: louis.fensterbank@upmc.fr (L. Fensterbank), anny.jutand@ens.fr (A. Jutand), cyril.ollivier@upmc.fr (C. Ollivier).
[†] Current address: School of Chemistry, University of Lincoln, Joseph Banks Laboratories, Lincoln, LN6 7DL, UK.

http://dx.doi.org/10.1016/j.tet.2016.08.039
0040-4020/

(II)—Grignard species, Cp(DIPHOS)FeMgBr.[21] Later, Oshima proposed catalytic conditions with the use of 5 mol % ferrous chloride and a Grignard reagent for the radical cyclization of iodo- and bromoalkenes to unsaturated or partially reduced tetrahydrofurans depending on the nature of the Grignard compound.[22]

To achieve a more effective system for catalytic reduction and thus avoid the formation of unsaturated products, a preliminary communication reported the reductive radical reactions of alkylhalides catalyzed by iron(II) dichloride (10 mol %) in the presence of sodium borohydride in acetonitrile (Scheme 1).[23] Direct reduction occurred in good yields, and unsaturated primary and secondary systems bearing either iodide or bromide radical precursors efficiently provided the corresponding products of tandem cyclization/reduction reactions.



Scheme 1. Iron(II)-mediated tandem cyclization/reduction reactions in the presence of $NaBH_4$ (previous work).[23]

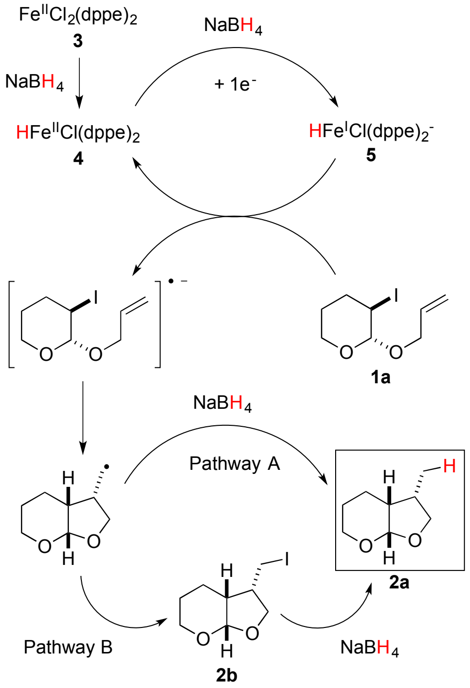
To gain more insight into the mechanism of these reactions, the iron(II) precatalyst [$FeCl_2(dppe)_2$] (**3**) (dppe=1,2-bisdiphenylphosphinoethane) was selected as a probe due to the stabilizing effect imparted by the bis-phosphine ligands. Electrochemical studies on **3** in the presence of sodium borohydride clearly identified the formation of an iron monohydride [$HFe^{II}Cl(dppe)_2$] (**4**) that upon reduction generated the anionic hydridoiron(I) [$HFe^{I}Cl(dppe)_2$]$^-$ (**5**). The catalytic activity of this species has been demonstrated by an increase of the observed reduction current of [$HFe^{II}Cl(dppe)_2$] (**4**) with the number of iodoacetal **1a** equivalents (Scheme 2).

However during the preparative electrolysis of iodide **1a** (in the absence of $NaBH_4$), the formation of the bicyclic byproduct **2b** resulting from iodine atom transfer (ca. 10% yield) was observed. This could suggest, as also recently proposed by Curran and Studer,[24] that under the standard conditions given in Scheme 1, the cyclization process could involve iodine atom transfer, followed by nucleophilic substitution of the resulting primary iodide with the borohydride to give **2a** (Scheme 2, pathway B). In sharp contrast, the corresponding bromide (**1b**) is presumably not sufficiently reactive to undergo the equivalent bromine atom transfer, yet the reductive cyclization reaction takes place in similar yields from this substrate.[25] It is even more difficult to conceive a bromine atom transfer taking place in the cyclization of the primary bromide **A** to give **B** as shown in Scheme 1. To follow up on the mechanistic investigations carried out on **1a**, analysis was extended to the bromoacetal derivative **1b**. These studies have provided new insights into this interesting transformation.

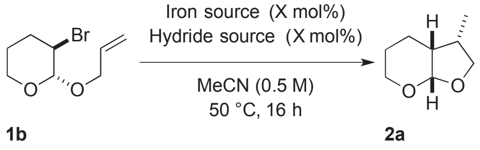
2. Results

2.1. Influence of reaction parameters

To complement the previous study, the influence of the iron and hydride sources and their respective loadings on the cyclization of bromoacetal **1b** was investigated as described in Scheme 3.



Scheme 2. Generation and reactivity of the anionic hydridoiron(I) active species ([$HFe^{I}Cl(dppe)_2$]$^-$) (**5**) for the reductive cyclization of **1a** via Pathway A (major) and Pathway B (iodine atom transfer. *Note*: Initiation by $NaBH_4$ alone is also possible).



Scheme 3. Iron(II)-mediated 5-exo-trig radical cyclization of unsaturated b-bromoacetal 1b in the presence of NaBH4.

2.1.1. Influence of the iron source. A variety of iron salts and iron complexes were screened under the general reaction conditions shown in Scheme 3 and a selection of the results are shown in Table 1 (see the Supplementary data for the complete table of results for bromoacetal **1b**, and results for iodoacetal **1a**). The bromoacetal **1b** was found to be more sensitive to the iron source than the corresponding iodoacetal **1a**: for example, while iodoacetal **1a** reacted well (62–65% yield) in the presence of iron(II) dichloride (98%), no reaction was observed with bromoacetal **1b** (Entry 1) or iron(III) trichloride (98%, Entry 4). In contrast, reaction with high purity iron(II) and (III) chlorides proceeded in similar, good yields (Entries 2 and 5), interestingly the results with high purity iron(II) dichlorides were dependent on the commercial

Table 1
Reactivity of **1b** in the presence of [Fe] or [Cu] (10 mol %) and sodium borohydride (150 mol %)[a]

Entry	[M], M=Fe, Cu	Purity%	Yield% (**2a**)
1	$FeCl_2$	98	0
2	$FeCl_2$[b]	99.99	78
3	$FeCl_2$[c]	99.99	39
4	$FeCl_3$	98	0
5	$FeCl_3$	99.99	80
6	[$FeCl_2(dppe)_2$] (**3**)	N.D.	78
7	$CuCl_2$	99.995	14

[a] Reaction conditions: **1b** (1.0 mmol, 0.5 M CH_3CN), [M] M=Fe, Cu (10 mol %), $NaBH_4$ (150 mol %), 50 °C, 16 h.
[b] Commercial supplier: Sigma–Aldrich.
[c] Commercial supplier: Alfa Aesar.