

Versatile electrochemically based preparation of unusual Grignard reagents containing electrophilic substituents

Henning Lund*, Heidi Svith, Steen Uttrup Pedersen¹, Kim Daasbjerg

Department of Chemistry, University of Aarhus, Langelandsgade 140, DK 8000 Aarhus C, Denmark

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Abstract

Upon electrochemical reduction of potassium perchlorate in dimethyl sulfoxide to potassium the strong dimethyl sulfoxide base (i.e. the conjugate base of dimethyl sulfoxide) is formed in the reaction of the alkali metal with the solvent. The electrolysis is performed in an undivided cell with a magnesium rod serving as sacrificial anode, thereby generating magnesium ions, which stabilize the generated dimethyl sulfoxide base through ion-pair formation. In a second non-electrochemical step, Grignard type reagents R_2Mg are obtained simply by letting the magnesium salt of dimethyl sulfoxide base deprotonate weakly acidic substrates ($pK_a < 26$ in dimethyl sulfoxide) added to the solution. The advantage of generating these reagents through a deprotonation route rather than by reduction of halogen-substituted compounds as in the classical approach is that the substrates may contain electrophilic groups, such as halogen, carbonyl or cyano. The R_2Mg reagents react with electrophiles akin to ordinary Grignard reagents as illustrated by the preparation of several substituted benzyldienefluorenes in nucleophilic addition reactions. The electrochemical properties of the products were investigated and a reasonable linear correlation of the first reduction potentials with the Hammett substituent coefficient σ^- was found.

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1. Introduction

Grignard reagents have for a century been important species employed in organic chemistry. The reagent is most often described as $RMgX$ although in reality there will be a Schlenk equilibrium between R_2Mg , MgX_2 , $RMgX$ and adsorbed species at magnesium [1,2]. In the classical approach, the reagent is formed in a reaction between an organic halide and magnesium in an inert solvent, generally, an ether. Although extremely useful, this approach has some limitations, as it prohibits the presence of other reactive and reducible functional groups in the same molecule. Electrophilic groups, such as carbonyl, nitro and cyano, along with acidic groups, such as alcohols, amines, thiols

and carboxylic acids, must be avoided because of their high reactivity towards the Grignard functionality [3].

Grignard reagents may be prepared in other ways than the classical one, such as employing highly reactive magnesium slurries in THF at $-78^\circ C$ [4], using an iodide-magnesium exchange reaction by treating *o*-iodonitrobenzene with phenylmagnesium chloride in THF at $-40^\circ C$ [5], or reacting an alkenyl iodide with isopropylmagnesium chloride and lithium chloride in dry THF [6]. Using these methods cyano groups, esters and even nitro groups [5] may be allowed in the Grignard reagent.

The aim of the present paper is to present another way of preparing Grignard type reagents which allows the presence of certain electrophilic groups. The first step in the new approach is an electrochemical generation of the strong dimethyl sulfoxide base (i.e. the conjugated base of dimethyl sulfoxide, DMSO) accomplished through a reduction of a potassium salt to the reactive and strongly reducing potassium metal in

* Corresponding author. Tel.: +45 89423905; fax: +45 86196199.

E-mail address: hlund@chem.au.dk (H. Lund).

¹ ISE member.

DMSO. This electrolysis is carried out in an undivided cell with a magnesium rod serving as sacrificial anode in order to prepare simultaneously the other important constituent of Grignard reagents, i.e. magnesium ions. In a second non-electrochemical step, this dimsyl base (now ion-paired with magnesium) is used to deprotonate weakly acidic substrates, thereby generating the target molecule in terms of a Grignard type reagent of the form R_2Mg . The great advantage of this procedure is that it allows the formation of R_2Mg reagents containing electrophilic substituents, such as halogen, carbonyl and cyano, which otherwise would be reduced by magnesium in the classical procedure for preparing such reactants.

A somewhat similar procedure has been used in forming strong bases from compounds having an N–H bond. Thus, electrochemical reduction of hexamethyldisilazane (HMDS) in DME containing 15% HMPA in an undivided cell with a sacrificial magnesium anode and a stainless steel grid cathode produced $[(Me_3Si)_2N]_2Mg$ which could deprotonate ketones having an α -hydrogen [7]. 2-Pyrrolidone and HMDS were similarly reduced at transition metal cathodes with a sacrificial magnesium anode. It was found that 2-pyrrolidone with $pK_a = 24.2$ (DMSO) [8] was reduced by a diffusion-controlled direct dissociative discharge mechanism, whereas the reduction of HMDS with $pK_a = 26$ (DMSO), involved a reduction of the solvent followed by a slow evolution of hydrogen from HMDS [9].

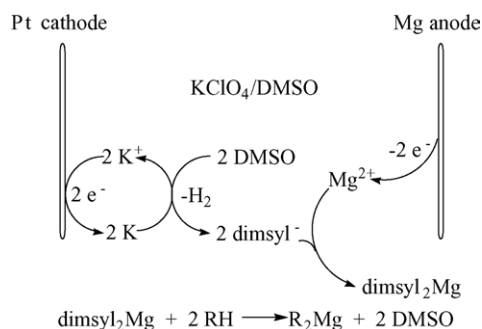
In the present paper, we have prepared Grignard reagents from fluorene, halogen-substituted fluorenes, acetophenone and phenylacetonitrile. The reagents have been employed in nucleophilic addition reactions involving carbonyl compounds, in most cases substituted benzaldehydes.

2. Results and discussion

One of the most useful strong bases employed within the organic chemistry community is the deprotonated DMSO, dimsyl. In principle, this base (along with hydrogen) may be prepared chemically by reacting an alkali metal (K, Na) or an alkali metal hydride (KH, NaH) with DMSO [10]. However, the latter procedure is somewhat hazardous and certainly for industrial purposes it will be associated with safety problems.

From this perspective, it would be desirable if the alkali metal could be generated in situ from the corresponding alkali ions. An attractive route is presented by the electrochemical approach outlined in Scheme 1. The electrochemical reduction of $KClO_4$ in DMSO in an undivided electrochemical cell using magnesium as anode produces in the first step the dimsyl base ion-paired with the magnesium ions generated at the anode.

The use of a galvanostatic (i.e. constant current) set-up is advantageous as this allows easy control of the amount of base produced simply through adjustment of the current and the electrolysis time. The current efficiency is close to 100%



Scheme 1. Proposed mechanism for the generation of the Grignard type reagent R_2Mg in the electrochemical approach.

as deduced from titration of the amounts of base produced. Note that if electrophilic impurities should be present in the solution, other and weaker bases might be generated along with dimsyl. In order to evaluate roughly the strength of the base(s) present we let the electrogenerated solution react with a weak acid, such as fluorene ($pK_a = 22.6$ in DMSO) [8]. The conversion of fluorene to fluorenone was found to be higher than 90% as determined from the recording of UV–vis spectra of the latter species (see Section 6). This result does not only illustrate the high efficiency of the electrochemical procedure outlined but also that electrogenerated dimsyl has a high stability in solution in the absence of electrophiles. In the synthetic applications described below we usually choose to employ a small excess of base. At the same time the set-up is simple requiring only two rods as electrodes and a power supply. The stabilizing effect exerted by magnesium ions on dimsyl is important because the further attack by potassium on DMSO [11] then is diminished. If the electrolysis were carried out in a divided cell the more reactive potassium salt of dimsyl would rather be produced. On the basis of the cyclic voltammograms of electrochemically generated dimsyl collected in Fig. 1 it is seen that the anodic peak potential is about 0.3 V less negative when dimsyl is ion-paired with Mg^{2+} than

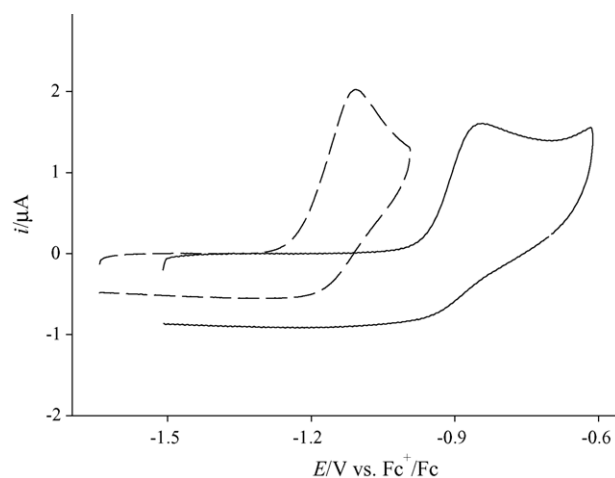


Fig. 1. Cyclic voltammograms of 2 mM magnesium ion-paired dimsyl (—) and 2 mM potassium ion-paired dimsyl (---) in 0.3 M $KClO_4$ /DMSO recorded at a scan rate of $0.5 V s^{-1}$.

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