

0040-4039(95)01240-0

**Lithium Hydride containing Complex Reducing Agent:
A new and simple activation of commercial lithium hydride.**

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Abstract : Commercially available lithium hydride, an essentially inert metal hydride, can be activated as a hydride source by *in situ* generated lithium alkoxide in the presence of a nickel salt. The obtained new reagent exhibited reducing properties *versus* alkyl or aryl halides, ketones, ethylenic or sulfurated compounds as well as coupling properties *versus* aryl halides when prepared in the presence of a ligand.

In spite of its advantageous properties,¹ commercially available lithium hydride has scarcely been used in organic synthesis, because of the lack of effective methods to activate the stable metal hydride as a nucleophile or base.² Several attempts to improve the reactivity of this reagent have been investigated. For example, Noyori and coll. described recently an efficient method to activate LiH by Me₃SiCl in the reductive silylation of carbonyl compounds.³ Zippi also showed that LiH, *in situ* generated by hydrogenolysis of BuLi in the presence of TMEDA, exhibited enhanced reactivity compared to commercial LiH.⁴ In this paper, we wish to report a new activation procedure for commercial LiH as a hydride source involving *in situ* generated alkoxides and a nickel salt according to the agregative activation principles.⁵

We have found that a mixture of lithium hydride, *tert*-butanol and nickel acetate heated at 63°C in THF (or DME)⁶ led to a new nickel-containing Complex Reducing Agent called LiH-NiCRA.⁷ The measurement of hydrogen evolution during the preparation of the reagent indicated the quantitative formation of *t*-BuOLi and a nickel (0) species.⁸

This new reagent exhibited interesting reducing properties *versus* various reducible organic compounds. Our main results are summarized in Table 1.

Table 1. Reduction of organic substrates by LiH-NiCRA.^a

| Run | Substrate | Solvent | Time (h.) ^b | Product | Yield (%) ^c |
|-----|----------------------------------|---------|------------------------|--|------------------------|
| 1 | 1-bromo-naphtalene | DME | 3.5 | naphtalene | 99 |
| 2 | 1-bromo-2-methyl-naphtalene | " | 4 | 2-methyl-naphtalene | 95 |
| 3 | 1-chloro-naphtalene | " | 6 | naphtalene | 95 |
| 4 | 1-bromo-dodecane | " | 1 | dodecane | 99 |
| 5 | 1-chloro-dodecane | " | 3 | dodecane | 98 |
| 6 | 1-bromo-adamantane | " | 3 | adamantane | 97 |
| 7 | 1-choro-adamantane | " | 24 | adamantane | 37 |
| 8 | styrene | THF | 4 | ethyl-benzene | 98 |
| 9 | 1-methyl-styrene | " | 20 | isopropyl-benzene | 99 |
| 10 | 4- <i>t</i> -butyl-cyclohexanone | " | 18 | 4- <i>t</i> -butyl-cyclohexanol (cis / trans = 10 / 90) | 94 |
| 11 | 3,5,5-trimethyl-cyclohexanone | " | 16 | 3,5,5-trimethyl-cyclohexanol (cis / trans = 6 / 94) | 74 |
| 12 | 3,3,5-trimethyl-cyclohex-2-enone | " | 2 | 3,3,5-trimethyl-cyclohexanone | 94 |
| 13 | styrene oxide | " | 24 | phenyl-2-ethanol phenyl-1-ethanol | 92 5 |
| 14 | dibenzothiophene | DME | 37 | biphenyl | 11 |

^a Reductions performed on a 10 mmole scale (runs 1-13) or on a 1 mole scale (run 14). ^b Time after which no evolution was observed. ^c Yields determined by GC using internal standard method (C₁₀-C₁₆).

It appeared that aromatic or primary alkyl bromides and chlorides were quantitatively reduced in 3-6 hours in DME (runs 1 to 7). However, a tertiary bromide (run 6) was reduced at almost the same rate as the corresponding primary halides. In contrast, a tertiary chloride (run 7) was slowly reduced yielding only 37 % of alkane after 24 hours. These results suggest that LiH-NiCRA exhibited attenuated reducing properties compared to the previously described NaH-NiCRA prepared from NaH.⁹ On the other hand, LiH-NiCRA allowed the efficient reduction of olefins and ketones (runs 8 to 11) while 3,5,5-trimethyl-cyclohex-2-enone was rapidly and selectively reduced into the corresponding ketone (run 12). Regioselective reduction of styrene oxide in phenyl-2-ethanol is also of some interest (run 13). Finally, we found that LiH-NiCRA exhibited some desulfurizing properties (run 14).

We next tried to prepared liganded LiH-NiCRA by the addition of triphenylphosphine or 2,2'-bipyridine, respectively called LiH-NiCRA-PPh₃ and LiH-NiCRA-bpy.⁶ As their analogues prepared from NaH, these reagents were very efficient in the coupling of aromatic bromides and chlorides as exemplified in table 2 (runs 1-4). Due to their attenuated reducing properties compared to LiH-NiCRA, the coupling yields were high with liganded LiH-NiCRA. Moreover, we found that LiH-NiCRA-PPh₃ and LiH-NiCRA-bpy exhibited a higher desulfurization efficiency than LiH-NiCRA (table 2, runs 5-6 compared table 1, run 14).

Table 2. Coupling reaction and desulfurization performed with liganded LiH-NiCRA.^a

| Run | Substrate | Reagent | Time (h.) ^b | Product | Yield (%) ^c |
|-----|--------------------|----------------------------|------------------------|-----------|------------------------|
| 1 | bromobenzene | LiH-NiCRA-PPh ₃ | 27 | biphenyl | 95 |
| 2 | bromobenzene | LiH-NiCRA-bpy | 16 | biphenyl | 98 |
| 3 | 1-bromo-naphtalene | LiH-NiCRA-bpy | 18 | binaphtyl | 94 |
| 4 | chlorobenzene | LiH-NiCRA-bpy | 26 | biphenyl | 93 |
| 5 | dibenzothiophene | LiH-NiCRA-PPh ₃ | 37 | biphenyl | 70 |
| 6 | dibenzothiophene | LiH-NiCRA-bpy | 40 | biphenyl | 90 |

^a Reductions performed in THF at 63°C on a 10 mmoles scale (runs 1-4) or on a 1 mole scale (runs 5-6). ^b Time after which no evolution was observed. ^c Yields determined by GC using internal standard method (C₁₀-C₁₆).

In order to determine the nature of the reaction intermediates involved in reductions by our new reagents, deuteration experiments were carried out on aromatic halides using commercially available LiD. After isolation by flash chromatography, the deuterium incorporation was measured by ¹H NMR and confirmed by analysis of the molecular ion peak ratio of deuterated - non-deuterated products. We found that reduction of 1-bromo-2-methyl-naphtalene and 2-bromo-anisole afforded respectively 47 % and 46 % of deuterium incorporation, based on the total reduction product. Quenching of the reaction by deuterium oxide did not increase the deuterium content. From these experiments and the coupling properties of our reagents, it seems reasonable to postulate the formation of an unstable aryl-nickel species leading to a radical or an anion which further reacts with LiD to give reduction products. These results also showed that the reaction intermediate reacts with a hydrogen source other than LiD. Thus, we

carried out the reduction of 1-bromo-2-methyl-naphtalene with LiH-NiCRA in THF-d₈. We obtained a 26 % deuterium incorporation showing that the solvent was a hydrogen source during the reduction. It must be implied that the third possible hydrogen source remains the alkyl chain of the alkoxide included in the reagent.

Examination of the potential use of LiH-NiCRA in selective reductions of organic compounds are currently investigated.

Acknowledgements: I thank Prof. P. Caubère for valuable discussions during this work.

References and notes

- 1 LiH possesses the highest lattice energy among metal alkali hydrides, a low sensitivity in air and is safe on storage. See for example: Cotton, F.A., Wilkinson, G., in *Advanced Inorganic Chemistry*, 4th Ed., John Wiley & Sons, New York, 1980, Part 2, chapters 7 and 8.
- 2 See for examples: Brown, H.C.; Krishnamurthy, S., *Tetrahedron*, 1979, 35, 567-603; Liu, H.J.; Lamoureux, G.V.; Llinas-Brunet, M., *Can. J. Chem.*, 1986, 64, 520-522. Klusener, P.A.A.; Brandsma, L.; Verkruijsse, H.D.; von Ragué Schleyer, P.; Friedl, T.; Pi, R., *Angew. Chem. Int. Ed. Engl.*, 1986, 25, 465-466.
- 3 Ohkuma, T.; Hashiguchi, S.; Noyori, R., *J. Org. Chem.*, 1994, 59, 217-221.
- 4 Zippi, E.M., *Synth. Commun.*, 1994, 24, 2515-2523.
- 5 Caubere, P., *Rev. Heteroatom Chem.*, 1991, 4, 78-139.
- 6 *General procedure of preparation and use of LiH-NiCRA*: *t*-BuOH (20 mmol) in 10 ml of dry DME (or THF) was added dropwise to a suspension of LiH (60 mmol), Ni(OAc)₂ (10 mmol) in dry DME (30 ml) at 65°C. After 5 h of stirring, the reagent was ready for use and the substrate could be added in dry DME (10 ml). LiH-NiCRA-bpy or LiH-NiCRA-PPh₃ were prepared in the same manner by the addition of 2,2'-bipyridine (20 mmol) or triphenylphosphine (40 mmol) to the initial mixture of LiH and Ni(OAc)₂. The reactions were monitored by GC analysis of small aliquots. The internal standard was hydrocarbon (C₁₀-C₁₆). After completion of the reaction, the excess of hydride was carefully destroyed by dropwise addition of water at 25°C until hydrogen evolution ceased. After classical workup and separation, products were characterized by comparison of their spectroscopic data with those of authentic samples.
- 7 LiH-NiCRA : Lithium hydride containing nickel Complex Reducing Agent. In the present paper we have adopted the convention of: Caubère, P., *Pure and Appl. Chem*, 1985, 57, 1875 -1882.
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(Received in France 29 May 1995; accepted 3 July 1995)