



Selective Reduction of Organic Compounds with Indium Hydride Reagents

Masafumi Yamada, Koji Tanaka, Shuki Araki, and Yasuo Butsugan*

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466, Japan

Abstract: Three indium hydride reagents (LiInH_4 , LiPhInH_3 , and $\text{LiPh}_2\text{InH}_2$) were prepared and successfully used for the selective reduction of various organic compounds.

Organoindium reagents¹ were recently introduced to organic synthesis and proved to be useful for several organic transformations. In particular, allylic indium reagents,² tetraorganoindate,³ indium carbenoid,⁴ and indium enolate⁵ were found to possess enough reactivity to make new carbon-carbon bonds with high selectivity under mild reaction conditions. In this paper, we describe the preparation of new indium hydride reagents and their use in the reduction of organic functional groups.

Wiberg and Schmidt first prepared indium hydride (InH_3), which was shown to have no reducing ability.⁶ They also prepared lithium indium hydride (LiInH_4) from InCl_3 and LiH , and briefly described on the reduction of several organic compounds with this reagent: acetamide, acetonitrile, butyric acid, and quinone were reported to be reduced, whereas butyraldehyde, benzaldehyde, and butyrolactone were inert.⁶ This unusual feature prompted us to reinvestigate the reactivity of LiInH_4 in detail, and we have now found that LiInH_4 readily reduces carbonyl compounds. LiInH_4 was prepared in ether according to the method of Wiberg and Schmidt.⁶ A substrate was added to this reductant and the reaction mixture was stirred at 0 °C for 1 h and then 12 h at room temperature. The results are shown in Table 1. Aldehyde was smoothly reduced to the corresponding alcohol in high yield. Reduction of ketone is less effective, giving a somewhat lower yield of alcohol. Acid chloride was converted to ester with this reagent. Ester, in turn, was very little reduced. Only with LiH , the above reductions did not occur at all.

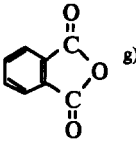
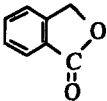

Table 1. Reduction of Carbonyl Compounds with LiInH_4 ^{a)}

| Substrate | Product | Yield (%) ^{b)} |
|---|---|-------------------------|
| <i>p</i> -ClC ₆ H ₄ CHO | <i>p</i> -ClC ₆ H ₄ CH ₂ OH | 93 |
| PhCH=CHCHO | PhCH=CHCH ₂ OH | 92 |
| <i>n</i> -C ₇ H ₁₅ CHO | <i>n</i> -C ₈ H ₁₇ OH | 89 |
| PhCOMe | PhCH(Me)OH | 64 (29) ^{c)} |
| <i>p</i> -BrC ₆ H ₄ COCl | <i>p</i> -BrC ₆ H ₄ COOCH ₂ C ₆ H ₄ Br- <i>p</i> | 84 |
| <i>n</i> -C ₇ H ₁₅ COCl | <i>n</i> -C ₇ H ₁₅ COOC ₈ H ₁₇ - <i>n</i> | 64 ^{d)} |
| <i>p</i> -BrC ₆ H ₄ COOEt | <i>p</i> -BrC ₆ H ₄ CH ₂ OH | 11 (86) ^{c)} |

a) All reactions were carried out with substrate (3 mmol), InCl_3 (3 mmol), and LiH (12 mmol) in Et_2O (20 ml).

b) Isolated yield. c) Recovery of the starting substrate. d) Octanoic acid, presumably formed via hydrolysis of the substrate during aqueous workup, was obtained in 22% yield.

Table 2. Reduction of Organic Compounds with LiPhInH₃^{a)} and LiPh₂InH₂^{b)}

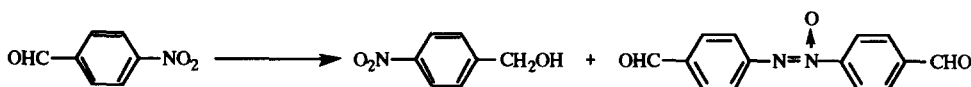
| Substrate | Product(s) | Yields (%) ^{c)} | |
|---|--|--------------------------|------------------------------------|
| | | LiPhInH ₃ | LiPh ₂ InH ₂ |
| <i>p</i> -BrC ₆ H ₄ CHO | <i>p</i> -BrC ₆ H ₄ CH ₂ OH | 57 (18) ^{d)} | 73 (4) ^{d)} |
| | <i>p</i> -BrC ₆ H ₄ CH(Ph)OH | 10 | 3 |
| <i>n</i> -C ₇ H ₁₅ CHO | <i>n</i> -C ₈ H ₁₇ OH | 56 | 71 |
| PhCH=CHCHO | PhCH=CHCH ₂ OH | 62 | 81 |
| | (PhCH=CHCH(OH)-) ₂ | 34 | 13 |
| PhCOMe | PhCH(Me)OH | 95 | 41 (35) ^{e)} |
| <i>n</i> -C ₆ H ₁₃ COMe | <i>n</i> -C ₆ H ₁₃ CH(Me)OH | 59 (28) ^{e)} | 6 (19) ^{e)} |
| <i>p</i> -BrC ₆ H ₄ COCl | <i>p</i> -BrC ₆ H ₄ CH ₂ OH | 48 (35) ^{d)} | 71 (15) ^{d)} |
| | <i>p</i> -BrC ₆ H ₄ CH(Ph)OH | 0 | 2 |
| <i>p</i> -BrC ₆ H ₄ COOEt ^{f)} | <i>p</i> -BrC ₆ H ₄ CH ₂ OH | 83 (10) ^{e)} | 95 |
|  |  | 22 | 66 |
|  | PhCH(Me)OH | 73 (67) ^{h)} | 90 (82) ^{h)} |
| | PhCH ₂ CH ₂ OH | (33) ^{h)} | (18) ^{h)} |
| <i>p</i> -BrC ₆ H ₄ CH ₂ Br | <i>p</i> -BrC ₆ H ₄ Me | 27 | 27 |
| | (<i>p</i> -BrC ₆ H ₄ CH ₂ -) ₂ | 9 | 5 |
| <i>p</i> -ClC ₆ H ₄ NO ₂ | <i>p</i> -ClC ₆ H ₄ N=N(O)C ₆ H ₄ Cl- <i>p</i> | 63 (0) ⁱ⁾ | 0 (93) ^{e)} |
| | <i>p</i> -ClC ₆ H ₄ N=NC ₆ H ₄ Cl- <i>p</i> | 24 (55) ⁱ⁾ | 0 |
| | <i>p</i> -ClC ₆ H ₄ NH ₂ | 13 (42) ⁱ⁾ | 0 |

a) All reactions were carried out with substrate (2 mmol), InCl₃ (4 mmol), LiH (12 mmol), and PhLi (4 mmol) in Et₂O (40 ml). b) All reactions were carried out with substrate (2 mmol), InCl₃ (4 mmol), LiH (8 mmol), and PhLi (8 mmol) in Et₂O (40 ml). c) Isolated yields. d) Yield of the corresponding carboxylic acid presumably formed via oxidation or hydrolysis of the substrate. e) Recovery of the starting substrate. f) 1.0 mmol of ethyl *p*-bromobenzoate was used. g) 0.5 mmol of phthalic anhydride was used. h) Ratio estimated by ¹H-NMR. i) Yield when 0.33 mmol of *p*-chloronitrobenzene was used.

The reducing ability of LiInH₄ was easily increased by the introduction of phenyl group(s) to the indium atom. LiPhInH₃ was prepared in the following manner. To a suspension of InCl₃ (4 mmol) and LiH (12 mmol) in ether (40 ml), PhLi (4 mmol) was added dropwise at 0 °C. The mixture was stirred for 1 h and then ultrasonicated at 10 °C for 2 h to furnish a gray suspension of LiPhInH₃. Although the concrete structure of this compound is not yet established, formulation of LiPhInH₃ was tentatively assigned based on the stoichiometric ratio of the reactants. LiPh₂InH₂ was similarly prepared by changing the amounts of

InCl₃, LiH, and PhLi to 4, 8, and 8 mmol, respectively. These indium hydrides were found to be effective for the selective reduction of organic compounds. Reduction was achieved by adding a substrate (2 mmol) to the reductant and the mixture was stirred at room temperature for 24 h. The results are summarized in Table 2. Although very small amounts of phenylation products were detected in the reactions of *p*-bromobenzaldehyde and *p*-bromobenzoyl chloride, hydride transfer generally occurred in preference over phenyl transfer. These reagents readily reduced aldehyde, ketone, acid chloride, and even ester to the corresponding alcohols. α,β -Unsaturated aldehyde was reduced via exclusive 1,2-reduction. Styrene oxide was converted to a mixture of α - and β -phenethyl alcohols. *p*-Bromobenzyl bromide gave a low yield of *p*-bromotoluene. *p*-Chlorobenzamide and *p*-chlorobenzonitrile were inert both to LiPhInH₃ and to LiPh₂InH₂. Concerning the mechanism of the reduction with the present lithium indium hydride reagents, the formations of the pinacol-type product in the reduction of cinnamaldehyde and the bibenzyl in the reduction of *p*-bromobenzyl bromide suggest that a single-electron-transfer mechanism may participate to some extent. The use of butyllithium in place of phenyllithium gave less satisfactory results.

When aldehyde, acid chloride, ester, and styrene oxide were reduced with LiPh₂InH₂, the yields of the corresponding products were higher than those with LiPhInH₃. But the results were reversed in the case of ketone. In particular, *p*-chloronitrobenzene was reduced only with LiPhInH₃. These results indicate that the reactivity and the selectivity of the phenyl-substituted indium hydrides can be controlled simply by changing the number of phenyl group on the central indium atom. Further example of the selective reduction was shown in Scheme 1. When *p*-nitrobenzaldehyde was treated with LiPh₂InH₂, only the reduction of the formyl group proceeded; whereas with LiPhInH₃, the nitro group was preferentially reduced to give the corresponding azoxy compound as the main product (Table 3).



Scheme 1

Table 3. Reduction of *p*-nitrobenzaldehyde

| | <i>p</i> -O ₂ NC ₆ H ₄ CH ₂ OH (%) | <i>p</i> -OHCC ₆ H ₄ N=N(O)C ₆ H ₄ CHO- <i>p</i> (%) | recovery (%) |
|------------------------------------|--|--|--------------|
| LiPh ₂ InH ₂ | 47 | 0 | 39 |
| LiPhInH ₃ | 21 | 30 | 43 |

It is well-known that NaBH₄ does not reduce ester and epoxide at room temperature;⁷ whereas LiPhInH₃ and LiPh₂InH₂ readily reduce these compounds. Nitrile, on the other hand, is reduced with LiAlH₄⁸ but not with LiPhInH₃ and LiPh₂InH₂. Therefore, the reducing power of these lithium indium hydride reagents is roughly intermediate between that of LiAlH₄ and NaBH₄. Further structural modification of lithium indium hydride should improve the reactivity and selectivity, and hence increase the utility of this new reagent in synthetic organic chemistry.

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