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UNSOLVATED MAGNESIUM DIISOPROPYLAMIDE (MDA) IN ORGANIC SYNTHESIS. THE REDUCTION OF ALDEHYDES AND KETONES TO ALCOHOLS.

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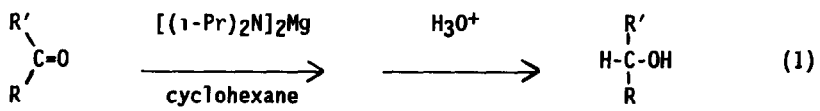
Summary: *A solution of unsolvated magnesium diisopropylamide in cyclohexane has been found to reduce aldehydes and ketones to the corresponding alcohols in good yield.*

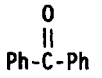
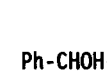
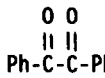
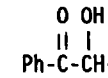
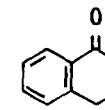
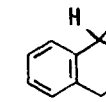
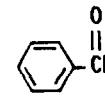
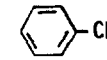
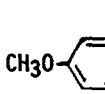
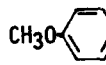
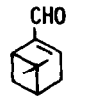
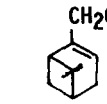
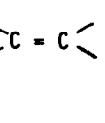
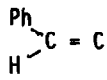
The use of main-group organometallic compounds as reducing agents for the conversion of carbonyls to alcohols is one of the most useful methods available for effecting such transformations.[1] The reduction of the carbonyl may be accomplished by use of a metal hydride directly, such as the reductions achieved by boron hydrides and organoaluminum hydrides,[2] or it may be brought about by transfer of hydride from the beta-carbon of a carbon framework appended to the metal (metalloid) atom.[3] Moreover, the transfer of hydride may be achieved from the beta-carbon of a compound whose metal center is bonded to a heteroatom.[4,5]

As part of our ongoing research dealing with the chemistry of unsolvated diorganomagnesium compounds (prepared and used in the total absence of donor solvent media), we are investigating the interaction of several structurally different compounds with a variety of functional groups. One such system involves the group of reagents possessing magnesium-heteroatomic bonds. We have found that a new reagent, unsolvated magnesium diisopropylamide (MDA)[6], will readily effect the reduction of ketones and aldehydes to alcohols in good yield in the absence of any donor solvent.



(1)

TABLE 1. REDUCTIONS OF KETONES AND ALDEHYDES WITH MDA

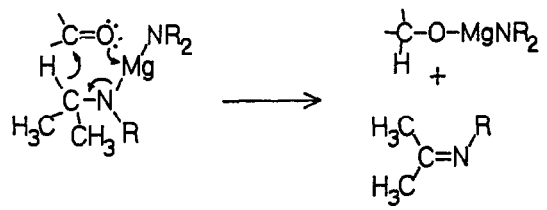
Entry	Substrate	Temp/Time °C/Hr	Main Product	Yield[a] %
1.		81/4.0		73[b]
2.		81/5		60[b]
3.		81/3		53[c]
4.		81/4		60[d]
5.		81/1.5		80[b]
6.		98/2.5		55[e]
7.		98/2		41[f]
8.		98/2		62[g]

(a) The yields reported are based on either isolated products after recrystallization or on the analysis of the total ion chromatogram (T.I.C.) product distribution after GC/MS analysis of the reaction mixture, and are not optimized. When the latter method was used, the products were identified by comparison with an authentic sample. The retention times as well as the fragmentation pattern of the products reported (Table 1) matched the authentic samples perfectly. (b) The yield reported is an isolated yield of analytically pure product. No other products were evident in the T.I.C. of the reaction mixture prior to or after recrystallization. (c) The remaining 47% of the products formed were identified as condensation products. (d) The remainder of the products were condensation products and amounted to 40%. (e) The remainder of the products were high molecular weight products. (f) The remaining 49% of the products formed were the Michael adduct products. (g) The other products formed were $PhCH_2CH_2CH_2OH$ (25%); $PhCH_2CH_2CHO$ (~ 5%) and 8% high molecular wt products. No Michael adduct was formed.

The reductions presented here are illustrated by the procedure for the conversion of benzophenone to benzhydrol. Thus, 4.56 g (25 mmol) of benzophenone were placed in a 100 ml airless-ware [R] flask and then 50 mmol of a 0.5 M magnesium diisopropylamide solution (in cyclohexane) were added slowly over a 10 min. period while maintaining the flask under an inert-gas atmosphere.[7] The reaction mixture was then heated at reflux for 4 h. The resulting product mixture was cooled to room temperature and then hydrolyzed with 20 ml of a deoxygenated 2N HCl solution. The hydrolysate was extracted thrice with ether and the ether extracts were combined, dried and finally submitted to solvents removal under reduced pressure yielding crude benzhydrol as a solid. Subsequent recrystallization of the crude from petroleum ether gave analytically pure benzhydrol 3.2 g (70%).[8]

To our knowledge, this constitutes the first example of such reductions by an unsolvated diorganomagnesium amide. Moreover, since the reaction proceeds cleanly for a variety of structurally different ketones and aldehydes, as in shown in table 1 and since the reagent can be easily prepared from commercially available n-Bu(sec-Bu)Mg (Lithco of America), we wish to report our findings at this time.

As a working hypothesis for further synthetic and mechanistic studies, we premise that these reductions proceed via hydride transfer from the carbon beta to the magnesium center.[9,10] i.e.



R = isopropyl

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6. The reagent can be prepared in a variety of ways. One method involves the reaction between an alkane solution of n-Bu(sec-Bu)Mg and diisopropylamine at a molar ratio of 1:2, $R_2Mg:R_2NH$. The reaction proceeds smoothly at room temperature yielding MDA in quantitative yield, based on the measured amount of evolved butanes according to the reaction depicted:

$$\text{n-Bu(sec-Bu)Mg} + 2\ R_2NH \xrightarrow[\text{R.T. 4h}]{} \text{MDA} + 2C_4H_{10}$$

Subsequent removal of the solvents from the MDA solution yielded a pale yellow solid, this was then analyzed for magnesium content. $C_{12}H_{28}N_2Mg$: Mg calcd 10.82 found 10.30.

7 Even though the reagent is not pyrophoric as a cyclohexane solution, the decomposition of the reagent is prevented by use of an inert atmosphere. Moreover, under these conditions the MDA solution has a shelf life of over 1 year.

8. The melting point range as well as the ^1H NMR spectrum and the mass spectrum were in agreement with those reported in the literature.

9. In order to test this postulate we performed the following: 1) the reaction between MDA and benzophenone was repeated under the conditions described (table 1 entry 1). Samples were removed at 15 min intervals during the course of reaction and analyzed by E.S. R. spectrometry. No E.S.R. signals were observed under these reaction conditions. Subsequent work-up of the reaction mixture and isolation of the products formed yielded only benzhydrol. 2) Unsolvated bis(diphenylamino)magnesium (BDPAM), which possesses no transferable beta hydrogen relative to the magnesium center, was prepared as described for the preparation of MDA (ref. 6 this paper). BDPAM was then allowed to react with benzophenone under the same reaction conditions described for the MDA-benzophenone experiment (entry 1). During this comparative experiment several things were evident. First, unlike the MDA-benzophenone experiments, admixture of the BDPAM + benzophenone at room temperature produced a blue colored reaction mixture (characteristic of the formation of the radical anion from benzophenone $Ph_2C\text{-}O$). Second, after the 4 hr reaction period at 81°C, the reaction mixture was hydrolyzed and the organic products were isolated via routine separation and purification procedures. Analysis by GC/MS indicated quantitative conversion of the benzophenone, but no benzhydrol was found. The major product formed, $C_{38}H_{31}NO$, was isolated in a 90% yield. We are currently attempting to elucidate the process involved in its formation.

10 The imine of acetone has been detected by GC/MS analysis of the reaction mixture prior to hydrolysis.

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