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A NOVEL REDUCING AGENT DERIVED FROM FORMIC ACID AND TWO EQUIVALENTS OF A GRIGNARD REAGENT: CHEMOSELECTIVE REDUCTION OF ALDEHYDES

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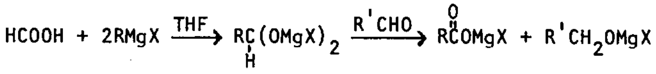
Summary: Aldehydes are reduced at a moderate rate by use of a novel reagent obtained by the addition of two molar equivalents of ethylmagnesium bromide to formic acid in tetrahydrofuran solution. Under similar conditions the reduction of ketones proceeds quite slowly.

Recently F. Sato and coworkers reported[1] a method for preparation of aldehydes that involved addition of two equivalents of a Grignard reagent to a solution of formic acid in tetrahydrofuran (THF), followed by acidification of the reaction mixture. They also indicated that the presumed intermediate (1) was stable in THF at room temperature. Since the latter species (1) bears some resemblance to the proposed intermediate in a Cannizzaro reaction,[2] we decided to examine its potential as a hydride donor to carbonyl compounds.



$$HCOOH + 2RMgX \xrightarrow{THF} R\underset{H}{C}(OMgX)_2 \xrightarrow{R'CHO} R\overset{O}{\overset{\|}{C}}OMgX + R'CH_2OMgX$$

1

The potential reducing agent (1, $R=CH_3CH_2$, X=Br) which we selected for initial studies was prepared by the addition of two molar equivalents of ethylmagnesium bromide[3] to a solution of formic acid in THF as described in the procedure given below. Subsequent addition of citral[3] (2:1 mixture of E:Z stereoisomers) and stirring for 20 minutes[4] at room temperature afforded, after isolation of the product[5] in the manner outlined below, a 3:1 mixture[6] of the desired alcohol (3,7-dimethyl-2,6-octadien-1-ol[7]) and unreduced aldehyde in 88% distilled yield.

Encouraged by these initial results, we examined similar reactions with p-tolualdehyde and decyl aldehyde. Using the standard conditions (35 min. at 20°C) outlined below, p-tolualdehyde[3] afforded p-methylbenzyl alcohol[7] in 94% yield. IR and NMR analysis of the reaction product[8] indicated the absence of any unreacted aldehyde. The reduction of decyl aldehyde[3] was also successful and resulted in a 75% distilled yield of a 9:1 mixture[9] of 1-decanol[7] and unreacted starting material.

Procedure: To a solution of 0.25 mL (6.6 mmoles) of formic acid[10] [assay (HCOOH):min. 98%] in 8 mL of anhydrous THF at 0°C under a nitrogen atmosphere was added dropwise slowly over 20 min. 4 mL of a 3 M solution of ethylmagnesium bromide[3] (12 mmoles) in ethyl ether. This mixture was subsequently stirred at room temperature for 30 min. before adding dropwise over 2 min. a solution of 3.3 mmoles of the carbonyl compound in 2 mL of anhydrous THF. After being stirred for 35 min. at 20°C, this mixture was cooled to 0°C and subsequently acidified by dropwise addition of 6 mL of 2 M aq. HCl. The reaction mixture was then poured into 60 mL of saturated brine and extracted with solvent ether (1x40 mL). The organic phase was washed successively with 50 mL portions of brine and saturated aqueous $NaHCO_3$ solution.[11] The organic layer was then dried ($MgSO_4$), the solvent removed in vacuo, and the product purified by evaporative (Kugelrohr) distillation.

When the above procedure was utilized for several representative ketones,[3] reduction[12] proceeded very slowly as shown by the results in Table I. This method therefore offers promise for selective reduction[13] of aldehydes in the presence of ketones. A more detailed study of this novel type of reducing agent (1), including its properties as the solvent and the nature of "R" are changed, and its reactivity with other functional groups is presently being initiated and results will be reported in a future article.

TABLE I

Starting Material	%Yield[a] (Distilled Product)	Ratio[b] of Ketone to Alcohol
propiophenone	93	91:9
4-phenyl-2-butanone	94	90:10
cycloheptanone	86	81:19

[a] VPC analysis indicated the ketone and corresponding reduction product to comprise >98% of the mixture. [b] This ratio was determined by VPC analysis (6'x1/8" 2½% Carbowax 20M column). Retention times: alcohol > ketone. IR and NMR spectra were consistent with the assigned structures.

REFERENCES

1. F. Sato, K. Ogura, H. Watanabe, and M. Sato, Tetrahedron Lett., 21, 2869 (1980).
2. For a review, see T.A. Geissman, Org. React., 2, 94-113 (1944).
3. Available from Aldrich Chemical Co., Milwaukee, Wis. U.S.A.
4. After a reaction time of 40 minutes, the product was a 9:1 mixture of alcohol and the corresponding aldehyde.
5. No citronellal or citronellol, products obtainable by 1,4-reduction of citral, could be detected by NMR analysis of this mixture.
6. This ratio was determined by NMR analysis (CH_2OH vs. CHO signals).
7. IR and NMR spectra were identical to those exhibited by the authentic compound sold by Aldrich Chemical Co.
8. NMR analysis failed to detect the presence of any p-tolylethylcarbinol, a by-product expected in the presence of excess ethylmagnesium bromide.
9. This ratio was determined by VPC analysis (6'x1/8" 2½% Carbowax 20M column, 185°C). The alcohol and aldehyde comprised >95% of this mixture.
10. Among the suppliers of "anhydrous" formic acid are Fluka (purum anhydrous HCOOH, 98% min.) and Eastman Organic Chemicals (formic acid, 97% min.).
11. If this wash was not done, the crude product was contaminated with a minor amount of propionic acid (the formation of which is consistent with our proposed mechanism for the reduction).
12. Anomalous results were obtained using cyclohexanone. Although its reduction was quite slow, >75% of the isolated material was a mixture of products derived from aldol-type condensations.
13. For previous methods to effect such a transformation see: P.A. Risbood and D.M. Ruthven, J. Org. Chem., 44, 3969 (1979); G.C. Andrews, Tetrahedron Lett., 21, 697 (1980) and references in footnote 3 in that paper.

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