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REDUCTION OF ACID CHLORIDES WITH SODIUM BOROHYDRIDE IN N,N-DIMETHYLFORMAMIDE: NATURE OF THE REACTION INTERMEDIATE AND A METHOD FOR ITS CONVERSION TO THE CORRESPONDING ALDEHYDE WITH MINIMAL ALCOHOL FORMATION

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Summary: By use of sodium borohydride under the proper reaction conditions, direct conversion of both aliphatic and aromatic acid chlorides to the corresponding aldehyde can be achieved in 80-95% yield.

One of the more difficult reductions to accomplish selectively is the conversion of an acid chloride to the corresponding aldehyde without overreduction to the alcohol. Until recently the most common methods of effecting this transformation involved the use of either lithium tri-tert-butoxyaluminum hydride[1] or catalytic hydrogenation (the Rosenmund reduction[2]) As a result of the utility of such conversions in organic synthesis, several novel reducing agents, among which are bis(triphenylphosphine)cuprous borohydride[3] and tetramethylammonium hydridoirontetracarbonyl,[4] have been developed in the past few years.

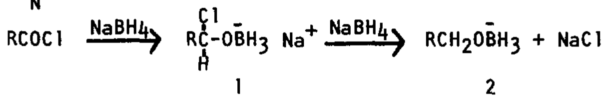
In view of its selectivity as a reducing agent, ease of handling, and low cost, sodium borohydride would seem to be an attractive reagent for effecting the selective reduction of an acid chloride to an aldehyde. Unfortunately, initial studies of this reduction[5] involved vigorous conditions and only alcohols were obtained. Even under mild reaction conditions (use of tetrabutylammonium borohydride in dichloromethane at -78°C), it was reported[6] that reduction of benzoyl chloride by borohydride was extremely rapid and did not stop at the aldehyde stage. A solution to this problem was uncovered by Johnstone and coworkers, who reported[7,8] that the intermediate aldehyde can indeed be isolated in fair to good yield if such reductions are conducted in acetonitrile in the presence of certain metal ions complexed with N,N-dimethylformamide (DMF).

Unfortunately, this metal-assisted borohydride reduction of acyl halides suffers from the low to moderate yields (24-58%) obtained with aliphatic compounds and results in a significant amount (always >10%) of alcohol from overreduction. We wish to report in this communication that $NaBH_4$ in a mixture of DMF-tetrahydrofuran (THF) is capable of converting both aliphatic and aromatic acyl chlorides to the corresponding aldehydes in high yield without the presence of any additional metal salts.

Addition of a 1M solution of $NaBH_4$ in DMF to m-chlorobenzoyl chloride in a THF-DMF solution at -70°C[9] resulted in a rapid reaction, yet surprisingly no precipitate of sodium chloride was observed if slightly less than one molar equivalent[10] of the metal hydride was utilized for the reduction. Using such reaction conditions, the major product was an aldehyde --

the exact amount varying greatly with the method by which the reaction was quenched! However, if more than one molar equivalent of NaBH$_4$ was added, the solution immediately turned cloudy and the sole product isolated was the corresponding alcohol from overreduction! This latter observation was initially quite perplexing since treatment of p-tolualdehyde under similar reaction conditions resulted in little, if any, reduction even after 5 min. at 0°C.

In order to explain the above observations, we suggest that in DMF solution[11] the initial reaction intermediate (1) is stable, yet in the presence of excess borohydride it undergoes facile reduction to afford a more potent reducing agent (2) which is capable of effecting a "chain reduction." Such results are consistent with the observations of Hutchins and coworkers, who reported[12] reduction of carbon-halogen bonds using NaBH$_4$ in aprotic solvents under S$_N$2 conditions.



$$RCOCl \xrightarrow{NaBH_4} R\overset{Cl}{\underset{H}{C}}\text{-}O\overset{-}{B}H_3\ Na^+ \xrightarrow{NaBH_4} RCH_2O\overset{-}{B}H_3 + NaCl$$

1 2

We have also discovered that a substantial amount of overreduction can occur while the reaction is being quenched (even in the presence of a strong acid such as HCl). After examining numerous methods to quench the reaction so as to quickly destroy excess hydride to minimize further reduction, we have found that a mixture of propionic acid-dilute hydrochloric acid-ethyl vinyl ether[13] gave the best results (Table I) for three representative acyl chlorides.

A more detailed study of this reduction, including its scope, is presently being initiated and results will be reported in a future article.

Procedure A[14]: To a solution of 5 mmoles of an aromatic acid chloride in 8mL of anhydrous THF and 2mL of DMF cooled to approximately -70°C (dry ice/n-propyl alcohol bath) was added dropwise slowly over 6 min. a solution of 4.4 mmoles of NaBH$_4$ dissolved in 4mL of DMF. Immediately thereafter 10mL of ethyl vinyl ether, followed in rapid succession by the reaction mixture, was added to a 250mL flask containing a well-stirred mixture of 20mL of propionic acid and 5mL of 2M aq. HCl (Caution: H$_2$ evolution[15]!). In order to minimize the time of contact between ethyl vinyl ether and this acidic mixture, 125mL of saturated brine was added after the mixture had been stirred for approximately 30 sec. 50mL of solvent ether was then introduced into the flask and stirring was continued for several minutes until H$_2$ evolution had ceased. The layers were then separated and the organic phase was washed successively with 15% aq. NaCl (1x100mL), 1M aq. NaOH (4x75mL--add 25mL of brine before separating each wash from the organic layer to prevent emulsions), and saturated brine (100mL). The organic layer was then dried (MgSO$_4$) and the solvent removed in vacuo.

Procedure B[14,16]: 4.4 mmoles of NaBH$_4$ was dissolved in 10mL of DMF, after which 15mL of anhydrous THF was added and the well-stirred mixture was cooled to -70°C. After several minutes, this mixture usually solidified and it was necessary to remove the bath and allow the flask to warm up gradually until the mixture could be considered a well-stirred slush. Once returned to the bath, no further difficulties were encountered stirring this heterogeneous mixture at -70°C. Next a solution of 5 mmoles of an aliphatic acyl chloride in 2mL of anhydrous THF was added dropwise over 30 sec. and the resulting mixture was stirred for an addi-

TABLE I

Starting Acid Chloride[a]	Reaction Mixture (mmol of $NaBH_4$: mmol of acid chloride)	% Yield (% Conversion)[b]	Ratio[c] of Aldehyde to Alcohol
m-chlorobenzoyl chloride	4.42 : 5.04; Procedure A	93(81)	6 : 1
lauroyl chloride	4.46 : 4.92; Procedure B	81(74)	19 : 1
10-undecenoyl chloride	4.30 : 4.78; Procedure B	80(72)	10 : 1

[a] Available from Aldrich Chemical Co., Milwaukee, Wis. U.S.A. [b] This yield is based on the molar amount of $NaBH_4$ utilized for the reaction and refers to distilled product. VPC analysis indicated the aldehyde (excluding the minor amount of alcohol present) to be >95% pure. The conversion is based on the amount of starting acid chloride (always used in slight molar excess). [c] For m-chlorobenzoyl chloride, this ratio was determined by NMR analysis (CHO vs. CH_2OH signals). For the aliphatic substrates, product ratios were determined by VPC analysis (6' x $^1/_8$'' SE-30 column). Retention times: alcohol > aldehyde. The aldehyde was further identified by coinjection with a known sample. IR and NMR spectra were consistent with those exhibited by the authentic compounds sold by Aldrich Chemical Co. All experiments were duplicated to ensure the reproducibility of these results.

tional 2 min. during which time it became homogeneous. The reaction was then quenched using the identical method described in procedure A.

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9. Although aldehydes are still obtained as one of the principal products, results are less satisfactory if the reaction is run at 0°C. Presumably there is less selectivity in the reaction of $NaBH_4$ with the acyl chloride vs. intermediate chloride 1. Furthermore, reaction of the acyl chloride (and intermediate chloride 1) with adventitious water can become a serious side-reaction at 0°C.
10. If 0.25 molar equiv. of $NaBH_4$ is used for this reduction, the major component in the product is unreacted starting material.
11. In the absence of DMF (i.e., in THF or diglyme solution, even at room temperature), no reduction occurs. Similar observations were reported[8] by Johnstone and coworkers; however, they proposed that the reduction proceeded via an intermediate acyl-DMF complex. Since IR analysis of a mixture of DMF and m-chlorobenzoyl chloride showed no indication of a rapid formation of such a complex, our results suggest that the enhanced nucleophilicity of $NaBH_4$ in a highly polar aprotic solvent such as DMF might be the primary factor in explaining the need for DMF.
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13. The critical need for ethyl vinyl ether was demonstrated by an experiment on lauroyl chloride similar to that reported in Table I. When ethyl vinyl ether in the quenching mixture was replaced by ethyl ether, the major product was lauryl alcohol! Similarly, it is important that the quenching mixture be acidic since use of a large volume of 3:1 (v/v) water:ethyl vinyl ether resulted in a 5:3 aldehyde:alcohol ratio for a reaction using m-chlorobenzoyl chloride.
14. All reactions were run under a nitrogen atmosphere. DMF, spectrophotometric grade, was purchased from Aldrich Chemical Co. and was not further purified.
15. If ethyl vinyl ether was either left out of this mixture or replaced by an equivalent volume of ethyl ether, H_2 evolution was considerably more vigorous.
16. If procedure A was used for lauroyl chloride, a substantial amount of the crude reaction product was neither alcohol nor aldehyde and may have been derived from ketene formation and subsequent transformations of the latter.

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