Tetrahedron. Vol. 25, pp. 5555 to 5569. Pergamon Press 1969. Printed in Great Britain

THE PREPARATION OF ALDEHYDES BY REDUCTION OF DIMETHYLAMIDES OF CARBOXYLIC ACIDS WITH SODIUM ALUMINOHYDRIDE

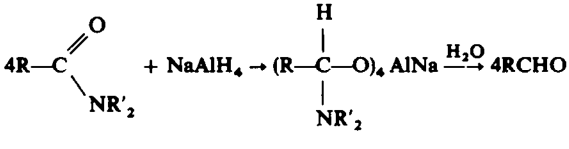
L. I. ZAKHARKIN, D. N. MASLIN and V. V. GAVRILENKO
Institute of Organo-Element Compounds, Academy of Sciences, Moscow, USSR

(*Received in the UK* 9 *June* 1969; *Accepted for publication* 5 *July* 1969)

Abstract—The selective reduction of N,N-disubstituted amides by sodium aluminohydride and alkoxyaluminohydrides has proved a useful synthetic route from carboxylic acids to the corresponding aldehydes. Dimethylamides of aliphatic, aromatic and heterocyclic acids of widely varying structural types have been reduced by sodium aluminohydride to aldehydes, in yields from 70 to 90%.

USE OF sodium aluminohydride[1, 2] in the reduction of organic compounds has been intensively investigated. Earlier we reported the reduction of carboxylic esters,[3] chloroanhydrides,[4] and nitriles[5] with sodium aluminohydride and its alkoxy derivatives.[6]

In addition to the reductions of N,N-disubstituted amides to aldehydes[7-10] we have studied the behaviour of several acid amides towards sodium aluminohydride in order to develop a general procedure for the preparation of aldehydes. The dimethyl derivatives of amides are readily available and give high yields of aldehydes on reduction.



$$4R-C(=O)NR'_2 + NaAlH_4 \rightarrow (R-CH(NR'_2)-O)_4AlNa \xrightarrow{H_2O} 4RCHO$$

As this reduction employing lithium aluminohydride has been reported to be very sensitive to the amide group,[11-13] we studied the effects of substituents on the aldehyde yield by reducing amides of butyric acid with sodium aluminohydride and its alkoxy derivatives. The reactions were carried out under standard conditions (1·5 hr at 0°). The results are summarized in Table 1.

In Table 1 results obtained by reducing these derivatives with lithium aluminohydride in ether[12] are shown for comparison. Thus yields of butyraldehyde are higher with $NaAlH_4$ than with $LiAlH_4$. THF is a more effective solvent than diethyleneglycol dimethyl ether (diglime). Sodium trimethoxy- and triethoxyaluminohydrides decrease the amide reactivity but increase the selectivity of the reaction. Sodium triethoxyaluminohydride is equivalent to lithium triethoxyaluminohydride in amide reduction.[12]

Except of N-butyrylaziridine, $NaAl(t\text{-}BuO)_3H$ reacts very slowly with the majority of the amides investigated, i.e. the reduction is sterically hindered. Consequently the

TABLE 1. YIELDS OF n-BUTYRALDEHYDE IN THE REDUCTION OF DISUBSTITUTED AMIDES OF n-BUTYRIC ACID BY SODIUM ALUMINOHYDRIDE AND SELECTED ALKOXY DERIVATIVES

Amide of n-butyric acid	Yield of aldehyde[a]% $NaAiH_4$ in THF	$NaAiH_4$ in DG	$Na(MeO)_3-AlH$ in THF	$Na(EtO)_3-AlH$ in THF	$Na(tBuO)_3-AlH$ in THF	$LiAlH_4$[e] in Et_2O
Dimethylamide	75	56	85	91	S.r.[b]	25
Diethylamide	43	24	42	50	S.r.[b]	22
Diisopropylamide	N.r.[c]	N.r.[c]	N.r.[c]	N.r.[c]	N.r.[c]	N.r.[c]
Piperidide	70	51	66	56	S.r.[b]	33
Aziridide	84	72	84	82	55[d]	88
N-Methylanilide	68					58
N-Ethylanilide	37	14	61	54	S.r.[b]	

[a] The reactions were carried out by adding the hydride reagents to the amide solution in THF or diglyme (DG) (I equivalent of the hydride per mole of the amide) at 0°. The reaction time was 1·5 hr. Hydride consumption was essentially complete except where otherwise indicated. The yield of aldehyde was determined by analysis with 2,4-dinitrophenyldrazone.[b] Slow reaction.[c] No reaction.[d] Only 0·64 mole of hydride was converted.[e] From Ref. 12.

amide group may provide a convenient means of protecting the carboxylic acid group from the reduction in polyfunctional molecules.

Although sometimes $NaAl(MeO)_3H$ and $NaAl(EtO)_3H$ give a better aldehyde yield than $NaAlH_4$ it is always more convenient to use $NaAlH_4$. This avoids the synthetic procedure of alkoxy derivatives and all four hydride equivalents of sodium aluminohydride are used for the amide reduction.

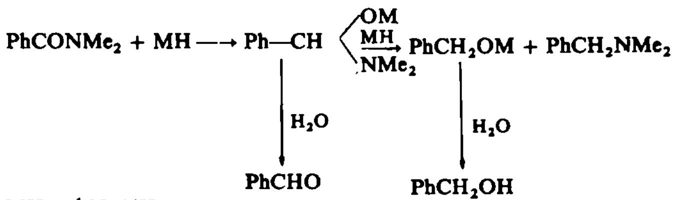
The high aldehyde yields obtained in the reduction of dimethylamides with sodium aluminohydride and the many readily available derivatives of carboxylic acids, promoted a detailed investigation of the reaction conditions in the reduction of reducing dimethylamides of capronic and benzoic acids. The results obtained in THF are summarized in Table 2.

TABLE 2. YIELDS OF ALDEHYDES AND OTHER PRODUCTS IN REDUCTION OF CAPRONIC AND BENZOIC DIMETHYLAMIDES BY SODIUM ALUMINOHYDRIDE UNDER VARIED CONDITIONS

Moles of $NaAlH_4$ per mole of amide	$n-C_5H_{11}CON(Me)_2$ Capraldehyde[b,c]% 0°	25°	$C_6H_5CON(Me)_2$[b] Benzaldehyde, % 0°	25°	Benzyl alcohol, % 0°	25°	N,N-Dimethylbenzamine, % 0°	25°	Starting amide, % 0°	25°
0·25	75	66	77	79	tr.[f]	tr.[f]	tr.[f]	tr.[f]	22	20
0·32	86	78	87	89	6	4	2	1	5	6
0·36	80	73	90	92	7	6	3	2	0	0
0·40	73	59	80	76	16	13	4	11	0	0
0·40		33[d]								
0·50	67	48	70	43	24	22	6	25	0	0
0·50		18[d,e]		9[d,e]		6[d,e]		85[d,e]		
1·0	17	0	43	29	42	33	15	38	0	0

[a] The reaction was carried out in THF at 0° or 25°; hydride was added to amide for 0·5 hr, mixture was stirred for further 1 hr and decomposed.[b] Isolated as 2,4-dinitropenylhydrazone.[c] Analysed by gas chromatografic method.[d] Amide added to hydride.[e] Reaction temp was 50–60°.[f] Traces.

Optimum results were obtained with the ratio of 0·32–0·36 mole sodium aluminohydride to amide, with yields of aldehydes in the range of 73 to 92%. The reaction may be carried out at 0° or room temperature but the lower temperature is preferable for aliphatic amides. If the sodium aluminohydride is added to the amide (to avoid a temporary excess of reducing agent), the aldehyde yields are higher. Gas chromatography of the reduction products of N,N-dimethylbenzamide with sodium aluminohydride indicated the formation of benzyl alcohol and N,N-dimethylbenzylamine together with benzaldehyde. The formation of alcohol in this reduction by lithium aluminohydride has been reported.[7,8] As seen from Table 2, formation of benzyl alcohol and benzaldehyde is favoured by a low temperature and the reverse order of reagent addition. If the ratio of $NaAlH_4$ to amide is increased from 0·36 to 1, the aldehyde yields are reduced while those of benzyl alcohol are increased. If the $NaAlH_4$ amide ratio is equal to 0·25 practically no alcohol or amine is produced. Thus the alcohol and tertiary amine formation is a secondary step of the reduction. The reaction may be described by the following scheme:



$$PhCONMe_2 + MH \longrightarrow Ph{-}CH\begin{cases}OM\\ NMe_2\end{cases} \xrightarrow{MH} PhCH_2OM + PhCH_2NMe_2$$

$$Ph{-}CH(OM)NMe_2 \xrightarrow{H_2O} PhCHO \qquad PhCH_2OM \xrightarrow{H_2O} PhCH_2OH$$

$MH = \frac{1}{4} NaAlH_4$

A high temperature (50–60°), regular order of the reagent addition and a molar ratio of $NaAlH_4$ to amide of 0·5, yielded N,N-dimethylbenzylamine as a main product, while at 0°, and a reverse order of addition yielded about 70% benzladehyde and 24% benzyl alcohol. Reduction of N,N-diethylbenzamide with lithium aluminohydride gave similar results:[11] regular order of the reagent addition at 34° provided 92% of N,N-diethylbenzylamine while the reverse order at −10° gave 35% benzaldehyde and 18% benzyl alcohol. The yields obtained by reduction of dimethylamides of different carboxylic acids with sodium aluminohydride are given in Table 3.

TABLE 3. YIELDS OF ALDEHYDES IN REDUCTION OF DIMETHYLAMIDES WITH SODIUM ALUMINOHYDRIDE IN TETRAHYDROFURAN[a]

Aldehyde from corresponding dimethylamide	Yield of aldehyde[b] %	Aldehyde from corresponding dimethylamide	Yield of aldehyde[b] %
n-Butyraldehyde	86	Benzaldehyde	92, 76[c]
Isobutyraldehyde	72	*p*-Toluic aldehyde	84
Isovaleraldehyde	78, 75[c]	*o*-Chlorobenzaldehyde	83
Capraldehyde	86	*p*-Chlorobenzaldehyde	90, 83[c]
Enanthaldehyde	80	*o*-Bromobenzaldehyde	49
Caprylaldehyde	86	Cinnamaldehyde	51
Palmitaldehyde	82, 78[c]	2-Furylaldehyde	88
Perfluorobutyraldehyde	80, 43[c]	2-Coumarilaldehyde	84
Sebacic aldehyde	77	Terephthalaldehyde	78, 64[c]

[a] Reaction conditions: 0·32–0·36 mole $NaAlH_4$ per mole of amide, reverse order of addition at 0°, mixture was kept at 20° for 1 hr. [b] As 2,4-dinitrophenylhydrazone. [c] Preparative isolation of aldehyde.

These results show that the reduction of dimethylamides with sodium aluminohydride can be applied to a variety of aliphatic, aromatic and heterocyclic acids. Unlike ester reduction to aldehydes,[3] dimethylamides provide good yields, both in the aliphatic (72–86%) and the aromatic (77–92%) series. Dimethylamides of *o*-bromobenzoic (49%) and cinnamic (51%) acids are an exception. Probably the steric hindrance in the first and concurrent addition to the double bond in the second reduce the aldehyde yields. Dimethylamides of dicarboxylic acids also can be reduced to dialdehydes in high yields.

We found that in the reduction of dimethylamides with lithium aluminohydride the yield of aldehydes is increased by using tetrahydrofuran instead of diethyl ether as the solvent. The results obtained in the reduction of butyric, enanthic and benzoic dimethylamides with $LiAlH_4$ in tetrahydrofuran (1 hr at 0°) are shown in Table 4, where for a comparison the data obtained in diethyl ether are also given.[12]

TABLE 4. REDUCTION OF DIMETHYLAMIDES WITH LITHIUM ALUMINOHYDRIDE

Aldehyde from corresponding dimethylamide	Yield of aldehyde[a] % $LiAlH_4$ in THF	 $LiAlH_4$ in Et_2O
n-Butyraldehyde	65	16–25[b]
Enanthaldehyde	66	31
Benzaldehyde	80	50–60[b]

[a] As 2,4-dinitrophenylhydrazones; conditions as described in footnote "a" of Table 1. [b] From Ref. 12.

A comparison of lithium and sodium aluminohydrides (Tables 3 and 4) shows that $NaAlH_4$ is more selective in TGF as is also the case in the reduction of carboxylic esters to aldehydes.[3]

EXPERIMENTAL

Sodium aluminohydride was obtained by direct synthesis from the elements[1, 2] or from lithium aluminohydride and sodium hydride.[14] Commerical grade lithium aluminohydride was employed. The aluminohydrides were dissolved in the freshly distilled dry solvents (THF, diglyme or diethyl ether), and the composition of the sols was established by analysis for hydride (by hydrolysis) and aluminium (with 8-hydroxyquinoline). Various sodium alkoxy aluminohydrides were obtained by adding the calculated amount of an alcohol to a standardized soln of sodium aluminohydride in THF or DG.[6]

N,N-Disubstituted amides were prepared from the corresponding chloroanhydrides and secondary amines in diethyl ether or benzene. Dimethylamides were in most cases prepared from chloroanhydrides and 25% aqueous dimethylamine.

Aldehyde yields in the reduction of various N,N-disubstituted butyric amides (Table 1) were determined as follows. A roundbottom flask, fitted with a stirrer, thermometer and dropping-funnel was flushed with N_2 and the N_2 atm maintained until the hydrolysis step. The THF or DG soln of hydride (1 equiv per mole of amide) was added dropwise over a period of 30 min to the stirred soln of 5–10 mmoles of amide in the same solvent at 0 or 5°. The reaction mixture was stirred for an additional hr at the same temp, and then an aliquot or all the soln taken for aldehyde analysis with 2,4-dinitrophenylhydrazine. The hydrazone ppt was filtered off, dried to constant weight.

In order to determined the products obtained by varying the ratio of sodium aluminohydride to dimethylamide (Table 2) the mixture after reaction was decomposed by the dropwise addition of 1–1·5 ml water. The precipitated hydroxide was separated and the soln was dried over $MgSO_4$, the solvent evaporated *in vacuo* and the products analysed by gas chromatography. In some cases the amide was added to the hydride reagent (normal addition); in others, the hydride was added to the amide (reverse addition).

In Table 3, the reagent was added during 0·5–1·0 hr to a stirred soln of the dimethylamide (0·32–0·35 mole of sodium aluminohydride per mole of amide) in THF at 0 or 5°; then the temp of the mixture was increased to room temp, the reaction mixture was stirred for 1 or 2 hr and then decomposed. The yields of aldehydes were determined by analysis with 2,4-dinitrophenylhydrazine. In a number of cases the reaction was conducted with preparative isolation of aldehydes.

Benzaldehyde. A soln of sodium aluminohydride (25 moles) in THF (50 ml) was added during 30 min to N,N-dimethylbenzamide (10·5 g; 70·5 mmoles) in THF (80 ml) cooled in ice water. The mixture was stirred for another hr and the temp then increased to room temp. Most part of THF was evaporated *in vacuo*, 100 ml of ether was added to the residue and the mixture decomposed with 3N H_2SO_4 (50 ml) with cooling. The etheral layer was separated, and the aqueous portion extracted 3 times with ether. The combined etheral extract were dried over $MgSO_4$, the solvent evaporated *in vacuo* and the residue distilled yielding benzaldehyde (5·7 g; 76%), b.p. 93–95°/42 mm, n_d^{20} 1·5450, 2,4-dinitrophenylhydrazone, m.p. 237–238° (from acetic acid) (Lit.[15] n_d^{20} 1·5456, 2,4-dinitrophenylhydrazone, m.p. 237°). A high boiling fraction (110–114°/42 mm, 0·68 g) was identified as benzyl alcohol (9% yield), n_d^{20} 1·5338, phenylurethane, m.p. 75–76° (from hexane) (Lit[15] m.p. 77°).

p-*Chlorobenzaldehyde.* Using a similar procedure, N,N-dimethyl-*p*-chlorobenzamide (12·4 g; 67·8 mmoles) reacted with sodium aluminohydride (25 mmoles) in THF. The mixture was worked up and the solvent evaporated *in vacuo* yielding *p*-chlorobenzaldehyde (7·8 g; 83%), m.p. 46–47°. The aldehyde distilled at 68–70° (2 mm) and no change in its m.p. was observed (Lit[15] m.p. 48°).

Palmitaldehyde. As described for benzaldehyde, palmitaldehyde (6·7 g; 78%; b.p. 149–151° at 2 mm, m.p. 31–32°, lit[15] m.p. 34°) was obtained from palmitic acid dimethylamide (10·1 g; 35·6 mmole) and sodium aluminohydride (13·5 mmole).

Terephthalaldehyde. A 1·0 M soln of sodium aluminohydride in THF (50 ml) was added with stirring and cooling to 0° to N,N-dimethylterephthalamide (16 g; 72·7 mmole) in the same solvent (60 ml). Stirring was continued for 2 hr at room temp and contents of the flask was poured on to crushed ice. The solid was pressed off to dryness and extracted several times with EtOH. After evaporation of the solvent and recrystallization from hot water, yielding terephthalaladehyde (6·2 g; 64%), m.p. 114–115° (Lit.[15] m.p. 118°).

Perfluorobutyric aldehyde. A 1·0 M $NaAlH_4$ soln (14 ml) was added to N,N-dimethylperfluorobutyramide (8·75 g; 36·4 mmole) in THF (40 ml) during 0·5 hr at −10°. The reaction mixture was stirred for 2 hr at 0–5°. The solvent was evaporated *in vacuo* created by a water-ejector and the residue was mixed with ether (50 ml). The mixture was decomposed slowly with water (5 ml) and then ice-cold 40% H_2SO_4 (35 ml) was added. The etheral layer was separated and the aqueous fraction extracted 3 times with ether. The etheral fractions were combined, dried over silica gel and distilled on a column (8–10 theor. plates). The fraction b.p. 90–95° (3·2 g) was placed in a flask equipped with a column, conc H_2SO_4 (15 ml) was added slowly through the dropping funnel and the mixture carefully heated. Perfluorobutyric aldehyde (1·44 g; 43%) was obtained, b.p. 28–29°, 2,4-dinitrophenylhydrazone, m.p. 105–106° (from CCl_4) (Lit.[16] m.p. 107°).

REFERENCES

[1] L. I. Zakharkin and V. V. Gavrilenko, *Dokl. Akad. Nauk SSSR* **145**, 793 (1962).
[2] E. C. Ashby, G. J. Brendel and H. E. Redman, *Inorg. Chem.* **2**, 499 (1963).
[3] L. I. Zakharkin, V. V. Gavrilenko and D. N. Maslin, I. M. Khorlina, *Tetrahedron Letters* 2087 (1963).
[4] L. I. Zakharkin, D. N. Maslin and V. V. Gavrilenko, *Zh. Org. Khim.* **2**, 2197 (1966).
[5] L. I. Zakharkin, D. N. Maslin and V. V. Gavrilenko, *Izv. Akad. Nauk SSSR, ser. khim.* 1511 (1964).
[6] L. I. Zakharkin, D. N. Maslin and V. V. Gavrilenko, *Zh. Obschch. Khim.* **36**, 200 (1966).
[7] V. Mićović and M. Mihailivić, *Lithium aluminium hydride in organic chemistry.* Izdavacko Preduzece, Beograd (1955).
[8] H. Gaylord, *Reduction with complex metal hydrides.* Interscience Publ., Inc., New York (1956), ch. 10.
[9] E. Mosettig, *Organic Reactions* Vol. VIII; pp. 218–257. Wiley, New York, N.Y. (1948).
[10] A. Hajos, *Komplexe Hydride.* VEB Deutsch. Verlag der Wissenschaften, Berlin (1966), s. 156–169.
[11] V. Mićović and M. Mihailivić, *J. Org. Chem.* **18**, 1190 (1953).
[12] H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.* **86**, 1089 (1964).
[13] H. A. Staab and H. Bräunling, *Liebigs Ann.* **654**, 119 (1962).
[14] L. I. Zakharkin and V. V. Gavrilenko, *Izv. Akad. Nauk SSSR, ser. khim.* 1146 (1962).
[15] *Tables for Identification of Organic Compounds, Supplement to Handbook of Chemistry and Physics.* Chemical Rubber Publishing Company, Cleveland (1960).
[16] D. R. Husted and A. H. Ahlbrecht, *J. Am. Chem. Soc.* **74**, 5424 (1952).