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A Convenient General Method for the Preparation of Aldehydes

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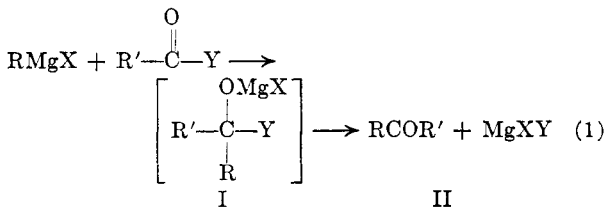
Ten aldehydes from both the aromatic and aliphatic series have been prepared by a two-step scheme. The crucial step in this scheme is the cleavage of an α-substituted *p*-dimethylaminobenzyl alcohol (III) by diazotized sulfanilic acid (Equation 2). The intermediate aminocarbinols are prepared from Grignard reagents and *p*-dimethylaminobenzaldehyde; the latter compound thus furnishes the formyl group in the final product.

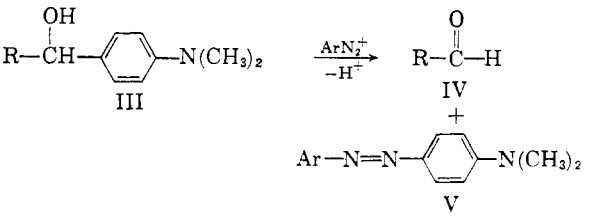
The synthesis of aldehydes and ketones by reactions involving organometallic reagents is sharply limited because of attack of the reagent upon the product. Thus the scheme of Equation 1 involving a Grignard reagent succeeds only if the intermediate (I) is sufficiently stable so that the carbonyl product (II) is not produced in the presence of the Grignard reagent, or if the product is itself unreactive toward the reagent because of special structural features such as steric hindrance.[1]



I II (1)

The preparation of methyl ketones from a Grignard reagent and acetic anhydride at low temperatures[2] is a useful technique based on the former principle, as is the reaction of the Grignard reagent with amides and nitriles.[1] The difficulties inherent in Equation 1 can also be surmounted by the use of organocadmium and organozinc reagents[1,3] which do not attack ketones readily. This paper reports a general method for the preparation of aldehydes by a scheme analogous to Equation 1, in which the free carbinol corresponding to I (R′ = H;Y = *p*-dimethylaminophenyl) is prepared and cleaved in a separate step. The technique has proved to be a convenient one for preparing small to moderate quantities of aldehydes in good yield and high purity.

The success of the method rests upon the ease with which *p*-dimethylaminophenylcarbinols (III) are cleaved by electrophilic reagents such as diazonium salts (Equation 2).



III IV V

This type of cleavage reaction was observed by Quilico and Freri[4] who showed that treatment of 4,4′-bis(dimethylamino)benzhydrol [III, R = *p*-$C_6H_4N(CH_3)_2$] with *p*-nitrobenzenediazonium sulfate produced the azobenzene (V, Ar = *p*-nitrophenyl). Ziegler and his collaborators identified benzaldehyde as a product of reaction of leuco-Malachite Green with *p*-nitrobenzenediazonium chloride[5] and also showed that a number of different *para* substituents could be displaced from aniline and phenol derivatives by diazonium salts.[6] Earlier investigators had shown that *p*-dimethyl-

(1) D. A. Shirley, *Org. Reactions*, **8**, 28 (1954).
(2) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).
(3) J. Cason, *Chem. Revs.*, **40**, 15 (1947).
(4) A. Quilico and M. Freri, *Gazz. chim. ital.*, **62**, 253 (1932).
(5) E. Ziegler and G. Snatzke, *Monatsh.*, **84**, 610 (1953).
(6) E. Ziegler, *Österr. Chemiker-Ztg.*, **53**, 31 (1952).

TABLE I

p-DIMETHYLAMINOPHENYLCARBINOLS (III)

p—$(CH_3)_2N$—C_6H_4—CHOH—R

R	Yield, %	M.P.	Analysis					
			Calcd.			Found		
			C	H	N	C	H	N
3-Methyl-1-butyl	55	50–51	75.97	10.47	6.33	75.88	10.37	6.39
2-Phenylethyl	74	69–71	79.96	8.29	5.48	79.81	8.04	5.62
Cyclohexyl	75	85–86	77.22	9.94	6.00	77.13	9.86	6.02
2-Chlorophenyl	50	94–95	68.84	6.17	5.36	68.86	6.12	5.34
2-Methoxyphenyl	58	79–80	74.68	7.44	5.44	74.81	7.27	5.35
3-Isopropylphenyl	60	53–54	80.25	8.61	5.20	80.31	8.40	5.24
2,5-Dimethylphenyl	60	73–74	79.96	8.29	5.48	80.05	8.29	5.48

aminobenzhydrol (III, R = C_6H_5) was cleaved in similar fashion by bromine,[7,8] nitrous acid,[8] and nitric acid.[8] In all this previous work attention was focused upon the non-carbonyl product, *i.e.*, the azobenzene derivative in the case of diazonium cleavage reactions. The carbonyl product was seldom isolated and characterized. Our attention was attracted to the synthetic possibilities of the reaction when it emerged in the form of a molecular rearrangement.[9]

Table I lists the amino carbinols (III) prepared from the appropriate Grignard reagent and *p*-dimethylaminobenzaldehyde. This inexpensive aldehyde thus serves as the source of the formyl group in the final product.

In Table II are listed the aldehydes prepared by cleavage of the amino carbinols (III) with diazotized sulfanilic acid at *p*H 5–6 and temperature 0–5°. Choice of this diazonium salt provides the necessary electrophilic reactivity and ensures that the by-product (methyl orange) can be easily eliminated because of its insolubility in ether. The conditions of the cleavage reaction are ideal for the manipulation of sensitive aldehydes. Ether extracts of the reaction mixtures contained nearly pure aldehydes as demonstrated by the distillation of colorless products with very little residue.

Smith and his students[10] have evaluated methods previously described for accomplishing the conversion of RMgX to RCHO. In favorable cases the yields of aldehyde-bisulfite addition compounds from the reaction of ethyl orthoformate or ethoxymethyleneaniline with the Grignard reagent were significantly higher than the yields reported here. However, our isolation of pure aldehyde probably constitutes a more realistic test of the synthetic applicability of the method. Furthermore, the scheme described here is a general one, working almost equally well for aliphatic aldehydes and

TABLE II

ALDEHYDES PREPARED BY EQUATION 2

Aldehyde	Yield, %	B.P./mm., found (reported)	2,4-DNP,[a] m.p., found (reported)
4-Methylpentanal	60	119–120/740 (121/747)[b]	99–100 (99)[b]
3-Phenylpropanal	64	71–72/1.5 (103/13)[c]	155–157 (149)[d]
Cyclohexanecarboxaldehyde	45, 69[e]	50–53/20 (55–57/20)[f]	175–176 (173–174)[f]
Benzaldehyde	80[g]	—	241–243 (237)[h]
2-Chlorobenzaldehyde	68	46–47/0.6 (132/60)[i]	208–209 (209)[j]
2-Methoxybenzaldehyde	75	79–80/1.5 (122/20)[k]	252–254 (249–250)[l]
3-Isopropylbenzaldehyde[m]	82	59–60/0.4	212–213[n]
2,5-Dimethylbenzaldehyde	72	58–59/1.0 (220/738)[o]	—
1-Naphthaldehyde	70	105/0.5 (150/13)[p]	256–257 (254–255)[q]
9-Phenanthraldehyde[r]	50	m.p. 100–101 (100–101)[s]	—

[a] 2,4-Dinitrophenylhydrazone. [b] H. Brunner and E. H. Farmer, *J. Chem. Soc.*, 1039 (1937). [c] E. Fischer and E. Hoffa, *Ber.*, **31**, 1992 (1898). [d] C. F. H. Allen and J. H. Richmond, *J. Org. Chem.*, **2**, 224 (1936). [e] Isolated as bisulfite addition compound. [f] M. Mousseron, R. Jacquier, and R. Zagdoun, *Bull. Soc. Chim.*, 1042 (1952). [g] Isolated as 2,4-dinitrophenylhydrazone. [h] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *Systematic Identification of Organic Compounds*, 4th ed., New York, J. Wiley & Sons, 1956, p. 283. [i] R. R. Dreibach and S. A. Shrader, *Ind. Eng. Chem.*, **41**, 2879 (1949). [j] A. K. Macbeth and J. R. Rice, *J. Chem. Soc.*, 151 (1935). [k] F. B. Garner and S. Sugden, *J. Chem. Soc.*, 2882 (1927). [l] E. K. Harwill and R. M. Herbst, *J. Org. Chem.*, **9**, 21 (1944). [m] Calcd. for $C_{10}H_{12}O$: C, 81.08; H, 8.11. Found: C, 80.91; H, 8.22. [n] Calcd. for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.87; N, 17.08. Found: C, 58.54; H, 4.85; N, 17.18. [o] L. Gattermann, *Ann.*, **393**, 219 (1912). [p] G. M. Badger, *J. Chem. Soc.*, 535 (1941). [q] B. A. Gingrass and W. A. Waters, *J. Chem. Soc.*, 3508 (1954). [r] The amino carbinol precursor of this aldehyde, prepared in the same manner as those in Table I, was used without purification. The yield may be taken as minimal. [s] C. A. Dornfeld and G. H. Coleman, *Org. Syntheses*, **Coll. Vol. III**, 701 (1955).

(7) G. J. Esselen and L. Clarke, *J. Am. Chem. Soc.*, **36**, 308 (1914).

(8) E. P. Kohler and R. H. Patch, *J. Am. Chem. Soc.*, **38**, 1205 (1916).

(9) M. Stiles and A. J. Sisti, *J. Org. Chem.*, **24**, 268 (1959).

(10) L. I. Smith and M. Bayliss, *J. Org. Chem.*, **6**, 437 (1941); L. I. Smith and J. Nichols, *J. Org. Chem.*, **6**, 489 (1941).

being relatively insensitive to steric and electronic effects in the aldehyde moiety.

EXPERIMENTAL[11]

p-Dimethylaminophenylcarbinols (III). The new amino carbinols listed in Table I were prepared from the appropriate alkyl- or arylmagnesium bromide and *p*-dimethylaminobenzaldehyde, except for the cyclohexyl derivative, which was prepared from cyclohexylmagnesium chloride. The halides (except *m*-bromocumene) and the aldehyde were commercial products. The Grignard reagents were prepared by reaction of the halides, in 2–3 volumes of ether, with a slight excess of magnesium. *p*-Dimethylaminobenzaldehyde was added as a solution in benzene, and the reaction was stirred at room temperature for 2–10 hr. Hydrolysis was accomplished in aqueous ammonium chloride, the ether layer was dried over calcium sulfate, and the residue was recrystallized from benzene–petroleum ether (b.p. 30–60°) [except in the case of 1-(4-dimethylaminophenyl)-4-methyl-1-pentanol, which was crystallized from petroleum ether alone].

p-Dimethylaminobenzhydrol, m.p. 69–70° (reported[12] 69–70°) was prepared by the reduction of the ketone with sodium borohydride. *p*-Dimethylaminophenyl-1-naphthylcarbinol, m.p. 98–99° (reported[13] m.p. 97–98°) was prepared as described previously.[13]

Preparation of the aldehydes. Sulfanilic acid (60 g., 0.31 mole) was dissolved in a solution of 18.4 g. of sodium carbonate in 200 ml. of water, and diazotized at 0–5° by the addition of 64 ml. of concd. hydrochloric acid and a solution of 24.4 g. of sodium nitrite in 75 ml. of water in portions. When diazotization was complete and a slight excess of nitrous acid was present, the solution was buffered by the addition of 70 g. of sodium acetate in 200 ml. of water (*p*H *ca.* 6). A solution of 0.20 mole of the amino carbinol in 500 ml. of acetone was then added, followed by an additional 250 ml. of acetone. The mixture, which became red in a few minutes, was allowed to stir under a nitrogen atmosphere at 0–5° for 30 min. and then for an additional 30 min. after the removal of the ice bath. The mixture was diluted with water and extracted with ether. After removal of solvent from the dried solution, the aldehyde was distilled under an atmosphere of nitrogen.

Methyl m-bromobenzoate, b.p. 69–70°/0.2 mm. (reported[14] b.p. 122.5°/15 mm.), was prepared in 84% yield from commercial *m*-bromobenzoic acid by the method of Clinton and Laskowski.[15]

m-Bromophenyldimethylcarbinol. A solution of 150 g. (0.70 mole) of methyl *m*-bromobenzoate in 300 ml. of ether was added to 2.25 moles of methylmagnesium bromide in 1.5 l. of ether and the mixture was stirred overnight. Hydrolysis with aqueous ammonium chloride was followed by isolation in the usual manner. The product, 130 g. (85%), distilled at 79–80°/0.24 mm.

Anal. Calcd. for $C_9H_{11}BrO$: C, 50.25; H, 5.16. Found: C, 50.10; H, 5.03.

m-Bromocumene.[16] *m*-Bromophenyldimethylcarbinol (130 g., 0.60 mole) was hydrogenolyzed in three batches, each utilizing 3 g. of 5% palladium-on-charcoal catalyst in 200 ml. of glacial acetic acid and 1 ml. of 70% perchloric acid, under 40 lb. initial hydrogen pressure, at room temperature. Approximately 1 hr. was required for each reaction. After removal of the catalyst the combined acetic acid solutions were combined and about 75% of the acetic acid was removed under reduced pressure. The residue was diluted with water and steam distilled. Fractional distillation yielded 96 g. (80%) of colorless liquid, b.p. 208–210° (reported[17] b.p. 208–210°).

ANN ARBOR, MICH.

(11) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting and boiling points were not corrected for stem exposure.

(12) K. Albrecht, *Ber.*, **21**, 3292 (1888).

(13) F. Sachs and L. Sachs, *Ber.*, **38**, 511 (1905).

(14) A. M. Kellas, *Z. Physik. Chem.*, **24**, 245 (1897).

(15) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(16) The synthesis of this compound was adapted from an unpublished procedure of Professor R. E. Ireland.

(17) E. C. Sterling and M. T. Bogert, *J. Org. Chem.*, **4**, 20 (1939).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensation of Alkyl Acetates with Benzophenone by Lithium Amide to Form β-Hydroxy Esters. Relative Ease of Self-condensation of Esters[1]

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The success of the aldol type of condensation of ethyl or isopropyl acetate with benzophenone by lithium amide in liquid ammonia to form the corresponding β-hydroxy ester was found to be dependent on minimizing the self-condensation of the alkyl acetate before adding the ketone to the reaction mixture. This was accomplished either by adding the ketone very soon after the ester or by employing excess reagent over the one equivalent required to form the intermediate lithio ester. This was not necessary with *t*-butyl acetate. When two equivalents of lithium amide were used, the monolithio derivative of the β-hydroxy ester first formed in the condensation was converted to the dilithio derivative of the β-hydroxy ester. This was demonstrated by adding benzyl chloride to the reaction mixture to form the α-benzyl derivative of the β-hydroxy ester. Consideration is given to the bearing of these results on the earlier general procedure for synthesizing β-hydroxy esters and to the relative ease of self-condensations of the alkyl acetates.

Recently[2] ethyl acetate was condensed with various ketones or aldehydes by means to two molecular equivalents of lithium amide in liquid ammonia to form the corresponding β-hydroxy esters. For example, this ester was condensed with benzophenone to give β-hydroxy ester I in

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).