RECENT ADVANCES IN ALDEHYDE SYNTHESIS

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ALDEHYDES occupy a central position in the series of oxidation levels found among organic compounds. They may act as electrophiles and also, by removal of an α-proton, give rise to nucleophilic anions. This variety of possible reactions makes them potentially very valuable as intermediates but complicates their synthesis since they are often unstable, particularly in basic or oxidising media. Examples are, however, widespread in Nature and exhibit widely differing but often highly important physiological activity, *e.g.*, glucose, pyridoxal phosphate, streptomycin, aldosterone, vanillin, or dolichodial.

It is the purpose of this review to indicate the developments which have taken place in the field of aldehyde synthesis since the last thorough review[1] was published in 1954,

The types of reactions discussed fall into eight groups, namely Hydrolysis and Hydration, Oxidation with no Skeletal Change, Reduction of Carboxylic acids and their Derivatives, Addition of One, Two, Three and Four Carbon Atoms, Skeletal Rearrangements.

Hydrolysis and Hydration

Substances at the same oxidation level as aldehydes such as acetals, aldimines, 1,1-dihalogenoalkanes, 1-halogenoalk-1-enes, etc., can generally be converted to aldehydes by hydrolysis. Acetylenes which are also at the same oxidation level usually give methyl ketones on hydration but butadiyne adds methanol to give 1-methoxybutenyne and hence various other derivatives of ethynylacetaldehyde or of acetylacetaldehyde which are valuable synthetic intermediates.[2]

The hydration of alk-1-ynes to aldehydes can be achieved in good yields by hydroboration with a hindered borane such as bis-1,2-dimethylpropylborane $(Me_2CH{-}CHMe{-})_2BH$, to give a mono-adduct, a vinylborane, and then oxidation of this to the aldehyde with hydrogen peroxide.[3]

A recently developed route to α-halogenoaldehydes from acetylenes involves the free-radical addition of a chloroamine to the triple bond. The chloroenamine formed is hydrolysed in the reaction medium to give the α-chloroaldehyde.[4]

$$RC{\equiv}CH \rightarrow RCCl{=}CHNR_2 \rightarrow RCHCl{-}CHO$$

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[1] O. Bayer in "Methoden der Organischen Chemie", Houben-Weyl, Stuttgart, 1954, 4th edn. vol. VII, part I,

[2] W. Franke, R. Kraft, and K. Kosswig in "Newer Methods of Preparative Organic Chemistry", Academic Press, London, 1963, vol. II, p. 3.

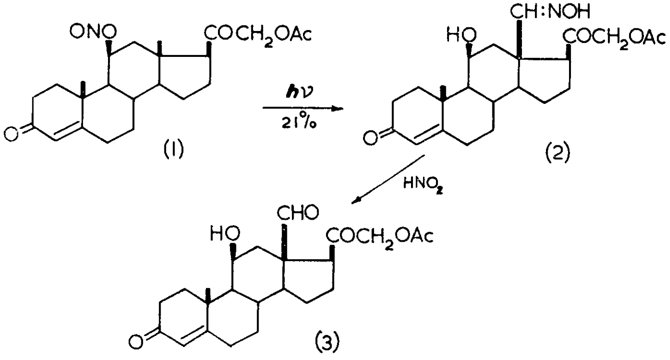
[3] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, 1961, **83**, 3834.

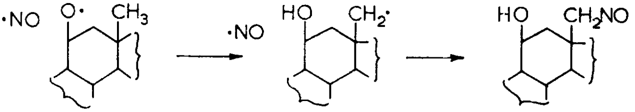
[4] F. Minisci and R. Galli, *Tetrahedron Letters*, 1965, 1679; F. Minisci, R. Galli, and G. Pollina, *Chimica e Industria*, 1965, **47**, 736.

Oxidation with no Skeletal Change

Oxidation of Methyl Groups.—The oxidation of "activated", allylic or benzylic, methyl groups can be achieved by a number of reagents.[5] For the oxidation of arylmethanes to benzaldehydes, chromium trioxide in acetic anhydride has been found to be a simpler modification of the Etard reaction.[6]

The oxidation of "unactivated" methyl groups may be achieved by a intramolecular radical reaction in which the specificity of attack is achieved as a result of the suitable relative positions of the two groups involved. The case of most interest for aldehyde synthesis is the Barton reaction[7] as exemplified by the synthesis of aldosterone acetate(3) from the corticosterone nitrite ester(1).[8] Photolysis of the nitrite groups produces nitric oxide and an alkoxyl radical which can abstract a hydrogen atom from a suitably situated methyl group. The carbon radical produced combines with the nitric oxide to form a nitrosomethyl group which isomerises to the aldoxime(2).





Other intramolecular radical reactions such as the decomposition of hypoiodites or the lead tetra-acetate oxidation of alcohols may yield aldehydes or their derivatives by a multi-stage process.[9] These will not be discussed here.

Oxidation of Primary Alcohols.—Two ionic schemes, (*a*) and (*b*), for the oxidation of a primary alcohol to an aldehyde are conceivable

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[5] Ref. 1, p. 135.

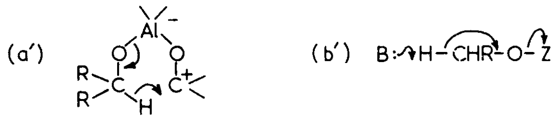
[6] J. Rocek and F. Šorm, *Chem. listy*, 1955, **49**, 306.

[7] A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, 1962, **17**, 35; M. Akhtar, *Adv. Photochem.*, 1964, **2**, 263.

[8] D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.*, 1960, **82**, 2641.

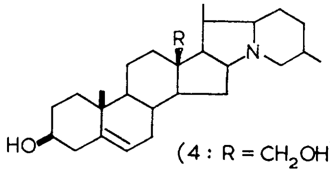
[9] Cf. K. Heusler and J. Kalvoda, *Angew. Chem.*, 1964, **76**, 518.

where B is a base and A an oxidant or hydride acceptor. Mechanism (a) probably occurs in the oxidation of ethanol to acetaldehyde by benzenediazonium salts[10] and, in a cyclic variant, (a′), in the Oppenauer oxidation[11] in which the aluminium alkoxide loses a hydride ion to a carbonyl compound. The strongly basic conditions used in the Oppenauer oxidation are conducive to condensation and polymerisation of the aldehyde produced and, particularly in the case of aliphatic aldehydes, good yields are obtained only in suitable cases under well chosen conditions.

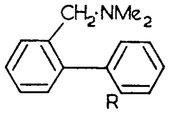


Mechanism (b) itself is not known but if the alcohol is converted to a derivative RCH_2–O–Z where Z is a better electron acceptor than H, the more facile reaction (b′) can occur and many examples of oxidation of this type are now known.

One of the best studied cases is that where Z = Cr^{VI} which occurs in the oxidation of alcohols by chromic acid.[12] Good conversions of primary alcohols to aldehydes are obtainable if strongly acidic media are avoided or if the alcohol is sterically hindered. Interesting examples are isorubijervine (4), which gives the hydroxy-aldehyde (5) with chromium trioxide in acetic acid,[13] and the amino-alcohol (6) which with t-butyl chromate gives the corresponding aldehyde (7) in 90% yield.[14] Chromium trioxide in pyridine[15] has been found useful, particularly for hindered aldehydes such as 2-ethyl-2-methylbutanal which is obtained from the alcohol in 88% yield.[16] A molar CrO_3 : alcohol ratio of 2:1 has been found to be the optimum in certain cases.[17]



(4 : R = CH_2OH)
(5 : R = CHO)



(6 : R = CH_2OH)
(7 : R = CHO)

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[10] N. C. Deno, H. J. Peterson, and G. S. Saines, *Chem. Rev.*, 1960, **60**, 7.

[11] C. Djerassi, *Org. Reactions*, 1951, **6**, 207.

[12] W. A. Waters, *Quart. Rev.*, 1958, **12**, 277.

[13] J. C. Sheehan, R. L. Young, and P. A. Cruickshank, *J. Amer. Chem. Soc.*, 1960, **82**, 6147.

[14] H-W. Bersch and A. v. Mletzko, *Arch. Pharm.*, 1958, **291**, 91; T. Suga, K. Kihara, and T. Matsuura, *Bull. Chem. Soc. Japan*, 1965, **38**, 893, 1503.

[15] J. R. Holum, *J. Org. Chem.*, 1961, **26**, 4814.

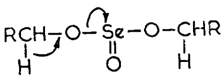
[16] S. Sarel and M. S. Newman, *J. Amer. Chem. Soc.*, 1956, **78**, 5416.

[17] R. C. Cookson, J. Hudec, S. A. Knight, and B. R. D. Whitear, *Tetrahedron*, 1963, **19**, 1995.

Other oxidising agents which have been used to prepare aldehydes are discussed below. Several are known to act by formation and cleavage of an ester as in (b′). The others may do so. Of the other metals of variable valency, Ru^{VIII} as RuO_4 will oxidise benzyl alcohol to benzaldehyde in 90% yield but converts aliphatic alcohols to acids.[18] Mn^{VII} is too strong an oxidising agent to be useful here but Mn^{IV} as MnO_2 is well known to give good yields of aldehydes from allylic or benzylic primary alcohols.[19] Recent studies[20,21] have shown that, with a large excess of reagent and in pure solvents, saturated primary alcohols are also oxidised to aldehydes (butanal 70%). Nickel peroxide has been found to give good yields of benzylic aldehydes but poor yields from saturated primary alcohols. Very little excess reagent is required unlike the case of MnO_2.[22] Pb^{IV} as $Pb(OAc)_4$ in pyridine solution will oxidise primary alcohols to aldehydes at room temperature (butanal 70%, cinnamaldehyde 91%).[23] If the alcohol has a δ-hydrogen atom, formation of tetrahydrofurans is usually a strongly competing reaction particularly in benzene where the mechanism is probably radical rather than ionic. Cu^{II} as $Cu(OAc)_2$ in the presence of oxygen has been found particularly useful for the oxidation of α-ketols, as in the $CH_2OH–CO–$ sidechain of steroids, to $CHO–CO–$,[24] and ceric ammonium nitrate in aqueous acetic acid effects oxidation of benzyl alcohols to benzaldehydes in excellent yield and under very mild conditions.[25]

Of the non-metals, halogens as X^+ have been used for allylic and benzylic alcohols. Thus iodine in the presence of silver trifluoracetate oxidises cinnamyl alcohol to cinnamaldehyde in 80% yield.[26] Potassium hypochlorite in methanol[27] and *N*-bromosuccinimide in carbon tetrachloride[28] have been used successfully for benzylic alcohols.

Selenium as SeO_2 has been used to convert various long-chain alcohols to their selenite esters which were then decomposed by heating under vacuum with ultraviolet irradiation when excellent yields of aldehydes were obtained along with water and elementary selenium.[29]



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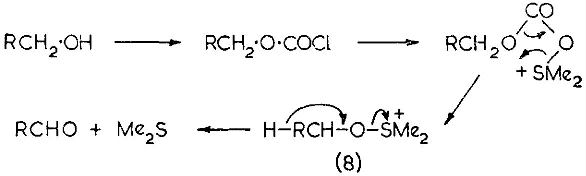
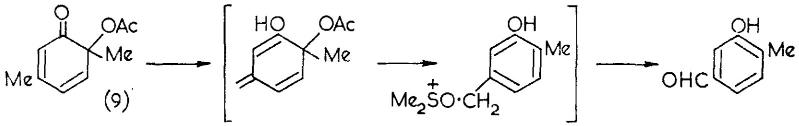
[18] L. M. Berkowitz and P. N. Rylander, *J. Amer. Chem. Soc.*, 1958, **80**, 6682.
[19] R. M. Evans, *Quart. Rev.*, 1959, **13**, 61.
[20] R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, 1959, **24**, 1051.
[21] I. T. Harrison, *Proc. Chem. Soc.*, 1964, 110.
[22] K. Nakagawa, R. Konaka, and T. Nakata, *J. Org. Chem.*, 1962, **27**, 1597.
[23] R. E. Partch, *Tetrahedron Letters*, 1964, 3071.
[24] M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, 1963, **28**, 2001; R. E. Beyler and F. Hoffman, *J. Amer. Chem. Soc.*, 1957, **79**, 5297.
[25] W. S. Trahanovsky and L. B. Young, *J. Chem. Soc.*, 1965, 5777.
[26] E. D. Bergmann and I. Shahak, *J. Chem. Soc.*, 1959, 1418.
[27] C. Y. Meyers, *J. Org. Chem.*, 1961, **26**, 1046.
[28] J. Blair, W. R. Logan, and G. T. Newbold, *J. Chem. Soc.*, 1956, 2443.
[29] H. P. Kaufmann and D. B. Spannuth, *Chem. Ber.*, 1958, **91**, 2127.

N^{IV} as N_2O_4 in carbon tetrachloride gives over 95% yields of a wide range of substituted benzaldehydes from the benzyl alcohols.[30] The mechanism probably involves the radical decomposition of the nitrite ester.[31]

The cases where Z = N^V and S^{IV} are particularly interesting. Benzylic alcohols are oxidised to aldehydes in good yield by boiling dimethyl sulphoxide in the presence of oxygen,[32] and all types of primary alcohol when treated with dicyclohexylcarbodiimide and phosphoric acid in dimethyl sulphoxide at room temperature give good yields of aldehydes (cholan-24-al 85%, *p*-nitrobenzaldehyde 92%).[33] It seems likely that this reaction proceeds[34] *via* the intermediate (8) which is probably also formed in the reaction of primary alcohols with, consecutively, phosgene, dimethylsulphoxide, and triethylamine. Seventy per cent yields of aliphatic aldehydes are obtainable by this modification which requires only very mild, and essentially neutral conditions.[35]



The same intermediate is probably formed in the reaction with dimethyl sulphoxide of primary alkyl iodides,[36] alkyl arenesulphonates[37,38] or "activated" alkyl chlorides or bromides, such as α-halogeno-ketones,[39] α-halogeno-esters,[40] and benzylic halides,[38] when 70—80% yields of aldehydes are obtainable—heating with sodium bicarbonate is usually found to be necessary. A similar intermediate has been invoked to explain the oxidation of quinol acetates, such as (9) which are obtained from phenols by the use of lead tetra-acetate, to aldehydes with dimethyl sulphoxide and sodium bicarbonate.[41]



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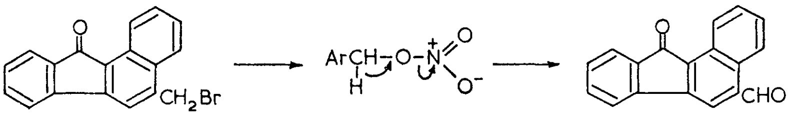
[30] B. O. Field and J. Grundy, *J. Chem. Soc.*, 1955, 1110.
[31] Cf. P. Gray and A. Williams, *Chem. Rev.*, 1959, **59**, 283.
[32] V. J. Traynelis and W. L. Hergenrother, *J. Amer. Chem. Soc.*, 1964, **86**, 298.
[33] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1963, **85**, 3027.
[34] S. G. Smith and S. Winstein, *Tetrahedron*, 1958, **3**, 317.
[35] D. H. R. Barton, B. J. Garner, and R. H. Wightman, *J. Chem. Soc.*, 1964, 1855.
[36] A. P. Johnson and A. Pelter, *J. Chem. Soc.*, 1964, 520.
[37] N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, 1959, **81**, 4113.
[38] H. R. Nace and J. J. Monagle, *J. Org. Chem.*, 1959, **24**, 1792.
[39] N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Amer. Chem. Soc.*, 1957, **79**, 6562.
[40] I. M. Hunsberger and J. M. Tien, *Chem. and Ind.*, 1959, 88.
[41] J. Leitich and F. Wessely, *Monatsh.*, 1964, **95**, 129.

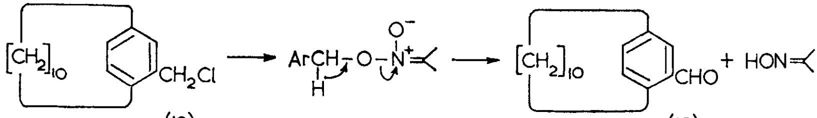
On heating a primary alkyl halide or toluene-*p*-sulphonate with an amine oxide an analogous reaction occurs *via* the intermediate RCH_2–O–NR_3^+, but the yields are not as good as in those cases using dimethyl sulphoxide.[42]

The conversion of benzyl nitrate to benzaldehyde by base is a well proven case of the ionic mechanism (b′) where Z = NO_2.[43] Benzyl nitrates may be obtained from the alcohols or the halides.[44] Thus the benzyl halide (10) is converted to the aldehyde (11) in 85% yield by treatment with silver nitrate and then base.[45]



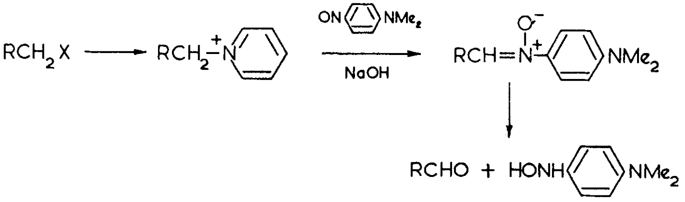
(10) (11)

Oxidation of Primary Halides.—As well as by the methods just mentioned, primary benzylic or allylic halides may be converted to aldehydes by reaction with the anion of a nitroalkane.[46] The intermediate, on treatment with base, gives the aldehyde plus an oxime. Thus 2,5-decamethylenebenzyl chloride (12) treated with 2-nitropropane and sodium methoxide gives 2,5-decamethylenebenzaldehyde (13) in 84% yield.[47]



(12) (13)

Recent developments in the use of the Kröhnke reaction have been



reviewed.[48] Only "activated" (benzylic, etc.) halides react but overall yields of the order of 80% are obtainable, often in cases where other methods are not suitable.

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[42] V. Franzen and S. Otto, *Chem. Ber.*, 1961, **94**, 1360; T. Kato, Y. Goto, and Y. Yamamoto, *J. Pharm. Soc. Japan*, 1964, **84**, 287; Cf. W. Feely, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, 1957, **22**, 1135.

[43] E. Buncel and A. N. Bourns, *Canad. J. Chem.*, 1960, **38**, 2457.

[44] R. Boschan, R. T. Merrow, and R. W. van Dolah, *Chem. Rev.*, 1955, **55**, 485.

[45] R. L. Letsinger and J. D. Jamison, *J. Amer. Chem. Soc.*, 1961, **83**, 193.

[46] Ref. 1, p. 202.

[47] A. T. Blomquist, R. E. Stahl, Y. C. Meinwald, and B. H. Smith, *J. Org. Chem.*, 1961, **26**, 1687.

[48] F. Kröhnke, *Angew. Chem.*, 1963, **75**, 317.

The Sommelet conversion of primary alkyl halides to aldehydes by reaction with hexamethylenetetramine[49] is generally not suitable for aliphatic aldehydes unless they are fully α-substituted but gives up to 80% yields with unhindered aromatic and heteroaromatic systems.

Primary Alkyl Nitro-compounds.—These can be converted to aldehydes by the Nef reaction.[50]

$$RCH_2{\cdot}NO_2 \xrightarrow[(ii)\,H^+]{(i)\,OH^-} RCH{=}\overset{+}{N}(OH)_2 \longrightarrow RCHO + [HNO] \longrightarrow N_2O + H_2O$$

Good yields are obtainable (butanal 85% from 1-nitrobutane).

Primary Alkyl Amines.—No good general way of oxidising these to aldehydes has been found. The Sommelet reaction[49] can be used in certain cases. Diazotisation of benzylamines in anhydrous dimethyl sulphoxide gives 60—80% yields of benzaldehydes.[51]

$$ArCH_2NH_2 \rightarrow ArCH_2^+ \rightarrow ArCH_2\text{–}O\text{–}\overset{+}{S}Me_2 \rightarrow ArCHO$$

Argentic picolinate oxidises amines of the type RCH_2NHR' to RCHO and NH_2R'. Yields are fairly good when R = aryl and R' = tertiary alkyl but poor when R' = H.[52] Hydrogen peroxide catalysed by sodium tungstate has been found to oxidise primary alkyl primary amines to aldoximes (*p*-carboxybenzaldoxime 91%, butyraldoxime 57%, acetaldoxime 5%).[53]

Reduction of Carboxylic Acids and their Derivatives

Carboxylic acids can be reduced to aldehydes in 20—80% yields with lithium in ethylamine[54] but many other functions are simultaneously reduced by the reagent. Diisobutyl aluminium hydride has been used also and gives 40—70% yields.[55]

Acid chlorides can be reduced by the Rosenmund,[56] Reissert,[57,58] or Grundmann[59] procedures or by using modified complex hydrides such as lithium tri-t-butoxyaluminium hydride, which gives good yields of alde-

[49] S. J. Angyal, *Org. Reactions*, 1954, **8**, 197.

[50] W. E. Noland, *Chem. Rev.*, 1955, **55**, 137.

[51] K. H. Scheit and W. Kampe, *Angew. Chem. Internat. Edn.*, 1965, **4**, 787.

[52] R. G. R. Bacon and W. J. W. Hanna, *J. Chem. Soc.*, 1965, 4962.

[53] K. Kahr and C. Berther, *Chem. Ber.*, 1960, **93**, 132; P. Burckard, J. P. Fleury and, F. Weiss, *Bull. Soc. chim. France*, 1965, 2730.

[54] A. W. Burgstahler, L. R. Worden, and T. B. Lewis, *J. Org. Chem.*, 1963, **28**, 2918.

[55] L. I. Zakharkin and I. M. Khorlina, *Zhur. obshchei Khim.*, 1964, **34**, 1029 (*Chem. Abs.*, 1964, **60**, 15724f).

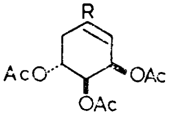
[56] E. Mosettig and R. Mozingo, *Org. Reactions*, 1948, **4**, 362; Y. Egawa, M. Suzuki, and T. Okuda, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 589.

[57] E. Mosettig, *Org. Reactions*, 1954, **8**, 218.

[58] W. E. McEwen and R. L. Cobb, *Chem. Rev.*, 1955, **55**, 511.

[59] H. K. Mangold, *J. Org. Chem.*, 1959, **24**, 405.

hydes from aromatic acid chlorides,[60] and sodium trimethoxyboron hydride which reduces the shikimic acid derivative (14) to the aldehyde (15) in 85% yield.[61]



(14: R = COCl)
(15: R = CHO)

A photolytic reduction of acid bromides is reported whereby benzoyl bromide, for example, on irradiation in ether for thirty hours gives 80% benzaldehyde, a hydrogen atom being transferred from the solvent to the initially formed benzoyl radical.[62]

Thiol esters, R·CO·SR′, can be reduced to aldehydes with lithium hydride[63] or with Raney nickel[57] preferably in the presence of *NN*′-diphenylethylenediamine.[64]

Esters of electron deficient acids such as *p*-nitrobenzoic and quinaldic acids[65] and perchloropropionic[66] and perchloropenta-2,4-dienoic acids[67] give fair yields of aldehydes with lithium aluminium hydride at −70°. Reduction by this reagent may also stop at the aldehyde level due to the formation of a particularly stable aluminium complex. Thus dimethyl aspartate, added at room temperature to excess lithium aluminium hydride and left for two hours gave a 69% yield of aminosuccindialdehyde, isolated as a bis-dinitrophenyl derivative.[68] For simple esters, di-isobutyl aluminium hydride at −70° (88% with ethyl butyrate),[69] sodium aluminium hydride at −50° (81% with methyl butyrate)[70] and sodium aluminium di-isobutyl dihydride[71] are all reported to give yields of the order of 60—90%. Phenyl esters are reported to give aldehydes in good yield on reduction with lithium tri-t-butoxyaluminium hydride.[72] Methyl linolenate has been reduced to the aldehyde by acyloin condensation, reduction of the ketol to a vicinal diol and subsequent cleavage by adding lead tetraacetate to give an 80% overall yield.[73]

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[60] H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, 1958, **80**, 5372; H. C. Brown and B. C. Subba Rao, *ibid.*, p. 5377; E. D. Bergmann and A. Cohen, *Tetrahedron Letters*, 1965, 1151.

[61] R. Grewe and H. Büttner, *Chem. Ber.*, 1958, **91**, 2452.

[62] U. Schmidt, *Angew. Chem.*, 1965, **77**, 169.

[63] P. Brandt, *Acta Chem. Scand.*, 1949, **3**, 1050.

[64] H. J. Bestmann and H. Schulz, *Chem. Ber.*, 1959, **92**, 530.

[65] H. Rutner and P. E. Spoerri, *J. Org. Chem.*, 1963, **28**, 1898.

[66] A. Roedig, F. Hagedorn, and G. Märkl, *Chem. Ber.*, 1964, **97**, 3322.

[67] A. Roedig and G. Märkl, *Annalen*, 1962, **659**, 1.

[68] W. Grassmann, H. Hörmann, and H. Endres, *Chem. Ber.*, 1955, **88**, 102.

[69] L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Letters*, 1962, 619.

[70] L. I. Zakharkin, V. V. Gavrilenko, D. N. Maslin, and I. M. Khorlina, *Tetrahedron Letters*, 1963, 2087; L. I. Zakharkin, V. V. Gavrilenko, and D. N. Maslin, *Izvest. Akad. Nauk S.S.S.R.*, *Ser. Khim.*, 1964, 926 (*Chem. Abs.*, 1964, **61**, 5505c).

[71] L. I. Zakharkin and V. V. Gavrilenko, *Izvest. Akad. Nauk S.S.S.R.*, *Odtel. khim. Nauk*, 1960, 2245 (*Chem. Abs.*, 1961, **55**, 14352i); L. I. Zakharkin and I. M. Khorlina, *ibid.*, 1964, 465 (*Chem. Abs.*, 1964, **60**, 15765d).

[72] P. M. Weissman and H. C. Brown, *J. Org. Chem.*, 1966, **31**, 283.

[73] E. J. Gauglitz and D. C. Malins, *J. Amer. Oil Chemists' Soc.*, 1960, **37**, 425.

Reduction of amides has been much studied as a method of obtaining aldehydes. With sodium in liquid ammonia, aliphatic acid amides give fair yields, aromatic acid amides good yields and amidines of both types excellent yields.[74] Lithium aluminium hydride reduction of *N*-methylanilides,[75] *N*-acylaziridines,[76] *N*-acylimidazoles,[77] and *N*-acylpyrazoles[78] or lithium triethoxyaluminium hydride reduction of dimethyl amides[79] gives 60—98% yields while diisobutylaluminium hydride reduction of *N*-methylanilides[80] seems to give slightly lower yields.

The McFadyen–Stevens decomposition or arenesulphonyl-hydrazides, $R.CO.NH.NH.SO_2Ar$, by heating with base[57] gives moderately good yields of aromatic aldehydes and of aliphatic ones if they have no α-hydrogens.[81]

Nitriles can be reduced to aldehydes by the Stephen procedure[57] which gives excellent yields from aromatic nitriles but often much lower yields with aliphatic and hindered aromatic ones. Partial hydrogenation over Raney nickel in the presence of various complexing agents such as hydrazine,[82] phenylhydrazine,[83] semicarbazide,[84] and*NN'*-diphenylethylenediamine,[85] has been studied. The aldehydes have to be recovered from the complexes formed but up to 90% yields are attainable. Excellent yields of aromatic aldehydes are obtained directly by reduction of the nitriles by Raney nickel in the presence of sodium hypophosphite in an aqueous medium[86] or with Raney nickel and formic acid.[87] The former method gives excellent yields of unsaturated aldehydes such as vitamin A aldehyde from the corresponding nitriles.[88] Of the hydride-reducing agents, lithium aluminium hydride may be used if the nitrile is hindered.[89,90] Excellent yields are claimed using di-isobutylaluminium hydride (butanal 93%).[91] Sodium triethoxyaluminium hydride gives good yields with aromatic and

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[74] A. J. Birch, J. Cymerman-Craig, and M. Slaytor, *Austral. J. Chem.*, 1955, **8**, 512.

[75] F. Weygand and R. Mitgau, *Chem. Ber.*, 1955, **88**, 301, and previous papers. S. S. Nigam and B. C. L. Weedon, *J. Chem. Soc.*, 1957, 3320.

[76] H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, 1961, **83**, 2016, 4549.

[77] H. A. Staab and H. Bräunling, *Annalen*, 1962, **654**, 119.

[78] W. Reid and F. J. Königstein, *Annalen*, 1959, **622**, 37.

[79] H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, 1964, **86**, 1089.

[80] L. I. Zakharkin and I. M. Khorlina, *Izvest. Akad. Nauk S.S.S.R., Odtel. khim. Nauk*, 1959, 2146 (*Chem. Abs.*, 1960, **54**, 10932b).

[81] M. Sprecher, M. Feldkimel, and M. Wilchek, *J. Org. Chem.*, 1961, **26**, 3665.

[82] S. Pietra and C. Trinchera, *Gazzetta*, 1955, **85**, 1705.

[83] A. Gaiffe, *Chimie et Industrie*, 1965, **93**, 259.

[84] H. Plieninger and G. Werst, *Chem. Ber.*, 1955, **88**, 1956.

[85] H. Plieninger and B. Kiefer, *Chem. Ber.*, 1957, **90**, 617.

[86] O. G. Backeberg and B. Staskun, *J. Chem. Soc.*, 1962, 3961.

[87] B. Staskun and O. G. Backeberg, *J. Chem. Soc.*, 1964, 5880; Cf. T. van Es and B. Staskun, *J.*, 1965, 5775.

[88] Netherland Appl., 6,401,332 (*Chem. Abs.*, 1965, **62**, 9182g); N. O. Pastushak and A. V. Dombrovskii, *Zhur. Org. Khim.*, 1965, **1**, 323.

[89] H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, 1964, **86**, 1085.

[90] W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *Annalen*, 1961, **641**, 196; see also Ref. 1, p. 306 and refs. quoted in Ref. 83.

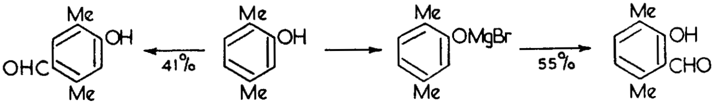
[91] L. I. Zakharkin and I. M. Khorlina, *Doklady Akad. Nauk S.S.S.R.*, 1957, **116**, 422 (*Chem. Abs.*, 1958, **52**, 8040f).

heteroaromatic nitriles but not with aliphatic ones,[92] and lithium trialkoxyaluminium hydrides have been used with success for both aromatic and aliphatic nitriles.[89] Esters and nitriles can be reduced to aldehydes in high yield by reaction with ethyl α-bromoisobutyrate and zinc, followed by borohydride reduction, and then pyrolysis of the β-hydroxy-ester formed (H. Lapin and R. Malzieu, *Bull. Soc. chim. France*, 1965, 1864, and previous papers).

Addition of One Carbon Atom

The formylation of an aromatic system, a double bond, or a carbanion by reaction with a formic acid derivative provides a general synthesis of R–CHO from R–H (or R–X *via* a metal derivative). Olah and Kuhn have made a thorough review of those formylations which are catalysed by protic or Lewis acids.[93] Of these the Gattermann–Koch reaction (CO + HCl) is useful for formylation of aromatic hydrocarbons and the Gattermann reaction (HCN) for hydrocarbons, phenols, phenol ethers, furans, chromans, and pyrroles. Recent developments in this field are the use of alkyl dichloromethyl ethers[94] and thio-ethers[95] and of formyl fluoride[96] to formylate hydrocarbons, hetero-aromatics, and phenols, and of carbon monoxide and hydrogen chloride in trifluoroacetic acid to formylate pyrones.[97]

The Reimer–Tiemann reaction[98] allows the formylation of phenols and pyrroles. Yields seldom exceed 50%, but high proportions of *ortho*-substitution occur. It has been shown recently that reaction of bromomagnesium phenoxides with ethyl orthoformate gives only the *ortho*-formylphenol in moderately good yield,[99] whereas the free phenol formylated with ethyl orthoformate and aluminium chloride gives only the *para*-formyl isomer.[94]



A recent surge of interest in the Vilsmeier reaction[100] has led to the realisation of a number of formylations of olefinic or potential olefinic

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[92] G. Hesse and R. Schrödel, *Annalen*, 1957, **607**, 24; Cf. L. I. Zakharkin, D. N. Maslin and V. V. Gavrilenko, *Izvest. Akad. Nauk, S.S.S.R., Odtel. khim. Nauk*, 1964, pp. 561 and 1511.

[93] G. A. Olah and S. J. Kuhn in "Friedel–Crafts and Related Reactions", Interscience, 1965, vol. III, part 2, p. 1153.

[94] A. Rieche, H. Gross and E. Höft, *Chem. Ber.*, 1960, **93**, 88; H. Gross, A. Rieche, and G. Matthey, *ibid.*, 1963, **96**, 308.

[95] H. Gross and G. Matthey, *Chem. Ber.*, 1964, **97**, 2606.

[96] G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, 1960, **82**, 2380.

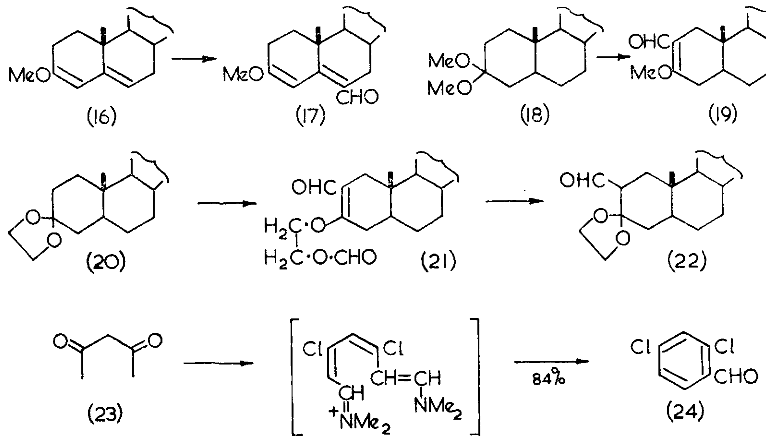
[97] L. L. Woods and P. A. Dix, *J. Org. Chem.*, 1961, 26, 1028.

[98] H. Wynberg, *Chem. Rev.*, 1960, **60**, 169.

[99] G. Casnati, M. Crisafulli, and A. Ricca, *Tetrahedron Letters*, 1965, 243.

[100] Ref. 93, p. 1211.

systems as well as of aromatic ones. Vilsmeier reagents are obtained from dialkylformamides, such as dimethylformamide and phosphorus oxychloride or phosgene, and can be considered to be complexes such as $[Cl_2PO–O–CH{=}NR_2]^+ Cl^-$. They react with aromatics, hetero-aromatics, and olefins which are rich in electrons and with substances such as ketals which can give rise to these, yielding immonium salts which on hydrolysis give aldehydes. Thus *NN*-dimethylaniline gives *p*-dimethylaminobenzaldehyde in 85% yield.[101] Recent developments include the formylation of enamines[102] and enol ethers,[100] and steroidal dienol ethers (16),[103] acyclic ketals (18),[104] and cyclic ketals (20).[105] 3-Keto-5α-steroids give 3-chloro-2-formyl-2-enes and 3-keto-5β-steroids 3-chloro-4-formyl-3-enes in accord with the direction of enolisation.[106] Acetylenes give β-chloroacroleins by addition of the elements of formyl chloride.[107] More complicated condensations may occur as in the case of acetylacetone(23), as a result of double formylation.[108]



The formylation of carbanions, as in the formation of α-hydroxymethylene derivatives from ketones, can be applied to unstabilised anions

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[101] H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1659.

[102] W. Ziegenbein, *Angew. Chem.*, 1965, **77**, 380.

[103] D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow, and D. M. Williamson, *Tetrahedron*, 1964, **20**, 597.

[104] D. Burn, G. Cooley, J. W. Ducker, B. Ellis, D. N. Kirk, and V. Petrow, *Tetrahedron Letters*, 1964, 733.

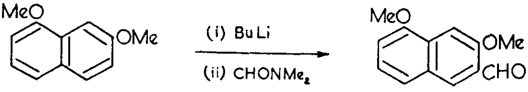
[105] R. D. Youssefyeh, *Tetrahedron Letters*, 1964, 2161.

[106] J. Schmitt, J. J. Panouse, A. Hallot, P. J. Cornu, H. Pluchet, and P. Comoy, *Bull Soc. chim. France*, 1964, 2753, 2760, 2768; K. Bodendorf and R. Mayer, *Chem. Ber.*, 1965, **98**, 3554.

[107] W. Ziegenbein and W. Franke, *Angew. Chem.*, 1959, **71**, 573; Vo-Quang Yen, P. Cadiot, and A. Willemart, *Bull. Soc. chim. France*, 1962, 10.

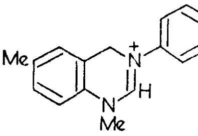
[108] A. Holy and Z. Arnold, *Coll. Czech. Chem. Comm.*, 1965, **30**, 53.

such as those in simple alkyl,[109] aryl,[110] vinyl,[111] or ethynyl[112] lithiums or Grignard reagents. The anion may be obtained from a halide or by hydrogen/metal exchange as in the cases of the ethynyl Grignards or 1,7-dimethoxynaphthalene (25) which by this procedure gives 84% of the 6-formyl derivative (26)[113] while normal Friedel–Crafts formylation should give the 4- or 8-formyl isomer.

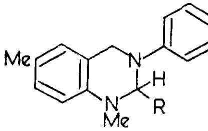


(25) (26)

Dimethylformamide and ethoxymethyleneaniline, EtOCH=NPh, appear to be the best reagents. Formic acetic anhydride, CHO–OCOCH$_3$, has been used but with much less success.[114] Grignard reagents react with the readily prepared formic acid derivative (27) presumably *via* (28) to give, after hydrolysis, the homologous aldehyde in excellent yield except in sterically hindered cases.[115] Formylation of aryl-lithiums with iron pentacarbonyl gives benzaldehydes in fair to moderate yields.[116]

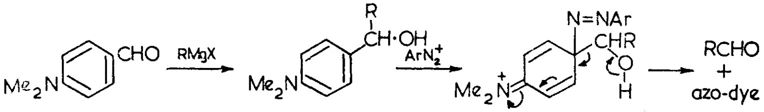


(27)



(28)

A more involved formylation of Grignard reagents is the sequence developed by Sisti.[117] Approximately 50% overall yields are attainable.



Formylations by nucleophilic reagents are also known. Formylation of phenols in an "abnormal" position can be achieved by reaction of the derived quinol acetates with sodio-nitromethane followed by a Nef reaction as shown.[118]

[109] Ref. 1, p. 64.

[110] W. J. Dale, L. Starr, and C. W. Stroble, *J. Org. Chem.*, 1961, **26**, 2225.

[111] J. Ficini and H. Normant, *Bull. Soc. chim. France*, 1964, 1294.

[112] E. R. H. Jones, L. Skattebøl, and M. C. Whiting, *J. Chem. Soc.*, 1958, 1054.

[113] R. A. Barnes and W. M. Bush, *J. Amer. Chem. Soc.*, 1959, **81**, 4705.

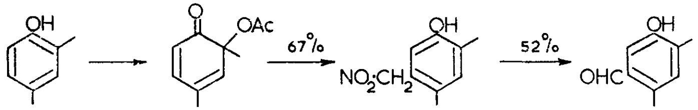
[114] W. R. Edwards and K. P. Kammann, *J. Org. Chem.*, 1964, **29**, 913.

[115] H. M. Fales, *J. Amer. Chem. Soc.*, 1955, **77**, 5118.

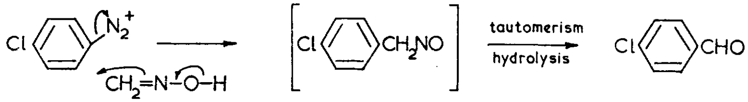
[116] M. Ryang, I. Rhee, and S. Tsutsumi, *Bull. Chem. Soc. Japan*, 1964, **37**, 341.

[117] M. Stiles and A. Sisti, *J. Org. Chem.*, 1960, **25**, 1691; A. Sisti, J. Burgmaster, and M. Fudim, *ibid.*, 1962, **27**, 279.

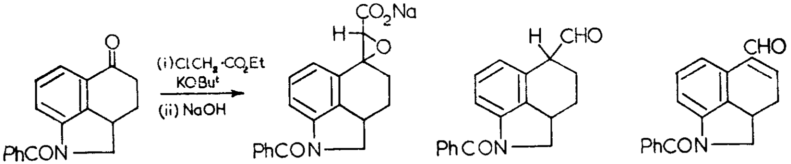
[118] V. Guth, J. Leitich, W. Specht, and F. Wessely, *Monatsh.*, 1963, **94**, 1262.



Aromatic amines can be converted to benzaldehydes by reaction of the corresponding diazonium salts with formaldoxime. For example, *p*-chloroaniline gives p-chlorobenzaldehyde in 60% yield.[119]



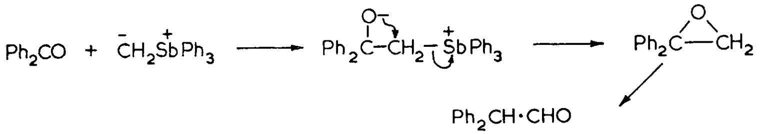
The Darzens–Claisen aldehyde synthesis can be modified to effect the conversion of a carbonyl compound to the next higher aldehyde either saturated or αβ-unsaturated. Thus the ketone (29) was converted as usual to the glycidate salt (30) which could either be decomposed to the saturated aldehyde (31) by treatment with sodium bisulphite or treated with pyridinium tribromide and then with semicarbazide to give the derivative of the unsaturated aldehyde (32).[120]



(29) (30) (31) (32)

The use of t-butyl chloracetate instead of the ethyl ester allows, in general, direct pyrolysis of the glycidate ester to the saturated aldehyde.[121]

The conversion of R_2CO to $R_2CH{\cdot}CHO$ can also be effected by a Wittig reaction using methoxymethylene triphenylphosphorane,[122] $MeOCH{=}PPh_3$, or, at least in the case of benzophenone, with a methyl triphenyl stibonium salt, $MeSbPh_3^+$, and phenyl-lithium which give diphenylacetaldehyde and triphenylantimony,[123] or also by reaction of the



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[119] W. F. Beech, *J. Chem. Soc.*, 1954, 1297; R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron* 1958, **2**, 1; S. D. Jolad and S. Rajagopal, *Chem. Ber.*, 1963, **96**, 592, and previous papers.

[120] E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Amer. Chem. Soc.*, 1956, **78**, 3087.

[121] E. P. Blanchard and G. Büchi, *J. Amer. Chem. Soc.*, 1963, **85**, 955.

[122] S. G. Levine, *J. Amer. Chem. Soc.*, 1958, **80**, 6150; G. Wittig and E. Knauss, *Angew. Chem.*, 1959, **71**, 127.

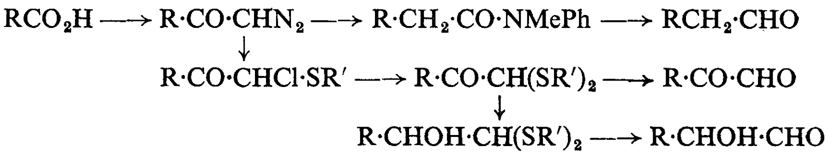
[123] M. C. Henry and G. Wittig, *J. Amer. Chem. Soc.*, 1960, **82**, 563.

ketone with an alkoxymethyl Grignard reagent and pinacol-type rearrangement of the carbinol produced.[124]

$$R_2CO + R'O{\cdot}CH_2MgCl \rightarrow HO{\cdot}CR_2{\cdot}CH_2OR' \xrightarrow{H^+} R_2CH{\cdot}CHO \text{ (65\% overall)}$$

Ketones, R_2CO, can be converted to the next higher α-hydroxyaldehydes, $R_2C(OH){\cdot}CHO$, by condensation with nitromethane followed by a Nef reaction.[50]

Carboxylic acids can be converted to aldehydes with one more carbon atom *via* the derived diazoketone by the routes shown.[125]



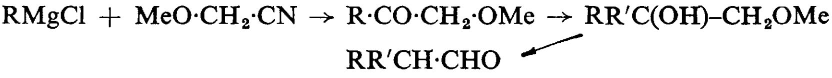
$$\begin{tikzcd}
RCO_2H \arrow[r] & R{\cdot}CO{\cdot}CHN_2 \arrow[r] \arrow[d] & R{\cdot}CH_2{\cdot}CO{\cdot}NMePh \arrow[r] & RCH_2{\cdot}CHO \\
 & R{\cdot}CO{\cdot}CHCl{\cdot}SR' \arrow[r] & R{\cdot}CO{\cdot}CH(SR')_2 \arrow[r] \arrow[d] & R{\cdot}CO{\cdot}CHO \\
 & & R{\cdot}CHOH{\cdot}CH(SR')_2 \arrow[r] & R{\cdot}CHOH{\cdot}CHO
\end{tikzcd}$$

Addition of Two Carbon Atoms

Methods are known for the conversion of alkyl halides, carbonyl compounds, and acids to aldehydes with two more carbon atoms. The condensation of an alkyl halide with the α-position of an aldehyde is probably best achieved by alkylation of the halogenomagnesium salt of the readily prepared aldimine such as (33).[126] Yields are high, little or no *N*-alkylation occurs and there is no rearrangement with allyl halides.

$$Me_2CH{\cdot}CHO \rightarrow\rightarrow \underset{(33)}{Me_2C{=}CH{-}NR{-}MgBr} \xrightarrow{\text{nBuI}}\rightarrow nBuCMe_2{-}CHO \text{ (70\%)}$$

Alternatively the alkyl halide may be converted to its Grignard derivative and this condensed with methoxyacetonitrile. The ketone produced can be reacted with another Grignard reagent and the resulting carbinol rearranged to give the aldehyde.[127] Vinylic Grignards give unsaturated aldehydes.[128]



$$\begin{tikzcd}
RMgCl + MeO{\cdot}CH_2{\cdot}CN \arrow[r] & R{\cdot}CO{\cdot}CH_2{\cdot}OMe \arrow[r] & RR'C(OH){-}CH_2OMe \arrow[dl] \\
 & RR'CH{\cdot}CHO &
\end{tikzcd}$$

A number of methods have been devised to circumvent the difficulties in performing the conversion of R_2CO to $R_2C{=}CR{\cdot}CHO$ which cannot be effected satisfactorily by direct reaction of the ketone with an acetalde-

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[124] H. Normant and C. Crisan, *Bull. Soc. chim. France*, 1959, 459; M. de Botton *Compt. rend.*, 1965, **260**, 4783, and previous papers.

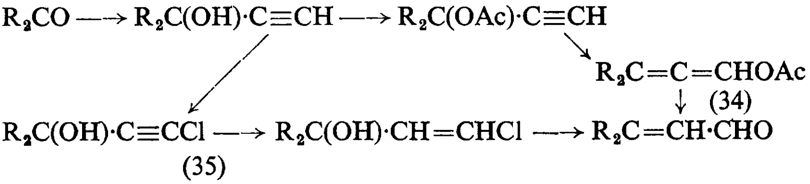
[125] F. Weygand and H. J. Bestmann, *Chem. Ber.*, 1957, **90**, 1230; 1958, **91**, 1043; 1959, **92**, 528.

[126] G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, 1963, **85**, 2178.

[127] M. Mousseron, M. Mousseron, L. Benezet, and G. Igolen, *Parfümerie u. Kosmetik*, 1959, **40**, 71.

[128] H. Normant, *Compt. rend.*, 1955, **240**, 1435.

hyde. The Wittig reagents, $Ph_3P{=}CR{\cdot}CHO$, react with aldehydes but not with ketones to give the desired homologue,[129] and the lithium salt of the aldimine, $LiCHR{\cdot}CH{=}NR'$, can be used in a normal Claisen aldol reaction.[130] Alternatively, an acetylenic anion may be used, but direct acid-catalysed rearrangement of the ethynyl carbinol gives a methyl ketone rather than the desired aldehyde. The required rearrangement can be effected indirectly as shown *via* an allenyl acetate (34)[131] (80% overall) or by partial reduction of the chloroacetylene (35).[132]



Modifications include the use of lithium chloroacetylide[133] or ethoxyethynyl magnesium bromide.[134]

An alternative "disguised" acetaldehyde unit is a vinyl ether. These react in the presence of Lewis acids with an aldehyde[135] or an acetal[136] to give homologues with two, or by repeated reaction, four or six more carbon atoms.

$$RCH(OR)_2 + R'CH{=}CH{\cdot}OR \rightarrow RCH(OR){\cdot}CHR'{\cdot}CH(OR)_2 \rightarrow RCH{=}CR'{\cdot}CHO$$

Similarly, ethyl β-bromovinyl ether reacts with acetals to give homologated α-bromoacetals ($R' = Br$).[137] Various aspects of the reaction have been reviewed recently.[138]

Acids can be homologated by reaction of their chlorides with acetylene under Friedel Crafts conditions and modification of the resulting vinyl chloride by reactions such as those shown.[139]

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[129] S. Trippett and D. M. Walker, *Chem. and Ind.*, 1960, 202; Netherland Appl., 6,413,904 (*Chem. Abs.*, 1965, **63**, 14926a).

[130] G. Wittig, H. D. Frommeld, and P. Suchanek, *Angew. Chem.*, 1963, **75**, 978.

[131] G. Saucy, R. Marbet, H. Lindlar, and O. Isler, *Helv. Chim. Acta*, 1959, **42**, 1945.

[132] M. Julia and J. M. Surzur, *Bull. Soc. chim. France*, 1956, 1615.

[133] H. G. Viehe, *Chem. Ber.*, 1959, **92**, 1270.

[134] J. F. Arens, *Adv. Org. Chem.*, 1960, vol. II, p. 157, and refs. therein.

[135] H. Saikachi and H. Ogawa, *J. Amer. Chem. Soc.*, 1958, **80**, 3642; R. I. Hoaglin, D. G. Kubler, and R. E. Leach, *ibid.*, p. 3069.

[136] R. I. Hoaglin and D. H. Hirsh, *J. Amer. Chem. Soc.*, 1949, **71**, 3468; O. Isler, H. Lindlar, M. Montavon, R. Rüegg, and P. Zeller, *Helv. Chim. Acta*, 1956, **39**, 249; K. C. Brannock, *J. Org. Chem.*, 1960, **25**, 258.

[137] B. M. Mikhailov and L. C. Povarov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1965, 282.

[138] L. A. Yanovskaya, *Reaktsii i Metody Issled. Organ. Soedin*, 1962, **11**, 231 (*Chem. Abs.* 1963, **59**, 7329); S. M. Makin and V. B. Mochalin, *Zhur. Vsesoyuz. Khim. obshch. im. D.I. Mendeleeva*, 1965, **10**, 114; O. Isler and P. Schudel, *Adv. Org. Chem.*, 1963, **4**, 128.

[139] S. Wakayama, S. Itoh, S. Yui, and H. Maekawa, *J. Chem. Soc. Japan*, 1957, **78**, 1525 (*Chem. Abs.* 1959, **53**, 21628a).

$$\begin{tikzcd}
\mathrm{RCOCl} \arrow[r] & \mathrm{RCO{\cdot}CH{=}CHCl} \arrow[r] & \mathrm{RCO{\cdot}CH_2{\cdot}CH(OMe)_2} \arrow[d] \\
& \mathrm{RCH{=}CH{\cdot}CHO} & \mathrm{RCH(OH){\cdot}CH_2{\cdot}CH(OMe)_2} \arrow[l]
\end{tikzcd}$$

Addition of Three Carbon Atoms

The reactions of anions, olefins, and aromatics with formic acid derivatives find a parallel in their reactions with the vinylogous compounds $\mathrm{CHO{-}CR{=}CRX}$, where X is an alkoxyl or amino group, to yield $\alpha\beta$-unsaturated aldehydes or, where X = H, to give saturated aldehydes by a Michael-type reaction. Thus Michael addition of a carbanion to acrolein gives a trishomoaldehyde.[140]

$$\mathrm{(EtO{\cdot}CO)_2CH^- + CH_2{=}CH{\cdot}CHO \rightarrow (EtO{\cdot}CO)_2{\cdot}CH{\cdot}CH_2{\cdot}CHO}\ 50\%$$

An analogous reaction of an alkyl or aryl magnesium halide with acrolein diethyl acetal gives in moderate yield a mixture of an allylic and a vinylic ether, the latter of which on hydrolysis gives an aldehyde. Bulky secondary or tertiary alkyl halides give higher proportions of the vinyl ethers.[141]

$$\begin{aligned}
&\mathrm{RMgX + CH_2{=}CH{\cdot}CH(OEt)_2 \rightarrow CH_2{=}CH{\cdot}CHROEt} + \\
&\qquad\qquad\qquad\qquad\qquad\qquad \mathrm{RCH_2CH{=}CHOEt} \\
&\qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow \\
&\qquad\qquad\qquad\qquad\qquad\qquad \mathrm{RCH_2CH_2CHO}
\end{aligned}$$

Similarly, good yields of aldehydes can be obtained by the Lewis acid-catalysed addition of alkyl and alkoxybenzenes to acrolein diesters.[142]

$$\begin{aligned}
&\mathrm{ArH + CHR{=}CR{-}CH(OAc)_2 \rightarrow ArCHR{-}CR{=}CHOAc} \rightarrow \\
&\qquad\qquad\qquad\qquad\qquad \mathrm{ArCHR{-}CHR{-}CHO}
\end{aligned}$$

Carbanions react quantitatively with β-phenoxyacrolein to give phenol and the sodium salt (36) which on acidification gives the unstable strongly acidic free aldehyde (37) or, on alkylation, the homologue (38).[143]

$$\begin{tikzcd}
\mathrm{R_2CH^- + PhOCH{=}CH{-}CHO} \arrow[rr] & & \mathrm{R_2C{=}CH{-}CH{=}CH{-}O^-Na^+}\ (36) \arrow[dl, "\mathrm{H^+}"'] \arrow[dr, "\mathrm{R'X}"] & \\
& \mathrm{R_2CH{-}CH{=}CH{-}CHO}\ (37) & & \mathrm{R_2CR'{-}CH{=}CH{-}CHO}\ (38)
\end{tikzcd}$$

(where R = acyl or ethoxycarbonyl)

Similarly, Grignard reagents react with β-alkoxyacroleins to give good yields of $\alpha\beta$-unsaturated aldehydes.[111] β-Ethoxyacrolein and $\beta\beta$-diethoxypropanal have been investigated as three carbon aldehyde units which by Grignard, Wittig, or Michael addition reactions can give trishomo-

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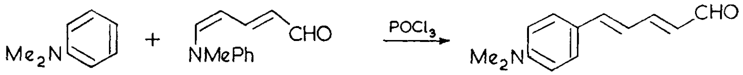
[140] Ref. 1, p. 96.

[141] R. Quelet, P. Berçot and J. d'Angelo, *Compt. rend.*, 1965, **260**, 1191.

[142] I. Scriabine, *Bull. Soc. chim. France*, 1961, 1194.

[143] R. Gélin and D. Makula, *Compt. rend.*, 1965, **260**, 589; Cf. *ibid.*, 1964, **258**, 5234.

aldehydes.[144] β-Aminoacroleins and 5-aminopentadienals can be used in a vinylogous Vilsmeier reaction to give ω-arylpolyenals with three or five more carbon atoms than the aromatic starting material,[145] or be reacted with Grignard reagents to give analogous products.[146]



Unsaturated aldehydes can also be obtained by the reaction of carbanions or Grignard reagents with acetoacetaldehyde acetal[147] to give (39) which could be converted to (40).

$\mathrm{MeCR(OH){\cdot}CH_2{\cdot}CH(OMe)_2}$ (39) $\mathrm{MeCR{=}CH{\cdot}CHO}$ (40)

Addition of Four Carbon Atoms

Alkyl halides[148] or carbonyl compounds[149] react with the anion of methoxybutenyne to give intermediates (41) or (42) which can be converted to various aldehydes with four more carbon atoms. Alternatively the carbonyl compound can be condensed with the methyl group of acetoacetaldehyde acetal to give analogous derivatives (43).[150]

$\mathrm{RC{\equiv}C{-}CH{=}CHOMe}$ (41) $\mathrm{R_2C(OH){-}C{\equiv}C{-}CH{=}CHOMe}$ (42)

$\mathrm{R_2C(OH){\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH(OMe)_2}$ (43)

Skeletal Rearrangements

Lastly a number of only remotely related reactions will be considered which give rise to aldehydes with a concomitant change in the skeleton of the starting material.

Ionic Rearrangements.—The rearrangement of epoxides may give aldehydes or ketones.[151] Whereas ketones are the usual products from

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[144] L. A. Yanovskaya, V. F. Kucherov, and B. G. Kovalev, *Izvest. Akad. Nauk S.S.S.R., Odtel. khim. Nauk*, 1962, 674 (*Chem. Abs.*, 1962, **57**, 16379); L. A. Yanovskaya, R. N. Stepanova, G. A. Kogan, and V. F. Kucherov, *ibid.*, 1963, 857 (*Chem. Abs.* 1963, **59**, 7368b).

[145] C. Jutz, *Chem. Ber.*, 1958, **91**, 850; *Angew. Chem.*, 1958, **70**, 270.

[146] C. Jutz, *Chem. Ber*,. 1958, **91**, 1867.

[147] Brit. Pat. 717,095 : 1954 (*Chem. Abs.*, 1955, **49**, 15955c); U.S. Pat. 2,676,990 : 1954 (*Chem. Abs.*, 1956, **50**, 408a).

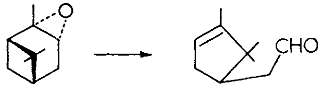
[148] M. Winter, *Helv. Chim. Acta*, 1963, **46**, 1792; and refs. therein.

[149] Ref. 2, p. 22.

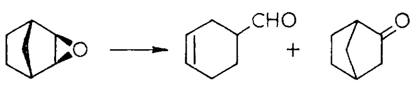
[150] U.S. Pat. 2,676,988 : 1954 (*Chem. Abs.*, 1956, **50**, 407g).

[151] R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 772.

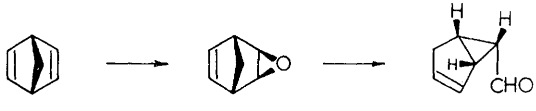
trisubstituted steroid epoxides,[152] 1-methylcyclohexene oxide gives only 1-formyl-1-methylcyclopentane with magnesium bromide at 0°,[153] and 1-methylcyclobutene epoxide is rearranged by mineral acids to give only 1-formyl-1-methylcyclopropane.[154] Various mono- and sesqui-terpene epoxides are also known to give aldehydes.[155] The acid used, the temperature, and the solvent all seem to affect the nature or the ratio of the products.[153,156] More complex rearrangements occur with pinene oxide (44)[157] and bicycloheptene oxide (46). The latter on passing through a column of "Carbowax" at 120° gives 47% of 4-formylcyclohexene (47) and 43% of bicycloheptanone (48).[158]



(44) (45)



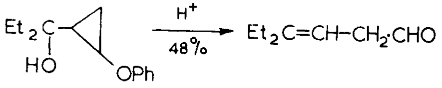
(46) (47) (48)



(49) (50) (51)

The bicycloheptadiene monoepoxide (50) transiently formed by epoxidation of the diene (49) rearranges under the epoxidation conditions to endo-6-formylbicyclo[3,1,0]hex-2-ene (51).[159]

Other small rings such as the cyclopropyl ether (52)[160] and the cyclobutanol (53)[161] may be opened by solvolysis to give aldehydes.



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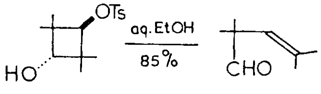

(53)

A fragmentation reaction leading to aldehydes is described by Weygand.[162] The ion (54) on treatment with phenyl lithium and hydrolysis of the intermediate enamine (55) gives oct-7-en-1-al (56) in 40% yield.

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[152] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 1957, 4596, 4765.

[153] S. M. Naqvi, J. P. Horwitz, and R. Filler, *J. Amer. Chem. Soc.*, 1957, **79**, 6283.

[154] J-L. Ripoll and J-M. Conia, *Bull. Soc. chim. France*, 1965, 2755.

[155] C. C. Kartha and K. K. Chakravarti, *Tetrahedron*, 1965, **21**, 139; H. H. Appel, C. J. W. Brooks, and K. H. Overton, *J. Chem. Soc.*, 1959, 3322; E. W. Warnhoff, *Canad. J. Chem.*, 1964, **42**, 1664.

[156] E. A. Braude, A. A. Webb, and M. U. S. Sultanbawa, *J. Chem. Soc.*, 1958, 3328.

[157] M. P. Hartshorn, D. N. Kirk, and A. F. A. Wallis, *J. Chem. Soc.*, 1964, 5494.

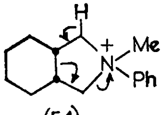
[158] J. K. Crandall, *J. Org. Chem.*, 1964, **29**, 2830.

[159] J. Meinwald, S. S. Labana, L. L. Labana, and G. Wahl, *Tetrahedron Letters*, 1965, 1789, and refs. therein.

[160] M. Julia and G. Tchernoff, *Compt. rend.*, 1957, **245**, 1246.

[161] L. J. Dolby and C. Wilkins, *Tetrahedron Letters*, 1964, 2379.

[162] H. Daniel and F. Weygand, *Annalen*, 1964, **671**, 111.



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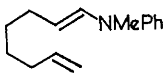
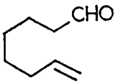
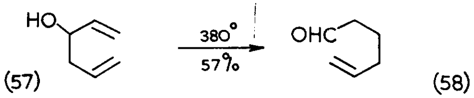


(55)



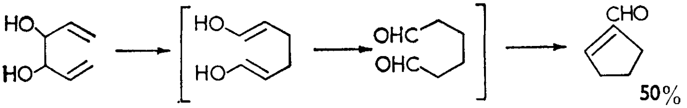
(56)

Thermal Rearrangements.—The production of aldehydes by a purely thermal rearrangement has the advantage that the aldehyde formed is not exposed to any ionic oxidising or basic medium. Two types of six-centre, thermal Cope rearrangements of considerable potential value have been discovered. Hexa-1,5-dien-3-ol (57) on heating gives hex-5-en-1-al (58).[163] Since the dienol is obtained from a Grignard reaction on acrolein this formally constitutes an aldehyde synthesis with addition of three carbon atoms. Its extention to the synthesis of substituted hexenals should be possible.

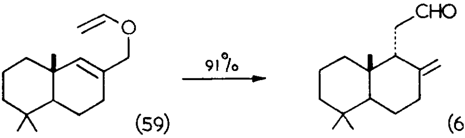


(57) (58)

The long known pyrolytic conversion of hexa-1,5-diene-3,4-diol over alumina at 280° to 1-formylcyclopentene [M. Urion, *Ann. Chim.* (*France*), 1934, **1**, 5] almost certainly proceeds analogously with formation and then cyclisation of hexan-1,6-dial.



The Cope rearrangement of allyl vinyl ethers also gives aldehydes. It provides a synthesis involving stereospecific addition of a two carbon chain in a position where it might otherwise be difficult to introduce such a unit.[164] Thus (59) gives (60) at 198°.[165] In favourable cases the rearrangement may occur at much lower temperatures. Thus divinyl carbinol treated with excess ethyl vinyl ether and mercuric acetate at 25° gives vinyl divinylcarbinyl ether which immediately rearranges even at that temperature to give hepta-4,6-dienal in 70% yield.[166]



(59) (60)

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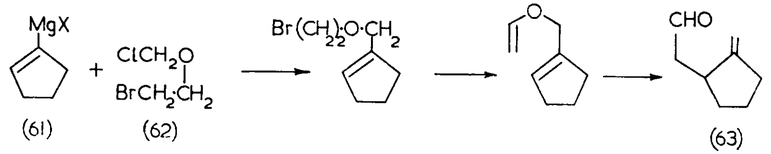
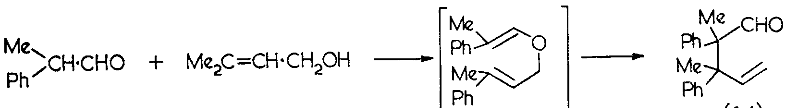
[163] A. Viola and L. A. Levasseur, *J. Amer. Chem. Soc.*, 1965, **87**, 1150.
[164] A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, 1961, **83**, 198.
[165] R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1118.
[166] S. F. Reed, *J. Org. Chem.*, 1965, **30**, 1663.

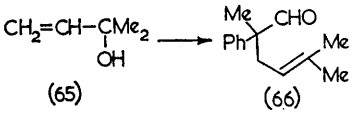
A recent extensive study[167] has shown that the vinyl ethers can be made not only by exchange as in the above cases but also by a synthesis starting with a vinyl magnesium halide such as (61) which ultimately gives (63). The dihalogenoether (62) is readily available from formaldehyde and ethylene bromohydrin.



Alternatively the condensation may be carried out without isolation of the intermediate allyl vinyl ether. Thus, heating 2-phenylpropionaldehyde with 3-methylbut-2-enol in benzene at 120° for 20 hours in the presence of toluene-*p*-sulphonic acid gives the aldehyde (64) in 70% yield. The acetal and enol ether of the propionaldehyde are probably intermediates. The isomeric alcohol (65) analogously gives (66). With isobutyraldehyde, however, cinnamyl alcohol and 1-phenylallyl alcohol *both* give the same product (67).



(64)



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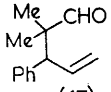

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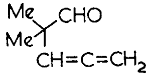

(68)

Allenic aldehydes can be prepared from ethynyl carbinols by the same method. Thus propargyl alcohol heated in diisopropylbenzene with excess butyraldehyde and a little toluene-*p*-sulphonic acid gives 40% yield of 2,2-dimethylpenta-3,4-dienal (68).[168]

A different type of six-centre pyrolytic reaction is the 1,5-hydrogen transfer occurring in the pyrolysis of allyl alkyl ethers such as diallyl ether (69) which has been used commercially to prepare acroleins.[169] Its extension to allyl ethers of other primary alcohols such as (70) has been investigated and shown to give excellent yields in certain cases and may thus provide an alternative to ionic oxidation for primary alcohols.[170]

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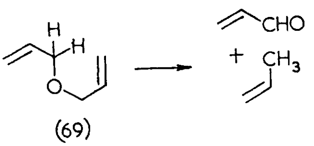
[167] P. Cresson, *Bull. Soc. chim. France*, 1964, 2618, 2629; H. Normant and P. Cresson, *Compt. rend.*, 1965, **260**, 1195.

[168] Brit. Pat. 971,751/1964 (*Chem. Abs.*, 1965, **62**, 446h), U.S. Patent 3,189,655/1965 (*Chem. Abs.*, 1965, **63**, 9816c).

[169] F. G. Watson, *Chem. Eng.*, 1947, **54**, Dec. 106.

[170] R. A. Malzahn, *Diss. Abs.*, 1963, **23**, 2698.



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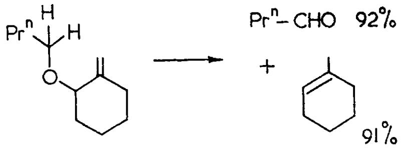
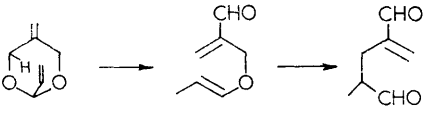


A reaction which may be a combination of these two six-centre reactions above has been discovered in the pyrolysis of 2-vinyl-5-methylene-1,3-dioxan (71) at 450° over glass beads which yields 46% of α-methyl-α'-methyleneglutardialdehyde (72).[171] This complex rearrangement may be accounted for as shown



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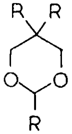

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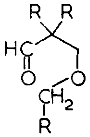

(74)

This is in contrast to the pyrolysis of 5,5-dialkyl-1,3-dioxans (73) which, over pumice or silica at 300°, give β-alkoxyaldehydes (74).[172].

The author thanks Professor G. Ourisson for his interest and the CIBA Fellowship Trust for their support during the preparation of this Review.

[171] F. Weiss, A. Isard, and R. Bensa, *Bull. Soc. chim. France*, 1965, 1358.

[172] C. S. Rondestvedt and G. J. Mantell, *J. Amer. Chem. Soc.*, 1962, **84**, 3307, 3319.