PREPARATION OF FORMYL-DEUTERATED BENZALDEHYDES BY DIRECT PHOTO-DEUTERATION OR BY PHOTOLYSIS OF PHENYLGLYOXYLIC ACID

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Summary

Two new photochemical methods are described to prepare D-1-benzaldehydes of high isotopic purity in good yield.

Key words: formyl-deuterated benzaldehydes, photodeuteration

Aromatic aldehydes are employed for numerous preparative purposes, and deuterated aldehydes are often useful to trace the course of reactions. We have elaborated two new methods to prepare formyl-deuterated benzaldehydes of high isotopic purity in good yield by photolysis of phenylglyoxylic acid (method A) or benzaldehyde and certain substituted benzaldehydes (method B) in the presence of deuterium oxide. The reactions are followed up by ^{1}H-N.M.R. spectroscopy. The isotopic purity of D-1-benzaldehyde or its p-chloro or -bromo derivatives can easily be checked by capillary column gas chromatographic separation$^{1)}$ of the deuterated and the undeuterated compounds giving results identical with N.M.R. determinations.

The comprehensive treatise of deuteration techniques and

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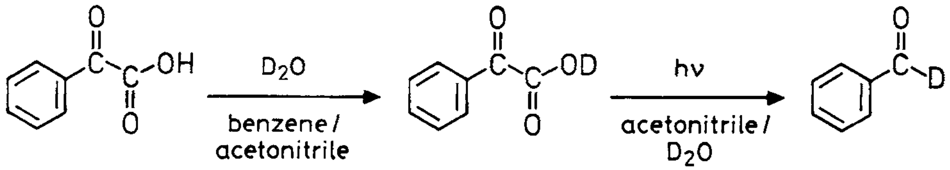
method A



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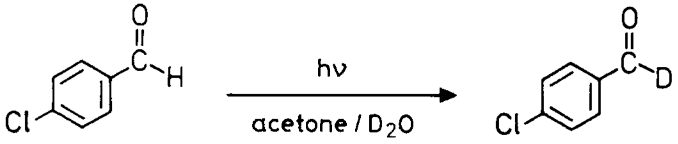
method B



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mechanisms by A.F. Thomas[2] presents at least ten methods to prepare formyl-deuterated benzaldehyde the most convenient being the dithiane method by Seebach et al.[3]. An analogue to our photochemical method A, although apparently not as simple and clean, is the thermal decarboxylation of phenylglyoxylic acid in the presence of bases[4-6]. Based on the photochemical decarboxylation of phenylglyoxylic acid[7-9], method A, starting with D-1-phenylglyoxylic acid, offers an experimentally very simple technique to prepare D-1-benzaldehyde of high purity. The D content of the product is defined by the D/H ratio of the water in the reaction medium. If a lower D content is satisfactory the reaction may as well be performed with the natural protium acid, or a cheaper D$_2$O quality may be used. The reaction proceeds with a quantum yield of 0.7[10].

Several dark chemical methods[2] for the preparation of unsubstituted D-1-benzaldehyde may as well be applied to substituted benzaldehydes. Some more recently published methods are the reaction of benzil[11)] or benzaldehydes[12)] with cyanide ion in the presence of D_2O, the silver carbonate oxidation of substituted deuteriobenzylalcohols[13)], the mercuric salt cleavage of deuterated triaryltrithianes[14)], reaction of benzonitriles with $SnCl_2$ and deuterium chloride[15)], deuterium oxide treatment of the salts obtained from aroyl chlorides with 3-methyl-1-phenyl-2-phospholene[16)], or the hydrolysis of 2-aryl 2-deuterio-1.3-benzodithiols with chloramine T and $HgCl_2$[17)].

Method B is of advantage for the preparation of substituted D-1-benzaldehydes. Considering the high prices of these compounds[18)] the direct photo-deuteration offers a simple and inexpensive new method of practical value. It is a one-step reaction, does not need other chemicals than commercially available aromatic aldehydes and deuterium oxide, and proceeds rapidly with a quantum yield of 1[10)] without producing any troublesome side products. However, the method is not universal[10)]. It works very well with, e.g., 4-fluoro-, 3- or 4-chloro-, 4-bromo-, 3- or 4-cyano or unsubstituted benzaldehyde and 2-, 3- or 4-pyridinealdehyde but it cannot be used with, e.g., 4- or 2-nitrobenzaldehyde or 2-naphthaldehyde. Work is in progress to further extend the scope of reaction B.

Experimental

All work - including preparation of solvents and undeuterated compounds - was done under dry argon atmosphere.

Method A.

D-1-Phenylglyoxylic Acid (α-Oxobenzeneacetic Acid (**2**)). The upper bulb of a double-bulb separatory funnel19) is charged with a solution of 13 g (0,087 mol) phenylglyoxylic acid20) (1, recryst. from CCl_4, colourless, m.p. 65-66 $^{\circ}C$) in a mixture of 80 ml benzene and 8 ml acetonitrile (passed through a 4 Å molecular sieve, distilled), the lower with 10 ml benzene/acetonitrile 10:1. The acid solution is washed with seven successive 1 ml-portions of deuterium oxide (Merck Uvasol min. 99.75% D) the first portion being absorbed by the organic solution. Each aqueous layer drained off from the upper bulb is washed by the benzene-acetonitrile solution in the bottom bulb; the aqueous phase should remain colourless. Without drying, the solvent is removed from the combined organic layers at 60 $^{\circ}C$/200 Torr and the residue is kept cool until it crystallizes. Drying is completed in high vacuum. Yield: 13 g 2, 97 ± 2% D. ^{1}H-N.M.R.: The H content of the acid is obtained from the difference of the integrated DOH signal intensities of the acid solution in CH_3CN/D_2O 3:1 and the pure solvent with reference to the intensity of an aromatic ring proton. The ^{13}C satellite signal of acetonitrile serves as instrumental calibration.

D-1-Benzaldehyde (3)

The slightly yellowish solution of 13 g (0.087 mol) 2 in 60 ml acetonitrile and 20 ml deuterium oxide (99.75% D, 1.1 mol) is distributed to four 25 ml Solidex irradiation tubes (17 mm Ø, 20 cm length). The tubes are placed in a merry-go-round apparatus within a Rayonet RPR 100 photoreactor equipped with 16 3500 Å lamps and a double-wall glass cylinder with Rappoldt Nr. 912) filter solution (5 mm, $\lambda > 330$ nm, 3 g $Pb(NO_3)_2$ and 650 g $NaBr \cdot 2H_2O$ per liter water). Stirring is accomplished by teflon-

coated magnetic bars which are moved up and down when the tubes pass by an arrangement of ring magnets[22]. The reaction is monitored by UV and ^{1}H-N.M.R. spectroscopy. UV: 1 mm cell, 400 nm region, isosbestic point at 412 nm. Phenylglyoxylic acid: λ_{max} 343 nm (ε 740), $\varepsilon_{400\ nm}$ = 80. Benzaldehyde: λ_{max} 330 nm (ε 29). N.M.R.: 1, δ (ppm) = 8.0 (*o*-H), 7.6 ± 0.2 (*m*-H, *p*-H); benzaldehyde, 7.8 (*o*-H), 7.6 ± 0.2 (*m*-H, *p*-H). The reaction is completed after 18 - 19 h when there are only minor changes in the UV and when the aromatic protons of the acid are hardly to be seen. The yellow solution is transferred to the top bulb of a double-bulb separatory funnel[19] together with 20 ml dichloromethane while the lower bulb is charged with 10 ml acetonitrile-dichloromethane 3 : 1 in order to wash the aqueous solution. After separation and washing of the deuterium oxide layer, the remaining organic layers are successively washed four times with 5 ml 10% Na_2CO_3 solution and then with water. Acidification of the sodium carbonate solution with 5 N H_2SO_4 followed by dichloromethane extraction yields a yellow mixture of acids: Benzoic acid (1%), 1 (5%), and *dl*- (1%) as well as *meso*-2.3-diphenyltartaric acid[23,24] (1%). The combined organic solutions are dried over $MgSO_4$ and concentrated to 25 ml at 40 °C/ 200 Torr. This liquid contains 6.8 g (73%) crude 3, > 99% D.
After vacuum distillation using a 300 mm FISCHER concentric tube column (b.p. 47 °C/5 Torr) an over-all-yield of 60% 3 is obtained. Isotopic purity > 99% D. GC separation[1] of deuterated (retention time 124,9 min) and undeuterated benzaldehyde (122,4 min): 110 m CW-1500, 100 °C.

Method B.

D-1-p-Chlorobenzaldehyde (5)

A solution of 4.023 g (0.029 mol) *p*-chlorobenzaldehyde (4, EGA, zone melted, m.p. 48-49 °C) in a mixture of 75 ml acetone (z.A., passed through 4 Å molecular sieve, distilled, containing ∿ 0.1% H_2O) and 25 ml deuterium oxide (99.75 % D) is placed in a Solidex glass immersion well irradiation apparatus and irradiated with an internal 125-watts high pressure mercury arc (Philips HPK 125). Essentially identical results are obtained when the same photoreactor is used as in method A. Prior to irradiation the H_2O/D_2O ratio of the solution has to be determined by N.M.R. (DOH peak at 4 ppm). The ^{13}C satellite signal of acetone (δ = 3.2 ppm) serves as a reference; for the solvent mixture given above its peak area equals 1.2% H_2O. Typically, 0.5% H_2O are found. After 2 h irradiation a 2 ml sample is diluted by 5 ml CH_2Cl_2, dried over $MgSO_4$, evaporated and measured by N.M.R. in $CDCl_3$. The remaining H-1 hydrogen content, α, is obtained from the CHO peak using the aromatic protons as reference.

The decay of the hydrogen content is given by $\alpha = e^{-kt}$. Therefore, from the measured value of α_1 after an irradiation time t_1, the irradiation time (t_2) necessary to arrive at a definite remaining hydrogen content, α_2, can be estimated by $t_2 = t_1 (\log \alpha_2/\log \alpha_1)$. E.g., after t_1 = 2 h, α_1 is found to be 0.22. Hence, for α_2 = 0.01, t_2 follows to be $\geq$ 6.1 h. After about 7 h of irradiation the yellow solution is diluted with 100 ml dichloromethane, the organic phase is separated under argon and the aqueous phase is washed three times with 5 - 10 ml dichloromethane. The combined organic solutions are dried over $MgSO_4$ and evaporated at 40 °C/200 Torr to give an oily residue which soon crystallizes. By extraction with dichloromethane insoluble *p*-chlorobenzoic acid (55 mg, 1%) is isolated. Yield: 4.1 g brownish crystals, containing 80% 5 of 98% D content. GC separation[1) on CW-1500 column, 120°, 46.9 min (1-H), 47.7 min (1-D). To purify the crude aldehyde vacuum sublimation (50-60 °C/50 - 100 Torr, stirring by magnetic bar) is used. On a 0.5 to 1 g scale it yields 68% pure white crystals of 5, m.p. 48-49 °C. The residues may be extracted with hot pentane and the extract used for another sublimation run which affords 3 - 4% pure aldehyde. Further digesting of the residues with dichloromethane leaves behind impure *p*-chlorobenzoic acid (m.p. 210 - 220 °C, 93 mg, 2%).

D-1-Benzaldehyde (3)

In a 500 ml immersion well apparatus the solution of 6.0 ml (0.06 mol) benzaldehyde in 400 ml acetone (as above) and 100 ml deuterium oxide (99.75% D) is irradiated as above with a 125 W high pressure mercury lamp for 14 h. A work-up procedure similar as above yields 6.9 - 7.3 g crude yellow oil, ∿ 75% 3, 98.5% D. Distillation gives 3.4 - 3.5 g (54 - 56%) pure 3, > 98% D-1. Lower conversion is observed at higher concentrations.

References

1. Frohn, H., Rauhut, U., Defoin, R. and Kuhn, H.J. - unpublished work.
2. Thomas, A.F. - Deuterium Labeling in Organic Chemistry, Appleton-Century-Crofts, Educational Division/Meredith Corp., New York 1971, pp. 518 (Out of print).
3. Seebach, D., Erickson, B.W. and Singh, G. - J. Org. Chem. 31: 4303 (1966)
4. Cohen, T. and Song, I.H. - J. Am. Chem. Soc. 87: 3780 (1965)
5. Althouse, V.E., Feigl, D.M., Sanderson, W.A. and Mosher, H.S.- J. Am. Chem. Soc. 88: 3595 (1966)

6. Craig, J.C. and Kray, L.R. - J. Org. Chem. 33: 871 (1968)
7. Corson, B.B., Sanhorn, N.E. and Van Ess, P.R. - J. Am. Chem. Soc. 52: 1623 (1930)
8. Leermakers, P.A. and Vesley, G.F. - J. Am. Chem. Soc. 85: 3776 (1963)
9. Mittal, L.J., Mittal, J.P. and Hayon, E. - J. Phys. Chem. 77: 1482 (1973)
10. Defoin, A., Defoin, R. and Kuhn, H.J. - publications in preparation.
11. Burgstahler, A.W., Walker, D.E., Kuebrich, J.P. and Schowen, R.L. - J. Org. Chem. 37: 1272 (1972)
12. Chancellor, T., Quill, M., Bergbreiter, D.E. and Newcomb, M.- J. Org. Chem. 43: 1245 (1978)
13. Fetizon, M., Henry, Y., Moreau, N., Moreau, G., Golfier, M. and Prange, T. - Tetrahedron 29: 1011 (1973)
14. Chattopadhyaya, J.B., Rama Rao, A.V. and Venkataraman, K. - Indian J. Chem. 11: 987 (1973)
15. Su, T.T. - J. Labelled Comp. 11: 613 (1975)
16. Scott, C.A., Smith, D.G. and Smith, D.J.H. - Synth. Commun. 6: 135 (1976)
17. Degani, I. and Fochi, R. - Synthesis 1976: 759
18. Merck, Sharpe & Dohme, catalog "Isotopes".
19. Houben-Weyl, Methoden der Organischen Chemie, I/2, p. 351 (1959)
20. Organic Syntheses Vol. 24, p. 16, John Wiley, New York, London 1944.
21. Rappoldt, M.P. - Ph.D. Thesis, Leiden 1958, p. 17
22. Straatmann, R. and Kuhn, H.J. - Mol. Photochem. 7: 203 (1976); EPA Newsletter January 1978, p. 21
23. Schönberg, A., Latif, N., Moubasher, R. and Sina, A. - J. Chem. Soc. 1951: 1364
24. Juday, R.E. - J. Org. Chem. 23: 1010 (1958)