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SYNTHESIS OF 1 - DEUTERIOALDEHYDES FROM METHYLENE - BIS - PYRIDINIUM CATIONS.

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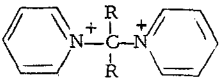
SUMMARY

A synthesis of 1-deuterio and 1-tritioaldehydes, especially arylaldehydes, from precursor gem-*dihalides is described. The scheme is especially useful when high label incorporation is desired.*

INTRODUCTION.

We report here the experimental procedure for a convenient and economical preparation of 1-deuterio or 1-tritiobenzaldehyde and other labelled aldehydes of high isotopic purity. In practical terms the process is limited to syntheses where the related gem-dihalides are inexpensive or readily available — primarily benzal type halides which are often favored commercial precursors of the unlabelled arylaldehydes. Our method, as exemplified by the exchange (in D_2O via the ylid IIa) and hydrolysis of the known benzal-bis-pyridinium dibromide (Ia) to benzaldehyde-1-d, has been outlined in a preliminary communication, (1, 2) but additional material is presented here to enable the experimenter to predict optimum reaction conditions for the preparation of other desired substrates.



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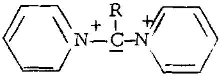


II

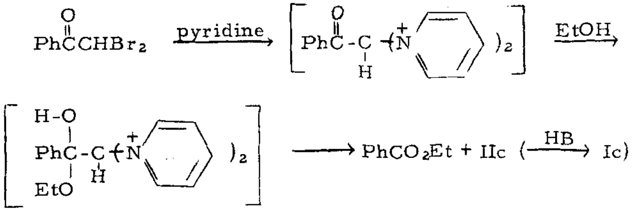
a: R = phenyl, b: R = p-anisyl, c: R = H

The synthesis of the bisiminium salts (Ia and Ic) which have previously been isolated by Kröhnke$^{(3,4)}$ as stable solids, has also been much improved by changes in reagent ratios, reaction times, and temperatures. For example, Ic has been obtained in 95% yield vs. 13% in earlier work.$^{(4)}$

RESULTS AND DISCUSSION.

The benzal (Ia), p-anisal (Ib), and methylene (Ic) bis-pyridinium dibromides were prepared in yields of 97%, 92%, and 95%, respectively, by treatment of the appropriate dibromides with pyridine. The salt (Ic) was also obtained in 73% yield from reaction of α,α-dibromoacetophenone with pyridine and ethanol in a process (Scheme A) which emphasizes the special stability of the cation ylid (II).

Scheme A:



(Hydrolytic loss of $PhCO_2Et$ could also occur at the monobromopyridinium cation level followed by pyridine substitution of the expelled bromomethylpyridinium cation.)

In accord with our predictions based on heterocyclic deprotonation studies,$^{(5)}$ the cations all exchanged the anticipated aliphatic protons for deuterium in neutral D_2O solutions. The exchange was slower in more acidic media as required for a deuteroxide initiated ionization mechanism. Kinetic data[*] was obtained for the salts, Ia: $k_1 = 4.5 \times 10^{-2} \text{min}^{-1}$ at pD 5.71-5.57[**] and 35° ($t_{\frac{1}{2}}$ = 15 min) and Ic: $k_1 = 3.5 \times 10^{-3} \text{min}^{-1}$ at pD 7.66-7.53[**] and 31° ($t_{\frac{1}{2}}$ = 200 min). The estimated deprotonation rate difference (relative k_2's) between Ia and Ic is about 10^3 in favor of the phenyl substituted compound. This is a normal rate acceleration attributed to the combined inductive and resonance stabilization by phenyl of the forming carbanion in a species too crowded and twisted to take much advantage of added delocalization into a new benzene ring. Measurements of the difference in kinetic or thermodynamic acidity between the model systems, diphenylmethane and triphenylmethane, vary from $10^{1.4}$ to $10^{2.5}$ in favor of the latter in less structure sensitive solvent-base systems.(6)

In a D_2O buffer at pD 6.7→5.4 (change due to liberation of pyridine) the hydrolysis of Ia to benzaldehyde-1-d could be accomplished by refluxing for three hours (time determined by following the increase in volume of oiled out product). Isotopic analysis indicated that equilibrium exchange was achieved prior to hydrolysis. For example, in one experiment the theoretical deuterium incorporation was 95%; the experimental value determined by NMR analysis was 95± 1%. The per cent deuterium in the benzaldehyde-1-d could easily be made *quantitative* by evaporating the D_2O *in vacuo* and including a second exchange step prior to the hydrolysis. The yield of pure benzaldehyde-1-d on a 20 gram product scale was 91% after steam distillation and redistillation. The unusual mechanism by which Ia is hydrolyzed

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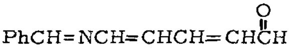
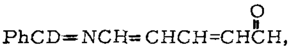
[*] Kinetics were measured by NMR in D_2O buffers using published techniques.(5) The rates were nicely first order in substrate for the first 1.5 half lives but tailed off thereafter. The salt (Ib) was too insoluble for a kinetic study.

[**] This is the pD drift during the kinetic runs for these very concentrated solutions; pD is defined here as an uncorrected pH meter reading in D_2O.

to benzaldehyde — a process in which one pyridinium ring is cleaved and later reformed — has already been reported,[1] and the isolation of the "enamine Schiff base" reaction intermediate,  $PhCH{=}NCH{=}CHCH{=}CH\overset{O}{\overset{\|}{C}}H$ or  $PhCD{=}NCH{=}CHCH{=}CH\overset{O}{\overset{\|}{C}}H$, is outlined in the Experimental.

In the synthesis of p-anisaldehyde-1-d from Ib under the conditions used for the exchange-hydrolysis of Ia, product with less than the equilibrium amount of deuterium was obtained presumably because of a less favorable exchange to hydrolysis rate ratio. However by adding Ib to a stirred suspension of excess magnesium oxide in D_2O at 0°, p-anisaldehyde-1-d containing the maximum possible amount of deuterium (96.4± 1%) was isolated in 74% yield on a small scale. The simple methylene bis-iminium cation (Ic) was more stable to hydrolysis than Ia or Ib, but formaldehyde-d_2 (>96% deuterium) was rapidly released in 10% K_2CO_3-D_2O (isolated as the dimedone derivative in 82% yield).

In order to extend this aldehyde-1-d or 1-t synthesis to other substrates, a knowledge of both the exchange and hydrolysis rates of the specific precursor (I) is required. The deprotonation rate of Ic provides a useful minimum value for the first order OD^- induced exchange (the ionization of compounds I with R = alkyl should be slightly less facile). Reasonable exchange rate estimates for other substrates may be calculated from the data for Ia and Ic modified by known effects of substituents on kinetic acidity in other systems.(5,6) The kinds of variation in required hydrolysis conditions to be expected with structure changes are outlined in the experimental. Since for most purposes aldehyde-1-d of 95% isotopic purity is sufficient, a one reaction pot exchange-hydrolysis will usually be the most convenient method for obtaining product from I. With R = alkyl, the K_2CO_3-D_2O method should be preferred; with R = aryl (or heteroaromatic) exchanging as fast or faster than Ia (electron withdrawing substituents), the phosphate buffer route is recommended; and with R = aryl exchanging much slower than Ia, the 0° MgO procedure should be best.[*]

EXPERIMENTAL.

Nmr spectra were obtained on a Varian HA-100 or A-60A spectrometer, infrared spectra on a Perkin Elmer 137 or 257 spectrometer, and mass spectra on an MS902 spectrometer.

Benzal-bis-pyridinium Bromide (Ia).

A solution of 40 g (0.16 mole) benzal bromide in 95 ml of pyridine in a 3-neck flask fitted with a mechanical stirrer and condenser topped by a drying tube was heated on a steam bath with stirring for 8 hr, then cooled to room temperature, and the precipitate triturated with $CHCl_3$, filtered, washed with $CHCl_3$, and dried *in vacuo*; yield 63 g (97%). The product could be further purified by dissolution in hot MeOH containing a few drops of conc HBr, clarified with activated charcoal, and then crystallized; mp 234° dec (lit.(3) 234°); nmr (D_2O) δ9.76(s, 1), 9.6(m, 4), 9.2(m, 2), 8.7(m, 4), 7.8(m, 5).

p-Anisal-bis-pyridinium Bromide (Ib).

A mixture of 5.3 g (0.02 mole) p-anisal bromide(8) and 12.8 ml pyridine was swirled for 5 min and then allowed to stand at room temperature overnight. The

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[*] A variation of our synthesis involving the conversion of aldehydes to 1-deuterioaldehydes without isolation of the intermediate gem-dibromides or bis-pyridinium salts has recently appeared.[7] Note the danger in using this procedure without ascertaining the ease and hydrolysis of the specific substrate (I). Note also that in this variant a complete recycling of the entire synthesis must be carried out to raise isotopic purity.

precipitate was triturated with acetone, filtered, washed with acetone, and dried *in vacuo*; yield 8.1 g (92%). An analytical sample was prepared from a MeOH solution containing one drop of conc HBr by precipitation with ether; mp 185° dec; nmr (D_2O) δ9.2-8.7(m,7), 8.5-8.1(m,4), 7.37 and 7.15(ABq, J = 9 cps, 4), 3.86(s, 3). Anal. Calcd for $C_{18}H_{18}Br_2N_2O$: C, 49.34; H, 4.14; Br, 36.47; N, 6.39. Found: C, 49.08; H, 4.24; Br, 36.40; N, 6.35.

Methylene-bis-pyridinium Bromide (Ic).

Method A. A solution of 20 g (0.115 mole) CH_2Br_2 and 130 ml pyridine was heated at 70° for 48 hr, the product worked up as above, and purified by dissolution in 3 parts warm dilute HBr followed by precipitation with acetone; yield 35 g (95%), mp 245-248° (lit.(4) 250° dec); nmr (D_2O) δ9.6(m,4), 9.1(m,2), 8.6(m,4), 7.55(s, 1).

Method B. (The published synthesis(4) was unsuccessful in our hands but the following method worked.) Pyridine (100 ml, 1.24 mole) was added to 137 g (0.49 mole) of crude α,α-dibromoacetophenone(4) dissolved in 100 ml of acetone. After stirring for one hr at 70°, 200 ml of 1:1 acetone-EtOH was added and the reaction mixture stirred 48 hr longer at 70°. The mixture was cooled, filtered, and purified as in Method A; yield 120 g (73%); mp 245-249° dec.

Dideuteriomethylene-bis-pyridinium Bromide.

Methylene-bis-pyridinium bromide (2.00 g, 6 mmole) was dissolved in 20 ml of a pD 7.7 buffer solution (0.40 g NaOH in 20 ml D_2O acidified with solid $NaH_2PO_4 \cdot H_2O$). After standing at 30° for 24 hr, the solution was made acidic to litmus with conc HBr and the deuterated salt precipitated with 200 ml acetone. The solid was reprecipitated twice with acetone from the minimum amount of 25% aqueous HBr; yield 1.85 g (87%); 94±2% D in the methylene position (nmr analysis).

Benzaldehyde-1-d.

The salt (Ia) (90 g, 0.22 mole) was dissolved in 160 ml of a pD 6.7 D_2O buffer (solution 0.5 M in Na_2HPO_4 and 0.33 M in $NaH_2PO_4 \cdot H_2O$). The initial reaction mixture pD of 6.2 dropped slowly with time and after 3 hr was down to pD 5.6 (if because of acidic impurities in the bisiminium cation sample the pD drops much further or faster, slowly add more Na_2HPO_4). The solution was then refluxed for 3 hr or until some time after the amount of oiled out benzaldehyde stopped increasing (end pD 5.4). (No hydrolysis took place when the bisiminium cation was refluxed for 24 hr in 1N HCl). The red solution was then acidified to pH 1-2 with conc HCl (to convert the pyridine to its salt) and steam distilled. The distillate was saturated with NaCl and then extracted with several small portions of ether (200 ml in all). The combined extracts were dried (Na_2SO_4), concentrated, and distilled; 21 g (91%) of benzaldehyde-1-d was obtained; bp 178°; ir (CCl_4) $_{\mu}$4.76, 4.88, 5.81. The product contained 95± 1% D on the aldehyde carbon (nmr analysis, weighed internal anisole standard); calculated D incorporation for complete equilibration of the reaction solution: 95%.

The % D could be increased by including a second exchange step (or using deuterated buffer salts) in the procedure above. The exchanged solution (just before the reflux-hydrolysis step) was taken to dryness at room temperature under high vacuum, D_2O added to the residue, the pD adjusted to pD 5.5 with NaOD-D_2O, and the solution again allowed to exchange overnight at room temperature before continuing with the hydrolysis step.

The above procedure was preferred over a more rapid exchange and hydrolysis with stronger base because the reaction seemed somewhat cleaner under the former conditions.

6-Aza-7-phenylhepta-2,4,6-triene-1-al ("The Enamine Schiff Base").

A solution of 2.0 g Ia in 15 ml of water was slowly titrated with scratching with 10% aqueous NaOH until a pale yellow solid stopped precipitating. This was filtered, washed with cold water, and dried in vacuo; yield 0.80 g (86%); recrystallized from pentane; mp 59-60° (lit.(3) 58°). Spectral data have been reported.(1)

The 7-deuterio "enamine Schiff base" was similarly prepared using D_2O and 10% NaOD; mp 57-58°. Both compounds were unstable at room temperature but could be kept for 2 weeks in the dark in the refrigerator with only minor decomposition.

Hydrolysis of the "Enamine Schiff Base".

A solution prepared by dissolving 5.0 g NaOH in 250 ml water followed by acidification to pH 6.8 with solid $NaH_2PO_4 \cdot H_2O$, was allowed to distill very slowly. The "enamine Schiff base" (5.0 g, 0.027 mole) in 75 ml dioxane was added dropwise (3 hr) to the slowly distilling mixture. Fifty ml of 2N aqueous NaOH was then slowly added followed by 100 ml water. The distillation was continued until 300 ml of distillate was collected. This was acidified to Congo red with conc HCl, extracted with 500 ml ether, the ether extract dried (Na_2SO_4), and concentrated on a rotary evaporator; 2.37 g (83%) of benzaldehyde was isolated. The aqueous layer above was taken to dryness yielding 1.58 g (51% assuming 1 eq) of crude pyridinium hydrochloride.

Benzaldehyde-1-d was isolated (34%, smaller scale) from the 7-deuterio "enamine Schiff base."

p-Anisaldehyde-1-d.

The salt (IB) (8.76 g, 0.02 mole) was added (1 hr) with stirring to a solution of 6.97 g (0.04 mole) K_2HPO_4 in 20 ml D_2O (pD 9.4) maintained at 0°. The solution was allowed to warm to room temperature and after 2 hrs was heated on a steam bath for an additional 2 hrs (pD after heating 7.1). The mixture was then acidified with H_2SO_4 and worked up by the steam distillation procedure described for the benzaldehyde-1-d preparation; yield 2.30 g (84%) with 79% D incorporation.

Repetition of this experiment using 0.80 g (0.02 mole) MgO in place of the K_2HPO_4 yielded product (74%) with the equilibrium 96.4±1% D incorporation (nmr analysis using internal benzothiazole weight standard); ir (CCl_4) μ 4.80, 4.90, 5.96. The pD of a saturated MgO suspension in D_2O is 10.8.

Formaldehyde-d_2 (Dideuteriomethylene-bis-dimedone).

The salt (Ic) could be reisolated after 1 hr in 5% $NaHCO_3$ solution (conditions under which the benzal salt immediately precipitated the "enamine Schiff base") and yielded a brown tar on treatment with aqueous NaOH. However, a clean reaction was obtained when Ic (2.00 g, 5.1 mmole) was dissolved in 25 ml 10% K_2CO_3-D_2O placed in a stoppered flask, and stirred for 9 hours; the solution was light yellow and the pH dropped from 12 to 9.5. A solution of 2.5 g (0.018 mole) dimedone in 25 ml of methanol was then added and the pH adjusted to 5 with rapid stirring by titration with conc HBr. (If the pH was taken to 5 prior to addition of the dimedone, the product had the same D content but was more difficult to purify because of contamination by dimedone.) The precipitated solid was filtered, washed with water, dissolved in 20 ml 2N NaOH, reprecipitated with conc HBr, filtered, and recrystallized from ethanol-water; yield 1.15 g (82%); mp 188-190° (lit.(9) 188° for undeuterated derivative). The product contained >96% D in the methylene position (nmr and MS analysis); otherwise it was identical with an authentic sample. In another experiment in which dimedone was present in the reaction mixture prior to the reaction start, the yield was 81% (94±2%D); nmr (CD_3CN) δ2.23(s, 8), 0.97(s, 12) (CH_2 at 3.11).

ACKNOWLEDGMENT

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