equilibration experiments. However, the 1-deuterium ^2H NMR signal overlapped with that for 1-α-*d*. Thus data for experiments with 1-α-*d* were corrected for the presence of the saturated contaminant. The exact amount of the contaminant was determined by capillary GC. Similarly, 1-γ-*D* contained ~2% 3-deuteriocyclohexanol. In this case the ^2H NMR signal is completely resolved from those for 1-α-*d* and 1-γ-*d* and thus this inert contaminant does not interfere with the equilibration measurements.

Results of the equilibrium studies are presented in Table I. Pseudo-first-order rate constants for equilibration (k_{eqn}) were obtained by quenching samples of reaction mixture with base at appropriate times and determining the deuterium distribution (amount of equilibration) by planimeter measurements of the ^2H NMR signals for 1-α-*d* and 1-γ-*d*. Reactions were followed from about 20% to 80% completion, and good first-order behavior was observed.

The equilibrium 1-α-*d*/1-γ-*d* ratios (K_{eqn}) were determined after 10 half-lives for equilibration. The equilibrium constants in Table I are average values (and average deviations) of three independent determinations. As would be expected, K_{eqn} is insensitive to change in solvent. This constant is also relatively insensitive to change in temperature; values for 30 and 90 °C are within combined experimental uncertainties.

The data in Table I show that for the temperature range investigated the equilibrium deuterium distribution is about 53.6% 1-α-*d* and 46.4% 1-γ-*d*. The equilibrium constant corresponds to a standard free-energy difference of ~90 cal/mol favoring the isomer with a sp^3 α-deuterium and a sp^2 γ-hydrogen over that with a sp^3 α-hydrogen and a sp^2 γ-deuterium. The magnitude of this thermodynamic deuterium isotope effect is similar to that estimated from the earlier data[1,2] by correcting for temperature differences and multiple deuterium atoms.

Experimental Section

General Methods. Proton-decoupled ^2H NMR spectra were determined with a JEOLCO FX-200 spectrometer operating at 30.6 MHz. Deuterium chemical shifts are relative to $CDCl_3$ set to 7.24 ppm. Fourier transform was used with a 2.40-s acquisition time and 2.0-s relaxation delay. Proton spectra were determined with a Brucker WP-200SY instrument. $LiAlD_4$ and $NaBD_4$ (98 atom % D) were obtained from Aldrich. Acetone was stored over $KMnO_4$, dried over $CaSO_4$, and fractionated. Conductivity water was obtained from a Millipore Super-Q filtration system. Aqueous acetone compositions are based on volumes of pure components at ambient temperature prior to mixing.

2-Cyclohexenol-α-*d* (1-α-*d*). Reduction of 2-cyclohexenone[4] by a cerium chloride catalyzed borodeuteride reduction[5] gave a 76% yield of 1-α-*d*, bp 78 °C (22 mm). Capillary GC (147 ft, UCON LB550, 80 °C) showed that this product contained ~2% 1,3-dideuteriocyclohexanol. This product had the following: ^1H NMR ($CDCl_3$) δ 5.84 (dt, 1 H, J = 10.1, 3.5 Hz), 5.79 (d, 1 H, J = 10.1 Hz), 3.48 (br s, 1 H (OH)), 1.5-2.1 (m, 6 H); ^2H NMR (acetone) δ 3.33 (98.5%), 1.3 (1.5%). The latter signal results from 1,3-dideuteriocyclohexanol.

2-Cyclohexenol-γ-*d* (1-γ-*d*). This compound was prepared in a similar manner by $CeCl_3$-$NaBH_4$ reduction of 3-deuterio-2-cyclohexenone.[4] This product had the following: ^1H NMR ($CDCl_3$) δ 5.75 (s, 1 H), 4.20 (br, d, 1 H, J = 3 Hz), 3.70 (s, 1 H (OH)), 1.4-2.0 (m, 6 H); ^2H NMR (acetone) δ 4.98.

Rates of Acid-Catalyzed Equilibration of 1-α-*d* and 1-γ-*d*. In typical experiments 15 mmol of labeled **1** was rapidly mixed with 100 mL of thermostated aqueous acetone containing the indicated concentration of $HClO_4$ (Table I). Aliquots of the thermostated reaction mixture were withdrawn at appropriate times and delivered into excess aqueous NaOH to quench the reaction. The quenched samples were saturated with salt, extracted with ether, dried, and distilled. Three aliquots were quenched after 10 half-lives for equilibration to determine the equilibrium deuterium distribution. Deuterium distributions were determined from relative peak areas (planimeter) for α-*d*- and γ-*d* signals. Pseudo-first-order rate constants were determined from slopes of ln (X-X_e) vs. time plots, in which X is the fraction of deuterium in the α position at various times and X_e is the fraction of deuterium in the α position after equilibration (10 half-lives). Data for the kinetic and equilibration experiments are presented in Table I.

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Registry No. 1-γ-*d*, 73741-72-7; 1-α-*d*, 55282-88-7.

A Convenient, General Synthesis of α-Trichloromethyl Carbinols

Jean M. Wyvratt,* George G. Hazen, and Leonard M. Weinstock

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

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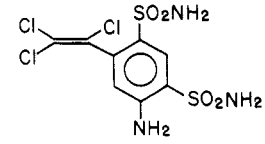
The condensation of chloroform with aldehydes and ketones under basic conditions is a standard method for the preparation of α-trichloromethyl carbinols, which serve as key intermediates in a variety of synthetic applications.[1] With highly reactive aldehydes such as nitrobenzaldehydes, the competing Cannizzaro reaction is often a serious problem resulting in low yields or exclusively Cannizzaro products.[2] This problem was overcome in the simple, high-yielding preparation of α-(trichloromethyl)-3-nitrobenzyl alcohol (**3**) described in this paper. We required **3** in our synthesis of clorsulon (**1**), used in the treatment of liver flukes in animals.[3]



1

Several reports describe the condensation of substituted benzaldehyde derivatives with chloroform in the presence of various bases to produce the corresponding α-(trichloromethyl)benzyl alcohols.[2a,4] With solid potassium hydroxide without solvent only Cannizzaro reaction products were obtained in the condensation of *m*-nitrobenzaldehyde (**2**) and chloroform.[2a] Phase-transfer conditions[4a] produced a mixture of nitrobenzoic acid, nitrobenzyl alcohol, and modest yields of α-(trichloromethyl)-nitrobenzyl alcohol. Potassium *tert*-butoxide in liquid ammonia at −75 °C has been reported to effect the desired condensation to form α-(trichloromethyl)-3-nitrobenzyl

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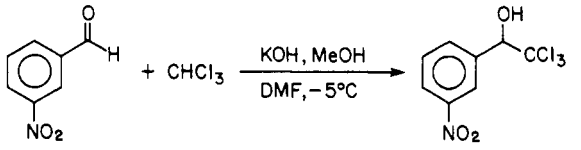
Table I. Yields of Trichloromethyl Carbinols

carbonyl compound	yield,[a,b] %
3-nitrobenzaldehyde	90
benzaldehyde	99
4-anisaldehyde	97
isobutyraldehyde	70
cyclohexanone	68

[a] All products exhibited the expected ^1H and ^{13}C NMR and MS characteristics. [b] Isolated yields after distillation or crystallization.

alcohol in 72% yield.[4b] The generation of trichloromethide anion in solution from the decomposition of trichloroacetic acid in dimethyl sulfoxide has been used to prepare α-(trichloromethyl)-4-nitrobenzyl alcohol in 60% yield.[4c]

In this paper we describe the preparation of α-(trichloromethyl)-3-nitrobenzyl alcohol in high yield with no detectable Cannizzaro product and demonstrate the generality of the method for the condensation of chloroform with other aldehydes and ketones. Initially, we examined potassium fluoride supported on alumina for this condensation since the nonnucleophilic fluoride base would prevent a Cannizzaro-type side reaction. While good yields of **3** could be obtained, this catalyst gave highly variable results.[5] The convenient and general method described herein avoids the preparation and variable activity of the supported base yet provides reproducible high yields. A mixture of chloroform (2.25 equiv) and 3-nitrobenzaldehyde (**2**) (1 equiv) in dimethylformamide (DMF) at −5 °C to −10 °C was treated with a methanolic solution of potassium hydroxide (0.7 equiv). After workup, the desired alcohol **3** was obtained in 98% yield and was crystallized to give analytically pure α-(trichloromethyl)-3-nitrobenzyl alcohol in 90% yield.



2 **3**

The use of solid bases and/or higher reaction temperatures resulted in lower yields of the desired carbinol. The homogeneous reaction medium, made possible by the methanol cosolvent, permitted more facile control of the reaction rate and temperature than when potassium hydroxide as a solid or supported on alumina[5] served as the base in DMF alone. With methanol as the sole solvent **3** did not form, but the desired condensation reaction occurred rapidly, although in lower yield, with solid sodium methoxide in DMF. The enhanced nucleophilicity of the trichloromethide anion in the DMF solvent[6] must contribute to the success of the procedure described.

The generality of this method for the condensation of chloroform with carbonyl compounds was examined and the results are summarized in Table I. The lower yields obtained with the aliphatic aldehyde and ketones reflect the formation of unwanted aldol condensation products as detected by ^1H and ^{13}C NMR. A survey of the reactions of trichloromethide anion with isobutyraldehyde[4a,d,7,8] and cyclohexanone[4a,d,8,9] showed yields lower or comparable to those described here. However, a 92% yield of 1-(trichloromethyl)cyclohexanol was obtained with lithium dicyclohexylamide as the base in tetrahydrofuran.[10]

This method permits the preparation of a variety of α-trichloromethyl carbinols in high yield by using the convenient potassium hydroxide base in methanol/DMF. Other workers have demonstrated the synthetic utility of such alcohols for the preparation of α-substituted carboxylic acids[1,2b,11,12] and α-halo ketones.[13]

Experimental Section

General Procedure. α-(Trichloromethyl)-3-nitrobenzyl Alcohol. To a solution of 3-nitrobenzaldehyde (200 g, 1.32 mol) and chloroform (238 mL, 2.97 mol) in 800 mL of DMF cooled to −9 °C under nitrogen was added dropwise a solution of potassium hydroxide (59.8 g, 0.92 mol) in 180 mL of methanol over a 2.7-h period. The deep purple reaction mixture was aged for 2 h at −8 °C before quenching over 40 min into 1.8 L of 1 N HCl and 1.8 L of toluene cooled to −5 °C. The quench mixture was stirred with cooling for an additional 0.5 h and then brought to ambient temperature. The toluene layer was separated and washed twice with 1.8 L of water. After treatment with 35 g of Darco G-60 charcoal for 1 h and filtration through Super-Cel the organic layer was washed with 1.8 L of aqueous 5% sodium bicarbonate solution and then 1.8 L of water. After evaporation to 550 mL the product **3** was crystallized by the addition of 450 mL of hexanes. The resulting slurry was cooled at 0 °C for 2 h and then the solid was collected by filtration and rinsed with hexanes. After drying 320 g (90% yield) of **3** was obtained: mp 91–95 °C; ^1H NMR δ 3.75 (1 H, d, J = 1 Hz), 5.25 (1 H, d, J = 1 Hz), 7.20–8.45 (5 H, m). Anal. Calcd for $C_8H_6NO_3Cl_3$: C, 35.52; H, 2.24; N, 5.18; Cl, 39.32. Found: C, 35.78; H, 2.23; N, 5.34; Cl, 39.38.

Registry No. **2**, 99-61-6; **3**, 54619-63-5; chloroform, 67-66-3; benzaldehyde, 100-52-7; *p*-anisaldehyde, 123-11-5; isobutyraldehyde, 78-84-2; cyclohexanone, 108-94-1; α-(trichloromethyl)benzyl alcohol, 2000-43-3; α-(trichloromethyl)anisyl alcohol, 14337-31-6; 1-(trichloromethyl)isobutyl alcohol, 32766-45-3; 1-(trichloromethyl)cyclohexanol, 3508-84-7.

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