hydrolysis of phosphonolecithins by lecithinase C (from *Cl. welchii*), are in progress in this laboratory.

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Convenient Deuterium Labeling for Mass Spectrometry *via* Exchange of Enolizable Hydrogen on a Gas–Liquid Chromatography Column

Sir:

The elucidation of electron-impact-induced fragmentation mechanisms and hydrogen rearrangement processes in organic molecules usually requires substitution of deuterium for hydrogen at certain positions. Direct exchange at activated sites in the molecule is carried out whenever desirable, and a wide variety of "wet" chemical procedures is available for this purpose.[1] A novel procedure is the application of column chromatography which is performed on alumina pretreated with deuterium oxide.[2]

We wish to report the quantitative exchange (96% average total incorporation) of enolizable hydrogen atoms in ketones which is effected during a single pass through a g.l.c. column pretreated with deuterium.[3] In order to ascertain the scope of such an effective exchange procedure, over 50 compounds of various structural types containing exchangeable hydrogen were examined. The compounds listed in Table I were chromatographed at the physical parameters indicated, in each case (but one) a single passage of the sample through the column was performed, and the collected sample was analyzed mass spectrometrically[4] for its deuterium content. The compounds examined were mainly ketones and showed a deuterium uptake on the average of about 96% (see Table I). Under these conditions tetrahydrodicyclopentadiene-8-one[5] failed to incorporate deuterium, as expected, since its enolization would require double bond formation at a bridgehead position. In addition a nitrile, a lactam (cotinine), and an amide were investigated; however, the latter proved to be less susceptible to efficient exchange. Employing this procedure, the results for aldehydes, esters, and lactones were less satisfactory and are currently the subject of further studies.

It is interesting to note that two successive passes of β-naphthyl methyl ketone over neutral, predeuterated alumina by column chromatography gave only

Table I

Deuterated compound[a]	Total deuterium exchange, %	G.l.c. conditions: column temp. (°C.)/retention time (min.)/flow rate (cc./min.)	Remarks
Methyl *n*-nonyl ketone-d_5	97	200/6/80	
2,11-Dodecanedione-d_{10}	93	200/50/80	
Cyclohexanone-d_4	91	160/3 × 4/60	3 passes, 5-ft. column
4-Isopropylcyclohexanone-d_4	96	180/12/40	
Carvomenthone-d_3	94	180/6/60	5-ft. column
Carvone-d_4	96	180/20/40	
Camphor-d_2	94	210/4/120	
Tetrahydrodicyclopentadiene-8-one	0	180/20/40	
cis-10-Methyl-2-decalone-d_4	96	180/35/40	
trans-10-Methyl-2-decalone-d_4	96	180/37/40	
$\Delta^{9(1)}$-10-Methyl-2-octalone-d_5	95	200/32/80	
cis-4,4,10-Trimethyl-5,6-methylene-7-decalone-d_2	90	210/37/120	Rapid loss of deuterium in inlet system
Phenylacetone-d_5	97	180/19/40	
Isovalerophenone-d_2	93	180/21/80	
β-Naphthyl methyl ketone-d_3	95	200/122/80	Ref. 2
Phenylacetonitrile-d_2	96	183/30/80	Measured at 10 e v. ionizing voltage to suppress M − 1 peaks; 96% represents a minimum value.
N,N-Diethylacetamide-d_3	42	200/4/80	
Cotinine-d_2 (5′-oxonicotine)	94	210/152/120	Measured at 10 e.v. ionizing voltage to suppress M − 1 peak; 96% represents a minimum value

[a] All compounds listed were, unless stated otherwise, chromatographed on a 10-ft. g.l.c. column.

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(1) For a comprehensive review of deuteration procedures, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1., Holden-Day Inc., San Francisco, Calif., 1964, Chapter 2.

(2) K. Mislow, M. A. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, Jr., *J. Am. Chem. Soc.*, **86**, 1710 (1964).

(3) The column packing consisted of Gaschrom Z (100-120 mesh) coated with 10% Carbowax 6000, and 10% KOD (prepared from KOH and D_2O (99.7%)). A 10-ft. column was ready for use after an initial injection of 300 μl. of D_2O and a stabilization period of a few hours. Regeneration of the column was not necessary during the entire course of the current investigation.

(4) All mass spectra were determined on a modified C.E.C. 21-103C mass spectrometer (for details of modifications and performance, see F. C. Walls and A. L. Burlingame, *Anal. Chem.*, in preparation) equipped with a heated glass inlet system operated at 200°. Most spectra were recorded at ionizing voltage 70 e.v., ionizing current 10–50 μa., and 160–180 v. per stage on the multiplier. Representative samples were determined employing a direct inlet system (see A. L. Burlingame, *Advan. Mass Spectrometry*, **3**, in press) and scanning the entire mass spectrum in 30 sec.

(5) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

39% exchange of the methyl protons,[2] whereas a single pass of this compound through our g.l.c. column resulted in *95% exchange.* In addition, the superiority of the g.l.c. approach is further emphasized upon comparison of results showing 16% incorporation of deuterium in di-*n*-hexyl ketone after two passes through the deuterated alumina column[2] with those obtained on 2,11-dodecanedione by our method. Even though the number of exchangeable hydrogens in this diketone is ten, compared with four in the di-*n*-hexyl ketone, a single pass of the former through the g.l.c. column resulted in a 93% uptake of deuterium.

The ease and rapidity with which exchange of enolizable hydrogens can be quantitatively achieved should make this method attractive for the high quality preparation of pure deuterated samples of synthetic and natural products available in only minute amounts (microgram range). Experiments are in progress on the application of the technique in a micro (capillary column gas chromatography) as well as a preparative scale.

Of course, introduction of tritium could be accomplished in an analogous fashion, with subsequent reduction of the functionality to obtain nonexchangeable tritium-labeled compounds for tracer experiments.

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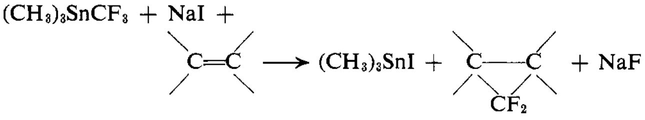
A New Method of Dihalocarbene Generation Based on Trihalomethylmetal Compounds

Sir:

It has been reported that trimethyl(trifluoromethyl)tin releases difluorocarbene at 150°.[1] We report here a procedure that allows utilization of this compound in CF_2 generation at 80° in a nonbasic medium to give, in the presence of olefins, *gem*-difluorocyclopropanes in very good yield. This procedure also can be used to generate CCl_2 from $C_6H_5HgCCl_2X$ (X = Cl and Br) at room temperature. Several examples serve to illustrate the utility of our method.

A mixture of 11.8 mmoles of $(CH_3)_3SnCF_3$, 15 mmoles of sodium iodide, and 100 mmoles of cyclohexene in 1,2-dimethoxyethane (DME) was heated under nitrogen at 80° for 12 hr. Gas chromatographic analysis of the filtered reaction mixture showed the presence of trimethyltin iodide[2] (90%) and 7,7-difluorobicyclo[4.1.0]heptane[3] (73%). A similar reaction with tetramethylethylene gave 1,1-difluorotetramethylcyclopropane[5] in 77% yield. This new procedure appears to generate CF_2 under the mildest conditions reported thus far and gives the best yields of *gem*-difluorocyclopropanes reported to date. We expect that trifluoromethylmercury compounds also would serve well in these reactions.



$$(CH_3)_3SnCF_3 + NaI + \text{>C=C<} \longrightarrow (CH_3)_3SnI + \text{>C—C<}(CF_2) + NaF$$

The application of these procedures to (trihalomethyl)mercurials was equally satisfactory. For example, to 7 mmoles of $C_6H_5HgCCl_3$ and 70 mmoles of cyclohexene in 25 ml. of benzene was added 7 mmoles of dry NaI in 5.5 ml. of DME. The mixture was stirred at 30° under nitrogen for 48 hr., then was filtered to remove C_6H_5HgI. G.l.c. analysis (G.E. SE-30 on Chromosorb W) of the filtrate after one high vacuum trap-to-trap distillation showed that 7,7-dichlorobicyclo[4.1.0]heptane[2] had been formed in 72% yield; chloroform[2] also was present (14%). These products were not formed under these conditions in the absence of sodium iodide. When this reaction was carried out at 80° during 4 hr., the dichloronorcarane and the chloroform yields were 72.4 and 7.2%, respectively. Dichloronorcarane was produced in 16% yield under these conditions when no sodium iodide was added. A similar reaction of the 1:1 $C_6H_5HgCCl_2Br$–NaI reagent system with cyclohexene at room temperature (4 hr.) gave 7,7-dichlorobicyclo[4.1.0]heptane (75%) and 7-bromo-7-chlorobicyclo[4.1.0]heptane (~1%). In the absence of sodium iodide, this reaction carried out under these conditions gave the dichloronorcarane in 1.5% yield.

These reactions involve intermediate formation of trihalomethide ion. This was shown when the $C_6H_5HgCX_3$ + NaI (1:1) reaction was carried out in anhydrous acetone. The major products obtained with $C_6H_5HgCCl_3$ at room temperature were chloroform[2] (34%), dimethyl(trichloromethyl)carbinol[2] (26%), and phenylmercuric iodide (93%); in a reaction carried out at reflux, these products were formed in yields of 59, 12, and 84%, respectively. The action of sodium iodide in acetone on $C_6H_5HgCCl_2Br$ at room temperature gave bromodichloromethane (43%) and dimethyl(bromodichloromethyl)carbinol[6] (15%) as major products. The formation of haloform, presumably by proton abstraction from acetone by CX_3^-, is essentially irreversible in the absence of strong base, hence $(CH_3)_2(CX_3)COH$ yields are low.

Further evidence for a CX_3^- intermediate is given by reactions in which acrylonitrile, an efficient trap for nucleophiles, was used as substrate. In one such reaction $C_6H_5HgCCl_2Br$, NaI, and acrylonitrile were used in 1:1.1:3 molar ratio; the reaction was carried out as described for the cyclohexene case in benzene–DME at room temperature during 4 hr. A similar work-up of the brown reaction mixture showed bromodichloromethane[2] (28.5%), 1,1-dichloro-2-cyanocyclopropane[2,7] (16%), and 4-bromo-4,4-dichlorobutyroni-

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(1) H. C. Clark and C. J. Willis, *J. Am. Chem. Soc.*, **82**, 1888 (1960).

(2) Identified by comparison of its infrared spectrum and g.l.c. retention time with those of an authentic sample.

(3) Refractive index and infrared spectrum agreed with literature data.[4] The yield of the difluoronorcarane under these conditions in the absence of NaI was *ca.* 1%.

(4) J. M. Birchall, G. W. Cross, and R. N. Haszeldine, *Proc. Chem. Soc.*, 81 (1960).

(5) N.m.r.: triplet (J = 2.0 c.p.s.) at 1.08 p.p.m. downfield from TMS (Varian A60, in CCl_4); $n^{25}D$ 1.3772; microanalysis satisfactory.

(6) M.p. 119–120°; identified by microanalysis and infrared and n.m.r. spectra.

(7) Prepared in 76% yield by the reaction of $C_6H_5HgCCl_2Br$ with acrylonitrile in benzene at 80°: D. Seyferth and R. J. Minasz, manuscript in preparation.