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CHLORODIFLUOROMETHANE AS A DIFLUOROMETHYLATING AGENT

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In the study of biologically active compounds the potency-enhancing effects of halomethyl groups have often been observed. Since the electrophilic nature of halomethylenes is clearly indicated by their solvolytic and olefin-addition reactions,[1-8] it was of interest to study the alkylation reactions of dihalo-

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[1] J. Hine, J. Am. Chem. Soc. 72, 2438 (1950) and subsequent papers.

[2] W. E. Doering and A. K. Hoffmann, ibid. 76, 6162 (1954); W. E. Doering and W. A. Henderson, ibid. 80, 5274 (1958).

[3] P. S. Skell and A. Y. Garner, ibid. 78, 5430 (1956).

[4] J. Hine and K. Tanabe, ibid. 80, 3002 (1958) and references therein.

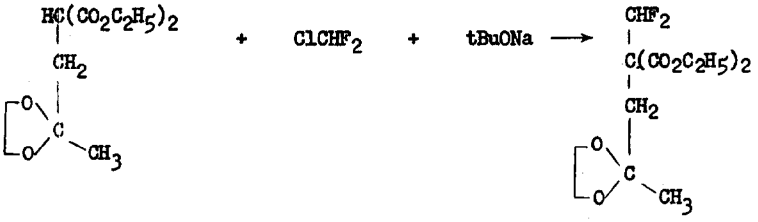
[5] J. Hine and J. J. Porter, ibid. 82, 6118 (1960); J. Hine, R. J. Rosscup and D. C. Duffey, ibid. 82, 6120 (1960).

[6] L. Z. Soborovskii and N. F. Baina, Zhur. Obschei Khim. 29, 1142 (1959); Chem. Abs. 54, 1263 (1960).

[7] J. M. Birchall, G. W. Cross and R. N. Haszeldine, Proc. Chem. Soc. 81 (1960).

[8] Also see reactions with triphenylphosphine, A. J. Speziale, G. J. Marco and K. W. Ratts, J. Am. Chem. Soc. 82, 1260 (1960); S. O. Grim and T. O. Read, ibid. 82, 1511 (1960).

methylene with various nucleophiles as a convenient method of introducing halomethyl groups. Difluoromethylene was first chosen as a model reagent both for the stability of the difluoromethyl group formed in the products and for the ready availability of its precursor chlorodifluoromethane ("Freon 22").[9] Some examples are itemized below. When the sodio derivative of a monoalkylmalonic ester in dimethoxyethane was treated with excess of chlorodifluoromethane, in the presence of sodium t-butoxide, the difluoromethylated derivative (b.p. 105-106° at 0.2 mm , $n_D^{23.5}$ 1.4325) was obtained in 60% yield after fractional distillation. The structure of the difluorinated product was established by elementary analyses ($C_{13}H_{20}O_6F_2$ Found: C, 50.65; H, 6.67; F, 11.58) and its characteristic NMR spectrum.[10] As chlorodifluoromethane was shown to be unreactive in the SN_2 type of reaction under the conditions employed,[4] the observed catalytic effect of excess sodium t-butoxide provided further support to the premise that difluoromethylene was involved as an active intermediate in this reaction.



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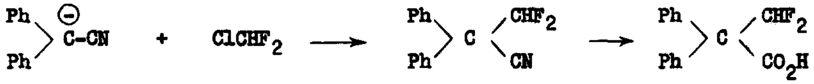
[9] Supplied by the Matheson Co., Inc., East Rutherford, N. J.

[10] We are indebted to Dr. N. R. Trenner and Mr. B. Arison of Merck Sharp & Dohme Research Laboratories for interpretations of the NMR spectra.

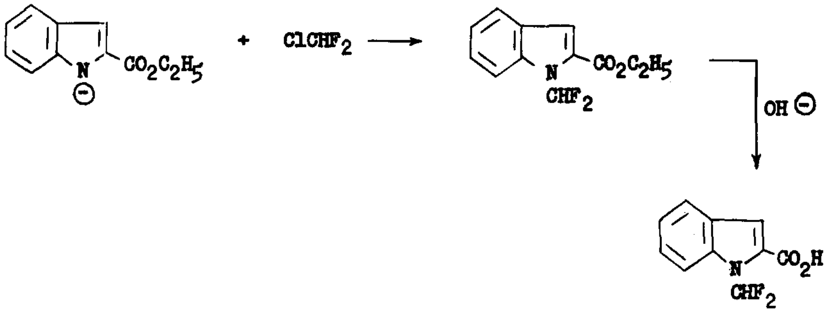
In a similar manner diethyl phenylmalonate was difluoromethylated to the expected ester (b.p. 110° at 0.22 mm , n_D^{23} 1.4741) in 80% yield ($C_{14}H_{16}O_4F_2$ Found: C, 60.03; H, 5.82; F, 10.18).

$$PhCH(CO_2C_2H_5)_2 + ClCHF_2 + tBuONa \longrightarrow Ph\text{-}\overset{\overset{\large CHF_2}{|}}{C}(CO_2C_2H_5)_2$$

Likewise, the anion of diphenylacetonitrile was difluoromethylated at 0° to give α-difluoromethyl-diphenylacetonitrile (m.p. 85°) in excellent yield ($C_{15}H_{11}NF_2$ Found: C, 74.44; H, 4.41; F, 5.89). Hydrolysis of the nitrile afforded α-difluoromethyl-diphenylacetic acid, m.p. 174-6° ($C_{15}H_{12}O_2F_2$ Found: C, 69.15; H, 5.06; F, 14.03).



In addition to the facile reactions of difluoromethylene with carbanions, treatment of the sodio derivative of 2-carbethoxyindole with chlorodifluoromethane at 0° readily gave N-difluoromethyl-2-carbethoxyindole (m.p. 95°), instead of a C-alkylated derivative, in very good yield ($C_{12}H_{11}NO_2F_2$ Found: C, 60.58; H, 4.51; F, 13.41). The structure assignment was based on its I.R. (no NH) and NMR spectra. The stability of the N-difluoromethyl group was demonstrated by the saponification of the ester to the corresponding acid (m.p. 184-6° dec.) with 1 N sodium hydroxide ($C_{10}H_7NO_2F_2$ Found: C, 57.09; H, 3.47; F, 16.77). The introduction of a highly electronegative difluoromethyl group at the N-atom apparently exerted a strong hypsochromic and a slight



hypochromic effect on the ultra-violet absorption of the parent 2-carbethoxyindole chromophore. The infrared spectrum of N-difluoromethyl-2-carbethoxyindole also indicated considerable interaction of the difluoromethyl group with the neighboring carbonyl group.

The alkylation of 2-hydroxypyridine and related compounds such as carbostyril has been rationalized in terms of the ambident ion theory.[11] When the sodio derivative of carbostyril was treated with difluoromethylene, a mixture of 2-difluoromethoxyquinoline (m.p. 34°, $C_{10}H_7NOF_2$ Found: C, 62.66; H, 3.77; F, 15.58), N-difluoromethyl-α-quinolone (m.p. 98°, $C_{10}H_7NOF_2$ Found: C, 61.94; H, 3.42; F, 17.06; N, 6.92) and two crystalline compounds of m.p. 145-8° ($C_{19}H_{13}N_2O_2F$ Found: C, 71.37; H, 4.03; N, 8.08) and m.p. 210-16° ($C_{28}H_{19}N_3O_3$ Found: C, 75.40; H, 4.19; N, 9.39) was obtained. The extent of O-alkylation observed was evidently indicative of the high electrophilicity

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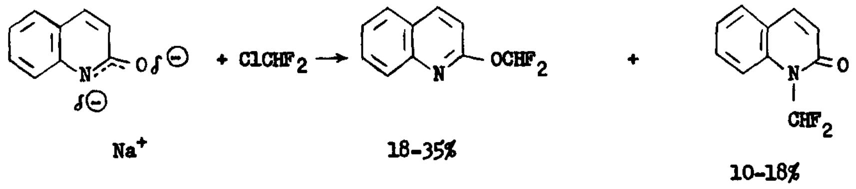
[11] N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, J. Am. Chem. Soc. 77, 6269 (1955) and references therein.



+ di- and tri-substituted methanes.

of the active species involved in the difluoromethylations. The isolation of the higher melting di- and possibly tri-substituted methanes was reminiscent of the formation of ortho esters and their thio-analogs in the solvolytic reactions of halomethylenes.[4,5] The yields of O- and N-difluoromethylated derivatives of carbostyril were substantially increased at the expense of higher melting byproducts when a proton donor like t-butanol was added. In accordance with the solvolytic mechanism postulated by Hine and co-workers, it may be rationalized that the intermediate ions $>N\text{-}\overset{\ominus}{C}F_2$ and $-O\text{-}\overset{\ominus}{C}F_2$ were also involved in this case.

Further exploration of this versatile reagent is being continued.