CHEMISTRY LETTERS, pp. 107-110, 1981.

FACILE SYNTHESIS OF DIALKYL FLUOROMALONATES AND THEIR DERIVATIVES

Nobuo ISHIKAWA* and Akio TAKAOKA

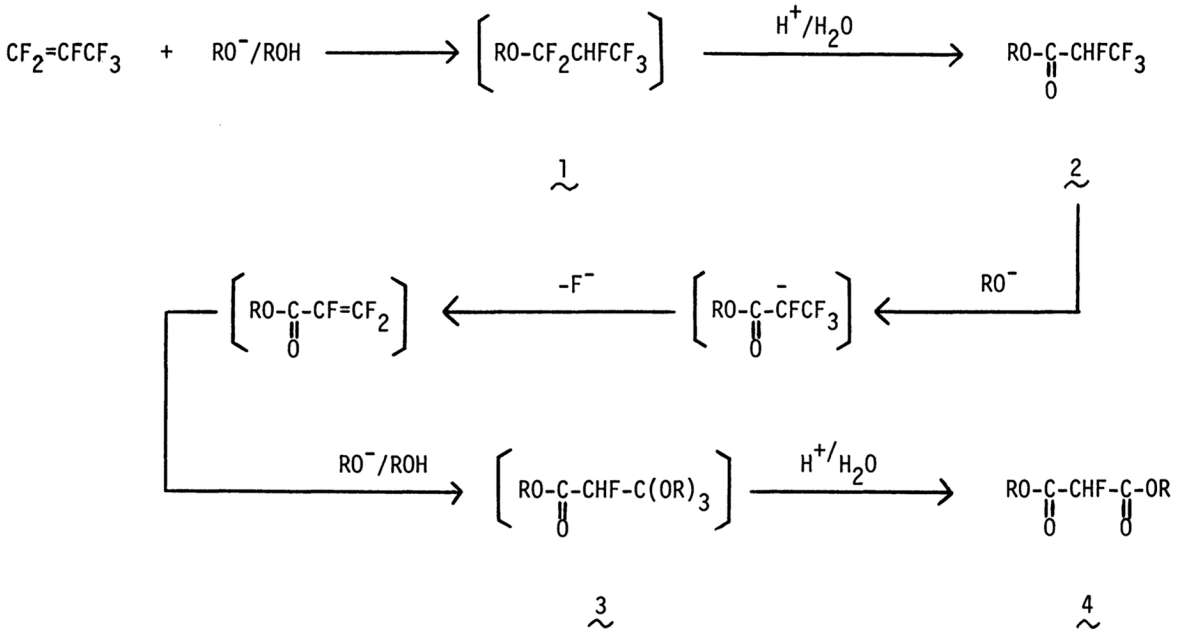
Department of Chemical Technology, Tokyo Institute of Technology

Ookayama, Meguro-ku, Tokyo 152

Dimethyl and diethyl fluoromalonates were prepared by the stepwise basic alcoholysis of hexafluoropropene in a total yield of 50 - 55%. These dialkyl fluoromalonates were alkylated with alkyl halides, and the resulting dialkyl α-fluoroalkylmalonates were cyclized with urea affording 5-fluorobarbituric acid derivatives.

Some sorts of monofluoro organic compounds have recently been attracting attentions owing to their biological activities[1] and some practical methods for monofluorination of organic molecules have been developed in these days.[2] However, practical methods to introduce one fluorine atom into a desired position of organic molecules are not common so far. On the other hand, the preparation of versatile monofluoro intermediates such as α-fluoro-β-diketones, β-diesters, and β-ketoesters from common organofluorine compounds such as fluorinated alkenes seem to be promising and useful. We have already revealed the preparation of α-fluoro-β-ketoesters from trifluoroethene or from hexafluoropropene very recently.[3] We now wish to report a simple preparative method for methyl and ethyl fluoromalonate, a typical α-fluoro-β-diester, from hexafluoropropene.

Dialkyl fluoromalonates have been prepared by 1) the condensation of ethyl fluoroacetate and ethyl chloroformate under basic conditions,[4] 2) the thermal decomposition of diethyl fluorooxaloacetate derived from ethyl fluoroacetate and diethyl oxalate,[4] 3) the halogen exchange reaction of diethyl chloromalonate with KF or KHF_2 at a high temperature,[5-7] 4) the fluorination of diethyl malonate with perchloryl fluoride (ClO_3F),[8] and 5) the Michael addition of a methoxide ion to trifluoroacrylic acid.[9] The starting materials for these methods, however, are rather expensive or toxic, and the procedures are tedious and give only poor yields. The present method, in contrast, uses a commercial perfluoroalkene of low toxicity as a starting material and the process is composed of only two step alcoholysis, with a total yield of 50 - 55%. The reaction proceeds as follows:



The nucleophilic reaction of hexafluoropropene with an alkoxide ion to give alkyl tetrafluoropropionate (2) was carried out in a similar way reported by Knunyants' group.[10] The second step, the dehydrofluorination of 2 followed by the alcoholysis of the terminal difluoromethylene group to give an orthoester (3) was achieved by using sodium alkoxide in an alcohol. The orthoester 3 was treated with an acid, affording dialkyl fluoromalonate (4).

For example, into a solution of sodium methoxide (94 g, 1.74 mole) in methanol (500 ml), hexafluoropropene gas (255 g, 1.70 mole) was introduced below 10 °C. The gas was completely absorbed in a course of ~3 h. After several hours of stirring at room temperature, the reaction mixture was thrown into ice water, and an oily layer was separated to give a crude product (400 ml) of 1,1,2,3,3,3-hexafluoropropyl methyl ether (1, R = Me).

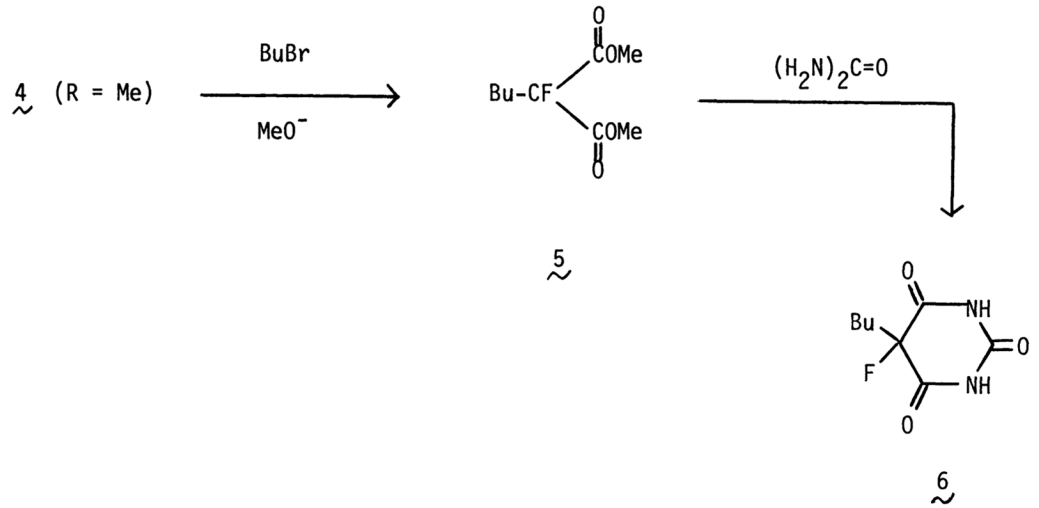
The product was placed in a polyethylene vessel and concentrated sulfuric acid (400 ml) was added dropwise keeping the temperature below 30 °C. The mixture was stirred for 1 h at room temperature and then was thrown into ice water, and an oily layer was separated. After being washed with aq. $NaHCO_3$ solution then with water, it was dried over $MgSO_4$. Distillation gave methyl 2,3,3,3-tetrafluoropropionate (2, R = Me) (203 g, 74%), bp 94 - 96 °C (Lit[10]: bp 95 °C). In a similar manner using sodium ethoxide in ethanol, ethyl 2,3,3,3-tetrafluoropropionate (2, R = Et), bp 108 - 109 °C (Lit[11]: bp 108 - 109 °C) was obtained in an 82% yield.

The methyl ester, 2 (R = Me), (203 g) was added gradually into a solution of sodium methoxide (205 g, 3.8 mole) in methanol (800 ml) keeping the temperature at 0 °C, and the mixture was stirred for 30 min at room temperature. The reaction mixture was acidified with conc. HCl, and after methanol was evaporated, an oily layer was extracted with diethyl ether. The ethereal extract was washed with

aq. $NaHCO_3$ solution, and then with water, and was dried over $MgSO_4$. Distillation under reduced pressure gave dimethyl fluoromalonate (4, R = Me) (107 g, 71%), bp 111 - 112 °C/ 45 mmHg (Lit[10]: bp 80 - 83 °C/ 13 mmHg). Diethyl fluoromalonate (4, R = Et), bp 110 - 111 °C/ 20 mmHg (Lit[10]: bp 82 - 83 °C/ 1 mmHg), was obtained similarly in a 63% yield.

The hydrogen atom of the fluoromethylene group of 4 was removed by an alkoxide ion as in the case of a normal active methylene group, and was replaced by an alkyl group by treating with alkyl halides. Further, the alkylated fluoromalonic esters thus obtained could be cyclized by the reaction with urea affording a series of 5-alkyl derivatives of 5-fluorobarbituric acid.

For example, 4 (R = Me) was butylated with butyl bromide in methanol containing sodium methoxide, giving dimethyl α-fluorobutylmalonate (5), bp 98 - 99 °C/ 3 mmHg,[12] in a 72% yield. When 5 was allowed to react with urea using sodium methoxide in methanol, 5-butyl-5-fluorobarbituric acid (6),[13] mp >260 °C, was obtained in a 71% yield.



5 6

References and Notes

1) Recent reviews: (a) R. Filler in "Organofluorine Chemicals and Their Industrial Applications," ed. by R. E. Banks, Ellis Horwood, London (1979), p.123, (b) W. G. M. Jones, ibid., p.154, (c) K. L. Kirk and L. A. Cohen in "Biochemistry Involving Carbon-Fluorine Bonds," ed. by R. Filler, Am. Chem. Soc., Washington (1976), p.23, and (d) R. W. Fuller and B. B. Molloy, ibid., p.77.

2) Review: C. M. Sharts and W. A. Sheppard in "Organic Reaction," Vol. 21, John Weiley New York (1974), p.125.

3) N. Ishikawa, A. Takaoka, H. Iwakiri, S. Kubota, and S. R. F. Kagaruki, Chem. Lett., 1980, 1107.

4) E. D. Bergmann, S. Cohen, and I. Shahak, J. Chem. Soc., 1959, 3286.

5) E. Gryszkiewicz-Trochimowski, A. Sporzynski, and J. Wnuk, Rec. Trav. Chim., 66, 413 (1947).

6) A. Y. Yakubovich and I. N. Belyaeva, Zhur. Obshch. Khim., 31, 2119 (1961).

7) Y. I. Bogodist and L. D. Protsenko, U.S.S.R.P 185,878 (1966); Chem. Abstr., 67, 2777r (1966).

8) H. Gershon, J. A. A. Renwick, W. K. Wynn, and R. D'Ascali, J. Org. Chem., 31, 916 (1966).

9) O. Paleta and J. Konarek, Collect. Czech. Chem. Commun., 38, 66 (1973).

10) M. D. Bargamova, Y. A. Cheburkov, B. L. Dyatkin, P. V. Petrovskii, and I. L. Knunyants, Izv. Akad. Nauk, SSSR, Ser. Khim., 1967, 611.

11) I. L. Knunyants, A. I. Shchenkotikhin, and A. V. Fokin, Izv. Akad. Nauk, SSSR, Otdel Khim. Nauk, 1953, 282.

12) Found: C, 52.60; H, 7.24%. Calcd for $C_9H_{15}FO_4$: C, 52.43; H, 7.28%. ^{19}F nmr (from ext. CF_3CO_2H in CCl_4): δ 88.5 ppm (t, J_{H-F} 21.1 Hz). ^1H nmr (CCl_4): δ 3.80 (s, OCH_3), 1.78 - 2.33 (m, CH_2CF), 1.18 - 1.46 (m, CH_2CH_2), 0.93 (t, CH_2CH_3).

13) Found: C, 47.11; H, 5.32; N, 13.42%. Calcd for $C_8H_{11}FO_3N_2$: C, 47.52; H, 5.48; N, 13.86%. ^{19}F nmr (DMSO): δ76.5 ppm (t, J_{H-F} 21.6 Hz). ^1H nmr (DMSO-d_6): 4.78 (s, NH), 1.6 - 2.1 (m, CH_2CF), 1.17 - 1.43 (m, CH_2CH_2), 0.85 (t, CH_2CH_3)

(Received October 31, 1980)