Tetrahedron Letters, Vol. 22, No. 15, pp 1421 - 1424 ,1981
Printed in Great Britain

0040-4039/81/151421-04$02.00/0

PREPARATION AND REACTIVITY OF AN α-(DIFLUOROMETHYLENE)-γ-LACTONE

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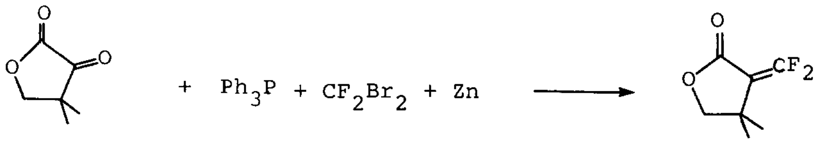
3-(Difluoromethylene)-4,4-dimethyloxolan-2-one, prepared by difluoromethylenation of 4,4-dimethyloxolan-2,3-dione, exhibits marked reactivity toward nucleophilic reagents.

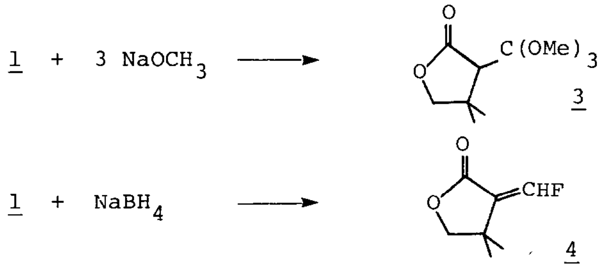
α-Methylene-γ-lactone structure is found in many naturally occurring terpenes and some of them are known to exhibit biological activities. Encouraged by this nature, a large number of synthetic methods to construct this unique functional moiety have been developed by now.[1)] As a part of our programs on organofluorine chemistry, we thought that introduction of fluorine atoms on the methylene carbon in α-methylene-γ-lactones would enhance their reactivity toward nucleophilic reagents, and might provide unique biologically active compounds. Thus, as the first entity of this class of compound we prepared 3-(difluoromethylene)-4,4-dimethyloxolan-2-one 1 and examined its reactivity.

When 4,4-dimethyloxolan-2,3-dione 2 was treated with triphenylphosphine-dibromodifluoromethane-zinc reagent[2)] in acetonitrile, expected difluoro-lactone 1[bp 58-66°C/0.2 Torr] was obtained in 56% yield as the sole product.[3)] The structure was determined by its spectroscopic properties.[4)] Especially, comparison of its mass spectrum with those of dichloro- and dibromo-analogues[5)] unambiguously supported the structure.

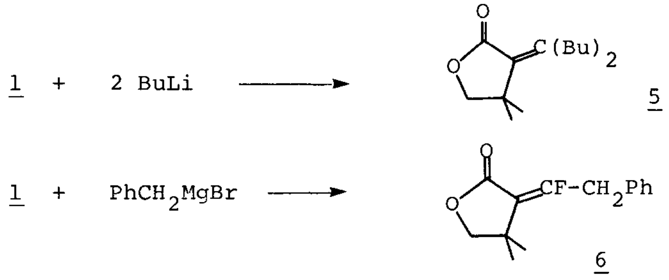


2 1

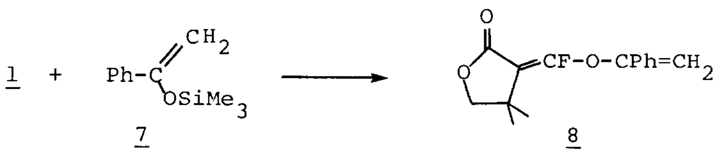
As expected, 1 was found to be quite labile toward various nucleophilic reagents. Brief treatment of 1 with excess sodium methoxide in methanol produced an orthoester 3.[5] Reduction of 1 could be achieved by sodium borohydride in methanol at 0°C producing monofluoromethylene lactone 4[6] (one isomer). Other nucleophilic reagents such as organolithium compound and



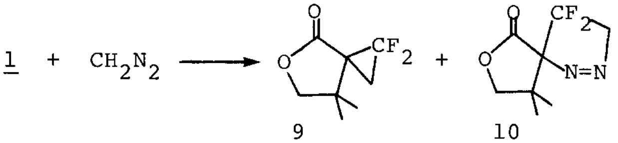
Grignard reagent reacted smoothly with 1 replacing one or two fluorine atoms. Thus, when 1 was treated with butyllithium in THF at -20°C, dibutylmethylene lactone 5[7] was isolated in 41% yield. On the other hand, reaction of 1 with benzylmagnesium bromide in THF at -50°C gave mono-substituted lactone 6[8] (one isomer) in 43% yield.



Interestingly, silyl enol ether 7 reacted (in refluxing DME for 1 hr) with 1 on oxygen and two isomeric vinyl ethers 8[9] were obtained in 36% and 11% yields.



Diazomethane was found to react with 1 slowly in ether at 0°C, and purification of the crude products by column chromatography on silica gel afforded difluorocyclopropane derivative 9[10] (19%) and pyrazoline 10[11] (22%). The latter was easily converted to 9 upon irradiation by high pressure mercury lamp. When crude reaction product from 1 + diazomethane in ether was directly photolyzed and then purified as above, 9 was isolated in 57% yield. In the ^{1}H-NMR spectra of 9 and 10, absorptions for one of the methyl groups appear as a doublet (J=2Hz) presumably due to through-space coupling with fluorine. Present method provides a new route to 1,1-difluorocyclopropane derivatives, which have been prepared by the addition of difluorocarbene intermediate upon olefins.[12]



9 10

In the above we have shown that 1 has a marked reactivity toward various nucleophiles, and in all cases 1,4-addition occured. Thus, 1 and its analogues seem to serve as versatil starting materials for the construction of fluorine substituted carbon skeleton. Examinations on other members of β,β-difluoro-α,β-unsaturated esters as well as on chloro-fluoro analogue of 1 are underway.

REFERENCES AND NOTES

1) For example; P. A. Grieco, Synth., 67 (1975).
2) S. Hayashi, T. Nakai, N. Ishikawa, D. J. Burton, D. G. Naae, and H. S. Kesling, Chem. Lett., 983 (1979).
3) We have found[5] that in dichloro- and dibromomethylenation of 2 by triphenylphosphine-carbon tetrahalide, both carbonyl groups of 2 participated and two dihalomethylenelactones were isolated. On the other hand, in the present case, reaction occurred only on the keto group.
4) NMR($CDCl_3$) δ 1.38(6H,s), 4.00(2H,s); IR 1780, 1725 cm^{-1}; MS m/e 162 (M^+); ^{19}F-NMR($CDCl_3$) δ (down field in ppm vs. external CF_3COOH) 5.1(d, J=5.2Hz), 11.2(d, J=5.2Hz).

5) M. Suda and A. Fukushima, Chem. Lett., 103 (1981).

6) NMR($CDCl_3$) δ 1.40(6H,s), 3.98(2H,s), 7.53(1H,d,J=78Hz); IR(neat) 3090, 1770, 1690, 1265, 1120, 760 cm^{-1}; MS m/e 144(10%, M^+).

7) NMR($CDCl_3$) δ 0.92(6H,bt), 1.27(6H,s), 1.15-1.80(8H,m), 2.4-2.7(4H,m), 3.91(2H,s); IR(neat) 1700, 1600, 1365, 1170, 1000 cm^{-1}; MS m/e 239 (2%, M^++1), 238(4, M^+).

8) mp 45-46°C. NMR($CDCl_3$) δ 1.34(6H,s), 3.93(2H,s), 4.14(2H,d,J=27Hz), 7.30(5H,s); ^{19}F-NMR($CDCl_3$) δ -3.15(d,J=27Hz); IR(KBr) 1750, 1695, 1600, 1285, 1265, 1175, 1050, 990, 720, 700 cm^{-1}; MS m/e 235(9%, M^++1), 234 (59, M^+); correct elemental analysis.

9) Major product; NMR($CDCl_3$) δ 1.35(6H,s), 3.95(2H,s), 4.82(1H,dd, J=3.6, 2.0Hz), 5.12(1H,d,J=3.6Hz), 7.2-7.7(5H,m); ^{19}F-NMR($CDCl_3$) δ 10.8(s); IR(neat) 3050, 1760, 1695, 1640, 1210, 1065, 1035, 1000 cm^{-1}; MS m/e 263(1%, M^++1), 262(2, M^+).

Minor product; NMR($CDCl_3$) δ 1.37(6H,s), 3.98(2H,s), 4.83(1H,dd, J=3.9, 2.7Hz), 5.28(1H, dd, J=3.9, 0.5Hz), 7.3-7.7(5H,m); ^{19}F-NMR($CDCl_3$) δ 10.2(s); IR(nujol) 1760, 1700, 1630, 1020 cm^{-1}; MS m/e 263(2%, M^++1).

10) bp 61-64°C/0.2Torr. mp 30-32°C. NMR($CDCl_3$) δ 1.10(3H,s), 1.22(3H,d, J=2Hz), 1.5-2.2(2H,m), 4.03(2H,s); ^{19}F-NMR($CDCl_3$) δ -53.8(ddd, J= 162, 12, 6Hz), -58.2(dddq, J=162, 12, 8, 2Hz); IR(neat) 3090, 2950, 1760, 1440, 1360, 1280, 1210, 1170, 1010, 960 cm^{-1}; MS m/e 177(177,M^++1).

11) mp 71—73°C. NMR($CDCl_3$) δ 1.31(3H,s), 1.41(3H,d, J=2Hz), 4.18(1H,d, J=8Hz), 4.6-5.1(3H,m); ^{19}F-NMR($CDCl_3$) δ -23.0(ddd, J=259, 26.5, 20Hz), -56.0(ddq, J=259, 5.5, 2Hz); IR(KBr) 3080, 1785, 1760, 1640, 1330, 1150, 1010, 885 cm^{-1}; MS m/e 177(1%); correct elemental analysis.

12) D. J. Burton and J. L. Hahnfeld, "Fluorine Chemistry Reviews", vol 8, p119.

(Received in Japan 4 January 1981)