CHEMISTRY LETTERS, pp. 755-758, 1982.

A USEFUL ZINC REAGENT FOR THE PREPARATION OF 2-OXO-1,1-DIFLUOROALKYLPHOSPHONATES

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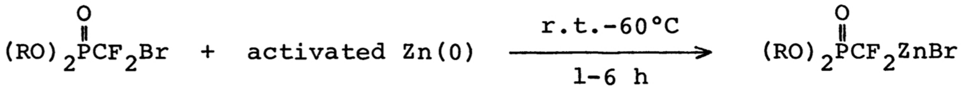
The treatment of dialkyl bromodifluoromethylphosphonates with activated zinc dust in various solvents gave dialkoxyphosphinyldifluoromethylzinc compounds 2, which were acylated with acid halides or fluorinated acid anhydride to afford dialkyl 2-oxo-1,1-difluoroalkylphosphonates in good yields.

In the literature there exist only scattered reports on fluorine-containing organozinc compounds, whose preparation is somewhat tedious in general. These zinc compounds have found little or no applicability in organic syntheses.[1)] For instance, it has been reported that perfluoropropyl-[2)] and perfluoroisopropylzinc iodide[3)] can be obtained by the reaction of the corresponding perfluoroalkyl iodides with zinc metal and that the propyl derivative is quite stable in dioxane at reflux, but the yields of the acylation of these zinc compounds with acid halides are very low.[2b)] Only recently has reasonable success been obtained in synthetic application of these reagents.[4)] In the course of our research on the chemistry of halofluoromethylphosphonates,[5)] we have now found that dialkyl bromodifluoromethylphosphonates react directly with activated zinc metal to form new dialkoxyphosphinyldifluoromethylzinc derivatives, which can react with acylating agents to give dialkyl 2-oxo-1,1-difluoroalkylphosphonates in good yields.



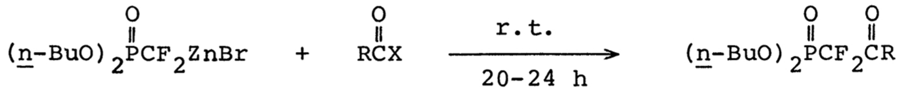
$$(RO)_2\overset{O}{\overset{\|}{P}}CF_2Br + \text{activated } Zn(0) \xrightarrow[\text{1-6 h}]{\text{r.t.-60°C}} (RO)_2\overset{O}{\overset{\|}{P}}CF_2ZnBr$$

1
a: R = Et
b: R = i-Pr
c: R = n-Bu

2
a: R = Et
b: R = i-Pr
c: R = n-Bu

Dialkyl bromodifluoromethylphosphonate (1)[5a] was treated at room temperature to 60°C under dry nitrogen with 1.1 equivalents of activated zinc dust in an ethereal solvent, such as dioxane, tetrahydrofuran, or triglyme. The resultant zinc compound (2)[6] was obtained as a colorless, clear solution and could be stored at room temperature for a long period, at least for several months, without any change. These zinc compounds had reasonably high thermal-stability. Thus, when the zinc reagent 2c in triglyme was successively heated at 100°C for 4 h, at 125°C for 4 h, and at 150°C for 4 h, ^{19}F NMR analyses revealed that the amount of decomposition was 49%, 70%, and 100%, respectively. Hydrolysis of 2 with water occurred reluctantly to give dialkyl difluoromethylphosphonate quantitatively.[7] The zinc reagents (2) also underwent bromination to regenerate the starting bromodifluoromethylphosphonate (1). Transmetallation of 2 took place with anhydrous mercury(II) bromide, but not with anhydrous cadmium(II) bromide in spite of a prolonged reaction time or an elevated temperature being used.

To illustrate the synthetic applicability of these organozinc reagents, attempts were made to prepare dialkyl 2-oxo-1,1-difluoroalkylphosphonates[9] *via* acylation of 2 with various acylating agents. Table I summarizes the results for the reactions of dibutoxyphosphinyldifluoromethylzinc bromide (2c).



$$(\underline{n}\text{-BuO})_2\overset{O}{\overset{\|}{P}}CF_2ZnBr + R\overset{O}{\overset{\|}{C}}X \xrightarrow[20\text{-}24\ h]{r.t.} (\underline{n}\text{-BuO})_2\overset{O}{\overset{\|}{P}}CF_2\overset{O}{\overset{\|}{C}}R$$

2c 3

Table I. The Reaction of 2c with Various Acylating Agents

RCOX	Yield of 3 (%)[a]	RCOX	Yield of 3 (%)[a]
CH_3COCl	86(77)	$(CF_3CO)_2O$	77
$CH_2ClCOCl$	80(69)	CF_3COOCH_3	0[b]
$(CH_3)_2CHCOCl$	82(72)	$CF_3CH_2OSO_2CF_3$	0[b]
PhCOBr	62	γ-butyrolactone	0[b]
$CH_3OCOCH_2CH_2COCl$	83(67)		

[a] Yields were determined by ^{19}F NMR analyses, and those in parentheses are based upon isolated materials.

[b] Reaction temperature, 60°C.

The acylation reaction with acid halides and with fluorinated acid anhydride smoothly proceeded to afford the desired products (3)[10)] in good yields, whereas acid fluorides, esters, lactones, and perhydro acid anhydrides did not react with 2c at all even though the reaction temperature was raised to 60°C. As shown in the case of succinic acid chloride monomethyl ester, the zinc reagent (2c) selectively attacks on the acid chloride function. Although the zinc reagents 2 obtained in the present study appear to have the reactivities similar to those of the corresponding cadmium reagent[5c)] toward acylating agents, the acylation of the former provides more excellent yields of the products than that of the latter.

A typical procedure for the reaction is as follows. To a solution of 2c (10 mmol), prepared from dibutyl bromodifluoromethylphosphonate (1c) and activated zinc dust in anhydrous triglyme, was added dropwise freshly distilled acetyl chloride (15 mmol) *via* a syringe under cooling with an ice-water bath. After the addition, the reaction mixture was stirred for 20 h at room temperature and then was poured into ice water. The organic layer was separated and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Distillation of the residual oil gave dibutyl 2-oxo-1,1-difluoropropylphosphonate in 77% yield.

As demonstrated above, the zinc reagents described herein can serve as a useful reagent for the preparation of 2-oxo-1,1-difluoroalkylphosphonate derivatives, which are extremely difficult to prepare by other methods. Further applications are now under way.

Acknowledgement. We wish to thank the Office of Army Research, the Air Force Office of Scientific Research, and the National Science Foundation for support of our programs.

References

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6) ^{19}F NMR spectra of the zinc reagents (2) showed a broad doublet at a field of -126.9 to -127.4 ppm (J, ~90 Hz) upfield from $CFCl_3$ as an internal reference in triglyme. ^{19}F NMR chemical shifts upfield from the standard are expressed negative, ^{31}P NMR chemical shifts downfield from the standard (external H_3PO_4) are expressed positive.

7) $(EtO)_2P(O)CF_2H$[8]: 77%, bp 95-96°C/15 mmHg, ^{19}F NMR δ -136.9 (dd, J = 48.9 and 90.9 Hz), ^{31}P NMR δ 4.73 (t, J = 90.9 Hz); $(i\text{-PrO})_2P(O)CF_2H$[8]: 79%, bp 66-68°C/2.3 mmHg, ^{19}F NMR δ -137.0 (dd, J = 48.7 and 90.9 Hz), ^{31}P NMR δ 2.79 (t, J = 90.9 Hz); $(n\text{-BuO})_2P(O)CF_2H$[8]: 75%, bp 88.0-90.5°C/2 mmHg, ^{19}F NMR δ -136.0 (dd, J = 48.7 and 90.9 Hz), ^{31}P NMR δ 4.85 (t, J = 90.9 Hz). All other spectroscopic and analytical data were compatible with the structural assignment. The treatment of 2c with deuterium oxide gave the deuterated phosphonate in 84% yield: $(n\text{-BuO})_2P(O)CF_2D$; bp 78-80°C/1.4 mmHg, ^{19}F NMR δ -136.5 (dt, J = 7.4 and 90.9 Hz), ^{31}P NMR δ 4.77 (tt, J = 3.7 and 90.9 Hz), ^{1}H NMR δ 0.95 (t, J = 6.6 Hz), 1.2-1.9 (m), and 4.22 (dt, J = 6.5 and 6.5 Hz).

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10) $(n\text{-BuO})_2P(O)CF_2COCH_3$: bp 70-72°C/0.1 mmHg, ^{19}F NMR δ -118.4 (d, J = 96.7 Hz), ^{31}P NMR δ 2.99 (t, J = 96.7 Hz); $(n\text{-BuO})_2P(O)CF_2COCH_2Cl$: bp 104.0-105.5°C/0.25 mmHg, ^{19}F NMR δ -118.6 (d, J = 93.8 Hz), ^{31}P NMR δ 3.27 (t, J = 93.8 Hz); $(n\text{-BuO})_2P(O)CF_2COCH(CH_3)_2$: bp 88.5-90°C/0.3 mmHg, ^{19}F NMR δ -117.7 (d, J = 96.0 Hz), ^{31}P NMR δ 3.47 (t, J = 96.0 Hz); $(n\text{-BuO})_2P(O)CF_2COPh$: ^{19}F NMR δ -110.0 (d, J = 96.4 Hz); $(n\text{-BuO})_2P(O)CF_2COCH_2CH_2COOCH_3$: bp 123-126°C/0.1 mmHg, ^{19}F NMR δ -118.9 (d, J = 95.2 Hz), ^{31}P NMR δ 2.75 (t, J = 95.2 Hz); $(n\text{-BuO})_2P(O)CF_2COCF_3$: ^{19}F NMR δ -74.7 (t, J = 8.4 Hz) and -117.0 (dq, J = 8.4 and 91.2 Hz). The structure assigned to each new compound was in good accord with its spectral and analytical data.

(Received March 11, 1982)