Journal of Fluorine Chemistry, 20 (1982) 121–126

Received: October 20, 1981

PRELIMINARY NOTE

Difluoromethylene Exchange In The Preparation Of Fluorinated *Bis*-Phosphonates

DONALD J. BURTON, TAKASHI ISHIHARA and RICHARD M. FLYNN

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242 (U.S.A.)

SUMMARY

The application of the Michaelis-Becker variation to the preparation of unsymmetrical *F*-methylene *bis*-phosphonates gives a mixture of both symmetrical and unsymmetrical *bis*-phosphonates. The reaction is best explained by dissociation of the intermediate *F*-methylene phosphonate ylide and carbene scrambling among the potential dialkyl phosphite anions.

Recently we reported the first high yield synthesis of halo-*F*-methyl phosphonates [1] *via* the reaction of trialkyl phosphites and halo-*F*-methanes. In contrast to the normal Michaelis-Arbuzov reaction, which involves a series of SN2 processes [2], the bromo-*F*-methyl phosphonate esters (1) are formed *via* a carbene trapping mechanistic sequence, Scheme 1.

$$(RO)_3P: \ + \ CF_2Br_2 \longrightarrow [(RO)_3\overset{+}{P}Br] \ + \ [:CF_2] \ + \ Br^-$$

$$(RO)_3P: \ + \ [:CF_2] \longrightarrow [(RO)_3\overset{+}{P}\text{-}\overset{-}{C}F_2]$$

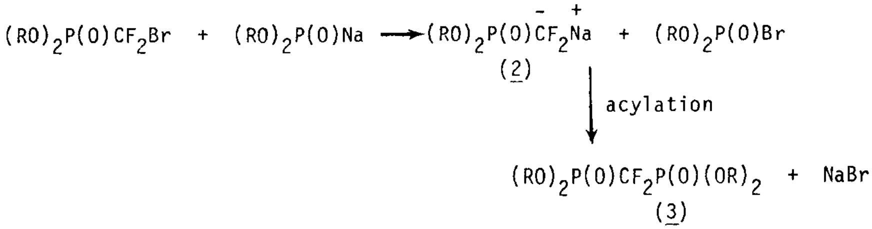
$$[(RO)_3\overset{+}{P}\text{-}\overset{-}{C}F_2] \ + \ [(RO)_3\overset{+}{P}Br] \longrightarrow [(RO)_3\overset{+}{P}CF_2Br] \ + \ (RO)_3P:$$

$$[(RO)_3\overset{+}{P}CF_2Br] \ + \ Br^- \longrightarrow RBr \ + \ \underset{(1)}{(RO)_2P(O)CF_2Br}$$

Scheme 1

0022-1139/82/0000-0000/$02.75

When esters, such as (1) were further reacted with sodium dialkyl phosphites, we obtained the first reported examples of *F*-methylene *bis*-phosphonates [3,4]. The mechanism of this Michaelis-Becker type reaction was shown *not* to involve SN2 displacement of bromide by phosphite, but rather positive halogen abstraction of bromine followed by *insitu* acylation of the phosphonate ylide (2), Scheme 2, to give the *bis*-phosphonate (3).



$$(RO)_2P(O)CF_2Br + (RO)_2P(O)Na \longrightarrow \underset{(2)}{(RO)_2P(O)\overset{-}{C}F_2\overset{+}{Na}} + (RO)_2P(O)Br$$

$$\Big\downarrow \text{acylation}$$

$$\underset{(3)}{(RO)_2P(O)CF_2P(O)(OR)_2} + NaBr$$

Scheme 2

Evidence for bromonium ion abstraction in the initial step was the formation of the reduced phosphonate when the reaction was carried out in the presence of dialkyl phosphite [3]. Additional evidence that proton quenching was faster than dissociation of (2) was obtained when bromo-*F*-methyl dibutylphosphonate was reacted with sodium diethyl phosphite in excess diethyl phosphite. The *only* reduced phosphonate observed was *F*-methyl-dibutylphosphonate [3].

We now wish to report that dissociation of (2) is competitive with the second step (acylation) in the *bis*-phosphonate reaction (Scheme 2). Thus, when bromo-*F*-methyl dibutylphosphonate was reacted with sodium diethyl phosphite in hexane, three *bis*-phosphonates were formed in the ratio 1:2:1 (see Table 1, Entry 1). When toluene was employed as the solvent, similar results were obtained (Entry 2, Table 1). Reversal of the roles of the *F*-methyl dibutylphosphonate and the sodium diethyl phosphite had little effect on the overall results (Entry 3, Table 1). Table 1 summarizes our results for a variety of these types of reactions. Table 2 summarizes the NMR data for the *bis*-phosphonates, [5]. In *all* cases the main product is the mixed *bis*-phosphonate. However, the main product is always accompanied by one or two symmetrical *bis*-phosphonates.

The formation of the *bis*-phosphonates observed in this reaction can be readily accommodated by the reaction mechanism outlined in Figure 1. Depending upon the ease of *insitu* acylation, stability of the intermediate phosphonate ylide, solvent, and concentration of the sodium dialkyl phos-

TABLE 1

$$(RO)_2P(O)Na + (R'O)_2P(O)CF_2Br \longrightarrow$$

Entry	R	R'	%^{a}	$[(RO)_2P(O)]_2CF_2$	$(RO)_2P(O)CF_2P(O)(OR')_2$	$[(R'O)_2P(O)]_2CF_2$	Solvent
1	Bu	Et	77	25	50	25	hexane^b
2	Bu	Et	80	25	61	14	toluene^c
3	Et	Bu	72	10	66	24	toluene^c
4	Bu	iso-Pr	65	—	53	47	hexane^b
5	Bu	iso-Pr	62	—	71	29	toluene^c
6	iso-Pr	Bu	83	16	78	6	toluene^c
7	Et	iso-Pr	69	—	84	16	toluene^c
8	iso-Pr	Et	74	7	90	3	toluene^c

[a] total % yield of <u>bis</u> phosphonates; [b] ratio of $(RO)_2P(O)Na/(R'O)_2P(O)CF_2Br$ is 1:1; [c] ratio of $(RO)_2P(O)Na/$-$(R'O)_2P(O)CF_2Br$ is 2:1.

TABLE 2

NMR data of *F*-methylene *bis*-phosphonates

Bis-Phosphonate	^{19}F (Φ*)	^{31}P (δ)	$^{13}C(CF_2$(δ)	Coupling Constants (Hz) $J_{P,F}$	$J_{C,F}$	$J_{C,P}$
$(EtO)_2P(O)CF_2P(O)(OEt)_2$	122.4(t)	-3.47(t)	116.3(t,t)	84.2	279.0	186.8
$(BuO)_2P(O)CF_2P(O)(OBu)_2$	122.3(t)	-3.64(t)	116.5(t,t)	85.6	279.4	186.8
$(iso\text{-}PrO)_2P(O)CF_2P(O)(OPr\text{-}iso)_2$	123.1(t)	-1.98(t)	115.8(t,t)	86.0	279.1	189.0
$(BuO)_2P(O)CF_2P(O)(OPr\text{-}iso)_2$	122.7(t)			85.8		
$(BuO)_2P(O)CF_2P(O)(OEt)_2$	122.2(t)			83.9		
$(iso\text{-}PrO)_2P(O)CF_2P(O)(OEt)_2$	122.6(t)			85.4		

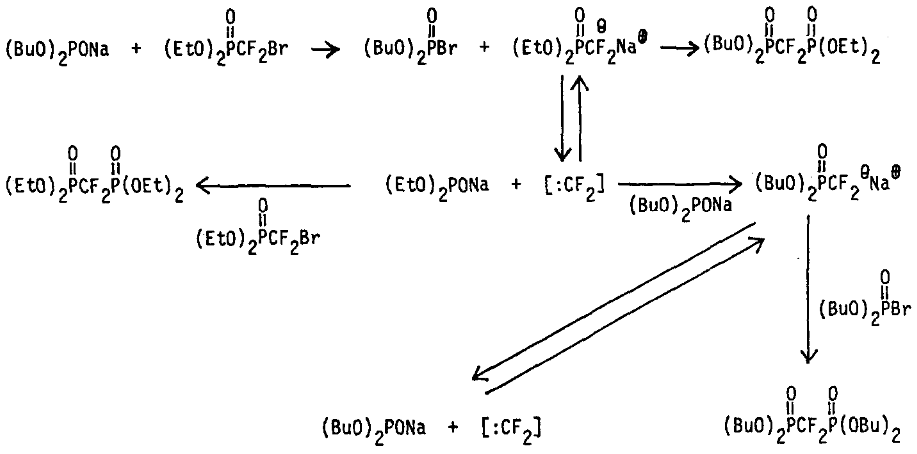


Fig.1. Mechanistic scheme for the reaction between $(BuO)_2PONa$ and $(EtO)_2P(O)CF_2Br$

phite [6], the amount of unsymmetrical bis-phosphonate product will vary relative to the symmetrical products - but the symmetrical by-products cannot be totally excluded.

It is not clear yet what the most important factor or factors are that control the scrambling of the difluorocarbene. From the available data, it appears that the scrambling occurs to maximize the $(iso\text{-}PrO)_2P(O)\bar{C}F_2$ ylide intermediate - but additional work is needed to clarify this point.

In conclusion, our Michaelis-Becker variation is an excellent route to symmetrical bis-phosphonates. Even when applied to the preparation of unsymmetrical bis-phosphonates, excellent yields of bis-phosphonates are obtained - but a mixture of products results from exchange of $[:CF_2]$.

We continue to search for a clean route to the unsymmetrical bis-phosphonates and to explore in detail the chemistry of (1) and (3). Future reports will detail these efforts.

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

1 D.J. Burton and R.M. Flynn, J. Fluorine Chem., 10 (1977) 329.

2 cf. A.K. Bhattacharya and G. Thyagarajan, Chem. Rev., 81 (1981) 415 for a review of the Michaelis-Arbuzov reaction.

3 D.J. Burton and R.M. Flynn, J. Fluorine Chem., 15 (1980) 263.

4 Abstracts of the 182nd American Chemical Society Meeting, New York, N.Y. August 1981, FLUO abstract No. 8. See also R.M. Flynn, Ph.D. Thesis, University of Iowa (1979) for the initial report of this type of dissociation process.

5 The identity of the symmetrical bis-phosphonates described in Table 1 were confirmed by spiking the NMR sample of the reaction mixture with authentic samples of each symmetrical bis-phosphonate.

6 In toluene, best results were obtained with a 2:1 ratio of the sodium dialkyl phosphite to bromo-F-methyl dialkylphosphonate. Similar ratio of products were obtained with a 1:1 ratio but the overall yield of bis-phosphonates was approximately 50% that described in Table 1.