Journal of Organometallic Chemistry, 309 (1986) C7–C10
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

Preliminary communication

RELATIVE REACTIVITIES OF TETRAALKYL ESTERS OF METHYLENE BISPHOSPHONIC ACID

DAVID W. HUTCHINSON* and GRAEME SEMPLE

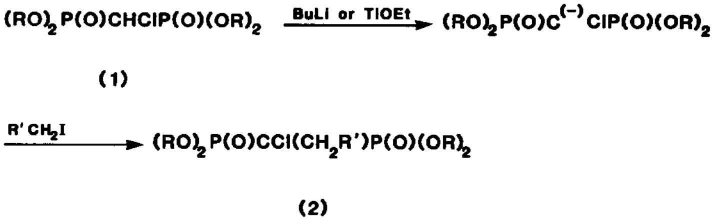
Department of Chemistry, University of Warwick, Coventry CV4 7AL, West Midlands (Great Britain)

(Received March 26th, 1986)

Summary

The synthesis in high yield of tetraisopropyl esters of *C*-alkylated methylene bisphosphonic acids can be achieved by the alkylation of the thallium salts of tetraisopropyl esters of the parent methylene bisphosphonic acids. Yields of *C*-alkylated products are markedly reduced when the tetraethyl or tetramethyl esters are used in this reaction. From a study of the ^{13}C and ^{31}P NMR spectra of the methylene bisphosphonates and their anions, this difference in reactivity is ascribed to steric factors.

Almost quantitative yields of *C*-alkylated esters (**2**) are formed from thallio derivatives of (**1**, R = i-Pr) or its bromo analogue and primary alkyl iodides (Scheme 1) [1]. However, under the same conditions, alkylation of the lithio, sodio or thallio derivatives of **1**, (R = Me or Et) gives very low (< 20%) yields of *C*-alkylated products. Furthermore, the rate of alkylation of the lithio derivative of **1** (R = i-Pr) is faster than the rate of alkylation of the lithio derivative of **1** (R = Et) and more side products are formed during the alkylation of the tetraethyl ester (Fig. 1). We



$$(RO)_2P(O)CHClP(O)(OR)_2 \xrightarrow{\text{BuLi or TlOEt}} (RO)_2P(O)C^{(-)}ClP(O)(OR)_2$$

(1)

$$\xrightarrow{R'CH_2I} (RO)_2P(O)CCl(CH_2R')P(O)(OR)_2$$

(2)

SCHEME 1. The alkylation of anions of tetra-esters of monochloromethylene bisphosphonate.

---

* To whom correspondence should be addressed.

0022-328X/86/$03.50

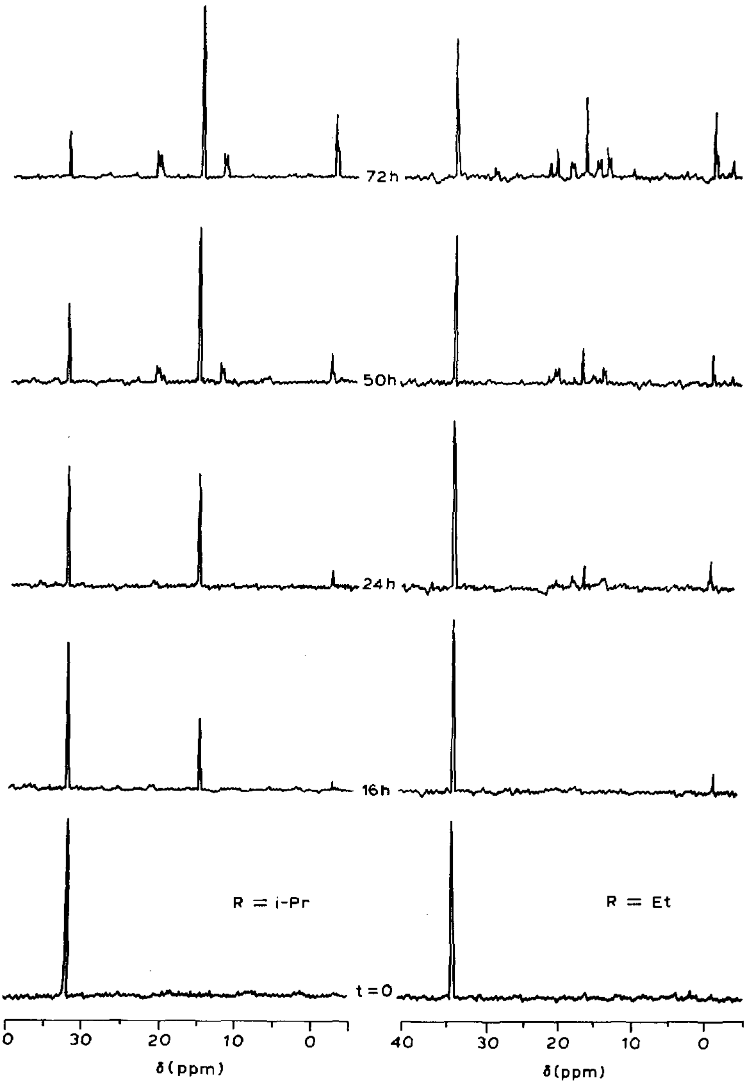


Fig. 1. The time course of alkylation of $[(RO)_2P(O)]_2CCl^-Li^+$ by n-butyl iodide in C_6D_6 at room temperature as studied by ^{31}P NMR spectroscopy. Spectra were recorded on a Bruker WH90 spectrometer at 36.4 MHz and were proton decoupled. The chemical shifts were recorded to an accuracy of ±0.5 ppm (downfield shifts positive) relative to H_3PO_4 as external standard.

have also observed by ^{31}P NMR spectroscopy that a number of products are formed when **1** (R = Me) is treated with n-butyllithium [2]. Cleavage of the C–P bond occurs and this can be avoided if t-butyllithium is used in place of n-butyllithium. While the rapid conversion of **1** (R = i-Pr) to its anion can be achieved at −78°C with one equivalent of methyllithium, the esters **1** (R = Me or Et) undergo extensive side reactions with methyllithium under these conditions.

$(RO)_2P(O)CH_2P(O)(OR)_2$ (**3**)

$(EtO)_2P(O)CH_2COOEt$ (**4**)

RCOCHR′COR (**5**)

TABLE 1

^{13}C AND ^{31}P NMR DATA FOR THE CENTRAL CARBON ATOM IN METHYLENE BISPHOSPHONATES (1 AND 3), THEIR ANIONS, TRIETHYL PHOSPHONOACETATE (4) AND PENTANE-2,4-DIONE (5)

(^{13}C NMR spectra were recorded in C_6D_6 at 22.63 MHz on a Bruker WH90 spectrometer and were proton decoupled with benzene as internal standard. Sodium salts were prepared by the addition of 1 equivalent of sodium hydride (50% dispersion in oil) to a solution in deuterobenzene of the protonated starting materials.)

Compound	^{13}C δ (ppm)	$J(^{13}C-^{31}P)$ (Hz)	^{31}P δ (ppm)
$[(MeO)_2P(O)]_2CHCl$ [a]	42.1	141.9	36.8
$[(MeO)_2P(O)]_2CCl^- Na^+$ [a]	30.2	236.9	15.5 [c]
$[(EtO)_2P(O)]_2CHCl$	43.9	141.9	34.6
$[(EtO)_2P(O)]_2Cl^- Na^+$	31.1	236.4	13.2 [c]
$[(i\text{-}Pro)_2P(O)]_2CHCl$	45.5	143.4	32.3
$[(i\text{-}PrO)_2P(O)]_2CCl^- Na^+$	33.8	234.3	11.5
$[(MeO)_2P(O)]_2CH_2$	24.0	135.3	23.0
$[(MeO)_2P(O)]_2CH^- Na^+$	7.3	217.5	45.5 [d]
$[(EtO)_2P(O)]_2CH_2$	26.1	135.3	19.3
$[(EtO)_2P(O)]_2CH^- Na^+$	8.6	217.7	41.5 [d]
$[(i\text{-}PrO)_2P(O)]_2CH_2$	28.5	136.8	40.5
$[(i\text{-}Pro)_2P(O)]_2CH^- Na^+$	11.1	214.7	22.0
$(EtO)_2P(O)CH_2COOEt$	34.7	133.8	–
$(EtO)_2P(O)CH^- COOEtNa^+$	40.3	219.1	–
$MeCOCH_2COMe$ [b]	52.8	–	–
$MeCOCH^- COMeNa^+$ [b]	96.9	–	–

[a] Recorded on a Bruker WH400 spectrometer at 100.62 MHz. [b] Taken from reference 6. [c] Li^+ salt. [d] Taken from reference 8.

The lithio and sodio derivatives of tetra-esters of methylene bisphosphonic acid (e.g. **1** or **3**) were studied by ^{13}C and ^{31}P NMR spectroscopy as these derivatives are considerably more soluble in organic solvents than their thallium analogues. The esters were dissolved in deuterobenzene at room temperature, the anions were formed by the addition of base and then NMR spectra were also recorded (Table 1). During the alkylation experiments (Fig. 1), an excess of butyl iodide was added in the NMR tube to the preformed anions and the reactions were monitored by ^{31}P NMR. The tetra-esters of methylene bisphosphonic acid were commercially available (Lancaster Synthesis). The tetra-esters of dichloromethylene bisphosphonic acid were prepared as previously described [1,3]. Treatment of these esters with methyl, n-butyl- or t-butyl-lithium (1.6 *M* in hexane, 1 equivalent) gave the corresponding esters of **1** [2]. The yield of **1** (R = i-Pr) was 75%, ^1H NMR ($CDCl_3$): δ 1.35 (24H, d, *J* 8 Hz), 3.9 (1H, t, *J* 20 Hz), 4.9 (4H, m) ppm. Analysis: Found: C, 40.92; H, 7.35; Cl, 9.74. $C_{13}H_{33}ClO_2P_2$ calcd.: C, 41.2; H, 7.72; Cl, 9.36%. The yield of **1** (R = Et) was 57%, ^1H NMR ($CDCl_3$): δ 1.4 (12H, t, *J* 7.4 Hz), 4.05 (1H, t, *J* 18.5 Hz), 4.35 (8H, m,) ppm. Analysis: Found: C, 33.4; H, 6.65; Cl, 11.5. $C_9H_{21}ClO_2P_2$ calcd.: C, 33.5; H, 6.56; Cl, 11.0%. The yield of 1 (R = Me) was 47%, ^1H NMR ($CDCl_3$): δ 3.7 (12H, m,), 4.0 (1H, t, *J* 18 Hz) ppm. Analysis: Found: C, 22.36; H, 5.29. $C_5H_{13}ClO_2P_2$ calcd.: C, 22.52; H, 4.91%.

The one-bond $^{13}C-^{31}P$ coupling constants between the phosphorus atoms and the central carbon atom in the anions of **1** and **3** are much larger than those found for the corresponding protonated compounds **1** and **3** (Table 1) suggesting that there is a change in hybridisation of the central atom from sp^3 to sp^2 when the anions are formed [4]. The ^{13}C chemical shifts indicate that the anions derived from **1** and **3** are not appreciably delocalised as the signals due to the central carbon atom shift upfield approximately 12–17 ppm on formation of the anions. These values may be compared with those obtained from the anion of triethyl phosphonoacetate (**4**) where the negative charge might be expected to be delocalised to some extent over the carbethoxy group. In this case, there is a downfield shift of 5.6 ppm of the signal due to the central carbon atom on formation of the anion. It has been reported for pentane-2,4-dione (**5**, R = Me; R′ = H) in solution in DMSO-d_6 that there is a large (44 ppm) downfield shift of the signal due to the central carbon atom on formation of the anion [5]. Presumably in this case there is considerable delocalisation of the negative charge, and it has been suggested from infrared evidence [6] that this anion is appreciably more delocalised than the anions of triethyl phosphonacetate or **3**.

One explanation for the difference in reactivities between the isopropyl esters of **1** or **3** and their ethyl and methyl analogues is that the bulky isopropyl groups distort the anion and prevent the two phosphoryl groups and the central carbon atom from achieving coplanarity. ^{13}C NMR evidence indicates that there is minimal delocalisation of charge in the anions of **1** or **3** and this distortion may result in the exposure of the negative charge on the central carbon atom to attack by electrophiles. Arguments invoking differences in coplanarity of anions of *β*-diketones have been used to explain differences in reactivities of these compounds [7]

Thus, in the synthesis of *C*-alkylated methylene bisphosphonate esters, we find that while excellent yields can be obtained when the thallio derivatives of tetraisopropyl esters are treated with primary alkyl iodides. Steric factors influence this reaction and considerably lower yields are obtained when either secondary alkyl iodides are used in this reaction or when the ethyl or methyl esters are employed.

References

1 D.W. Hutchinson and G. Semple, J. Organomet. Chem., 291 (1985) 145.
2 D. Seyferth and R.S. Marmor, J. Organomet. Chem. 59 (1973) 237.
3 J.D. Curry, U.S. Patent 3,624,188, 1971.
4 J.B. Stothers, Organic Chemistry (Vol. 24), Carbon-13 NMR Spectroscopy, Academic Press, 1972, Part III, p. 321.
5 C.A. Wilkie and D.T. Haworth, J. Inorg. Nucl. Chem., 40 (1978) 195.
6 F.A. Cotton and R.A. Schunn, J. Am. Chem. Soc., 85 (1963) 2394.
7 H.O. House, in W.A. Benjamin (Ed.), Modern Synthetic Reactions 2nd. edit., 1972, Ch 9, p. 499.
8 O.T. Quimby, J.D. Curry, D.A. Nicholson, J.B. Prentice and C.H. Roy, J. Organomet. Chem., 13 (1968) 199.