Journal of Organometallic Chemistry, 291 (1985) 145–151
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

SYNTHESIS OF ALKYLATED METHYLENE BISPHOSPHONATES VIA ORGANOTHALLIUM INTERMEDIATES

DAVID W. HUTCHINSON and GRAEME SEMPLE
Department of Chemistry, University of Warwick, Coventry, West Midlands, CV4 7AL (Great Britain)

(Received February 25th, 1985)

Summary

Thallium(I) derivatives of esterified methylene bisphosphonates can be readily obtained by treating the latter with thallium(I) ethoxide under anhydrous conditions. Alkylation of the thallium(I) derivatives by a range of primary alkyl iodides takes place smoothly, and significantly higher yields are obtained than for the corresponding reactions with lithio or sodio derivatives.

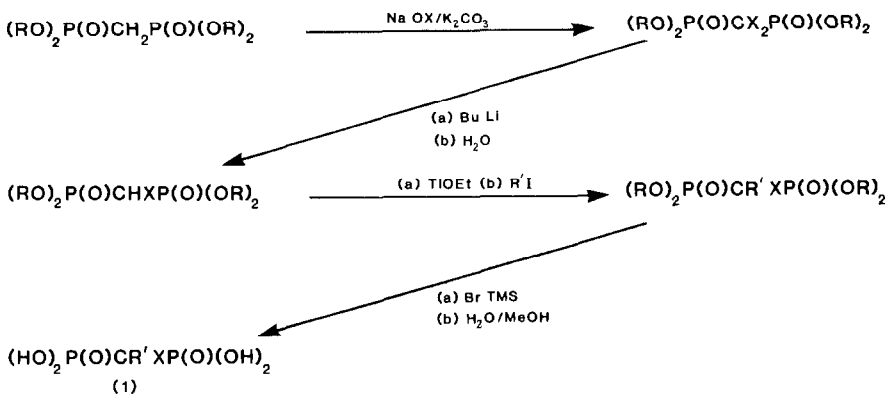
Introduction

Halogenated methylene bisphosphonic acids, e.g., **1** where (R^1 = Cl or Br, R^2 = H) or ($R^1 = R^2$ = Cl or Br) are inhibitors of the RNA transcriptase of influenza virus A and this inhibitory activity has been correlated with the effectiveness of these compounds as chelators of zinc ions [1]. Highly polar compounds such as **1** are not taken up readily by cells and hence we have turned our attention to the synthesis of *C*-alkylated monohalogenomethylene bisphosphonic acids **1** where R^1 = alkyl, R^2 = Cl or Br as these compounds should cross lipid membranes more readily than the unalkylated analogues.

$(HO)_2P(O)CR^1R^2P(O)(OH)_2$
(1)

There are two methods available for the synthesis of **1** (R^1 = alkyl, R^2 = Cl or Br). The first involves the alkylation of the tetraisopropyl ester of methylene bisphosphonic acid **1a** followed by halogenation and removal of the esterifying groups. This route has been reported previously, the sodio derivative of tetraisopropyl **1a** was alkylated and the product then halogenated with a sodium hypohalite. However, yields were poor as $\leqslant 25\%$ alkylation [2] and 45% halogenation [3] occurred. Our studies have shown that it is more efficient to invert the two steps as the yields are much higher and the products are more readily purified (Scheme 1). Monohalogenation of tetraisopropyl **1a** cannot be accomplished in a single step in good yield [2]

0022-328X/85/$03.30



where: R = i - Pr
R' = Me, Et, Pr, n-Bu, n-Hex, CH_2Ph
X = Cl or Br

SCHEME 1

but the monodehalogenation of **1** ($R^1 = R^2$ = Cl or Br) can readily be achieved using either fluoride ion [4] or n-butyllithium [5]. We find that alkylation of the tetraisopropyl esters of monochloromethylene **1e** and monobromomethylene **1m** bisphosphonic acids occurs in high yield when thallium(I) ethoxide is used as base to generate the mono-anion followed by treatment of the latter with a primary alkyl iodide. Alkylation of tetraisopropyl **1a** can be carried out in a similar manner when an excess of thallium(I) ethoxide is used as base. Hydrolysis of the tetraisopropyl esters of the *C*-alkylated products is most efficiently carried out on a small scale via the formation of the tetra(trimethylsilyl) esters with bromotrimethylsilane. The *C*-alkylated monochloromethylene bisphosphonic acids are inhibitors of the RNA transcriptase of influenza virus A, a full report of their biological activities will be published elsewhere.

Results and discussion

The alkylation of organophosphorus compounds by means of their thallium derivatives has not previously been reported although quantitative *C*-alkylation of *β*-diketones has been achieved via stable organothallium intermediates [6]. We have obtained isolated yields of more than 80% of the closely analogous tetra esters of *C*-alkylated monochloromethylene bisphosphonates by means of organothallium intermediates (Table 1). Such high yields could not be obtained when butyllithium, sodium hydride or sodium metal were used to form the reactive intermediates. For example, when tetraisopropyl **1e** was treated with either sodium metal or sodium hydride followed by iodomethane, ^{31}P NMR analysis of the reaction showed the presence of tetraisopropyl *C*-methyl monochloromethylene (**1f**) and tetraisopropyl *C*-dimethyl methylene **1** ($R^1 = R^2$ = Me) bisphosphonates in the ratio 9/1. When iodoethane or iodobutane were reacted with the sodio derivative of tetraisopropyl **1e** complex mixtures of products were obtained, ^{31}P NMR analysis showed the presence of $< 45\%$ tetraisopropyl (**1**; R^1 = Cl, R^2 = Et or Bu) and ca. 30% of *C*-dial-

TABLE 1

CHARACTERISATION OF ALKYLATED METHYLENE BISPHOSPHONATES

Compound			Tetraisopropyl esters			Tetra sodium salts		
No.	R^1	R^2	Alkylation by ^{31}P NMR (%)	Yield isolated (%)	Parent ion(s) ($M+H$) in CIMS	Analyses (Found (calcd.) (%))		
						C	H	P
1a	H	H	–	–	345	4.73	0.81	23.5
						(4.55)	(0.76)	(23.5)
1b	H	Me	72	47	359	8.67	1.27	20.8
						(8.63)	(1.44)	(22.3)
1c	H	Et	68	45	373	13.96	3.74	22.15
						(12.33)	(2.05)	(21.23)
1d	H	n-Bu	74	49	401	18.64	2.70	19.52
						(18.75)	(2.50)	(19.38)
1e	Cl	H	–	–	379, 381	3.84	1.76	19.30
						(4.02)	(0.34)	(20.77)
1f	Cl	Me	98	80	393, 395	7.75	2.22	20.40
						(7.70)	(0.96)	(19.84)
1g	Cl	Et	97	81	407, 409	11.5	2.19	18.07
						(11.03)	(1.53)	(18.99)
1h	Cl	n-Pr	97	78	421, 423	14.37	2.66	19.61
						(14.10)	(2.06)	(18.21)
1i	Cl	n-Bu	96	78	435, 437	14.81	2.90	16.70
						(16.93)	(2.54)	(17.5)
1j	Cl	n-Hex	96	79	463, 465	21.40	3.89	16.37
						(21.96)	(3.40)	(16.21)
1k	Cl	CH_2Ph	99	82	469, 471	23.11	2.39	16.75
						(24.70)	(1.80)	(15.96)
1l	Cl	i-Pr	15	–	421, 423	–	–	–
1m	Br	H	–	–	423, 425	3.80	1.95	17.60
						(3.50)	(0.30)	(18.10)
1n	Br	Me	93	70	437, 438	6.09	1.72	–
						(6.70)	(0.84)	–
1o	Br	Et	87	63	451, 453	9.70	1.51	18.01
						(9.70)	(1.35)	(16.70)

kylated products (Table 2). These results confirm the observation of Quimby et al. [3] who found that monoalkylation of tetraisopropyl **1a** did not occur in high yield by this route. We obtained a good yield of tetraisopropyl **1f** when butyllithium was used to generate the mono-anion of tetraisopropyl **1e** before alkylation of the latter with iodomethane. However, poor yields of *C*-monoalkylated products were obtained with other iodoalkanes. Thus, the thallium(I) intermediate is unique in giving high yields of *C*-monoalkylated products with a range of iodoalkanes.

Treatment of the thallium salt of tetraisopropyl **1e** with bromohexane gave a 36% yield (by ^{31}P NMR) of tetraisopropyl *C*-n-hexyl monobromomethylene bisphosphonate **1j** compared with a 96% yield with iodohexane. This is in accordance with observations by Taylor et al. on the *C*-alkylation of β-diketones [6]. Although these authors reported that the alkylation of thallium(I) salts of β-diketones took place in high yield with 2-iodopropane, we have found that the equivalent reaction with esterified methylene bisphosphonates is very sluggish and we could only obtain 15% of tetraisopropyl *C*-isopropyl monochloromethylene bisphosphonate **1l** at elevated temperatures with prolonged reaction times. Presumably steric hindrance by

TABLE 2

ALKYLATIONS OF TETRAISOPROPYL SODIOCHLOROMETHYLENE BISPHOSPHONATE

	Alkylating Agent					
	MeI		EtI		BuI	
	Yield by ^{31}P NMR (%)	^{31}P Chemical shift (δ)	Yield by ^{31}P NMR (%)	^{31}P Chemical shift (δ)	Yield by ^{31}P NMR (%)	^{31}P Chemical shift (δ)
Starting material	2	11.4	15	11.4	19	11.4
Monoalkylated product	89	14.8	44	14.7	39	14.7
Dialkylated product	9	25.6	30	25.3	26	25.3
Others	–	–	11	two peaks	16	three peaks

the bulky groups around the central carbon atom in our compounds is an important factor in this reaction with secondary iodoalkanes.

Alkylation of the monobromo derivative **1m** proceeded less cleanly than for the monochloro analogue. Fair yields of *C*-monoalkylated compounds could be isolated when the formation of the thallium salt was performed at low temperature ($-20°C$). When the salt was prepared at room temperature, up to 25% (by ^{31}P NMR) of side products were formed presumably due to positive halogen abstraction as has been observed in our earlier experiments [4] and by others [7]. The increased tendency of the monobromo derivative to undergo positive halogen abstraction can be correlated with the ionisation potentials of the two halogens [8] and presumably a monoiodo derivative would undergo dehalogenation even more rapidly. Best yields for monoalkylation of tetraisopropyl **1a** occurred at 30°C with an excess (1.4 equiv.) of thallous ethoxide. Presumably the formation of the monoanion is comparatively difficult in the absence of a chlorine atom on the central carbon atom.

All tetra esters were analysed by ammonia chemical ionisation mass spectrometry (CIMS) with ammonia as reagent gas [9]. In every case an intense ion corresponding to $(M + H)^+$ was observed, together with peaks corresponding to the successive loss of propene residues (Table 1). In the case of tetraisopropyl esters of longer chain *C*-alkylated monohalogenated methylene bisphosphonates **1h–j** and **1p** a second decomposition pathway of the parent $(M + H)^+$ ions was possible involving elimination of hydrogen halide from the bridge carbon atom.

The ^{1}H and ^{31}P NMR spectra of the acids are listed in Table 3. The tetraisopropyl esters had very similar ^{1}H NMR spectra with the addition of peaks in the regions δ 4.8–5.0 (m, methine protons, 4H) and 1.35–1.5 ppm (d, methyl protons, 24H, J 7 Hz). In the ^{1}H NMR spectrum of tetraisopropyl *C*-benzyl monochloromethylene bisphosphonate **1k**, four separate doublets were observed in the region δ 1.17–1.35 ppm. The extremely bulky substituents around the bridge carbon atom have restricted rotation and the separation of the doublets due to the methyl groups are presumably due to diastereotopic effects as there are several prochiral centres in the molecule.

The hydrolysis of the tetraisopropyl esters in concentrated hydrochloric acid [10] does not give high yields of the corresponding free acids. Treatment of the esters with an excess of bromotrimethylsilane followed by aqueous methanol gave quanti-

TABLE 3

NMR DATA OF ALKYLATED METHYLENE BISPHOSPHONANTES

Compound	^{31}P Chemical shift (δ(ppm))		^{1}H chemical shifts (δ(ppm)) of Na_4-salts in D_2O spin–spin coupling constants (J) in Hz
	(i-Pr)$_4$-ester ($CDCl_3$)	Na_4-salt (D_2O)	
1a	17.2	18.0	2.40 (t, 2H, J 21)
1b	22.0	23.2	1.44 (t, 3H (d), J 18, 8 (d), 2.25 (t, 1H (q), J 23, 7.5 (q)
1c	21.9	22.7	1.10 (t, 3H, J 8), 1.7–2.0 (m, 3H)
1d	22.0	22.7	0.90 (t, 3H, J 7), 1.35 (2H sext, J 7), 1.55 (2H, quint, J 7), 1.75–2.0 (m, 2H), 2.25 (t, 1H (t), J_1 23, J_2 7.5)
1e	11.4	13.2	3.90 (t, 1H, J 20)
1f	14.8	17.8	1.85 (5, 3H, J 15)
1g	14.75	17.2	1.17 (t, 3H, J 7.5), 2.25 (m, 2H)
1h	14.8	17.3	0.87 (t, 3H, J 7.5), 1.65 (2H, sext., J 7.5), 2.10 (m, 2H)
1i	14.7	17.3	0.86 (t, 3H, J 7.5), 1.32 (2H, sext., J 7), 1.62 (2H, quint., J 7.5), 2.15 (m, 2H)
1j	14.75	17.3	0.86 (t, 3H, J 7.5), 1.30 (m, 6H), 1.75 (2H, quint., J 7.5), 2.15 (m, 2H)
1k	13.7	16.9	3.40 (s, 2H, J 13), 7.25 (m, 3H), 7.40 (m, 2H)
1l	14.8	17.2	–
1m	11.4	12.9	3.75 (t, 1H, J 20)
1n	14.9	17.8	2.02 (t, 3H, J 15)
1o	14.7	17.5	1.14 (t, 3H, J 8), 2.18 (m, 2H, J 8)

tative yields of the free acids [11,12]. This reaction is much cleaner than when iodotrimethylsilane [13] is used in place of the bromo derivative. Thus, the combination of the use of thallium(I) ethoxide to form the monoanions of esterified methylene bisphosphonates with the use of bromotrimethylsilane to remove the esterifying groups from the alkylated products results in significantly increased yields of *C*-alkylated methylene bisphosphonic acids compared with previously reported procedures.

Experimental

Instrumentation

^{1}H NMR spectra of sodium salts of the free acids were recorded at 220 MHz (Table 3) on a Perkin–Elmer R34 spectrometer using deuterium oxide as solvent and 3-(trimethylsilyl)-1-propane sulphonic acid as internal standard. ^{31}P NMR spectra were recorded to an accuracy of ± 0.5 ppm (downfield shifts positive) at 36.44 MHz on a Bruker WH90 spectrometer using H_3PO_4 as external standard. Chemical ionisation mass spectra with ammonia as reagent gas were obtained with an MS80 mass spectrometer with a DS55 data system (Kratos Analytical Instruments). Analyses were carried out by Elemental Micro-Analysis Ltd. (Beaworthy, Devon, U.K.).

Preparation of methylene bisphosphonates

(i) Tetraisopropyl dichloromethylene bisphosphonate. Tetraisopropyl methylene bisphosphonate (30 g, 0.09 mol; Lancaster Synthesis Ltd., Morecambe, Lancs.,

U.K.) was treated with excess sodium hypochlorite as previously described [3]. Flash column chromatography of the product on silica with 40–60 petroleum ether/acetone (2/1, v/v) as eluant gave a white solid (29.7 g, 82%). ^{31}P NMR analysis indicated that the only phosphorus-containing species present was the title compound (δ 6.86 ppm in $CDCl_3$). The structure was confirmed by CIMS when the principal ions were $(M + H)^+$ 413, 415, 417 in the ratio 9/6/1 due to the compounds with ^{35}Cl and ^{37}Cl isotopes.

(ii) Tetraisopropyl dibromomethylene bisphosphonate. Tetraisopropyl methylene bisphosphonate (10 g, 0.029 mol) was treated with an excess of potassium hypobromite prepared in situ as described [4]. Flash column chromatography of the product on silica using 40–60 petroleum ether/acetone (8/1, v/v) as eluant gave a pale brown oil (11.4 g, 78%). ^{31}P NMR analysis indicated that the only phosphorus-containing species present was the title compound (δ 6.74 ppm in $CDCl_3$). The structure was confirmed by CIMS when the principal ions were $(M + H)^+$ 500, 502, 504, in the ratio 1/2/1.

*(iii) Tetraisopropyl esters of monochloromethylene (**Ie**) and monobromomethylene (**Im**) bisphosphonic acids.* Tetraisopropyl dichloromethylene bisphosphonate (5 g, 0.012 mol) was treated with n-butyllithium (1 equiv.) as described [6] to give tetraisopropyl monochloromethylene bisphosphonate acid (**1e**) (3.25 g, 71%) after chromatography on silica with elution with 40–60 petroleum ether/acetone (7/1, v/v). In a similar reaction, tetraisopropyl dibromomethylene bisphosphonate (5 g, 0.01 mol) gave the tetraisopropyl ester of monobromomethylene bisphosphonic acid **1m** (2.7 g, 64%).

(iv) Tetraisopropyl C-alkyl monochloromethylene bisphosphonates. A standard procedure was used to prepare the tetraisopropyl *C*-alkyl monochloromethylene bisphosphonates listed in Table 1 and the preparation of tetraisopropyl ester of *C*-ethyl monochloromethylene bisphosphonic acid **1g** given below is a typical example. Analytical data (^{31}P NMR spectra and ammonia CIMS) are also given in Table 1.

Tetraisopropyl **1e** (0.5 g, 0.0013 mol) was dissolved in dry, freshly distilled tetrahydrofuran (10 ml) and the solution stirred for 40 min under nitrogen at room temperature in a 100 ml 3-necked flask fitted with a drying tube and a rubber septum. Thallium(I) ethoxide (95 μl, 0.0013 mol) was added and the stirring continued for 40 min during which time the solution became cloudy. Iodoethane (5 ml, 0.032 mol) was added by syringe via the septum and the mixture heated under reflux for 2 h. The solution was then cooled and the orange thallium(I) iodide removed by passing the reaction mixture through a short column of Florisil and eluting with 40–60 petroleum ether/acetone (1/1, v/v) (120 ml). The eluant was concentrated in vacuo to an oil which ^{31}P NMR analysis showed contained $\geqslant$ 97% tetraisopropyl **1g**. The latter was purified by flash chromatography on silica with elution with 40–60 petroleum ether/acetone (6/1, v/v) to give the pure tetraisopropyl **1g** (0.44 g, 81%). During the preparations of tetraisopropyl **1h** and **1i** the reaction vessel was kept dark as the alkyl iodides are light sensitive. In the preparation of tetraisopropyl **1k**, the thallium intermediate was treated with a mixture of benzyl iodide and bromide prepared, in an efficient fume hood, as follows. Benzyl bromide (5 g, 0.029 mol) was added to a solution of sodium iodide (4.4 g, 0.03 mol) in acetone (25 ml). The mixture was stirred at room temperature fo 10 min, filtered and then concentrated in vacuo. This mixture (which was shown by ^{1}H NMR to be a 4/1

mixture of benzyl iodide and benzyl bromide) was used immediately in the alkylation reaction.

(v) Tetraisopropyl C-alkyl monobromomethylene bisphosphonates. The above procedure was used for the *C*-alkylation of tetraisopropyl monobromomethylene bisphosphonate. In the case of the *C*-ethyl derivative, ^{31}P NMR analysis of the reaction showed that the tetraisopropyl esters of **1o** (87%, δ 14.7 ppm), dibromomethylene (8%, δ 17.2 ppm) and *C*-diethyl methylene (4%, δ 25.3 ppm) bisphosphonic acids were present. Column chromatography of the mixture on silica eluting with 40–60 petroleum ether/acetone (5/2, v/v) gave pure tetraisopropyl **1o** in 61% as a colourless oil.

(vi) Alkylation of tetraisopropyl sodio-chloromethylene bisphosphonate was carried out as described [3], ^{31}P NMR Analyses of the product mixtures are shown in Table 2.

(vii) Alkylation of tetraisopropyl lithio-chloromethylene bisphosphonate. The lithium salt of tetraisopropyl monochloromethylene bisphosphonate was prepared as described above, an excess of either iodomethane or bromomethane was added and after the mixture had been heated under reflux for a short time, excess saturated sodium bicarbonate was added. The alkylated products were obtained from this reaction in the usual manner as oils. ^{31}P NMR analysis revealed the presence of the following products: (a) methylation reaction: tetraisopropyl esters of **1f** 65%, **1e** 20%, and dichloromethylene (15%) ethylation reaction: tetraisopropyl esters of **1g** 36%, **1e** 12%, and dichloromethylene 25% bisphosphonic acids together with trace amounts of four unidentified compounds.

(viii) Hydrolysis of tetraisopropyl esters of methylene bisphosphonic acids. Bromotrimethylsilane (2.5 fold excess) was added to each of the esters under dry nitrogen and the mixture stirred at room temperature for $\geqslant$ 20 h, the mixture was then lyophilised and excess aqueous methanol added. The aqueous methanol was removed in vacuo, further aqueous methanol was added and the solution evaporated again. This procedure was repeated 4 times. The residues were dissolved in a little water and isolated as the tetrasodium salt by ion exchange chromatography on Dowex 50 (2 $\times$ 15 cm). In all cases isolated yields were in excess of 90%.

References

1 P.A. Cload and D.W. Hutchinson, Nucleic Acids Res., 11 (1983) 5621.
2 O.T. Quimby, J.D. Curry, D.A. Nicholson, J.B. Prentice and C.H. Roy, J. Organomet. Chem., 13 (1968) 199.
3 O.T. Quimby and J.B. Prentice, U.S. Patent No. 3, 772, 412 (1973).
4 D.W. Hutchinson and G. Semple, Phosphorus and Sulfur, 21 (1984) 1.
5 D. Seyferth and R.S. Marmor, J. Organomet. Chem., 59 (19730 237.
6 E.C. Taylor, G.H. Hawks III and A. McKillop, J. Am. Chem. Soc., 90 (1968) 2421.
7 D.J. Burton and R.M. Flynn, J. Fluor. Chem., 15 (1980) 263.
8 A.J. Downs and C.J. Adams, The Chemistry of Chlorine, Bromine, Iodine and Astatine, Pergamon, Oxford, 1973, Chapter 1, p. 1109.
9 P.A. Cload and D.W. Hutchinson, Org. Mass Spectrom., 18 (1983) 59.
10 H.R. Hays and T.J. Logan, J. Org. Chem., 31 (1966) 3391.
11 C.E. McKenna and J. Schmidhauser, J. Chem. Soc., Chem. Commun., (1979) 739.
12 N. Lalinde, B.E. Tropp and R. Engel, Tetrahedron, 39 (1983) 2369.
13 G.M. Blackburn and D. Ingleson, J. Chem. Soc., Perkin Trans. I, (1980) 1150.