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THE PHOSPHONYLPHOSPHINYL DIANION: A CONVENIENT SYNTHON FOR THE PREPARATION OF BIOLOGICALLY INTERESTING PHOSPHONYLPHOSPHINYL (P-C-P-C-) COMPOUNDS

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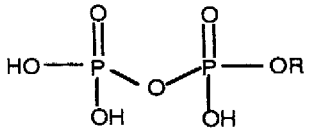
Abstract: *The formation of the (((diisopropyloxyphosphinyl)methyl)isopropyloxyphosphinyl)methyl dianion,* $(iPrO)_2P(O)CH^-P(O)(iPrO)CH_2^-$, *is reported and its application to the synthesis of phosphonylphosphinyl (P-C-P-C-) compounds, including analogs of biologically interesting diphosphates, is presented.*

The diphosphate functional group is prevalent in biochemical processes. Accordingly, it is of much interest to synthesize appropriate analogs[1] of naturally occurring diphosphates, **1**. Such compounds have potential to be used either therapeutically, or to serve as mechanistic probes, or both. One class of analogs which has only recently become available is the phosphonylphosphinyl (P-C-P-C-) class of compounds[2], wherein both the bridging oxygen atom between the two phosphorus atoms of the diphosphate moiety and the oxygen ester atom are replaced by methylene groups, as in **2**.



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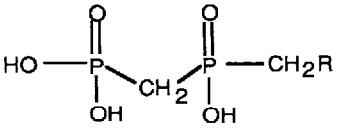
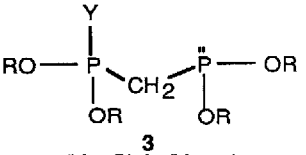


2a-f

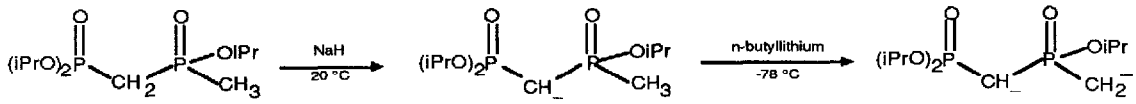


3
a (Y = O) **b** (Y = ··)

Recently it was demonstrated that this interesting class of compounds could be prepared via an Arbuzov reaction between the phosphonylphosphonite **3a** and a suitable homoalkyl halide and that two such analogs were good inhibitors of the 1'-4-condensation reaction between isopentenyl diphosphate and geranyl diphosphate catalyzed by avian liver farnesyl diphosphate synthetase[2]. Similarly, Farrington et al.[3], using a methylene bisphosphonite **3b**, synthesized a P-C-P-C- compound designed to be a tetrahedral transition state analog which was found to be an effective inhibitor of glutamine synthetase. Although these previous methods are functional, they rely upon the phosphonylphosphonite **3a** (or the analogous methylene bisphosphonite **3b**), a reagent which is both difficult to prepare and with which it is cumbersome to work. These facts, in combination with the positive results obtained from the enzymatic studies, prompted us to seek a more facile route to P-C-P-C- compounds.

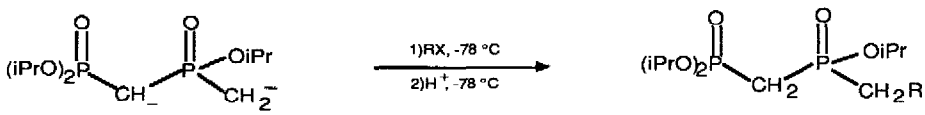
We reasoned that the dianion of a phosphonylphosphinate could serve as an efficient and effective synthon for P-C-P-C- compounds. Grieco and Pognowski[4] (following the work originally of Wolfe et al.[5], and later improved by Weiler[6]) provided precedent by showing that the dianion of ß-keto phosphonates could be readily generated and alkylated with a variety of electrophiles. Accordingly, we were able to treat (((diisopropyloxyphosphinyl)methyl)iso-propyloxyphosphinyl)methane, **4a**[7], with an equivalent of sodium hydride (NaH) at room temperature in

tetrahydrofuran (THF) followed by the addition of an equivalent of n-butyllithium (nBuLi) at -78 °C to give the corresponding dianion **4b**.



4a **4c** **4b**

Treatment of **4b** at -78 °C with an equivalent of a number of electrophiles, followed by acidification, readily afforded the desired products **5a-f** [8]. Although yields have not been maximized, the alkylations occur in moderate to good yields (Table 1) with the exception of hindered halogen electrophiles such as isopropyl bromide and isobutyl bromide which were plagued by competing elimination. However, in those instances, we were able to suppress competing elimination through the use of the triflate ester leaving group[9]. Replacement of the halide leaving group with a triflate resulted in a greater than three-fold increase in yield in the case of the isobutyl system (**5f**), and a greater than ten-fold increase in yield in the case of the isopropyl system (**5b**).



4b **5a-f**

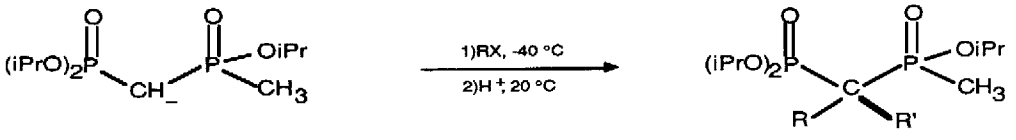
Table 1: Reactions of $(iOPr)_2P(O)CH^-P(O)(iOPr)CH_2^-$ with various electrophiles[10].

Comp.	RX	Time[a](min)/Temp	% Yield[c]	GC/MS[e] M^+ (Calc)
5a	EtI	20 / -78 °C	60 (63)	328.15 (328.32)
5b	$(CH_3)_2CHBr$	b	(0)	- (342.35)
"	$(CH_3)_2CHI$	b	(<2)	342.20 "
"	$(CH_3)_2CHOS(O)_2CF_3$*	20 / -78 °C	21 (24)	342.05 "
5c	$(CH_3)_2C{=}CHCH_2Br$	5 / -78 °C	78 (87)	368.45 (368.38)
5d	Geranyl Bromide	20 / -78 °C	53 (56)	436.55 (436.50)
5e	$C_6H_5CH_2Br$	20 / -78 °C	42 (53)[d]	390.55 (390.39)
5f	$(CH_3)_2CHCH_2Br$	b	13 (14)	356.40 (356.37)
"	$(CH_3)_2CHCH_2OS(O)_2CF_3$*	10 / -78 °C	49 (51)	356.30 "

* CAUTION: Highly Toxic. **a)** Reactions were usually complete within 5 min. **b)** Allowed to warm to room temperature after addition of electrophiles at -78 °C. **c)** All of the compounds were isolated as clear or pale yellow oils after purification by silica gel chromatography and were greater than 99% pure by GC/MS, except **5f**. Yields in brackets are calculated by GC/MS. **d)** 1,2-Diphenylethane was detected in 15% yield by GC/MS. **e)** Performed on an HP 5995 GC/MS equipped with a 10 meter cross-linked silicon gum capillary column.

Verification that alkylation of **4b** occurred in the desired manner was accomplished in several ways. Proton-proton correlation (COSY) experiments and proton-phosphorus (^1H-^{31}P HETCOR) correlation experiments performed on compound **5d** revealed that the P-CH_2-P methylene protons were isolated from the rest of the protons in the molecule. Further evidence was inferred from the absence of the three-proton doublet at δ 1.64 in all isolated products. Control experiments were also conducted wherein the treatment of the monoanion **4c** with iodoethane at temperatures greater than -40 °C readily afforded the expected pair of diastereomers **6a-b**[11]. These compounds,

monoalkylated at the methylene group between the phosphorus atoms, were analyzed by GC/MS and differed in all respects (except for M^+) from the racemate **5a**, isolated from the alkylation of the dianion **4b**. We also synthesized the dialkylated species **6** (R = R' = Et) in a similar manner. GC/MS analysis of this compound revealed that it too differed completely from the racemate **5a**.



4c **6**

a (R =H, R'=Et) **b** (R = Et, R'=H)

Application of a standard method[12] (treatment with bromotrimethylsilane at 40 °C for 48 hr followed by hydrolysis with water and methanol) allowed the quantitative conversion of the phosphonylphosphinates **5c-d** into the corresponding free acid derivatives **2c-d**[13].

In conclusion, the present method demonstrates the utility of the phosphinylphosphinate dianion for the preparation of P-C-P-C- compounds. The stability and availability of starting materials, the thermally mild reaction conditions (-78 °C), and the generality towards several unhindered and hindered systems make the present method a convenient choice for the synthesis of P-C-P-C- compounds, including diphosphate analogs, from the appropriate electrophiles[14].

Acknowledgements: Support for this research was provided by a Bristol-Myers Company Grant of Research Corporation, a DuPont College Science Grant (1987-88), and the American Cancer Society - Oregon Division.

References and Notes

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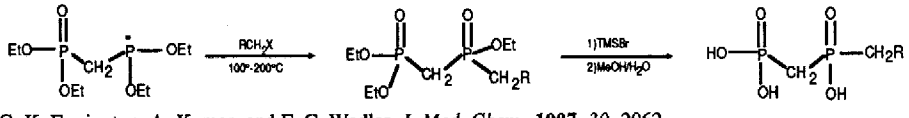

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7. Compound **4** was prepared by a method similar to that of M. P. Teulade, P. Savignac, E. E. Aboujaoud and N. Collignon, *J. Organomet. Chem.*, **1986**, *312*, 283. A flame-dried flask was charged with 45 mL of THF, cooled to -78 °C (IPA/CO_2) and nBuLi (25 mL of a 2.74 M solution in hexane) was quickly added. With rapid stirring, diisopropyl methylphosphonate (12 mL of a 2.05 M solution in THF) was added dropwise during a 45 min period. After completion of the addition, the solution was allowed to slowly warm to room temperature and after 8.5 hr this solution was quenched with 70 mL of 1 M HCl. The organic layer was separated and the aqueous phase extracted with methylene chloride (2 x 50 mL). The organic extracts were combined and solvent removed *in vacuo* to yield 10.1 g of a slightly cloudy colorless liquid, which proved to be a mixture of starting material and product **4a**. Excess starting material (1.76 g) was removed in vacuo (30 °C, 0.005 torr, 6 hr, CO_2/acetone trap). The residue was purified on silica gel (7:3 EtOAc:IPA, R_f 0.76) to yield 6.8 g (69%) of a slightly yellow liquid. GC/MS M^+ = 300.15 (FW = 300.27); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.33 (18H, CH_3-CH), 1.64 (3H, d, P-CH_3), 2.32 (2H, dd, P-CH_2-P, $^2J_{P,H}$ =17.3Hz, 17.7Hz), 4.6-4.8 (3H, m, O-CH-CH_3) ; ^{31}P NMR (36.2 MHz, $CDCl_3$) δ 42.9 and17.6 (doublets $^2J_{P,P}$=3.4Hz).
8. The following procedure was typical. A flame-dried flask equipped with a rubber septum and a magnetic stir bar was charged with 1.1 mmole of NaH (26.4 mg) and 5.0 ml of freshly distilled THF. At room temperature, 1.0 mmole (306 μL) of compound 4a was added

dropwise via syringe to the well-stirred heterogeneous solution. There was an immediate evolution of gas which persisted for 1-2 min after completion of the addition. The solution was allowed to stir for 1.5 hr and then cooled to -78 °C (acetone/CO_2). nBuLi (1.1 mmole) was added dropwise via syringe and the solution was stirred for 10-15 min at -78 °C whereupon 1.1 mmole of the appropriate electrophile was added dropwise via syringe and the resulting solution stirred for the appropriate amount of time at -78 °C. The solution was quenched at -78 °C with a 0.5 M solution of benzoic acid (2.2 mmole) in THF, the organic layer was extracted with methylene chloride (2 x 25 mL) and washed with 5% sodium bicarbonate. The crude oils were purified by flash chromatography on silica gel using EtOAc:IPA .

(((Diisopropyloxyphosphinyl)methyl)isopropyloxyphosphinyl)propane (5a). R_f = 0.54 (9:1 EtOAc:IPA); GC/MS M^+ = 328.15 (FW = 328.32); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, dt, **CH_3** at C3, $^3J_{H,H}$ = 7.2 Hz, $^4J_{P,H}$ = 1.5 Hz) 1.3-1.4 (18H, m, **CH_3**-CH, $J_{H,H}$ = 6.0 Hz), 1.67 (2H, m, **CH_2** at C2) 1.9 (2H, m, **CH_2** at C1) 2.34 (1H, dd, P-HC**H**-P, $^2J_{P,H}$ = 17.1 Hz, $^2J_{P',H'}$ = 20.6 Hz) 2.35 (1H, dd, P-**H**CH-P, $^2J_{P,H}$ = 16.7 Hz, $^2J_{P',H'}$ = 20.8 Hz) 4.63-4.83 (3H, m, O-**CH**-CH_3); ^{31}P NMR (36.2 MHz, $CDCl_3$) δ 17.9, 45.5 (doublets, $^2J_{P,P}$ = 3.4 Hz).

1-(((Diisopropyloxyphosphinyl)methyl)isopropyloxyphosphinyl)-2-methylpropane (5b). R_f = 0.75 (7:3 EtOAc:IPA); GC/MS M^+ = 342.05 (FW = 342.35); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, d, **CH_3**-CH-CH_2, $^3J_{H,H}$ = 6.5 Hz) 1.08 (3H, d, **CH_3**-CH-CH_2, $^3J_{H,H}$ = 6.6 Hz) 1.32-1.38 (18H, m, **CH_3**-CH, $J_{H,H}$ = 6.1 Hz), 1.65-2.05 (2H, m, **CH_2** at C1) 2.15 (1H, m, **CH_3**-CH-CH_2, $J_{apparent}$ = 6.6 Hz) 2.36 (2H, ddd, nonequivalent P-C**H**(**H**)-P) 4.64-4.84 (3H, m, O-**CH**-CH_3).

1-(((Diisopropyloxyphosphinyl)methyl)isopropyloxyphosphinyl)-4-methyl-3-pentene (5c). R_f = 0.52 (9:1 EtOAc:IPA); GC/MS M^+ = 368.45 (FW = 368.38); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25-1.35 (18H, m, **CH_3**'s, $^3J_{H,H}$ = 6 Hz) 1.62 (3H, s, **CH_3**-C) 1.67 (3H, s, **CH_3**-C) 1.88-2.22 (2H, m, **CH_2** at C1) 2.22-2.37 (2H, m, **CH_2** at C2 obscured by P-CH_2-P methylene protons) 2.32 (2H, ddd, nonequivalent P-C**H**(**H**)-P) 4.62-4.82 (3H, m, CH_3-**CH**-O) 5.09 (1H, t, C-**CH**-CH_2, $^3J_{H,H}$ = 7 Hz); ^{31}P NMR (36.2 MHz, $CDCl_3$) δ 18.0, 45.6 (doublets, $^2J_{P,P}$ = 4.3 Hz).

(*E*)-1-(((Diisopropyloxyphosphinyl)methyl)isopropyloxyphosphinyl)-4-8-dimethyl-3-7-nonadiene (5d). GC/MS M^+ = 436.55 (FW = 436.50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32-1.35 (18H, m, **CH_3**-CH, $^3J_{H,H}$ = 6.1 Hz), 1.57 (3H, s, **CH_3**-C), 1.62 (3H, s, **CH_3**-C), 1.67 (3H, d, **CH_3**-C, $J_{apparent}$ = 0.8Hz), 1.88-2.1 (6H, m, **CH_2**'s at C1, C5 and C6), 2.22-2.38 (2H, m, CH_2 at C2, obscured by the P-C-P CH_2) 2.3-2.43 (2H, ddd, nonequivalent P-C**H**(**H**)-P, $^2J_{P,H}$ = 17.0 Hz, $^2J_{P,H'}$ =17.3 Hz, $^2J_{P',H}$ = 20.2 Hz, $^2J_{P',H'}$ = 20.6 Hz), 4.66-4.86 (3H, m, O-**CH**-CH_3), 5.07 (1H, tt, **CH** at C3, $^3J_{H,H}$ = 6.9 Hz) 5.14 (1H, dt, **CH** at C7, $^3J_{H,H}$ = 7 Hz)

1-(((Diisopropyloxyphosphinyl)methyl)isopropyloxyphosphinyl)-2-phenylethane (5e). GC/MS M^+ = 390.55 (FW = 390.39); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3-1.4 (18H, m, **CH_3**'s, $^3J_{H,H}$ = 6 Hz), 2.15-2.4 (2H, m, **CH_2** at C1), 2.35 (2H, dd, P-**CH_2**-P, $^2J_{P,H}$ = 17.0 Hz, $^2J_{P',H}$ = 20.7 Hz), 2.96 (2H, m, **CH_2** at C2), 4.7-4.84 (3H, m, O-**CH**-CH_3), 7.2-7.38 (5H, phenyl); ^{31}P NMR (36.2 MHz, $CDCl_3$) δ 17.6, 44.4 (doublets, $^2J_{P,P}$ = 4.2 Hz).

1-(((Diisopropyloxyphosphinyl)methyl)isopropyloxyphosphinyl)-3-methylbutane (5f). This product contained a slight impurity which could not be removed by silica gel chromatography or reverse phase C18 HPLC. R_f = 0.74 (9:1 EtOAc:IPA); GC/MS M^+ = 356.30 (FW = 356.37); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (6H, d, **CH_3**-CH-CH_2, $^3J_{H,H}$ = 6.5 Hz) 1.3-1.38 (18H, m, **CH_3**-CH-O, $^3J_{H,H}$ = 6.0 Hz) 1.35-1.70 (3H, m, CH at C3 and CH_2 at C2) 1.85-2.0 (2H, m, CH_2 at C1) 2.35 (1H, dd, P-C**H**(H)-P, $^2J_{P,H}$ = 16.8 Hz, $^2J_{P',H}$ =20.8 Hz) 2.37 (1H, dd, P-CH(**H**)-P, $^2J_{P,H'}$ = 16.7 Hz, $^2J_{P',H'}$ = 21.0 Hz) 4.6-4.8 (3H, m, CH_3-**CH**-O).

9. The use of sulfonate esters to suppress undesirable elimination was recently reported by V. J. Davisson, A. B. Woodside, T. R. Neal, K. E. Stremler, M. Muehlbacher and C. D. Poulter, *J. Org. Chem.*, **1986**, *51*, 4768. It should be noted that triflate electrophiles are usually employed with extremely weak nucleophiles (For a review see P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis*, **1982**, 85.). The observed suppression of elimination through the use of triflates is consistent with HSAB observations and HOMO/LUMO molecular orbital theory (for example see I. Fleming, Frontier Orbitals and Organic Chemical Reactions, John Wiley & Sons, New York, **1977**, p45, p84-85).
10. It is interesting to note that while the dianions studied by Weiler (*cf.* ref. 6), and presumably those of Grieco and Pognowski (*cf.* ref. 4), were found to be completely unreactive at -78 °C, the phosphinate dianion of the present study readily reacts at this temperature.
11. These diastereomers were separable by capillary GC and had identical mass spectra.
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13. Several of the free acid derivatives were treated with a slight excess of diazomethane, in diethyl ether, to give the ((dimethoxy)phosphinylmethyl)methoxyphosphinates in approximately 75% yield (calculated by GC/MS).
14. After submission of this manuscript an article was published describing the preparation P-C-P-C- and P-CF_2-P-C- compounds *via* a several step synthesis. This method may be more useful for certain applications (See: S. C. Biller, C. Forster, E. M. Gordon, T. Harrity, W. A. Scott, C. P. Ciosek, Jr., *J. Med. Chem.*, **1988**, *31*, 1869).

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