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SYNTHESIS OF ACYLOXYALKYL ACYLPHOSPHONATES AS POTENTIAL PRODRUGS OF THE ANTIVIRAL, TRISODIUM PHOSPHONOFORMATE (FOSCARNET SODIUM)[1,2]

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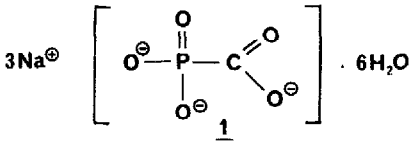
Abstract: *Bis(trimethylsilyl) acylphosphonates via their silver salts couple with iodoalkyl esters to provide an efficient synthesis of the corresponding acyloxyalkyl esters as potential prodrugs of the antiviral agent, trisodium phosphonoformate. These compounds were tested as inhibitors of* **HIV-1** *in chronically infected H9 cells.*

The development of reverse transcriptase inhibitors is regarded as one of the more fruitful approaches to human acquired immunodeficiency syndrome (**AIDS**) chemotherapy.[3] Trisodium phosphonoformate (**1**) is a potent and reasonably selective inhibitor of **HIV-1** reverse transcriptase and has received attention as a potential **AIDS** drug.[3,4] However, due to its highly ionic nature, **1** does not readily cross mucosal or cellular membranes.[4] Clinically, this necessitates its repeated high-dose intravenous administration . We envisioned that suitable lipophilic and bio-reversible analogs,[5] such as the acyloxyalkyl esters, might serve as useful (*i.e.*, orally available and able to cross cellular membranes) prodrug forms of **1**. Reported herein is a general synthetic method providing ready access to diacyloxyalkyl acylphosphonates of **1** and similar compounds.



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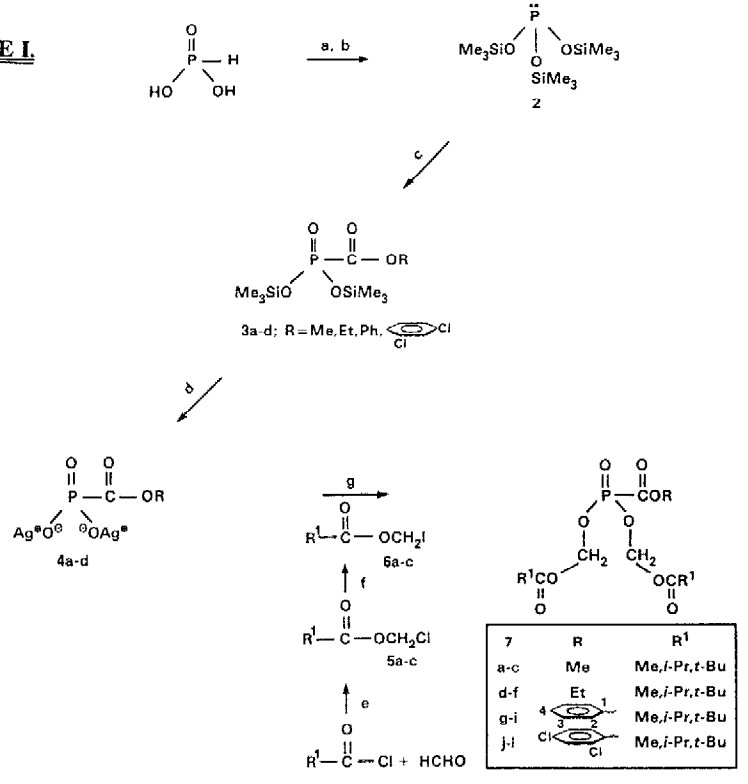
Our initial attempts to synthesize a variety of acyloxyalkyl esters of foscarnet using published procedures[6] were not successful and accordingly we devised an alternate route, displayed in **Scheme I**, to our synthetic targets. The novel and key feature of the present approach is the conversion of the bis(trimethylsilyl) acylphosphonates (**3a-d**) to the corresponding disilver salts (**4a-d**) and their subsequent and facile coupling with iodoalkyl esters to furnish the title compounds. Thus, silylation of anhydrous phosphorous acid with trimethylsilyl chloride followed by heating the resulting product mixture with sodium at 140-150 ^{o}C for 22 h, furnished tris(trimethylsilyl) phosphite (**2**) in an overall isolated yield of *ca.* 65%.[7] The Arbuzov reaction of **2** with either alkyl- or aryl- chloroformates gave the corresponding bis(trimethylsilyl) alkoxy- and aryloxy-carbonylphosphonates (**3a-d**) in isolated yields of *ca.* 80-95%.[8] The silyl phosphonates **3a-d** were converted to the dianilinium salts with aniline in methanol and subsequently to the corresponding monopyridinium salts by ion-exchange chromatography over AG® 50W-X8 (Pyridinium form). All intermediates were characterized by ^{1}H, ^{13}C and ^{31}P-NMR spectroscopy.

SCHEME I.



(a) TMSCl, $N(Et)_3$, THF/ether (b) Na, 140-150°C, 22 hrs. (c) ROCOCl
(d) $AgNO_3$/MeOH/H_2O (e) $ZnCl_2$ (cat.), 75°C, 5-6 hrs.
(f) NaI, CH_3CN, 25°C, 12 hrs. (g) toluene, −78°C, 8 hrs; 25°C, 6 hrs

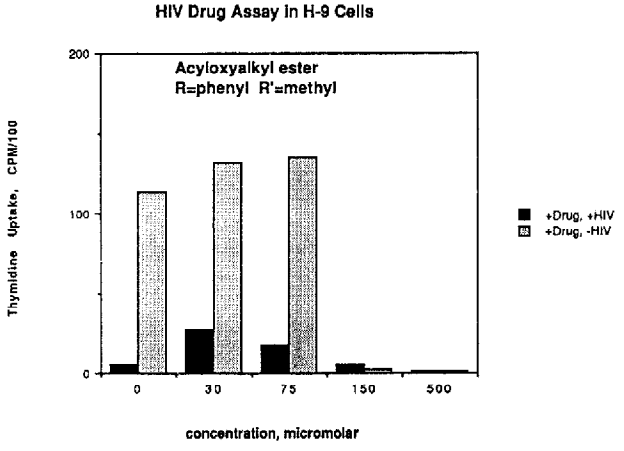


FIGURE 1. Inhibition of the cytopathic effect of HIV-1 by 7g and DMSO in H9 cells. The H9 cells were exposed to HIV-1 and various concentrations of 7g (solid columns) and same concentrations of 7g without the virus (open columns). On day 5, the total viable cells were counted as previously described.[11]

The chloroalkyl esters (**5a-c**) were prepared by the reaction of the corresponding acid chlorides with paraformaldehyde in the presence of catalytic amounts of zinc chloride.[9] Treatment of **5a-c** with sodium iodide in dry acetonitrile gave the corresponding iodoalkyl esters **6a-c** in overall yields of 50-60% for the two steps. Attempts to effect the direct coupling of the silyl phosphonates with the chloroalkyl esters, under a variety of conditions, failed. However, by converting the silyl phosphonates with aqueous methanolic silver nitrate to the disilver salts **4a-d** and reacting them with iodoalkyl esters **6a-c** in dry toluene, the target prodrugs **7a-l** were obtained in yields of *ca.* 60-65%.

Certain of the NMR spectral features of the compounds **7a-l** deserve mention. In the proton-decoupled ^{13}C-NMR spectra, the carbonyl attached to the phosphorus appeared as *doublets* at *ca.* δ 165 *ppm* with $^{1}J_{C\text{-}P}$ between 282 and 290 *Hz*[10] and the -O-CH_2-O- carbons appeared as *doublets* at *ca.* δ 82 *ppm* with $^{2}J_{C\text{-}P}$ between 5 and 6 *Hz*. In the coupled ^{31}P-NMR spectra, *quintets* were observed at *ca.* δ -9 *ppm* with $^{3}J_{P\text{-}H}$ = 12 *Hz*.

The prodrugs **7a-l** were found to be stable when stored either neat or as solutions in aprotic solvents at -20°C. However, some of the herein described acyloxyalkyl esters proved to be unsuitable prodrug forms of **1**. They were ineffective in inhibiting **HIV-1** replication[11] and were, moreover, toxic to the host cells (**Figure 1**). Their inability to inhibit viral replication is associated with their hydrolytic behavior and will be detailed in a forthcoming article.

Typical experimental procedures:[12]

Synthesis of **3c**: Tris(trimethylsilyl) phosphite (**2**) (3.5 g, 11.73 mmol) was added to a dry 25 mL flask under an argon atmosphere. The flask was surrounded by an ice bath and phenyl chloroformate (1.84 g, 1.62 mL, 11.75 mmol) was slowly added over a period of 15 m. The contents were stirred at 25 °C for 12 h and then heated at 60-80 °C for 3h with continuous stirring. Vacuum distillation of the reaction mixture gave **3c** as a clear, colorless, viscous liquid (145-155 °C, 0.45 mm Hg, 3.22 g, 78%). ^{1}H-NMR ($CDCl_3$/ ext. TMS): δ *ppm* 0.36 (*s*, 18H), 7.05-7.50 (*m*, 5H). ^{13}C-NMR ($CDCl_3$/TMS): δ *ppm* 0.8 (CH_3Si), 121.1 (*C*-2), 126.5 (*C*-4), 129.6 (*C*- 3), 149.9 (*C*-1, *d*, *J* = 8.7 Hz), 166.7 (*CO*, *d*, *J* = 287 *Hz*). ^{31}P-NMR ($CDCl_3$) (relative to external trimethyl phosphate): δ *ppm* -25.5 (*s*).

Synthesis of **6c**: To a solution of sodium iodide (17.56 g, 117 mmol), in dry acetonitrile (100 mL), was added **5c**[9] (12.70 g, 85 mmol) over a period of 30 m at 25 °C in the dark. A white precipitate of NaCl began to appear immediately. The contents were stirred for 12 h. The precipitate was filtered, and the acetonitrile was removed from the filtrate *in vacuo*. The filtrate was taken up in toluene (70 mL), washed with aqueous sodium bisulfite (5%, 2 X 40 mL) then water (1 X 40 mL); the toluene layer was then dried over anhydrous sodium sulfate. Toluene was removed *in vacuo* and distillation of the resulting pale yellow oil gave **6c** as a clear, colorless liquid (48-50 °C, 3 mm Hg, 14.2 g, 70%). ^{1}H-NMR ($CDCl_3$): δ *ppm* 1.19 (*s*, 9H), 5.91 (*s*, 2H). ^{13}C-NMR ($CDCl_3$): δ *ppm* 26.4 (CH_3), 31.4 (CH_2), 38.7 (*-C-*), 176.0 (*CO*).

Synthesis of **7i**: *Methanol and distilled water were degassed and sparged with argon before use. The reaction was performed under an argon atmosphere in the dark.* A 100 mL flask fitted with a 20 mL pressure equalizing addition funnel was purged with argon. The phosphonate **3c** (1.13 g, 3.26 mmol) was placed in the flask and was cooled to 0-5°C. Methanol (4 mL) was introduced into the flask and the contents stirred for 5 m. A

solution of silver nitrate (1.11 g, 6.52 mmol) in 75% methanol (15 mL) was then added to the flask. The white crystalline silver salt **4c** precipitated almost instantly. After stirring at 0-5 ^{O}C for 15 m, the reaction mixture was filtered under an argon atmosphere. The disilver salt **4c** thus obtained was dried *in vacuo* (0.5 mm Hg) for 1 h (yield, 0.9 g, 70%) and placed in a dry argon-purged flask. Dry toluene (2 mL) was added to the flask and the contents were cooled to -78^{O}C. Freshly distilled **6c** was taken up in dry toluene (6 mL) and added over a period of 30 m. After stirring at -78^{O}C for 8 h, the reaction mixture was allowed to warm to 25^{O}C and remain there for 6 h with constant stirring. The resulting red colored reaction mixture was filtered through a 0.45μm *acrodisc* filter and the yellow precipitate of silver iodide was washed thoroughly with toluene. The filtrate and washings were combined and extracted with cold, aqueous sodium bisulfite solution (5%, 2 X 25 mL) followed by a cold water wash (1 X 25 mL). The solvent was removed *in vacuo* to give a pale yellow oil. This was dried *in vacuo* (0.5 mm Hg) for several hours to give **7i** as an oil (0.41 g, 57%). ^{1}H-NMR ($CDCl_3$): δ *ppm* 1.18 (*s*, 18H), 5.80 (*m*, 4H), 7.10 - 7.59 (*m*, 5H). ^{13}C-NMR ($CDCl_3$): δ *ppm* 26.7 (CH_3), 38.7(*C*-), 82.6 (-CH_2-, *d*, *J* = 6.1 *Hz*), 121.2 (*C*-2), 126.8 (*C*-4), 129.6 (*C*-3), 149.9 (*C*-1, *d*, *J* = 10.2 *Hz*), 163.6 (*CO*, *d*, *J* = 289 *Hz*), 176.9 (*CO*). ^{31}P-NMR ($CDCl_3$): δ -9.60 (*quintet*, *J* = 12 *Hz*).

References and Notes:

1. *R.P.I. dedicates this paper to Professor S. K. Pradhan of Bombay University Department of Chemical Technology, Bombay-400019, India, on the occasion of his 60th birthday.*
2. *This research was supported by the Office of the Director, NIH, with funds earmarked for AIDS Targeted Antiviral Research.*
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12. Complete data for all compounds will be presented in a forthcoming paper.

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