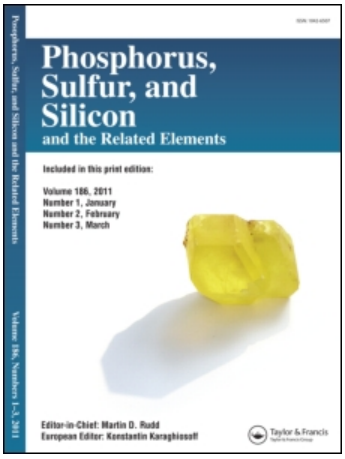

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SIMPLE AND CONJUGATE BIFUNCTIONAL THIOPHOSPHONATES: SYNTHESIS AND POTENTIAL AS ANTI-VIRAL AGENTS

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Abstract The synthesis and antiviral potential of some thiophosphonocarboxylates, bisthiophosphonates and related nucleoside conjugates is summarized.

INTRODUCTION

Thiophosphonoformic acid (TPFA), a thio analogue of the anti-viral agent phosphonoformic acid (PFA), is facilely synthesized by Lawesson's reagent (LR) thionation of trimethyl PFA to trimethyl TPFA ($(CH_3O)_2P(O)CO_2CH_3$ –> $(CH_3O)_2P(S)CO_2CH_3$), followed by alkaline hydrolysis.[1] Compared to PFA, TPFA has a similar IC_{50} for inhibition of human immunodeficiency virus (HIV-1) reverse transcriptase (RT), and also for inhibition of HIV-1 p24 expression in human cells *in vitro*, but is 2–3x less inhibitory to human α DNA polymerase.[1, 2] TPFA is slowly converted to PFA in the p24 antigen capture assay, raising the possibility that it could function to some degreee as a prodrug of the latter compound.[2] The replacement of S for O in PFA might also affect bioavailability, toxicity or other pharmacological properties of the drug. In this brief overview,we present our recent work on: 1) Lawesson synthesis of phosphonoacetate and bisphosphonate analogues of TPFA, and their evaluation as HIV-1 inhibitors; 2) *in vivo* chemistry and pharmacokinetics of TPFA bearing on its potential as an anti-viral drug; 3) synthesis and HIV-1 inhibition characteristics of novel TPFA conjugates with AZT and several other dideoxynucleosides. New compounds were characterized by ^1H, ^{13}C and ^{31}P NMR and by elemental analysis.

RESULTS AND DISCUSSION

LR thionation of phosphonocarboxylates $(RO)_2P(O)CXYCO_2R$, **1** (**1a**: R = Me, XY = HH; **1b**: R = Et, XY = HH; **1c**: R = Me, XY = HCl; **1d**: R = Me, XY = ClCl) regioselectively gave the thiophosphoryl derivatives $(RO)_2P(S)CXYCO_2R$, **2** (**2a–2d**) (32–67%), whereas bisphosphonate esters $(RO)_2P(O)CH_2P(O)(OR)_2$, **3** (**3a**: R = Me; **3b**, R = Et; **3c**, R = *i*Pr) and the phosphinylmethylphosphonate ester $(EtO)PhP(O)CH_2P(O)(OEt)_2$, **4** were dithionated by LR, giving $(RO)_2P(S)CH_2P(S)(OR)_2$, **5a–5c** (13–50%) and $(EtO)PhP(S)CH_2P(S)(OEt)_2$, **6** (10%), respectively. Yields were higher for substrates having a

more electron-withdrawing P(O) substituent (Me_3TPFA > **1**; **1d** > **1c** > **1a**) but decreased with bulkier phosphonate ester alkyl groups in the series **3a–c**.

Pathways for complete and partial hydrolysis of **2** and **5** were explored[3]. Trisodium thiophosphonoacetate (Na_3^+TPAA, **7**) was obtained from the trimethyl ester **1a** by either BTMS/OH^- or direct alkaline hydrolysis, but these methods were unsuccessful with the α-chloro TPAA esters **1c** and **1d**. Tetramethyl methylenebis[thiophosphonate] **3a** was converted to its Na_2^+ *sym* –O,O-dimethyl (**8**), Na_2^+ S,S-dimethyl (**9**) and Na_4^+ (**10**) salts by reaction with BTMS/NaOH, NaI and ITMS[3]/NaOH, respectively. Thiono –> thiolo rearrangement (as in **9**) was also observed when trimethyl phosphonocarboxylates (*e.g.* **2a**) were monodemethylated with NaI. Unlike trisodium TPFA (**11**) or trisodium PFA (**12**), none of the thiophosphonates, or partial esters thereof, thus prepared showed significant activity in the p24 inhibition assay, suggesting that further efforts be concentrated on **11**.

HPLC-EC analysis of plasma or urine from felines dosed with **11** reveals that TPFA is partly metabolized *in vivo* to PFA. Thus, in 6 h 42.3% of TPFA administered i.v. (800 μg/kg) was excreted (urine) as 23.5% TPFA, 13.8% PFA and 5.0% of a metabolite identified by GC-MS and ^{31}P NMR as thiophosphophosphorous acid (TPA).[4] Mean oral bioavailability of TPFA in enteric-coated capsules was > 2x greater for TPFA (22%; 28% including PFA from TPFA) vs. PFA (8%). In a similar study[5] using a canine model, partial conversion *in vivo* of TPFA (400 μg/kg dosage; 95% of dose) to PFA (8.3%) and TPA (8.6%) was also observed (balance recovered as TPFA), and oral bioavailability of TPFA was > 3x vs. PFA (44.5% vs. slightly more than 12%) with cimetidine pretreatment. In the same model, PFA (400 μg/kg) caused a dramatic decrease (>70%) in creatinine clearance, whereas TPFA had essentially no effect on this sensitive measure of renal function.

Our results prompted us to investigate synthesis of novel O,O-dimethyl (**13–16**) and O-methyl (**17-20**) thiono TPFA conjugates of dideoxynucleoside HIV inhibitors: AZT, ddA, ddI and ddC. The dimethyl esters were prepared in 35–45% yield by condensing the nucleoside partner with the phosphonyl chloride $CH_3O_2P(S)Cl(OCH_3)$ **21**, obtained by treatment of Me_3PFA with PCl_5 in CCl_4 followed by LR thionation. Preliminary HIV-1 p24 inhibition data for some of these compounds gave apparent IC_{50} values of 0.09–23 μM (**13–15**), compared to 1–10 μM for **17–19**. Reference IC_{50} values for conjugate moieties were 0.05–0.06 (AZT), 0.3–0.8 (ddA), 0.5–1 (ddI) and 10–15 (TPFA) μM. Investigation of conjugate reactivities under assay conditions is in progress.

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