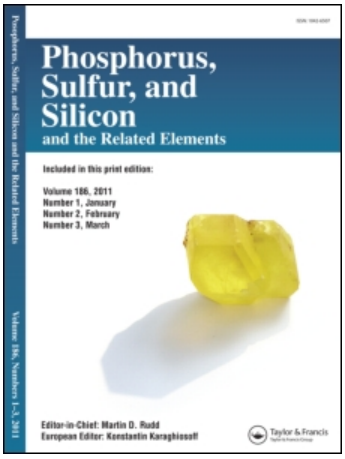

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Synthetic Approaches to Biologically Active Bisphosphonates and Phosphonocarboxylates

CHARLES E. MCKENNA, BORIS A. KASHEMIROV and ZENG-MIN LI

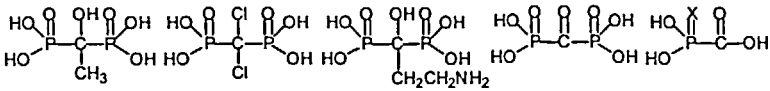
Department of Chemistry, University of Southern California, Los Angeles, CA 90089-0744, USA

Some current and potential therapeutic uses of bisphosphonates and phosphonocarboxylates are summarized. The feasibility of synthesizing α-hydroxy α-alkyl/aryl methyl-enebisphosphonates via Grignard addition to tetraalkyl carbonylbisphosphonates **6** is demonstrated, and a new synthesis of **6** under very mild conditions is described.

Keywords: anti-resorptive; cancer; anti-viral; AIDS; foscarnet; thiophosphonoformate; carbonylbisphosphonate; etidronate

INTRODUCTION

Bisphosphonates have increasingly found applications in medicine. The earliest bisphosphonates demonstrated to possess biological activity were methylenebisphosphonates bearing simple α-alkyl, α-halo and/or α-hydroxy substituents, with specific affinity for bone. Etidronate (EHDP, **1**) and clodronate **2** in particular have been



1 **2** **3** **4** **5**

extensively studied and widely used in treating Paget's disease and osteoporosis.[1] Recent structure-activity studies in several pharma laboratories have identified impressively potent new antiresorptive bisphosphonates for more effective treatment of osteoporosis.[2, 3]

Since the recent FDA approval of pamidronate **3** for multiple myeloma and breast cancer bone disease, bisphosphonates have rapidly become the standard treatment for cancer-linked hypercalcemia and osteolytis in the USA. In 1998 the potential of bis-

phosphonates as anti-cancer drugs is receiving further attention following reports that **2** exhibited unexpected anti-metastatic activity in cancer patients, decreasing the tumor burden in bone and perhaps also in soft tissue.[4]

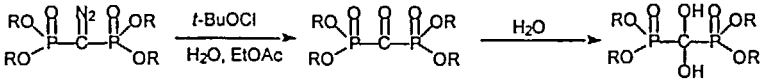
To date no bisphosphonate-based anti-viral drug has emerged. Carbonylbisphosphonate **4**, which potently inhibits (EC_{50} = 13 μM) the pyrophosphate-dependent phosphofructokinase from *T. gondii*, an AIDS-related parasite[5] and selectively inhibits certain mammalian DNA polymerases[6] is one of the few bisphosphonates demonstrated to inhibit HIV-1 replication in vitro.[7] The structurally related phosphonocarboxylates are thus far represented in the clinic by a single anti-viral drug—intravenous foscarnet (**5a**, X = O)—which is an alternate therapy for CMV retinitis in AIDS. Foscarnet also significantly inhibits HIV-1 reverse transcriptase (RT) in vitro. Interest in foscarnet as a possible component in combination anti-retroviral therapy in AIDS has been stimulated by the observation that foscarnet-resistant HIV mutants show increased susceptibility to nucleoside RT inhibitors, e.g. AZT.[8] Unfortunately, foscarnet is severely limited by its inadequate oral bioavailability and reduced potency in vivo. The search for an effective strategy to overcome these limitations has engendered synthetic approaches to **5a** analogues ranging from thioderivatization (e.g. **5b**, X = S)[9] to the creation of lipid prodrugs.[10]

Although significant progress has been made over the past decade, it is likely that realization of the full medical potential of both bisphosphonates and phosphonocarboxylates remains in the future, pending further advances in drug design informed by better understanding of the mechanisms of action and pharmacological properties of these compounds. The development of new synthetic routes to specific classes of bisphosphonates and phosphonocarboxylates can obviously benefit this process. In this report we describe the first practical, facile synthesis of tetraalkyl carbonylbisphosphonates **6** and preliminarily explore their potential as synthons for preparation of α–alkyl α-hydroxy methylenebisphosphonates via carbanion addition chemistry.

RESULTS AND DISCUSSION

We previously reported the synthesis of several examples of **6** by treating the corresponding diazo compounds **7** with *t*-butyl hypochlorite (*t*-BuOCl) in formic acid, followed by pyrolysis under vacuum.[11] An adaptation of Regitz' method to prepare vicinal tricarbonyl compounds,[12] this approach afforded the first examples of **6**, but suffers from several disadvantages: the pyrolytic vacuum distillation step is difficult and unreliable; yields are poor and variable; and the ketones **6** are contaminated with α,α-dichloro side products which resist removal by distillation. Use of *t*-BuOCl in dry acetonitrile, said to convert 2-diazo-1,3-dicarbonyl compounds into 1,2,3-tricarbonyl derivatives via spontaneous decomposition of an α-chloro α-*t*-butoxy diacyl intermediate,[12] also gives unsatisfactory results with **7**.

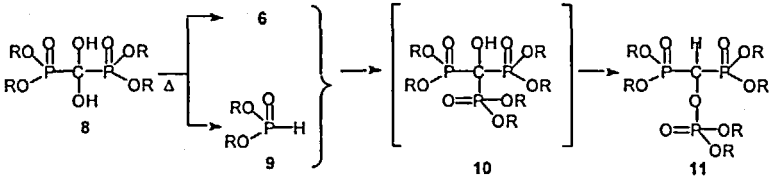
We have now discovered that brief (several minutes) reaction at or below room temperature of *t*-BuOCl with **7** in ethyl acetate containing *several equivalents of H_2O* provides the corresponding ketones **6** in almost quantitative yield (~95%). The reaction displays a short induction period, with an accelerating release of gas. After quenching with chlorotrimethylsilane (to destroy excess H_2O) and removal of volatiles in vacuo, essentially pure **6** remains ready for use in situ in subsequent reactions.



7 (R = Me, Et, *i*-Pr) **6** **8**

The results can be rationalized as follows. Efficient transfer of a positive chlorine atom from *t*-BuOCl[13] to the diazo carbon of **7** is promoted by protonation of the *t*-butyloxy oxygen, facilitating departure of *t*-BuOH. Loss of N_2 and attack by H_2O then generates an unstable α-chloro alcohol intermediate which eliminates HCl to produce **6**. Activation of *t*-BuOCl by the HCl released would lead to an increasing acceleration of the reaction. H_2O as a weak acid may initiate the early, slow reaction. Sufficient H_2O must be available as a competing nucleophile to suppress diversion of the α-chloro cation intermediate by Cl^- into α,α-dichloro side product. However, excess H_2O may react with the desired ketone product (the Me and *i*-Pr **6** hydrates (**8**) can be isolated as crystalline compounds). In ethyl acetate, reaction of **6** with a small excess of H_2O is relatively slow, permitting timely quenching with chlorotrimethylsilane.

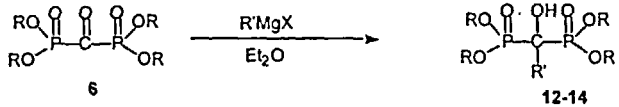
When heated, the hydrates **8** are converted into bisphosphono phosphates **11** (scheme below). Evidence supporting the proposed trisphosphonate intermediate **10** was provided by direct reaction of *i*-Pr **6** with dimethyl phosphite, which yielded a binary mixture of **11** isomers, one corresponding to C -> O migration of a $(MeO)_2P(O)$ group and the other to C -> O migration of a $(i\text{-PrO})_2P(O)$ group in **10**.



8 **9** **10** **11**

Addition of carbon nucleophiles to **6** should generate the ester precursor of an α,α-disubstituted bisphosphonate having the α-hydroxy "bone hook"[3] present in many active anti-resorptives. Notwithstanding the propensity of α-hydroxyphosphonates to eliminate phosphite anion under basic conditions, we find that simple alkyl, aryl and

benzyl Grignard reagents readily convert Et or *i*-Pr **6** to the corresponding α-hydroxy α-alkyl, α-aryl and α-benzyl methylenebisphosphonates (**12-14**; **12** is the tetraisopropyl ester of **1**) in 40-75% isolated yields. Further exploration of **6** addition chemistry is in progress.



6 **12-14**

12: R = *i*-Pr, R' = Me; **13**: R = *i*-Pr, R' = Ph; **14**: R = Et, R'= CH_2Ph

Acknowledgments

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