Faculty of Science
Chemistry Department

Synthesis of Mono- and Bis-Phosphonates *via* Transformations of P*III* and P*V* Synthons as Bone Diseases Treatment Agents

A DISSERTATION

For

The Degree of Doctor of Philosophy
in Organic Chemistry

By

Eman Sabry A. Abd-Elmoniem

B. Sc. (Al-Azhar University)
M. Sc. (Cairo University)

National Research Center

Presented to

Department of Chemistry
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Ain-Shams University

Cairo, Egypt

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Under Supervision

Prof. Dr. Galal H. Sayed
Prof. Dr. Wafaa M. Abdou (D. Sc.)
Prof. Dr. Neven A. F. Ganoub

Cairo, Egypt
2015

APPROVAL SHEET OF THE DISSERTATION

ENTITLED

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Eman Sabry A. Abd-Elmoniem

The Candidate dedicates this

Dissertation

to

My late father and my mother,

for their endless love, support and

encouragement throughout my life.

Thank you both for giving me strength to

reach for the stars and chase my

dreams.

My husband, my sisters,

for their encouragement and push,

and to my beloved kids

Habiba & Nour

Abbreviations

TAP	Trialkyl phosphite
DAP	Dialkyl phosphite
TMP	Trimethyl phosphite
TEP	Triethyl phosphite
T*i*PrP	Triisopropyl phosphite
DMP	Dimethyl phosphite
DEP	Diethyl phosphite
TPP	Triphenylphosphine
TPPO	Triphenylphosphine oxide
HWE	Horner-Wadsworth-Emmons
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TEA	Triethylamine
r.t.	Room temperature
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
LDA	Lithium diisopropylamide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DMF	*N*,*N*-Dimethylformamide
LiH	Lithium hydride
SAR	Structure-activity Relationship
NMR	Nuclear Magnetic Resonance
CAMM	Computer-assisted molecular modeling

ABSTRACT

Name: Eman Sabry Aziz Abd-Elmoneim

Title: Synthesis of Mono- and Bis-Phosphonates *via* Transformations of P*III* and P*V* Synthons as Bone Diseases Treatment Agents

Degree: Philosophy of Doctor (Ph.D.)

The thesis focuses on the phosphorus chemistry. The general part includes the most interesting reactions of alkyl phosphites, mainly, trialkyl and dialkyl phosphites, with C=X electrophiles (aldehydes, ketones, aldimines, ketimines, isocyanates, isothiocyanates, and activated olefins. The original work, contains four parts; all relied on applying a variety of phosphorus reagents on different substrates, that characterized by the presence of nitrogen containing heterocycles, such as pyridazine or triazole core structure for the purpose of pharmacological evaluation. According to the structures of the products and the data base (Molecular assisted molecular modeling), new synthesized phosphorus compounds were pharmacologically evaluated, e.g., as anti-nociceptive, anti-inflammatory, anti-microbial, antiarthritis or anticancer agents. The structure-activity relationship was studied in most cases.

In the first part, a high-yielding general synthesis of imidazophosphor esters-based tetrazolo[1,5-*b*]pyridazine was described. A conjugated reaction between 3,6-diazidopyridazine and different types of phosphonyl carbanion reagents followed by intramolecular cyclization afforded the target products, using sodium

ethanolate solution as the reaction medium. Among the products, 5 compounds, at 50 mg/kg dose showed notable anti-nociceptive and anti-inflammatory activity with low toxic-effect.

In the second part, three different series of phosphonate derivatives, *β*-amino- and fused thiadiazolo/thiadiazine-phosphonates were synthesized using addition and/or addition-cyclization protocol of Horner-Wadsworth-Emmons (HWE) reagents to 1,2,4-triazole-3-thiols. The design of potentially antimicrobial and anticancer phosphor esters accounted to the results of the computer-assisted molecular modeling. All synthesized phosphonates are evaluated for their *in vitro* antimicrobial activities while anticancer properties were determined for eight out of twenty new phosphonates. The tested phosphonates, except compounds that have a nitrile moiety exhibit from moderate to significant antimicrobial activity. Nevertheless, the most active compounds are the fused thiadiazole-phosphonates that inhibited the growth of both Gram-negative and Gram-positive bacteria better than *β*-aminophosphonates and fused thiadiazolophosphonates. In parallel, the antitumor activity screenings of selected phosphonates representing each series are also tested. Their antitumor properties against ten carcinoma cell lines including breast, ovarian, prostate, and liver were investigated. The results showed that all tested compounds reflected remarkable antitumor activity against breast, and prostate carcinoma cell lines, whereas a moderate to good effect was observed on ovarian and liver carcinoma cell lines.

In the third part, two different protocols for the synthesis of a variety of *N*-methylenebisphosphonates (*N*-MBPs) and their relevant

bisphosphonic acids were reported, from (i) coupling of azido-substrates with the phosphorus reagent, tetraethyl methylene-bisphosphonate catalyzed by sodium ethanolate (EtONa); (ii) involved three-component one-pot synthesis, by applying tetraethyl methylene-bisphosphonate in an alkaline solution to carbodiimide- or Schiff-base derivatives, initially was generated *in situ*. The synthesized aminobis-phosphonates were pharmacologically evaluated for their antiarthritis/ anti-inflammatory activities. Furthermore, the structure-activity relationship were studied. The docking studies were also performed.

In the fourth part, a new and an efficient conjugated addition reaction of phosphorus reagents (trialkyl- or dialkyl phosphites) with 2-azido-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile was developed and furnished spiro-triazaphosphole-oxides and phosphoramidate derivatives. Contrary to these results, linear substituted phosphoramidates were obtained from the reaction of the azide with dimethyl-, diethyl-, and diisopropyl phosphites. Reaction of hexaalkylphosphorus triamides with the same substrate afforded the corresponding phosphoric triamides in the presence of a protonating agent (dil alcohol). The new synthesized phosphorus compounds are reported and evaluated for anticancer activities.

Keywords: Imidazophosphor; α-aminophosphonates; β-enaminobis-phosphonates; Horner-Wadsworth-Emmons reagents; spiro-triaza-phosphole-oxides; *N*-methylenebisphosphonates; anti-nociceptive; anti-inflammatory; anticancer; docking studies.

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Contents **Page**

Overview of Phosphonation of C=X Compounds

(Reactions of TAP/DAP with aldehydes, ketones, aldimines, ketimines, isocyanates, isothiocyanates, and activated olefins)

1. Introduction:

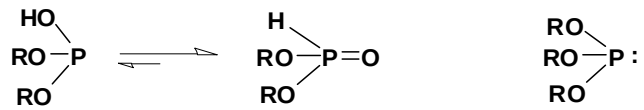
Phosphorus compounds play an important role in life. Phosphate is commonly known to be a part of the DNA and RNA backbone. Also, di-and triphosphates (ADP/ATP) are considered the key of energy in human life as they are widely present in all living organisms. For example, they act as post-translational modification of proteins, in particular in signal transduction. Phosphorus compounds occur mainly in the oxidation states *III* and *V* valencies whereby the latter one is more stable and the only oxidation state in minerals containing phosphorus.

A century after the discovery of the phosphonates, they have become very important compounds. They are recognized for their use and efficiency as reagents in organic synthesis and for their biological and industrial importance. The vast literature devoted to phosphonate chemistry reflects an exciting field with many opportunities for research and development. The value of phosphorus reagents stems from a combination of easy access and the reactions of anions on carbon adjacent to the phosphoryl group.

Tervalent phosphorus, P*III*, compounds, the workhorse of organophosphorus chemistry, have the general formula X_3P, where X can be alkyl, aryl, alkyl amine, alkoxy, aryloxy, alkylthio, or halogen. These reagents carry a lone pair of electrons, which endows basicity and nucleophilicity on the molecule. In general,

phosphines are much weaker bases than amines but they are still strong nucleophiles. Almost all reactions of value in synthesis depend on this nucleophilicity. Thus, the reactions and reactivity are enormous because P*III* reagents react by nucleophilic attack at saturated and unsaturated carbon, oxygen, sulfur, halogen, and nitrogen to give intermediates that either break down *in situ* to the target unphosphorylated products or can be used in a second reaction as synthons in their own right.

Alkyl phosphite esters are derived from phosphorous acid, could be primary [$ROP(OH)_2$], secondary [$(RO)_2POH$] or tertiary [$(RO)_3P$] phosphite esters. Dialkyl-(DAP) and trialkyl phosphites (TAP) are more known reagents in organophosphorus chemistry as they are the most reactive ones, stable, and they are commercially available. DAP, are, however, less of nucleophilic property and in sequel are less reactive than TAP. This observation was attributed to the presence of dialkyl phosphites in equilibrium with dialkylphosphonates as displayed in the following forms:

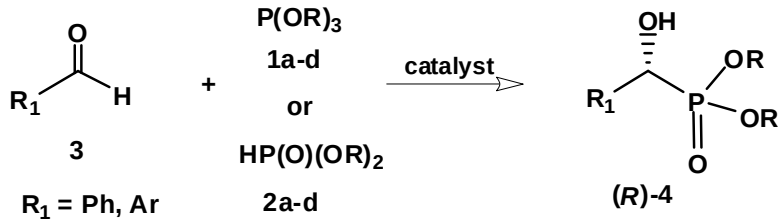


Dialkyl phosphites **Dialkyl phosphonates** **Trialkyl phosphites**

The general part of this thesis presents the most interesting reactions of alkyl phosphites, mainly, TAP/DAP with C=X electrophiles (aldehydes, ketones, aldimines, ketimines, iso-cyanates, isothiocyanates, and activated olefins. We have attempted to be encyclopedic with respect to the topics with the important interactions but not in citing all examples of every reaction.

2. Reactions with Aldehydes:

Reactions of tri and dialkyl phosphites with aldehydes afforded α-hydroxy phosphonates. In most cases, they are based on Abramov[1] reactions in the presence of acids or bases or Pudovik [2] reactions. Both reactions employ similar mechanisms in which nucleophilic phosphorous compound attacks the carbonyl center of aldehydes. Also, the three component reaction of tri and dialkyl phosphite with aldehyde and amine or imine (Kabachnik–Fields reaction)[3] afford α-amino phosphonates. Hydroxyphosphonates consist an attractive class of biologically active compounds as well as they are useful as synthetic intermediates (Scheme 1).



1a, 2a, R = Me; 1b, 2b, R = Et
1c, 2c, R = *i*-Pr; 1d, 2d, R = Bu

Scheme 1

A number of synthetic methods for the preparation of α-hyroxyphosphonates have been reported during the past two decades.[4] Most of these methods have disadvantage of long reaction time or hard conditions. In addition, in the presence of a base the reaction is usually accompanied by phosphonate-phosphate rearrangement, and by reverse processes such as Abramov retro-reaction. Because the biological activities of α-hyroxyphosphonates usually depend on the absolute configuration, catalytic enantioselective synthesis of these compounds has been explored. It

is found that a chiral Lewis base (LB*)/$SiCl_4$ complex could activate prochiral aldehydes and facilitate enantioselective attack of trialkyl phosphites to yield trichlorosilylated α-hydroxy-phosphonates after Arbuzov-type liberation of the corresponding alkyl chloride (figure 1).[5]

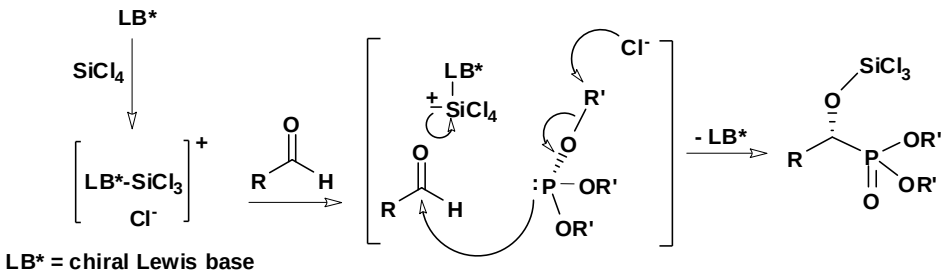


Figure 1

Enantioselective phosphonylation of benzaldehyde (**3**) with tri/dialkyl phosphites **1/2** was investigated by using (S)-BINAP dioxide (BINAPO) as a chiral Lewis base catalyst afforded the optically active α-hydroxyphosphonate **4**. By adding $SiCl_4$ dropwise to the solution of **3**, the phosphite, and iPr$_2$NEt in CH_2Cl_2 at -78 ˚C, the corresponding hydroxyphosphonates **4** were obtained in good yields (≈75-90%) with a moderate enantioselectivity.[5] Triethyl phosphite gave the highest enantioselectivity. On the other hand, it was found that Pudovik-type reactions with dialkyl phosphites **2a-d** were also promoted by silicon tetrachloride and the BINAPO catalyst. However, the selectivities were lower than those with trialkyl phosphites.[5]

In a systematic study, treating aromatic or aliphatic aldehydes with trialkylphosphite in the presence of trimethylsilylchloride TMSCl in a concentrated ethereal solution of lithium perchlorate at