β-Hydroxyimino Phosphorus Derivatives. An Efficient Tool in Organic Synthesis

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Abstract: The purpose of this review article is to illustrate synthetic aspects of functionalized phosphorus derivatives containing an oximo moiety at the beta-position. First section will be focused on the synthesis of phosphine oxides, phosphonates or phosphonium salts containing an oxime group. The synthesis of these derivatives comprises the carbon–phosphorus single bond construction by reaction of haloximes with phosphorus derivatives, nucleophilic addition of phosphorus reagents to carbonyl compounds, or nucleophilic addition of phosphorus reagents to nitro olefins. This section will also concentrate on the most practical routes for the synthesis of the target compounds, through carbon–nitrogen double bond formation, which are as follows: condensation processes of carbonyl compounds and hydroxylamine derivatives or addition of hydroxylamines to allenes or alkynes. The preparative use of beta-oximo phosphorus derivatives as synthetic intermediates will be discussed in a second section, comprising olefination reaction, oxidation of oximes to nitrile oxides by reaction at the C-N double bond of the oxime moiety, oxidation of these substrates to nitrosoalkenes, reduction to the corresponding hydroxylamines and some reactions at the hydroxyl group of the hydroximino moiety.

Keywords: β-Hydroxyimino phosphorus derivatives, α-haloximes, nitro olefins, nitrile oxides, nitrosoalkenes.

1. PREPARATION OF β-HYDROXYIMINO PHOSPHORUS DERIVATIVES

Some general synthetic methods exist for the preparation of β-hydroxyimino phosphorus derivatives. This section will be focused on the synthesis of substituted phosphoxide, phosphonate or phosphonium salts containing an oxime moiety at the β-position. Depending on the type of bond formed in the reaction, some strategies for the preparation of these derivatives can be highlighted (Scheme 1). Section 1.1 outlines their preparation through carbon–phosphorus single bond construction by reaction of α-haloximes with phosphorus derivatives (route a), nucleophilic addition of phosphorus reagents to carbonyl compounds (route b2) or nucleophilic addition of phosphorus reagents to nitro olefins (route a3). Section 1.2 will concentrate on the most practical routes for the synthesis of the target compounds, through carbon–nitrogen double bond formation, which are as follows: condensation processes (route b1) and addition of hydroxylamines to allenes or alkynes (route b2).

1.1. Carbon-Phosphorus Single Bond Formation

1.1.1. Reaction of α-Haloximes with Phosphines and Phosphites

Alkylation of phosphines and phosphites constitutes an important entry to phosphorated oximes through C-P bond formation. Thus, reaction of oximes 2, generated from condensation reaction of bromopyruvate 1 with O-methyl hydroxylamine, with trimethylphosphine (R = Ph), describes a general method through a C-P bond forming process for the preparation of oxime phosphonium salt 3a.

Similarly, β-phosphorylated oximes 3b or 3c can be obtained by means of Arbuzov reaction of oximes 2 with trimethylphosphite (R = OMe) (Scheme 2) [1]. The alkylation of phosphines and phosphites with haloximes strategy has also been extended for the preparation of other substituted oximes derived from phosphonium salts [2] or phosphonates [3]. Similarly, when bromoacetophenone was used, functionalized oximes derived from phosphine oxides and phosphonates were obtained in good yields [4].

In a similar way, condensation reaction of 3-bromopyruvate 4 with hydroxylamine hydrochloride leads to α-haloimine 5. Its protection with dihydropyrane affords O-THP oxime 6, which can be converted into oxime derived from phosphonium salt 7 in very good yield on reaction with triphenylphosphine (Scheme 3) [5].

The base-catalyzed reaction for the formation of oxime derived from phosphonium salt 9 might be explained by three paths: an attack by phosphorus atom on α-carbon in the conjugate base of the oxime (path A), an initial attack of the base on the oxime carbon followed by displacement of bromine with PP3 (path B), or the preliminary replacement of bromine with base followed by displacement with PP3 (path C), as shown in Scheme 4 [6]. Path C was ruled out by control experiments, which showed that (2-phenyl-2-oximinoethyl)pyridinium bromide neither reacted with PP3 nor catalyzed the reaction of 8 with PP3, whereas a catalytic amount of pyridine lead to the exclusive formation of 9 under the identical conditions. Although there is no positive evidence, the catalytic reaction may be rationalized by path A or B, which would have somewhat of an SN1 character since the transition states are stabilized by mesomeric electron release from the nearby anionic sites.

1.1.2. Nucleophilic Addition of Phosphorus Reagents to Carbonyl Compounds

Nucleophilic addition of phosphorus reagents to carbonyl compounds represents an easy strategy for the preparation of α-hydroxy-phosphorylated compounds. This procedure has been applied to the keto-oxime 10 for the preparation of an α-hydroxy-β-oximo phosphine oxide derivative 11. In this way, addition of dimethyl phosphine oxide to keto-oxime 10 in the presence of BuOK...
Scheme 1.

C-P Bond Formation

N
R1
P
R2
O
X = Hal

C=N Bond Formation

H2NOR2
P
PR1
H2NOR2

Scheme 2.

O
O
R1O2C
Br
H2NOMe·HCl
EtOH

R1O2C
Br
R1O2C
MeO

Scheme 3.

EtO2C
O
H2NOH·HCl
CHCl3/MeOH

Scheme 4.
leads to the potassium salt of phosphinylated oxime 11 (Scheme 5) [7].

Scheme 5.

1.1.3. Nucleophilic Addition of Phosphorus Reagents to Nitro Olefins

Nitro olefins are useful intermediates in the synthesis of some biological active natural products. Due to the strong electron withdrawing properties of the nitro group, conjugated nitroalkenes are excellent Michael acceptors with a variety of nucleophiles. Several papers describe the addition of phosphorus nucleophiles to nitro olefins as Michael acceptors. Krueger et al. [8] reported that trimethylphosphite reacted with β-nitrostyrene 12 in tert-butyl alcohol to produce phosphorylated aldoxime 15 through C–P bond formation. A reaction pathway which is consistent with the experimental and spectroscopic results is proposed in Scheme 6. The mechanism involves initial attack of trimethylphosphite at the γ-carbon of β-nitrostyrene 12, to form a zwitterion 13, which rearranges to the proposed cyclic intermediate 14. Methoxide ion attack on 14 affords the oxime 15. This compound was characterized unambiguously by x-ray crystallography [8a].

The above-mentioned study was followed by other authors [9], who reported the addition reaction of triethylphosphite to β-nitrostyrene 12. As reported in Scheme 7, reaction of nitroalkene 12 with 3.2 equivalents of triethylphosphite leads to a mixture of diphosphonate 16, nitrile 17 and phosphorylated oximes 18 and 19 as traces.

C–P Bond creation with the formation of a β-oxime phosphonate derived from sugars has also been observed in the reaction of β-nitro sugar 20 with trimethylphosphite. In this case, a mixture of alkene 21 and phosphorylated aldoxime 22 were obtained in very low yield (Scheme 8) [10].

Phosphorylated haloximes can be prepared from the reaction of conjugated nitroalkenes with diethyl phosphite. In such a way, treatment of conjugated nitroalkenes 23 with diethyl phosphite in the presence of a base such as sodium hydride and subsequent addition of HCl gives haloximes 24 in very good yield (Scheme 9) [11].

Scheme 6.

Scheme 7.

Scheme 8.
1.2. Carbon-Nitrogen Double Bond Formation

1.2.1. Condensation Reaction Formation

Condensation reaction of a β-keto phosphorus substituted compounds with hydroxylamines to give aldoximes or ketoximes, represents a simple route for the preparation of β-oximo phosphorus derivatives via a carbon–nitrogen double bond-forming process. This is one of the most common synthetic ways for the preparation of oximes. Arbuzov reaction of bromoacetaldehyde diethyl acetal (25) with triethylphosphate affords phosphorylated acetal 26 with a C-P bond formation process (Scheme 10) [12]. Deacetalization under acidic conditions and condensation with hydroxylamine hydrochloride in the presence of a base give aldoxime 28 in good yield.

Similarly, nucleophilic addition of hydroxylamine to the keto carbonyl group of diethyl β-ketopropylphosphonate (29a) (R = OEt, R1 = Me) in aqueous solution around pH = 7 leads to β-oximo phosphonate 31a (Scheme 11) [13]. Using 1H and 31P NMR spectroscopy, during the reaction, it was possible to detect the carbino-ester hydrolysis which appear to involve internal assistance by the phosphorus atom by the OH oxygen to form a pentaco-valent intermediate. Following this strategy, β-oximo phosphine oxides 31b (R = Ph) have been synthesized by our group using triethylamine as the base (Scheme 11) [14].

Some phosphorylated oximes have been tested as N-methyl-D-aspartate (NMDA) receptor antagonists. Since it appeared that the binding potency and relatively good bioavailability of 33 could be related to the β-ketophosphonic acid functionality, Whitten et al. [15] sought to modify the ketone with similar, less readily enolizable groups. Thus, a mixture of syn- and anti-oximes or their ethers 34 were synthesized through condensation reaction of readily available hydroxylamines with (R)-4-oxo-5-phosphonovaleric acid (33) by standard procedures (Scheme 12).

Alkylation of the anion derived from diethyl methylphosphonate (35) with methyl iodide followed by addition of trimethylammonium affords phosphorylated oxime 37 by condensation reaction of aldehyde 36 with hydroxylamine (Scheme 13) [17]. Related phosphorylated oximes have been obtained in 86% yield by using the same conditions when starting from methyl diphenylphosphine oxide [18].

This approach has been also used for the preparation of β-oximo phosphine oxides 40a (R = Ph) and β-oximo phosphonates 40b (R = OEt) containing a fluoroalkyl substituent [19]. Hence, metallation of alkyl diphenylphosphine oxides 38a or alkylphosphonates 38b with LDA and subsequent treatment with fluorinated esters affords fluorine substituted β-ketophosphine oxides 39a or β-ketophosphonates 39b, respectively (Scheme 14). The condensation of ketones 39 with hydroxylamine hydrochloride in the presence of pyridine gives fluorinated oximes 40a or 40b.

This method developed for the preparation of β-ketophosphonates using anions derived from alkyl phosphonates has been expanded to cyclic ketophosphonates, and thus, cyclic phosphorylated oximes by condensation reaction with hydroxylamines were reported. The diester 42 resulting from NiCl2-catalyzed Arbuzov reaction of diethyl methylphosphonate and ethyl iodobenzoate 41, reacts with 3 equivalents of potassium tert-butoxide in diethyl ether effecting cyclization to 43. The corresponding phosphorylated oximes 44 resulted from oximation reaction of ketone 43 with the appropriate hydroxylamine (Scheme 15) [20].

Similarly, condensation of phosphate anions derived from 45 with diesters can be used for the preparation of 3-phosphonopyruvate...
derivatives 46 (Scheme 16) [21]. Oximation of these derivatives 46 affords functionalized oximes 47 in good yields.

β-Oximo phosphine oxides 50 can be obtained by C–N double bond formation through condensation reaction of hydroxylamine with β-keto phosphine oxides 49, previously prepared on treatment of stannyloxiranes 48 with lithium diphenylphosphine (Scheme 17) [22].

Oximes containing a phospholene ring can be prepared by quaternization reaction of trivalent P-bromophospholene 51. Thus, reaction of bromophospholene 51 with α-chloroketone 52 afforded functionalized phospholene P-oxide 53, which after condensation reaction with hydroxylamine hydrochloride give phosphorylated oxime 54 (Scheme 18) [23].

Other oximes containing a phospholene ring have been prepared through a condensation reaction of ethyl formate with the anion derived from phospholene P-oxide 55 [24]. The corresponding aldehyde obtained 56 is condensed with hydroxylamine hydrochloride affording oxime phospholene 57 (Scheme 19).

Minami et al. [25] have reported a synthetic methodology for the preparation of α-formylvinylphosphonates 60, precursors of oximes 61. Allylic alcohols 58, prepared by trapping anions derived from vinylphosphonates with aldehydes and ketones, can react in acidic conditions to afford vinylphosphonates 60 in very good yields. This reaction probably proceeds via a mechanism which included attack of water on an allylic carbocation 59 stabilized by the oxygen atom. The C–N double bond formation in 61 takes place by treatment of 60 with hydroxylamine and pyridine in ethanol under reflux (Scheme 20).

1.2.2. Nucleophilic Addition of Hydroxylamines to Allenyl or Alkynyl Derivatives

A different approach can also be applied for the preparation of phosphorylated oximes though C–N double bond formation. This strategy involves conjugative addition of hydroxylamine to the
acetylenic C–C-triple bond of tetraethyl ethynyldiphosphonate 62, and subsequent tautomerization of the N-hydroxyenamine 63.[26]. Through this procedure, oxime bisphosphonate 64 can be synthesized in 85% yield (Scheme 21).

Scheme 20.

![Scheme 20](image)

In a similar way, nucleophilic addition of unsubstituted hydroxylamine (R3 = H), O-methylhydroxylamine (R3 = Me) or O-silyl substituted hydroxylamines (R3 = SiMe3, SiMe2tBu) to allenyl phosphine oxides 65a (R = Ph) or phosphonates 65b (R = OEt) represents an easy procedure for the preparation of β-oximo phosphine oxides 67a (R = Ph) or β-oximo phosphonates 67b (R = OEt), via functionalized enamines 66, in good yields (Scheme 22) [27].

1.3. Ring Opening of 1,2,5-Oxazaphospholines

Umani-Ronchi et al. [2c] report the reaction between nitrile oxides 68 and phosphonium ylides 69 as a useful method for the preparation of 1,2,5-oxazaphosph(V)ol-2-ines 70. The successful transformation of 70 into the corresponding 2-hydroxyimino phosphonium salts 71 involves the ring opening of 70 by P–O bond cleavage by the action of hydrobromic [2c] or hydrochloric acid [28] (Scheme 23). In a similar way, oxime ethers phosphonium salts 72 can be obtained by ring opening of 1,2,5-oxazaphospholines 70 on treatment with iodomethane [28] (Scheme 23). The use of nitrile oxides for the synthesis of such heterocycles 70, and thus these β-oximo phosphonium salts 71 and 72, offers a more limited route of synthesis, when compared with the Arbuzov reaction of α-haloximes and phosphines [2] (see Scheme 2). This is because of the limited availability of nitrile oxides 68, which usually are less easily obtained than α-haloximes. Moreover, the reaction requires the use of phosphonium ylides 69 instead of simple phosphines.
2. REACTIVITY. PREPARATIVE USE OF $\beta$-HYDROXYIMINO PHOSPHORUS DERIVATIVES AS SYNTHETIC INTERMEDIATES

$\beta$-Hydroxyimino phosphorus derivatives are bifunctional compounds and contain an oxime moiety and a phosphorated group linked by a carbon atom. Characteristic reactions of the oxime function such as the oxidation of these substrates to nitrosoalkenes and nitrile oxides, reduction to the corresponding hydroxylamines and some reactions at the hydroxyl group of the hydroxyimino moiety has been reported, while the presence of phosphorous functional groups confers an additional preparative interest to these substrates because they can be used for the construction of selective C-C double bonds by means of the Wittig reactions or related processes [29] (Scheme 24).

2.1. Olefination Reaction

One of the most representative examples of the reactivity of $\alpha$-carbanions derived from some phosphorus derivatives entails the C-C double bond forming process, through Wittig reaction [29] or related processes with carbonyl compounds. For carbon–carbon double bond construction, not only phosphonium salts (Wittig reaction) but also phosphine oxide derivatives (Horner reaction) or phosphonates (Horner-Wadsworth-Emmons reaction) are very useful reagents. For this reason, $\beta$-oximo phosphorus compounds can be excellent starting materials for the selective preparation of $\alpha,\beta$-unsaturated oximes. Moreover, this is a very useful method for the preparation of 1-azabuta-1,3-dienes, important building blocks for the preparation of six-membered nitrogen containing heterocycles. For example, Boger et al. have described the preparation of $N$-
sulfonyl-1-azabuta-1,3-dienes 75, based on the use of the stabilized Wittig reagent containing an oximo group 7, and their participation in inter [5, 30] and intramolecular [31] [4+2] cycloaddition reactions. 4-Substituted N-sulfonyl-1-azabuta-1,3-dienes 75 are prepared through Wittig reaction of the stabilized phosphorane generated in situ from the phosphonium salt 7 with aldehydes, followed by acid-catalyzed removal of the tetrahydropyranyl (THP) group, O-phenylsulfinyl or O-methylsulfinyl formation, and subsequent in situ homolytic rearrangement to provide 75 (Scheme 25). 1-Azadienes, prepared through Wittig olefination reaction of -oximo phosphonium salts, have been also used as building blocks for the preparation of indole-3-piruvic acid oxime ethers by Heck cyclization [32].

Our group [27] reported an efficient method for the preparation of α,β-unsaturated oximes through olefination reaction, starting from oximes containing phosphorated functional groups. Consequently, β-oximo phosphine oxides 67a (R = Ph) can be suitable precursor for the homologation of oximes into their vinylogous compounds. Oximes 67a (R = Ph) are treated with a base such as methyl lithium, followed by addition of aromatic, heteroaromatic and aliphatic aldehydes and ketones leading to 1-azadienes 76 with high E-stereoselectivity of the carbon–carbon double bond, isolated as a mixture of syn- and anti-isomers, and in good yields (Scheme 26). This olefination reaction is not restricted to β-oximo phosphine oxides 67a (R = Ph) since oximes derived from phosphonates 67b (R = OEt) can also be used in this approach.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>Yield (%)</th>
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<tr>
<td>76a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Bu</td>
<td>81</td>
</tr>
<tr>
<td>76b</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2-C₆H₄N</td>
<td>72</td>
</tr>
<tr>
<td>76c</td>
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<td>H</td>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph-OC₆H₄</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>76e</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>p-MeC₆H₄</td>
<td>88</td>
</tr>
<tr>
<td>76f</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Bu</td>
<td>77</td>
</tr>
<tr>
<td>76g</td>
<td>H</td>
<td>H</td>
<td>SiMe₃/Bu</td>
<td>H</td>
<td>p-MeC₆H₄</td>
<td>80</td>
</tr>
<tr>
<td>76h</td>
<td>H</td>
<td>Me</td>
<td>SiMe₃/Bu</td>
<td>H</td>
<td>p-MeC₆H₄</td>
<td>71</td>
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<tr>
<td>76i</td>
<td>SiMe₃/Bu</td>
<td>H</td>
<td>p-MeC₆H₄</td>
<td>80</td>
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<td>Me</td>
<td>Me</td>
<td>H</td>
<td>Bu</td>
<td>65</td>
</tr>
</tbody>
</table>

Scheme 26.
There has been considerable interest in vinyl glycines as antibiotics, enzyme inhibitors and synthetic intermediates. The β-aminophosphonium salt 77, a vinyl glycine synthon derived from serine, is tedious to prepare and has to be used as its free acid to avoid β-elimination. Oxime phosphonium salt 3a (P = PPh₃+ Br⁻) provide advantages as an amino acid synthon. Reaction of phosphorane derived from salt 3a, generated from the treatment of 3a with a base, with aldehydes gave the required 1-azabuta-1,3-dienes 78 with yields ranging from 50 to 99% (Scheme 27). Butyl lithium was the initial base chosen for the generation of phosphorane derived from 3a. However, owing to the partially stabilized nature of this phosphorane, it was reasoned that a weaker base would suffice. The preferred choice was potassium carbonate in DMF, which requires no special precautions and has provided excellent yields. To increase the versatility of this approach, reactions of ketones was required. Hence, Horner-Wadsworth-Emmons (H-W-E) olefination reaction of phosphorylated oxime 3c (P = P(O)(OMe)₂) with sodium hydride and the corresponding ketone leads to the final azadienes 78 in 24-54% yield. Finally, the vinyl glycine derivatives 79 were obtained in good yields by reduction of α,β-unsaturated oximes 78 with zinc in formic acid (Scheme 27) [1].

An illustration of the olefination reaction of a phosphorylated oxime as the key step in the synthesis of natural products is present in the total synthesis of radiosumin 84, a strong trypsin inhibitor from the blue-green alga plectonema radiosum (Scheme 28) [3a,33]. This structurally intriguing dipeptide 84 is composed of

![Scheme 27](image1)

<table>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>78</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
<th>79</th>
<th>Yield (%)</th>
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<tr>
<td>3a</td>
<td>Et</td>
<td>78a</td>
<td>H</td>
<td>Et</td>
<td>50</td>
<td>79a</td>
<td>84</td>
</tr>
<tr>
<td>3a</td>
<td>Et</td>
<td>78b</td>
<td>H</td>
<td>iPr</td>
<td>99</td>
<td>79b</td>
<td>94</td>
</tr>
<tr>
<td>3a</td>
<td>Et</td>
<td>78c</td>
<td>H</td>
<td>Ph</td>
<td>98</td>
<td>79c</td>
<td>65</td>
</tr>
<tr>
<td>3a</td>
<td>Et</td>
<td>78d</td>
<td>H</td>
<td>p-CF₃C₆H₄</td>
<td>99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>Me</td>
<td>78e</td>
<td>Et</td>
<td>Et</td>
<td>24</td>
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</tr>
<tr>
<td>3c</td>
<td>Me</td>
<td>78f</td>
<td>–(CH₃)₂–</td>
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<td>79f</td>
<td>49</td>
</tr>
<tr>
<td>3c</td>
<td>Me</td>
<td>78g</td>
<td>–(CH₃)₂S(CH₃)₂–</td>
<td></td>
<td>54</td>
<td>79g</td>
<td>37</td>
</tr>
</tbody>
</table>

![Scheme 28](image2)
two unusual, novel α-amino acids: 2-amino-3-(4-amino-2-cyclohexen-1-ylidene)propionic acid (Aayp) (82) and 2-amino-3-(4-amino-2-cyclohexylidene)propionic acid (Aacp) (83). Stereoselective Horner-Wadsworth-Emmons reaction of oxime 3c with aminocyclitol ketone 80 furnished one of the building blocks 81 for the construction of Aacp derivative 82. The other, Aacp derivative 83 needed for the preparation of radiosumin 84, was prepared in five steps starting from the common intermediate 82.

Furthermore, the high efficiency of this protocol has been also applied to the total synthesis of naturally occurring amino acid 2,6-diaminopimelic acid (DAP) (87) found in both bacteria and higher plants (Scheme 29) [34]. Condensation of the aldehyde 85, with the stabilized phosphorane three carbon synthon derived from 3a, affords the corresponding unsaturated oxime ester 86. This compound serve as a versatile intermediate to a variety of DAP analogues, since one can selectively reduce the oxime and the olefinic moieties.

2.2. Reactions at the C-N Double Bond

2.2.1. Oxime Reductions

Through a simple oxime-amine reduction, fluorine containing β-amino phosphine oxides or phosphonates may be prepared in satisfactory yields [19]. For this goal, treatment of fluorine containing p-toluenesulfonyl oxime 88a derived from phosphine oxides or p-toluenesulfonyl oxime 88b derived from phosphonates with NaBH₄ at low temperature gives fluorine containing β-amino phosphine oxide 89a or phosphonates 89b,c in a regioselective fashion [19] (Scheme 30). In a similar way, β-aminophosphonate derivatives [35] have been prepared starting from phosphinacyl-aldehyde oximes, by means of an oxime-hydroxylamine reduction employing the pyridine-borane complex [36].

2.2.2. Oxidation Reactions

2.2.2.1. Nitrile Oxide Formation

Nitrile oxides have been much more frequently used in organic synthesis, especially in the elaboration of complex molecules, than any other 1,3-dipoles [37]. The importance of nitrile oxide is based on its high reactivity toward a wide range of olefins, both electron–poor and –rich types, forming isoxazolines which are flexible building blocks through their ability to function as masked forms of β-hydroxyketones [38] and γ-amino alcohols [39], after the N–O bond cleavage. Phosphorus functionalized nitrile oxides undergo regioselective 1,3-dipolar cycloadditions to olefins or acetylenes to furnish good yields of 2-isoxazolines or isoxazoles bearing a phosphorus substituent. For example, Tsuge et al. reported the first synthesis of phosphorus functionalized nitrile oxide and its cycloaddition with a variety of olefins. Nitrile oxide 91 is successfully accessible by the bromination of 28 with NBS (N-bromosuccinimide) followed by dehydrobromination of haloxime 90 with triethylamine. This nitrile oxide 91 has been trapped as cycloadduct with a variety of olefinic dipolarophiles giving the corresponding isoxazolines 92 as single regioisomers and in good yield (Scheme 31) [12d,e]. Cycloaddition of phosphorus functionalized nitrile oxide 91 to acetylenic alcohols affords compounds 93. This approach has been reported in the synthesis of E-isomers of furanone derivatives which are essential part of the framework of furanone natural products such as geiparvarin [40] (Scheme 31). Other dipolarophiles such as allyl [41] and homoaeryl alcohol [42] or α,β-unsaturated esters [43] have been used for the cycloaddition reaction to 91 to give terpene, pyridine or furanone derivatives, respectively. Likewise, isoxazolinophosphonates and isoxazolephosphonates substituted at 4- and 5-positions have been obtained by cycloaddition of olefins and acetylenes to 91 [12c].

This method developed for the cycloaddition reaction of nitrile oxides with dipolarophiles was subsequently expanded to the preparation of α-alkoxyacarbonyl-β-diketones by Jones et al. [12b]. Phosphorylated isoxazole derivative 96, resulting from the cycloaddition of nitrile oxide 91 with enamines 95, was used as starting material for the construction of C-C double bonds when they were treated under basic conditions with a variety of aldehydes and ketones (benzaldehyde, propanone, cyclohexanone, but-2-enal and (E)-2-methylbut-2-enal) to afford the 3-alkenylisoxazoles 97 (Scheme 32). Treatment of 97 with hexacarbonylmolybdenum in moist acetonitrile gives efficient access to α-alkoxyacarbonyl-β-diketones 98 in excellent yields. Early work by Warren et al. [18] shows the viability to performing the cycloaddition of nitrile oxide, olefination

![Scheme 29.](image)

![Scheme 30.](image)
reaction and cleavage with Mo(CO)$_6$ of isoxazole ring, for the regiospecific synthesis of derived leukotriene analogues using phosphine oxides.

The synthetic utility of this approach has been recently demonstrated in the preparation of 1β-methylcarbapenem 100 which showed markedly antibacterial activity as well as high stability to DHP-1 against *Pseudomonas aeruginosa* isolates and advanced pharmacokinetic profiles in rat and dog than those of meropenem (Scheme 33) [12a].

Recently, phosphonated dihydroisoxazole nucleosides have been prepared via 1,3-dipolar cycloaddition reaction of nitrile oxides with the corresponding vinyl nucleobases for antiviral studies [44]. This synthesis has been performed in a one-step process as shown in Scheme 34. The nitrile oxide 91, derived *in situ* from aldoxime 28 by treatment with NBS under basic conditions, was added to the vinyl nucleobases to give the racemic nucleosides 101. This reaction showed a complete regioselectivity obtaining the 5-isomer as an exclusive product.

The synthetic value of nitrile oxide cycloaddition is now growing as shown in its wide applications to natural product synthesis. For example, Carreira *et al*. [17,45] reported the stereoselective syntheses of epothilones A and B via magnesium-mediated hydroxyl-directed nitrile oxide cycloadditions with allyl alcohols, inspired by the work of Kanemasa [46]. In this regard, the cycloadditions of the versatile oxime 37 with chiral allyl alcohols is the key to the Carreira’s strategy. Oxidation of 37 to nitrile oxide 103 was followed by highly diastereoselective cycloaddition with an allyl alcohol 104, containing and additional sterocenter, to furnish 105 as a single syn-diastereomer at the isoxazoline oxygen (Scheme 35). Furthermore, these authors have applied the diastereoselective nitrile oxide cycloaddition of homoallylic alcohols in the synthesis of polyketide building blocks [47].

### 2.2.2.2. Nitrosoalkene Formation

Nitrosoalkenes are functionalized nitroso derivatives, and the presence of an adjacent double bond in conjugation with the nitroso moiety introduces new reactivity centers in these substrates and
then increases the synthetic value of these compounds. Therefore, the usefulness of nitrosoalkenes [48] as conjugate addition acceptors [49], coupled with the easy conversion of the nitroso group into other functionalities, such as oximes and ketones [50], or their ability to act as dienes in hetero-Diels-Alder reactions for the preparation of 1,2-oxazine derivatives [51], have been reported. The synthesis of nitrosoalkenes containing a phosphorus substituent at C-4 has been scarcely explored. Only one example of the preparation of these systems has been recently reported by our group [52]. As outlined in Scheme 36, for the preparation of phosphorylated nitrosoalkenes 108 the required bromooximes 107 are easily accessible from reaction of functionalized oximes 106 with an excess of base and subsequent addition of bromine. Nitrosoalkenes 108 have been prepared in almost quantitative yield through base-mediated dehydrohalogenation of α-bromooximes 107. These functionalized nitrosoalkenes are useful Michael acceptors and thus, conjugate addition of nucleophilic reagents such as ammonia, primary and secondary amines or optically active amino esters furnish α-aminophosphine oxides (R = Ph) and phosphonates (R = OEt) 109 in a highly regioselective fashion (Scheme 36) [52]. More recently, these nitrosoalkenes 108 have been used for the preparation of five-membered nitrogen containing heterocycles such as N-hydroxypyrrole derivatives 110, through conjugate addition of enamines at the terminal carbon atom of the heterodiene 108, ring closure (formally a [3+2] dipolar cycloaddition), and elimination of the pyrrolidine residue (Scheme 36) [53]. The synthesis of similar N-hydroxypyrroles is also reported by other authors via conjugate
addition of enolates derived from ketones to phosphorylated α-chloroximes [54].

2.3. Reactions at the OH Group of the Oxime Moiety

2.3.1. Cyclization Reactions

Some reports [2b,c,28a] describes the preparation of oxazaphospholine intermediates 70 by treatment of oxime phosphonium salts 71 with a base. These oxazaphospholines are readily converted, on pyrolysis at 100–150 °C, into 2H-azirines 111 by an initial P–C bond cleavage [55], subsequent loss of triphenylphosphine oxide and ring-contraction (Scheme 37).

A convenient synthesis of phosphono-substituted heterocyclic compounds has been recently reported through vinylphosphonates via condensation-intramolecular 1,4-addition sequence [25]. α-Formylvinylphosphonates 60 are treated with hydroxylamine hydrochloride and pyridine in ethanol under reflux to afford 4-phosphono isoxazoles 112. Treatment of the independently prepared oxime 113 with pyridine in ethanol under reflux afforded the isoxazole 112a in quantitative yield (Scheme 38). This result demonstrates that the oxime 113 clearly underwent the 5-endo-trigonal cyclization to give the isoxazole 112a.

2.3.2. Dehydration of Oximes

Acetic anhydride-mediated dehydration of oximes can be applied to aldoxime 15 for the preparation of substituted phosphonate carbonitrile 115a. The formation of nitrile 115a apparently preceded by acylation of the starting aldoxime 15 with formation of the intermediate acetate 114, and subsequent elimination of acetic acid (Scheme 39) [8c]. A similar behaviour has been observed by our group starting from O-tosyl aldoximes and diethyl cyanomethylphosphonate 115b was obtained [56].
2.3.3. O-Functionalization Reactions

Functionalized O-tosyloximes 116, can be easily accomplished by simple reaction of phosphorylated oximes derived from phosphonate 31 (R = OEt) or phosphine oxide 31 (R = Ph) with tosyl chloride in pyridine (Scheme 40). The synthesis of these phosphorylated tosyl ketoximes 116 has been applied to the asymmetric preparation of phosphorylated 2H-azirines 117 and 118 through the modified Neber reaction [57,58]. The same approach has been applied to the synthesis of 2H-azirines 119 as building blocks for the preparation of oxazoles [59], and α- and β-aminophosphonates [14,35]. p-Tosyloximes 116 derived from phosphonates and phosphate oxides can also be used as synths for the preparation of phosphorus substituted pyrazines 119 and 120 [60]. Treatment of p-tosyloximes derived from phosphonates 116 (R = OEt) with primary or secondary amines (α-methylbenzylamine, diethylamine or piperidine) at room temperature give pyrazines 119. Similarly, pyrazines 120 can be obtained from p-tosyloximes derived from phosphate oxides 116 (R = Ph) in the presence of piperidine (Scheme 40). The formation of these pyrazines suggests the dimerization of vinyl nitrene intermediates or unstable nitrite ylide dipoles, generated from oximes 116, followed by oxidation. In the case of pyrazines 120, loss of diphenyl phosphate oxide (HPOPh2) takes place.

O-Functionalization reaction of fluoroalkyl ketoximes 121 for the preparation of fluoroalkyl p-toluenesulfonyl ketoximes 122 have been recently reported by our group [19]. For this purpose, p-toluenesulfonyl chloride in the presence of a base such as sodium hydride was necessary for the tosylation of oximes 121 (Scheme 41). O-Functionalized oximes 122 have been applied to the stereoselective synthesis of fluoroalkyl substituted aziridine-2-phosphate oxides and phosphonates 123–125 by diastereoselective addition of methoxide, imidazole, benzenethiol, and Grignard reagents (Scheme 41).

3. CONCLUSIONS

The versatility and synthetic interest of functionalized β-hydroxyimino phosphorus derivatives are outlined. Most of the published strategies in the preparation of phosphine oxides, phosphonates or phosphonium salts containing an oxime moiety at the beta-position, refer to the carbon–nitrogen double bond construction or the carbon–phosphorus single bond formation reactions.

Condensation reaction of β-keto phosphorus substituted compounds with hydroxylamines has been so far the most employed strategy to the preparation of phosphorylated oximes through carbon–nitrogen double bond formation, while alkylation of phosphines and phosphites can be considered a remarkable synthetic procedure to achieve β-oximo phosphorus derivatives via a carbon–phosphorus single bond-forming process. Although the application of the hydrophosphinylation of N-protected α-amino aldehydes has become a useful and versatile method for the synthesis of the very interesting α-hydroxy-β-amino phosphonic acid derivatives, only a report has reported the nucleophilic addition of phosphorus reagents to

<table>
<thead>
<tr>
<th>31</th>
<th>R</th>
<th>R'</th>
<th>116 Yield (%)</th>
<th>2H-Azirine Yield (%)</th>
<th>Pyrazine Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31a</td>
<td>OEt</td>
<td>Me</td>
<td>73</td>
<td>117a 90</td>
<td>119a 97</td>
</tr>
<tr>
<td>31b</td>
<td>OEt</td>
<td>Et</td>
<td>70</td>
<td>117b 95</td>
<td>119b 98</td>
</tr>
<tr>
<td>31c</td>
<td>OEt</td>
<td>Ph</td>
<td>35</td>
<td>117c 69</td>
<td></td>
</tr>
<tr>
<td>31d</td>
<td>Ph</td>
<td>Me</td>
<td>61</td>
<td>118a 96</td>
<td>120a 70</td>
</tr>
<tr>
<td>31e</td>
<td>Ph</td>
<td>Et</td>
<td>58</td>
<td>118b 95</td>
<td>120b 68</td>
</tr>
</tbody>
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Scheme 40.
keto-oximes for the synthesis of α-hydroxy-β-oximo phosphine oxides in moderate yield. The use of the enantioselective metal-catalysed version of this reaction could offer a very efficient method for the preparation of optically pure α-hydroxy-β-oximo phosphonic acid derivatives.

Characteristic reactions of the oxime function such as the oxidation or the reduction of these substrates have been reported. Therefore, these polyfunctional compounds can be used in the elaboration of complex molecules such as natural products epothilones A and B, phosphonated dihydroisoxazole nucleosides, and α-amino phosphorus derivatives and biologically active compounds. Moreover, the presence of phosphorus functional groups can be used for the construction of selective C–C double bonds by means of the Wittig reaction or related processes. These bifunctional β-hydroxyimino phosphorus derivatives are excellent synthetic intermediates in preparative organic chemistry and in medicinal chemistry for the synthesis of a wide number of acyclic and heterocyclic compounds, some of them presenting biological activity. The use of enantioselective processes could use the synergy of both moieties (oximo and phosphorated groups) and open a new and efficient way for the preparation of optically pure functionalized organophosphorus derivatives and biologically active compounds.

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REFERENCES


Goerlich, J. R.; Schmutzler, R. α-Hydroxyphosphonohexafluorobutane and –sulfuride through addition of dimethylphosphorohexafluorobutane and –sulfur to functionalized organophosphorus derivatives and biologically active compounds.

Scheme 41.


