Article

Direct Synthesis of Phosphonates and α-Amino-phosphonates from 1,3-Benzoxazines

Oscar Salgado-Escobar 1, Alexis Hernández-Guadarrama 1, Ivan Romero-Estudillo 2 and Irma Linzaga-Elizalde 1,*

1 Centro de Investigaciones Químicas-IICBA, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62209 Cuernavaca, Morelos, México; pyrel@hotmail.com (O.S.-E.); alexis13975@hotmail.com (A.H.-G.)
2 CONACYT-Centro de Investigaciones Químicas-IICBA, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62209 Cuernavaca, Morelos, México; ivan.romeroest@uaem.mx

* Correspondence: linzaga@uaem.mx; Tel.: +52-777-329-7997

Received: 22 November 2018; Accepted: 11 January 2019; Published: 15 January 2019

Abstract: A straightforward and novel method for transformation of readily available 1,3-benzoxazines to secondary phosphonates and α-aminophosphonates using boron trifluoride etherate as catalyst is developed. The formation of phosphonates proceeds through ortho-quinone methide (ο-QM) generated in situ, followed by a phospha-Michael addition reaction. On the other hand, the α-aminophosphonates were obtained by iminium ion formation and the subsequent nucleophilic substitution of alkylphosphites. This method can be also used for the preparation of o-hydroxybenzyl ethers through oxa-Michael addition.

Keywords: phosphonates; α-aminophosphonates; o-quinone methide; o-hydroxybenzyl ethers; 1,3-benzoxazines

1. Introduction

The α-aminophosphonic acids are probably the most important analogues of α-amino acids attributed to their structural analogy obtained by isosteric substitution of planar carboxylic acid (CO₂H) by tetrahedral phosphonic acid (PO₃H₂) [1–3]. This kind of compounds have been widely studied and used in agriculture, industry and medicinal chemistry [4–9]. In this context, the phosphonates and α-aminophosphonates also constitute an interesting class of compounds which have been utilized in the production of dental additives [10,11], dispersants, corrosion inhibitors [12–14], in fire retardants [15–17], as well as for preventing deposit formation [18]. Due the different applications, several efforts have been developed for the preparation of phosphonates and α-aminophosphonates [19,20].

In general, the main strategy for the synthesis of phosphonates including the Michaelis-Arbuzov [21] and Michaelis-Becker [22] reactions. On the other hand, the α-aminophosphonates are commonly prepared by Kabachnik-Fields [23–25] or Pudovik reactions [26,27]. In this context, Chen [28] and Huang [29] described a practical method for the preparation of ortho-hydroxybenzyl phosphonates by phospha-Michael addition of phosphites to ortho-quinone methides (ο-QMs). Particularly, the o-hydroxybenzyl phosphonates have been used for the preparation of 1,2-benzoxaphospholes with interesting antioxidants properties [30,31] and as anticancer agents [32].

Considering the high value of these compounds and in connection with our recent work [33], we report herein an innovative methodology for the synthesis of secondary phosphonates and α-aminophosphonates from the reaction of 1,3-benzoxazines with diethyl or triethyl phosphate using catalytic amounts of boron trifluoride etherate. In addition, when the 1,3-benzoxazines was treated with alcohols under reflux conditions provided the corresponding ethers in good yields.
2. Results and Discussion

Initially, 1,3-benzoxazines 1a–h were prepared from the corresponding 2-(benzylamino)phenols following procedures described in the literature [34–36]. In the next step, the study of the reaction conditions for the synthesis of the phosphonate 2b and α-aminophosphonate 3b were started. For this purpose, the reaction of the 1,3-benzoxazine 1b and triethyl phosphite under different conditions (solvents, temperature and using boron trifluoride etherate as catalyst) was examined in order to find the best reaction conditions (Table 1). At first, the 1,3-benzoxazine 1b was treated with triethyl phosphite in ethanol obtaining the α-aminophosphonate 3b in 28% yield (Table 1, entry 1). In entry 2 was carried out the reaction at 26 °C in presence of catalytic amounts of boron trifluoride etherate (20 mol%) using DCM as solvent afforded the α-aminophosphonate 3b in 27% yield. On the other hand, using the same solvent at 40 °C and without catalysts the result was similar (3b; 28% yield, entry 3). In the next experiments, using MeCN as solvent at 26 and 82 °C without catalyst, product reaction was not formed (entries 4 and 5).

Alternatively, when MeCN was used in presence of catalytic amounts of boron trifluoride etherate (10 mol%) at 26 °C the phosphonate 2b in 18% yield was afforded (entry 6). On the other hand, from the reaction of the 1,3-benzoxazine 1b with triethyl phosphite and increasing amount of boron trifluoride etherate at 20 and 50 mol%, 2b in 28% yield was obtained in both cases (entries 7 and 8). Then 2.7 equivalents of triethyl phosphite were used and the phosphonate 2b was isolated in 28% yield (entry 9). In entry 10 the reaction mixture was refluxed in MeCN with the presence of boron trifluoride etherate (20 mol%), from these, the phosphonate 2b and α-aminophosphonate 3b in 30 and 47% yield respectively were afforded.

Table 1. Study of the reaction of 1,3-benzoxazine 1b with triethyl phosphite.

| Entry | Solvent | Temp. (°C) | P(OEt)3 (Eq) | BF3·OEt2 (mol%) | Yield (%) |
|-------|---------|------------|--------------|----------------|-----------|
| 1     | EtOH    | 78         | 1.0          | -              | 3b; 28    |
| 2     | DCM     | 26         | 1.0          | 20             | 3b; 27    |
| 3     | DCM     | 40         | 1.5          | -              | 3b; 28    |
| 4     | MeCN    | 26         | 1.0          | -              | No product|
| 5     | MeCN    | 82         | 1.0          | -              | No product|
| 6     | MeCN    | 26         | 2.0          | 10             | 2b; 18    |
| 7     | MeCN    | 26         | 2.1          | 20             | 2b; 28    |
| 8     | MeCN    | 26         | 2.2          | 50             | 2b; 28    |
| 9     | MeCN    | 26         | 2.7          | 50             | 2b; 28    |
| 10    | MeCN    | 82         | 3.0          | 20             | 2b; 30, 3b; 47 |
| 11    | MeCN    | 82         | 3.5          | 20             | 2b; 28, 3b; 47 |
| 12    | Hexane  | 26         | 3.6          | 20             | No product|

In another experiment, an increase to 3.5 equivalents of the triethyl phosphite under similar conditions did not improve the yield (entry 11). When hexane was used as solvent, no products were observed (Table 1, entry 12).

With these results the formation of the phosphonate was favored when triethyl phosphite, boron trifluoride etherate in catalytic quantities and a polar solvent as acetonitrile at room temperature were used, besides, the reaction was cleaner and the 1,3-benzoxazine that not reacted was recovered.

Under the optimized conditions, the 1,3-benzoxazines 1a–h were reacted with triethyl phosphite in presence of boron trifluoride etherate (20 mol%) in acetonitrile (Scheme 1). When the 1,3-benzoxazines 1b, 1e and 1g were used, the o-hydroxybenzyl phosphonates 2b, 2e and 2g were formed in 28–40%
yields. The o-hydroxybenzyl phosphonates are valuable building block for the synthesis of a wide range of compounds. [29,30,37,38]. From 1,3-benzoxazines 1a, 1d and 1h the α-amino-phosphonates 3a, 3d and 3h were obtained in 6–89% yields (Scheme 1).

![Scheme 1](image1)

Scheme 1. Synthesis of phosphonates and α-aminophosphonates from 1,3-benzoxazines.

The mechanism in Scheme 4 below shows an equilibrium in the ring-opening benzoxazines via iminium ion or α-Quinone Methide (α-QMs) intermediates. Considering that the stabilization of the iminium ions is directly affected by the steric effect of the substituent (H > Me > n-Bu > s-Bu > C₆H₅ ≥ p-ClC₆H₄ > p-MeC₆H₄ > m-MeC₆H₄), the aminophosphonates with H and Me as substituents were formed in better yields. On the other side, the phosphonates were formed according to the stabilization of the substituent in α-QMs intermediates (H > Me > n-Bu > s-Bu > C₆H₅ ≥ p-ClC₆H₄ > p-MeC₆H₄ > p-MeC₆H₄ > m-MeC₆H₄).

In order to study others phosphorus sources, the reaction of the 1,3-benzoxazines 1a–h, diethyl phosphite and boron trifluoride etherate as catalyst in MeCN were carried out (Scheme 2). To our satisfaction only the α-aminophosphonates 3a–h were detected in 24–96% yield. We found that the 1,3-benzoxazines 1a and 1h with hydrogen and methyl substituents show the best yields (96 and 80%, respectively), whereas, the 1,3-benzoxazines 1d, 1g and 1h with bulky substituents furnished the α-aminophosphonates 3d, 3g and 3h in moderate yields (Scheme 2). Due to the fact benzyl and o-hydroxybenzyl groups are attached to the nitrogen atom, both move away from each other avoiding the steric hindrance, which causes them to be oriented towards the double bond of the iminium ion inhibiting the access of the phosphite. However, the 1,3-benzoxazine ring opening produces the reaction between the phenolate and hydrogen atom of diethyl phosphite tautomer (Ar-O=H-O-P), this facilitate the attack to form the C-P bond, this effect does not occur when triethyl phosphite is used.

![Scheme 2](image2)

Scheme 2. Direct conversion of 1,3-benzoxazines 1a–h to α-aminophosphonates 3a–h.

With the results obtained in the phosphorylation of o-QMs, next we explored the direct transformation of 1,3-benzoxazine 1e. Thus, 1e was treated with 3-chloro-1-propanol at 70 °C for 12 h affording the oxa-Michael adduct 5a in 53% yield. The ether product is a versatile intermediate to obtain more complex compounds [29,39–41] (Scheme 3).
A proposed reaction pathway is depicted in Scheme 4. The formation of α-aminophosphonates can be explained through protonation of the oxygen by the hydrogen of diethyl phosphite which promotes the ring-opening generating the iminium ion, the subsequent phosphorylation provides the corresponding α-aminophosphonates. On the other hand, when triethyl phosphite is used the electronic delocalization of electron pair of nitrogen could generate the ring opening of 1,3-benzoxazines producing the iminium ion (path A) [42,43] which is attacked by the triethyl phosphite to give the α-aminophosphonates. When the oxygen was activated (path B) it promoted o-QM formation following by phospha-Michael addition reaction [28] with P(OEt)3 to produce the corresponding phosphonates.

Scheme 3. Preparation of phenol ether 5e from the direct transformation of the 1,3-benzoxazine 1e.

Scheme 4. Proposed reaction pathway for the ring-opening of 1,3-benzoxazines to generated phosphonates and α-aminophosphonates.

3. Materials and Methods

3.1. General Information

Reagents were obtained from commercial suppliers and were used without further purification. Melting points were determined in a Fischer Johns apparatus (Pittsburgh, PA, USA) and are uncorrected. NMR spectra were recorded on Varian System instrument (Palo Alto, CA, USA) at 400 MHz for 1H- and 100 MHz for 13C- and a Varian Gemini at 200 MHz for 1H- and 50 MHz for 13C-. The spectra were obtained in CDCl3 solutions using TMS as an internal reference. 31P chemical shifts are reported relative to H3PO4 as an internal reference. High-resolution Cl+ and FAB+ mass experiments were performed on a JEOL HRMStation JHRMS-700 (Akishima, Tokyo, Japan). The purification of all compounds was carried out by column chromatography using (silica gel 230–400 mesh). The dichloromethane and acetonitrile were refluxed on phosphorous pentoxide and hexane with sodium and benzophenone. Formaldehyde (30%) was used for the reactions.
3.2. General Procedure to Obtain the 1,3-benzoxazines 1a-h

A mixture of 2-(benzylamino)-phenol (1.0 eq.) and formaldehyde solution (1.3 eq.) in dichloromethane was stirred at 37 °C for 1 h using a modified Dean-Stark trap. The crude product was purified by flash chromatography using hexane:EtOAc (99:01) or by recrystallization in methanol.

3.2.1. 3-Benzyl-3,4-dihydro-2H-1,3-benzoxazine (1a)

The 1H- and 13C-NMR data for the compound 1a were identical to those reported in the literature [36].

3.2.2. 3-Benzyl-4-methyl-3,4-dihydro-2H-1,3-benzoxazine (1b)

According to the general procedure, a mixture of 2-[1-(benzylamino)ethyl]phenol (1.0 g, 4.40 mmol) and formaldehyde (0.17 g, 5.72 mmol, 0.46 mL) in dichloromethane (10 mL) was reacted. After purification, 1b (1.01 g, 99%) was obtained as a colorless oil. 1H-NMR (CDCl3, 400 MHz): δ 1.46 (d, J = 7.2 Hz, 3H), 3.74 (q, J = 6.4 Hz, 1H), 3.79 (d, J = 13.6 Hz, 1H), 4.01 (d, J = 14.0 Hz, 1H), 4.73 (d, J = 10.4 Hz, 1H), 5.01 (d, J = 10.0 Hz, 1H), 6.83–7.38 (m, 9H). 13C-NMR (CDCl3, 100 MHz): δ 24.1, 52.8, 56.4, 77.7, 116.8, 120.6, 127.4, 127.7, 128.5, 128.9, 129.0, 129.1, 138.3, 154.3. HRMS (Cl+): calculated for C16H18NO [M + H]+, m/z 240.1389; found for [M + H]+, m/z 240.1378.

3.2.3. 3-Benzyl-4-butyl-3,4-dihydro-2H-1,3-benzoxazine (1c)

According to the general procedure, a mixture of 2-[1-(benzylamino)pentyl]phenol (1.0 g, 3.71 mmol) and formaldehyde (0.14 g, 4.83 mmol, 0.40 mL) in dichloromethane (15 mL) was reacted. After purification 1c (1.01 g, 97%) was obtained as a colorless oil. 1H-NMR (CDCl3, 400 MHz): δ 0.86 (t, J = 7.0 Hz, 3H), 1.13–1.88 (m, 6H), 3.48 (dd, J = 9.8, 3.8 Hz, 1H), 3.69 (d, J = 13.4 Hz, 1H), 4.00 (d, J = 13.4 Hz, 1H), 4.68 (dd, J = 10.4, 1.6 Hz, 1H), 4.96 (d, J = 10.4 Hz, 1H), 6.80–7.35 (m, 9H). 13C-NMR (CDCl3, 50 MHz): δ 14.2, 22.5, 28.5, 37.9, 56.9, 57.2, 77.8, 116.6, 120.4, 124.9, 127.4, 127.6, 128.4, 128.8, 129.3, 138.7, 153.7. HRMS (Cl+): calculated for C19H23NO [M + H]+, m/z 282.1780; found for [M + H]+, m/z 282.1788.

3.2.4. 3-Benzyl-4-(s-butyl)-3,4-dihydro-2H-1,3-benzoxazine (1d)

According to the general procedure, a mixture of 2-[1-(benzylamino)-2-methylbutyl]phenol (0.47 g, 1.74 mmol) and formaldehyde (0.06 g, 2.27 mmol, 0.18 mL) in dichloromethane (10 mL) was reacted. After purification 1d (0.44 g, 91%) was obtained as a colorless oil. 1H-NMR (CDCl3, 400 MHz): δ 0.83 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 7.6 Hz, 3H*), 0.94 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H*), 1.15–1.27 (m, 3H), 1.52–1.63 (m, 1H*), 1.69–1.85 (m, 2H*), 3.64 (d, J = 13.6 Hz, 1H), 3.66 (d, J = 13.2 Hz, 1H*), 3.93 (d, J = 13.2 Hz, 1H), 3.95 (d, J = 13.2 Hz, 1H*), 4.68 (dd, J = 10.4, 0.8 Hz, 1H), 4.69 (d, J = 10.4 Hz, 1H*), 4.97 (d, J = 10.0 Hz, 1H), 5.00 (d, J = 10.0 Hz, 1H*), 6.82–7.36 (m, 9H, 9H*). 13C-NMR (CDCl3, 100 MHz): δ 11.2, 11.9*, 16.1, 16.5*, 25.5, 26.1*, 40.3, 40.8*, 57.5, 57.8*, 61.9, 62.2*, 78.0, 78.5*, 116.5, 116.6*, 116.9, 119.3*, 119.5, 119.7*, 122.4, 122.7*, 127.4, 127.9, 128.0*, 128.4*, 129.4, 129.5*, 130.0, 130.3*, 138.7, 138.8*, 153.7, 154.0*. HRMS (Cl+): calculated for C19H23NO [M + H]+, m/z 282.1780; found for [M + H]+, m/z 282.1845.

3.2.5. 3-Benzyl-4-phenyl-3,4-dihydro-2H-1,3-benzoxazine (1e)

According to the general procedure, a mixture of 2-[(benzylamino)phenyl)methyl]phenol (0.80 g, 2.76 mmol) and formaldehyde (0.10 g, 3.58 mmol, 0.30 mL) in dichloromethane (15 mL) was reacted. After crystallization in methanol 1e (1.04 g, 100%) was isolated as a white solid m.p. = 88–90 °C. 1H-NMR (CDCl3, 400 MHz): δ 3.91 (d, J = 13.6 Hz, 1H), 4.06 (d, J = 13.6 Hz, 1H), 4.63 (dd, J = 10.4, 4.6 Hz, 1H), 4.76 (d, J = 9.6 Hz, 1H), 4.78 (s, 1H), 6.88–7.44 (m, 14H). 13C-NMR (CDCl3, 100 MHz): δ 56.7, 60.2, 78.1, 116.9, 120.4, 128.3, 128.5, 128.6, 129.2, 129.4, 138.6, 143.6, 154.3. HRMS (Cl+): calculated for C21H19NO [M + H]+, m/z 302.1576; found for [M + H]+, m/z 302.1561.

Molecules 2019, 24, 294
5 of 12
3.2.6. 3-Benzyl-4-(m-tolyl)-3,4-dihydro-2H-1,3-benzoxazine (1f)

According to the general procedure, a mixture of 2-[(benzylamino)(m-tolyl)methyl]phenol (1.0 g, 3.30 mmol) and formaldehyde (0.12 g, 4.29 mmol, 0.34 mL) in dichloromethane (15 mL) was reacted. After purification 1f (0.89 g, 86%) was obtained as a colorless oil. 1H-NMR (CDCl3, 200 MHz): δ 2.31 (s, 3H), 3.93 (d, J = 13.4 Hz, 1H), 4.08 (d, J = 13.2 Hz, 1H), 4.66 (d, J = 10.0 Hz, 1H), 4.77 (s, 1H), 4.82 (d, J = 10.0 Hz, 1H), 6.93-7.49 (m, 13H). 13C-NMR (CDCl3, 50 MHz): δ 21.7, 56.7, 60.4, 78.1, 80.9, 116.8, 120.4, 126.3, 127.7, 128.4, 128.5, 129.5, 129.9, 130.0, 130.2, 130.3, 137.9, 138.5, 143.5, 154.3. HRMS (Cl+: calculated for C22H21NO [M + H]+, m/z 317.1780; found for [M + H]+, m/z 317.1830.

3.2.7. 3-Benzyl-4-(p-tolyl)-3,4-dihydro-2H-1,3-benzoxazine (1g)

According to the general procedure, a mixture of 2-[(benzylamino)(p-tolyl)methyl]phenol (0.3 g, 0.98 mmol) and formaldehyde (0.03 g, 1.27 mmol, 0.10 mL) in dichloromethane (10 mL) was reacted. After crystallization in methanol 1g (0.23 g, 76%) was obtained as a white solid m.p. = 80–83 °C. 1H-NMR (CDCl3, 400 MHz): δ 2.31 (s, 3H), 3.91 (d, J = 13.2 Hz, 1H), 4.06 (d, J = 13.6 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 4.78 (s, 1H), 4.82 (d, J = 10.0 Hz, 1H), 6.91–7.45 (m, 13H). 13C-NMR (CDCl3, 50 MHz): δ 21.1, 56.6, 60.4, 78.1, 116.9, 120.4, 126.3, 127.7, 128.5, 128.6, 129.2, 129.5, 129.9, 130.0, 130.3, 137.2, 138.5, 143.5, 154.4. HRMS (Cl+: calculated for C22H21NO [M + H]+, m/z 317.1780; found for [M + H]+, m/z 317.1810.

3.2.8. 3-Benzyl-4-(4-chlorophenyl)-3,4-dihydro-2H-1,3-benzoxazine (1h)

According to the general procedure, a mixture of 2-[(benzylamino)(4-chlorophenyl)methyl]phenol 6 (0.88 g, 2.73 mmol) and formaldehyde (0.09 g, 3.27 mmol, 0.26 mL) in dichloromethane (15 mL) was reacted. After purification 1h (0.89 g, 86%) was obtained as a colorless oil. 1H-NMR (CDCl3, 200 MHz): δ 3.88 (d, J = 13.2 Hz, 1H), 4.06 (d, J = 13.4 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.69 (d, J = 10.2, 1.6 Hz, 1H), 5.29 (s, 1H), 6.87–7.44 (m, 13H). 13C-NMR (CDCl3, 50 MHz): δ 56.5, 59.3, 77.8, 116.8, 119.5, 120.3, 127.6, 128.2, 128.5, 129.2, 130.0, 130.3, 133.1, 138.2, 141.9, 154.0. HRMS (Cl+: calculated for C22H21ClNO [M + H]+, m/z 335.1078; found for [M + H]+, m/z 336.1156.

3.3. General Procedure for Preparation of 2-hydroxybenzylphosphonates 2b, 2e, 2g and α-Aminophosphonates 3a, 3d, 3h

A mixture of 1,3-benzoxazine 1a–h (1.0 eq.), triethyl phosphate (1.0 eq.) and boron trifluoride etherate (20 mol%) in acetonitrile was stirred under nitrogen atmosphere at 26 °C for 72 h. Then, the solvent was evaporated under reduced pressure. The crude was dissolved in dichloromethane (1.0 mL), a saturated solution of ammonium chloride (1.0 mL) was added and the reaction mixture was stirred for 15 min. The organic phase was extracted with dichloromethane and dried with anhydrous sodium sulfate. Finally, the solvent was removed under reduced pressure and the crude was purified by flash chromatography using hexane:EtOAc (80:20).

3.3.1. Diethyl-[1-(2-hydroxyphenyl)ethyl]phosphonate (2b)

According to the general procedure, a mixture of 1,3-benzoxazine 1b (0.10 g, 0.41 mmol), triethyl phosphate 0.06 g (0.41 mmol, 0.07 mL) and boron trifluoride etherate (0.01 g, 0.08 mmol, 0.01 mL) in acetonitrile (3 mL) was reacted. After purification 2b (0.03 g, 28%) was obtained as a colorless oil. 1H-NMR (CDCl3, 400 MHz): δ 1.21 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.57 (dd, J = 18.0, 7.6 Hz, 3H), 3.85 (dq, J = 23.6, 7.6 Hz, 1H), 3.89-4.08 (m, 4H), 6.87-7.20 (m, 4H). 13C-NMR (CDCl3, 100 MHz): δ 13.2 (d, J = 4.4 Hz), 16.2, 34.7 (d, J = 136.2 Hz), 63.0 (d, J = 7.3 Hz), 63.1 (d, J = 7.3 Hz), 119.5, 120.9, 124.3 (d, J = 7.4 Hz), 128.7 (d, J = 7.2 Hz), 129.2 (d, J = 7.3 Hz), 155.4 (d, J = 4.4 Hz). 31P-NMR (CDCl3, 161.90 MHz): δ 31.12. HRMS (Cl+: calculated for C12H19O4P [M + H]+, m/z 259.1099; found for [M + H]+, m/z 259.1110.
3.3.2. Diethyl-[(2-hydroxyphenyl)(phenyl)methyl]phosphonate (2e)

According to the general procedure, a mixture of 1,3-benzoxazine 1e (0.20 g, 0.66 mmol), triethylphosphite (0.11 g, 0.66 mmol, 0.11 mL) and boron trifluoride etherate (0.01 g, 0.13 mmol, 0.01 mL) in acetonitrile (5 mL) was reacted. After purification 2e (0.08g, 40%) was obtained as a white solid, m.p. = 157–159 °C. 1H-NMR (CDCl₃, 400 MHz): δ 1.12 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), 3.74-4.16 (m, 4H), 4.72 (d, J = 26.6 Hz, 1H), 6.78-7.53 (m, 9H). 13C-NMR (CDCl₃, 100 MHz): δ 16.3, 18.3, 47.0 (d, 1JCP = 136.2 Hz), 63.5 (d, 2JCP = 7.0 Hz), 64.0 (d, 2JCP = 7.4 Hz), 119.5, 121.0, 123.7, 129.1, 129.5, 129.7, 130.0, 131.1, 132.5, 137.2, 155.3. 31P-NMR (CDCl₃, 161.90 MHz): δ 28.78. HRMS (Cl⁺): calculated for C₁₇H₂₃O₄P [M + H]⁺, m/z 321.1256; found for [M + H]⁺, m/z 321.1306.

3.3.3. Diethyl-[(2-hydroxyphenyl)(p-toly)methyl]phosphonate (2g)

According to the general procedure, a mixture of 1,3-benzoxazine 1g (0.10 g, 0.31 mmol), triethyl phosphite (0.05 g, 0.31 mmol, 0.05 mL) and boron trifluoride etherate (0.009 g, 0.06 mmol, 0.009 mL) in acetonitrile (3 mL) was reacted. After purification 2g (0.04 g, 30%) was obtained as a white solid, m.p. = 151–153 °C. 1H-NMR (CDCl₃, 400 MHz): δ 1.13 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.32 (s, 3H), 3.88 (m, 2H), 4.03 (m, 2H), 4.69 (d, J = 26.4 Hz, 2H), 6.79-7.39 (m, 8H). 13C-NMR (CDCl₃, 100 MHz): δ 16.3, 21.2, 47.3 (d, 1JCP = 136.2 Hz), 63.4, 64.0, 119.5, 121.0, 123.7, 129.1, 129.5, 129.7, 130.0, 131.1, 131.2, 132.5, 137.2, 155.3. 31P-NMR (CDCl₃, 161.90 MHz): δ 28.78. HRMS (Cl⁺): calculated for C₁₈H₂₅O₄P [M + H]⁺, m/z 335.1412; found for [M + H]⁺, m/z 335.1419.

3.3.4. Diethyl[(benzyl(2-hydroxybenzyl)amino)methyl]phosphonate (3a)

According to the general procedure, a mixture of 1,3-benzoxazine 1a (0.20 g, 0.88 mmol), triethylphosphite (0.16 g, 0.88 mmol, 0.15 mL) and boron trifluoride etherate (0.02 g, 0.17 mmol, 0.02 mL) in acetonitrile (5 mL) was reacted. After purification 3a (0.28g, 89%) was obtained as a colorless oil 1H-NMR (CDCl₃, 200 MHz): δ 1.29 (t, J = 7.0 Hz, 3H), 2.87 (d, J = 11.6 Hz, 2H), 3.75 (s, 2H), 3.95, (s, 2H), 4.05 (dq, J = 7.2, 7.2 Hz, 4H), 6.72-7.33 (m, 9H). 13C-NMR (CDCl₃, 50 MHz): δ 16.5, 16.6, 47.9 (d, 1JCP = 158.3 Hz), 58.8 (d, J = 6.4 Hz), 59.1 (d, J = 9.9 Hz), 62.2, 62.4, 116.5, 119.5, 121.9, 127.9, 128.7, 129.3, 129.6, 129.9, 136.6, 157.4. 31P-NMR (CDCl₃, 80.9 MHz): δ 21.92. HRMS (Cl⁺): calculated for C₁₉H₂₆NO₄P [M + H]⁺, m/z 364.1679; found for [M + H]⁺, m/z 364.1724.

3.3.5. Diethyl[benzyl[1-(2-hydroxyphenyl)-2-methylbutyl]amino]methyl]phosphonate (3d)

According to the general procedure, a mixture of 1,3-benzoxazine 1d, (0.20 g, 0.83 mmol), triethylphosphite (0.15 g, 0.83 mmol, 0.14 mL) and boron trifluoride etherate (0.02 g, 0.16 mmol, 0.02 mL) in acetonitrile (5 mL) were reacted. After purification 3d (0.12g, 37%) was obtained as a colorless oil The compound was characterized as diastereomeric mixture. 1H-NMR (CDCl₃, 400 MHz): δ 0.53 (d, J = 6.8 Hz, 3H), 0.72 (dd, J = 5.2 Hz, 5.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H*), 1.09 (d, J = 6.8 Hz, 3H*), 1.22 (t, J = 7.2 Hz, 3H, 3H*), 1.23 (t, J = 7.2 Hz, 3H, 3H*), 1.91 (dq, J = 7.2, 2.8 Hz, 2H), 1.95 (dq, J = 7.2, 2.8 Hz, 2H*), 2.22–2.35 (m, 1H, 1H*), 3.26 (dd, J = 16.8, 3.2 Hz, 1H), 3.28 (dd, J = 16.8, 3.2 Hz, 1H*), 3.32 (d, J = 7.6 Hz, 1H, 1H*), 3.59 (d, J = 16.0 Hz, 1H), 3.64 (d, J = 14.0 Hz, 2H, 2H*), 3.68 (dd, J = 14.0, 4.0 Hz, 1H*), 4.04-4.14 (m, 2H, 2H*), 4.23–4.33 (m, 2H, 2H*), 6.89-7.33 (m, 9H, 9H*), 10.40 (s, 1H, 1H*). 13C-NMR (CDCl₃, 100 MHz): 10.7, 11.2*, 16.4, 16.5, 16.6, 17.2*, 25.9, 27.3, 33.5, 33.9, 44.9 (d, 1JCP = 121.8 Hz), 45.0 (d, 1JCP = 122.6 Hz*), 58.0, 62.1, 62.2*, 71.1, 71.8*, 116.9, 117.1*, 119.0, 119.1*, 122.3, 125.0*, 127.5, 127.5*, 128.5, 128.5*, 128.8, 128.9*, 129.2, 129.2*, 132.9, 138.5*, 148.0, 148.1*. 31P-NMR (CDCl₃, 161.90 MHz): δ 26.01, 26.36* HRMS (Cl⁺): calculated for C₂₃H₃₄NO₄P [M + H]⁺, m/z 420.2305; found for [M + H]⁺, m/z 420.2286.

3.3.6. Diethyl[(benzyl[(4-chlorophenyl)(2-hydroxyphenyl)methyl]amino)methyl]phosphonate (3h)

According to the general procedure, a mixture of 1,3-benzoxazine 1h (0.20 g, 0.59 mmol), triethylphosphite (0.10 g, 0.59 mmol, 0.1 mL) and boron trifluoride etherate (0.01 g, 0.11 mmol, 0.01 mL)
in acetonitrile (5 mL) were reacted. After purification 3h (0.01g, 6%) was obtained as a colorless oil. 1H-NMR (CDCl$_3$, 200 MHz): δ 1.29 (t, J = 7.2 Hz, 6H), 3.22 (dd, J = 16.6, 7.0 Hz, 1H), 3.43 (dd, J = 16.5, 4.8 Hz, 1H), 3.73-4.37 (m, 4H), 3.82 (dd, J = 6.2, 3.2 Hz, 2H), 4.10 (dd, J = 7.9, 7.2 Hz, 1H), 5.06 (s, 1H), 6.69-7.36 (m, 13H), 10.83 (s, 1H). 13C-NMR (CDCl$_3$, 50 MHz): δ 16.4, 16.5, 45.0 (d, J$_{1C-P}$ = 124.5 Hz), 57.6, 61.9 (d, J$_{3C-P}$ = 7.5 Hz), 67.0, 122.4, 122.5, 125.6, 127.6, 128.5, 128.7, 129.5, 130.12, 132.5, 133.3, 137.0, 138.0. 31P-NMR (CDCl$_3$, 161.90 MHz): δ 24.64. HRMS (Cl$^+$): calculated for C$_{25}$H$_{26}$ClN$_4$O$_4$P [M + H]$^+$, m/z 474.1603; found for [M + H]$^+$, m/z 474.1653.

3.4. General Procedure for Preparation of α-Aminophosphonates 3a–h

A mixture of 1,3-benzoxazines 1a–h (1.0 eq.), diethyl phosphate (1.0 eq.) and boron trifluoride etherate (0.2 eq.) was stirred at 26 °C for 48 h in acetonitrile, then, the solvent was evaporated under reduced pressure and re-dissolved in dichloromethane. Afterward, a saturated solution of ammonium chloride was added and the reaction mixture was stirred for 15 min. Finally, the organic phase was extracted with dichloromethane and dried over anhydrous sodium sulfate. The solvent was eliminated under reduced pressure and the crude was purified by flash chromatography using hexane:EtOAc (80:20).

3.4.1. Diethyl[[benzyl(2-hydroxybenzyl)amino]methyl]phosphonate (3a)

According to the general procedure, a mixture of 1,3-benzoxazine 1a (0.3 g, 1.33 mmol), diethyl phosphate (0.18 g, 1.33 mmol, 0.17 mL) and boron trifluoride etherate (0.03 g, 0.26 mmol, 0.03 mL) in acetonitrile (5 mL) were reacted during 48 h. The reaction crude was purified by flash chromatography using hexane:EtOAc (80:20). After purification 3a (0.46 g, 96%) was obtained as a colorless oil.

3.4.2. Diethyl[[benzyl[1-(2-hydroxyphenyl)ethyl]amino]methyl]phosphonate (3b)

According to the general procedure, a mixture of 1,3-benzoxazine 1b (0.10 g, 0.41 mmol), diethyl phosphate (0.05 g, 0.41 mmol, 0.07 mL) and boron trifluoride etherate (0.01 g, 0.08 mmol, 0.01 mL) in acetonitrile (3 mL) were reacted. After purification 3b (0.12 g, 80%) was obtained as a colorless oil. 1H-NMR (CDCl$_3$, 200 MHz): δ 1.25 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.47 (d, J = 6.6 Hz, 1H), 2.92 (d, J = 12.2 Hz, 2H), 3.48 (d, J = 12.8 Hz, 1H), 3.79-4.19 (m, 4H), 4.45 (q, J = 7.0 Hz, 1H), 6.78-7.34 (m, 9H). 13C-NMR (CDCl$_3$, 50 MHz): δ 10.3, 16.4, 16.6, 44.2 (d, J$_{1C-P}$ = 159.1 Hz), 54.9 (d, J$_{3C-P}$ = 7.6 Hz), 57.0 (d, J$_{3C-P}$ = 6.0 Hz), 62.2 (d, J$_{2C-P}$ = 9.1 Hz), 62.4 (d, J$_{2C-P}$ = 7.5 Hz), 116.7, 119.3, 126.5, 127.3, 127.8, 128.6, 129.0, 129.8, 137.0, 157.1. 31P-NMR (CDCl$_3$, 80.9 MHz): δ 26.19. HRMS (Cl$^+$): calculated for C$_{20}$H$_{28}$NO$_4$P [M + H]$^+$, m/z 378.1756; found for [M + H]$^+$, m/z 378.1783.

3.4.3. Diethyl[[benzyl[1-(2-hydroxyphenyl)pentyl]amino]methyl]phosphonate (3c)

According to the general procedure, a mixture of 1,3-benzoxazine 1c (0.30 g, 1.06 mmol), diethyl phosphate (0.14 g, 1.06 mmol, 0.13 mL) and boron trifluoride etherate (0.03 g, 0.21 mmol, 0.03 mL) in acetonitrile (5 mL) were reacted. After purification 3c (0.26 g, 58%) was obtained as a colorless oil. 1H-NMR (CDCl$_3$, 200 MHz): δ 0.90 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 6.8 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.37 (q, J = 7.2 Hz, 2H), 1.78-1.88 (m, 2H), 1.95-2.05 (m, 2H), 2.91 (d, J = 16.0 Hz, 1H), 3.00 (dd, J = 16.0, 7.2 Hz, 1H), 3.20 (d, J = 13.2 Hz, 1H), 3.92-4.07 (m, 4H), 4.03 (d, J = 13.2 Hz, 1H), 4.15 (d, J = 10.0 Hz, 2H), 6.81-7.34 (m, 9H), 9.60 (s, 1H). 13C-NMR (CDCl$_3$, 100 MHz): δ 14.2, 16.5, 16.6, 23.1, 26.0, 29.5, 44.4 (d, J$_{1C-P}$ = 155.3 Hz), 55.1 (d, J$_{3C-P}$ = 7.3 Hz), 62.1 (d, J$_{2C-P}$ = 5.8 Hz), 62.3 (d, J$_{2C-P}$ = 5.9 Hz), 63.2, 117.2, 119.2, 125.2, 127.8, 128.5, 128.7, 128.9, 129.9, 137.6, 157.3. 31P-NMR (CDCl$_3$, 161.90 MHz): δ 25.71. HRMS (Cl$^+$): calculated for C$_{23}$H$_{34}$NO$_4$P [M + H]$^+$, m/z 420.2305; found for [M + H]$^+$, m/z 420.2355.

3.4.4. Diethyl[[benzyl[1-(2-hydroxyphenyl)-2-methylbutyl]amino]methyl]phosphonate (3d)

According to the general procedure, a mixture of 1,3-benzoxazine 1d (0.30 g, 1.06 mmol), diethyl phosphate (0.14 g, 1.06 mmol, 0.13 mL) and boron trifluoride etherate (0.03 g, 0.21 mmol, 0.03
mL) in acetonitrile (5 mL) was reacted. After purification 3d (0.16 g, 37%) was obtained as a colorless oil. The compound was characterized as diastereomeric mixture.

3.4.5. Diethyl([benzyl][2-hydroxyphenyl](phenyl)methyl)amino)methyl)phosphonate (3e)

According to the general procedure, a mixture of 1,3-benzoxazine 1e (0.20 g, 0.66 mmol), diethyl phosphite (0.09 g, 0.66 mmol, 0.08 mL) and boron trifluoride etherate (0.018 g, 0.13 mmol, 0.016 mL) in acetonitrile (5 mL) was reacted. After purification 3e (0.19 g, 65%) was obtained as a colorless oil. 

$^{1}$H-NMR (CDCl₃, 400 MHz): δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H), 2.86 (dd, $J = 15.6, 5.6$ Hz, 1H), 2.99 (dd, $J = 18.0, 15.6$ Hz, 1H), 3.64 (d, $J = 13.2$ Hz, 1H), 4.14 (d, $J = 12.8$ Hz, 1H), 3.85–4.00 (m, 2H), 4.04–4.14 (m, 2H), 5.48 (s, 1H), 6.70–7.47 (m, 14H), 10.74 (s, 1H). $^{13}$C-NMR (CDCl₃, 100 MHz): δ 16.4, 16.6, 44.4 (d, $^{1}$C-P = 156.0 Hz), 55.1, (d, $^{2}$C-P = 6.5 Hz), 62.2 (d, $^{2}$C-P = 6.5 Hz), 69.3 (d, $^{2}$C-P = 6.5 Hz), 117.1, 119.4, 124.6, 124.8, 127.9, 128.5, 128.7, 128.9, 129.1, 129.9, 130.2, 130.4, 136.4, 157.2. $^{31}$P-NMR (CDCl₃, 161.90 MHz): δ 27.89. HRMS (Cl⁺): calculated for C$_{25}$H$_{30}$NO$_{4}$P [M + H]$^+$, m/z 440.1992; found for [M + H]$^+$, m/z 440.2004.

3.4.6. Diethyl([benzyl][2-hydroxyphenyl](m-tolyl)methyl)amino)methyl)phosphonate (3f)

According to the general procedure, a mixture of 1,3-benzoxazine 1f (0.3 g, 0.95 mmol), diethyl phosphite (0.13 g, 0.95 mmol, 0.12 mL) and boron trifluoride etherate (0.027 g, 0.19 mmol, 0.024 mL) in acetonitrile (6 mL) was reacted. After purification 3f (0.15 g, 35%) was obtained as a colorless oil. 

$^{1}$H-NMR (CDCl₃, 400 MHz): δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 3H), 2.37 (s, 3H), 2.87 (dd, $J = 15.6, 5.6$ Hz, 1H), 2.99 (dd, $J = 18.0, 15.6$ Hz, 1H), 3.66 (d, $J = 13.2$ Hz, 1H), 3.82–4.02 (m, 2H), 4.04–4.17 (m, 2H), 4.09 (d, $J = 13.2$ Hz, 1H), 5.41 (s, 1H), 6.70–7.47 (m, 13H), 10.79 (s, 1H). $^{13}$C-NMR (CDCl₃, 100 MHz): δ 16.5 (d, $^{3}$C-P = 5.0 Hz), 16.6 (d, $^{3}$C-P = 5.0 Hz), 44.4 (d, $^{1}$C-P = 155.0 Hz), 55.1, (d, $^{3}$C-P = 6.0 Hz), 62.3 (d, $^{2}$C-P = 6.0 Hz), 69.5 (d, $^{2}$C-P = 6.0 Hz), 117.1, 119.4, 124.7, 127.3, 127.9, 128.6, 128.7, 128.9, 129.1, 129.2, 130.0, 130.3, 131.0, 136.5, 138.5, 157.2. $^{31}$P-NMR (CDCl₃, 161.90 MHz): δ 28.52. HRMS (Cl⁺): calculated for C$_{26}$H$_{32}$NO$_{4}$P [M + H]$^+$, m/z 454.5404; found for [M + H]$^+$, m/z 454.5454.

3.4.7. Diethyl([benzyl][2-hydroxyphenyl](p-tolyl)methyl)amino)methyl)phosphonate (3g)

According to the general procedure, a mixture of 1,3-benzoxazine 1g (0.25 g, 0.79 mmol), diethyl phosphite (0.10 g, 0.79 mmol, 0.10 mL) and boron trifluoride etherate (0.02 g, 0.15 mmol, 0.02 mL) in acetonitrile (5 mL) was reacted. After purification 3g (0.086 g, 24%) was obtained as a colorless oil. 

$^{1}$H-NMR (CDCl₃, 400 MHz): δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 3H), 2.37 (s, 3H), 2.84 (dd, $J = 15.6, 5.2$ Hz, 1H), 2.98 (dd, $J = 18.0, 16$ Hz, 1H), 3.60 (d, $J = 13.2$ Hz, 2H), 3.82–4.00 (m, 2H), 4.04–4.15 (m, 2H), 5.44 (s, 1H), 6.69–7.36 (m, 13H), 10.83 (s, 1H). $^{13}$C-NMR (CDCl₃, 100 MHz): δ 15.6, 15.6, 44.4 (d, $^{1}$C-P = 157.0 Hz), 55.1, (d, $^{2}$C-P = 7.0 Hz), 62.3 (d, $^{2}$C-P = 7.0 Hz), 69.0 (d, $^{2}$C-P = 7.0 Hz), 117.1, 119.3, 124.7, 127.3, 127.9, 128.7, 128.9, 129.5, 130.0, 130.3, 136.4, 138.2, 157.3. $^{31}$P-NMR (CDCl₃, 161.90 MHz): δ 22.55. HRMS (Cl⁺): calculated for C$_{26}$H$_{32}$NO$_{4}$P [M + H]$^+$, m/z 454.5404; found for [M + H]$^+$, m/z 454.5444.

3.4.8. Diethyl ((benzyl)(4-chlorophenyl)(2-hydroxyphenyl)methyl)amino)methyl)phosphonate (3h)

According to the general procedure, a mixture of 1,3-benzoxazine 1h (0.21 g, 0.63 mmol), diethyl phosphite (0.086 g, 0.63 mmol, 0.081 mL) and boron trifluoride etherate (0.017 g, 0.12 mmol, 0.02 mL) in acetonitrile (5 mL) was reacted. After purification 3h (0.15 g, 50%) was obtained as a colorless oil.

3.5. 2-(3-Chloropropoxy)(phenyl)methyl)phenol (5e)

A mixture of 1,3-benzoxazine 1e (0.15g, 5 mmol) and 3-chloro-1-propanol (0.5 mL, 0.56 g, 5.9 mmol) was stirred at 70 °C for 12 h at 70 °C. Then, the crude was purified by flash chromatography using hexane:EtOAc (80:20), to give 5e (0.072 g, 53%) $^{1}$H-NMR (CDCl₃, 200 MHz): δ 2. (dq, $J = 6.2, 1.6$ Hz,
2H), 3.80 (m, 4H), 5.55 (s, 1H), 7.02 (m, 9H), 7.80 (br, 1H). $^{13}$C-NMR (CDCl$_3$, 50 MHz): δ 32.6, 41.7, 66.4, 85.2, 117.3, 120.0, 124.9, 127.3, 127.6, 128.4, 128.8, 129.0, 129.4, 129.6, 139.9, 155.5. HRMS (CI$^+$): calculated for C$_{16}$H$_{17}$O$_2$Cl [M + H]$^+$, m/z: 277.0917; found for [M + H]$^+$, m/z 277.0880.

4. Conclusions

We have developed a novel “one-pot” method for the synthesis of secondary benzyl phosphonates and α-aminophosphonates from 1,3-benzoxazines. The phosphonates were obtained through direct o-QM formation, followed by a phospha-Michael addition reaction and the α-aminophosphonates by iminium ion formation and the subsequent alkylphosphites addition. In addition, this synthetic methodology was used to the preparation a valuable o-hydroxybenzyl ether derivative, which makes it a useful and efficient method for the synthesis of phosphonates, α-aminophosphonates and benzyl ethers.

Author Contributions: I.L.-E. provided the concepts of the work, interpreted the results and prepared the manuscript. O.S.-E., A.H.-G., I.R.-E., they carried out the experimental work and interpreted the results. All authors read and approved the final manuscript.

Acknowledgments: The authors thank the Consejo Nacional de Ciencia y Tecnología (CONACYT) of México for financial support through project 807 and Laboratorio Nacional de Estructura de Macromoléculas (LANEM) as well O.S.-E. thank CONACYT for Graduate Scholarship 248543. I.R.-E. also thank CONACYT for Cátedra contract 942. We thank Blanca E. Dominguez-Mendoza and V. Labastida-Galván for the determination of the NMR spectra and HRMS.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Moonen, K.; Laureyn, I.; Stevens, C.V. Synthetic methods azaheterocyclic phosphonates and their biological activity. Chem. Rev. 2004, 104, 6177–6215. [CrossRef] [PubMed]
2. Wu, D.; Niu, J.Q.; Ding, Y.H.; Wu, X.Y.; Zhong, B.H.; Feng, X.W. Antiviral effects of three novel derivatives of adefovir on the replication of hepatitis B virus. Med. Chem. Res. 2012, 21, 1179–1187. [CrossRef]
3. Kafarski, P.; Lejczak, B. Biological activity of aminophosphonic acids. Phosphorus Sulfur Silicon Relat. Element. 1991, 63, 193–215. [CrossRef]
4. Sasaki, M. Current status of organophosphorus insecticide and stereochemistry. Phosphorus Sulfur Silicon Relat. Element. 2008, 183, 291–299. [CrossRef]
5. Lindsay, C.I.; Hill, S.B.; Hearn, M.; Manton, M.; Everall, N.; Bunn, A.; Heron, J.; Fletcher, I. Mechanism of action of phosphorus based flame retardants in acrylic polymers. Polym. Int. 2000, 49, 1183–1192. [CrossRef]
6. Kafarski, P.; Lejczak, B. Aminophosphonic acids of potential medical importance. Curr. Med. Chem. 2001, 1, 301–312. [CrossRef]
7. Lejczak, B.; Kafarski, P. Biological activity of aminophosphonic acids and their short peptides. Top. Heterocycl. Chem. 2009, 20, 3–63. [CrossRef]
8. Naydenova, E.D.; Todorov, P.T.; Troev, K.D. Recent synthesis of aminophosphonic acids as potential biological importance. Amino Acids 2010, 38, 23–30. [CrossRef]
9. Orsini, F.; Sello, G.; Sisti, M. Aminophosphonic acids and derivatives. Synthesis and biological applications. Curr. Med. Chem. 2010, 17, 264–289. [CrossRef]
10. Moszner, N.; Zeuner, F.; Fisher, U.K.; Rheinberger, V. Monomers for adhesive polymers, 2. Synthesis and radical polymerisation of hydrolytically stable acrylic phosphonic acids. Macromol. Chem. Phys. 1999, 200, 1062–1067. [CrossRef]
11. Cabasso, I.; Smid, J.; Sahni, S.K. Radiopaque polymers based on acrylated phosphonate esters derived from polyols. J. Appl. Polym. Sci. 1990, 41, 3025–3042. [CrossRef]
12. Salasi, M.; Sharabi, T.; Roayaei, E.; Aliolfkhazraei, M. The electrochemical behavior of environment-friendly inhibitors of silicate and phosphonate in corrosion control of carbon steel in soft water media. Mater. Chem. Phys. 2007, 104, 183–190. [CrossRef]
13. Kavipriya, K.; Rajendran, S.; Sathiyabama, J.; Prabha, A.S. A critical review of corrosion inhibition by phosphonic acids. Eur. Chem. Bull. 2012, 1, 366–374. [CrossRef]
14. Knepper, T.P. Synthetic chelating agents and compounds exhibiting complexing properties in aquatic environment. *Trends Analytic. Chem.* 2003, 22, 708–724. [CrossRef]

15. Canadell, J.; Hunt, B.J.; CooK, A.G.; Mantecon, A.; Cadiz, V. Flame retardance and shrinkage reduction of polystyrene modified with acrylate-containing phosphorus and crosslinkable spiro-orthoester moieties. *Polym. Degrad. Stab.* 2007, 92, 1482–1490. [CrossRef]

16. Singh, H.; Jain, A.K. Ignition, combustion, toxicity, and fire retardancy of polyurethane foams: A comprehensive review. *J. Appl. Polyom. Sci.* 2009, 111, 1115–1143. [CrossRef]

17. Ai, H.; Xu, K.; Liu, H.; Chen, M.; Zhang, X. Synthesis, characterization, and curing properties of novel phosphorus-containing naphtophosphoryl epoxy systems. *J. Appl. Polyom. Sci.* 2009, 113, 541–546. [CrossRef]

18. Herrera-Taboada, L.; Guzmán, M.; Neubecker, K.; Goethlich, A. Process and Polymer for Preventing Ba/Sr Scale with a Detectable Phosphorus Funtionality. U.S. Patent US 12/520,624, 8 July 2010.

19. Demmer, Ch.S.; Krogsgaard-Larsen, N.; Bunch, L. Review on modern advances of chemical methods for the introduction of a phosphonic acid group. *Chem. Rev.* 2011, 111, 7981–8006. [CrossRef]

20. Ordoñez, M.; Rojas-Cabrera, H.; Catiiviela, C. An overview of stereoselective synthesis of α-aminophosphonic acids and derivates. *Tetrahedron* 2009, 65, 17–49. [CrossRef]

21. Ma, X.; Xu, Q.; Li, H.; Su, Ch.; Yu, L.; Zhang, X.; Cao, H.; Han, L.B. Alcohol-based Michaelis-Arbuzov reaction: An efficient and environmentally-benign method for C-P(O) bond formation. *Green Chem.* 2018, 20, 3408–3413. [CrossRef]

22. Sharova, E.V.; Artyushin, O.I.; Odinet, L.L. Synthetic routes to carbamoylmethylphosphoryl compounds-extractants for the processing of spent nuclear fuels. *Russ. Chem. Rev.* 2014, 83, 95–119. [CrossRef]

23. Fan, W.; Queneau, Y.; Popowycz, F. The synthesis of HMF-based α-amino phosphonates via one-pot Kabachnik—Fields reaction. *RSC Adv.* 2018, 8, 31496–31501. [CrossRef]

24. Fields, E.K. The Synthesis of esters of substituted amino phosphonic Acids. *J. Am. Chem. Soc.* 2018, 140, 11957–11974. [CrossRef] [PubMed]

25. Cytlak, T.; Skibinska, M.; Kaczmarek, P.; Kazmierczak, M.; Rapp, M.; Kubickia, M.; Koroniak, H. Functionalization of α-hydroxyphosphonates as a convenient route to N-tosyl-α-aminophosphonates. *RSC Adv.* 2018, 8, 11957–11974. [CrossRef]

26. Bálint, E.; Taji, A.; Anna Adám, Á.; Csontos, I.; Karaghioso, K.; Czugle, M.; Ábrányi-Balogh, P.; Keglevich, G. The synthesis of α-aryl-α-aminophosphonates and α-aryl-α-aminophosphine oxides by the microwave-assisted Pudovik reaction. *Beilstein J. Org. Chem.* 2017, 13, 76–86. [CrossRef] [PubMed]

27. Ordoñez, M.; Viveros-Ceballos, J.L.; Romero-Estudillo, I. Stereoselective Synthesis of α-Aminophosphonic Acids through Pudovik and Kabachnik-Fields Reaction. In *Amino Acid-New Insights and Roles in Plant and Animal*, 1st ed.; Asao, T., Asaduzzaman, M., Eds.; InTechOpen: Rijeka, Croatia, 2017; Chapter 6; pp. 127–151. ISBN 978-953-51-3242-4.

28. Chen, Z.; Shi, Q.; Wang, G.; Chen, S.; Hu, J. Straightforward synthesis of bifunctional phosphorus phenols via phospination of in situ generated o-quinone methides. *Molecules* 2018, 23, 1240. [CrossRef] [PubMed]

29. Huang, H.; Kang, J.Y. Organocatalytic phosphorylation of in situ formed o-quinone methides. *Org. Lett.* 2017, 19, 5988–5991. [CrossRef]

30. Pérez-Prieto, J.; Galian, R.E.; Miranda, M.A.; Catalina, F.; Martín-Vargas, N.; López-Ortiz, F. Benzo[d]-1,2-oxazaphosphines as precursors of stabilized C-centered radicals. *Org. Lett.* 2004, 6, 561–564. [CrossRef]

31. Pérez-Prieto, J.; Galian, R.E.; Oña-Burgos, P.; Morant-Miñana, M.C.; Miranda, M.A.; López-Ortiz, F. Influence of substitution at the benzylic position on the behavior of stereoisomeric phosphorus compounds as precursors of stabilized carbon-centered radicals. *Org. Lett.* 2005, 7, 3869–3872. [CrossRef]

32. Kalla, R.M.N.; Lee, H.R.; Cao, J.; Yoo, J.W.; Kim, I. Phospho sulfonic acid: An efficient and reciclabale solid acid catalyst for the solvent-free synthesis of α-hydroxyphosphonates and their anticancer properties. *New J. Chem.* 2015, 39, 3916–3922. [CrossRef]

33. Salgado-Escobar, O.; Chavelas-Hernández, L.; Domínguez-Mendoza, B.E.; Linzaga-Elizalde, I.; Ordoñez, M. Synthesis of chiral 1,4,2-oxazaphosphines. *Molecules* 2015, 20, 13794–13813. [CrossRef]

34. Palmieri, G.; Cimarelli, C.; Volpini, E. Ready N-alkylation of enantiopure aminophenols: Synthesis of tertiary aminophenols. *Tetrahedron* 2001, 57, 6089–6096. [CrossRef]
35. Palmieri, G. Synthesis of enantiopure o-hydroxybenzylamines by stereoselective reduction of 2-imidoylphenols: Application in the catalytic enantioselective addition of diethylzinc to aldehydes. *Eur. J. Org. Chem.* 1999, 805–811. [CrossRef]

36. Andreu, R.; Ronda, J.C. Synthesis of 3,4-Dihydro-2H-1,3-benzoxazines by Condensation of 2-Hydroxylaldehydes and Primary Amines: Application to the Synthesis of Hydroxy-Substituted and Deuterium-Labeled Compounds. *Synth. Commun.* 2008, 38, 2316–2329. [CrossRef]

37. Aliouane, N.; Helesbeux, J.-J.; Douadi, T.; Khan, M.A.; Bouet, G.; Chafaa, S.; Duval, O. Synthesis of new benzylic di-, tri-, and tetraphosphonic acids as potential chelating agents. *Phosphorus Sulfur Silicon Relat. Elem.* 2011, 186, 354–364. [CrossRef]

38. Gibadullina, E.M.; Shaekhov, T.R.; Voronina, Y.K.; Pudovik, M.A.; Burilov, A.R. Reactions of [(3,5-Di-tert-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl]phosphonates with Phenols. *Russ. J. Org. Chem.* 2018, 54, 530–536. [CrossRef]

39. Zengwei, L.; Zhaobin, W.; Jianwei, S. Organocatalytic asymmetric nucleophilic addition to o-quinone methides by alcohols. *Org. Lett.* 2015, 17, 6058–6061. [CrossRef]

40. Malhotra, B.; Gandelman, K.; Sachse, R.; Wood, N.; Michel, M.C. The design and development of fesoterodine as a prodrug of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of tolterodine. *Curr. Med. Chem.* 2009, 16, 4481–4489. [CrossRef]

41. Greene, M.A.; Yonova, I.M.; Williams, F.J.; Jarvo, E.R. Traceless directing group for stereospecific nickel-catalyzed alkyl-alkyl cross-coupling reactions. *Org. Lett.* 2012, 14, 4293–4296. [CrossRef]

42. Kawaguchi, A.W.; Sudo, A.; Endo, T. Polymerization-depolymerization system sased on reversible addition-dissociation reaction of 1,3-benzoxazines with thiol. *ACS Macro Lett.* 2013, 2, 1–4. [CrossRef]

43. Metlushka, K.E.; Kashemirov, B.A.; Zheltukhin, V.F.; Sadkova, D.N.; Buchner, B.; Hess, C.; Kataeva, O.N.; McKenna, C.E.; Alfonsov, V.A. 1-(α-Aminobenzyl)-2-naphthol: A new chiral auxiliary for the synthesis of enantiopure α-aminophosphonic acids. *Chem. Eur. J.* 2009, 15, 6718–6722. [CrossRef] [PubMed]

**Sample Availability:** Samples of the compounds are not available from the authors.

© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).