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A Sustainable Improvement of ω-Bromoalkylphosphonates Synthesis to Access Novel KuQuinones

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Abstract: Owing to the attractiveness of organic phosphonic acids and esters in the pharmacological field and in the functionalization of conductive metal-oxides, the research of effective synthetic protocols is pivotal. Among the others, ω-bromoalkylphosphonates are gaining particular attention because they are useful building blocks for the tailored functionalization of complex organic molecules. Hence, in this work, the optimization of Michaelis–Arbuzov reaction conditions for ω-bromoalkylphosphonates has been performed, to improve process sustainability while maintaining good yields. Synthesized ω-bromoalkylphosphonates have been successfully adopted for the synthesis of new KuQuinone phosphonate esters and, by hydrolysis, phosphonic acid KuQuinone derivatives have been obtained for the first time. Considering the high affinity with metal-oxides, KuQuinones bearing phosphonic acid terminal groups are promising candidates for biomedical and photo(electro)chemical applications.

Keywords: ω-bromoalkylphosphonates; KuQuinones; phosphonate esters; diethyl phosphonates; organic phosphonic acids; Arbuzov reaction; triethyl phosphite; phosphonate ester hydrolysis; dibromoalkane; anchoring group

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1. Introduction

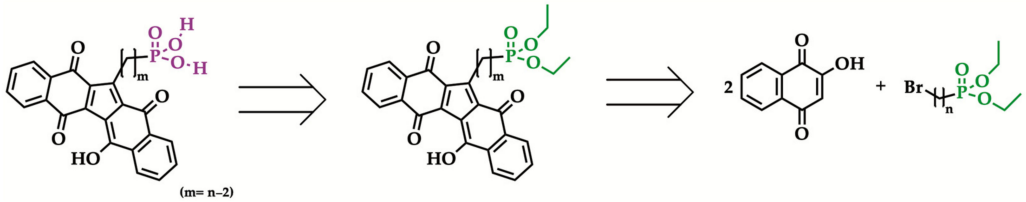
Phosphonic acid (PA) functionalization of organic compounds is of great interest in various scientific areas. Several pharmacologically active compounds bearing a PA group (or the corresponding phosphonate salt) have been developed over the years [1,2]. Organic phosphonic acid derivatives, such as phosphonoformic or phosphonoacetic acids and many others, resulted in promising antiviral drugs [3,4] and, recently, the aromatic analogue, phosphonobenzoic acid, has been object of a theoretical study on Covid-SARS [5]. Additionally, fosmidomycin and its α-substituted derivatives are effective anti-malarian drugs [6], while fosfomycin is a widely used antibiotic [7]. Notably, the presence of a phosphonic acid group significantly improves organic molecules hydrophilicity, which is an essential feature for biomedical application [8].

PAs are also optimal hydrogen bond donors and acceptors; therefore, they are employed in supramolecular chemistry, for metal-organic frameworks and organic proton conductors [9–12]. The dianionic nature of the deprotonated form of PA is pivotal for covalently binding different metal oxides, in mono-, bi- or tri-dentate architectures [13]. In fact, PA is a robust anchoring group, widely adopted for organic molecules immobilization on metal oxide surfaces and nanoparticles [14–21]. Therefore, phosphonic acid functionalization of organic and metallorganic photosensitizers is a proficient tool to decorate metal oxides for their application in dye-sensitized solar cells, photoelectrochemical devices [22,23] as well as in organocatalysis [24–27].

With respect to photoelectrochemical applications, we have been recently involved in the use of metal-free quinoid compounds, i.e., KuQuinones (KuQs), as photosentisiz-

ers on indium-tin oxide (ITO) [28], NiO [29] and on SnO_2 [30], due to their favorable electrochemical and photophysical properties [31]. In this respect, terminal hydroxy or carboxylic acid functionalities were introduced in KuQuinone structure to ensure a stable and effective metal oxide binding. Additionally, differently functionalized KuQs were tested as anti-proliferative agents against ovarian and colon cancer cells, with promising results [32,33].

In an attempt to extend KuQuinones application in the photo(electro)chemical and biomedical fields, the synthesis of new KuQuinone phosphonic acid derivatives was investigated. As a matter of fact, compared to carboxylates, PAs are better anchoring groups in terms of stability [34,35], bond strength [36–38] and monolayer deposition reproducibility [39]. Additionally, PA functionalization is expected to enhance KuQ pharmacological applications. In this framework, according to the previously reported synthetic procedure, to obtain new KuQuinone phosphonic acid derivatives, the synthesis of suitable ω-bromoalkylphosphonate esters was required (Scheme 1) [32].



Scheme 1. Retrosynthetic analysis to obtain new KuQuinone phosphonic acid derivatives [32].

The first synthesis of alkylphosphonate esters has been proposed more than 100 years ago by Michaelis and Arbuzov [40,41]. Optimized reaction conditions required the use of an alkyl bromide with an excess of triethyl phosphite. Reactions proceeded solventless, at high temperatures, with good yields. Later, the synthesis of ω-bromoalkylphosphonates was also experienced with Arbuzov's reaction [41]. Here, a dibromoalkane was used as the substrate. Nevertheless, such reactions lacked selectivity, because the di-substitution process occurred; therefore, a large excess of the dibromoalkane was required [42–46]. In that respect, although the authors claimed that the unreacted substrate can be recovered by fractional distillation and reused, it is worth mentioning that such a recovery procedure is actually problematic and time-consuming, because of the very similar boiling points of the reaction components. Therefore, in this paper, optimization of Michaelis–Arbuzov reaction conditions for the synthesis of ω-bromoalkylphosphonate esters is investigated, using an equimolar amount of reagents, to enhance process sustainability. The synthesized compounds are adopted for the synthesis of new KuQuinone derivatives.

2. Materials and Methods

All commercial reagents and solvents were purchased from Sigma Aldrich/MerckLife Science (KGaA, Darmstadt, Germany), with the highest degree of purity, and they were used without any further purification. UV-vis absorption spectra were recorded with a UV-Vis 2450 (Shimadzu, Kyoto, Japan) spectrophotometer. ATR-IR spectra were recorded with a FT-IR Nicolet iS50 (Thermo Scientific, Madison, WI, USA) spectrometer. Melting points were measured using a Büchi 512 melting point apparatus (Büchi, Flawil, CH) and all values were uncorrected. GC-MS analyses have been performed with a (Shimadzu, Kyoto, Japan) GCMS QP2010 Ultra system. ^{1}H-NMR and ^{31}P-NMR spectra were recorded with a Bruker AM400 NMR spectrometer (Bruker, Billerica, MA, USA) operating frequency of 400 MHz. Reactions with MW have been performed with a Microwave Accelerated Reaction System, Model MARS Xpress 5-CEM (CEM Corporation, Matthews, NC, USA). High-resolution mass spectra (HRMS) were recorded with a Bruker Compact QTOF instrument (Bruker, Billerica, MA, USA). Spectra have been acquired in positive or negative ion mode, with a mass resolution of R = 30,000.

2.1. Optimized Procedure for the Synthesis of Diethyl ω-Bromoalkylphosphonate

Glassware was flamed under nitrogen flow. The reaction flask was connected to a distillation apparatus, in order to distill the bromoethane produced during the process. A total of 75 mmol of α,ω-dibromoalkane were pre-heated at 140 °C; 75 mmol of triethyl phosphite were then added dropwise, within 2 h. The mixture was stirred for an additional hour and monitored by GC-MS. Pure diethyl ω-bromoalkylphosphonate was isolated by vacuum fractional distillation, with satisfactory yield. Product characterization has been performed with GC-MS, ^{1}H and ^{31}P NMR in $CDCl_3$ (see Supplementary Materials). Reactions have been performed in duplicate and good reproducibility was observed.

Diethyl 6-bromohexylphosphonate (**1**). Colorless oil (9.19 g, 30.5 mmol, 40% yield). MS (EI, 70 eV): *m/z* = 221 $[M - Br]^+$; *m/z* = 152 $[^{\bullet}CH_2P(=OH)(OCH_2CH_3)_2]^+$; *m/z* = 125 $[152\text{-}C_2H_3]^+$ [47,48]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.322 (t, *J* = 7.09 Hz, 6H), δ 1.366–1.509 (m, 4H), δ 1.562–1.667 (m, 4H), δ 1.819–1.908 (m, 2H), δ 3.402 (t, *J* = 6.74 Hz, 2H), δ 4.030–4.160 (m, 4H); ^{31}P NMR ($CDCl_3$, 400 MHz): δ 32.248 (s, 1P).

Diethyl 5-bromopentylphosphonate (**2**). Colorless oil (8.17 g, 29.5 mmol, 40% yield). MS (EI, 70 eV): *m/z* = 207 $[M - Br]^+$; *m/z* = 152 $[^{\bullet}CH_2P(=OH)(OCH_2CH_3)_2]^+$; *m/z* = 125 $[152\text{-}C_2H_3]^+$ [47,48]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.322 (t, *J* = 7.06, 6H), δ 1.475–1.739 (m, 6H), δ 1.826–1.920 (m, 2H), δ 3.404 (t, *J* = 6.72 Hz, 2H), δ 4.013–4.166 (m, 4H); ^{31}P NMR ($CDCl_3$, 400 MHz): δ 31.926 (s, 1P).

Diethyl 4-bromobutylphosphonate (**3**). Colorless oil (4.24 g, 15.5 mmol, 20% yield). MS (EI, 70 eV): *m/z* = 193 $[M - Br]^+$; *m/z* = 165 $[193\text{-}C_2H_4]^+$; *m/z* = 137 $[165\text{-}C_2H_4]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.326 (t, *J* = 7.05, 6H), δ 1.730–1.821 (m, 4H), δ 1.918–2.002 (m, 2H), δ 3.409 (t, *J* = 6.56 Hz, 2H), δ 4.042–4.156 (m, 4H).; ^{31}P NMR ($CDCl_3$, 400 MHz): δ 31.400 (s, 1P).

2.2. General Procedure for the Synthesis of 1-[n-(Diethyl phosphonyl) alkyl]KuQuinone

5.75 mmol of 2-hydroxy-1,4-naphthoquinone, 12 mmol of ω-bromoalkylphosphonate, 8 mmol of Cs_2CO_3, 0.33 mmol of sublimated ferrocene and 22 mL of dimethyl sulfoxide were mixed at 114 °C, for 41 h. The crude was then diluted with 100 mL of dichloromethane, filtered and extracted with NaCl saturated aqueous solution. The organic phase was subsequently dried over Na_2SO_4, filtered and concentrated. Purification was carried out by chromatography column (SiO_2/$CHCl_3$). The sample was dried and then further purified by precipitation with chloroform/hexane. The product was characterized by UV-vis and IR spectroscopy, HRMS, ^{1}H, ^{13}C and ^{31}P NMR in $CDCl_3$ (see Supplementary Materials).

1-[4-(Diethyl phosphonyl)butyl]KuQuinone (**4**). Purple powder (103.94 mg, 0.2 mmol, 7% yield) mp 185–188 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.303 (t, *J* = 7.08 Hz, 6H), δ 1.593–1.802 (m, 6H), δ 3.350–3.423 (t, *J* = 7.28 Hz, 2H), δ 4.026–4.147 (m, 4H), δ 7.622–7.729 (m, 4H), δ 8.102–8.199 (m, 4H), δ 18.072 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 181.052 and 177.973 (C=O); δ 136.089, 135.692, 135.127, 133.150, 131.905, 127,798, 127.341, 125.753 (aromatic carbons); δ 59.894, 27.354, 23.433, 22.360, 20.465, 16.428 (aliphatic carbons). ^{31}P NMR ($CDCl_3$, 400 MHz): δ 32.686 (s, 1P). UV−vis in $CHCl_3$ [λ_{max}, nm (ε, $M^{-1}cm^{-1}$)]: 569 (14,919); 532 (12,240). HRMS: *m/z* $[M + Na]^+$ calculated for $C_{29}H_{27}NaO_7P$ 541.1387; found 541.1394.

1-[3-(Diethyl phosphonyl)propyl]KuQuinone (**5**). Purple powder (145.21 mg, 0.3 mmol, 10% yield) mp 204–206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.281 (t, *J* = 7.08 Hz, 6H), δ 1.862–2.053 (m, 4H), δ 3.486 (t, *J* = 7.09, 2H), δ 3.991–4.152 (m, 4H), δ 7.628–7.780 (m, 4H), δ 8.120–8.238 (m, 4H), δ 18.150 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 180.876 and 178.090 (C=O); δ 135.664, 135.133, 133.125, 132.638, 131.836, 127,827, 127.344, 125.515 (aromatic carbons); δ 61.437, 26.312, 24.920, 22.263, 16.524 (aliphatic carbons). ^{31}P NMR ($CDCl_3$, 400 MHz): δ 32.337 (s, 1P). UV−vis in $CHCl_3$ [λ_{max}, nm (ε, $M^{-1}cm^{-1}$)]: 567 (14,851); 529 (11,351). HRMS: *m/z* $[M + Na]^+$ calculated for $C_{28}H_{25}NaO_7P$ 527.1230; found 527.1234.

1-[2-(Diethyl phosphonyl)ethyl]KuQuinone (**6**). Purple powder (152.60 mg, 0.3 mmol, 11% yield) mp 220–222 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.423 (t, *J* = 7.00 Hz, 6H), δ 2.102–2.224 (m, 2H), δ 3.602–3.702 (m, 2H), δ 4.157–4.320 (m, 4H), δ 7.645–7.764 (m, 4H), δ 8.163–8.228 (m, 4H), δ 18.147 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 30.835 (s, 1P). δ 180.888 and 178.309 (C=O); δ 135.613, 135.183, 133.164, 132.404, 131.861, 127,925, 127.363, 125.434 (aromatic carbons); δ 61.827, 24.772, 20.637, 16.621 (aliphatic carbons). ^{31}P NMR ($CDCl_3$, 400 MHz). UV−vis in $CHCl_3$ [λ_{max}, nm (ε, $M^{-1}cm^{-1}$)]: 563 (14,544); 526 (11,367). HRMS: *m/z* $[M + Na]^+$ calculated for $C_{27}H_{23}NaO_7P$ 513.1074; found 513.1069.

2.3. Hydrolysis of Diethyl Phosphonate KuQuinone Derivatives

Glassware was flamed under nitrogen flow before use. A total of 0.1 mmol of diethyl phosphonate KuQuinone and 5 mmol of NaI were mixed in 16 mL of dry acetonitrile: chloroform solution (1:1 *v/v*) until a deep purple solution was observed. Subsequently, 5 mmol of bromotrimethylsilane were added and the mixture was stirred for 4 h, at 40 °C, under an inert atmosphere. The crude was then diluted with 15 mL of chloroform, filtered and concentrated under vacuum, obtaining the bis-(trimethylsilyl)phosphonate intermediate, as a brownish oil. The silyl ester was converted to the corresponding acid by hydrolysis with 30 mL of methanol, under magnetic stirring, within an hour. Phosphonic acid, in form of a purple precipitate, was isolated by vacuum filtration, washed with diethyl ether and characterized by ^{1}H and ^{31}P NMR in DMSO-d_6, IR and HRMS (see Supplementary Materials).

1-[4-(Dihydroxyphosphonyl)butyl]KuQuinone (**7**). Purple powder (44.83 mg, 0.097 mmol, 97% yield) mp > 250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.493–1.617 (m, 6H), δ 7.529–7.697 (m, 4H), δ 7.891–8.035 (m, 4H). ^{31}P NMR (DMSO-d_6, 400 MHz): δ 26.653 (s, 1P). HRMS: *m/z* $[M - H]^-$ calculated for $C_{25}H_{18}O_7P$ 461.0796; found 461.0786.

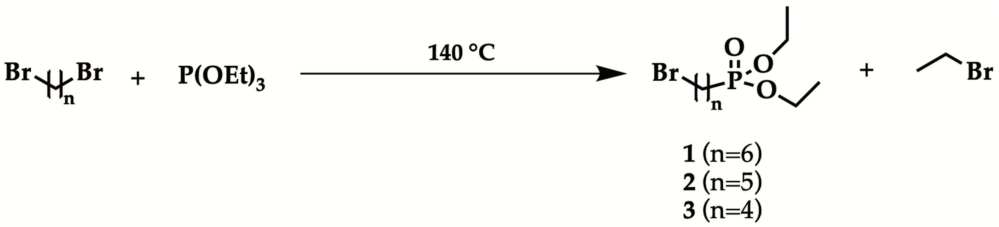
1-[3-(Dihydroxyphosphonyl)propyl]KuQuinone (**8**). Purple powder (42.56 mg, 0.095 mmol, 95% yield) mp > 250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.493–1.617 (m, 6H), δ 7.529–7.697 (m, 4H), δ 7.891–8.035 (m, 4H). ^{31}P NMR (DMSO-d_6, 400 MHz): δ 26.534 (s, 1P). HRMS: *m/z* $[M - H]^-$ calculated for $C_{24}H_{16}O_7P$ 447.0639; found 447.0625.

1-[2-(Dihydroxyphosphonyl)ethyl]KuQuinone (**9**). Purple powder (43.38 mg, 0.1 mmol, 100% yield) mp > 250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.692–1.847 (m, 2H), δ 7.509–7.677 (m, 4H), δ 7.921–8.045 (m, 4H). ^{31}P NMR (DMSO-d_6, 400 MHz): δ 26.483 (s, 1P). HRMS: *m/z* $[M - H]^-$ calculated for $C_{23}H_{14}O_7P$ 433.0483; found 433.0478.

3. Results and Discussion

Synthesis of diethyl ω-bromoalkylphosphonates has been explored, in order to optimize Arbuzov reaction conditions [41]. Previous works on phosphonate esters monofunctionalization of dibromoalkanes highlighted that a high excess (from 3 to 20 equivalents) of substrate was required to avoid di-substitution reaction [42–46]. In this study, 1,4-dibromobutane, 1,5-dibromopentane and 1,6-dibromohexane have been selected as substrates to perform Arbuzov synthesis. The reactions have been carried out solventless, at 140 °C, using equimolar amount of triethyl phosphite with respect to the substrate, in order to improve process sustainability, thus reducing waste (Scheme 2). The reactions were monitored by GC-MS. Products isolation has been performed by fractional distillation under vacuum. The results are reported in Table 1.

Solvent-free Arbuzov reaction between triethyl phosphite and 1,4-dibromobutane, in equimolar amount, was performed following a previously reported procedure (Table 1, Entry 1) [49,50]. However, in the adopted conditions, GC-MS analysis revealed that diethyl ethylphosphonate was the main product. As a matter of fact, during the Arbuzov reaction, bromoethane is formed as a byproduct (Scheme 3a) and it readily reacted with triethyl phosphite, leading to diethyl ethylphosphonate, in a high amount (Scheme 3b). Only traces of diethyl 4-bromobutylphosphonate (**3**) and the di-substituted product were detected.

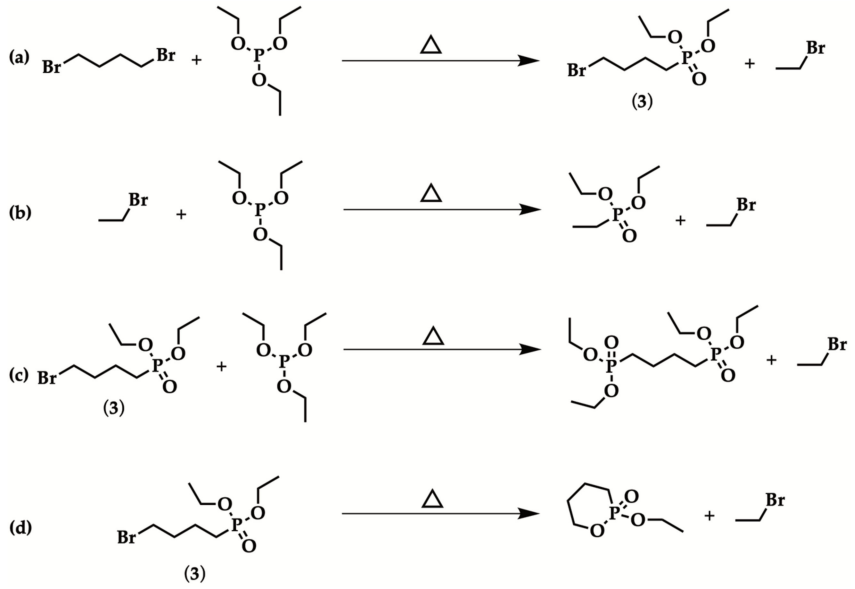


Scheme 2. Diethyl ω-bromoalkylphosphonates synthesis.

Table 1. Optimization of reaction conditions for the synthesis of diethyl ω-bromoalkylphosphonate. Conditions: α,ω-dibromoalkane (75 mmol): triethyl phosphite (75 mmol); T = 140 °C.

Entry	$Br(CH_2)_nBr$	Reaction Time	Isolated Yield (%)
1	n = 4	12 h	-
2 [a]	n = 4	12 h	-
3 [b]	n = 4	5 min	-
4 [a,c]	n = 6	90 min	5
5 [a,d]	n = 6	3 h	40
6 [a,d]	n = 5	3 h	40
7 [a,d]	n = 4	3 h	20 [e]

[a] Bromoethane distilled during the reaction. [b] microwave irradiation at 150 W. [c] triethyl phosphite dropwise addition within 30 min. [d] triethyl phosphite dropwise addition within 2 h. [e] isolated by column chromatography (ethyl acetate/Al_2O_3).



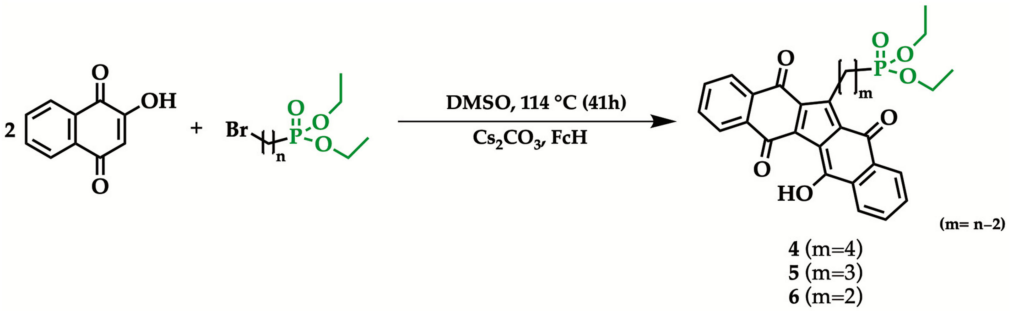
Scheme 3. (**a**): Arbuzov reaction for the synthesis of **3**; (**b**–**d**) concurrent processes: diethyl ethylphosphonate generation (**b**), di-phosphonation (**c**) and cyclization (**d**).

To improve the experimental conditions, the same reaction was performed while distilling the generated bromoethane (Table 1, Entry 2); this was also useful to monitor the progress of the reaction. Product analysis pointed out that di-substitution reaction (Scheme 3c) and intramolecular cyclization of **3** (Scheme 3d) occurred, thus forming a stable six-membered heterocycle [44]. Additionally, in this case, only traces of the mono-substituted product were detected. Microwave irradiation was attempted [51,52], using equimolar reactants ratio, and an irradiation power of 150 W for 5 min; however, the reaction lacked in selectivity (Table 1, Entry 3).

In order to avoid cyclization reaction to a stable 6-membered ring, 1,6-dibromohexane was used as the substrate, experimenting with the synthesis of diethyl 6-bromohexylphosphonate

(**1**). Moreover, to promote mono-substitution reaction, triethyl phosphite was added dropwise in 30 minutes [44]. However, in such conditions, di-phosphonation process was again the predominant one, while **1** was isolated in very low yield (Table 1, Entry 4). It is noteworthy that slower triethyl phosphite addition (in about two hours) allowed to achieve **1**, with high selectivity and satisfactory yield (40%, Table 1 Entry 5). Thus, such an optimized procedure was employed to synthesize diethyl 5-bromopentylphosphonate (**2**) (40% yield, Table 1, Entry 6) and **3** (20% yield, Table 1, Entry 7), in acceptable yields. Nevertheless, in the case of **3,** it was necessary to further purify the product, since the intramolecular cyclization side-reaction occurred (Scheme 3d).

The obtained diethyl ω-bromoalkylphosphonates (**1**–**3**) were then employed as reagents to synthesize new KuQuinone derivatives (**4**–**6**), bearing a diethyl phosphonate terminal group. KuQ synthesis was executed following the previously reported one-pot procedure [32], in which 2-hydroxy-1,4-naphthoquinone is reacted with an excess of an appropriate alkyl bromide, in the presence of a base and ferrocene (FcH) in catalytic amount (Scheme 4). Overall, three KuQuinone phosphonate derivatives, differing in side-chain length, were synthesized with yields (7 to 11%, Table 2) that compare well with that of other KuQuinone analogues [29,30,33].



Scheme 4. Synthesis of KuQuinone phosphonate esters **4**–**6**.

Table 2. Synthesis of KuQuinone diethyl phosphonate derivatives. Reaction conditions: 5.75 mmol of 2-hydroxy-1,4-naphthoquinone, 12 mmol of bromoalkylphosphonate, 8 mmol of Cs_2CO_3, 0.33 mmol of FcH, in 22 mL of DMSO, at 114 °C, for 41 h.

Reagent	Product	Yield (%)
1	**4**	11
2	**5**	10
3	**6**	7

To achieve KuQuinone phosphonic acids, KuQ-phosphonate esters hydrolysis was performed [53]. Reaction with 48% hydrobromic acid, at reflux, was first studied [54]. Despite the harsh conditions adopted, the phosphonic acid was not obtained. Acid hydrolysis was then performed with 0.5 M of hydrochloric acid, under microwave irradiation, with no results, likely because of the poor KuQuinone solubility in water [55]. Additionally, hydrolysis with bromotrimethylsilane (TMSBr) [56–58] was not successful. At this point, considering a seminal work by Morita [59], KuQuinone phosphonate ester hydrolysis has been performed with TMSBr in the presence of NaI (Table 3). In fact, because of the higher nucleophilicity of the iodide compared to other halides, trimethylsilyl intermediate formation is favored. Therefore, the reaction was carried out, dissolving 0.1 mmol of KuQ phosphonate ester in dry chloroform/acetonitrile (1:1), with a large excess of NaI and TMSBr (5 mmol), under N_2 atmosphere, at 40 °C. After 4 h, the generated intermediate (trimethylsililphosphonate ester) was converted to the corresponding acid by methanolysis at room temperature (Scheme 5). The reaction was checked with TLC and interrupted when the ester band disappeared. In these conditions, almost quantitative conversions of KuQuinone phosphonate esters **4**–**6** to phosphonic acids **7**–**9** were achieved.

Table 3. Hydrolysis of KuQuinone phosphonate esters. Conditions: 0.1 mmol of diethyl phosphonate KuQuinone, 5 mmol of NaI, 5 mmol of bromotrimethylsilane, in 16 mL of dry CH_3CN: $CHCl_3$ (1: 1), at 40 °C, 4 h, under N_2 atmosphere. Then, silyl ester hydrolysis was performed with 30 mL of methanol.

Reagent	Product	Yield (%)
4	**7**	100
5	**8**	95
6	**9**	97

Scheme 5. Hydrolysis of KuQuinone phosphonate esters.

Note that KuQ phosphonate esters were highly soluble in all conventional organic solvents. Conversely, phosphonic acid derivatives were insoluble in apolar organic solvents and they showed only poor solubility in methanol and dimethyl sulfoxide. Solubility was significantly enhanced in water in the presence of a base, which allows phosphonic acid deprotonation and dissolution [60].

Therefore, KuQ phosphonic acid characterization was performed with NMR in DMSO-d_6. ^{1}H NMR spectra were characterized by a large and intense peak at about 3.4 ppm, which is typical of organic phosphonic acids (Figures S13, S17 and S21), being attributable to the hydroxyl groups of PA moiety, as well as to water traces [61]. Such intense peak overlaps with some KuQ aliphatic signals in the ^{1}H NMR spectrum of the products, that are also broad and not well-resolved, likely because of the compound's low solubility in DMSO. Conversely, KuQuinones characteristic peaks were clearly observed in the aromatic region of the spectra. On the other hand, ^{31}P NMR analysis unambiguously confirmed the effectiveness of the hydrolysis [62]. In fact, by comparing the ^{31}P NMR spectra in DMSO-d_6 of the phosphonate esters with the corresponding phosphonic acids (Figure 1), a shift of about 5 ppm fields was observed, according to literature data [62].

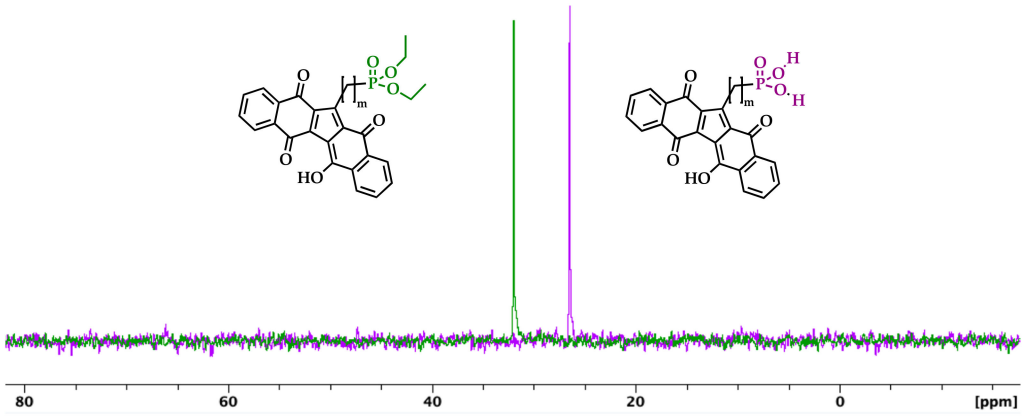


Figure 1. ^{31}P NMR spectra of **8** (purple) and **5** (green) in DMSO-d_6.

4. Conclusions

In this paper, Arbuzov reaction for the synthesis of ω-bromoalkylphosphonates has been optimized. In fact, the main drawback in published synthetic procedures of ω-bromoalkylphosphonates was the large excess of the substrate, i.e., a α,ω-dibromoalkane, in order to prevent the di-substitution side process. Here, we report that slow dropwise addition of triethyl phosphite to 1 equivalent a α,ω-dibromoalkane leads to the desired product, with satisfactory yields. Importantly, reactions occur at 140 °C, while distilling bromoethane, that is formed as the first byproduct. Note that reactions performed using 1,4-dibromobutane as the substrate lead to a high amount of the cyclization side-product, thus lowering yields.

The optimized reaction conditions allow to significantly reduce the amount of the substrate, consequently reducing α,ω-dibromoalkane waste. Moreover, substrate scope can be further extended to obtain a library of ω-bromoalkylphosphonates.

The synthesized ω-bromoalkylphosphonates have been experimented in the synthesis of KuQuinone diethyl phosphonate derivatives, following a previously reported procedure. Hence, novel KuQuinone phosphonate esters have been synthesized and their hydrolysis with TMSBr and NaI allowed to access new KuQuinone phosphonic acids, with almost quantitative yields.

The introduction of a phosphonate ester in KuQ side chain sensibly enhances the solubility of such compounds in organic solvents. More importantly, a phosphonic acid functionality is strategic to exploit KuQuinones in different applications, such as in photo(electro)chemical devices anchored on suitable metal oxide nanoparticles, as well as in photocatalysis and biomedical applications.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/org2020010/s1, Figure S1: ^{1}H NMR spectrum of **1** in $CDCl_3$; Figure S2: ^{31}P NMR spectrum of **1** in $CDCl_3$; Figure S3: Mass spectrum of **1**; Figure S4: ^{1}H NMR spectrum of **2** in $CDCl_3$; Figure S5: ^{31}P NMR spectrum of **2** in $CDCl_3$; Figure S6: Mass spectrum of **2**; Figure S7: ^{1}H NMR spectrum of **3** in $CDCl_3$; Figure S8: ^{31}P NMR spectrum of **3** in $CDCl_3$; Figure S9: Mass spectrum of **3**; Figure S10: ^{1}H NMR spectrum of **4** in $CDCl_3$; Figure S11: ^{13}C NMR spectrum of **4** in $CDCl_3$; Figure S12: ^{31}P NMR spectrum of **4** in $CDCl_3$; Figure S13: HRMS spectrum of **4**; Figure S14: UV-vis spectrum of **4**; Figure S15: ATR-IR spectrum of **4**; Figure S16: ^{1}H NMR spectrum of **7** in DMSO-d_6; Figure S17: ^{31}P NMR spectrum of **7** in DMSO-d_6; Figure S18: HRMS of **7**; Figure S19: ATR-IR spectrum of **7**; Figure S20: ^{1}H NMR spectrum of **5** in $CDCl_3$; Figure S21: ^{13}C NMR spectrum of **5** in $CDCl_3$; Figure S22: ^{31}P NMR spectrum of **5** in $CDCl_3$; Figure S23: HRMS spectrum of **5**; Figure S24: UV-vis spectrum of **5** in $CHCl_3$; Figure S25: ATR-IR spectrum of **5**; Figure S26: ^{1}H NMR spectrum of **8** in DMSO-d_6; Figure S27: ^{31}P NMR spectrum of **8** in DMSO-d_6; Figure S28: HRMS spectrum of **8**; Figure S29: ATR-IR spectrum of **8**; Figure S30: ^{1}H NMR spectrum of **6** in $CDCl_3$; Figure S31: ^{13}C NMR spectrum of **6** in $CDCl_3$; Figure S32: ^{31}P NMR spectrum of **6** in $CDCl_3$; Figure S33: HRMS spectrum of **6**; Figure S34: UV-vis spectrum of **6** in $CHCl_3$; Figure S35: ATR-IR spectrum of **6**; Figure S36: ^{1}H NMR spectrum of **9** in DMSO-d_6; Figure S37: ^{31}P NMR spectrum of **9** in DMSO-d_6; Figure S38: HRMS spectrum of **9**; Figure S39: ATR-IR spectrum of **9**.

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