Heteroatom Chemistry
Volume 20, Number 6, 2009

# Microwave Michaelis–Becker Synthesis of Diethyl Phosphonates, Tetraethyl Diphosphonates, and Their Total or Partial Dealkylation

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*Received 14 April 2009; revised 16 June 2009*

ABSTRACT: *Diethyl phosphonates and tetraethyl alkyldiphosphonates were efficiently and rapidly prepared via the Michaelis–Becker reaction, under microwave irradiation. These compounds were then hydrolyzed to phosphonic and diphosphonic acids or selectively monodealkylated to give monoesters of phosphonic acids and symmetrical diethyl esters of diphosphonic acids. These reactions were also achieved rapidly in satisfactory yields with microwave methodology. This methodology was applied with success to the functionalization of a polymer resin.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:369–377, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20561

## *INTRODUCTION*

Among organophosphorus compounds, phosphonic acids (or phosphonate) have generated considerable synthetic interest for their numerous uses. Phosphonic analogues of naturally occurring phosphates or carboxylic acids have attracted attention due to their antibacterial, antiviral, antibiotic, pesticidal, and enzyme inhibitory properties [1–5]. Moreover, molecules containing phosphonate moiety have elicited many interest for their chelating properties with applications in imaging, catalysis, and ion exchange [6,7]. Finally, phosphonate containing polymers have been widely studied as fire retardant, promoters for paints and adhesives, as ion exchanger, or in extraction systems [8–13]. Among the methods described for the formation of carbon phosphorus bound Michaelis–Arbuzov [14] and Michaelis–Becker reactions (MA and MB, respectively) represent the easiest and more used synthetic pathways toward the obtaining of phosphonate. Although very efficient methods for reactive and simple substrates, these reactions suffer from some drawbacks (such as length of reaction time, need of high reaction temperatures, and by-products formation) and are sometimes less efficient for unreactive substrates such as fatty alkyl halides [15]. While microwave dielectric heating had been widely exploited in several organic chemistry areas to accelerate and improve reactions yields [16,17], it has not been often applied to phosphorus chemistry. Less than 15 studies were conducted [18–21]. To the best of our knowledge, few studies dealt with the MA reaction [22,23] and none with MB, though these two reactions using or evolving through ionic species are particularly fitted for microwave applications.

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Herein, we propose to study the use of microwave technology for MB reactions especially with unreactive fatty halides or secondary alkylhalides and we showed the interest of such methodology for the diphosphonic compounds synthesis. We, moreover, studied several microwave-assisted solutions for the cleavage of alkyl phosphonates to obtain phosphonic acids or partial esters. We finally applied this methodology to the functionalization of a polymer resin.

## *RESULTS AND DISCUSSION*

We first wanted to apply the microwave technology to relatively unreactive substrates such as 1-bromododecane on which studies with MA reactions have already been conducted using conventional heating with trimethyl or triethyl phosphite [15]. We performed the reaction using the MA or MB methodology in the same conditions (such as same vessel, same quantities, and same stoichiometry) using whether classical oil bath heating or microwave irradiation (Scheme 1).

Using MA methodology, reactions were conducted without solvent, and in both heating modes the reaction media was preheated prior to the alkyl halide addition to avoid formation of methyl or ethylphosphonate. With the MB methodology, we first carried out the reaction in the presence of a solvent, e.g., acetonitrile. The 1-bromododecane was added to a suspension of sodium diethylphosphite in acetonitrile at room temperature and then heated in an oil bath or using microwave. For both methodologies, various experimental conditions were studied: varying temperature, reaction time, irradiation power, and ratio of reagents. The optimal conditions are presented in Table 1. One must note that for each reaction an increase in the reaction time, ratio of reactants, or of irradiation power did not improve yields. The optimal ratio of reactant used was $P(OR)_3/RBr = 2$ in the case of the MA methodology, and $NaP(OEt)_2/R'Br = 1.1$ in the case of the MB methodology. The conversion ratio of dodecylbromide to the desired dialkyl dodecylphosphonate (**1a** or **1b**) was measured by integrating $^1H$ NMR signals corresponding to the two compounds. As described by Pelaprat et al. [15], we integrated the signal corresponding to the proton of terminating methyl on the alkyl chain at 0.86 ppm (noted $h_{CH_3}$) and the signal corresponding to the methylene proton bearing the bromine at 3.4 ppm (noted $h_{CH_2Br}$). The following relation gave the conversion ratio noted X (Eq. (1)):

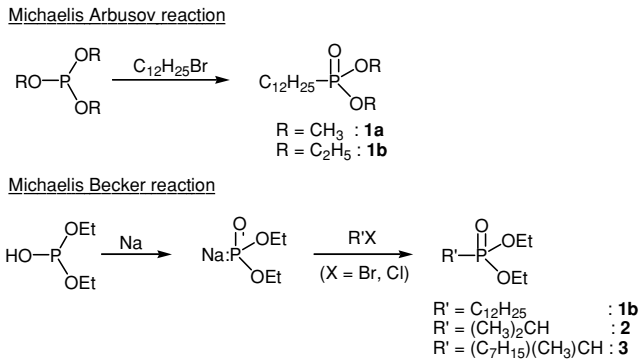
$$\frac{(h_{CH_2Br})/2}{(h_{CH_3})/3} = 1 - X \qquad (1)$$

Using MA methodology, we found that as reported by Villemin et al. [22], microwave irradiation decreases the reaction time, but for 1-bromododecane no considerable enhancement in yield was noted. The reaction still did not go to completion whatever the conditions tried; the reaction with trimethylphosphite remaining more difficult than with diethylphosphite. With microwave dielectric heating, only traces of methyl or ethyl phosphonate were observed; using oil bath, formation of ethylphosphonate was observed and methyl phosphonate was the main product. Finally, when using triethylphosphite compound, **1b** was separated from the unreacted 1-bromododecane on silica gel chromatography and isolated with 55% yield. Using MB methodology the results were remarkable. Not only the time reaction was drastically decreased, but also the conversion ratio was greatly improved. Moreover, olefin by-product was never observed. Nevertheless, the irradiation power must be kept under 150 W because temperature could increase very quickly (within few seconds). One must note that the reaction could even be done without any solvent with the same results. Using the best condition, the diethyldodecylphosphonate **1b** was obtained in

**TABLE 1** Reaction Conditions for the Obtaining of Compound **1a** and **1b** with MA or MB Methodology

| *Method* | *Oil Bath Heating* | | | *Microwave Irradiation* | | |
|---|---|---|---|---|---|---|
| Reaction type | MA | MA | MB | MA | MA | MB |
| Compound | **1a** | **1b** | **1b** | **1a** | **1b** | **1b** |
| Time | 20 h | 04 h | 24 h | 50 min | 40 min | 03 min |
| *X* | 0.08 | 0.66 | 0.20 | 0.20 | 0.62 | 0.98 |
| T | 112 | 160 | 85 | 112[a] | 160[a] | 85[a] |
| Power (W) | – | – | – | 150 | 250 | 120 |

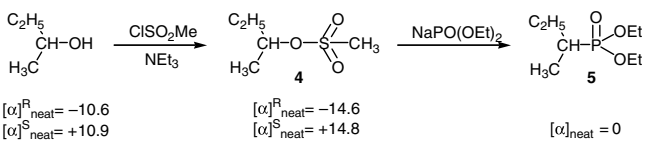
[a]Programmed $T_{max}$.



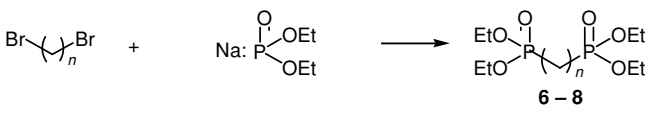

**SCHEME 1**

95% yield after purification by silica gel chromatography. We then tried to reproduce this result with 1-chlorododecane. Chloroalkanes are known to be less reactive in MA or MB reactions than bromoalkanes. Applying MB microwave methodology, the corresponding phosphonate **1b** was obtained with 35% yield (after purification on silica gel chromatography) within 15 min. This was an appreciable yield, because it was higher than those obtained with 1-bromododecane within 24 h under conventional heating.

In a second step, we tried to evaluate whether the MB reaction using microwave methodology was possible with secondary halogenoalkane. We choose 2-bromopropane and 2-bromononane as substrates. The reaction was carried out using the following optimized conditions: 150 W, 40 min. The dialkyl phosphonates **2** and **3** were obtained with 30% yield after purification on silica gel column chromatography. As the reaction did not go to completion, we checked by $^1$H NMR in the reaction media that formation of nonene by-product did not occurred using bromononane. Only unreacted starting material remained. We furthermore tried to study the mechanism of our reaction with secondary substrates. In the literature, there have been several kinetic investigations of the Arbuzov reaction [14], but there are only few reports on the Michaelis–Becker reaction mechanism [24]. It seems well established to undergo through an SN2 mechanism and was proved in some conditions [25]. Using microwave, the influence of solvent on the reaction yield was consistent with the SN2 mechanism. Use of DMF slightly increased the speed of the reaction (yield of phosphonate **2** was increased for the same reaction time), whereas use of THF decreased it (data not shown). To further prove the SN2 mechanism, we carried out reactions with both enantiomerically pure R and S *sec*-butyl methylsulfonate and we measured specific optical rotation for the obtained phosphonate products (Scheme 2). Unfortunately, racemization occurred. Nevertheless the reaction did not evolved through an SN1 type mechanism as using *iso*-butyl methylsulfonate no rearrangement product was observed. So this result could be explained by the possibility of attack on the carbon–halogen bond with retention of configuration due to the apical attack. This phenomenon exists for nucleophile able of expanding their valence shells such as phosphorus species [26].




**SCHEME 2**




**SCHEME 3**

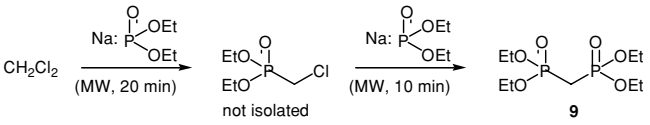
In a third part of this work, we wanted to evaluate this methodology of the synthesis of diphosphophosphonate. Diphosphonic acids (and diphosphonates) have numerous applications ranging from the simplest one, tetraethylmethylene diphosphonate that is an useful intermediate for the synthesis of bioactive compound, to longer one ($n = 3$–12) which could have several applications, such as metals extraction, obtaining of porous materials, and so on [27–32]. The preparation of these compounds has already been reported for short alkyl chains using the Arbuzov reaction, but appreciable yields are needed for the use of triethylphosphite excess and long-time reactions [29,33]. We therefore applied the conditions developed for the MB reaction from bromododecane to several dihalogeno-alkanes (Scheme 3).

The reactions were done in the same conditions (such as same vessel, same quantities, and same stoichiometry) using the conventional method: oil bath heating in refluxing acetonitrile or using microwave irradiation at 100 W.

For compounds **6–8**, we showed that at least 2 h was required by thermal heating for almost completion of reactions in contrast with microwave dielectric heating where only 2–3 min was sufficient (see Table 2). The diphosphonates were then purified by silica gel column chromatography. The most impressive result was the synthesis of tetraethyl methylenediphosphonate **9** from sodium diethyl phosphite and dichloromethane (Scheme 4): The previously described method [34] implies at least a

**TABLE 2** Comparison of the MB Conditions for Obtaining of Compounds **6–8**

| | | | *Oil Bath Heating* | | *Microwave Irradiation* | |
|---|---|---|---|---|---|---|
| *Compound* | *X* | *n* | *Time (h)* | *Yield (%)* | *Time (min)* | *Yield (%)* |
| **6** | Br | 6 | 1.5 | 85 | 2 | 96 |
| **7** | Br | 10 | 2 | 90 | 3 | 90 |
| **8** | Br | 12 | 2 | 95 | 3 | 95 |




SCHEME 4

1-month stirring time to obtain a 50% yield, whereas using microwave the same results were achieved within 30 min.

The reaction was carried out in two steps when using microwave technology. A first equivalent of sodium phosphite was irradiated for 20 min in dichloromethane until no sodium phosphite remained in the mixture and then, after evaporation of the dichloromethane, a second equivalent of sodium phosphite was added and irradiated for 10 min. The tetraethyl methylenediphosphonate **9** was separated from the diethyl chloromethylphosphite by distillation under reduced pressure and was obtained with a yield of 50%.

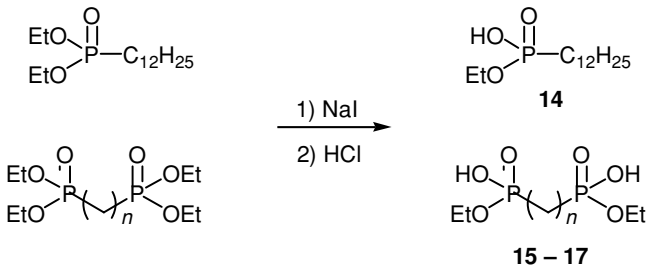
Mineral acid hydrolysis of alkyl phosphonates represents a more general pathway toward obtaining phosphonic acid(s) [35]. We, therefore, tried to apply microwave irradiation to this reaction. Unfortunately, although water is described as one of the best solvent for microwave reaction, we have not been able to conclude whether there was any sensible improvement in the reaction time. So we turned toward the alternative mild methods employing silylating agents [36,37]. It was already demonstrated that using trimethylsilylbromide the cleavage of phosphonates esters proceeds faster under microwave conditions without compromising product yields [38]. We applied the described conditions to our mono- or diphosphonates with success. We also decided to evaluate the other silylating solution often used and less expensive: the mixture of trimethylsilylchloride and sodium iodide (Scheme 5) [37].

The reaction was carried out in acetonitrile for all our compounds and followed by $^{31}P\{^{1}H\}$ NMR. The $^{31}P\{^{1}H\}$ NMR spectrum showed the apparition of a new peak around 26 ppm corresponding to the silylated intermediate; the end of the reaction corresponds to the total disappearance of the initial peak around 32 ppm. After a methanolysis step, conversions of alkyl phosphonates into phosphonic acids were found to be quantitative. Reactions were completed within 2 min using bromotrimethylsilane or the mixture of trimethylsilylchloride and sodium iodide. But in the latter case, the purification was sometimes tedious that explains why we had lower products yields.

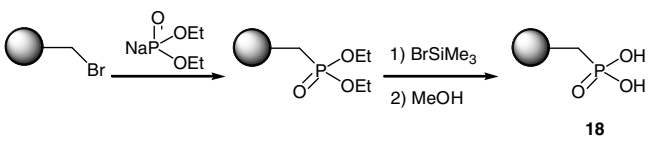
We, then, evaluated the microwave synthesis of partial phosphonic esters of our phosphonate and diphosphonate compounds. The obtaining of monoalkyl esters of alkyl phosphonates could be of great interest for several applications (biological or extraction) [32,39–41]. Besides beneficial application, use of monoalkyl alkylphosphonate in the identification of phosphorus chemical warfare agents is noteworthy [42]. Apart from the use of thiolates [43], sodium iodide is the usual reactant to monodealkylate, a phosphonate, and could even be used on diphosphonate to realize symmetric monodealkylation [44]. Reactions were performed in methanol under microwave irradiation to give, after acidification, ethyl dodecylphosphonic acid **14** and symmetrically substituted diethyl alkyldiphosphonic acids **15–17** (Scheme 6). Good yields in isolated products (60%–75%) were obtained in less than 30 min reaction, whereas on conventional heating similar reaction took several hours for the same results [44].

Finally, we applied this methodology to the functionalization of a polymer resin. We choose a NovaSyn® TG bromo resin: a composite of low cross-linked polystyrene and 3000–4000 MW polyethylene glycol in which the ends of the PEG chains have been bromofunctionalized (see Scheme 7). It was treated by an excess of sodium diethylphosphonate in acetonitrile under microwave irradiation (70 W, 4 min). The cleavage of the esters was achieved with trimethylsilylbromide using microwave activation. The functionalization was qualitatively assessed by staining resin beads with phosphomolybdenic acid


SCHEME 5




SCHEME 6

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SCHEME 7

and was qualitatively calculated by conductometric and acidic titration methods. Loading in phosphinic acids functions was found to be equal to the loading in brominated functions as provided by the supplier.

## *CONCLUSION*

In conclusion, we propose herein an efficient and rapid method enabling the synthesis of phosphonate or diphosphonate from various alkylhalides. This method was based on development of the Michaelis–Becker reaction under microwave irradiation. We showed that phosphonates or diphosphonates were obtained with better yields and in less time than when using classical heating technology. No olefin products were produced during these reactions. Moreover, this methodology permits the use of less reactive fatty halides or secondary halides substrates. The reaction mechanism under microwave irradiation was studied with secondary substrates. Evidences of the SN2-type mechanism were found, but racemization occurred probably due to an apical attack. Microwave technology was further used to hydrolyze phosphonic esters. As already described in the literature, use of bromotrimethylsilane followed by methanolysis enables the complete, rapid, and efficient hydrolysis of phosphonic esters. We showed that the inexpensive mixture of chlorotrimethylsilane/sodium iodide could afford the same results. Furthermore, we showed that under microwave irradiation sodium iodide partially hydrolyzed phosphonic ester functions. Finally, we successfully applied this methodology to functionalization of a polymer resin.

## *EXPERIMENTAL*

### *General*

All experiments under microwave irradiations were run in open vessel, using a CEM-Discover monomode microwave apparatus. The irradiation was done at a fixed power for 2–5 min irradiation followed by return at room temperature. This ensured no local heating especially with heterogeneous media such as with sodium phosphonate and the polymer resin. All reagents were commercial grade and were used without purification unless otherwise noted. Trialkyl and dialkylphosphites were distilled before use. All solvents were distilled before use. Dichloromethane and acetonitrile were distilled from $P_2O_5$. Methanol was distilled from sodium. The NovaSyn® TG bromo was bought from Novabiochem (Merck-chemicals, Fontenay-sous-bois, France). NMR spectra were recorded with a VARIAN Unity Inova 500 MHz ($^{13}$C: 125.9, $^{1}$H: 500.6 MHz, $^{31}$P: 200.7 MHz) or a VARIAN Gemini 200 MHZ ($^{13}$C: 50.3 MHz, $^{1}$H: 200 MHz, $^{31}$P: 80.9 MHz) spectrometer in $CDCl_3$or $CD_3OD$. Chemical shifts ($\delta$) are given in ppm. The solvent peak was used as a reference for $^{1}$H NMR and $^{13}$C NMR. The values are, respectively, 7.26 and 77.2 ppm for $CDCl_3$, 3.31 and 49.0 ppm for $CD_3OD$. $^{31}$P spectra were recorded with phosphoric acid (85%) as external reference. The IR spectra were recorded using a Nicolet FTIR 380 spectrometer. The mass spectra were run on a MALDI–TOF mass spectrometer (Biflex IV, Bruker Daltonique) with 2,5-dihydroxybenzoic acid as matrix. Optical rotations were measured on a 314 Perkin–Elmer polarimeter. All melting points were recorded using a Stuart SMP3 melting point apparatus and are uncorrected.

### *General Procedure for the Conventional and the Microwave Arbuzov Synthesis of Dialkyl Dodecylphosphonates (***1a–1b***)*

The trialkylphosphites (40 mmol) were first heated at approximately 100°C, then dodecylbromide was added in an appropriate ratio. The mixture was then heated at 160°C (triethyl phosphite) or 112°C (trimethyl phosphite) for 4–20 h. Using microwave, the trialkylphosphites were irradiated until the temperature reached 100°C, dodecylbromide (20 mmol) was added, and the mixture was irradiated again for 40–50 min. All experiments were run under argon atmosphere. The evolution of the reaction was monitored by $^{31}$P. The excess of trialkylphosphite was evaporated under reduced pressure. The desired phosphonate was separated from the unreacted bromide by flash chromatography. The bromide was eluted with hexane/ethyl acetate (90/10), then the phosphonate was recovered with pure ethyl acetate.

### *General Procedure for the Mickaelis–Becker Synthesis of Diethyl Phosphonates (***1b, 2, 3***) and Tetraethyl Diphosphonates (***6–8***)*

A solution of diethylphosphite (6.1 g, 44 mmol) in acetonitrile (15 mL) was degassed with argon under magnetic stirring for approximately 10 min. Metallic sodium (1.1 g, 44 mmol) was added to the solution by small portions at 0°C. The solution was stirred until

the sodium completely dissolved; this required only few minutes. The alkyl bromide or dibromide (40 or 20 mmol) was then added. A reflux condenser was then placed, and the setup was closed with a calcium chloride tube. The reaction mixture was then irradiated or heated according to the microwave or classic method. The solvent was then evaporated, and $H_2O$ (50 mL) and diethyl ether (150 mL) were added to the residue. The crude product was extracted, and the organic layer was washed, respectively, with NaOH (1 M) (2 × 50 mL), HCl (1 M) (2 × 50 mL), and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated.

In the case of compound (**1b, 2, 3**), the crude yellow oils were purified by column chromatography over a silica column using, first *n*-hexane gradually enriched with ethyl acetate then the desired products were recovered by methanol (5%) in ethyl acetate.

*Diethyldodecylphosphonate (***1b***).* Classical heating: 4 h, 160°C, yield: 60% (the MA reaction); 24 h, 85°C, yield: 20% (the MB reaction). Microwave: 40 min, 250 W, yield 55% (the MA reaction); 03 min, 120 W, yield 95% (the MB reaction). $^{31}P\{^1H\}$ NMR ($CDCl_3$ 80.9 MHz, 298 K): 32.0. $^1H$ NMR ($CDCl_3$, 500 MHz, 298 K): 0.81 (t, 3H, $^3J_{H-H}$ = 7.0 Hz, C**H**$_3$(CH$_2$)$_{10}$CH$_2$P), 1.18–1.29 (m, 18H, CH$_3$ (C**H**$_2$)$_9$ CH$_2$CH$_2$P) 1.25 (t, 3H, $^3J_{H-H}$ = 7.0 Hz, C**H**$_3$CH$_2$OP), 1.66 (m, 2H, C**H**$_2$CH$_2$P), 1.75 (m, 2H, C**H**$_2$P), 4.01 (m, 4H, **CH**$_2$OP). $^{13}C$ $\{^1H\}$NMR ($CDCl_3$, 125.9 MHz, 298 K): 14.3 (s, **C**H$_3$(CH$_2$)$_{11}$P), 16.6 (d, $^3J_{C-P}$ = 5.8 Hz, **C**H$_3$CH$_2$OP), 22.4 (d, $^2J_{C-P}$ = 5.8 Hz, C**H**$_2$CH$_2$P), 22.8 (s, CH$_3$**C**H$_2$(CH$_2$)$_{10}$P), 25.7 (d, $^1J_{C-P}$ = 140.6 Hz, **C**H$_2$P), 29.2–29.4–29.5–29.7–29.8–29.9 (s, CH$_3$CH$_2$CH$_2$(**C**H$_2$)$_6$CH$_2$CH$_2$CH$_2$P), 30.7 (d,$^3J_{C-P}$ = 15.6 Hz, **C**H$_2$CH$_2$CH$_2$P), 32.0 (s, CH$_3$CH$_2$ **C**H$_2$ (CH$_2$)$_9$ P), 61.6 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_2$OP). *m/z* ($MH^+$): 307.17, Calcd: 307.23.

*Diethylisopropylphosphonate (***2***).* Microwave: 10 × 2 min, 100 W, yield: 30%. $^{31}P$ $\{^1H\}$ NMR ($CDCl_3$, 80.9 MHz, 298 K): 35.8, $^1H$ NMR ($CDCl_3$, 500 MHz, 298 K): 1.11 (dd, 6H, $^3J_{H-H}$ = 6.5 Hz, $^3J_{H-P}$ = 11.7 Hz C**H**$_3$CH-P), 1.25 (t, 6H, $^3J_{H-H}$ = 6.9 Hz, C**H**$_3$CH$_2$OP), 4.03 (dd, 4H, $^3J_{H-H}$ = $^3J_{H-P}$ = 6.5 Hz C**H**$_2$OP). $^{13}$ C $\{^1H\}$NMR ($CDCl_3$, 125.9 MHz, 298 K): 16.1 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_3$CHP), 16.6 (d, $^3J_{C-P}$ = 5.8 Hz, **C**H$_3$CH$_2$OP), 25.8 (d, $^1J_{C-P}$ = 142.6 Hz, **C**HP), 61.7 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_2$OP).

*Diethyl Nonan-2-phosphonate (***3***).* Microwave: 35 min, 100 W, yield: 30% $^{31}P$ $\{^1H\}$ NMR ($CDCl_3$, 80.9 MHz, 298 K): 35.8. $^1H$ NMR ($CDCl_3$, 500 MHz, 298 K): 0.86 (t, 3H, $^3J_{H-H}$ = 6.5 Hz, C**H**$_3$ (CH$_2$)$_6$CHP), 1.13 (dd, 3H, $^3J_{H-H}$ = 6.5 Hz, $^3J_{H-P}$ = 19.0 Hz C**H**$_3$ CH-P), 1.20–1.35 (m, 16H, CH$_3$C**H**$_2$C**H**$_2$(C**H**$_2$)$_2$C**H**$_2$CH$_2$CHP and C**H**$_3$CH$_2$OP), 1.44 (m, 2H, C**H**$_2$CHP), 1.75 (m, 1H, C**H**P), 4.09 (m, 4H, CH$_2$OP). $^{13}C$ $\{^1H\}$ NMR ($CDCl_3$, 125.9 MHz, 298 K): 13.2 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_3$CHP), 14.3 (s, **C**H$_3$ (CH$_2$)$_6$CHP), 16.6 (d, $^3J_{C-P}$ = 5.8 Hz, **C**H$_3$CH$_2$OP), 22.8 (s, CH$_3$ **C**H$_2$(CH$_2$)$_5$CHP), 27.6 (d, $^3J_{C-P}$ = 13.6 Hz, **C**H$_2$CH$_2$CHP), 29.3–29.5 (s, CH$_3$CH$_2$CH$_2$ (**C**H$_2$)$_2$CH$_2$CH$_2$CHP), 30.0 (d, $^2J_{C-P}$ = 3.9 Hz, **C**H$_2$CHP), 30.9 (d,$^1J_{C-P}$ = 140.3 Hz, **C**HP), 32.0 (s, CH$_3$CH$_2$**C**H$_2$ (CH$_2$)$_2$CH$_2$CH$_2$CHP), 61.6 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_2$OP).

*Synthesis of Diethyl Phosphonate (***5***).* This compound was prepared as described above using the mesylate **4** instead of an alkyl bromide. Microwave: 20 min, 100 W: yield: 20% $^{31}P$ $\{^1H\}$ NMR ($CDCl_3$, 80.9 MHz, 298 K): 35.5. $^1H$ NMR ($CDCl_3$, 500 MHz, 298 K): 0.96 (t, 3H, $^3J_{H-H}$ = 7.3 Hz, C**H**$_3$CH$_2$CHP), 1.14 (dd, 3H, $^3J_{H-H}$ = 7.3 Hz, $^3J_{H-P}$ = 11.7 Hz C**H**$_3$CH-P), 1.29 (t, 6H, $^3J_{H-H}$ = 7.3 Hz C**H**$_3$CH$_2$OP), 1.65–1.85 (m, 2H, CH$_3$C**H**$_2$CHP), 4.07 (m, 4H, C**H**$_2$OP). $^{13}C$ $\{^1H\}$NMR ($CDCl_3$, 125.9 MHz, 298 K): 12.2 (d, $^3J_{C-P}$ = 13.7 Hz, **C**H$_3$CH$_2$CHP), 12.8 (d, $^2J_{C-P}$ = 3.9 Hz, C**H**$_3$CHP), 16.7 (d, $^2J_{C-P}$ = 3.9 Hz, **C**H$_3$CH$_2$-OP), 23.2 (d, $^2J_{C-P}$ = 3.9 Hz, CH$_3$**C**H$_2$CHP), 27.6 (d, $^3J_{C-P}$ = 13.6 Hz, **C**H$_2$CH$_2$CHP), 32.0 (d,$^1J_{C-P}$ = 140.6 Hz, **C**HP), 61.5 (d, $^2J_{C-P}$ = 7.8 Hz, **C**H$_2$OP).

*Tetraethyl Hexane-1, 6–diyldiphosphonate (***6***).* Classical heating: 1 h, 30–85°C, yield: 85%. Microwave: 2 min, 100 W, yield: 95%. $^{31}P$ $\{^1H\}$ NMR ($CDCl_3$, 80.9 MHz, 298 K): 32.0. $^1H$ RMN ($CDCl_3$, 500 MHz, 298 K): 1.26 (m, 12H, $^3J_{H-H}$ = 6.7 Hz, CH$_3$), 1.43 (m, 2H, C**H**$_2$CH$_2$CH$_2$P), 1.57 (m, 4H, C**H**$_2$CH$_2$P), 1.66 (m, 4H, C**H**$_2$P), 4.0 (m, 8H, CH$_2$OP). $^{13}C$ $\{^1H\}$ NMR ($CDCl_3$, 125.9 MHz, 298 K): 16.6 (d, $^3J_{C-P}$ = 5.8 Hz, CH$_3$), 22.2 (d, $^2J_{C-P}$ = 5.9 Hz, CH$_2$CH$_2$P), 25.6 (d, $^1J_{C-P}$ = 142.6 Hz, **C**H$_2$P), 31.6 (t, $^3J_{C-P}$ = 15.6 Hz, **C**H$_2$CH$_2$P), 61.5 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_2$OP). *m/z* ($MH^+$): 359.09. Calcd 359.16.

*Tetraethyl Decane-1,10-diyldiphosphonate (***7***).* Classical heating: 2 h, 85°C, yield: 90%. Microwave: 3 min, 100 W, yield: 90%. $^1P$ $\{^1H\}$ NMR ($CDCl_3$, 80.9 MHz, 298 K): 33.0, $^1H$ NMR ($CDCl_3$, 500 MHz, 298 K): 1.20 (m, 10H, C**H**$_2$CH$_2$CH$_2$P), 1.25 (t, 12H, $^3J_{H-H}$ = 7.0 Hz, CH$_3$), 1.49–1.52 (m, 4H, C**H**$_2$CH$_2$P), 1.59–1.66 (m, 4H, CH$_2$P), 4.00 (m, 8H, C**H**$_2$OP). $^{13}C$ $\{^1H\}$ NMR ($CDCl_3$, 125.9 MHz, 298 K): 16.6 (d, $^3J_{C-P}$ = 5.8 Hz, **C**H$_{3)}$, 22.5 (d, $^2J_{C-P}$ = 3.9 Hz, **C**H$_2$CH$_2$P), 25.8 (d, $^1J_{C-P}$ = 140.6 Hz, **C**H$_2$P), 29.17–29.33–29.42–29.56 (s, **C**H$_2$CH$_2$CH$_2$CH$_2$P), 30.7 (d, $^3J_{C-P}$ = 17.6 Hz, C**H**$_2$CH$_2$CH$_2$P), 61.5 (d, $^2J_{C-P}$ = 7.8 Hz, **C**H$_2$OP). *m/z* ($MH^+$): 415.25. Calcd: 415.23.

*Tetraethyl Dodecane-1, 12- diyldiphosphonate (**8**).* Classical heating: 2 h, 85°C, yield: 90%. Microwave: 3 min, 100 W, yield: 90%. $^{31}P$ $\{^1H\}$ NMR ($CDCl_3$, 80.9 MHz, 298 K): 33.6. $^1H$ NMR ($CDCl_3$, 500 MHz, 298 K): 1.24 (s, 12H, C**H**$_2$CH$_2$CH$_2$CH$_2$P), 1.30 (t, 12H, $^3J_{H-H}$ = 7.0 Hz, $CH_3$), 1.31–1.33 (m, 4H, C**H**$_2$ CH$_2$CH$_2$P), 1.51–1.56 (m, 4H, C**H**$_2$CH$_2$P), 1.63–1.71 (m, 4H, C**H**$_2$P), 4.05 (m, 8H, C**H**$_2$OP). $^{13}C$ $\{^1H\}$ NMR ($CDCl_3$, 125.9 MHz, 298 K): 16.6 (d, $^3J_{C-P}$ = 5.8 Hz, $CH_3$), 22.5 (d, $^3J_{C-P}$ = 3.9 Hz, **C**H$_2$CH$_2$P), 25.8 (d, $^1J_{C-P}$ = 140.6 Hz, **C**H$_2$P), 29.2–29.5–29.7 (s, **C**H$_2$CH$_2$CH$_2$CH$_2$P), 30.7 (d, $^3J_{C-P}$ = 17.5 Hz, **C**H$_2$CH$_2$ CH$_2$P), 61.6 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_2$OP). **IR** (KBr) $\nu$/(cm$^{-1}$): 1248 (P=O), 1030 (P–O).

*Synthesis of Tetraethyl Methylenediphosphonate (**9**).* Synthesis of compound **9** was compared to the methodology originally described by Villemin et al. (1 month reaction, yield 50% after distillation). Using microwave irradiation, it was obtained as follows:. An excess of dichloromethane (15 mL) was added to a solution of sodium diethylphosphite (20 mmol) in acetonitrile (15 mL) prepared as described before. A reflux condenser was then placed, the setup closed with a calcium chloride tube. The reaction mixture was then irradiated for a total of 20 min at 100 W. To avoid rapid evaporation of dichloromethane, the irradiation was done in 10 × 2 min runs separated by quick cooling in an ice bath. After evaporation of the unreacted dichloromethane, an equivalent of sodium diethylphosphite (20 mmol) in acetonitrile (15 mL) was added to the reaction mixture. The mixture was then irradiated for 10 min. After evaporation of the solvent, the residue was treated as described for compounds (**6–8**). The crude yellow oil was purified by vacuum distillation to give colorless oil (yield 50%). $^{31}P$ $\{^1H\}$ RMN ($CDCl_3$, 80.9 MHz, 298 K): 19.4. $^1H$ NMR ($CDCl_3$, 200 MHz, 1298 K), 1.30 (t, 12H, $^3J_{H-H}$ = 6.8 Hz, $CH_3$), 2.40 (t, $^3J_{H-P}$ = 21.0 Hz, 2H, C**H**$_2$P), 4.10 (m, 8H, C**H**$_2$OP).

## *Synthesis of Diphosphonic Acids*

*Synthesis of Diphosphonic Acids Using Bromotrimethylsilane.* The compounds are obtained according to the method originally descried by Kishore et al. [38].

*Synthesis of Diphosphonic Acids Using Chlorotrimethylsilane and Sodium Iodide.* Phosphonate (3 g) was dissolved in acetonitrile; this solution was saturated with argon, and 6 equiv. of $ClSiMe_3$ and 6 equiv. of sodium iodide were added (except for obtaining compound **10** 3 equiv was used). A reflux condenser was placed, and the setup was closed with a calcium chloride tube. The reaction mixture was then irradiated at 50 W for 2–3 min. After evaporation of the solvent and the $ClSiMe_3$, the silylated intermediaries were hydrolyzed with methanol by stirring for 10 min (followed by $^{31}P$ NMR). The methanol was evaporated; acetonitrile was added to the residue, the stirring of this solution resulted in the formation of a beige solid. The solid was filtered off, washed several time with cold acetone.

*Dodecylphosphonic acid (**10**).* Aspect: White powder. mp: 96°C. Isolated yield: 80%. $^{31}P$ $\{^1H\}$ NMR ($CD_3OD$, 80.9 MHz, 298 K): 34.0. $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): 0.9 (t, 3H, $^3J_{H-H}$ = 6.7 Hz, C**H**$_3$ (CH$_2$)$_{10}$CH$_2$P), 1.29 (m, 18H, CH$_3$ **(C**H$_2$)$_8$ CH$_2$ CH$_2$CH$_2$P) 1.41(m, 2H, C**H**$_2$CH$_2$CH$_2$P), 1.57–1.71 (m, 4H, C**H**$_2$C**H**$_2$P). $^{13}C\{^1H\}$ NMR ($CD_3OD$, 125.9 MHz, 298 K): 14.5 (s, **C**H$_3$(CH$_2$)$_{11}$P), 23.8 (s, CH$_3$CH$_2$(CH$_2$)$_{10}$P), 24.0 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_2$CH$_2$ P), 28.2 (d, $^1J_{C-P}$ = 138.9 Hz, **C**H$_2$P), 30.4–30.6–30.7–30.9 (s, CH$_3$CH$_2$CH$_2$**(C**H$_2$)$_6$**C**H$_2$CH$_2$CH$_2$P), 31.9 (d,$^3J_{C-P}$ = 15.6 Hz, **C**H$_2$CH$_2$CH$_2$P), 33.2 (s, CH$_3$CH$_2$**C**H$_2$(CH$_2$)$_9$ P), 61.6 (d, $^2J_{C-P}$ = 5.8 Hz, **C**H$_2$OP). *m/z* (MH$^+$): 251.14. Calcd 251.17.

*Hexane-1,6-diyldiphosphonic acid (**11**).* Aspect: White powder. mp: 198°C. Isolated yield: 75%. $^{31}P$ $\{^1H\}$ NMR ($CD_3OD$, 80 MHz, 298 K): 31.0, $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): 1.45 (m, 4H, C**H**$_2$CH$_2$CH$_2$P), 1.60–1.73 (m, 8H, C**H**$_2$C**H**$_2$P). $^{13}C$ $\{^1H\}$ NMR ($CD_3OD$, 125 MHz, 298 K): 23.3 (s, **C**H$_2$CH$_2$P), 28.0 (d, $^1J_{C-P}$ = 138.6 Hz, **C**H$_2$P), 31.3 (d, $^3J_{C-P}$ = 15.6 Hz, **C**H$_2$ CH$_2$CH$_2$P). *m/z* (MH$^+$): 246.97. Calcd 247.14.

*Decane-1,10-diyldiphosphonic acid (**12**).* Aspect: white powder. Mp: 170°C. Isolated Yield: 82%. $^{31}P$ $\{^1H\}$ NMR ($CD_3OD$, 80.9 MHz, 298 K): 31.4. $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): 1.23 (m, 8H,C**H**$_2$CH$_2$CH$_2$CH$_2$P), 1.31–1.33 (m, 4H, C**H**$_2$CH$_2$CH$_2$P), 1.51–1.54 (m, 4H, C**H**$_2$CH$_2$P), 1.56–1.63 (m, 4H, CH$_2$P). $^{13}C$ $\{^1H\}$ NMR ($CD_3OD$, 125.9 MHz, 298 K): 24.0 (d, $^2J_{C-P}$ = 3.9 Hz, **C**H$_2$CH$_2$P), 28.2 (d, $^1J_{C-P}$ = 138.7 Hz, **C**H$_2$P), 30.4–30.6–30.8 (s, **C**H$_2$ CH$_2$CH$_2$CH$_2$P), 31.8 (d, $^3J_{C-P}$ = 17.6 Hz, **C**H$_2$CH$_2$CH$_2$P).

*Dodecane-1,12-diyldiphosphonic acid (**13**).* Aspect: white powder. mp: 172°C. Isolated yield: 90%. $^{31}P$ $\{^1H\}$ NMR ($CD_3OD$, 80.9 MHz, 298 K): 33.4. $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): 1.25 (s, 12H,C**H**$_2$CH$_2$CH$_2$CH$_2$P), 1.33 (m, 4H,C**H**$_2$CH$_2$CH$_2$P), 1.49–1.56 (m, 4H, C**H**$_2$CH$_2$P), 1.55–1.63 (m, 4H, CH$_2$P). $^{13}C$ $\{^1H\}$ NMR ($CD_3OD$, 125.9 MHz, 298 K):

24.0, (d, $^2J_{C-P}$ = 5.8 Hz, **CH2**$CH_2P$), 28.2 (d, $^1J_{C-P}$ = 138.6 Hz, **C**$H_2P$), 30.3–30.6 (s, **C**$H_2CH_2CH_2CH_2P$), 31.8 (d, $^3J_{C-P}$ = 15.6 Hz, **C**$H_2CH_2CH_2P$). IR (KBr) $\nu$/($cm^{-1}$): 2345(OH), 1235 (P=O).

### *Synthesis of Diethyl Diphosphonic Acid Esters (**15–17**)*

Tetraethyl phosphonates (10 mmol) were mixed with sodium iodide (40 mmol), 5 mL of methanol was added, and the reaction mixture was irradiated at 100 W for 30–40 min (by 10 min run followed by cooling to room temperature). 50 mL of diethyl ether was added to separate the unreacted products. The precipitate was then acidified with concentrated HCl. After evaporation to dryness, the desired products were dissolved in chloroform. The formed salts were filtered of, and the solution was evaporated to give a clear yellow powder. The same procedure was used for the monodealkylation of compound **1b**.

*Ethyl Hydrogen Dodecylphosphonate (**14**).* Aspect: thick oil. Isolated yield: 50%. $^{31}P$ $\{^1H\}$ NMR ($CD_3OD$, 80.9 MHz, 298 K): 32.9.$^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): 0.9 (t, 3H, $^3J_{H-H}$ = 7.0 Hz, C**H**$_3(CH_2)_{10}CH_2P$), 1.29–1.34 (m, 19H, $CH_3$(C**H**$_2)_8CH_2CH_2CH_2P$ and C**H**$_3CH_2OP$), 1.41 (m, 2H, C**H**$_2CH_2CH_2P$) 1.67 (m, 2H, C**H**$_2CH_2P$), 1.77 (m, 2H, C**H**$_2P$), 4.09 (m, 2H, C**H**$_2OP$). $^{13}C$ $\{^1H\}$ NMR ($CD_3OD$, 125.9 MHz, 298 K): 14.7 (s, **C**$H_3(CH_2)_{11}P$), 16.9 (d, $^3J_{C-P}$ = 5.8 Hz, **C**$H_3CH_2OP$), 23.6 (d, $^2J_{C-P}$ = 5.8 Hz, **C**$H_2CH_2P$), 23.9 (s, **C**$H_3$**C**$H_2(CH_2)_{10}P$), 26.0 (d, $^1J_{C-P}$ = 141.1 Hz, **C**$H_2P$), 30.4–30.7–30.8–30.9–31.0 (s, $CH_3CH_2CH_2$ **(C**$H_2)_6CH_2CH_2CH_2P$), 30.7 (d,$^3J_{C-P}$ = 15.6 Hz, **C**$H_2CH_2CH_2P$), 33.2 (s, $CH_3CH_2$**C**$H_2$ $(CH_2)_9$ P), 63.1 (d, $^2J_{C-P}$ = 5.8 Hz, **C**$H_2OP$).

*Diethyl Hexane-1,6-diylbis(hydrogen Phosphonate) (**15**).* Aspect: beige powder. mp: 296°C Isolated yield: 60%. $^{31}P$ $\{^1H\}$ NMR ($CD_3OD$, 200 MHz, 298 K): 27.5. $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): 1.23 (t, $^3J_{H-H}$ = 7.5 Hz, 6H, C**H**$_3$), 1.38 (m, 4H, C**H**$_2CH_2CH_2P$), 1.50–1.57 (m, 8H, C**H**$_2$C**H**$_2P$), 3.88 (td, 8H, $^3J_{H-H} \approx {}^3J_{P-H}$ = 7.5 Hz, C**H**$_2OP$). $^{13}C$ $\{^1H\}$ NMR ($CD_3OD$, 500 MHz, 298 K): 17.3 (d, $^3J_{C-P}$ = 5.8 Hz, $CH_3$), 25.0 (d, $^2J_{C-P}$ = 3.9 Hz, **C**$H_2CH_2P$), 28.0 (d, $^1J_{C-P}$ = 135 Hz, **C**$H_2P$), 32.4 (d, $^3J_{C-P}$ = 15.6 Hz, **C**$H_2CH_2CH_2P$**)**, 60.6 (d, $^2J_{C-P}$ = 5.7 Hz, **C**$H_2OP$). *m/z* ($MH^+$): 302.97. Calcd: 303.10.

*Diethyl Decane-1,10-diylbis(hydrogen Phosphonate) (**16**).* Aspect: white powder. mp: 86°C. Isolated yield: 65%. $^{31}P$ $\{^1H\}$ NMR ($CD_3OD$, 80.9 MHz, 298 K): 33.3. $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): 1.30 (m, 6H, $CH_3$), 1.32 (m, 8H, C**H**$_2CH_2$ $CH_2CH_2P$), 1.39–1.42 (m, 4H, C**H**$_2CH_2CH_2P$), 1.54–1.63 (m, 4H, CH2 $CH_2P$), 1.68–1.75 (m, 4H, $CH_2P$), 4.05 (td, 8H, $^3J_{H-H} \approx {}^3J_{P-H}$ = 7.4 Hz, C**H**$_2OP$). $^{13}C$ $\{^1H\}$NMR ($CD_3OD$, 125.9 MHz, 298 K): 16.9 (d, $^3J_{C-P}$ = 5.8 Hz, **C**$H_3$), 23.7 (d, $^2J_{C-P}$ = 3.9 Hz, **C**$H_2CH_2P$), 26.9 (d, $^1J_{C-P}$ = 140.6 Hz, **C**$H_2P$), 30.4–30.6–30.8 (s, **C**$H_2$ $CH_2CH_2CH_2P$), 31.7 (d, $^3J_{C-P}$ = 17.6 Hz, **C**$H_2CH_2$ $CH_2P$), 62.2 (d, $^2J_{C-P}$ = 5.8 Hz, **C**$H_2OP$).

*Diethyl Dodecane-1,12-diylbis(hydrogen Phosphonate) (**17**).* Aspect: white powder. mp: 83°C. Isolated yield: 75%. $^{31}P$ $\{^1H\}$ NMR ($CD_3OD$, 80.9 MHz, 298 K): 35.6. $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): 1.29, (m, 6H, $CH_3$), 1.40 (m, 4H, C**H**$_2CH_2CH_2P$), 1.56–1.58 (m, 4, C**H**$_2CH_2P$), 1.60–1.72 (m, 4, $CH_2$C**H**$_2P$), 4.07, (m, 4H, C**H**$_2OP$). $^{13}C$ $\{^1H\}$ NMR ($CD_3OD$, 125.9 MHz, 298 K): 16.9 (d, $^3J_{C-P}$ = 5.8 Hz, **C**$H_3$), 23.8 (d, $^2J_{C-P}$ = 3.9 Hz, **C**$H_2CH_2P$), 27.0 (d, $^1J_{C-P}$ = 140.6 Hz, **C**$H_2P$), 30.3–30.6–30.7 (s, **C**$H_2$ $CH_2CH_2CH_2P$), 1.7 (d, $^3J_{C-P}$ = 15.6 Hz, **C**$H_2CH_2CH_2P$), 62.2 (d, $^2J_{C-P}$ = 5.8 Hz, **C**$H_2OP$). *m/z* ($MH^+$): 387.21. Calcd 387.20. IR (KBr) $\nu$/($cm^{-1}$): 2557(OH), 1222 (P=O).

### *Synthesis of Phosphonic Acid Functionalized Resin (**18**)*

The NovaSyn® TG bromo resin (1 g, substitution 0.3 mmol $g^{-1}$) was suspended in acetonitrile (10 mL) in a round-bottom flask equipped with a reflux condenser. Sodium phosphate (6 equiv, 1.8 mmol) prepared as previously described was added to the flask and the reaction mixture was then irradiated for 5 min (5 × 1 min) at 70 W ($T_{max}$ = 80°C). The resin was filtrated, washed successively with water, acetonitrile, dichloromethane, and diethylether and dry in a desiccator overnight. The resin phosphonate was suspended in acetonitrile (10 mL) in a round-bottom flask equipped with a reflux condenser and an argon bubbling. An excess of trimethylsilylbromide (0.7 mL, 6 mmol) was added, and the reaction mixture was irradiated (50 W, 2 × 2 min.). Methanol was added (10 mL) at 0°C, and the reaction was stirred for 2 h. The resin was then, filtrated, washed successively with dichloromethane, and diethylether and dry in a desiccator overnight. To calculate the loading of the obtained resin, 3 × 100 mg of the resin was treated overnight with an aqueous sodium hydroxide solution. Conductometric titration was done on the remaining solutions, and they were also titrated with an HCl solution. Both methodology gave a loading of 0.3 mmol $g^{-1}$.

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