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Synthesis of the N-Butyl Ester and N-Butylamide of Methyl-Phenylphosphinic Acid – Two Case Studies

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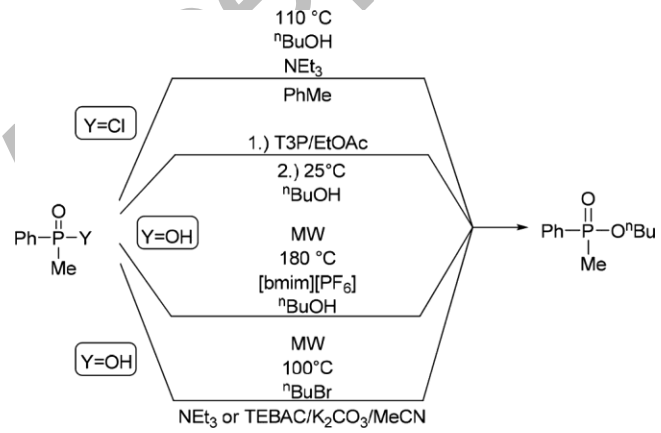
Abstract

n-Butyl methyl-phenylphosphinate and methyl-phenylphosphinic n-butylamide were synthesized by different methods comprising the reaction of methyl-phenylphosphinyl chloride with ^{n}BuOH or ^{n}BuNH$_2$, respectively, the T3P®-promoted derivatization of methyl-phenylphosphinic acid with ^{n}BuOH or ^{n}BuNH$_2$, the microwave-assisted direct esterification of the model phosphinic acid, and finally the alkylating esterification with n-butyl bromide under phase transfer catalytic and MW-assisted conditions. The different methods, mostly elaborated by us, were compared from practical and environmentally-friendly points of view.



KEYWORDS: phosphinic acid; esterification; amidation; T3P® reagent; microwave; phase transfer catalysis

INTRODUCTION

Most often, phosphinates and phosphinic amides are synthesized from the corresponding phosphinic chloride intermediates.[1–5] Even industrial syntheses are based on this approach. However, phosphinic chlorides are relatively expensive, and the hydrochloric acid formed from them on phosphinylation means an environmental burden, and should be removed by a base, in most cases by a tertiary amine. Not speaking about the by far not quantitative atomic efficiency. Direct derivatization of phosphinic acids is, in general, not possible. Two authors of this paper were, who elaborated the microwave (MW)-assisted direct esterification of phosphinic acids. Using the alcohols in 15-fold quantity, and performing the reactions at 200–220 °C in a closed vessel, especially with longer carbon atom chain alcohols ($n \geq 4$), the phosphinates were obtained in most cases in 70–95% yields.[6–9] The esterification of phosphinic acids is thermoneutral, and has a rather high ($\geq$100 kJ·mol^{-1}) enthalpy of activation.[10] Such reactions may be promoted by the beneficial effect of the statistically occurring local overheatings appearing on MW irradiation.[11,12] It is noteworthy that the MW-assisted direct amidations remained incomplete that is the consequence of the endothermicity of the reactions.[13] Another possibility for the preparation of phosphinates is the alkylating esterification.[14] A MW-assisted version was developed for the solid–liquid phase reaction of phosphinic acids with alkyl halides in the presence of K_2CO_3, and in the absence of any solvent. It was found that the alkylations with alkyl halides of normal reactivity were enhanced by the

use of triethylbenzylammonium chloride (TEBAC) as the phase transfer catalyst.[7,15] Recently, the trimeric n-propylphosphonic anhydride (T3P®)–promoted esterification and amidation of phosphinic acids were also described by us.[16,17] In our earlier derivatizations, mainly phenyl-*H*-phosphinic acid and cyclic phosphinic acids, such as 1-hydroxy-phospholene 1-oxides, 1-hydroxy-phospholane oxides, and a 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxide served as the starting phosphinic acids.[7,18]

In this paper, we wished to compare the different possibilities for the derivatizations (esterification and amidation) of methyl-phenylphosphinic acid and its chloride.

RESULTS AND DISCUSSION

1.) Synthesis Of N-Butyl Methyl-Phenylphosphinate (3a) And Methyl-Phenylphosphinic N-Butylamide (4) Via Methyl-Phenylphosphinic Chloride

First, the traditional method starting from methyl-phenylphosphinic chloride (**2**) was followed during the preparation of the target compounds (Scheme 1). In our case, the phosphinic chloride **2** was obtained from methyl-phenylphosphinic acid (**1**) by reaction with thionyl chloride in dichloromethane. Then, the intermediate (**2**) was reacted with 2 equivalents of n-butanol (Scheme 1/(1)) and with 1.1 equivalents of n-butylamine (Scheme 1/(2)) in boiling toluene, in both cases, in the presence of 1 equivalent of triethylamine, and for 2 h. After removing the amine salt by filtration, the organic phase was concentrated. The crude products were purified by flash column chromatography to afford the phosphinate (**3a**) or the phosphinic amide (**4**) in yields of 93% and 89%, respectively.

2.) The T3P®-Assisted Esterification And Amidation Of Methyl-Phenylphosphinic Acid (1) (Scheme 2 And 3)

Methyl-phenylphosphinic acid (**1**) was first reacted with 1.1 equivalents of the T3P® reagent in ethyl acetate. In this stage, the mixed anhydride shown by formula **5** was formed. This way of activation is well-known, and the reaction sequence has been evaluated by us by quantum chemical calculations.[19] Then, 3 equivalents of n-butanol was added to intermediate **5** at 25 °C. After a 1 h's stirring, the purification of the crude product obtained after removing the T3P® reagent by hydrolysis and evaporation of the volatiles led to ester **3a** in a yield of 81% (Table 1, entry 1). Carrying out the esterification at 85 °C, either on conventional heating for 30 min, or on MW irradiation for 20 min, the yields of phosphinate **3a** were similar (~78%) (Table 1, entries 2 and 3). In order to make the synthesis more atom-economical and cheaper, we tried to decrease the quantity of the T3P® reagent. For this, the previous protocols were repeated using only 0.66 equivalents of the T3P®. No matter if a longer reaction (1.5 h) was allowed, at 25 °C the yield was only 52% (Table 1, entry 4). The thermal and the MW-assisted variations at 85 °C led to a yield of 61% and 80%, respectively (Table 1, entries 5 and 6). It can be seen that the experiments covered by entries 1, 3 and 6 gave practically the same results. One may conclude that increasing the temperature from 25 to 85 °C, MW irradiation allows a faster esterification. At the same time, decreasing the quantity of the T3P® reagent from 1.1 to 0.66 equivalents, application of a temperature of 85 °C and a somewhat longer reaction time leads to a similar result under MW.

The T3P®-assisted amidation of methyl-phenylphosphinic acid (**1**) was performed similarly applying 1.1 equivalents of the activating agent and 3 equivalents of n-buthylamine. After a 1 h's stirring at 25 °C, the work-up afforded the phosphinic amide (**4**) in a yield of 65%.

3.) Direct Esterification Of Methyl-Phenylphosphinic Acid (1)

As was mentioned in the Introduction, the direct esterification of phosphinic acids is possible under MW conditions. n-Butanol is, however, not a too efficient reagent due to its volatility. At a temperature of 220 °C, the pressure is ~18 bar that is close to the limit of the MW reactor applied. Regarding the direct esterification of methyl-phenylphosphinic acid **1** and n-butanol measured in 15-fold excess, the conversion was only 15% after a reaction time of 3 h (Table 2, entry 1). Performing the esterification at a lower temperature of 180 °C, but in the presence of 10% of [bmim][PF_6] as an additive, the conversion was 100% after 1.5 h, and the target phosphinate (**3a**) was isolated in a yield of 73% (Table 2, entry 2). As a matter of fact, ionic liquids used in catalytic quantities may have a positive influence on the course of different reactions [20,21] including esterifications.[22]

To use a more efficient alcohol, the esterification was also performed with n-octanol. Irradiation at 200 °C for 2 h, or at 180 °C for 20 min, this latter in the presence of 10% of [bmim][PF_6], resulted in the formation of n-octyl phosphinate **3b** in conversions of 32% and 100%, respectively (Table 2, entries 3 and 4). In the latter case, the yield of **3b** was 92%.

4.) Alkylating Esterification Of Methyl-Phenylphosphinic Acid (1)

The next option was the synthesis of the phosphinate (**3a**) by alkylating esterification. Methyl-phenylphosphinic acid (**1**) was reacted with 1.2 equivalents of n-buthyl bromide in the presence of K_2CO_3 and 5% of TEBAC in acetonitrile, at 100 °C on MW irradiation. Allowing a reaction time of 2 h, phosphinate **3a** was obtained in a yield of 89% after the work-up comprising filtration, concentration in vacuum, and purification by flash chromatography (Table 3, entry 1). In the absence of the phase transfer catalyst, the yield was decreased by 44% (Table 3, entry 2). On conventional heating at 100 °C for a longer reaction time of 5 h in the presence of 5% of TEBAC, the yield was only 67% (Table 3, entry 3) referring to the beneficial effect of MW irradiation. In the last case, the alkylating esterification was carried out using triethylamine as the base, but without any solvent. The yield of this homogeneous accomplishment was 89% (Table 3, entry 4). It can be seen that the heterogeneous phase transfer catalytic approach (Table 3, entry 1) and the homogeneous variation (entry 4), both under MW conditions, led to the best results.

The comparison of the different methods for the preparation of n-butyl methyl-phenylphosphinate (**3a**) are shown in Table 4. The classical synthesis involving the phosphinylation of ^{n}BuOH by reaction with MePhP(O)Cl is rather efficient (the yield of **3a** is 93%), but the use of a P-chloride may mean a drawback regarding cost, environmental burden, and atomic efficiency that is only 47%. Moreover, there was need for toluene as the solvent.

The preparation of phosphinate **3a** from methyl-pehylphosphinic acid **1** via its activation by reaction with the T3P® reagent can be realized under mild conditions, and with a rather good yield (81%). At the same time, the T3P® reagent is expensive, and the atomic efficiency is as low as 37%, if 1 equivalent of the T3P® reagent is used. It is, however, possible to reduce the quantity of T3P® to 0.66 equivalents, but in this case a somewhat higher temperature (85 °C) is needed under MW conditions.

The third possibility comprises the MW-assisted IL-catalyzed direct esterification of phosphinic acid **1**, providing the phosphinate (**3a**) in a yield of 73%. The excess of the alcohol served as the solvent. An obvious advantage of this method is the good atomic efficiency of 92% that is the best in the series discussed. The need for 180 °C as the optimum temperature is compensated by a relatively short reaction time.

The synthesis via *O*-alkylation of phosphinic acid **1** with n-butyl bromide was performed in two ways. In the first variation, the esterification was performed under solid-liquid phase transfer catalytic conditions applying TEBAC as the catalyst, and K_2CO_3 as the base in acetonitrile, under MW-assisted conditions. The other way included the use of triethylamine in a homogeneous phase accomplishment. Both protocols led to good yields of 89%. However, the need for n-butyl bromide as the reagent, and the atomic efficiency of 54% (in case of TEA) or 49% (in case of K_2CO_3) may be problematic.

In summary, the MW-assisted direct esterification may be the method of choice if the phosphinate (**3a**) is prepared in a small (0.5 g) scale. The larger scale realization justifies the utilization of the classical method starting from the phosphinic chloride (**2**). Regarding the preparation of methyl-phenylphosphinic n-butylamide (**4**), the synthesis via phosphinylation of n-butylamine with MePhP(O)Cl (**2**) remains the practical method of choice, but the approach utilizing T3P®-activated phosphinic acid (**1**) may also be a good possibility. The atomic efficiency of the two methods mentioned is 47% and 36%, respectively.

In conclusion, four methods for the preparation of n-butyl methyl-phenylphosphinate (**3a**) were applied, and critically evaluated. From among the four protocols, three methods were based on synthetic approaches developed by us.[15,16,22] The direct MW-assisted esterification seemed to be the best. In respect of the target amide, it may be synthesized by both methods starting either from the *P*-chloride (**2**) and n-butylamine, or from the acid (**1**), the T3P® reagent and butylamine.

EXPERIMENTAL

The ^{31}P, ^{13}C, ^{1}H NMR spectra were taken on a Bruker DRX-300 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. The couplings are given in Hz. Mass spectrometry was performed on a ZAB-2SEQ instrument.

GC was carried out on an HP5890 series 2 GC-FID chromatograph, using a 15 m × 0.18 mm Restek, Rtx-5 column with a film layer of 0.20 μm. The temperature of the

column was initially held at 40 °C for 1 min, followed by programming at 25 °C/min up to 300 °C, and a final period at 300 °C (isothermal) for 10 min. The temperature of the injector was 290 °C, and of the FID detector 300 °C. The carrier gas was H_2.

The MW-assisted reactions were carried out in a CEM Discover microwave reactor equipped with a stirrer and a pressure controller applying 100–300 W irradiation.

Procedure For The Traditional Esterification And Amidation Via Phosphinic Chloride 2

To 0.50 g (3.2 mmol) of methyl-phenylphosphinic acid (**1**) in 5 mL of dry dichloromethane was added 0.28 mL (3.8 mmol) of thionyl chloride and the mixture was stirred at 26 °C for 24 h. Then the solvent was evaporated, and the volatiles were removed in vacuum. The 0.55 g (~100%) of methyl-phenylphosphinic acid chloride (**2**) so obtained was taken up in 3 mL of dry toluene, and the resulting solution was added dropwise to a mixture of 0.32 mL (3.5 mmol) of n-butanol (or 0.35 mL (3.5 mmol) of n-butylamine) and 0.45 mL (3.2 mmol) of triethylamine in 3 mL of toluene at 60 °C. The contents of the flask were stirred at reflux for 2 h. Then, the amine-hydrochloride salt was removed by filtration, and the filtrate evaporated. The crude product so obtained was purified by column chromatography (3% methanol in chloroform, silica gel) to afford 0.63 g (93%) of n-butyl methyl-phenylphosphinate (**3a**) (or 0.60 g (89%) of methyl-phenylphosphinic n-butylamide (**4**)).

Procedure For The Esterification And Amidation Of Methyl-Phenylphosphinic Acid (1) In The Presence Of T3P® Reagent (Table 1/Entry 1 And Scheme 3)

A mixture of 0.12 g (0.75 mmol) methyl-phenylphosphinic acid (**1**) and 0.55 mL (0.84 mmol) of T3P® reagent (50 wt.% ethyl acetate solution) was stirred for 10 min. To the resulting mixture 0.21 mL (2.3 mmol) of n-butanol or 0.23 mL (2.3 mmol) of n-butylamine was added, and the contents of the flask were stirred for 1 h. The excess of the T3P® reagent was hydrolyzed with 7 mL of 10% $NaHCO_3$ solution, and after separation the aqueous phase was washed with 15 mL of ethyl acetate. The combined organic phases were dried (Na_2SO_4), and concentrated in vacuum. The crude product so obtained was passed through a thin (ca. 3–4 cm) layer of silica gel using ethyl acetate as the eluent to give 0.13 g (81%) of phosphinate **3a** or 0.11 g (65%) of phosphinic amide **4** as colourless oils.

Procedure For The MW-Assisted Direct Esterification Of Methyl-Phenylphosphinic Acid (1) (Table 2/Entries 2 And 4)

A mixture of 0.12 g (0.75 mmol) of methyl-phenylphosphinic acid (**1**), 11.0 mmol of the alcohol (1.0 mL of n-butanol or 1.8 mL of n-octanol), and 10% (15.5 μL) of [bmim][PF_6] was measured in a sealed tube that was irradiated in the MW reactor equipped with a pressure controller at 180 °C for 1.5 h and 20 min, respectively. (The pressure developed was 18 and 2 bar, respectively.) Then, the excess of the alcohol was removed under reduced pressure, and the residue so obtained purified by flash column chromatography using silica gel and ethyl acetate as the eluent to afford phosphinates **3a** [0.12 g (73%)] and **3b** [0.19 g (92%)] as oils.

Procedure For The Alkylating Esterification Of Methyl-Phenylphosphinic Acid (1) (Table 3/Entries 1 And 4)

Method A: A mixture of 0.12 g (0.75 mmol) of methyl-phenylphosphinic acid, 0.10 mL (0.90 mmol) of n-butyl bromide, 0.11 g (0.83 mmol) of K_2CO_3 and 8.6 mg (0.038 mmol) of TEBAC in 1 mL of acetonitrile was stirred under MW irradiation at 100 °C for 2 h. The reaction mixture was then taken up in 50 mL of ethyl acetate, and the suspension was filtrated. The solid was washed with 5 mL of ethyl acetate. Evaporation of the combined organic phases provided the crude product that was passed through a thin (ca. 3-4 cm) layer of silica gel using ethyl acetate as the eluent to give 0.15 g (89%) of phosphinate **3a** as an oil.

Method B: A mixture of 0.12 g (0.75 mmol) of methyl-phenylphosphinic acid (**1**), 0.10 mL (0.90 mmol) of n-butyl bromide and 0.12 mL (0.83 mmol) of triethylamine was stirred under MW irradiation at 100 °C for 0.5 h. The crude product was passed through a thin (ca. 3-4 cm) layer of silica gel using ethyl acetate as the eluent to give 0.15 g (89%) of phosphinate **3a** as a colourless oil.

SUPPLEMENTARY INFORMATION

Supplementary data (^{31}P, ^{13}C, ^{1}H NMR and HRMS characterization data for compounds **3a,b** and **4**) associated with this article can be found via the "Supplementary Content" section of this article's webpage.

ACKNOWLEDGEMENT

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Table 1. T3P®–promoted esterification of methyl-phenylphosphinic acid (1) with n-butanol

T3P® (eq.)	T (°C)	Mode of heating	t (h)	Yield (%)	Entry
1.1	25	–	1	81	1
1.1	85	Δ	0.5	77	2
1.1	85	MW	0.33	79	3
0.66	25	–	1.5[a]	52	4
0.66	85	Δ	0.5[b]	61	5
0.66	85	MW	0.5	80	6

[a] No change on further stirring.

[b] No change on further heating.

Table 2. Direct esterification of methyl-phenylphosphinic acid (1) with n-butanol

R	T (°C)	t (h)	p (bar)	Catalyst	Conversion (%)	Yield (%)	Entry
Bu	220	3	18	–	15	–	1
Bu	180	1.5	14	10% [bmim][PF_6]	100	73 (**3a**)	2
Oct	200	2	2.5	-	32	–	3
Oct	180	0.33	2	10% [bmim][PF_6]	100	92 (**3b**)	4

Table 3. Alkylating esterification of methyl-phenylphosphinic acid (1) with n-butyl bromide

Base	TEBAC	Solvent	Mode of heating	t (h)	Yield (%)	Entry
K_2CO_3	5%	MeCN	MW	2	89	1
K_2CO_3	–	MeCN	MW	2[a]	45	2
K_2CO_3	5%	MeCN	Δ	5[b]	67	3
Et_3N	–	–	MW	0.5	89	4

[a] No change on further irradiation.

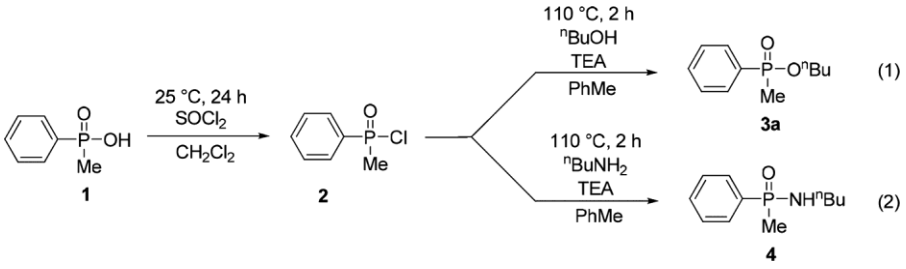
[b] No change on further heating.

Table 4. Comparison of the different methods for the preparation of PhMeP(O)O^{n}Bu

Reaction	Phosphinylation	Phosphinylation	Phosphinylation	O-alkylation
Reagents	PhMeP(O)Cl	PhMeP(O)OH	PhMeP(O)OH	PhMeP(O)OH
	BuOH	T3P®	^{n}BuOH	^{n}BuBr
	NEt_3 (1 equiv.)	^{n}BuOH	[bmim][PF_6] (cat.)	NEt_3*
Solvent	PhMe	EtOAc	BuOH	–*
Temperature [°C]	110	25	180	100
Mode of heating	Δ		MW	MW
Reaction time [h]	2	0.33	1.5	0.5
Yield [%]	93	81	73	89
Adventage	Efficient synthesis	Mild conditions	good atomic efficiency	Efficient synthesis
Disadvantage	need for P-chloride	need for expensive T3P	relatively high temperature	need for ^{n}BuBr

*or TEBAC (cat.)/K_2CO_3 (1 equiv.)/MeCN leading to a yield of 89%

Scheme 1.



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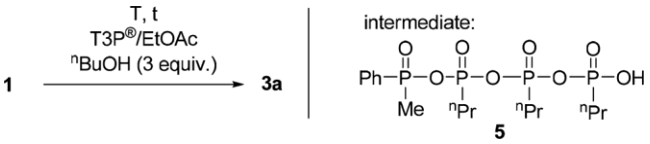

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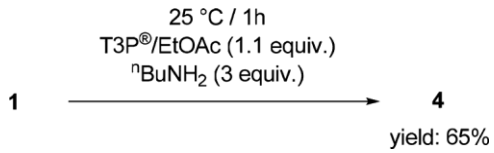
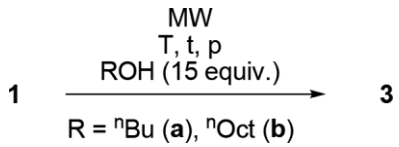


Scheme 4



Scheme 5.