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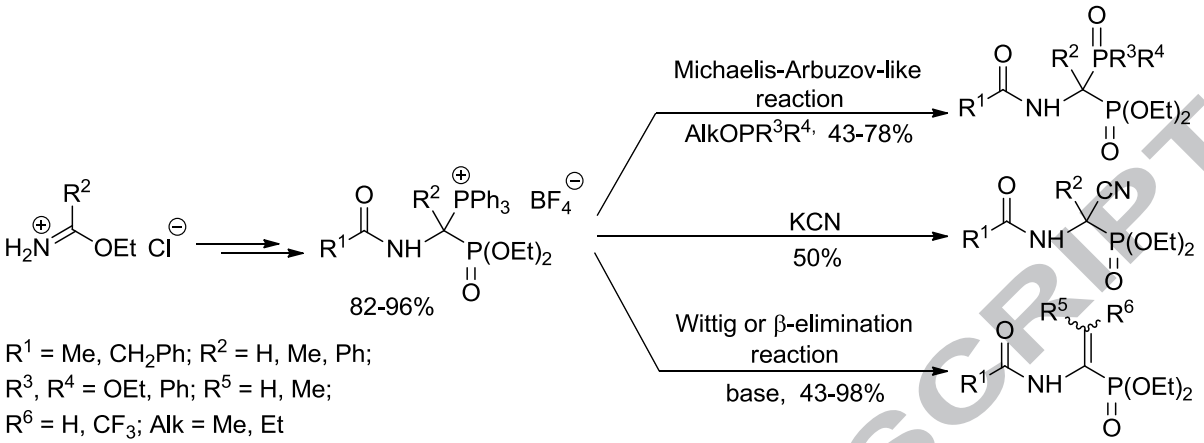
Graphical Abstract



R^1 = Me, CH_2Ph; R^2 = H, Me, Ph;
R^3, R^4 = OEt, Ph; R^5 = H, Me;
R^6 = H, CF_3; Alk = Me, Et

1-(*N*-Acylamino)-1-triphenylphosphoniumalkylphosphonates: general synthesis and prospects for further synthetic applications

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Dedicated to the memory of Professor Jerzy Suwiński (1939-2017)

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Abstract

A general approach for the synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates from readily accessible alkyl imidate hydrochlorides has been developed. The three-step synthesis involves acylation of the imidate hydrochloride with an acyl chloride, the Michaelis–Becker-like addition of diethyl phosphite to the *N*-acylimidate and subsequent nucleophilic substitution of the ethoxy group of the 1-ethoxyphosphonate derivative with triphenylphosphonium tetrafluoroborate. 1-(*N*-Acylamino)-1-triphenylphosphoniumalkylphosphonates were demonstrated to be promising intermediates for further synthetic transformations toward α-functionalized derivatives of α-aminophosphonic acids and α,β-dehydro-α-aminophosphonates.

Keywords: *N*-acylimidates, 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates, α,β-dehydro-α-aminophosphonates, bisphosphonates

Introduction

α-Aminophosphonic acids **1**, as phosphorus analogues and mimetics of α-amino acids, exhibit a variety of important biological activities.[1–4] In the last decade our research group has developed effective methods for the synthesis of 1-(*N*-acylamino)alkylphosphonium salts **2** and demonstrated their efficiency as highly reactive α-amidoalkylating agents in reactions with a variety of nucleophiles.[5–7] 1-(*N*-Acylamino)-1-triphenylphosphoniumalkylphosphonates **4** can be considered both as a subclass of 1-(*N*-acylamino)alkylphosphonium salts **2** and phosphonium derivatives of α-aminophosphonic acids **1**, as they include both the triphenylphosphonium group of phosphonium salts **2** and the

phosphonate group of compounds **1** (Fig.1). It could be assumed that nucleophilic substitution of the triphenylphosphonium group at the α-position of compounds **4** would enable the simple synthesis of variously α-functionalized α-aminophosphonic acid derivatives. It could also be expected that the Wittig reaction of phosphonium salts **4** with a proton at the α-position (R^2 = H) would enable the direct synthesis of important α,β-dehydro-α-aminophosphonic acid derivatives. The elimination of triphenylphosphonium tetrafluoroborate from phosphonium salts **4** with a proton at the β-position ($R^2 = R^6R^7CH$) represents another pathway towards α,β-dehydro-α-aminophosphonic acid derivatives.

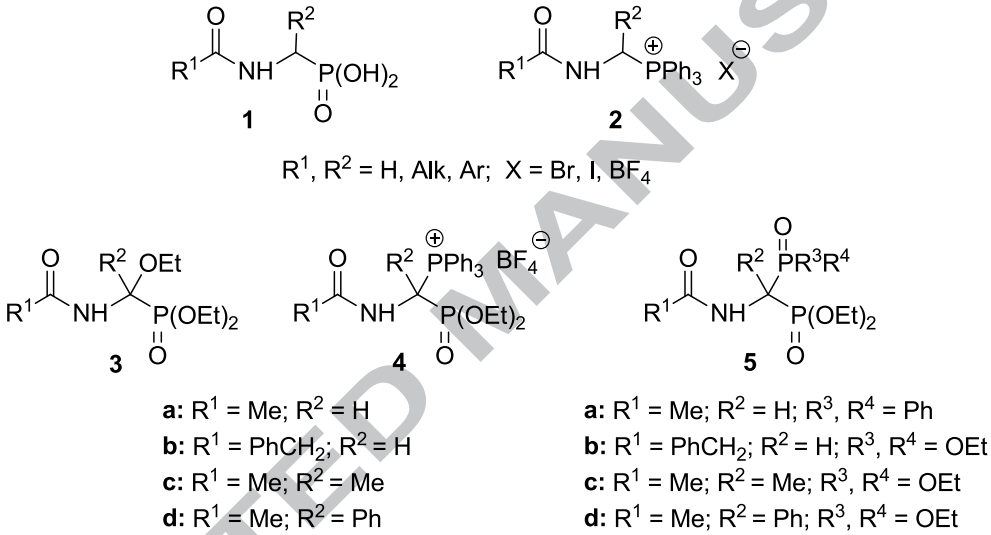
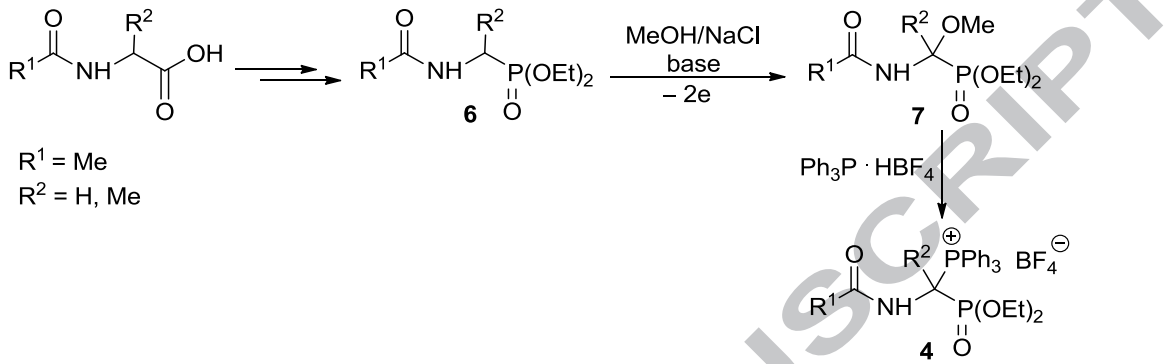


Figure 1. General structures of α-aminophosphonic acids **1** and their α-functionalized derivatives **3, 5** as well as 1-(*N*-acylamino)triphenylphosphonium salts **2** and 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4**.

Recently, we reported a method for the synthesis of hitherto unknown diethyl 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4** by electrochemical oxidative α-methoxylation of diethyl 1-(*N*-acetylamino)alkylphosphonates **6** to 1-(*N*-acetylamino)-1-methoxyalkylphosphonates **7**, followed by substitution of the methoxy group with triphenylphosphonium tetrafluoroborate (Scheme 1).[8] We also showed the usefulness of these compounds in the synthesis of α-aminobisphosphonates **5** as well as their phosphonyl-phosphinyl and phosphonyl-phosphinoyl unsymmetrical analogues.[8] However, the reaction scope for the synthesis of compounds **4** was proven to be limited. Electrochemical α-methoxylation of 1-(*N*-acetylamino)alkylphosphonates was possible only in the case of compounds **6** with small substituents at the α-position (R^2 = H or Me). Attempts to extend

this method to 1-(*N*-acetylamino)alkylphosphonates with more bulky substituents at the α-position (R^2 = Ph or *i*Pr) failed, as electrochemical oxidation in methanol gave intractable mixtures of many compounds in these cases.

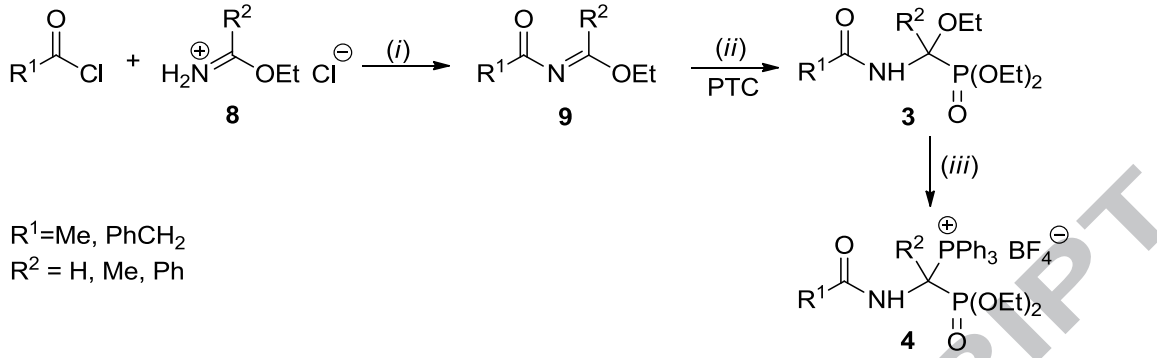


Scheme 1. Synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4** *via* electrochemical α-methoxylation of 1-(*N*-acylamino)alkylphosphonates **6** followed by substitution of the methoxy group with triphenylphosphonium tetrafluoroborate.[8]

Herein, we report a more general strategy for the synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumphosphonates **4** based on *N*-acylimidates **9** as starting compounds (Scheme 2). The oxidation state of the imine carbon in *N*-acylimidates **9** and in the α-carbon in 1-(*N*-acylamino)-1-triphenylphosphoniumphosphonates **4** are the same, thus the difficult oxidation step in the discussed syntheses has been omitted. The second part of this paper demonstrates the potential applications of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates as new reagents for the synthesis of variously α-functionalized α-aminophosphonic acid derivatives.

Results and Discussion

Imidate salts **8** are a well-known class of compounds most commonly synthesized from nitriles *via* the Pinner synthesis, but are also available from amides or lactams *via* *O*-alkylation. Imidoesters, their less stable free bases, can be obtained from imidoyl halides by reaction with alkoxide or phenolate anions.[9–11] The acylation of *N*-unsubstituted imidate salts with acetyl chloride in the presence of triethylamine to *N*-acetylimidates **9** was carried out by modification of the procedures described by Alves and co-workers and Inoue and co-workers (Scheme 2).[12,13] In the case of *N*-acylformimidates, the acylation products were too unstable to be isolated and were therefore reacted *in situ*.



Scheme 2. Synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4** from imidate hydrochlorides **8** *via* 1-(*N*-acylamino)-1-ethoxyalkylphosphonates **3**. Reagents and conditions: (*i*) acyl chloride, Et_3N, Ar atmosphere, 0-20 ºC, 2-18 h, 76-87%; (*ii*) $HP(O)(OEt)_2$, K_2CO_3, 18-crown-6, 20 ºC, 4-120 h, 38-78%; (*iii*) $Ph_3P{\cdot}HBF_4$, 20-85 ºC, 0.1-6 h, 82-96%.

The Michaelis-Becker-like addition of diethyl phosphite to *N*-acylimidates 9 under PTC conditions in hexane in the presence of K_2CO_3 and the appropriate crown ether (18-crown-6) at room temperature resulted in the expected 1-(*N*-acylamino)-1-ethoxyphosphonates **3a-d** (Scheme 2, Table 1). The reaction progress was monitored by ^1H and ^{31}P NMR spectroscopy, thus determining the optimal reaction time. The obtained 1-alkoxy derivatives of 1-aminophosphonic acid are a rare class of compounds. Pudovik and co-workers described the synthesis of dimethyl and diethyl 1-(*N*-acetylamino)-1-ethoxy-1-phenylmethylphosphonates (**3**, R^1 = Me, R^2 = Ph) *via* the addition of diethyl phosphite to the corresponding *N*-acetylimidate in the presence of sodium methoxide or sodium ethoxide.[14] In contrast to the well-known electrochemical α-alkoxylation of 1-(*N*-acylamino)acid esters,[15] the analogous alkoxylation of 1-(*N*-acylamino)phosphonic acid esters **6** to 1-(*N*-acylamino)-1-alkoxyphosphonic acid esters was reported in the literature only twice and, as was already mentioned, the scope of application of the electrochemical alkoxylation of these compounds proved to be very limited.[8,16]

Table 1. Synthesis of 1-(*N*-acylamino)-1-ethoxyalkylphosphonates **3** *via* the Michaelis-Becker-like reaction.

Entry	***R¹***	***R²***	***Procedure[a]***	***Time [h]***	***Yield [%]***
3a	Me	H	*B*[b]	18	49[c]
3b	CH_2Ph	H	*B*[b]	18	38[c]
3c	Me	Me	*A*	4	78

3d	Me	Ph	*A*	120	57

[a] PTC reaction conditions: ethyl *N*-acylimidate (2 mmol), diethyl phosphite (2.4 mmol), K_2CO_3 (2.72 mmol), 18-crown-6 (0.27 mmol), hexane (6.4 mL), 20 °C. [b] Procedure B differs from procedure A in that ethyl *N*-acylformimidates were *in situ* subjected to the Michaelis-Becker-like reaction. [c] The yield of product was calculated relative to the starting formimidate hydrochloride due to the instability of the intermediate *N*-acyl derivative.

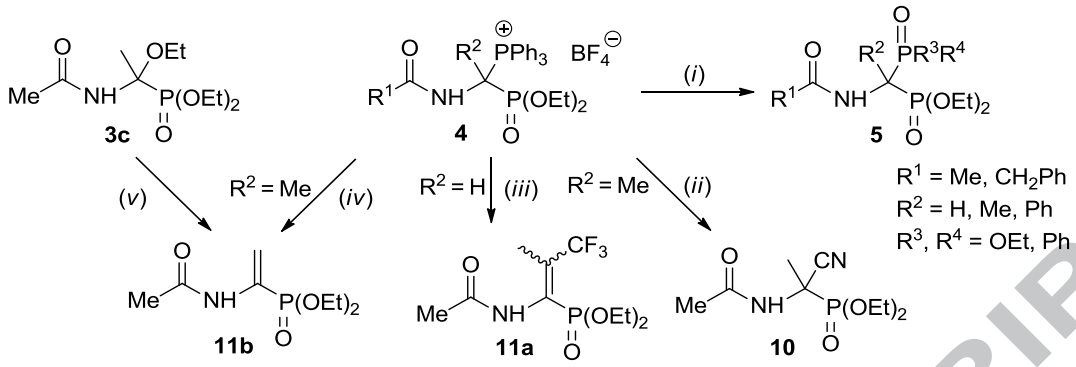
As recently demonstrated, the electrophilic reactivity of the α-carbon in 1-(*N*-acylamino)-1-alkoxyalkylphosphonates **7** was relatively low.[8] Our attempts to transform these compounds to the corresponding α-(*N*-acylamino)bisphosphonates **5** in the Michaelis–Arbuzov-like reaction with triethyl phosphite failed.[8] To enhance the electrophilic activity of the 1-ethoxy derivatives of 1-aminophosphonic acid, the 1-ethoxy group was successfully displaced by the triphenylphosphonium group in the presence of catalytic methyltriphenylphosphonium iodide, thus obtaining the hitherto unknown 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4a-d** in good yields (Scheme 2, Table 2). The optimal reaction time was determined based on NMR experiments. The synthesized phosphonium salts were purified by dissolution in CH_2Cl_2 and precipitation of the crystalline salt with Et_2O.

Table 2. Synthesis of 1-(*N*-acylamino)-1-triphenylphosphoniumphosphonates **4** from the corresponding 1-ethoxyphosphonate derivatives **3.**

Entry	***R*^{1}**	***R*^{2}**	***Procedure***	***temp. [°C]***	***Time [h]***	***Yield [%]***
4a	Me	H	*C*[a]	85	6	86
4b	CH_2Ph	H	*C*[a]	85	4	93
4c	Me	Me	*D*[b]	20	0.1	96
4d	Me	Ph	*D*[b]	20	0.75	82

Reaction conditions: diethyl 1-(*N*-acylamino)-1-ethoxyalkylphosphonate (0.8 mmol), $Ph_3P{\cdot}HBF_4$ (0.8 mmol), CH_2Cl_2 (5 mL). [a] 85 °C, reduced pressure. [b] 20 °C, atmospheric pressure.

As expected, preliminary experiments proved that the obtained 1-triphenylphosphonium derivatives of 1-aminophosphonic acid **4a-d** were compounds of high and diversified reactivity (Scheme 3).



Scheme 3. Potential applications of 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4** for the α-functionalization of α-aminophosphonic acid derivatives. Reagents and conditions: (*i*) $R^3R^4POR^5$, $(iPr)_2EtN$, $Ph_3P^+Me\ I^-$, 20-60 ºC, 0.3-6 h, 43-78%; (*ii*) KCN, 18-crown-6, 20 ºC, 24 h, 50%; (*iii*) $MeC(O)CF_3$, K_2CO_3, 18-crown-6, 50 ºC, 4 h, 43%; (*iv*) $(iPr)_2EtN$, 20 ºC, 5 h, 98%; (*v*) TBD, 20 ºC, 24 h, 62%.

It was demonstrated that the phosphonium group of phosphonium salts **4** can easily be displaced by triethyl phosphite or methyl (diphenyl)phosphonite in a Michaelis–Arbuzov-like reaction to give α–(*N*-acylamino)alkylenebisphosphonates **5** or their phosphonyl-phosphinoyl asymmetrically substituted analogue, typically in good yields (Scheme 3, Table 3). As before, the optimal reaction time was determined by ^1H and ^{31}P NMR spectroscopy.

It was also demonstrated that the phosphonium group of phosphonium salts **4c** can easily be displaced by a carbon nucleophile, e.g. the cyanide anion with formation of a new C_α-C bond (*cf* compound **10**).

We also proved that phosphonium salt **4a** with a proton at the α-position underwent the Wittig reaction with trifluoroacetone under PTC conditions to give the corresponding α,β-dehydro-α-aminophosphonic acid ester **11a**. Moreover, β-elimination of phosphonium tetrafluoroborate from 1-(*N*-acylamino)-1-triphenylphosphoniumphosphonate with a proton at the β-position (**4c)** in the presence of Hünig's base offers another route to the important α,β-dehydro-α-aminophosphonic acid derivative **11b**. It is noteworthy that we were also able to transform 1-(*N*-acylamino)-1-ethoxyethylphosphonate **3c** into the same α,β-dehydro-α-aminophosphonic acid derivative **11b** by the β-elimination of ethanol, although this reaction required a much stronger base [1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)] and a longer reaction time, and resulted in a much lower yield. α,β-Dehydro-α-aminophosphonic acid

derivatives are widely used for asymmetric synthesis of α-aminophosphonic acids by stereoselective hydrogenation in the presence of chiral catalysts.[17]

Table 3. Michaelis–Arbuzov-like reaction of diethyl 1-(*N*-acylamino)-1-triphenylphosphoniumalkyl-phosphonate tetrafluoroborates **4** with phosphorus nucleophiles

Substrate			***Nucleophile***			***temp. [ºC]***	***Time [h]***	***Product***	
Entry	***R¹***	***R²***	***R³***	***R⁴***	***R⁵***			***Entry***	***Yield [%]***
4a	Me	H	Ph	Ph	Me	60	4	**5a**	78
4b	CH_2Ph	H	EtO	EtO	Et	60	4	**5b**	73
4c	Me	Me	EtO	EtO	Et	20	6	**5c**	70
4d	Me	Ph	EtO	EtO	Et	0	0.3	**5d**	43

Reaction conditions: diethyl 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonate tetrafluoroborate (0.5 mmol), phosphorus nucleophile (0.75 mmol), $Ph_3P^+Me\ I^-$ (0.12 mmol), $(iPr)_2EtN$ (0.05 mmol), CH_2Cl_2 (1.5 mL).

Conclusion

In conclusion, the Michaelis–Becker-like addition of diethyl phosphite to readily accessible *N*-acylimidates followed by displacement of the ethoxy group by triphenylphosphonium tetrafluoroborate was proven to be a novel and general method for the synthesis of hitherto unknown 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonates **4a-d**. The charged triphenylphosphonium group at the α-position of compounds **4** can be displaced by diversified nucleophiles to give variously α-functionalized α-aminophosphonic acid derivatives. Both the Wittig reaction of phosphonium salts **4** which are able to generate phosphonium ylides ($R^2 = H$) and the β-elimination of triphenylphosphonium tetrafluoroborate from phosphonium salts with hydrogen at the β-position ($R^2 = R^6R^7CH$) enable easy access to important α,β-dehydro-α-aminophosphonic acid derivatives.

Supplementary data (for online publication)

^1H, ^{13}C and ^{31}P NMR spectra of all synthesized compounds **3**, all phosphonium salts **4** and new bisphosphonates **5b,d** as well as derivatives **10** and **11a,b** are presented in the *Supplementary data* file.

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Declarations of interest: none.

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Highlights

1. Hitherto unknown 1-amino-1-phosphoniumalkylphosphonate salts were described.
2. A general approach for α-functionalization of α-aminophosphonates was developed.
3. Two effective pathways toward α,β-dehydro-α-aminophosphonates were proposed.
4. A new route for the synthesis of bisphosphonates was reported.
5. Transformation of *N*-acylimidates into aminophosphonate derivatives was described.

Graphical Abstract