RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2023, **13**, 18908

A method for the synthesis of unsymmetric bisphosphoric analogs of α-amino acids†

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Received 5th May 2023
Accepted 14th June 2023

DOI: 10.1039/d3ra02981f

rsc.li/rsc-advances

Herein, we describe the first universal strategy for the synthesis of unsymmetric phosphonyl–phosphinyl and phosphonyl–phosphinoyl analogs of *N*-protected 1-aminobisphosphonates. The proposed user-friendly procedure, based on a one-pot reaction of the α-ethoxy derivatives of phosphorus analogs of protein and non-protein α-amino acids with triphenylphosphonium tetrafluoroborate and an appropriate phosphorus nucleophile (diethyl phenylphosphonite or methyl diphenylphosphinite), provides good to very good yields of 53–91% under mild catalyst-free conditions (temperature: rt to 40 °C, time: 1 to 6 hours). The progress of the transformation, running through the corresponding phosphonium salt as a reactive intermediate, was monitored by ^{31}P NMR spectroscopy, which is a convenient tool for the identification of the transient species formed here. In this paper, we present the full characteristics of the spectroscopic properties of all 13 synthesized models of structurally diverse *N*-protected unsymmetric bisphosphoric analogs of α-amino acids. Therefore, these results contribute to increasing the practical applicability of our recently reported synthesis protocol of symmetric models of α-aminobisphosphonates derivatives and thus justify its universality.

Introduction

1,1-Bisphosphoric derivatives, due to their confirmed biological activity, not only enjoy unwavering interest, but even gain more and more importance because of the huge potential of compounds with this type of structure. The essential feature that guarantees the biological activity of 1,1-bisphosphoric derivatives is the presence of the P–C–P skeleton, which is resistant to enzymatic hydrolysis and additionally provides them with an affinity for hydroxyapatite (HA) present in the bone matrix due to the ability to chelate metals such as magnesium and calcium by phosphonyl groups.[1] One of the subclasses of bisphosphoric compounds are their derivatives that contain an amino group on the bridge carbon atom and thus are characterized by the presence of the P–C(N)–P moiety, of which the most known group are geminal 1-amino-1,1-bisphosphonates.[2] These compounds can be considered phosphorus analogs of α-amino acids, functionalized with an additional phosphonyl group. The biological activity of 1,1-bisphosphonates is well known since they are an important class of drugs currently used to treat osteoporosis and other diseases such as Paget's disease, hypercalcemia, or bone metastases.[3,4] The wide range of their potential applications is also associated with other properties including antiviral,[5] antibacterial,[6] antiparasitic,[7,8] and herbicidal.[9] Furthermore, they have also a significant potential to be used in targeted anticancer therapies as drug delivery systems to bone tissue[10] or in the synthesis of new diagnostic agents for bone tissue imaging by MRI or PET.[11] Another group of 1-amino-1,1-bisphosphoric compounds, namely their unsymmetric derivatives, including phosphonyl–phosphinyl and phosphonyl–phosphinoyl analogs (Fig. 1), may be equally interesting. However, such compounds

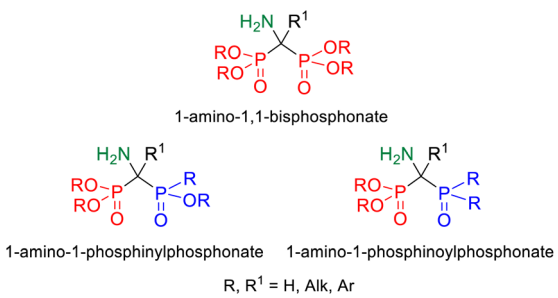

Fig. 1 Comparison of the structures of 1-amino-1,1-bisphosphonate and its unsymmetric phosphonyl–phosphinyl and phosphonyl–phosphinoyl analogs.

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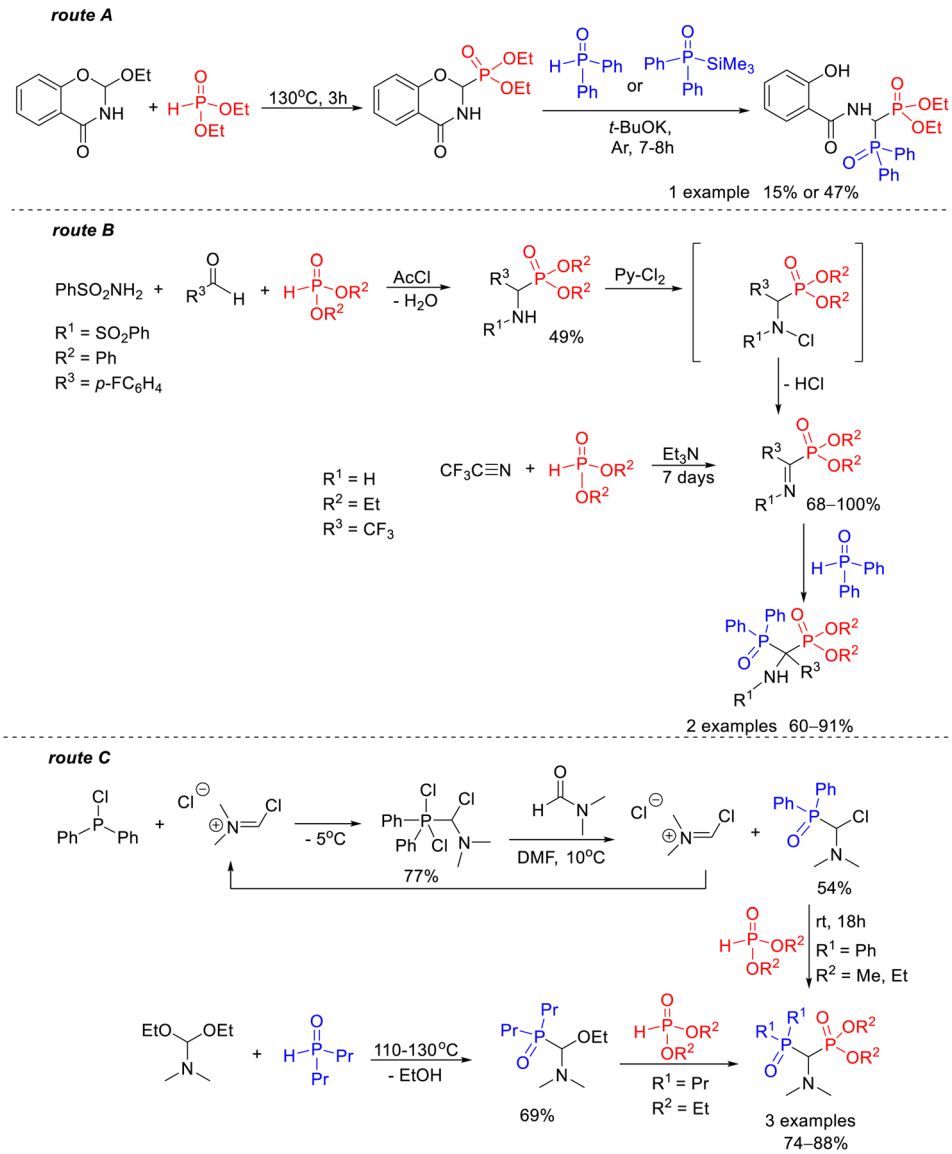
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra. See DOI: https://doi.org/10.1039/d3ra02981f

of the P–C(N)–P skeleton have been much less explored so far; hence, their potential has not yet been fully discovered.

The only studies found in the literature that indicate the biological potential of these compounds were reported by Ebetino. *In vitro* studies on HA crystal growth inhibition and *in vivo* studies on antiresorptive activity of phosphonyl–phosphinyl derivatives of (*N*-pyridyl)-1-amino-1,1-bisphosphonates have shown that they have both the ability to interact with HA crystals and antiresorptive activity, but to a lesser extent compared to their symmetric bisphosphonate analogs.[12] However, this feature may be desirable, especially when the high affinity for bone tissue and the strong chelating effects of symmetric bisphosphonates are the cause of their toxicity. This knowledge can then be used in the design of therapeutics with appropriate antiresorptive potency. The limited number of data on the biological activity of these compounds may be due to their much lower availability, the synthesis of which must be performed stepwise to allow the introduction into the molecule of two different phosphorus groups. This contrasts with the preparation of symmetric derivatives of 1-amino-1,1-bisphosphonates, where in most known synthetic routes both Cα–P bonds are formed simultaneously between a central carbon atom and two identical molecules of the phosphorus nucleophile.[13–16] Therefore, the search for not only an effective but also a universal method to obtain this type of unsymmetric bisphosphoric derivatives remains a challenge that attracts the attention of scientists. It should be emphasized that the usefulness of most of the methods reported in the literature for the preparation of phosphonyl–phosphinoyl analogs of 1-aminobisphosphonates has been demonstrated



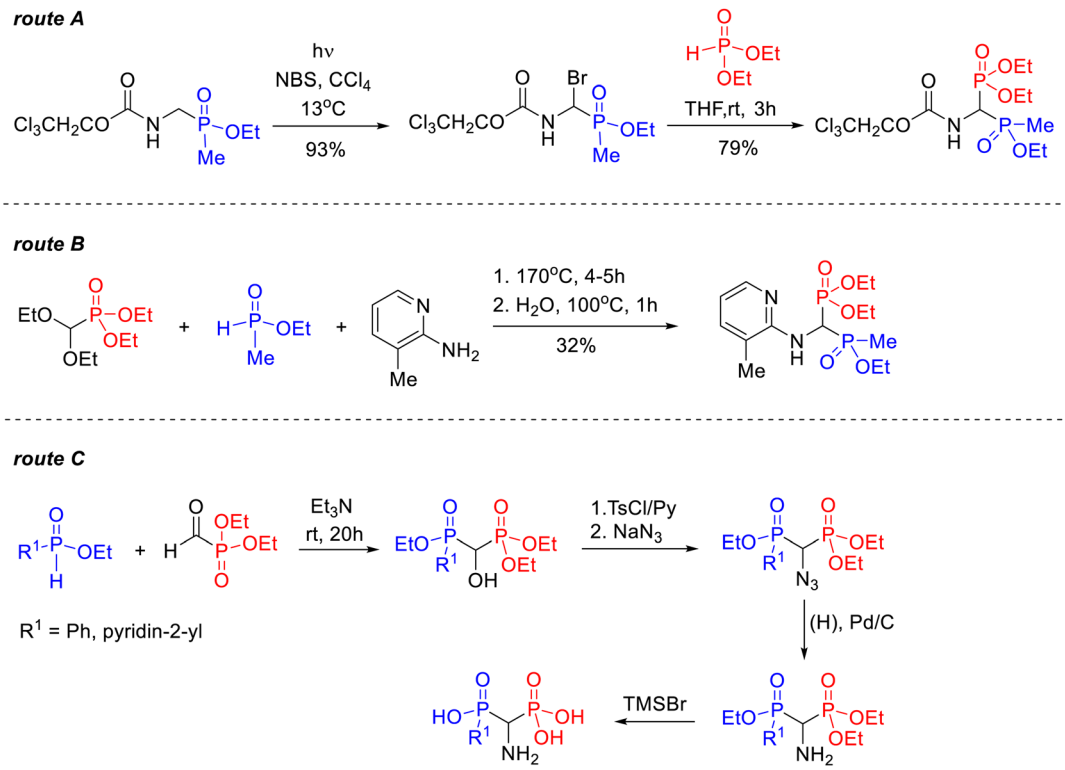
Scheme 1 Known routes for the synthesis of 1-amino-1-phosphinoylalkylphosphonate derivatives: reaction of diethyl 2,3-dihydro-4*H*-1,3-benzoxazin-4-one-2-phosphonate with diphenylphosphine oxide[17] or diphenyl(trimethylsilyl)phosphine oxide[18] (route A); reaction of diphenylphosphine oxide with activated iminophosphonates (route B);[19,20] reaction of dialkyl phosphite with *N*,*N*-dialkylamine derivatives of phosphine oxide functionalized at the α-position by chlorine atom[21] or ethoxy group[22] (route C).

for a limited number of synthesized models, often single (Scheme 1).

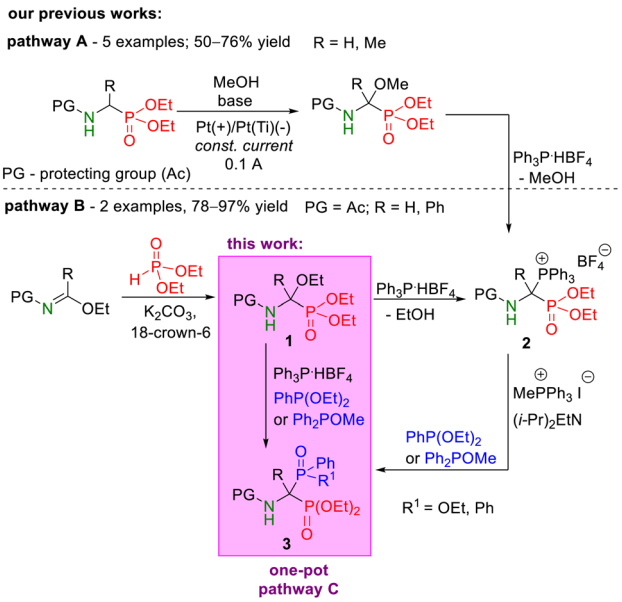
Such an example is the synthesis of diethyl 1-(*N*-salicyloylamino)-1-diphenylphosphinoylmethylphosphonate described by Kostka and Kotyński, one of the first methods for the preparation of this type of bisphosphoric derivative that was carried out with a yield of 15% or 47% depending on the type of nucleophile used (Scheme 1, route A).[17,18] In addition to that, there are only two known routes for the preparation of 1-amino-1-phosphinoylalkylphosphonates. One of them consists of the reaction of diphenylphosphine oxide with iminophosphonate derivatives activated by the presence of trifluoromethyl[19] or a *p*-fluorophenyl group[20] at the α-carbon atom provided the desired product in yields of 60–91% (Scheme 1, route B). The other involves the reaction of dialkyl phosphite with *N*,*N*-dialkylamine derivatives of phosphine oxide functionalized at the α-position by a nucleofugal group such as chlorine[21] or ethoxy[22] (Scheme 1, route C).

Similarly, only a few mentions of synthetic methods have been found in the literature for phosphonyl–phosphinyl analogs of 1-amino-1,1-bisphosphonates. One of the first was the two-stage procedure, reported by Schrader and Steglich, in which diethyl 1-(*N*-2,2,2-trichloroethoxycarbonylamino)-1-(ethoxymethylphosphinyl) methylphosphonate was obtained *via* the corresponding 1-bromo-1-aminoethoxymethylphosphinic acid derivative (Scheme 2, route A).[23] In 1997, Ebetino *et al.* described the synthesis of diethyl 1-[*N*-(3-methylpyridin-2-yl)amino]-1-(etoxymethylphosphinyl)methylphosphonate prepared in 32% yield in the reaction of diethyl dietoxymethylphosphonate with 2-amino-3-methylpyridine and ethyl methylphosphinate (Scheme 2, route B).[12] In 2003, a four-step method was patented for the synthesis of two models of 1-aminophosphinylmethylphosphonic acids through azide derivatives, however, no yield data was provided (Scheme 2, route C).[24]

In recent years, our research group has developed effective procedures for the transformation of α-alkoxyphosphonates into target 1-amino-1,1-bisphosphoric derivatives in the Michaelis–Arbuzov-type reaction.[25–28] These routes proceed through 1-(diethoxyphosphoryl)phosphonium salts as reactive intermediates, and they have been tested in the synthesis of both symmetric and unsymmetric bisphosphoric derivatives. The starting α-alkoxy derivatives of the phosphorus analogs of α-amino acids were synthesized by electrochemical oxidation of diethyl 1-(*N*-acylamino)alkylphosphonates[25] or by adding diethyl phosphite to ethyl *N*-acylimidates.[26] Recently, we published a simplified variant of this procedure, performed using the one-pot method in a catalyst-free system, whose usefulness has been tested so far in the synthesis of a number of symmetric 1-amino-1,1-bisphosphonates.[27] Since this procedure has great potential to become a general route in the synthesis of 1-amino-



Scheme 2 Known routes for the synthesis of 1-amino-1-phosphinylalkylphosphonate derivatives: reaction of 1-bromo-1-amino-ethoxymethylphosphinic acid derivative with diethyl phosphonate (route A);[23] reaction of diethyl diethoxymethylphosphonate with 2-amino-3-methylpyridine and ethyl methylphosphinate (route B);[12] synthesis of 1-aminophosphinylmethylphosphonic acids through reduction of azide derivatives (route C).[24]



Scheme 3 Synthetic pathways for the preparation of phosphonyl–phosphinyl and phosphonyl–phosphinoyl analogs of 1-aminobisphosphonates from α-functionalized derivatives of phosphorus analogs of α-amino acids, such as diethyl 1-(*N*-acetylamino)-1-triphenylphosphoniumalkylphosphonate tetrafluoroborates **2** obtained from α-methoxyphosphonates (pathway A)[25] or α-ethoxyphosphonates (pathway B).[26,28]

1,1-bisphosphoric derivatives, it seemed justified to explore its applicability in the synthesis of unsymmetric phosphonyl–phosphinyl and phosphonyl–phosphinoyl derivatives.

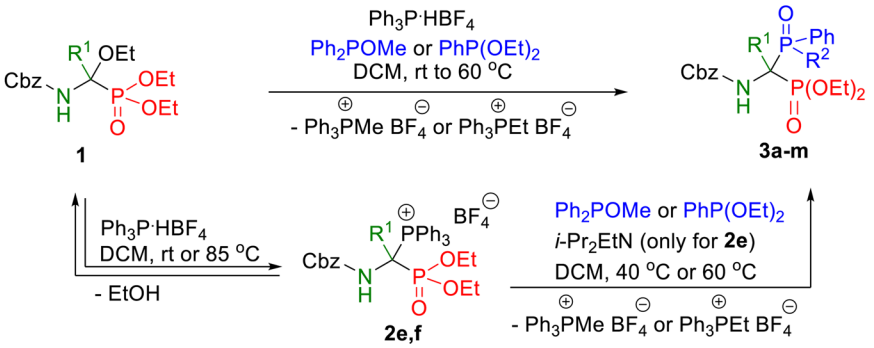
In this paper, we present the synthesis and full spectroscopic characteristics of selected analogs of 1-aminophosphinyl and 1-aminophosphinoylphosphonate derivatives (Scheme 3, pathway C) that can be obtained according to our one-pot strategy.

Results and discussion

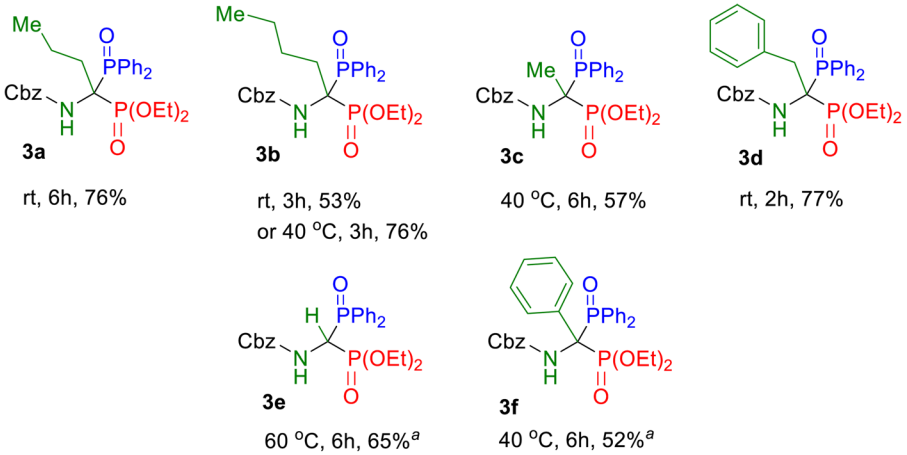
By analogy to the recently published synthesis of 1-amino-1,1-bisphosphonates, here also the models of unsymmetric bisphosphonate derivatives, which we defined as the target compounds, possessed at the α position a side chain identical to those characteristic for natural α-amino acids, both protein and non-protein, since we assumed that its type may have an impact on the biomedical profile of the compound. In all synthesized products, the benzyloxycarbonyl group was used as the protection of the amino group because of the ease of its deprotection.

The starting diethyl 1-(*N*-benzyloxycarbonylamino)-1-ethoxyalkylphosphonates **1** were synthesized according to a recently described two-step protocol[27] consisting of acylation of imidate hydrochlorides with benzyl chloroformate followed by the Michaelis–Becker-like addition of diethyl phosphite to ethyl *N*-acylimidates. Our research on the transformation of diethyl 1-(*N*-acylamino)-1-ethoxyalkylphosphonates into unsymmetric phosphonyl–phosphinoyl derivatives of 1-amino-1,1-bisphosphonates has begun from a series of exploratory experiments with the use of selected models of α-ethoxy derivatives **1** according to the newly developed one-pot procedure, using methyl diphenylphosphinite as nucleophile (Scheme 4). After performing initial optimization experiments for all models of the intended phosphonyl–phosphinoyl analogs of 1-aminobisphosphonates, the syntheses were repeated on a larger scale according to optimized procedures to isolate and characterize the spectroscopic properties of compounds **3** (Scheme 4A). Therefore, for the **1a–d** substrate models, a one-pot procedure was successfully applied, and the Michaelis–Arbuzov-type reaction proceeded smoothly in dichloromethane, at room temperature or 40 °C in 2–6 hours (Scheme 4A). It was observed that in the case of product **3b**, despite the satisfactory course of its synthesis at room temperature (53% yield), it turned out to be advantageous to increase the reaction temperature to 40 °C, resulting in a significantly higher yield of 76%. However, the synthesis of compound **3d** carried out for 1 hour at elevated temperature provided a slightly lower yield of the expected product (64%) compared to that obtained at room temperature (77%). Only, syntheses from the phosphorus analog of glycine **1e** and the phosphorus analog of phenylglycine **1f** did not lead to the expected products **3e** or **3f**, even at elevated temperature. It was not surprising at all in the case of the bisphosphorus analog of glycine, because the same result was observed for the reaction of this model with triethyl phosphite, which we wrote in our previous work (see ref. [27]). As we found, this is probably due to the lack of a substituent at the α position of the substrate model **1e** that stabilizes the iminophosphonate derivative, formed here as an intermediate. For substrate model **1f**, the main obstacle in the effective performance of the intended reaction may be the steric hindrance associated with the accumulation of aromatic rings (present both in the substrate structure and in the nucleophile) at the reaction center. Furthermore, according to the plausible mechanism for the formation of the intermediate diethyl 1-(*N*-acylamino)-1-triphenylphosphoniumalkylphosphonate tetrafluoroborate **2** proposed in our previous article,[27] the low conversion of α-ethoxyphosphonate **1** during the one-pot transformation can also be explained by the unfavorable equilibrium state associated with the reversible nature of this reaction, which in the presence of the released ethanol is shifted toward substrate **1** (Scheme 4). To overcome this problem, it was decided to divide the procedure into two steps, consisting of ethanol removal after phosphonium salt preparation and subsequent use of the synthesized salts **2e,f** *in situ* in the Michaelis–Arbuzov-type reaction with methyl diphenylphosphinite. Therefore, phosphonium salts **2e,f** were obtained by dissolving the α-ethoxyphosphonate **1e,f** and phosphonium tetrafluoroborate in dichloromethane at room temperature, then after 40 minutes, the solvent from the reaction mixture was evaporated and the residue was dried under reduced pressure for 1 or 5 hours at room or elevated temperature (Table 1).

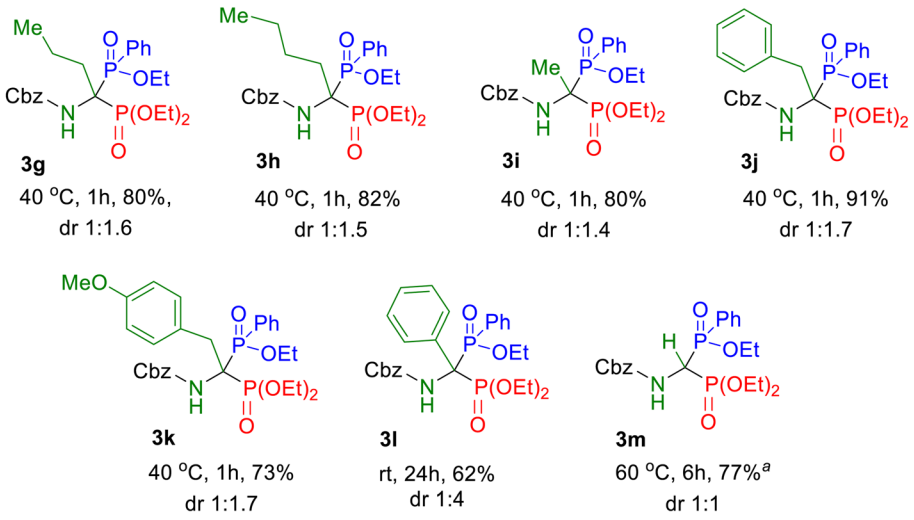
Subsequently, the crude phosphonium salts **2e,f** were dissolved *in situ* in the selected solvent and a phosphorus nucleophile was added, performing the further reaction at room temperature or increased temperature. A catalytic amount of Hünig's base was additionally introduced into the reaction



A: *phosphonyl-phosphinoyl analogs*



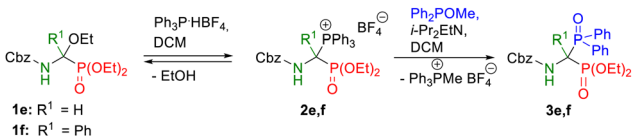
B: *phosphonyl-phosphinyl analogs*



[a] - from phosphonium salt **2e,f** used in situ; yield calculated according to starting α-ethoxyphosphonate **1e,f**.

Scheme 4 Scope of the Michaelis–Arbuzov-type reaction in the synthesis of phosphonyl–phosphinoyl and phosphonyl–phosphinyl analogs of 1-aminobisphosphonates. Conditions: substrate **1** (1.0 mmol), $Ph_3P{\cdot}HBF_4$ (1.1 mmol, 1.1 equiv.), Ph_2POMe or $PhP(OEt)_2$ (1.5 mmol, 1.5 equiv.), DCM (5.0 mL). Isolated yield.

Table 1 Screening of reaction conditions in the synthesis of phosphonyl–phosphinoyl analogs of 1-aminobisphosphonates **3e,f** from phosphonium salts **2e,f** used *in situ*[a]



Entry	Substrate model	R^1	Drying temperature of salt 2 [°C]	Drying time [h]	Solvent	Reaction temperature [°C]	Hünig's base	Substrate **1** conversion[b] [%]
1	**1e**	H	70	1	DCM	60	+	52
2	**1e**	H	70	1	MeCN	70	+	42
3	**1e**	H	85	5	DCM	60	+	92
4	**1f**	Ph	rt	1	DCM	25	−	60
5	**1f**	Ph	rt	1	MeCN	40	−	75
6	**1f**	Ph	rt	1	DCM	40	−	89

[a] Conditions: substrate **1e,f** (0.1 mmol), $Ph_3P \cdot HBF_4$ (0.11 mmol, 1.1 equiv.), DCM (0.5 mL), next, after drying crude salt **2e,f**, Ph_2POMe (0.15 mmol, 1.5 equiv.), *i*-Pr_2EtN (0.03 mmol, 0.3 equiv.), DCM (0.5 mL). $^+$Denotes the addition of Hünig's base as a catalyst. $^-$Denotes that the experiment was carried out without the addition of Hünig's base. [b] The conversion was estimated from the ^{31}P NMR spectrum after 6 h of reaction.

mixture in the case of the phosphonium salt model **2e**. To monitor the progress of the reaction, samples were taken from the reaction system for spectroscopic analysis, usually after 3, 6 and 24 hours of reaction (see Table 1).

This modification of the one-pot procedure brought surprising results. In the case of model **3e**, slight progress of the reaction course was observed (Table 1, entries 1–3), with the ^{31}P NMR spectra showing the intense signal of substrate **1e**, still dominant in the reaction mixture in relation to the low signals of the expected product **3e**. As for model **3f**, a significant improvement was found in the progress of the explored reaction. In each of the variants tested, the **3f** product signals were observed in the ^{31}P NMR spectra of the reaction mixtures. In the case of the reaction performed at room temperature in the second step, the conversion of substrate **1f** was around 60% (Table 1, entry 4). Comparing the recorded spectra of reaction mixtures obtained in syntheses carried out in different solvents, it was again found that for the reaction in dichloromethane, the resulting spectrum was of the higher purity of the baseline and a higher degree of substrate conversion (Table 1, entries 5, 6).

Finally, unsymmetric products **3e,f** were successfully synthesized in a stepwise procedure by the primary formation of the intermediate phosphonium salt **2e,f** and its further use *in situ* in the Michaelis–Arbuzov-type reaction. The difference in the synthesis of both models was that compound **3f** was obtained by heating the reaction mixture in the second step at 40 °C for 6 h, after the previous synthesis of the phosphonium salt **2f** carried out at room temperature for 40 minutes, while model **3e** was synthesized similarly to our recently published procedure,[27] that is, first, the phosphonium salt **2e** was obtained by heating the homogeneous residue after evaporation of the solvent from a solution, prepared by combining α-ethoxyphosphonate **1e** and triphenylphosphonium tetrafluoroborate, at 85 °C under reduced pressure for 5 hours. Next, the crude phosphonium salt **2e**, after dissolving in DCM and treatment with methyl diphenylphosphinite in the presence of a catalytic amount of Hünig's base, was subjected to the Michaelis–Arbuzov-type reaction carried out at 60 °C for 6 hours, resulting in a good yield of the target product **3e** (65%, Scheme 4A).

The one-pot protocol was further explored for the synthesis of **3g–m** derivatives of 1-amino-1-phosphinylalkylphosphonates (Scheme 4B). It was found that selected *N*-protected α-ethoxyaminophosphonates **1** subjected to the Michaelis–Arbuzov-type reaction with triphenylphosphonium tetrafluoroborate and diethyl phenylphosphonite at 40 °C for 1 hour resulted in the desired products **3g–k** with high yields (73–91%). We showed that the phosphonyl–phosphinyl derivative of phenylglycine **3l** can be synthesized in the one-pot protocol with a good yield of 62%, while this result was obtained in the reaction carried out at room temperature for 24 h unlike the standard reaction conditions (40 °C, 1 h) used in the synthesis of most models of bisphosphoric phosphonyl–phosphinyl analogs. As expected, the one-pot method failed to give the glycine derivative product **3m**. The desired product **3m** was successfully synthesized in a stepwise procedure identical to that used in the synthesis of the unsymmetric product **3e**. Similarly to the synthesis of the phosphonyl–phosphinoyl analogs **3a–f**, also in that case for the synthesis of the phosphonyl–phosphinyl analogs **3g–m**, the progress of the reaction was controlled by ^{31}P NMR spectroscopy to evaluate the conversion of α-ethoxyaminophosphonate **1** (Fig. 2) The phosphonyl–phosphinyl analogs of 1-aminobisphosphonates **3g–m** were obtained as mixtures of diastereomers (dr 1 : 1–1 : 4) with very good yields (62–91%). Only product **3l** (dr 1 : 4) was separated and isolated as single isomers by gravity column chromatography. Unfortunately, attempts to separate other diastereomeric mixtures **3g–k,m**, both by gravity column chromatography and by HPLC, failed (see ESI†).

The purification process for all of the synthesized esters of 1-(*N*-benzyloxycarbonylamino)alkylenebisphosphoric acids **3a–m**, regardless of the procedure used for their synthesis, consisted of extraction with toluene from the reaction mixture and further

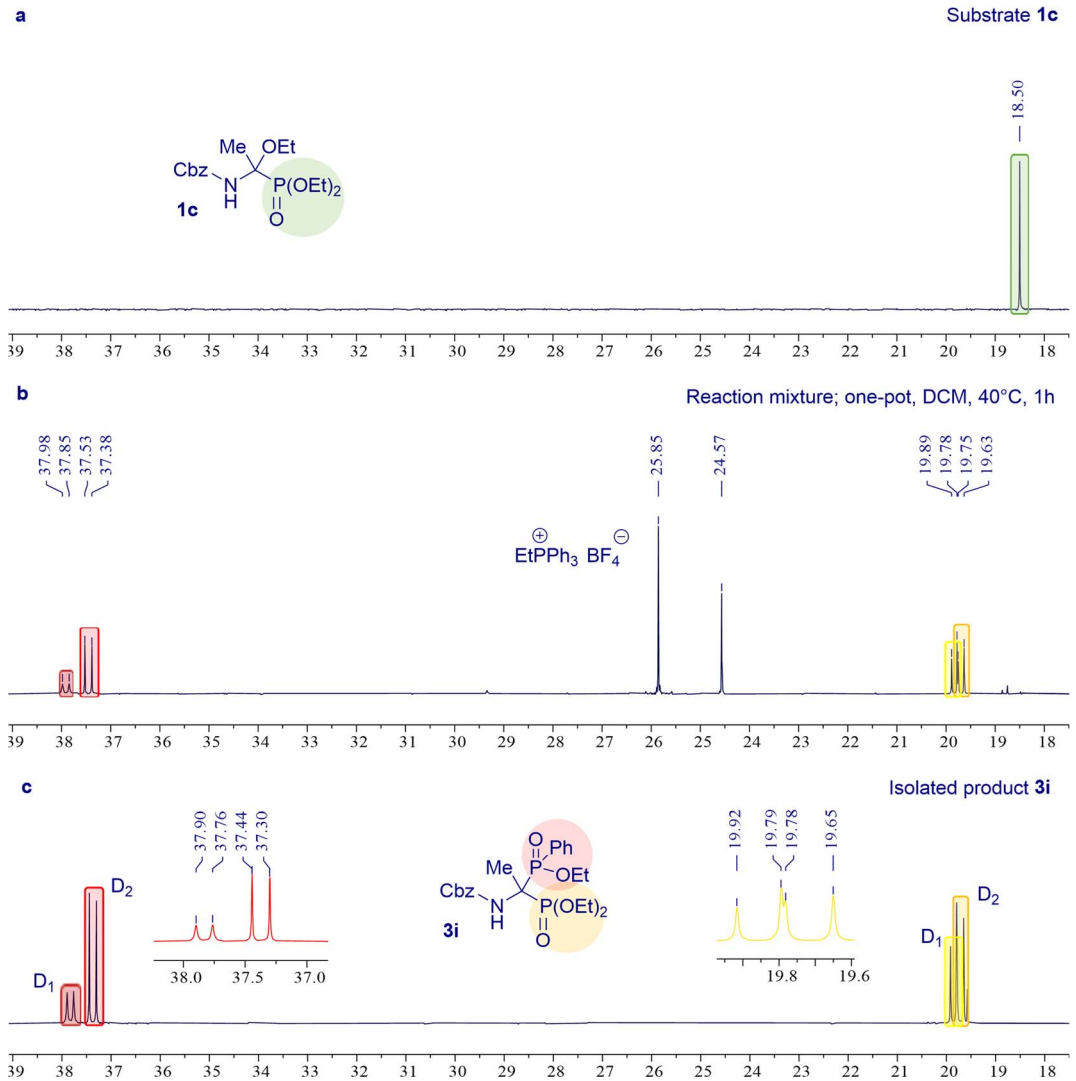


Fig. 2 (a) ^{31}P NMR spectrum of α-ethoxyphosphonate **1c**. (b) ^{31}P NMR spectrum of the reaction mixture obtained in the synthesis of **3i** carried out at 40 °C for 1 h. (c) ^{31}P NMR spectrum of isolated product **3i**.

purification of the extracts by twice column chromatography. For all reactions performed, yields of 52–91% for isolated products **3a–m** were reported (Scheme 4A and B).

Considering the prospects for the further use of synthesized models of unsymmetric analogs of 1-aminobisphosphonates **3**, it is planned to subject them to a hydrolysis reaction and then to biological tests to evaluate their cytotoxicity in selected tumor cell lines. Another research direction involves the acylation of obtained bisphosphoric derivatives with the use of appropriate chloroacyl chlorides to produce the building blocks that are useful in the synthesis of ligands, which after complexing with paramagnetic ions can be further used as potential contrast agents for imaging of bone tissue by MRI.

Conclusions

In conclusion, our efforts to extend the procedure previously developed for the synthesis of *N*-protected bisphosphonic analogs of α-amino acids, to their unsymmetric diethyl phosphonyl–ethoxyphenylphosphinyl and diethyl phosphonyl–diphenylphosphinoyl analogs resulted in success. In most cases, the one-pot strategy performed under mild conditions in an autocatalytic system worked very well here. This easy-to-follow procedure consisted only of mixing the starting 1-(*N*-acylamino)-1-ethoxyphosphonates with triphenylphosphonium tetrafluoroborate and the appropriate phosphorus nucleophile (diethyl phenylphosphonite or methyl diphenylphosphinite) in dichloromethane and then leaving the reaction mixture at room temperature or slightly elevated temperature to 40 °C for 1 to 6 hours. Further extraction of the reaction mixture followed by purification by column chromatography furnished the expected structurally diverse both protein and non-protein *N*-protected 1-aminobisphosphoric derivatives with good to very good yields (52–91%). The one-pot procedure was not applicable only in the case of both unsymmetric bisphosphoric analogs of glycine and for the phosphonyl–phosphinoyl derivative of phenylglycine; therefore, a stepwise method of reaching the final compounds turned out to be necessary. The results presented in this article

in the form of 13 new compounds, combined with our achievements published in the previous article,[27] constitute the universality of the protocol developed for the transformation of ethoxyphosphonate into a 1-amino-1,1-bisphosphoric derivative through the corresponding phosphonium salt as a reactive intermediate. The wide range of various bisphosphoric compounds with the P–C(N)–P skeleton obtainable by this procedure emphasizes its synthetic importance.

Conflicts of interest

There are no conflicts to declare.

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