α-Amino acid derivatives with a $C_α$-P bond in organic synthesis

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Dedicated to Prof. Jan Epsztajn on the occasion of his 75th birthday

Abstract

α-Amino acid derivatives with a $C_α$-P bond have been used for a wide range of chemical transformations, including synthesis of many kinds of bioactive compounds, e.g. non-proteinogenic α-amino acids, α,β-dehydro-α-amino acids, dehydropeptides, β-lactam antibiotics and glycopeptides. The present review is focused on methods of synthesis of the title compounds, their properties and application in organic synthesis.

Keywords: α-Triphenylphosphonioglycinates, α-triphenylphosphonio-α-amino acid derivatives, α-(dialkoxyphosphoryl)glycinates, β-lactam antibiotics, Wittig reaction, Wadsworth-Emmons reaction

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1. Introduction

Chemical literature deals with the four most important kinds of α-amino acid derivatives with a C_α-P bond: esters of *N*-acyl-α-triphenylphosphonio-α-amino acids **1**, the most important of which are *N*-acyl-α-triphenylphosphonioglycinates (**1a**, R^3 = H), phosphonium ylides derived from glycine with the nitrogen atom incorporated into a β-lactam ring **2**, α-(dialkoxyphosphoryl)glycinates **3** and their analogues with a tertiary nitrogen atom included into a β-lactam structure **4** (Figure 1).

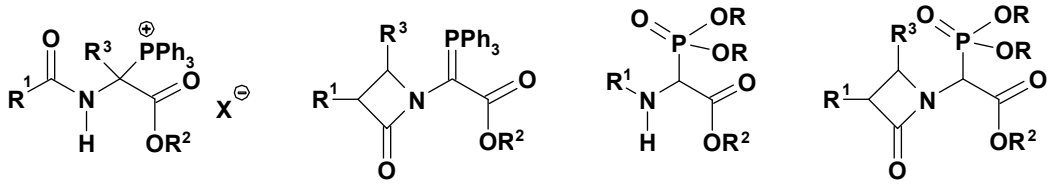


Figure 1

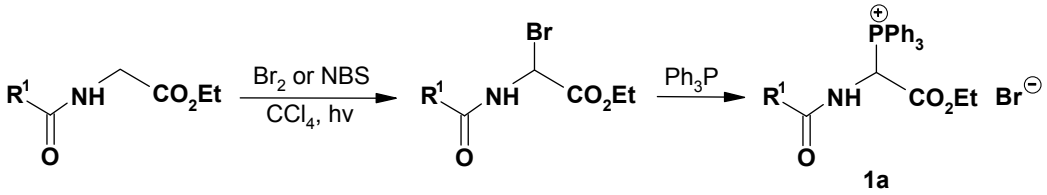
The great interest in these compounds is due to their many applications in organic synthesis. *N*-Acyl-α-triphenylphosphonio-α-amino acid esters **1**, described for the first time by Kober and Steglich only in 1983,[1] are used in syntheses of α-amino acid derivatives as synthetic equivalents of the glycine α-cation.[2-5] Recently, their applications in the synthesis of α,β-dehydro-α-amino acids in the Wittig reaction,[6] as well as their transformation to *N*-acyl-α-(dialkoxyphosphoryl)glycinates **3b**, have also been described.[7] Ylides **2** have been applied in Woodward's synthesis of β-lactam antibiotics since 1978.[8] At the present time, α-(dialkoxyphosphoryl)glycinates derived from β-lactams **4** are being used for this purpose. α-(Dialkoxyphosphoryl)glycinates **3** have been gaining importance since 1973, when they were used for the first time by Ratcliffe and Christensen for the synthesis of β-lactam antibiotics.[9,10] Nowadays, they have become the crucial synthetic tool for the synthesis of α,β-dehydro-α-amino acids, dehydropeptides and glycopeptides in the Wadsworth-Emmons reaction.

The present review deals with the methods of synthesis, the properties and synthetic applications of the α-amino acid derivatives with a C_α-P bond, mentioned above.

2. *N*-Acyl-α-triphenylphosphonio-α-amino acid esters

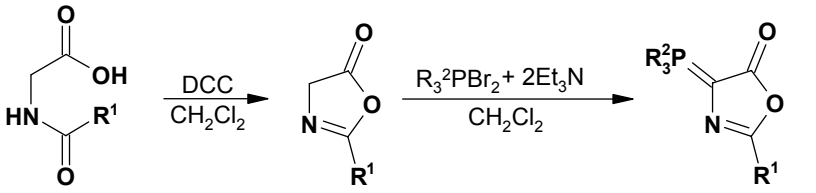
2.1. Synthesis of *N*-acyl-α-triphenylphosphonio-α-amino acid esters

Among this group of compounds, the *N*-acyl-α-triphenylphosphonioglycinates (**1a**, R^3 = H) are the best known. They were obtained for the first time in 1983 by Kober and Steglich in reaction of ethyl *N*-acyl-α-bromoglycinates with triphenylphosphine.[1] α-Bromoglycine derivatives were obtained *in situ* by photochemical bromination of the corresponding glycine derivatives with bromine or *N*-bromosuccinimide in tetrachloromethane (Scheme 1).



Scheme 1

In 1996 a simple and effective method for synthesizing 4-phosphoranylidene-5(4*H*)-oxazolones **5** from *N*-acylglycine was described.[11,12] The method consists in the transformation of *N*-acylated glycine into the corresponding 5(4*H*)-oxazolone **6** followed by the phosphorylation of this compound *in situ* with dibromotriphenylphosphorane or dibromotributylphosphorane in the presence of triethylamine (Scheme 2).

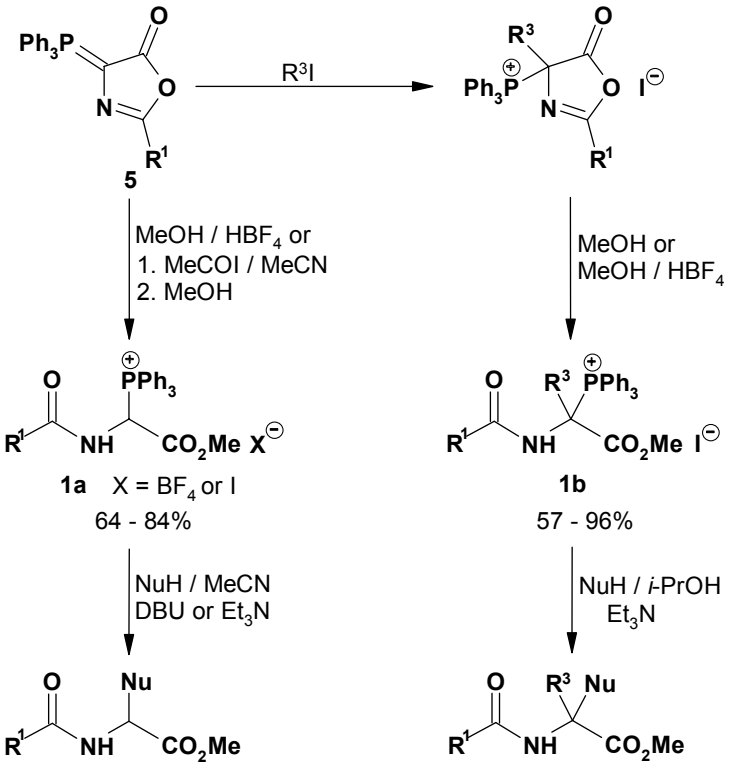


Scheme 2

Phosphoranylidene-5(4*H*)-oxazolones **5** can be easily transformed into *N*-acyl-α-triphenylphosphonioglycinates (**1a**, R^3 = H) as well as esters of other *N*-acyl-α-triphenylphosphonio-α-amino acids (**1b**, R^3 = alkyl) (Scheme 3).

The most convenient method of synthesizing *N*-acyl-α-triphenylphosphonioglycinates (**1a**, X = BF_4) consists in treating a solution of phosphoranylideneoxazolones **5** in methanol with an

ethereal solution of tetrafluoroboric acid.[2,4] An alternative synthesis of *N*-acyl-α-triphenylphosphonioglycinates with an iodide counterion (**1a**, X = I) consists in the reaction of 4-phosphoranylidene-5(4*H*)-oxazolone **5** with acetyl iodide in acetonitrile, followed by the reaction of the acylation product with methanol.[2,4] The synthesis of *N*-acyl-α-triphenylphosphonio-α-amino acids **1b** with an alkyl substituent at the α-position by alkylation of phosphoranylideneoxazolones **5** with alkyl halides,[12,13] followed by the opening of the oxazolone ring with methanol or methanol in the presence of an acidic catalyst (Scheme 3), has been described, too.[4]



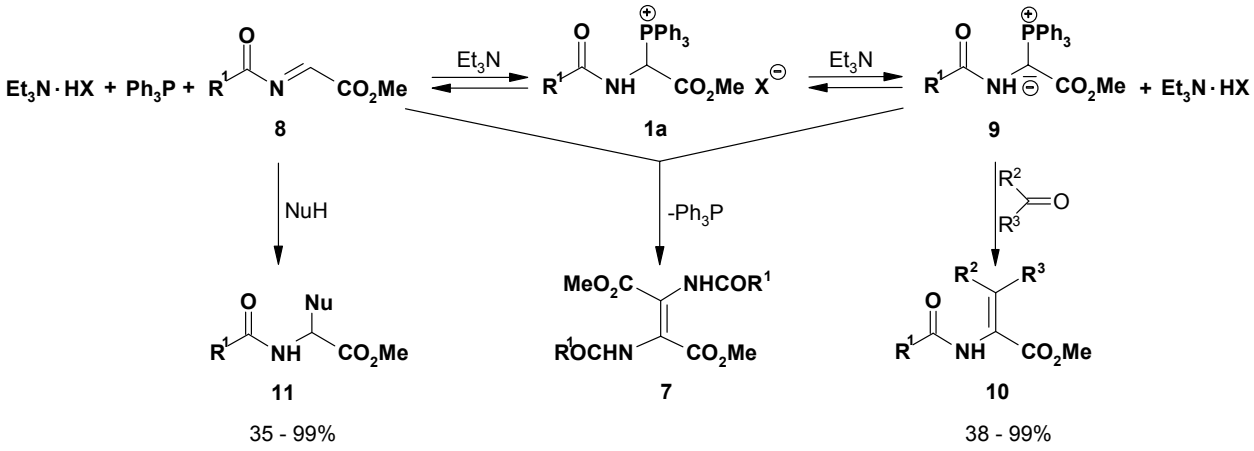
Scheme 3

2.2 *N*-Acyl-α-triphenylphosphonio-α-amino acid esters - properties and application in synthesis

N-Acyl-α-triphenylphosphonio-α-amino acid esters **1a** and **1b** are stable, crystalline compounds, not sensitive to moisture, and easily purified by crystallization.[2-4] They are easily accessible from *N*-acylglycine even on a kilogram scale (Scheme 2 and 3). These features, as well as their diversified reactivity, make them interesting reagents in organic synthesis.

In 1983 Kober and Steglich noticed that the treatment of *N*-benzoyl-α-triphenylphosphonioglycinate **1a** (R^1 = Ph, X = Br) with triethylamine results in the formation of the corresponding 1,2-di(acylamino)fumaric acid diester **7**. Based on this observation, they

assumed that *N*-benzoyl-α-triphenylphosphonioglycinate, in the presence of triethylamine, was transformed to a mixture of the corresponding *N*-acyliminoacetate **8** and *N*-acyl-α-triphenylphosphoranylideneglycinate **9**, which reacted slowly with each other to the fumaric acid derivative **7** (Scheme 4).[1]



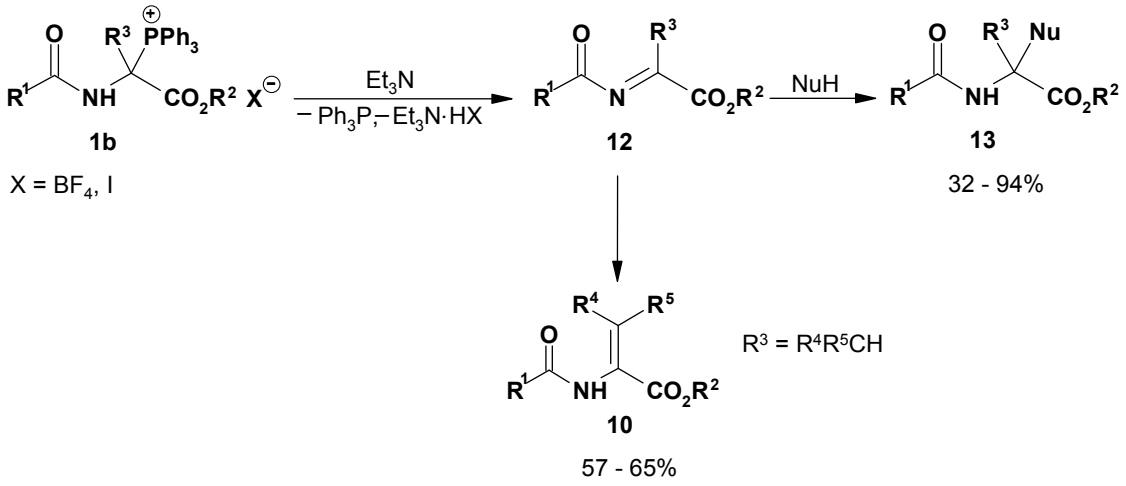
Scheme 4

This hypothesis has been confirmed experimentally by Mazurkiewicz and Grymel, who demonstrated spectroscopically that the treatment of *N*-acyl-α-triphenylphosphonioglycinates **1a** (R^1 = *t*-Bu, Ph; X = BF_4) with bases resulted in the immediate disappearance of the starting ester. Detailed analyses of ^{1}H- and ^{13}C-NMR spectroscopic data led to the conclusion that the reaction mixture contained the corresponding phosphonium ylide derived from glycine **9** and *N*-acyliminoacetate **8,** which remained in an equilibrium (Scheme 4).[14] Attempts to isolate ylide **9** and *N*-acyliminoacetate **8** from the reaction mixture failed, probably because of the instability of both these compounds.[14] Both components of the equilibrium mixture are highly reactive compounds, which makes *N*-acyl-α-triphenylphosphonioglycinates an interesting starting point in organic synthesis.

Thus, *N*-acyl-α-triphenylphosphonioglycinates react as precursors of phosphonium ylides **9** with aliphatic or aromatic aldehydes in the presence of Et_3N in the Wittig reaction in mild conditions yielding the corresponding α,β-dehydro-α-amino acid derivatives **10** in good or even very good yields (Scheme 4).[6] *N*-Acyliminoacetates **8**, again**,** generated *in situ* from *N*-acyl-α-triphenylphosphonioglycinates **1a**, add a variety of nucleophilic reagents, including oxygen, sulfur, nitrogen, carbon and even phosphorus nucleophiles, usually in very good or excellent yields, which eventually leads to the functionalization of the glycine α position by a nucleophilic reagent according to the elimination-nucleophilic addition mechanism (Scheme 4).[2-4] The especially interesting displacement of the triphenylphosphonium group with dimethylphosphite or trimethyl phosphite, which transforms *N*-acyl-α-triphenylphosphonioglycinates **1a** into *N*-acyl-α-(dialkoxyphosphoryl)glycinates **3b** will be discussed in Section 4.1.3 of this paper.

Thus, *N*-acyl-α-triphenylphosphonioglycinates may be considered to be synthetic equivalents of the glycine α-cation. If *N*-acyliminoacetate **8** or ylide **9** are not caught in their reaction with a nucleophile or a carbonyl compound, respectively, the ylide reacts as a nucleophile with *N*-acyliminoacetate, which eventually gives dimethyl 1,2-di(acylamino)fumarate.[1,14]

Similarly as in the case of *N*-acyl-α-triphenylphosphonioglycinates **1a**, *N*-acyl-α-triphenylphosphonio-α-amino acid esters **1b** with an alkyl substituent at the α-position under the influence of triethylamine undergo immediate transformation to the corresponding ester of α-(*N*-acylimino)alkanecarboxylic acid **12**; however in such a case, as is to be expected, esters **12** are the only primary reaction product. If esters **12** possess a hydrogen at the β-position, they can undergo tautomerization to the corresponding α,β-dehydro-α-amino acid derivatives **10**, which can be isolated in good yields (Scheme 5).[4,14] The addition of a nucleophile results, in this case, in a double functionalization of the glycine α-position with an alkyl group and a nucleophilic agent.[4]



Scheme 5

3. Phosphorus ylides derived from glycine with a nitrogen atom incorporated into a β-lactam ring

β-Lactam ring-containing compounds, such as penicillins, ampicillin, amoxicillin, cephalosporins and carbapenems, belong to the most important and most famous class of antibiotics.[15,16] They are derivatives of parent systems such as cephem, carbacephem, oxacephem, penem and carbapenem (Figure 2).

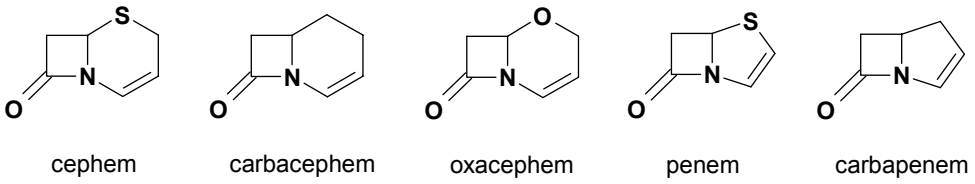
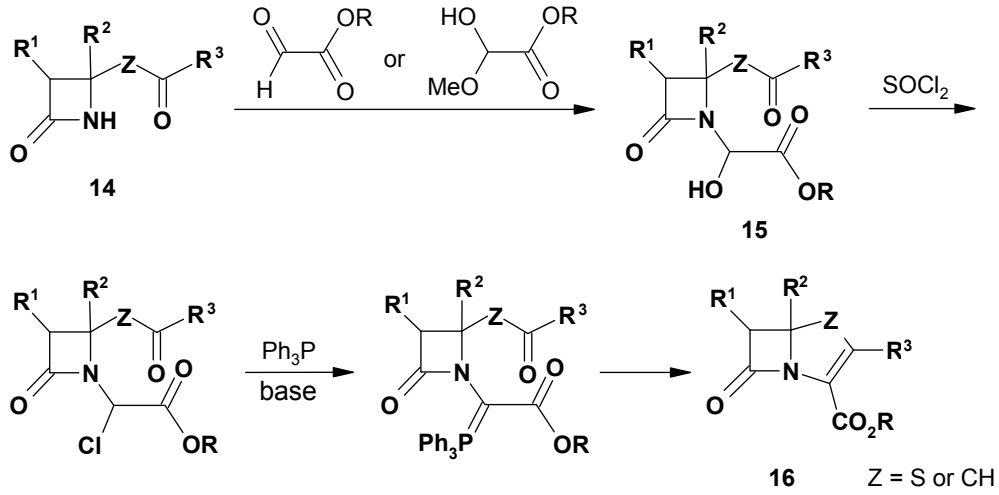


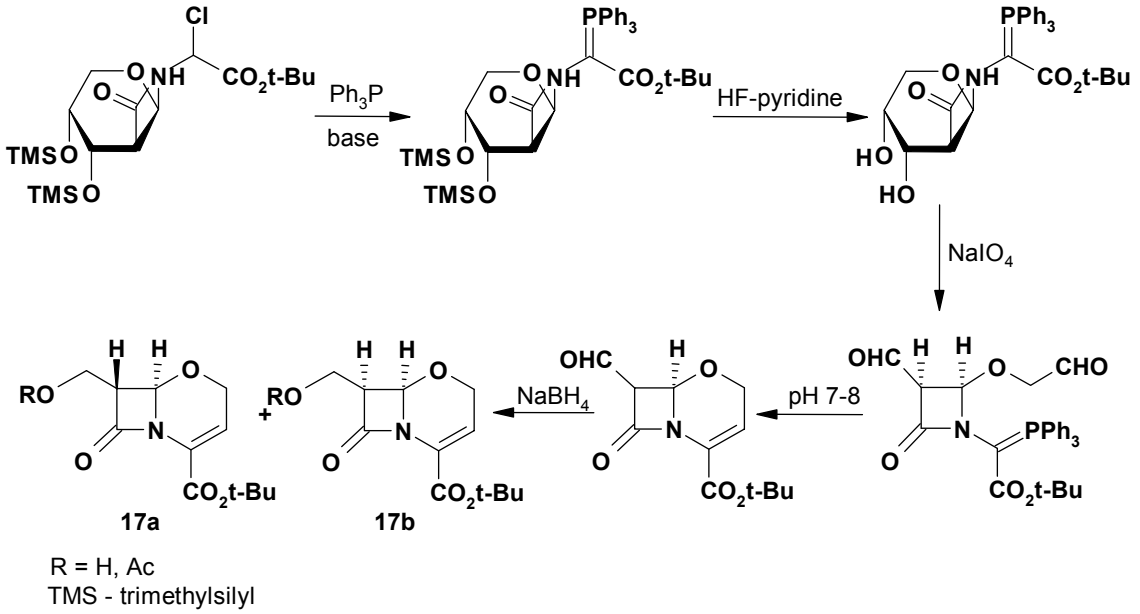
Figure 2

As has already been mentioned, attempts to isolate phosphonium ylides **9** derived from *N*-acyl-α-triphenylphosphonioglycinates failed, because they are generated from the corresponding phosphonium salts simultaneously with *N*-acyliminoacetates **8**, and react easily with the latter compounds to 1,2-di(acylamino)fumarates **7** (Scheme 4). On the other hand, a special class of relatively stable phosphonium ylides **2** derived from glycine, with the nitrogen atom incorporated into a β-lactam ring, is well known. Their stability is probably caused by the lack of hydrogen at the nitrogen atom in the parent phosphonium salts, which makes it impossible to form an iminoacetic acid derivative. The discussed ylides are widely used for the synthesis of bicyclic β-lactam antibiotics. One of the earliest methods of synthesizing them, described by Woodward, consists in the treatment of the corresponding β-lactams **14** with glyoxylic acid esters[17-22] or their hemiacetals,[8,23,24] which yields the corresponding α-hydroxyglycine derivatives **15**. The latter compounds react with thionyl chloride, followed by their reaction with triphenylphosphine in the presence of bases. β-Lactam antibiotics **16** derived from penem-3-carboxylic acid (Z = S)[8,19,23,24] and carbapenem-2-carboxylic acid (Z = CH)[21] were synthesized using this method (Scheme 6).



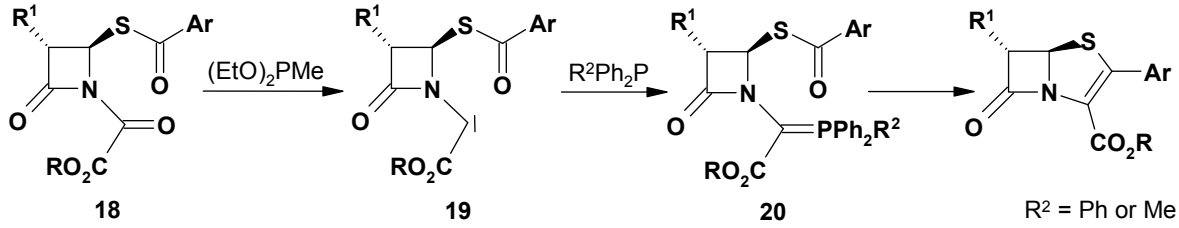
Scheme 6

In a similar way Grodner and Chmielewski obtained 1-oxa-3-cephem-4-carboxylic acid derivatives **17a-b** (Scheme 7).[22]



Scheme 7

In 1995 Hussain and Morgan described another interesting method of synthesizing phosphonium ylides **20** from *N*-oxalated β-lactams **18**, which consists in the transformation of the latter compound under the influence of diethylmethylphosphonite into carbene **19** and trapping the carbene with phosphine (Scheme 8).[25]



Scheme 8

4. Synthesis, properties and application of α-(dialkoxyphosphoryl)glycinates

Since 1973, when Ratcliffe and Christensen used α-(dialkoxyphosphoryl)glycinates **3** in the synthesis of cephalosporins,[9,10] again and again, new information has appeared in the literature devoted both to the methods of synthesizing these important compounds and their application in organic syntheses.

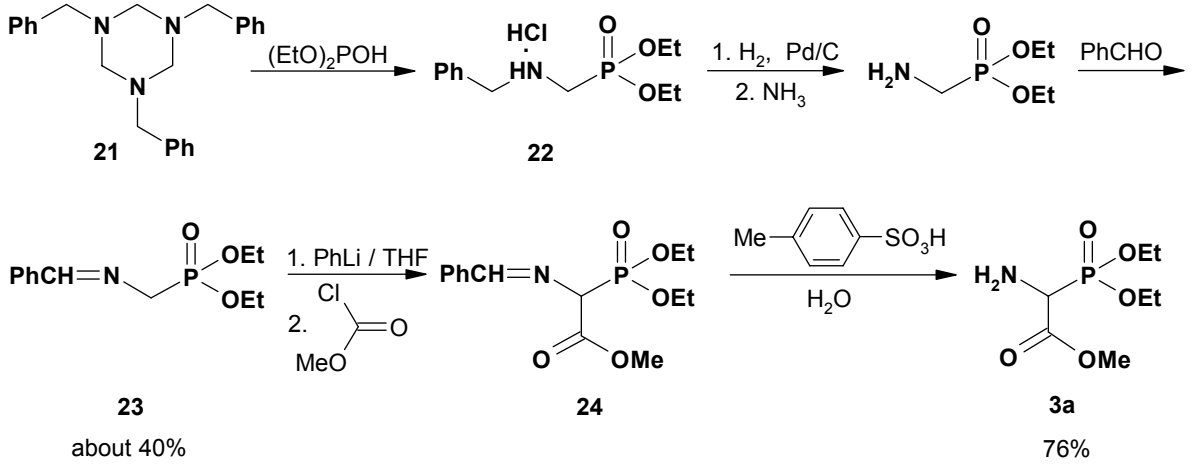
4.1. Synthesis of α-(dialkoxyphosphoryl)glycinates

As the number of described methods of synthesizing α-(dialkoxyphosphoryl)glycinates **3** is considerable, these methods will be further on classified in this paper, depending on which of the three bonds of the C_α atom is formed the last, as follows:

- formation of the C_α-COOR bond,
- formation of the C_α-N bond,
- formation of the C_α-P bond.

4.1.1. Formation of the C_α–COOR bond

One of the earliest methods of synthesizing α-(dialkoxyphosphoryl)glycinates consisted in the acylation of the carbanion generated from Schiff base **23** with methyl chloroformate, followed by the removal of the benzylidene group. The Schiff base **23** derived from ethyl aminomethylphosphonate was obtained in the reaction of 1,3,5-tribenzylhexahydro-s-triazine **21** with diethyl phosphite followed by the hydrogenolytic debenzylation of ethyl *N*-benzylaminomethylphosphonate hydrochloride **22**, and the condensation of the obtained amine with benzaldehyde (Scheme 9).[9]

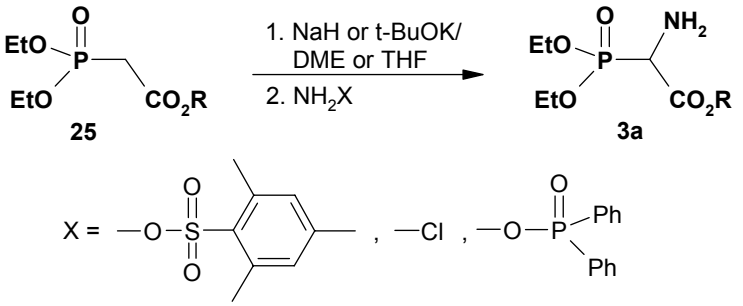


Scheme 9

4.1.2. Formation of the C_α–N bond

Among methods in which the final step is the formation of the C_α-N bond, two sub-groups may be distinguished: (i) the direct electrophilic amination of dialkoxyphosphorylacetic acid derivatives **25**, and (ii) methods consisting in a multi-step formation of the C_α-N bond.

Several methods of synthesizing α-(diethoxyphosphoryl)glycinates **3a** by the direct electrophilic amination of enolates derived from dialkoxyphosphorylacetates **25** have been described (Scheme 10).



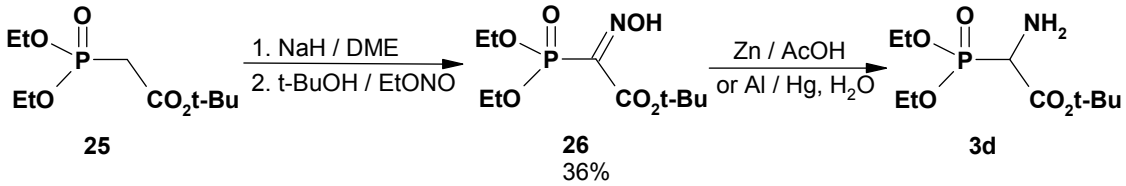
Scheme 10

Amination with *O*-mesitylenesulfonylhydroxylamine, carried out in DME in the presence of sodium hydride gives the expected α-(diethoxyphosphoryl)glycinates in about 40% yield.[26] The explosive properties of *O*-mesitylenesulfonylhydroxylamine are the main drawback of this method.[26]

Chloramine in the presence of sodium hydride or potassium *t*-butoxide was also used for the amination of diethoxyphosphorylate **25** giving the amination product **3a** in 24-84% yields (Scheme 10).[27] This method does not seem to be a suitable process for large scale preparations, because of the difficulty of generating the hazardous chloramine in a large quantity.[27]

O-(Diphenylphosphinyl)hydroxylamine, which can be prepared easily from hydroxylamine hydrochloride and diphenylphosphinyl chloride, seems to be a better reagent for C_α-amination of diethoxyphosphorylacetates **25**.[28] Benzyl diethoxyphosphorylacetate (**25**, R = $PhCH_2$) was aminated with this reagent in THF at –78°C in the presence of sodium hydride, obtaining the amination product **3a** in 60-74% yields.[28-30]

Electrophilic amination of the α-position of diethoxyphosphorylacetates can also be performed in a few steps, e.g. by the reaction of the enolate anion derived from the ester **25** with ethyl nitrite, followed by the reduction of the obtained oxime **26** with zinc in acetic acid or aluminum amalgam (Scheme 11).[27,31] The low yield of the oxime synthesis is the main limitation of this method.[27]

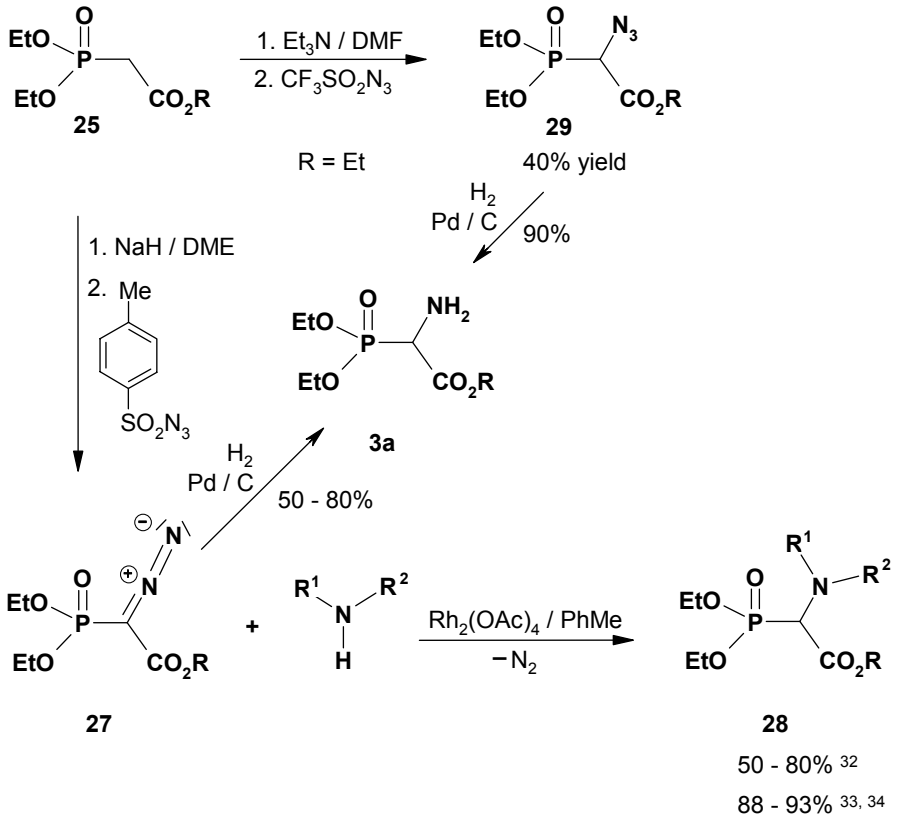


Scheme 11

It has also been shown that the reaction of the enolate anion of *t*-butyl diethoxyphosphorylacetate (**25**, R = *t*-Bu) with tosyl azide in 1,2-dimethoxyethane at 0°C leads

to the corresponding diazo derivative **27** with a yield of 81% (Scheme 12).[27] Subsequent catalytic hydrogenation of the latter compound using 10% palladium on charcoal in methanol gave the desired amination product **3a** in a good yield.[27]

Diazo derivatives of diethoxyphosphorylacetates **27** were also used as precursors of rhodium carbenoids in N-H insertion reactions catalyzed by rhodium (II) acetate.[32] A wide range of amines (R^1 = aryl, R^2 = H) and amides (R^1 = acyl, R^2 = H or alkyl) was used in this reaction to get the amination product in moderate to good yields.[32-34] It should be noted, that both tosyl azide and diazo compound **27** are potentially explosive.[32]



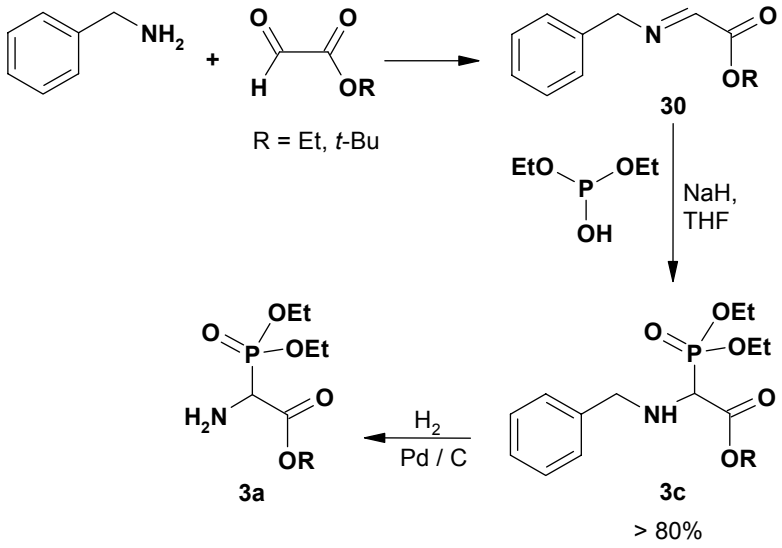
Scheme 12

The amination of diethoxyphosphorylacetates can also be carried out via the azido derivative **29** (R = Et), which was obtained in the reaction of the corresponding starting compound **25** with trifluoromethanesulfonyl azide in a yield of 40%.[35] Catalytic hydrogenation of the azide **29** gave the corresponding α-(diethoxyphosphoryl)glycinate **3a** in a 90% yield (Scheme 12).[35]

4.1.3. Formation of the C_α–P bond

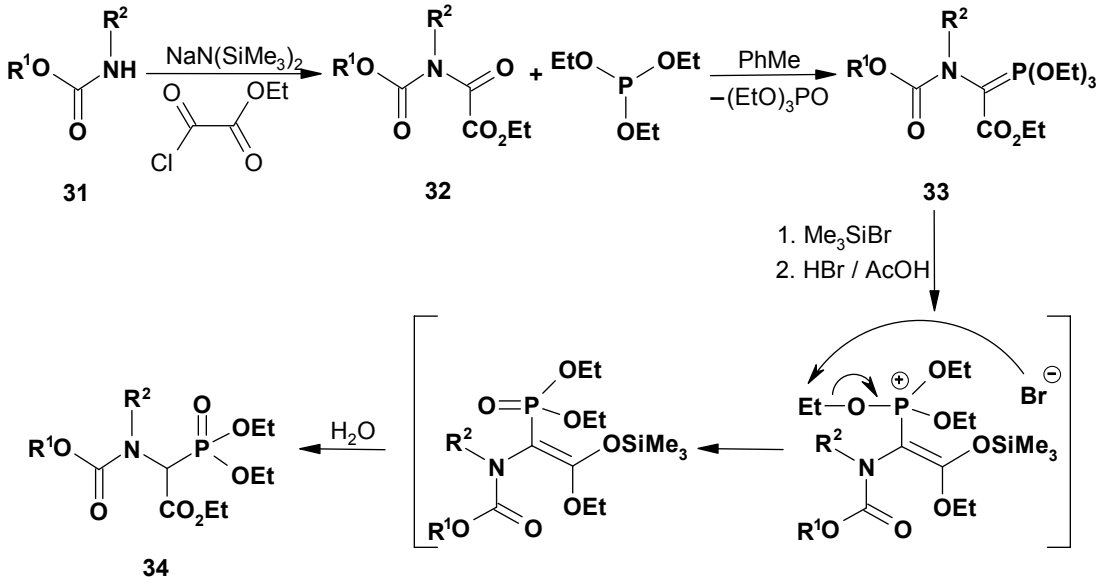
Several methods of synthesizing α-(diethoxyphosphoryl)glycinates by the formation of a C_α-P bond have also been described. One of them consists in the addition of diethyl phosphite to the

Schiff base **30** in the presence of sodium hydride. The addition product **3c** was then catalytically hydrogenated to the corresponding α-(diethoxyphosphoryl)glycinate **3a** in a quantitative yield (Scheme 13).[35]



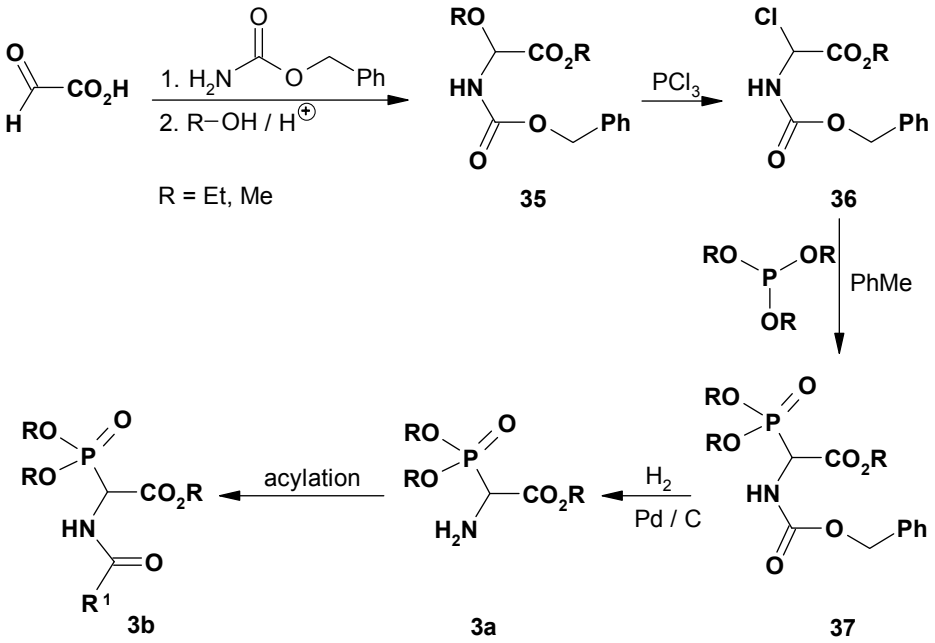
Scheme 13

Seki *et al.* developed a method for synthesizing α-(diethoxyphosphoryl)glycinates consisting in the treatment of *N*-oxalylcarbamates **32** with triethyl phosphite which yields the unstable triethoxyphosphoranylidene derivatives **33**. These latter compounds were reacted with bromotrimethylsilane and then with hydrogen bromide in acetic acid to get α-(diethoxyphosphoryl)glycinate derivatives **34** with a yield exceeding 80% (Scheme 14).[36,37]



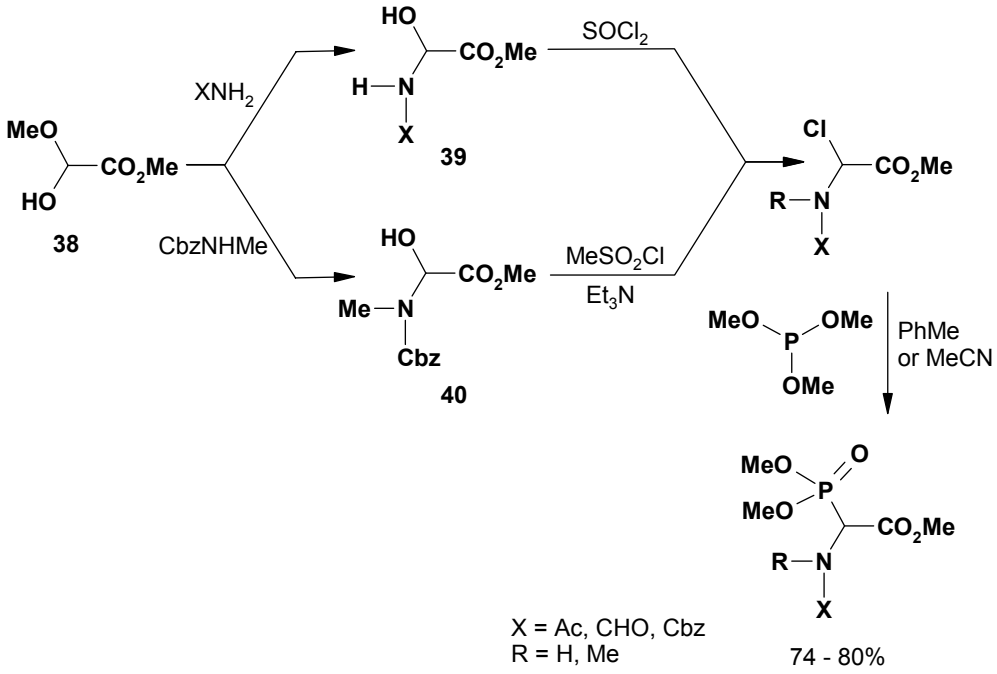
Scheme 14

The multi-step synthesis of *N*-benzyloxycarbonyl-α-(diethoxyphosphoryl)glycinates **37** by the Michaelis-Arbuzov reaction of α-chloroglycinates **36** with trialkyl phosphites described by Schmidt *et al.* is the most frequently used method for the preparation of these compounds.[38,39] α-Alkoxyglycinates **35** were obtained from glyoxylic acid and benzyl carbamate. Its reaction with PCl_3 followed by the reaction with trialkyl phosphite gave *N*-benzyloxycarbonyl-α-(dialkoxyphosphoryl)glycinates **37** in 80-90% yield. *N*-Acyl-α-(dialkoxyphosphoryl)glycinates with other *N*-protecting groups can be obtained by catalytic hydrogenation of the benzyloxycarbonyl group and reacylation (Scheme 15).[38]



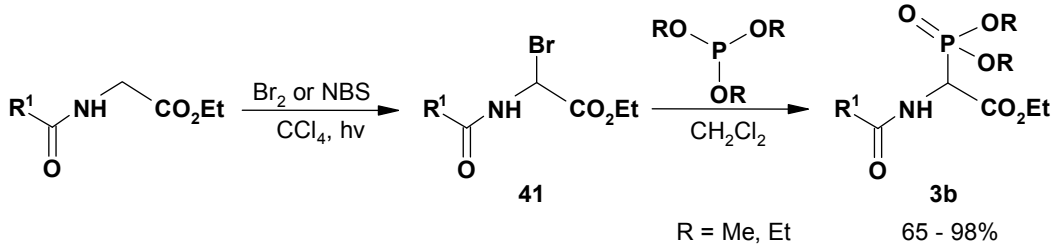
Scheme 15

The synthesis of *N*-formyl-, *N*-acetyl- and *N*-benzyloxycarbonyl-α-(dialkoxyphosphoryl)glycinates according to Schmidt's modified procedure has been described, too (Scheme 16). Condensation of methyl glyoxylate hemiacetal **38** with the corresponding amides yielded *N*-acylamino-α-hydroxyglycinates **39-40**, which were treated with $SOCl_2$ or methylsulfonyl chloride and then with trimethyl phosphite resulting in the expected *N*-acyl-α-(dialkoxyphosphoryl)glycinates in good yields.[40,41]



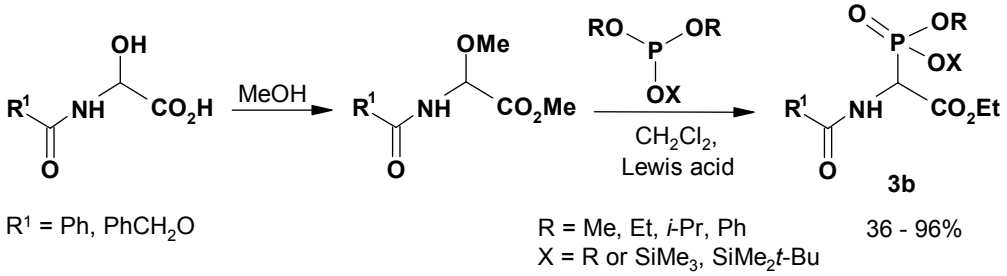
Scheme 16

The similar synthesis of *N*-acyl-α-(dialkoxyphosphoryl)glycinates from *N*-acyl-α-bromoglycinates **41** and trialkyl phosphite in the Michaelis-Arbuzov reaction was described by Kober and Steglich (Scheme 17).[1]



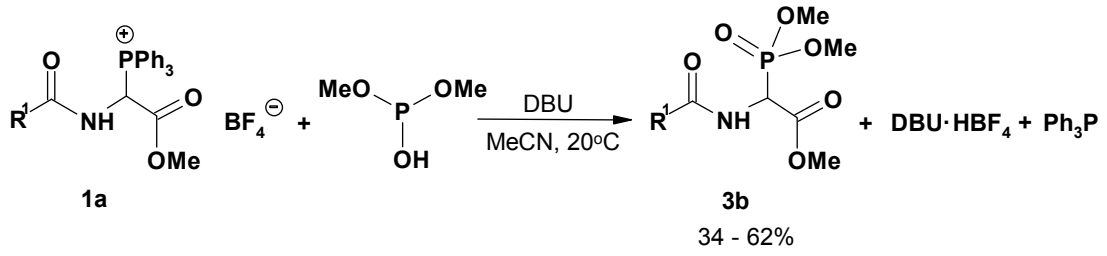
Scheme 17

The synthesis of *N*-acyl-α-phosphorylglycinates by the direct displacement of the methoxy group in methyl *N*-acyl-α-methoxyglycinates with trialkyl- or dialkyltrimethylsilyl phosphites in the presence of Lewis acids, like $BF_3 \cdot OEt_2$, $AlCl_4$, $TiCl_4$ or $SnCl_4$ has been described, too (Scheme 18).[42]



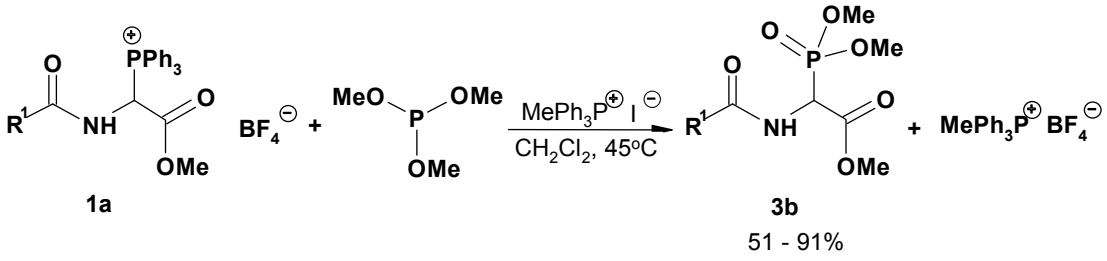
Scheme 18

Recently, two convenient methods for synthesizing *N*-acyl-α-(dialkoxyphosphoryl)glycinates from easily available *N*-acyl-α-triphenylphosphonioglycinates **1a** have been described. The first one consists in the displacement of the triphenylphosphonium group by dimethylphosphite in the Michaelis-Becker type reaction (Scheme 19).[43]



Scheme 19

In the second method, methyl esters of *N*-acyl-α-triphenylphosphonioglycine tetrafluoroborates **1a** are transformed into α-(dialkoxyphosphoryl)glycinates **3b** in the Michaelis-Arbuzov type reaction with trimethylphosphite in the presence of catalytic amounts of methyltriphenylphosphonium iodide (Scheme 20).[7,43]

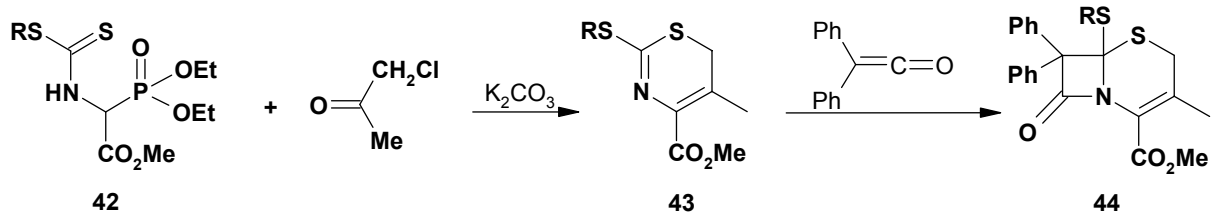


Scheme 20

4.2 α-(Dialkoxyphosphoryl)glycinates in synthesis of β-lactam antibiotics

Historically the first, and also one of the most important applications of α-(dialkoxyphosphoryl)glycinates is their use in syntheses of bicyclic and polycyclic β-lactam antibiotics derived from cephem, carbacephem, penem and carbapenem, both natural ones and those obtained synthetically (Figure 2). α-(Dialkoxyphosphoryl)glycinates are used as key intermediates at the stage of closing a five- or six-membered carbo- or heterocyclic ring fused with a β-lactam ring in the final structure.

Early information provided in literature in the years 1973-1977 described the procedure of closing of a six-membered thiazine ring in the Wadsworth-Emmons reaction of α-(diethoxyphosphoryl)glycinates **42** with chloroacetone.[9,10,26] A 2-cephem skeleton of (±)-cephalotin **44** was obtained by cycloaddition of diphenylketene to the thiazine derivative **43** (Scheme 21).[26]

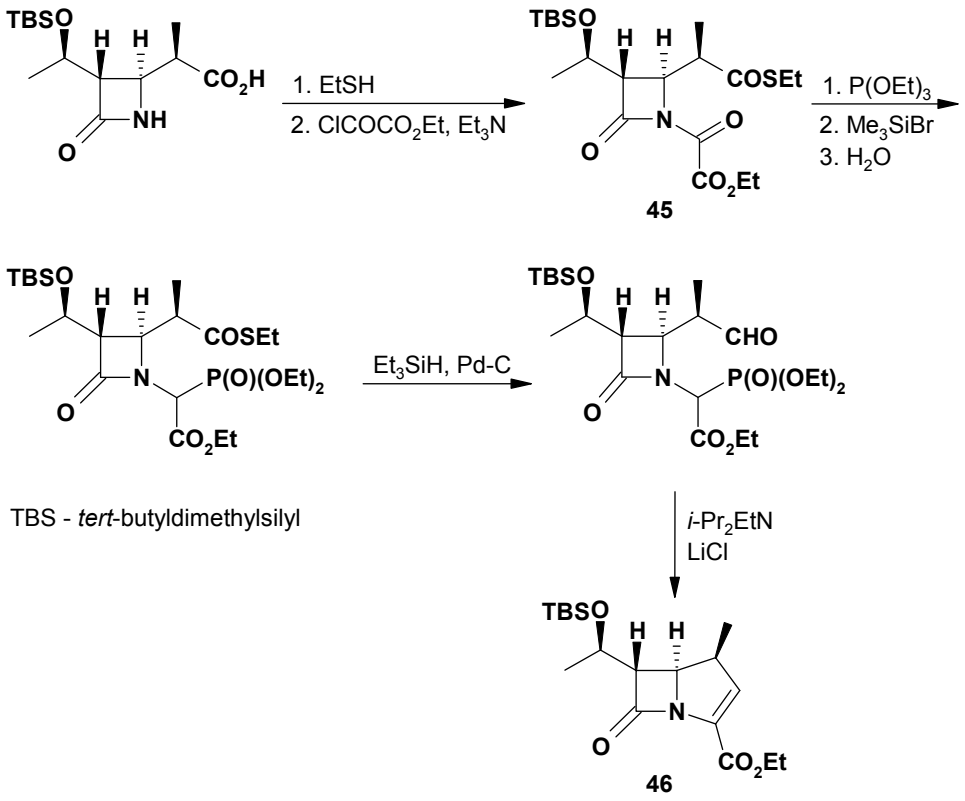


42 **43** **44**

R = Me or H

Scheme 21

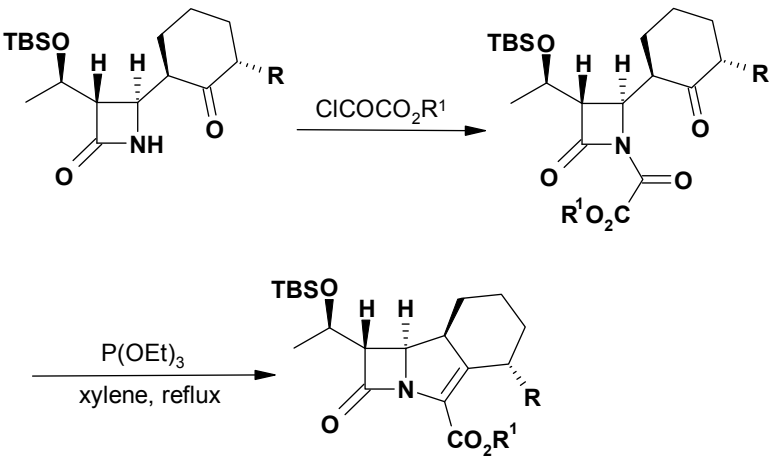
β-Lactam antibiotics derived from 2-carbaphenemic acid **46** were obtained by the intramolecular Wadsworth-Emmons reaction, which gave the unsaturated 5-membered ring condensed with the previously formed β-lactam ring (Scheme 22).[36,44,45]



Scheme 22

The α-(diethoxyphosphoryl)glycinate moiety was synthesized by *N*-acylation of β-lactam with ethyl oxalyl chloride followed by the reaction of the obtained oxamate **45** with triethyl phosphite and bromotrimethylsilane, the mechanism of which is analogous to the one shown in Scheme 14.

A similar method was used for the synthesis of fused tricyclic carbapenems, which bear the name "trinems"(Scheme 23).[15,46]

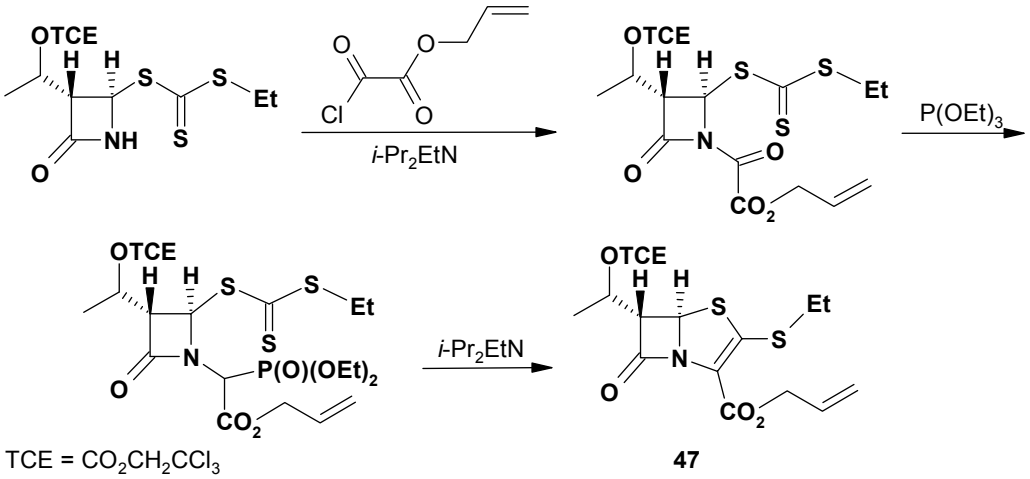


R^1 = benzyl or allyl

TBS - *tert*-butyldimethylsilyl

Scheme 23

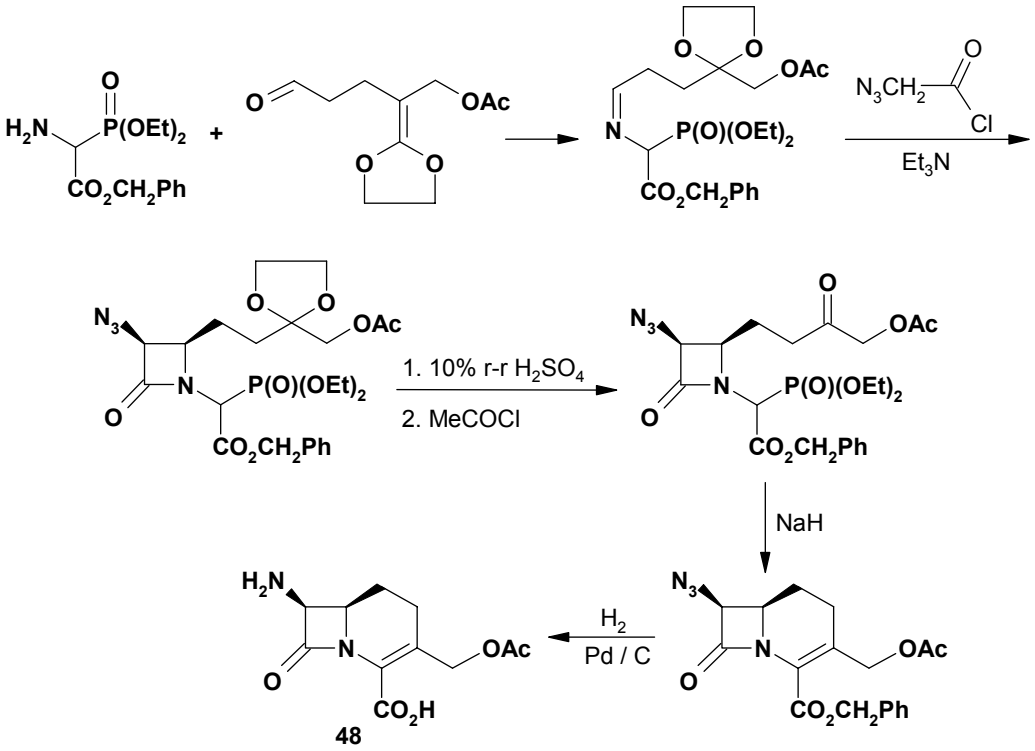
Similarly, the Wadsworth-Emmons reaction was applied for the synthesis of β-lactam antibiotics derived from penem **47** (Scheme 24).[47]



TCE = $CO_2CH_2CCl_3$ **47**

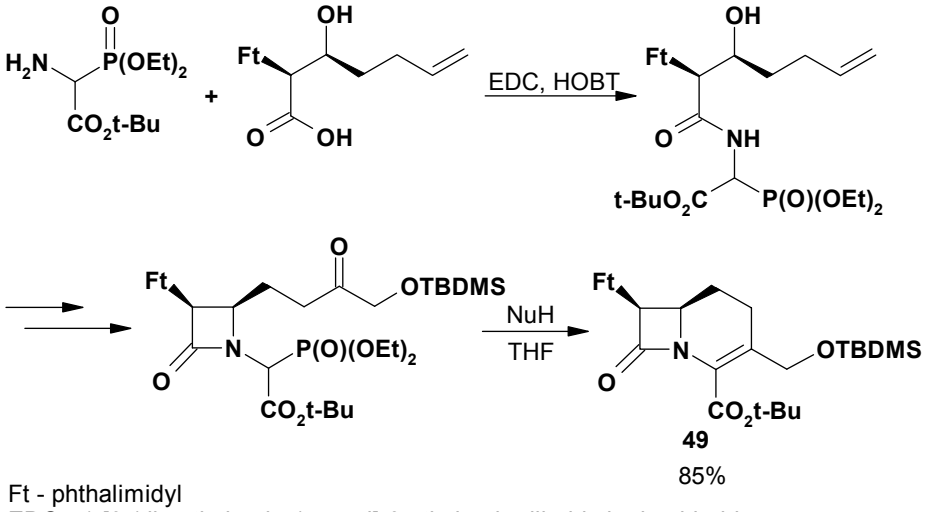
Scheme 24

Another example of the application of α-(diethoxyphosphoryl)glycinates in the intramolecular Wadsworth-Emmons reaction for the synthesis of β-lactam antibiotics is the total synthesis of the racemic form of (±)-7-amino-1-carbocephalosporanic acid **48** (Scheme 25).[48]



Scheme 25

Later, a similar, total asymmetric synthesis of a carbacephem derivative **49** was described (Scheme 26).[29]



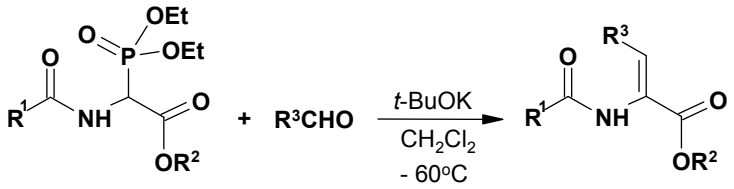
Ft - phthalimidyl
EDC - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
HOBT - 1-hydroxybenzotriazole
TBDMS - *tert*-butyldimethylsilyl

Scheme 26

4.3. α-(Dialkoxyphosphoryl)glycinates in the synthesis of α,β-dehydro-α-amino acids and other bioactive compounds by the Wadsworth-Emmons reaction

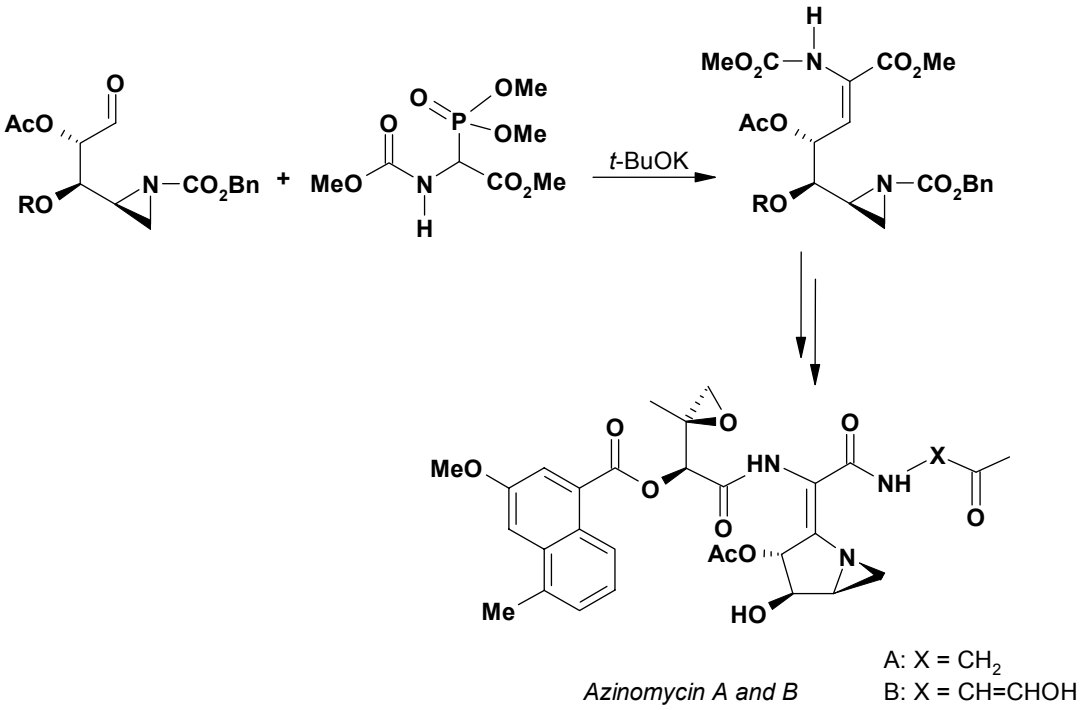
The widest application of α-(dialkoxyphosphoryl)glycinates is their use in the Wadsworth-Emmons synthesis of α,β-dehydro-α-amino acids.[7,30,38,49-73] The latter compounds are common components of naturally occurring peptides;[71,74-77] apart from that, their hydrogenation using Wilkinson-type chiral catalysts is considered to be one of the most general methods for the enantioselective synthesis of α-amino acids.[71-72,76]

The synthesis of α,β-dehydro-α-amino acids, including their synthesis from α-(dialkoxyphosphoryl)glycinates in the Wadsworth-Emmons reaction, was the subject matter of a few excellent reviews.[60,71-73] The most frequently used and very useful procedure for preparing a wide variety of α,β-dehydro-α-amino acids from *N*-acyl-α-(dialkoxyphosphoryl)glycinates **3b** was developed by Schmidt *et. al*.[38] Schmidt's method consists in the condensation of *N*-acyl-α-(dialkoxyphosphoryl)glycinates with aromatic, heteroaromatic or aliphatic aldehydes in CH_2Cl_2 at –60°C in the presence of potassium *t*-butoxide, which gives yields in the range of 80-95% (Scheme 27).[38] Under such conditions, *Z*-isomers are formed preferentially from aldehydes, whereas ketones do not react. Other bases, e.g. NaH, or LDA can also be employed (Scheme 27).



Scheme 27

More recently many new interesting examples of the application of the Wadsworth-Emmons reaction of α-(dialkoxyphosphoryl)glycinates **3a-c** for syntheses of bioactive α,β-dehydropeptides,[41,78-84] peptides[85] and glycoproteins[86-88] have been described.



Scheme 28

For example, it was used for the total synthesis of cyclic heptapeptide microcystin-LA – a serine-threonine phosphatase inhibitor[41] as well as for the synthesis of α,β-dehydropeptides related to the azinomycin A and B antitumor antibiotics.[80-84]

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