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Synthesis of α-aminophosphonates and related derivatives under microwave conditions

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Academic Editor: name

Received: date; Accepted: date; Published: date

Abstract: α-Aminophosphonates and related derivatives represent one of the most important class of organophosphorus compounds. The most widely applied synthetic routes towards α-aminophosphonates involve the Kabachnik-Fields condensation and the Pudovik reaction. In this paper the microwave (MW)-assisted catalyst- and mostly solvent-free syntheses of various α-aminophosphonates and α-aminophosphine oxides are discussed. Bis(aminophosphonate) derivatives were also prepared by the double Kabachnik-Fields reaction. Furthermore, the synthesis of amino-methylenebisphosphonates and amino-methylenebisphosphine oxides is also described.

Keywords: α-aminophosphonates; α-aminophosphine oxides; amino-methylenebisphosphonates; Kabachnik-Fields reaction; Pudovik reaction; microwave

1. Introduction

These days, α-aminophosphonates and related derivatives are in the focus due to their broad spectrum of biological activity [1]. They are important targets in bio- [1,2], medicinal- [3–6] and pesticide chemistry [7–9]. One of the most common synthetic routes towards α-aminophosphonates and α-aminophosphine oxides is the Kabachnik-Fields (phospha-Mannich) reaction, involving the condensation of an amine, an oxo compound and a >P(O)H species, such as a dialkyl phosphite or a secondary phosphine oxide [10–13]. The other main route is the Pudovik (aza-Pudovik) reaction of imines with >P(O)H reagents [14,15]. Most of the papers dealing with the two routes mentioned above suggest the use of special catalysts, with or without the use of a solvent [13,16–18].

In this paper, the MW-assisted synthesis of α-aminophosphonates and α-aminophosphine oxides by the catalyst- and solvent-free Kabachnik-Fields condensation is summarized. The preparation of bis(aminophosphonates) and bis(aminophosphine oxides) by the double Kabachnik-Fields reaction, as well as the utilization of the latter compounds are also discussed. Another „green" accomplishment of the synthesis of α-aryl-α-aminophosphonate derivatives, the Pudovik reaction is also summarized. Finally, the synthesis of amino-methylenebisphosphonates and amino-methylenebisphosphine oxides is described.

2. Results and Discussion

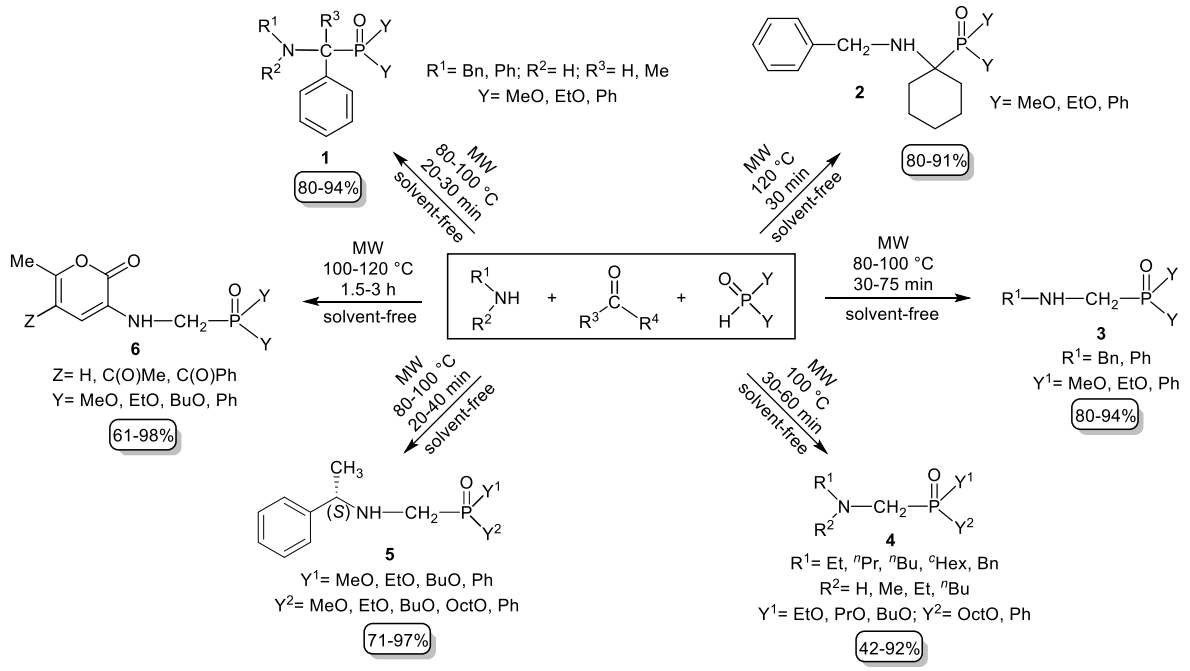
2.1. Synthesis of α-aminophosphonates and α-aminophosphine oxides by MW-assisted Kabachnik-Fields reactions

In the Kabachnik-Fields reaction of amines, oxo compounds and >P(O)H reagents, a number of α-aminophosphonate derivatives (**1-6**) could be synthesized by the solvent- and catalyst-free MW-assisted Kabachnik–Fields reaction (Scheme 1). By the condensation of aniline or benzyl amine, benzaldehyde or acetophenone and dialkyl phosphites or diphenylphosphine oxide, the corresponding products (**1**) were prepared at 80–100 °C for 20–30 min in yields of 80–94% [19].

When cyclohexanone was applied as the oxo-reagent, a slightly higher temperature was necessary to furnish the corresponding aminophosphonate derivatives (**2**). Starting from paraformaldehyde, several compounds containing N-CH_2-P moiety (**3-6**) were also prepared [19–23]. As a P-chiral building block, ethyl octyl phosphite (Y^1=EtO; Y^2= OctO) or alkyl phenyl-*H*-phosphinates (Y^1=EtO, PrO, BuO; Y^2= Ph) were utilized in the three-component condensation [20,21]. The synthesis of optically active α-aminophosphonates (**4**) was elaborated using (*S*)-α-phenylethylamine as the amine component [22]. Using 3-amino-6-methyl-2*H*-pyran-2-ones, a series of heterocyclic α-aminophosphonate derivatives (**6**) was obtained in yields 61–98% [23].

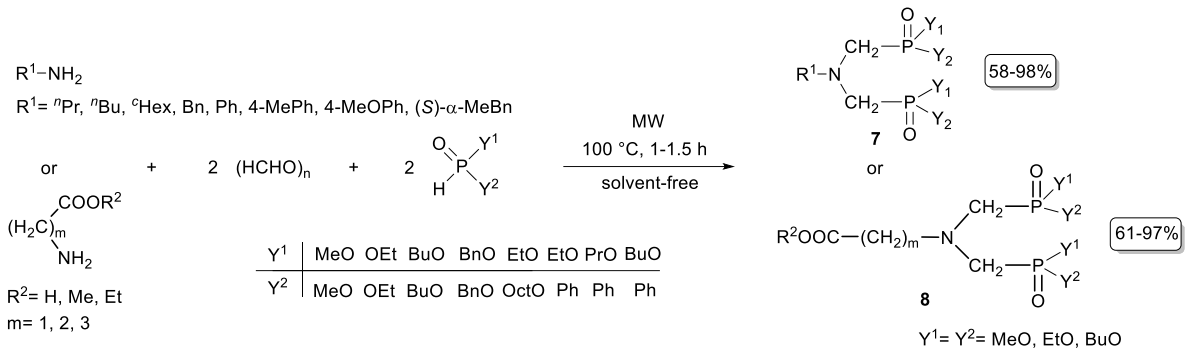
The Kabachnik-Fields reaction of benzylamine, benzaldehyde and triethyl phosphite or diethyl phosphite was also studied in water. It was found that in case of triethyl phosphite, *p*-toluenesulfonic acid (PTSA) had to be used as the catalyst, however, using diethyl phosphite, the reaction could be performed without any catalyst, in a solvent-free manner [24].

As a new development, the flow Kabachnik-Fields reaction is also being studied in a self-designed continuous flow MW system [25].



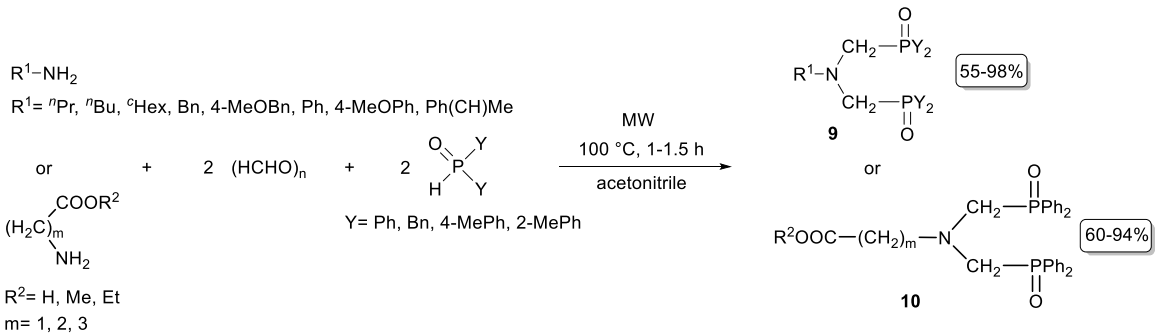
Scheme 1. Synthesis of α-aminophosphonates and α-aminophosphine oxides**.**

As an extension, double Kabachnik–Fields reactions were also performed using two equivalents of paraformaldehyde and two equivalents of dialkyl phosphites or alkyl phenyl-*H*-phosphinates (Scheme 2). Starting from primary amines, a few new bis(aminophosphonates) (**7**) were synthesized under MW irradiation without any catalysts and solvents in yields of 58–98% [26–28]. Using chiral building blocks, such as (*S*)-α-phenylethylamine or assymmetric >P(O)H reagent, the synthesis of chiral derivatives was also carried out [20–22]. α-, β- and γ-Amino acids and esters were also suitable amine components in the condensation. The corresponding bis(dialkoxyphosphonylmethyl)amino acid derivatives (**8**) were obtained in yields of 61–97% [29,30].



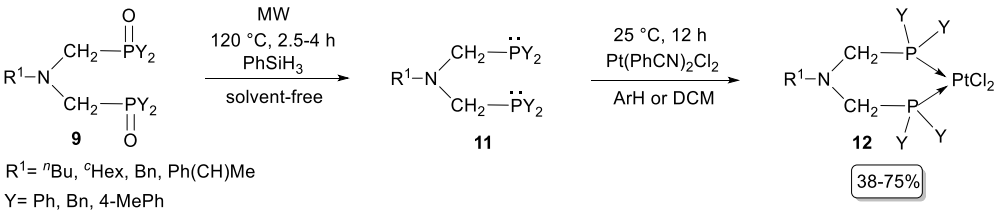
Scheme 2. Synthesis of bis(aminophosphonates) and bis(aminophosphinates).

The double Kabachnik–Fields condensations were also carried out applying secondary phosphine oxides (Scheme 3) [26–30]. To overcome the heterogeneity of the reaction mixture, the reactions were carried out in acetonitrile. The corresponding bis(phosphinoylmethyl)amines (**9** and **10**) were prepared at 100 °C in moderate to high yields.



Scheme 3. Synthesis of bis(aminophosphine oxides) (**9** and **10**).

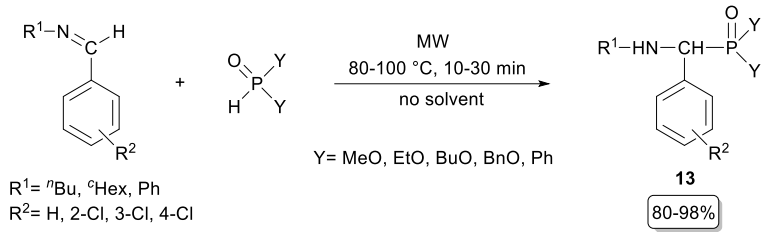
The utilization of the bis(phosphine oxides) (**9**) was also studied. After double deoxygenation of the bis(phosphine oxides) (**9**) with phenyl silane under MW irradiation, the bisphosphines (**11**) obtained were converted to ring platinum complexes (**12**) by reaction with dichlorodibenzonitrile platinum(II) (Scheme 4) [28,31]. The complexes (**12**) proved to be effective catalysts in the hydroformylation of styrene.



Scheme 4. Synthesis of ring platinum complexes (**12**).

2.2. MW-assisted synthesis of α-aryl-α-aminophosphonates and α-aryl-α-aminophosphine oxides by the Pudovik reaction

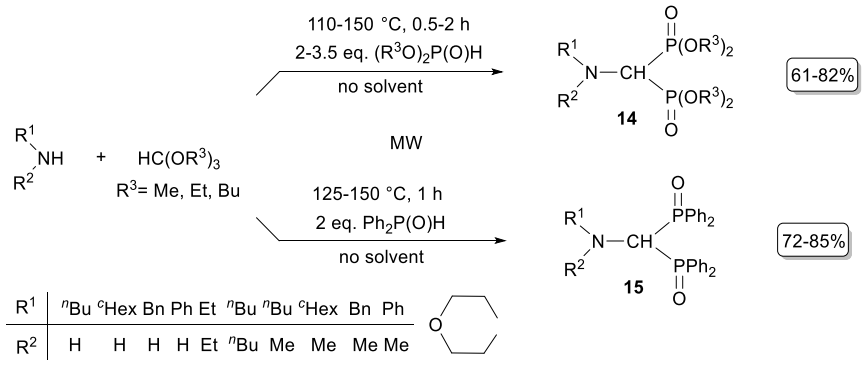
A „green" accomplishment of the (aza-)Pudovik reaction for the synthesis of α-aryl-α-aminophosphonates (**13**, Y= alkoxy) and α-aryl-α-aminophosphine oxides (**13**, Y= Ph) was also investigated [32]. The addition of dialkyl phosphites and diphenylphosphine oxide to imines was carried out under catalyst- and solvent-free MW-assisted conditions.



Scheme 5. MW-assisted synthesis of α-aryl-α-aminophosphonate derivatives (**13**) by the Pudovik reaction

2.3. MW-assisted synthesis of amino-methylenebisphosphonates and amino-methylenebis(phosphine oxides) by three-component condensations

Finally, amino-methylenebisphosphonates (**14**) and amino-methylenebis(phosphine oxides) (**15**) were prepared by the catalyst- and solvent-free three-component condensation of an amine, an orthoformate and dialkyl phosphites or diphenyl phosphine oxide under MW conditions [33]. The yields fell in the range of 61–85%.



Scheme 6. MW-assisted synthesis of amino-methylenebisphosphonates (**14**) and amino-methylenebis(phosphine oxides) (**15**).

3. Conclusion

In summary, several novel mono- and bis(aminophosphonates), as well as related aminophosphine oxides were synthesized by the single and double MW-assisted Kabachnik-Fields reactions. It was proved that under the conditions investigated, there is no need for any catalyst and, in most cases, for any solvent. The bis(aminophosphines) obtained by the deoxygenation of bis(aminophosphinoyl)amines were utilized as bidentate P-ligands in platinum complexes. Furthermore, α-aryl-α-aminophosphonate derivatives were prepared by the (aza-)Pudovik reaction under MW irradiation. Finally, the synthesis of amino-methylenebisphosphonates and amino-methylenebis(phosphine oxides) was accomplished by the three-component condensation of amines, orthoformiates and >P(O)H reagents.

Acknowledgments: This project was supported by the National Research, Development and Innovation Fund (PD111895 and K119202).

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