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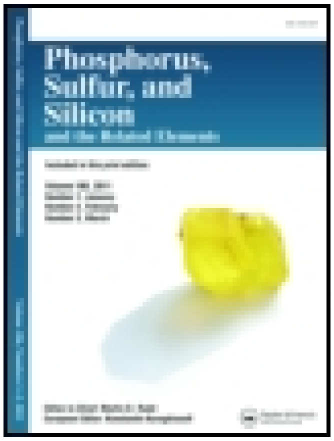

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Synthesis of α-Aminophosphonate Derivatives by Microwave-Assisted Kabachnik-Fields reaction

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SYNTHESIS OF α-AMINOPHOSPHONATE DERIVATIVES BY MICROWAVE-ASSISTED KABACHNIK-FIELDS REACTION

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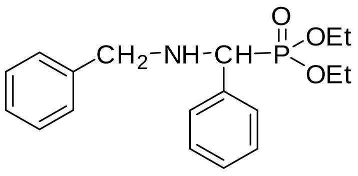
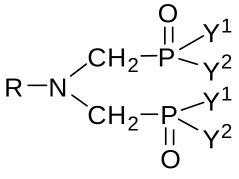
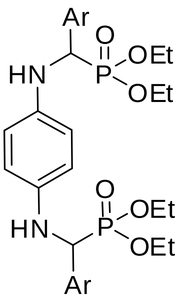
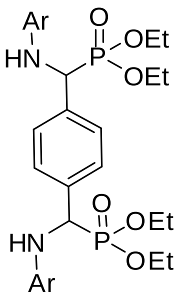
Abstract *The synthesis of aminophosphonates was studied in aqueous solution using triethyl phosphite and under solvent-free and microwave-assisted conditions using >P(O)H species and starting from primary amines or α-, β- and γ-amino acid derivatives. The synthesis of bisaminophosphonates from suitable bifunctional compounds was also investigated in the presence of the T3P® reagent.*









Keywords Kabachnik–Fields reaction, Microwave, α-Aminophosphonate, Ring platinum complex

One of the most convenient and widespread method for the synthesis of α-aminophosphonates is the condensation of an amine, oxo compound and >P(O)H species that is called the Kabachik-Fields reaction.[1] In our research group, these kind of condensations were studied before.[2,3] In this paper, our recent results are summarized on the synthesis of novel α-aminophosphonates.

1.) Kabachnik-Fields reactions using triethyl or diethyl phosphite in water

The model reaction investigated was the condensation of benzylamine, benzaldehyde and triethyl phosphite (TEP) or diethyl phosphite (DEP) at room temperature in water.[4] First, we studied the hydrolysis of TEP to DEP (Scheme 1), and the formation of imine from the aldehyde (Scheme 2). It was found that both processes were relatively fast (with reaction times of 1 h and 6 min, respectively).

In the Kabachnik-Fields reaction of benzylamine, benzaldehyde and TEP in water, the maximum composition of the α-aminophosphonate **1** was 95% after a reaction time of 10 h using 2 equivalents of the phosphite in the presence of 10% of *p*-toluenesulfonic acid (Scheme 3). Using DEP as the P-component, the reaction was slower, and the maximum ratio of the α-aminophosphonate **1** was 76% after 1 day. The condensation was not complete even at a higher temperature.

Therefore, this reaction was carried out in the absence of water at 100 °C under conventional heating and also under MW conditions. It was found that the condensation was complete under both variations, however, under MW irradiation the reaction was much faster. In conclusion, in the condensation with DEP, there is no need for any solvent, water and catalyst as compared to the reaction with TEP. In addition, the TEP is malodorous and the use of excess of this reagent means extra cost. We can say that DEP is preferable to be used in this condensation.

2.) Double Kabachnik-Fields reactions of primary amines

The condensation of primary amines, two equivalents of paraformaldehyde and two equivalents of the >P(O)H species, such as dialkyl phosphites, alkyl phenyl-*H*-phosphinates, diarylphosphine or oxaphosphorine oxide derivatives was carried out under MW conditions at 100 °C, in the absence of catalyst and, in most cases, without any solvent (Scheme 4).[5-7] When diarylphosphine oxides were used as the P-component, the condensations were performed in acetonitrile due to the heterogeneity of the reaction mixtures. The corresponding bis(phosphinoylmethyl)amines (**2**) were obtained in 55-98% yield.

We wished to study the utilization of these bisphosphinoyl compounds, therefore the bis(diphenylphosphinoylmethyl)amines (**2**, Y=Ph) were subjected to double deoxygenation applying phenylsilane (Scheme 5).[5-7] The diphosphines (**3**) obtained were reacted with dichlorodibenzonitrile platinum to furnish ring platinum complexes (**4**) in yields of 38–60%. These complexes (**4**) showed good activity and chemoselectivity, along with an unexpected regioselectivity as catalyst in the hydroformylation of styrene.[7]

3.) Double Kabachnik-Fields reactions of amino acid derivatives

The condensation of α-, β- and γ-amino acid derivatives was studied with two equivalents of paraformaldehyde and two equivalents of dialkyl phosphites or diphenyl phosphine oxide (Scheme 6).[8-9] The condensations were carried out under MW irradiation at 100 °C for 1 h in the absence of catalyst and, except of the reaction with diphenylphosphine oxide, without any solvent. The bis(aminophosphonates) (**5**) expected were obtained in high yields.

In a few cases, comparative thermal experiments were also performed to evaluate the potential of the MW technique. The yields of the thermal control experiments were 7-39% lower indicating the beneficial role of the MW irradiation.

4.) Synthesis of bis(α-aminophosphonates) from bifunctional compounds

We have also studied the synthesis of bisaminophosphonates starting from bifunctional compounds, such as 1,4-phenylenediamnine and terephthalic aldehyde.[10] First the reaction of 1,4-phenylenediamine, two equivalents of aromatic aldehydes and two equivalents of TEP or DEP was investigated in the presence of propylphosphonic anhydride (the T3P® reagent) (Scheme 7). The condensations were performed in ethylacetate/dichloromethane at room temperature, and it was found that the reactions took place through the monoaminophosphonates (**6**) as the intermediates. The bisaminophosphonates (**7**) were obtained in 66-87% yields. It was observed that the condensations with TEP, in most cases, were faster and more efficient, than the reactions with DEP.

Finally, the reation of terephthalic aldehyde was studied with aniline derivatives (Scheme 8).[10] The condensations were also performed at room temperature and resulted in the formation of the corresponding bis(aminophosphonates) (**8**) in shorter reaction times, as compared to the reactions with 1,4-phenylenediamine.

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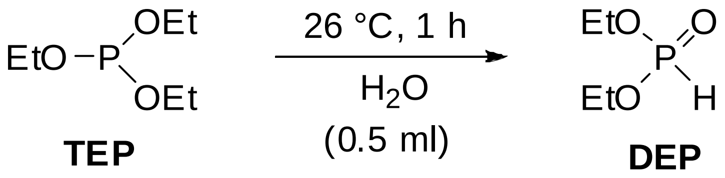
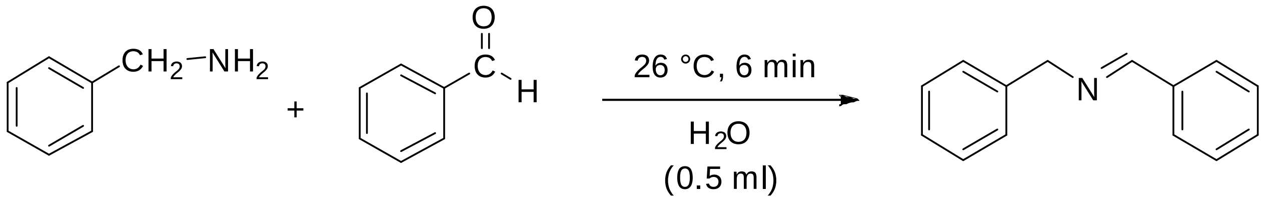
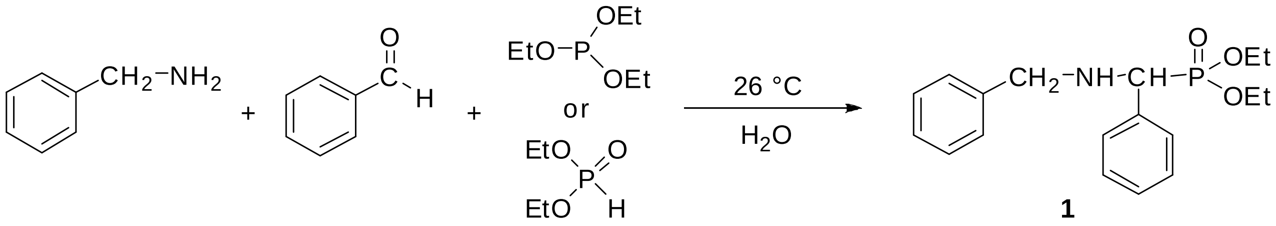


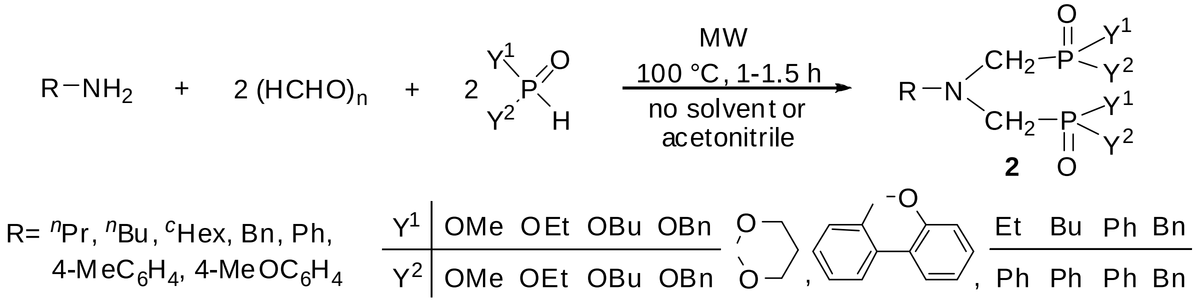
Scheme 1



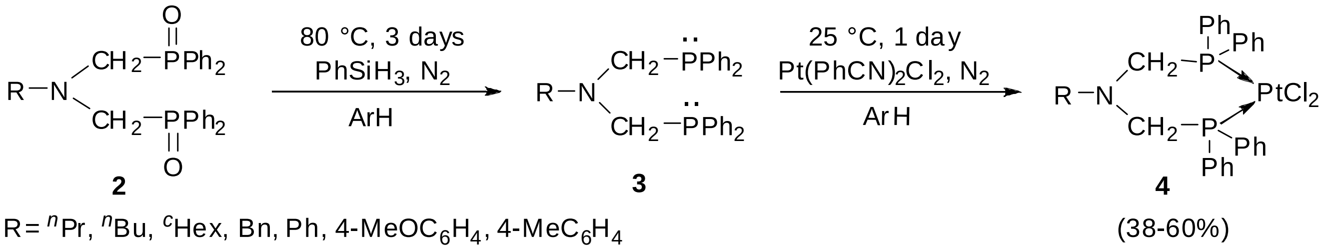
Scheme 2



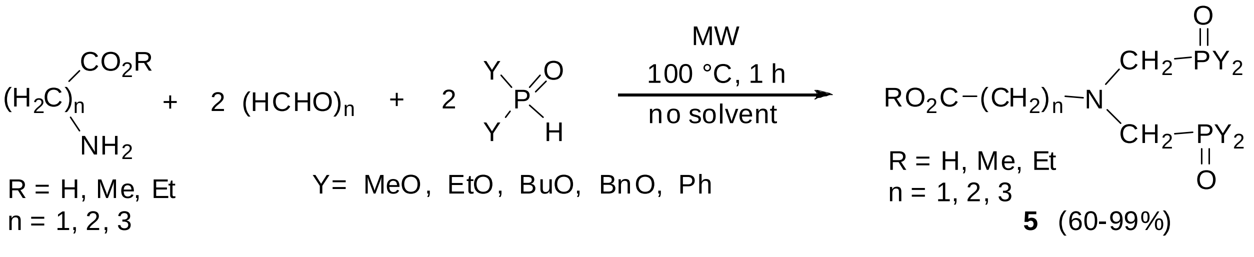
Scheme 3



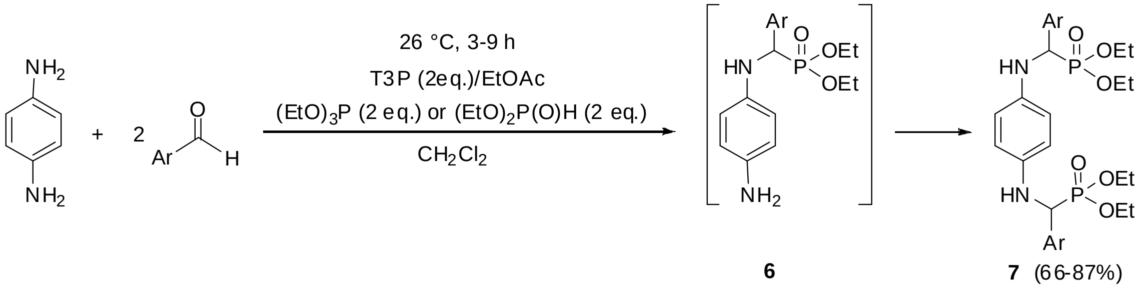
Scheme 4



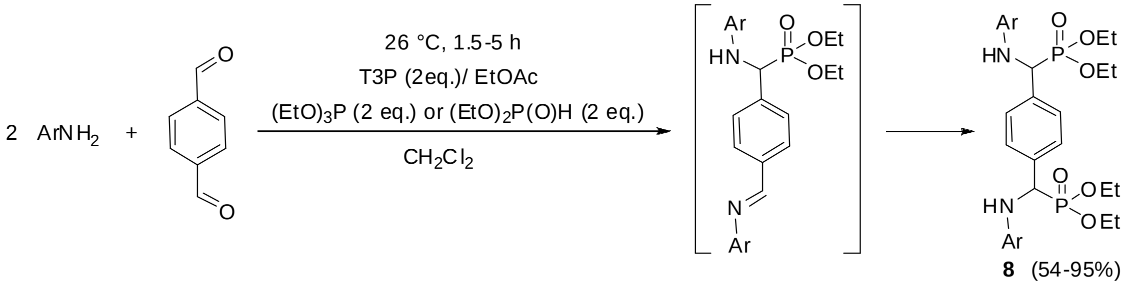
Scheme 5



Scheme 6



Scheme 7



Scheme 8