Synthetic Methods

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One-Pot Tandem 1,4–1,2-Addition of Phosphites to α,β-Unsaturated Imines for the Synthesis of Glutamic Acid Analogues**

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Amino phosphonates and their corresponding amino phosphonic acids are known as amino acid mimetics and, therefore, affect the physiological activity of the cell.[1] The synthesis of 1-alkylamino phosphonates by a reaction of a dialkyl phosphite and an imine under thermal conditions had been described in the early 1950s.[2] However, dialkyl phosphites are generally considered to be poor nucleophiles because they exist predominantly in a $\sigma_4\lambda_5$ configuration.[3] Dialkyl trimethylsilyl phosphites were presented by Afarinkia et al. as excellent mild phosphonylation agents because the more nucleophilic $\sigma_3\lambda_3$ form of the dialkyl phosphite reagent could be obtained by O-silylation with trimethylsilyl chloride (TMSCl) in dichloromethane and triethylamine as the base.[4] Furthermore, exclusive 1,2-addition to α,β-unsaturated imines containing a phenyl group was reported by the same authors using diethyl trimethylsilyl phosphite.[5] During our research into azaheterocyclic phosphonates,[6] we planned to use this phosphonylation reaction with α,β-unsaturated imines **5a–d** derived from cinnamaldehyde. The diethyl trimethylsilyl phosphite was prepared in situ, as described previously.[4] The reaction mixture consisted mainly of the 1,2-adduct **9a** (^{31}P NMR: $\delta = 24.44$ ppm) and residual starting material after 24 h of reaction with the imine **5a**. However, several small ^{31}P NMR signals were present and became more abundant upon prolonged reaction times. The minor peaks appeared as two doublets ($J = 9.7$ Hz) next to two singlets and could be assigned to be the double-addition product **6a** (two diastereomers, ratio: 27:73) after its isolation in very low yield by column chromatography. The same type of product was obtained using imines **5b–d** in increasing amounts proportional to the steric bulk of the *N*-substituent, which also explains the decreasing yields of 1,2-adducts when more sterically demanding *N*-substituents were used in the original

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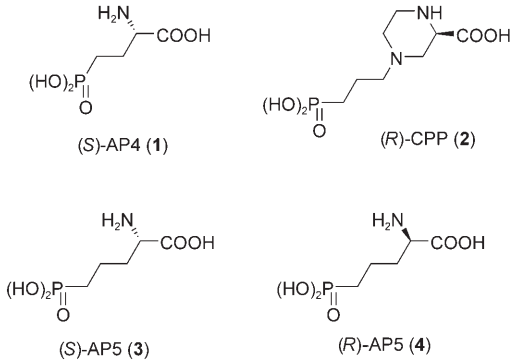
report.[5] With a *N*-phenyl substituent, however, only 1,2-addition was observed.

The obtained diphosphonates can be of major importance because of their high similarity to glutamic acid. (*S*)-Glutamic acid (Glu) is the main excitatory neurotransmitter in the central nervous system (CNS) and operates through two main heterogeneous classes of receptors: ionotropic and metabotropic Glu receptors (iGluRs and mGluRs, respectively). Both classes are further subdivided into several subclasses, but the number of functional receptors in the CNS is not known. Selective Glu agonists and antagonists are not only important for the characterization of different Glu receptor subtypes, but also for the treatment of CNS diseases, such as epilepsy, Huntington's disease, Parkinson's disease, dementia, chronic pain, and so forth. Therefore, the Glu receptor field has been, and continues to be, in a state of almost explosive development.[7] A number of phosphonic acid Glu analogues are known as potent selective Glu antagonists or agonists (Scheme 1). Substitution of the carboxylate group by a bioisosteric phosphonic acid group is known to increase receptor selectivity. For example, (*S*)-AP4 (**1**) is shown as a group III mGluR agonist, some tenfold more potent than Glu.[9] (*S*)-AP5 (**3**) activates the same group III receptors, but with markedly lower potency and selectivity. (*R*)-AP5 (**4**) on the other hand can not be shown to interact with mGluRs, but is a potent and selective competitive *N*-methyl D-aspartate (NMDA; iGluR) antagonist.[8] The diphosphonic acid derivative of AP4 has been tested several times as a Glu analogue without any activity so far.[10] However, further research into new bioisosteres has been indicated as a fruitful path to new subtype-selective mGluR ligands.[7]



Scheme 1. Selected examples of phosphonic acid Glu analogues with GluR-agonist or -antagonist activity.

The previous results prompted us to look for appropriate reaction conditions to achieve higher yields of the desired Glu bioisosteres. When the imine **5b** was added to two equivalents of diethyl trimethylsilyl phosphite, prepared in situ, complete conversion of the imine into the 3-phosphonyl 1-alkylamino phosphonate (PAP) **6c** was achieved after 72 h at reflux. However, when the diethyl trimethylsilyl phosphite was filtered first to remove the triethylammonium salts, no reaction occurred at all when the imine was added. Also no reaction was observed on addition of LiCl or TMSCl, even though the latter was said to act as a catalyst in the reaction mechanism proposed by Afarinkia et al.[4] Addition of NH_4Cl led to approximately the same result as obtained before (complete conversion in 72 h) and acidification of the reaction medium was observed. Therefore, $(NH_4)_2SO_4$ was selected as a more acidic salt to replace the triethylammonium salts after filtration, thus leading to a remarkable acceleration of the reaction rate (complete conversion after 3 h of reflux). Moreover, when diethyl trimethylsilyl phosphite was mixed with an imine in dry dichloromethane, the reaction proceeded violently upon addition of one equivalent of concentrated sulfuric acid to yield **6c** as a single product in 30 minutes at room temperature. Also with other α,β-unsaturated imines, complete conversion into the corresponding PAP was observed.[11] Diastereomeric ratios were determined from ^{31}P and ^{1}H NMR integration measurements (see Table 1).

As the reaction of imine **5b** with diethyl trimethylsilyl phosphite catalyzed by sulfuric acid proceeds too rapidly to detect any reaction intermediates, triethylammonium chloride was selected as a less potent catalyst to monitor the reaction as a function of time. Rapid disappearance of **5b** was observed, whereas the amount of the 1,2-adduct grew accordingly to a maximum. The PAP **6c** was formed more slowly, however, finally becoming the only end product of the reaction (see Figure 1). This kind of behavior suggests that the imine is protonated first by the acid and becomes activated towards nucleophilic attack of the dialkyl trimethylsilyl phosphite (Scheme 2). 1,2-Addition is clearly the fastest reaction pathway and the *N*-trimethylsilyl 1-alkylamino-phosphonate **9** is formed after nucleophilic attack of the nitrogen atom at the trimethylsilyl group of phosphonium salt **8**. These three steps all occur in an equilibrium which was demonstrated in a separate experiment (Scheme 3). When dimethyl (1-amino-1-phenylmethyl)phosphonate (**14**) was N-silylated using TMSCl and subsequently treated with a large excess of diethyl trimethylsilyl phosphite, diethyl phosphonate **15** was mainly recovered along with small amounts of **14**. When the same experiment was repeated without silylation and using diethyl phosphite, no exchange at all occurred. This clearly demonstrated the reversibility (**8**⇌**9**) of the reaction and the leaving-group capacity of the intermediate positively charged phosphonium group.

The initial equilibrium allows two possible routes to the PAP **6** (Scheme 2). The first (pathway A) is complete reversion into the iminium salt **7** followed by a slow 1,4-addition, whereas the second (pathway B) starts with an S_N'-like substitution of the phosphonium group. Both routes yield the same intermediate enamine **10**, which subsequently isomerizes to the imine **11**. A final 1,2-addition then yields PAP **6**, which only shows phosphonyl exchange at the 1 position.

However, enamine **10** or imine **11**, the suggested intermediates in this reaction mechanism (Scheme 2), were never observed. Furthermore, the proposed reaction mechanisms require an external proton source, as one equivalent of protons is incorporated in the final product **6**. Therefore, an experiment was performed using only 0.1 equivalents of sulfuric acid together with 2.0 equivalents of $P(OEt)_2OTMS$.

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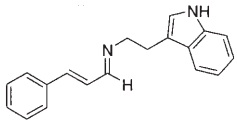
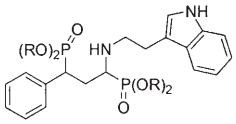
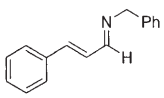
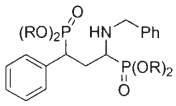
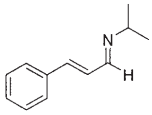
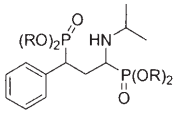
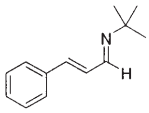
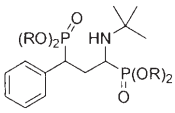
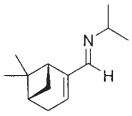
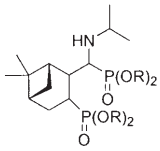
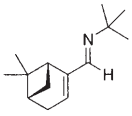
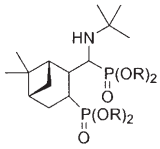
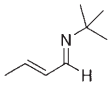
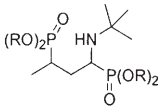
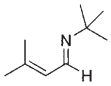
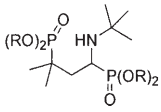
Table 1: Conversion of imines **5** to PAP **6** using $P(OR)_2OTMS$ (2 equiv) and H_2SO_4 (1 equiv).

	Imine	Product		Yield[a] [%]	d.r. [%]
5a			**6a** (R = Et)	82	29:71
5b			**6b** (R = Me) **6c** (R = Et)	70 80	19:81 29:71
5c			**6d** (R = Me) **6e** (R = Et)	77 78	32:68 33:67
5d			**6f** (R = Me) **6g** (R = Et)	82 85	49:51 36:64
5e			**6h** (R = Me)	46	22:78
5f			**6i** (R = Me)	20	12:88
5g			**6j** (R = Me)	74	36:64
5h			**6k** (R = Me)	60	–

[a] Yield after column chromatography or acid–base extraction.

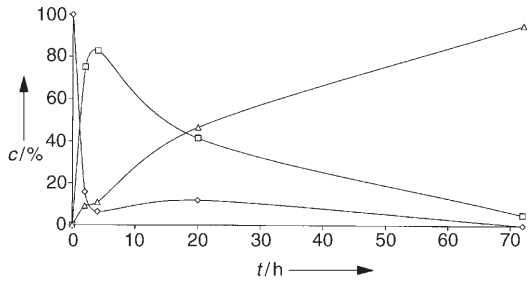


Figure 1. Composition (c) of the reaction mixture during the reaction of **5b** (◇) with $P(OEt)_2OTMS$ in the presence of $HNEt_3Cl$, measured by NMR spectroscopy. 1,2-Adduct **9** (□) appears as an intermediate in the reaction, whereas PAP **6c** (△) seems to be the final product.

The reaction proceeded very sluggishly under these conditions, and the formation of **6** was stopped completely after 3–4 h as expected. From that point, the concentration of **10** started to increase (^{31}P NMR: $\delta = \pm 27$ ppm in the reaction medium), while the rest of the imine **7** was slowly consumed (Figure 2). However, addition of water for the work-up led to the conversion of **10** into **6** and some of the imine **7** into the 1,2-adduct using the remaining phosphite in the reaction mixture. This result shows that water can also act as a proton source for this reaction. The structure of intermediate imine **11** was confirmed in a separate experiment (Scheme 4) using subequivalent amounts of sulfuric acid or the non-protic Lewis acid $AlCl_3$ as an activator, together with a limiting amount of diethyl trimethylsilyl phosphite (0.9 equivalents). Under these conditions, there was no free phosphite in the work-up and the intermediate 1,4-adduct **16** was obtained in a mixture of **6** and starting material **5**. The structure of **16** was confirmed after hydrolysis to the corresponding aldehyde **17** and comparison with literature data.[12]

From the evolution of the reaction intermediates as a function of the reaction time (Figure 2), it is clear that the 1,2-adduct **9** is not a real intermediate of the PAP formation. After the initial 1,2-adduct formation (which can also be noticed in Figure 1), the 1,2-addition is also blocked by the absence of protons. Furthermore, the observation that a considerably higher reaction rate results for imines bearing more sterically demanding N-substituents (tBu > iPr > Bn ≫ Ph) is in favor of the tandem addition, as the 1,2-addition should be slowed down by the steric bulk. One case of a

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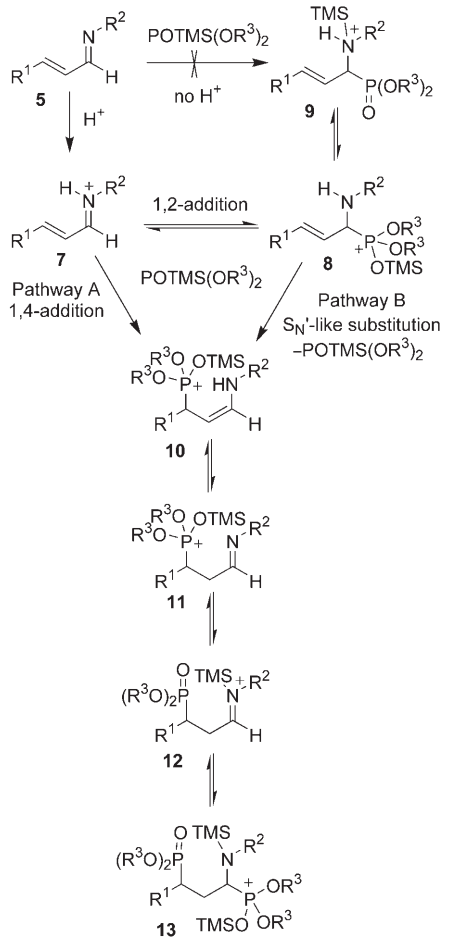
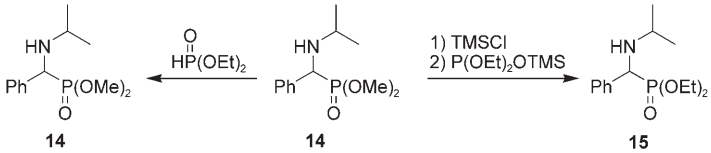


Scheme 2. Suggested reaction mechanisms.



Scheme 3. Phosphonyl exchange reactions.

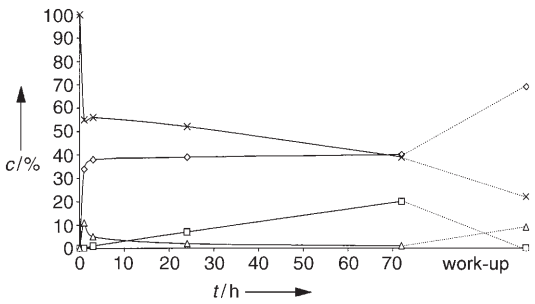
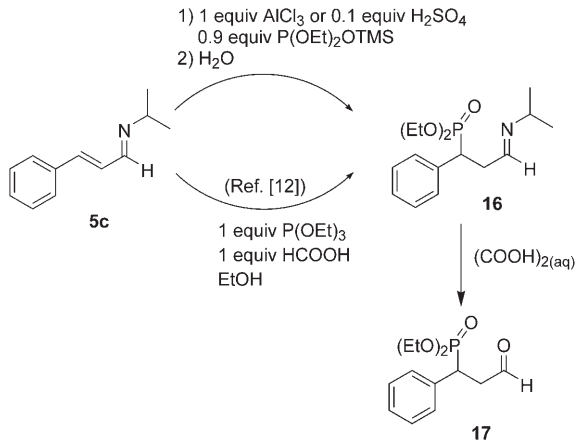


Figure 2. Composition (*c*) of the reaction mixture during the reaction of **5c** (×) with $P(OEt)_2OTMS$ in the presence of 0.1 equivalents of H_2SO_4, measured by NMR spectroscopy. Only a small amount of 1,2-adduct **9** (△) is formed, whereas PAP **6c** (◇) is formed initially very quickly. When the reaction stops because of a lack of protons, the concentration of intermediate enamine **10** (□) starts to increase.



Scheme 4. Isolation and identification of the intermediate 1,4-adduct.

double addition of ketene silyl acetals to α,β-unsaturated imines has been reported, which also proceeded in a 1,4–1,2-tandem fashion.[14]

In summary, our observations in this field lead to a new insight regarding the use of dialkyl trimethylsilyl phosphite which contradicts earlier research:[5] when this reagent is present in its apparently most nucleophilic form, dialkyl trimethylsilyl phosphite fails to react either in a 1,2- or a 1,4-addition in the absence of a protic acid. Furthermore, it has been demonstrated that dialkyl phosphite itself is able to convert imines into the corresponding 1-aminoalkyl phosphonates with complete 1,2-regioselectivity.[2,13] However, in a sufficiently acidic medium, dialkyl trimethylsilyl phosphite is able to convert α,β-unsaturated imines **5** into diphosphonates **6** in one step through a sequential tandem 1,4–1,2-addition (pathway A of Scheme 2).[15] As the free phosphonic acids of diphosphonates[16] are potential Glu agonists or antagonists, our future research will be directed towards the synthesis of enantiopure PAP derivatives.[17]

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Keywords: amino acids · Michael addition · phosphorylation · reaction mechanisms · regioselectivity

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[16] PAPs **6** can be dealkylated using TMSBr, see: C. E. McKenna, M. T. Higa, N. H. Cheung, M. C. McKenna, *Tetrahedron Lett.* **1977**, 155; an example with a general experimental procedure is included in the Supporting Information.
[17] Spectral data, general procedures, sample spectra, and additional mechanistic evidence are available in the Supporting Information.

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