JOC*Note*

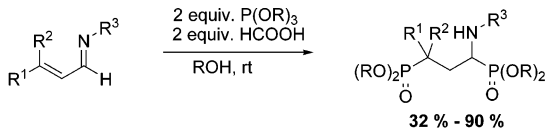
Tandem Addition of Trialkyl Phosphites to α,β-Unsaturated Imines: A Comparison with Silylated Phosphites

Ellen Van Meenen, Kristof Moonen,† Annelies Verwée, and Christian V. Stevens*

Research Group SynBioC, Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

chris.stevens@UGent.be

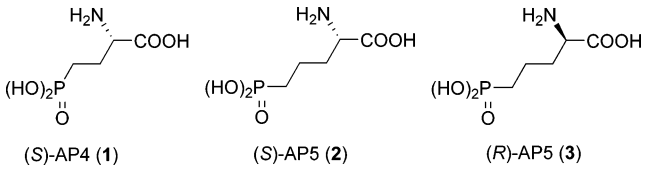
Received June 19, 2006



R = Me, Et; R^1 = Ph, Furan-2-yl, Me; R^2 = Me, H; R^3 = Ph, *i*Pr, allyl, Bn, *p*-OMe-Bn

Trialkyl phosphites were evaluated for addition reactions to α,β-unsaturated imines. An acidic medium is required to allow consecutive 1,4- and 1,2-addition to occur. In this manner, 3-phosphonyl-1-aminophosphonates, phosphonic acid analogues of glutamate, are obtained in good yields (32−90%). The reaction is mainly influenced by the steric bulk of the nitrogen substituent: less steric N-substituents lead to better yields of the tandem adducts.

Glu agonists or antagonists are not only important for the characterization of different Glu receptor subtypes, but also for the treatment of central nervous system diseases, such as epilepsy, Huntington's disease, Parkinson's disease, dementia, and chronic pain. Substitution of the carboxylate group by a bioisosteric phosphonic acid is known to increase receptor selectivity. Several phosphonic acid analogues of glutamate have shown important activities in this area such as (*S*)-AP4 **1**, (*S*)-AP5 **2**, and (*R*)-AP5 **3**. Where **1** and **2** are group III metabotropic Glu Receptor (mGluR) agonists,[1] phosphonic acid analogue **3** is a potent and selective competitive *N*-methyl D-aspartate (NMDA, ionotropic GluR) antagonist.[2] Further research into new bioisosters has been indicated as a fruitful path to new subtype-selective mGluR ligands.[3]



(*S*)-AP4 (**1**) (*S*)-AP5 (**2**) (*R*)-AP5 (**3**)

Recently, we reported for the first time a tandem 1,4−1,2-addition of dialkyl trimethylsilyl phosphite to α,β-unsaturated imines **4** derived from cinnamaldehyde.[4] As a consequence of the fast but reversible 1,2-addition of dialkyl trimethylsilyl phosphite to aldimines, this reaction was erroneously reported earlier to proceed with complete 1,2-regioselectivity.[5] Because of the double addition of dialkyl trimethylsilyl phosphite under acid catalysis, we were able to obtain 3-phosphonyl-1-aminophosphonates **6**,[4] which can be considered as glutamate analogues and may therefore be of interest as selective Glu agonists or antagonists.[3]

The unique reactivity of dialkyl trimethylsilyl phosphite toward α,β-unsaturated imines **4** has prompted us to evaluate the reactivity of other phosphorus nucleophiles. In particular, the resemblance of trialkyl phosphites to dialkyl trimethylsilyl phosphites, suggests these nucleophiles as potential tandem addition candidates. Both phosphite reagents occur in the highly nucleophilic $\sigma_3\lambda_3$ form.

Addition of trialkyl phosphite to α,β-unsaturated imines **4** was reported to proceed with complete 1,4-regioselectivity when a steric nitrogen substituent (*t*-Bu) was used as described by Teulade and Savignac.[6] In this case, imine **4a** was treated with 0.96 equiv of triethyl phosphite in ethanol. A slight excess of formic acid (1.04 equiv) was added to dealkylate the intermediate phosphonium ion. However, when the reaction was repeated with 1 equiv of triethyl phosphite and *i*-Pr imine **4b**, a small amount of 3-phosphonyl-1-aminophosphonate **6b** could be detected in the crude reaction mixture after standard aqueous workup and ^{31}P NMR analysis.[7] With an *N*-phenyl substituent, the 3-phosphonyl-1-aminophosphonate **6c** even becomes the major product next to a considerable amount of unreacted starting material **4c** since only 1 equiv of triethyl phosphite is added (Scheme 1).

These results prompted us to search for appropriate reaction conditions to achieve complete conversion of the imines **4** to the 3-phosphonyl-1-aminophosphonates **6**. The reaction proceeded vigorously upon addition of 2 equiv of formic acid to a mixture of 2 equiv triethyl phosphite and the substrate **4** in ethanol. Complete conversion to the 3-phosphonyl-1-aminophosphonates **6** was obtained in typically 30 min at room temperature. The more sterically demanding *i*-Pr derivative **4b** required 24 h to achieve complete conversion, and the *t*-Bu-

† K. Moonen is aspirant of the Fund for Scientific Research (FWO Vlaanderen).

* To whom correspondence should be addressed. URL: http://www.synbioc.ugent.be.

10.1021/jo061256b CCC: $33.50
Published on Web 09/02/2006

(1) (a) Tanabe, Y.; Nomura, A.; Masu, M.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *J. Neurosci.* **1993**, *13*, 1372; (b) Nakajima, Y.; Iwakabe, H.; Akazawa, C.; Nawa, H.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *J. Biol. Chem.* **1993**, *268*, 11868; (c) Okamoto, N.; Hori, S.; Akazawa, C.; Hayashi, Y.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *J. Biol. Chem.* **1994**, *269*, 1231.

(2) (a) Bräuner-Osborne, H.; Krogsgaard-Larsen, P. *Br. J. Pharmacol.* **1998**, *123*, 269; (b) Johansen, P. A.; Chase, L. A.; Sinor, A. D.; Koerner, J. F.; Johnson, R. L.; Robinson, M. B. *Mol. Pharmacol.* **1995**, *48*, 140.

(3) For excellent reviews on ligands for glutamic receptors, see: Danbolt, N. C. *Prog. Neurobiol.* **2001**, *65*, 1. Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609.

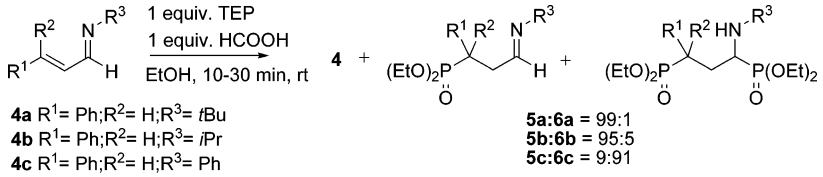
(4) Moonen, K.; Van Meenen, E.; Verwée, A.; Stevens, C. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7407.

(5) Afarinkia, K.; Cadogan, J. I. G.; Rees C. W. *Synlett* **1992**, 123.

(6) Teulade, M.; Savignac, P. *Synthesis* **1987**, 1037.

(7) Phosphonyl-1-aminophosphonates **6** are generally formed as a mixture of two diastereomeric pairs. One pair can generally be recognized in the ^{31}P spectrum as two doublets ($J_{PP} \approx 10$ Hz), while the other one usually gives two singlets.

SCHEME 1. Addition of 1 equiv of Triethyl Phosphite to α,β-Unsaturated Imines 4



SCHEME 2. Proposed Reaction Mechanism of the Tandem 1,4−1,2-Addition of Trialkyl Phosphite to α,β-Unsaturated Imines 4

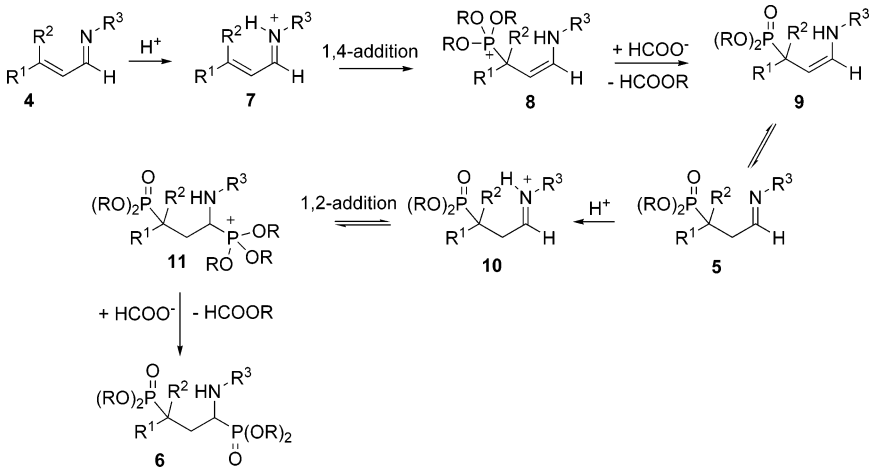


TABLE 1. Addition of 2 equiv of Trialkyl Phosphite to α,β-Unsaturated Imines 4

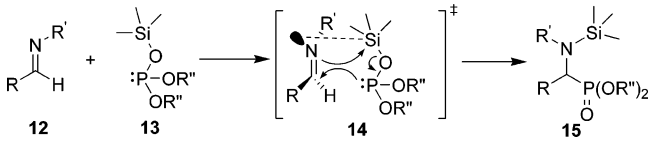
imine	R^1	R^2	R^3	R	prod	time at rt	yield[a] (%)	diast ratio
4a	Ph	H	*t*-Bu	Et	**6a**	*exclusive 1,4-addition*		
4b	Ph	H	*i*-Pr	Et	**6b**	24 h	90	38/62
4c	Ph	H	Ph	Et	**6c**	30 min	86	21/79
4c	Ph	H	Ph	Me	**6d**	30 min	86	34/66
4d	Ph	H	Bn	Et	**6e**	30 min	78	33/67
4e	Ph	H	allyl	Et	**6f**	30 min	70	72/28
4f	Ph	H	*p*-OMeBn	Et	**6g**	3 h	72	36/64
4g	Me	Me	Ph	Et	**6h**	30 min	54[b]	
4h	Me	Me	Bn	Et	**6i**	55 h	59	
4i	furan-2-yl	H	Ph	Et	**6j**	30 min	65[b]	22/78
4i	furan-2-yl	H	Ph	Me	**6k**	2 h	32[c]	25/7

[a] Yield after acid−base extraction; [b] Yield after column chromatography of the evaporated reaction mixture since the product decomposed during acidic aqueous workup; [c] Yield after acid−base extraction and additional column chromatography.

imine **4a** even only reacted in a 1,4-fashion (Table 1). This reactivity is opposite to the results obtained using dialkyl trimethylsilyl phosphite as a nucleophile. Using dialkyl trimethylsilyl phosphite, the highly steric *t*-Bu group is the best N-substituent to obtain double adducts, while phenyl, a less sterically demanding nitrogen substituent, resulted only in the 1,2-adducts.[4]

As was the case for the dialkyl trimethylsilyl phosphite tandem addition,[4] the acid also plays a crucial role in the trialkyl phosphite addition. Next to the imine activation and enamine tautomerization, the acid (or its conjugated base) is required for dealkylation of the phosphonium intermediates (Scheme 2). From these experimental results, it was clear that both addition reactions of trialkyl phosphite or dialkyl trimethylsilyl phosphite to α,β-unsaturated imines **4** proceed very fast in acidic media, yielding the corresponding diphosphonates **6** in high yields and purity. Both reactions proceed via the tandem 1,4−1,2-addition

SCHEME 3. Push−Pull Mechanism[9]



mechanism (Scheme 2), which is also indicated by the occurrence of 1,4-adducts as intermediates (especially with highly steric demanding nitrogen substituents) and the similar diastereomeric ratios of the final products.[4]

In the case of trialkyl phosphite, the 1,4-addition is clearly favored, causing no 1,2-adduct to appear in the reaction mixture. The 1,4-adduct is the sole reaction intermediate or end product in case the subsequent 1,2-addition is blocked (e.g., due to steric hindrance). Previous research showed that the mechanism is more complicated for the dialkyl trimethylsilyl phosphite addition.[4] In that case, the 1,2-addition is favored kinetically over the 1,4-addition, causing the 1,2-adducts to appear very fast in the reaction mixture. Therefore, it should be concluded that trialkyl phosphite is more sterically demanding in this type of reactions than dialkyl trimethylsilyl phosphite, which is quite surprising at first sight comparing the OEt to the OTMS group.

A possible explanation for this unexpected behavior of dialkyl trimethylsilyl phosphite can be found in the reaction mechanism of dialkyl trimethylsilyl phosphite additions described in the literature.[8] In this mechanism, coordination of the nitrogen lone pair with the silicon atom is suggested, which brings the (bulky) nucleophile in close proximity of the electrophilic center. Because of the presence of both a nucleophilic and an electrophilic center in the silylated phosphite **13**, the subsequent transformation then occurs via a classical "push−pull" mechanism (Scheme 3).[9]

(8) Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3467.

The 1,4-addition of dialkyl trimethylsilyl phosphite, on the other hand, probably proceeds similarly to that of trialkyl phosphite, i.e., without prior coordination with nitrogen. Furthermore, the fast 1,2-addition of dialkyl trimethylsilyl phosphite has proven to be a reversible reaction, which makes the 1,2-adduct only a transient intermediate. Therefore, only limited amounts of substrate (imine) are available for the 1,4-addition, causing it to be the rate-determining step, which nevertheless is favored by sterically demanding nitrogen substituents. The final 1,2-addition proceeds again smoothly through nitrogen−silicon coordination.

When trialkyl phosphite is used, no 1,2-adduct formation is observed because of the lack of coordination. 1,4-Addition proceeds through a classical nucleophilic attack. The final 1,2-addition is now the rate-determining step, which is disfavored by the sterically demanding nitrogen substituents. This is the reason Teulade and Savignac only reported 1,4-addition to the steric *t*-Bu-imines.[6] These exceptional reaction kinetics, rather than simply steric differences, explain the opposite reactivity order for both reagents.

The generality of this method has been proven by selecting different nitrogen substituents, both aromatic and aliphatic α,*β*-unsaturated aldimines and different phosphorus nucleophiles (Table 1). When trimethyl phosphite (R = Me) was used, instead of triethyl phosphite, methanol was chosen as a solvent (in stead of ethanol) to prevent transesterification; however, the reaction appeared to slow and more impurities were formed. Therefore, the solvent is probably an important factor influencing the reactivity of both nucleophiles.

In addition, Kabachnik−Fields-type three-component reactions are often employed for the preparation of α-aminoalkyl phosphonates.[10] To investigate the possibility that the above-described tandem 1,4−1,2-addition also operates under these conditions, the method reported by Kudrimoto and Bommena was selected as a model.[11] This method involves a solvent-free three-component reaction between an aldehyde, an amine, and a trialkyl phosphite, which was reported to yield exclusively α-aminoalkyl phosphonates under the action of (bromodimethyl)sulfonium bromide ($Me_2S{\cdot}Br_2$), even when an α,*β*-unsaturated aldehyde was used. However, when cinnamaldehyde was reacted with *i*-Pr-amine or aniline in the presence of 2 equiv of trimethyl phosphite and 0.1 equiv of $Me_2S{\cdot}Br_2$, small amounts of 3-phosphonyl-1-aminophosphonates **6b**,**d** could be detected by ^{31}P NMR[7] in the crude reaction mixture after standard aqueous workup. Evaluating different time−temperature combinations, however, never resulted in complete conversion to the 3-phosphonyl-1-aminophosphonates **6b**,**d** (maximum up to 60% in the reaction mixture). The catalysis of this reaction by (bromodimethyl)sulfonium bromide seems to be less efficient than the acid catalysis discussed in the previous paragraph. Furthermore, the water that is liberated during the condensation reaction is required for the dealkylation of the intermediate phosphonium ions as the reaction did not proceed when aldimines were used directly in the reaction. Addition of water during the reaction using preformed aldimines again led to the formation of 3-phosphonyl-1-aminophosphonate **6** (in small amounts). Dealkylation of the phosphonium intermediates by water was confirmed by the detection of methanol or ethanol in the reaction mixture.

In conclusion, the tandem 1,4−1,2-addition of trialkyl phosphites to α,*β*-unsaturated imines was studied and was found to be perfectly supplementary to the method previously reported using dialkyl trimethylsilyl phosphites.[4] While the latter method only allowed the preparation of 3-phosphonyl-1-aminophosphonates with considerably sterically demanding nitrogen substituents (e.g., *i*-Pr, *t*-Bu), addition of trialkyl phosphites proceeded smoothly with little sterically demanding nitrogen substituents due to the different reactivity of trialkyl phosphite (higher tendency toward 1,4-addition than 1,2-addition). The results presented here, together with our previous research,[4,12] lead to a better understanding of the special reactivity and regioselectivity of three different phosphorus nucleophiles toward α,*β*-unsaturated nucleophiles: dialkyl phosphites,[12] dialkyl trimethylsilyl phosphites[4] and trialkyl phosphites. By selecting the appropriate phosphorus reagent and reaction conditions, it is now possible to obtain 1,2-, 1,4-, and 1,2−1,4-adducts in high yields and purity. Furthermore, the spectroscopic characteristics of 3-phosphonyl-1-aminophosphonates **6** have been properly assessed, which allows their identification as potential minor impurities in so-called exclusive α-aminophosphonylation protocols in the future.

Experimental Section

General Procedure for the Synthesis of 3-Phosphonyl-1-aminoalkyl Phosphonates 6. α,*β*-Unsaturated imine **4** (5 mmol) was dissolved in 15 mL of absolute ethanol (or methanol in case of trimethyl phosphite) in an oven-dried flask. Under a nitrogen atmosphere, 10 mmol of triethyl phosphite (or trimethyl phosphite) and 10 mmol of formic acid were added consecutively. When complete conversion was obtained (see Table 1), the solvent was evaporated under reduced pressure. The crude product was dissolved in 25 mL of diethyl ether and poured into 25 mL of 1 M aqueous HCl. The aqueous phase was washed twice with 15 mL of diethyl ether and made basic by addition of 1 N NaOH and extracted three times with 20 mL of dichloromethane. The 3-phosphonyl-1-aminophosphonate **6** was obtained in satisfactory purity after drying ($MgSO_4$) and evaporation of the solvent. To obtain the 3-phosphonyl-1-aminophosphonate perfectly pure, column chromatography with silica gel as a stationary phase and a mixture of CH_3CN, CH_2Cl_2, and MeOH (80/18/2) as a mobile phase was appropriate.

Product Characterization of One Representative Example: [3-(Dimethoxyphosphonyl)-3-phenylamino-1-phenylpropyl]phosphonic Acid Dimethyl Ester (6d). The product was obtained as a mixture of two diastereomeric pairs (ratio: 34/66). ^1H NMR δ (300 MHz, ppm): 2.29 (2H, multiplet), 2.52−2.71 (2H, multiplet), 3.38−3.83 (4H, multiplet), 3.48 (3H, d, J_{HP} = 10.5 Hz), 3.49 (3H, d, J_{HP} = 10.5 Hz), 3.54 (3H, d, J_{HP} = 10.2 Hz), 3.65 (3H, d, J_{HP} = 11.0 Hz), 3.68 (3H, d, J_{HP} = 10.5 Hz), 3.69 (3H, d, J_{HP} = 10.5 Hz), 3.71 (3H, d, J_{HP} = 9.1 Hz), 3.78 (3H, d, J_{HP} = 10.2 Hz), 6.34 (2H, d, J = 8.3 Hz), 6.43 (2H, d, J = 8.3 Hz), 6.46−6.61 (2H, multiplet), 6.78−7.15 (4H, multiplet), 7.16−7.37 (10H, multiplet). ^{13}C NMR δ (75 MHz, ppm): 31.1 (d, J = 8.1 Hz, CH_2), 32.1 (CH_2), 39.9 (dd, J_{CP} = 139.6 Hz, J_{CP} = 13.8 Hz, CH), 40.2 (dd, J_{CP} = 137.3 Hz, J_{CP} = 8.1 Hz, CH), 48.1 (dd, J_{CP} = 154.6 Hz, J_{CP} = 16.2 Hz, CH), 48.6 (dd, J_{CP} = 155.9 Hz, J_{CP} = 11.5 Hz, CH), 52.6 (d, J_{CP}

(9) Wozniak, L.; Chojnowski, J. *Tetrahedron* **1989**, *45*, 2465.

(10) (a) Chandrasekhar, S.; Narsihmulu, C.; Shameem Sultana, S.; Saritha, B.; Jaya Prakash, S. *Synlett* **2003**, 505. (b) Heydari, A.; Karimian, A.; Ipaktschi, J. *Tetrahedron Lett.* **1998**, *39*, 6729. (c) Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar; V., Narsihmulu, C. *Tetrahedron Lett.* **2001**, *42*, 5561. (d) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141. (e) Kaboudin, B.; Rahmani, A. *Synthesis* **2003**, 2705. (f) Kaboudin, B.; Nazari, R. *Tetrahedron Lett.* **2001**, *42*, 8211.

(11) Kudrimoto, S.; Bommena, V. R. *Tetrahedron Lett.* **2005**, *46*, 1209.

(12) Van Meenen, E.; Moonen, K.; Acke, D.; Stevens, C. V. *Arkivoc* **2006**, *i*, 31.

= 6.9 Hz, CH_3), 52.8 (d, J_{CP} = 6.9 Hz, CH_3), 53.4 (d, J_{CP} = 5.8 Hz, CH_3), 53.5 (d, J_{CP} = 5.8 Hz, CH_3), 113.6 (CH), 113.9 (d, J_{CP} = 10.4 Hz, CH), 118.1 (CH), 118.5 (CH), 127.6 (CH), 127.69 (CH), 127.74 (CH), 128.56 (CH), 128.59 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 129.2 (CH), 129.25 (CH), 129.28 (CH), 129.33 (CH), 129.4 (CH), 129.5 (CH), 129.57 (CH), 129.63 (CH), 129.7 (CH), 134.17 (d, J = 6.9 Hz, C), 135.88 (C), 146.12 (C), 146.63 (C). ^{31}P NMR δ (121 MHz, ppm): 28.47, 28.74 (d, J_{PP} = 9.7 Hz), 30.76, 31.30 (d, J_{PP} = 9.7 Hz). IR ν (cm^{-1}): 3301 (N-H), 1243 (br, P═O), 1043 (br, P-O). MS *m*/*z*: 428 ($[M + H]^+$, 100), 318 ($[M + H - PO(OMe)_2]^+$, 10).

Acknowledgment. We thank the Fund for Scientific Research Flanders and the Ghent University Research Fund for financial support of this research.

Supporting Information Available: General experimental methods, experimental procedures, and characterization data (^{1}H NMR, ^{13}C NMR, ^{31}P NMR, MS, IR) and ^{13}C NMR spectra of the compounds **6b**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061256B