One-Pot Tandem 1,4- and 1,2-Addition of Phosphites to α,β-Unsaturated Hydrazones

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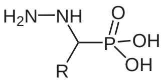
Abstract: The 1,4- and 1,2-addition of phosphites to α,β-unsaturated hydrazones was investigated. When silylated phosphites and trialkyl phosphites were compared, trialkyl phosphites gave better conversions and subsequently higher yields. A variety of hydrazones were evaluated as substrate in this reaction, which yield 3-phosphonyl-1-hydrazinoalkyl phosphonates.

Key words: phosphorylations, tandem addition, hydrazones, amino acids, Michael additions

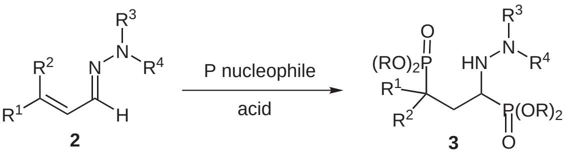
α-Hydrazinoalkyl phosphonic acids **1** (Figure 1) and their derivatives have been found to have an interesting protecting effect against the phytotoxic action of chloroacetanilide herbicides.[1] Limited research was performed to establish a general route to this type of compounds.[2] Among the specific methods, the lithium perchlorate/diethyl ether catalyzed multicomponent reaction of an aldehyde, a hydrazine, and silylated phosphite[2e] or the binary reagent $(MeO)_3P/Me_3SiCl$[2f] seems to be the most straightforward. However, this method is only applicable to aliphatic aldehydes.



1

Figure 1 α-Hydrazinoalkyl phosphonic acid

As a continuation of our studies on the behavior of different phosphorus nucleophiles and the chemistry of azaheterocyclic phosphonates,[3] the addition of silylated phosphites and trialkyl phosphites to α,β-unsaturated hydrazones **2** is presented in this paper (Scheme 1). In this reaction, two phosphonate moieties are introduced in one single reaction to form 3-phosphonyl-1-hydrazinoalkyl phosphonates **3**. Our previous research showed that both reagents are able to perform a tandem 1,4–1,2-addition to α,β-unsaturated imines.[4,5] A mechanistic study proved a different reactivity of both phosphorus reagents. Trialkyl phosphites show a higher tendency to perform 1,4-addition than 1,2-addition, where a reverse reactivity is noticed with silylated phosphites. To evaluate the scope of these reactions, hydrazones **2**, which were anticipated to be much less reactive compared to imines, have now been evaluated as possible substrates.



Scheme 1 Synthesis of 3-phosphonyl-1-hydrazinophosphonates **3**

To synthesize the substrates **2**, an α,β-unsaturated aldehyde was dissolved in methanol in the presence of one equivalent of the hydrazine or hydrazide. After one hour at 0 °C, the solvent was evaporated in vacuo and the products were recovered in excellent yields (95–99%).

The first part of the research comprised the evaluation of silylated phosphite as a phosphorus nucleophile and was based on the work of Afarinkia and co-workers for the synthesis of α-aminophosphonates.[6] O-Silylation of dialkyl phosphite provided the more nucleophilic $\sigma_3\lambda_3$ reagent.[7] In these experiments the hydrazone **2** was dissolved in dry dichloromethane, and 5 equivalents of silylated phosphite were added. This mixture was heated to reflux temperature after which 0.5 equivalents of sulfuric acid were added.

Follow-up of the reaction by ^{31}P NMR (whenever possible, conversions were calculated from integrations in the ^{31}P NMR) had shown a very slow and incomplete conversion.[8] Imines, on the other hand, showed vigorous reaction upon addition of sulfuric acid (the solvent starts to boil) and the reactions were complete after one hour at room temperature.[4] As seen in Table 1, the results were not really satisfying and only two derivatives **3b**,**d** showed an acceptable yield (the conversion was not determined for **3a** and **3b**). Next to the incomplete conversion, the low yields can also be explained by the work-up. An acid–base extraction was required to remove the excess of phosphite. However, a lot of side products remained in the crude reaction mixture, which made flash chromatography inevitable for further purification.[9] These phosphono

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Table 1 Reaction of Hydrazones **2** with Dimethyl Trimethylsilylphosphite in Acidic Medium

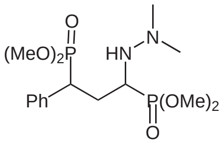
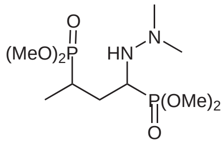
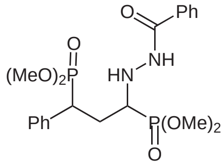
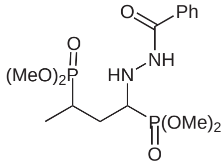
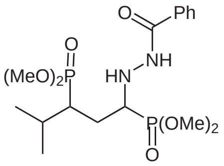
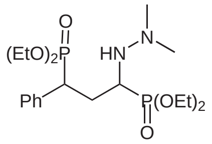
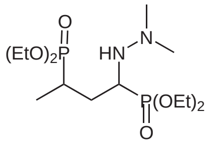
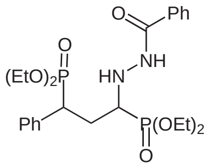
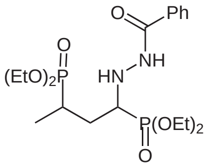
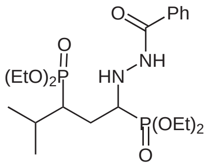
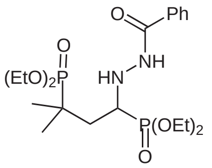
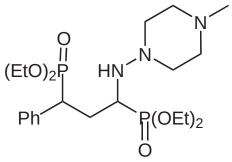
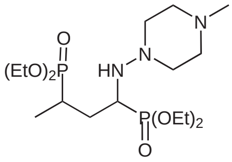
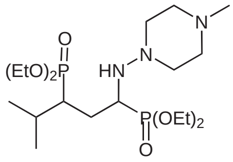
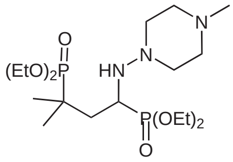
	Product	Conversion (%)	Isolated yield (%)
3a		–	18
3b		–	55
3c		46	32
3d		90	75
3e		35	19

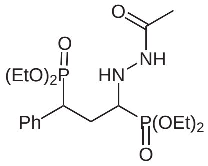
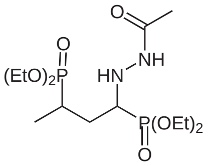
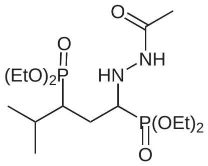
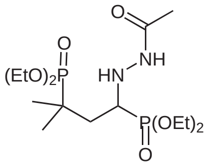
Table 2 Reaction of Hydrazones **2** with Triethyl Phosphite in Acidic Medium

	Product	Time (d)	Conv. (%)	Isolated yield (%)
3f		1	–	52
3g		1	70	21
3h		2	–	57
3i		1	98	78
3j		7	76	53
3k		4	89	64
3l		5	86	64
3m		2	91	76
3n		7	81	47
3o		8	21	18

hydrazino phosphonates **3**, however, were to a great extent retained on the column, leading to the low yields listed in Table 1.

Because of these unsatisfactory results, another method was evaluated before further optimization of the reaction conditions. In this case, a trialkyl phosphite was used as the phosphorus nucleophile. Literature showed that this reagent can perform a 1,4-addition to α,β-unsaturated imines.[10] Furthermore, our own research showed that for this methodology, the combination triethyl phosphite in ethanol was preferred over trimethyl phosphite in methanol.[5] Therefore, the starting hydrazone **2** was dissolved in absolute ethanol, and 5 equivalents of triethyl phosphite were added (when less phosphite was used, say 2 equivalents, the yield was <5% so that the 1,2-to-1,4-addition ratio could not be easily determined). After the reaction was brought to reflux temperature, 5 equivalents of formic acid were added to the mixture.[11] A sufficient amount of formic acid is crucial to obtain a good conversion in this reaction. Also here, the reaction was monitored by ^{31}P NMR, which showed a slow reaction (several days).[8] The conversion, however, was higher than in the first case.

Table 2 Reaction of Hydrazones **2** with Triethyl Phosphite in Acidic Medium (continued)

	Product	Time (d)	Conv. (%)	Isolated yield (%)
3p		3	84	55
3q		1	–	62
3r		6	89	58
3s		4	66	42

An acid–base extraction was used to obtain the pure products. The excess of phosphite was removed during the acidic extraction. It was, however, necessary to use diethyl ether at this stage, and not dichloromethane, in order to prevent excessive loss of the product in the organic phase. In most cases, no further chromatographic purification was necessary, which avoided additional losses.

As can be seen from Table 2 (**3f**–**j**) the yields are generally higher than with the first method (Table 1). Therefore the scope of this reaction was investigated by making a series of derivatives (Table 2; the conversion was not determined for **3f** and **3h**). From these results some conclusions can be drawn concerning the steric influence of the β-substituents. In general, the reaction proceeds slower when the substituents become more sterically demanding. The unexpected behavior of the cinnamaldehyde-derived substrates in this respect can be caused by the extended conjugated system. The lower reactivity of hydrazones compared to imines can be explained by the less electrophilic C=N double bond. Using acyl-substituted hydrazones, the electrophilicity of the C=N bond is again increased. However, not in all the cases a significant effect could be noticed.

In summary we have broadened the scope of the previously described tandem 1,4- and 1,2-addition of phosphites.[4,5] Hydrazones **2** (derived from hydrazines or hydrazides) are, despite the lower reactivity in comparison to imines, appropriate substrates for the synthesis of 3-phosphonyl-1-hydrazinophosphonates **3** in one step.

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

(8) The phosphonylated adduct appears in the ^{31}P NMR spectrum as a major and minor diastereomeric pair. One gives two singlets and the other two doublets (^{31}P coupling).

(9) A suitable solvent mixture for flash chromatography is MeCN–CH_2Cl_2–MeOH (81:17:3).

(10) Teulade, M.-P.; Savignac, P. *Synth. Commun.* **1987**, *19*, 1037.

(11) **Detailed Description of the Procedure**
In an oven-dry flask, hydrazone **2** (2 mmol) is dissolved in abs. EtOH. To this solution, triethyl phosphite (10 mmol, 5 equiv) is added. This mixture is brought to reflux temperature under an N_2 atmosphere and formic acid (5 equiv) is added by a syringe. The reaction is followed with ^{31}P NMR. When no changes are observed anymore (after several days) the reaction is stopped. The solvent is evaporated and the residue redissolved in Et_2O (20 mL). After pouring into 3 N HCl (30 mL) this system is extracted 3 times with Et_2O (20 mL). The aqueous phase is made basic with 3 N NaOH and extracted three times with CH_2Cl_2 (20 mL). The combined organic layers are dried over $MgSO_4$. After filtration, the solvent is evaporated in vacuo. ^{1}H NMR, ^{13}C NMR, IR, and MS spectra were entirely consistent with the assigned structures. Selected example: [1-(*N′*-Benzoylhydrazino)-3-(diethoxyphosphoryl)but-yl]phosphonic acid diethyl ester (**3i**): Ratio A:B = 47:53 (^{31}P NMR). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19–1.41 [15 H (A) + 15 H (B), m, CHCH_3 (A + B), P(O)OCH$_2$CH_3 (A + B)], 1.67–1.87 [2 H (A), m, CHCH_2CH], 2.10–2.29 [2 H (B), m, CHCH_2CH], 2.32–2.55 [1 H (A) + 1 H (B), m, CHP], 3.27–3.36 [1 H (B), m, NCHP], 3.58–3.67 (1 H (A), m, NCHP], 4.02–4.30 [8 H (A) + 8 H (B), m, P(O)OCH_2CH$_3$], 7.40–7.53 [6 H, m, CH(Ph) (A + B)], 7.80–7.86 [4 H, m, CH(Ph) (A + B)], 8.77 (1 H, br s, NH (B)], 8.79 [1 H, br s, NH (B)], 9.22 [1 H, br s, NH (A)], 9.24 [1 H, br s, NH (A)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.16 [d, $^2J_{CP}$ = 4.6 Hz, CHCH_3 (B)], 15.36 [d,

$^{2}J_{CP}$ = 4.6 Hz, CH*C*H$_3$ (A)], 16.38, 16.46, 16.54, 16.61 [P(O)OCH$_2$*C*H$_3$ (A + B)], 26.61 [dd, $^{1}J_{CP}$ = 140.8 Hz, $^{3}J_{CP}$ = 9.2 Hz, CHP (A)], 27.02 [dd, $^{1}J_{CP}$ = 143.1 Hz, $^{3}J_{CP}$ = 13.9 Hz, CHP (B)], 28.00 [CH*C*H$_2$CH (B)], 28.78 [d, $^{2}J_{CP}$ = 2.3 Hz, CH*C*H$_2$CH (A)], 55.58 [dd, $^{1}J_{CP}$ = 155.8 Hz, $^{3}J_{CP}$ = 6.9 Hz, NCHP (A)], 55.65 [dd, $^{1}J_{CP}$ = 161.5 Hz, $^{3}J_{CP}$ = 13.9 Hz, NCHP (B)], 61.79 [d, $^{2}J_{CP}$ = 6.9 Hz, P(O)O*C*H$_2$CH$_3$], 61.88 [d, $^{2}J_{CP}$ = 6.9 Hz, P(O)O*C*H$_2$CH$_3$], 62.52 [d, $^{2}J_{CP}$ = 6.9 Hz, P(O)O*C*H$_2$CH$_3$], 62.71 [d, $^{2}J_{CP}$ = 6.9 Hz, P(O)O*C*H$_2$CH$_3$] 62.83 [d, $^{2}J_{CP}$ = 6.9 Hz, P(O)O*C*H$_2$CH$_3$], 63.13 [d, $^{2}J_{CP}$ = 6.9 Hz, P(O)O*C*H$_2$CH$_3$], 126.97, 128.63, 131.70, 131.81 [*C*H(Ph) (A + B)], 132.53 [C$_q$(Ph) (A)], 132.57 [*C*$_q$(Ph) (B)], 165.64 [C=O (A)], 165.98 [C=O (B)] ppm. ^{31}P NMR (121 MHz, CDCl$_3$): δ = 25.72 [d, J_{PP} = 1.5 Hz (A)], 26.16 [d, J_{PP} = 7.4 Hz (B)], 34.47 [d, J_{PP} = 7.4 Hz (B)], 35.11 [d, J_{PP} = 1.5 Hz (A)] ppm. IR: 3413 (NH), 1648 (C=O), 1229 (P=O), 1052, 1027 (P–O) cm^{-1}. MS: *m/z* (%) = 465 (100) [M + H]$^{+}$.