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Diastereoselective synthesis of α-substituted β-amidophosphonates

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Abstract—A simple and general asymmetric synthesis of β-amidophosphonates is described. The method involves the highly selective addition (up to 95% d.e.) of diethyl phosphite to various chiral α,β-unsaturated carboxylic amides derived from chiral aminoalcohols.

Phosphonic acids and their derivatives have been prepared and studied as isosteric analogs of carboxylic acids. Phosphorylated aminoacids[1] (Fig. 1) are of particular interest and have found widespread use as enzyme inhibitors,[2] antiviral drugs,[3] antibiotics[4] and neurodrugs.[5] Phaclofen, a γ-aminophosphonic acid, was described as the first selective $GABA_B$ antagonist.[6] They are also known to exhibit strong herbicidal activity.[7] Furthermore, aminophosphonic acids are found as constituents of natural products.[8] Generally, biological activity is strongly dependent upon the chirality α or β to the phosphorus atom.

Numerous synthetic methods for α- and β-aminophosphonates have been developed during the past two decades,[9] whereas fewer methods have been devoted to γ-aminophosphonate preparations. Although their synthesis has been already reported,[10] these methods lack versatility and their application to optically active compounds and polysubstituted derivatives appears to be difficult. One of the most versatile pathways for the formation of carbon phosphorus bonds is the Pudovik reaction[11] involving the addition of compounds containing a labile P–H bond with unsaturated activated systems to afford racemic[12] or optically active[13] products. Particularly attractive was the possibility of developing an asymmetric version of the method described by Barycki[12] involving conjugate addition of diethyl phosphite anions to α,β-unsaturated amides.

Diastereoselective conjugate additions of organometallic reagents to chiral α,β-unsaturated oxazolines,[14] oxazolidinones,[15] or amides[16] is a valuable method for the asymmetric synthesis of optically active β-substituted or α,β-disubstituted carbonyl compounds.

We report in this article the stereocontrolled synthesis of α-substituted β-amidophosphonates utilizing a method that capitalizes on the highly diastereofacial addition of the diethyl phosphite anion to an α,β-unsaturated amide derived from a chiral aminoalcohol.

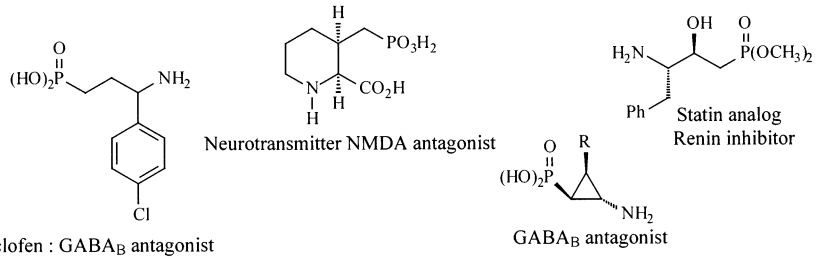

Figure 1. Examples of biologically active γ-aminophosphonic acids.

Keywords: asymmetric synthesis; phosphonic acids and derivatives; Michael addition.

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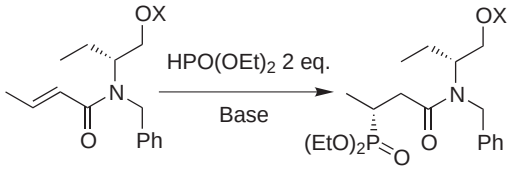
Table 1. Diastereoselective 1,4-addition of diethyl phosphite to crotonyl amides **1a**,**b**



1a: X = H
1b: X = CH_2Ph

2a
2b

Entry	Amide	Base[a]	Product (yield %)	% D.e.[b]
1	**1a**	*n*- or *s*-BuLi	**2a** (30)	70
2	**1a**	LDA	**2a** (55)	70
3	**1a**	LDA, TMEDA	**2a** (32)	66
4	**1a**	LDA, BF_3/OEt_2	**2a** (0)	0
5	**1a**	NaH	**2a** (50)	92
6	**1b**	NaH	**2b** (45)	30

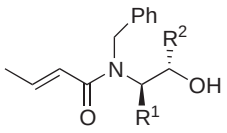
[a] 2 equiv. of base and 2 equiv. of diethyl phosphite were used.
[b] Measured on the crude product by ^{31}P NMR or by HPLC.

Crotonamide (**1a**) was first selected to study the diastereoselectivity of such an addition (Table 1). Compound **1a** was easily prepared in 74% yield by condensation of *trans*-crotonyl chloride with (*R*)-*N*-benzylaminobutanol in a biphasic system (CH_2Cl_2, aq. NaOH). The Michael adduct (**2a**) was obtained in moderate yield by treating diethyl phosphite (2 equiv.) with a base (2 equiv.), followed by reaction of the resulting anion with **1a** in THF at −78°C. Use of alkyllithiums as bases (entry 1) led to a similar diastereoselectivity (d.e.: 70%); the low yields were due to mono- and disubstitution of the phosphonate ethoxy group of the resulting adduct by the corresponding butyl anions. Using LDA improved the yields but left the d.e. unchanged (entry 3). On the other hand, the addition of TMEDA to LDA afforded the expected Michael adduct with a reduced yield (entry 3). Attempted activation with a Lewis acid completely inhibited the reaction. Finally, the best results were obtained by using NaH (2 equiv.) (entry 5). Neither the replacement of THF by Et_2O nor the use of TMSCl to displace the equilibrium of the reaction toward the formation of the β-amidophosphonate increased the chemical yields or the diastereoselectivity. The reaction could be performed at higher temperatures (−20°C, 0°C or rt) or with a large excess of diethyl phosphite anion without any change in diastereoselectivity but with slightly lower yields.

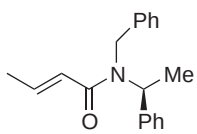
In order to assess the importance of a free hydroxyl group (which could be involved in a chelation process as previously suggested[16]), benzyl *O*-protected crotonamide **1b** was synthesized in the usual manner starting from (*R*)-*O*-benzylaminobutanol. When **1b** was treated with $(EtO)_2P(O)H$ and NaH to give the Michael adduct, a significantly lower diastereoselectivity was observed (entry 6).

We then turned our attention to the influence of the chiral auxiliary (Table 2). A series of aminoalcohols were used to prepare crotonyl amides **1c**–**e** which were employed in a Michael addition type reaction with the diethyl phosphite anion. The same diastereoselectivities as with aminobutanol were observed with valinol and phenylglycinol derivatives (entries 1 and 2), showing the relative unimportance of the nature of the group α to the nitrogen atom. But introduction of a substituent α to the oxygen atom of the aminoalcohol dramatically decreased the diastereoselectivity (entry 3). The same results were observed when α-methylbenzylamine or (*S*)-4-benzyl-2-oxazolidinone were used as chiral auxiliaries (entries 4 and 5), confirming our hypothesis that the presence of a free hydroxy group is necessary to get high diastereoselection. Oxazolines (**1h**,**i**) were prepared in 78 and 54% yields, respectively, from the correspond-

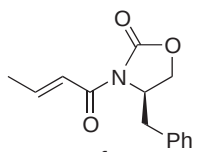
Table 2. Diastereoselective 1,4-addition of diethyl phosphite to crotonyl amides **1c**–**i**[18]



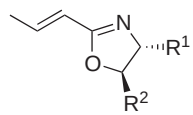
1c : R^1=iPr; R^2=H
1d : R^1=Ph; R^2=H
1e : R^1=Me; R^2=Ph



1f



1g



1h : R^1=Ph; R^2=H
1i : R^1=Me; R^2=Ph

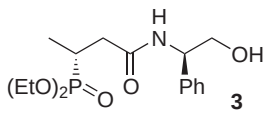
Entry	Amide	Base[a]	Product (yield %)	% D.e.[b]
1	**1c**	NaH	**2c** (53)	92
2	**1d**	NaH	**2d** (50)	92
3	**1e**	NaH	**2e** (55)	24
4	**1f**	NaH	**2f** (27)	45
5	**1g**	NaH	**2g** (45)	40
6	**1h**	LDA	**2h** (55)	80
7	**1i**	LDA	**2i** (60)	80

[a] 2 equiv. of base and 2 equiv. of diethyl phosphite were used.
[b] Measured on the crude product by ^{31}P NMR or by HPLC.

ing secondary amides by treatment with MsCl and Et_3N. When used with our described conditions, these products led to Michael adducts in very low yields. Using LDA instead of NaH allowed us to obtain satisfactory yields (55–60%), but only moderate d.e. (80%).

To evaluate the scope of the reaction, we then studied the influence of the double bond substituent on the diastereoselectivity. Unsaturated amides derived from (*R*)-*N*-benzylphenylglycinol were prepared by condensation with the corresponding acyl chlorides. The results of Michael addition are given in Table 3. Chemical yields were independent of the substituents (52–55%) unlike diastereoselectivity, which was highly dependent on electronic nature of the substituent R (entry 3). Indeed, we observed that when R is an alkyl group, the diastereoselectivity is always higher than 90%, but when we changed R to a phenyl, the diastereoselectivity dropped to 45%.

NMR studies did not allow the determination of the configuration of the newly-created asymmetric center. This problem was solved by an X-ray analysis of derivative **3**.[17] The relative configuration is opposite to the one observed by Mukaiyama and Brown[16] indicating a different mechanism for the conjugate addition. Currently, we favor a chelated process in which the nitrogen substituent induces steric hindrance in the vicinity of the double bond.



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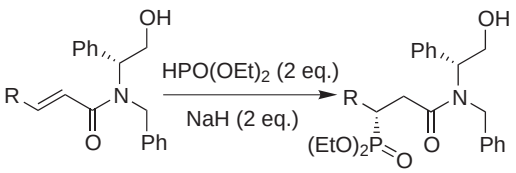
In conclusion, an asymmetric synthesis of substituted amidophosphonates has been developed. Our strategy allows the preparation of a large variety of functionalized derivatives. Particularly attractive is the possibility of gaining access to new γ-aminophosphonic acids in enantiomerically pure form. Such an application and new experiments to clarify the mechanism are in progress and will be reported in due course.

Table 3. Diastereoselective 1,4-addition of diethyl phosphite to amides **1j**–**l**: influence of the β substituent



1j : R=Et
1k : R=iPr
1l : R=Ph

2j
2k
2l

Entry	Amide	Product (yield %)	% D.e.[a]
1	**1j**	**2j** (52)	>95
2	**1k**	**2k** (55)	90
3	**1l**	**2l** (55)	45

[a] Measured on the crude product by ^{31}P NMR or by HPLC.

Acknowledgements

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17. After simple transformation, the major isomer of compound **2d** was shown to possess an *R* configuration by simple comparison of its ^{31}P NMR spectra with the known absolute configuration compound **3** derivative. Full details concerning the synthesis of this product and X-ray crystallographic data will be furnished in the forthcoming full paper.
18. Typical procedure for the 1,4-addition step
Synthesis of **2d**: Diethyl phosphite (1.16 mL, 9 mmol) was added to a suspension of NaH (0.206 g, 8.6 mmol) in anhydrous THF (20 mL) under an inert atmosphere at room temperature. After stirring for 1 h, the mixture was cooled to −20°C, and a solution of amide **1d** (1 g, 4.29 mmol) diluted in THF (10 mL) was added. After stirring for 5 h at −20°C, water (10 mL) was added and the compound was extracted with dichloromethane (3×20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude mixture was purified by column chromatography on silica gel (EtOAc/MeOH: 95/5) to provide **2d** (0.8 g) with 50% yield.
Description of the major diastereoisomer (presence of rotamers): **^{31}P NMR** ($CDCl_3$): δ 34.52 and 35.75; **^{1}H NMR** ($CDCl_3$): δ 1.09 (dd, $J=6.9$ and 17.9 Hz, 3H, P-CH-C$\underline{H}_3$), 1.16–1.24 (m, 6H, (C$\underline{H}_3$-CH_2-O)$_2$), 2.14–2.22 (m, 1H, P-CH-C$\underline{H}_2$), 2.22 (s, 1H, O$\underline{H}$), 2.59–2.68 (m, 2H, P-CH-C$\underline{H}_2$, P-C$\underline{H}$-CH_2), 3.93–4.09 (m, 6H, (CH_3-C$\underline{H}_2$-O)$_2$, C$\underline{H}_2$-OH), 4.41 and 4.6 (2d, $J=17.7$ Hz, N-C$\underline{H}_2$-C_6H_5), 5.65 and 5.62 (2d, $J=4.4$ Hz, 1H, N-C$\underline{H}$), 6.94–7.28 (m, 10H, $\underline{H}$ ar.); **^{13}C NMR** ($CDCl_3$): δ 14.9 (d, $J=5.2$ Hz, P-CH-$\underline{C}H_3$), 16.8 and 16.9 (2d, $J=5.7$ Hz, ($\underline{C}H_3$-CH_2-O)$_2$), 28.7 (d, $J=142.6$ Hz, P-$\underline{C}$H-CH_2), 35.9 (P-CH-$\underline{C}H_2$), 49.5 (N-$\underline{C}H_2$-C_6H_5), 61.9 (N-$\underline{C}$H), 62.0–62.4 (m, (CH_3-$\underline{C}H_2$-O)$_2$), 63.3 ($\underline{C}H_2$-OH), 126.4–129.3 (m, $\underline{C}$ ar.), 137.6 and 137.8 ($\underline{C}$ ar. quat.), 173.8 (d, $J=12.5$ Hz, $\underline{C}$=O).; **MS(IC)** m/z 434 $(M+1)^+$, 403 (2.5), 326 (2.5), 314 (10), 209 (1); **HRMS** $(MH)^+$ 434.2096 found 434.2098.