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Synthesis of α-amino phosphonates by diastereoselective addition of diethyl phosphite sodium salt to aldimines derived from Betti base

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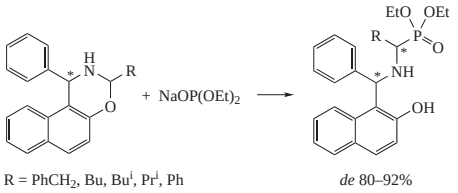
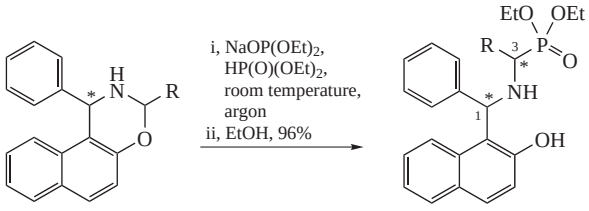
A diastereoselective (*de* 80–92%) synthesis of α-amino phosphonates was accomplished by reaction of diethyl phosphite sodium salt with 3-R-1-phenyl-2,3-dihydro-1*H*-naphth[1,2-*e*]-[1,3]oxazines being the products of aminoacetalization of aldehydes with 1-(α-aminobenzyl)-2-naphthol (Betti base).



α-Amino phosphonic acids, which are analogues of natural amino acids, exhibit a wide range of biological activity[1] and are used as building blocks for synthesis of physiologically active phosphonopeptides.[1,2] The Pudovik reaction is the most convenient method for their preparing. We have previously reported that the Betti base [1-(α-aminobenzyl)-2-naphthol[3]] is an effective chiral auxiliary for the synthesis of enantiopure α-aminobenzylphosphonates synthesis. Reaction of triethyl phosphite with enantiopure Betti base benzimines (which are in equilibrium with the corresponding 3-aryl-1-phenylnaphthoxazine cyclic forms in solution[4]) in the presence of trifluoroacetic acid affords the target compounds with *de* up to 84%.[5] Mostly, the major diastereomer can be easily separated by crystallization and then transformed to enatiopure α-aminobenzylphosphonic acid by treatment with HCl. However, in living organisms the process of biosynthesis involves exclusively α-aminoalkanecarboxylic acids. Unfortunately, 3-alkyl-1-phenylnaphthoxazines, which are the precursors of α-aminoalkylphosphonates (α-aminoalkanecarboxylic acid analogues), do not react with trialkyl phosphites in the presence of trifluoroacetic acid. We obtained the desired α-aminoalkylphosphonates using halotrimethylsilanes instead of trifluoroacetic acid in the reaction of alkyl-substituted Betti base imines (oxazines) with triethyl phosphite with *de* up to 75%.[6] However, in this case, isolation of major diastereomers caused some difficulties.

Herein, we successfully used diethyl phosphite salts in the reaction with 3-alkyl-1-phenylnaphthoxazines **1a**–**d**. Note that according to the literature[7] reactions of lithium or sodium salts of dialkyl esters of phosphorous acid with imines derived from chiral amines or amides often proceed with high diastereoselectivity.

Reactions of 3-benzyl-, 3-butyl-, 3-isobutyl- and 3-isopropyl-1-phenylnaphthoxazines **1a**–**d** with an excess of diethyl phosphite sodium salt were carried out at room temperature under argon atmosphere, using diethyl phosphite as a solvent (Scheme 1). The reaction mixtures were vigorously stirred for 6 h at room temperature, followed by the addition of 96% ethanol. The volatiles were then removed *in vacuo* and the obtained diastereomeric products were analyzed by NMR.† The ^{1}H and $^{31}P\{^{1}H\}$



	R	*de* of **2** (%)
a	$PhCH_2$	90
b	Bu	80
c	Bu^i	82
d	Pr^i	86
e	Ph	92

Scheme 1

spectra of these samples in each case contained two sets of α-aminoalkylphosphonates signals, one of which was in a large excess, indicating the high stereoselectivity of the reaction (*de* of 80–90%). Major diastereomers from diastereomeric mixtures **2a** and **2d** were isolated by crystallization from hexane–cyclohexane mixture. Phosphonates **2b** and **2c** were characterized as diastereomeric mixtures.

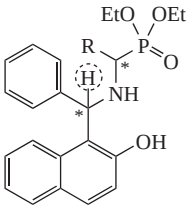
Due to the high diastereoselectivity of studied processes it was interesting to test 1,3-diphenylnaphthoxazine **1e** in the same reaction (see Scheme 1). The diastereomeric α-aminobenzylphosphonates **2e** formed had in fact *de* value as 92% which was greater than that (80%) in the case[5] of reaction **1e** + $P(OEt)_3$ + + CF_3CO_2H.

The important point was the relative configurations of chiral centers in resulting amino phosphonates. In our previous work it was established by X-ray single crystal diffraction that reaction **1e** + $P(OEt)_3$ + CF_3CO_2H afforded the major diastereomer with (*RR*/*SS*)-configuration.[5] However, in the reaction **1e** + $P(OEt)_3$ + + $HalSiMe_3$ the major diastereomer **2c** had (*RS*/*SR*)-configuration[6] at C(1) and C(3) chiral centers. Herein, in the reaction **1a**–**e** + + $NaOP(OEt)_2$ the major diastereomers always have (*RR*/*SS*)-configuration.

Comparison of the ^{1}H NMR spectra of the individual diastereomers of these phosphonates with the spectra of the initial

† For details, see Online Supplementary Materials.

Table 1 Comparison of the methine protons chemical shifts (ppm) for (*RR*/*SS*) and (*RS*/*SR*) α-amino phosphonates of type **2**.



R	(*RR*/*SS*), δ_H (working frequency/MHz)	(*RS*/*SR*), δ_H (working frequency/MHz)
CH_2Ph	6.17 (500)	6.33 (500)
Bu	6.12 (500)	6.41 (500)
Bu^i	6.24 (400)	6.51 (400)
Pr^i	6.27 (500)	6.46 (500)
Ph	5.55 (400)	6.15 (400)
4-BrC_6H_4[5]	5.49 (400)	6.14 (400)
4-MeC_6H_4[5]	5.56 (400)	6.16 (400)

reaction mixtures revealed a characteristic feature that allowed us to clearly determine the configuration of formed diastereomers. Thus, the indicative are the signals of methine protons at C(1) carbon atom. For (*RR*/*SS*)-stereoisomers, these protons exhibit a relatively upfield chemical shift ($\Delta\delta$ ~ 0.15–0.3 ppm for α-aminoalkyl- and ~0.6 ppm for α-aminobenzylphosphonates) in comparison with those of (*RS*/*SR*)-diastereomer (Table 1). Thus, we have a tool for determination of the relative configuration of diastereomers chiral centers of α-amino phosphonates obtained using a Betti base as the chiral auxiliary.

Comparison of stereochemical results of all three preparation methods of Betti base amino phosphonic derivatives from its imine (oxazine) (triethyl phosphite with trifluoroacetic acid[5], triethyl phosphite with halotrimethylsilanes[6] and the diethyl phosphite sodium salt) shows their significant difference depending on the nature of the substituents. The reaction of 1,3-diphenylnaphthoxazines always gives mostly (*RR*/*SS*)-products regardless of the preparation method. However, in the reactions of 3-alkyl-1-phenylnaphthoxazines with halotrimethylsilanes the major products are (*RS*/*SR*)-diastereomers. Oppositely, the interaction of 3-alkyl-1-phenylnaphthoxazines with diethyl phosphite sodium salt leads to (*RR*/*SS*)-diastereomers as major products. In our opinion, the reason of such difference in stereoselectivity of the addition reactions of phosphites to Betti base imines is the different nature of the electrophilic centers (proton, trimethylsilyl group or sodium cation) involved in the transition state. In case of the proton or sodium cation having a small size and bearing localized positive charge, the nucleophilic attack preferably occurs from the one side of prochiral imine group because another side is blocked by naphthyl fragment. In the case of bulky trimethylsilyl group, change in the position of the naphthyl fragment would occur due to strong steric interactions, which in some cases makes the attack from the previously hindered side more preferable. Thus, using the Betti base as a chiral auxiliary allows one to purposefully synthesize the α-amino phosphonic acids derivatives of the desired configuration.

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We dedicate this study to the 100th anniversary of our teacher A. N. Pudovik.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.09.009.

References

1 *Aminophosphonic and Aminophosphinic Acids*, eds. V. P. Kukhar and H. R. Hudson, John Wiley & Sons, Chichester, 2000.

2 V. P. Kukhar and V. D. Romanenko, in *Amino Acids, Peptides and Proteins in Organic Chemistry. Vol. 2. Modified Amino Acids, Organocatalysis and Enzymes*, ed. A. B. Hughes, Wiley-VCH, Weinheim, 2009, pp. 189–260.

3 C. Cardellicchio, M. A. M. Capozzi and F. Naso, *Tetrahedron: Asymmetry*, 2010, **21**, 507.

4 (*a*) I. Szatmári, T. A. Martinek, L. Lázár and F. Fülöp, *Tetrahedron*, 2003, **59**, 2877; (*b*) I. Szatmári, T. A. Martinek, L. Lázár, A. Koch, E. Kleinpeter, K. Neuvonen and F. Fülöp, *J. Org. Chem.*, 2004, **69**, 3645.

5 K. E. Metlushka, B. A. Kashemirov, V. F. Zheltukhin, D. N. Sadkova, B. Büchner, C. Hess, O. N. Kataeva, Ch. E. McKenna and V. A. Alfonsov, *Chem. Eur. J.*, 2009, **15**, 6718.

6 K. E. Metlushka, D. N. Sadkova, L. N. Shaimardanova, K. A. Nikitina, A. I. Tufatullin, O. N. Kataeva and V. A. Alfonsov, *Russ. Chem. Bull., Int. Ed.*, 2014, **63**, 1390 (*Izv. Akad. Nauk, Ser. Khim.*, 2014, 1390).

7 (*a*) M. Ordóñez, H. Rojas-Cabrera and C. Cativiela, *Tetrahedron*, 2009, **65**, 17; (*b*) M. Ordóñez, J. L. Viveros-Ceballos, C. Cativiela and F. J. Sayago, *Tetrahedron*, 2015, **71**, 1745, and references therein.

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