Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 1, pp. 21-24, 1996

0957-4166/96 $15.00 + 0.00

0957-4166(95)00411-4

Asymmetric Synthesis of α-Aminophosphonates via Diastereoselective Addition of Phosphite to Chiral Imine Derivatives

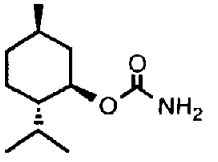
Sung-Kee Chung* and Dong-Ho Kang

Department of Chemistry, Pohang University of Science & Technology, Pohang, 790-784, Korea

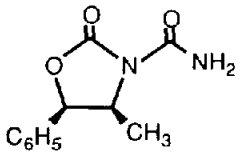
Abstract: One pot three component reactions employing homochiral (1*S*)-(+)-camphorsulfon-amide-derived carbamate, aldehydes and diethyl phosphite at 0°C was found to give protected (*S*)-α-aminophosphonates in high enantiomeric purities.

In the recent years the synthesis of α-aminophosphonates has received an increasing amount of attention because they are considered to be structural analogues of the corresponding α-amino acids and transition state mimics of peptide hydrolysis. In these connections, the utilities of α-aminophosphonates as peptide mimics,[1] haptens of catalytic antibodies,[2] enzyme inhibitors,[3] antibiotics and pharmacologic agents[4] are well documented. A variety of synthetic approaches to optically active α-aminophosphonates are available with varying degrees of enantiomeric purities.[5] The most commonly employed methods involve nucleophilic addition of phosphites to imine and oxoiminium derivatives,[6] alkylation of anionic[7] or cationic[8] phosphonoglycine equivalents, electrophilic amination of phosphorus-stabilized anions,[9] and hydrogenation of dehydroaminophosphonate derivatives.[10] The nucleophilic addition of dialkylphosphite to imines appears to be the most general approach to the asymmetric synthesis of α-aminophosphonates due to its operational simplicity and accessibility of the necessary starting materials, but the enantiomeric excess of this reaction is as a rule not very high with a few reported exceptions.[5,6] We have recently reexamined this approach with several recyclable chiral auxiliaries and wish to report a highly promising diastereoselective route to α-aminophosphonates.

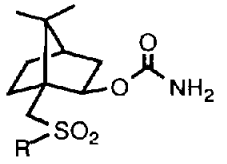
We have chosen for our study the carbamate and urea derivatives such as compounds **A**-**C** as the recyclable chiral auxiliary, since they are easily prepared[11] from the readily available starting material, (1*R*, 2*S*, 5*R*)-(-)-menthol, (1*R*, 2*S*)-(-)-ephedrine[12] and (1*S*)-(+)-10-camphorsulfonic acid,[13] respectively. After



A



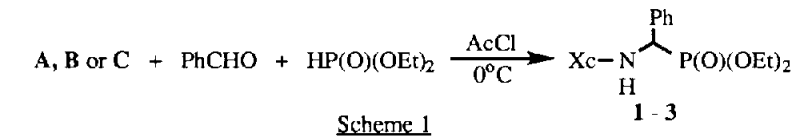
B



C 1. R= N(cyclohexyl)$_2$
2. R= N(*i*Pr)$_2$
3. R= 2,4,6,-trimethylphenyl

considerable experimentation in generating *N*-acylimine or *N*-acyliminium ion species incorporating these chiral auxiliaries under various reaction conditions[14], the one pot three component reaction procedure with

the chiral carbamate (or urea), an aldehyde and diethyl phosphite in acetyl chloride at 0 °C was found to be most convenient and satisfactory.[15] Thus, when the three component reactions were carried out with each of the chiral auxiliaries **A**-**C** and benzaldehyde the protected α-amino phosphonates were obtained in good yields (Scheme 1). The diastereoselectivities of the reactions were determined by either ^{1}H- and ^{31}P-nmr, or their conversion to the Mosher amide followed by the ^{1}H- and ^{19}F-nmr analysis, and are listed in Table 1. The ^{31}P-nmr of product **1** showed two resonances at δ 22.58 and 22.47 with the integral ratio of 57.2 : 42.8, leading to the % de of 14.4. The ^{1}H-nmr of product **2** displayed two doublets at δ 0.93 and 0.84 for the 4'-methyl group with the integral ratio of 65.9 : 34.1, indicating the % de to be 34.1.



Scheme 1

The diastereomeric ratios of products **3a-c** could not be determined on the basis of nmr analysis, and they were converted to the corresponding Mosher amide[16] by a series of reactions: 1) hydrolysis in 8N HCl, 2) phthalic anhydride and Et_3N in toluene, 3) triethyl orthoformate, 4) hydrazine in EtOH, 5) (*R*)-(+)-MTPA-Cl and Et_3N in CH_2Cl_2. The Mosher amide prepared from the racemic α-amino-phenyl-methylphosphonic acid showed two resonances at δ 3.5 and 3.4 in its ^{1}H-nmr spectrum, and two signals at δ 5.1 and 5.0 in its ^{19}F-nmr, thus providing clear experimental bases for determining the diastereoselectivity of **3**. From the results shown in Table 1, it is evident that the camphorsulfonamide-based chiral auxiliaries **C1-3** are all very effective in inducing the chirality transfer, whereas chiral auxiliaries **A** and **B** are not. In particular, the reaction with chiral auxiliary **C1** gave the best result, providing essentially a single diastereomer.

Table 1

compound	Xc	Yield(%)	mp(°C)	$[\alpha]_D$ [a]	% de [b]
1	**A**	71	85-6	-38.2	14.4
2	**B**	84	oil	+36.9	34.1
3a	**C1**	75	111-2	-30.9	>99
3b	**C2**	73	95-6	-39.8	96.4
3c	**C3**	77	105-6	-24.1	96.7

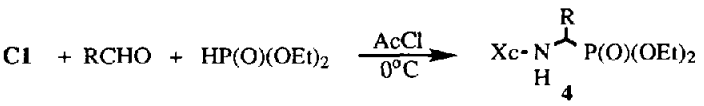
a. condition of (c 1.0, $CHCl_3$)

b. based on nmr of Mosher amide(see the text)

Next, we investigated the three component reactions with chiral auxiliary **C1** and diethyl phosphite with a number of different aldehydes, and the results are shown in Table 2. It is clear that aromatic aldehydes work very well, giving essentially a single diastereomer of α-aminophosphonates in good chemical yields. The reason why cyclohexylaldehyde gives a much lower diastereoselectivity is not clear. Perhaps, it may be due to the higher rotational freedom about the C_α-alkyl bond in the *N* - acylimine or iminium ion intermediate. This is an important issue that needs to be examined in order to extend the scope

of the present methodology, and is under study by means of computational chemistry.

Table 2



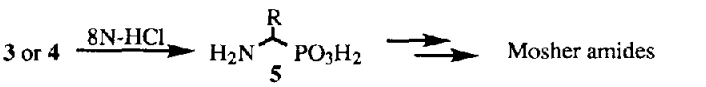
Compound	R	Yield(%)	mp(°C)	$[\alpha]_D$ [a]	% de [b]
4a	p-anisyl	76	166-8	-31.3(c 1.0)	>99
4b	α-naphthyl	79	185-6	-24.15(c 1.05)	>99
4c	p-tolyl	75	152-4	-31.5(c 1.03)	>99
4d	cyclohexyl	71	106-9	-21.94(c 1.1)	56

a. measured in $CHCl_3$

b. based on nmr analyses of Mosher amides

In order to determine the absolute stereochemistry of the synthetic α-aminophosphonates, the specific rotations were determined after hydrolysis of **3** and **4** en route to the Mosher amides, and they are listed in Table 3. In the case of phenyl α-amino-phenyl-methylphosphonate **5a**, the specific rotation was -17.8 as opposed to the literature value of -18.0.[5b] The observed rotation indicates that the absolute configuration is (*S*), and that the optical purity based on the rotation is consistent with the one based on the nmr analyses of the Mosher amide. Furthermore, the (*S*)-configuration is most likely attained by the backside attack of the phosphorus nucleophile onto the *s-cis*/*E* conformation of the *N*-acylimine species, an observation in accord with previous reports utilizing the Oppolzer chiral auxiliary.[17] On this basis, the absolute configurations of compounds **5b-d** are also assumed to be (*S*).[18]

Table 3



Compound	R	Yield(%)	mp(°C)	$[\alpha]_D$ [a]
5a	phenyl	70	280-2	-17.8(c 1.0)
5b	p-anisyl	69	310-2	-25.81(c 0.58)
5c	α-naphthyl	71	287-9	-30.45(c 0.9)
5d	p-tolyl	68	280-3	-28.2(c 1.0)
5e	cyclohexyl	52	267-9	-20.36(c 0.5)

a. measured in 1.0N-NaOH

In summary, we have found a procedure in which a highly diastereoselective addition of phosphite occurs onto the camphorsulfonamide-derived carbamoylimine species to give protected α-aminophosphonates in high enantiomeric purities. Scope and applications of this procedure are currently under study.[19]

Acknowledgment. We wish to thank Korea Science & Engineering Foundation and POSCO for financial support of this work.

References and Notes

1. P. Kafarski and B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, **1991**, *63*, 193.
2. R. Hirschmann, A. B. Smith III, C. M. Taylor, P. A. Benkovic, S. D. Taylor, K. M. Yager, P. A. Sprengler and S. J. Venkovic, *Science*, **1994**, *265*, 234.
3. (a) M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, J. M. Wood, *J. Med. Chem.*, **1989**, *32*, 1652. (b) P. P. Giannousis and P. A. Bartlett, *ibid.*, **1987**, *30*, 1603.
4. (a) F. R. Atherton, C. H. Hassall and R. W. Lambert, *ibid.*, **1986**, *29*, 29. (b) C. H. Hassall in *Antibiotics*, Ed. F. E. Halm, Springer-Verlag, Berlin, **1983**, Vol. VI, pp. 1-11. (c) P. Wieczorek, M. Kaczanowska, B. Lejczak and P. Kafarski, *Pestic. Sci.*, **1990**, *30*, 43. (d) S. Bajusz, A. Ronai, J. I. Szekely , A. Turan, A. Juhasz, A. Pathy, E. Miglecz and I Bezetei, *FEBS Lett.*, **1989**, *117*, 308. (e) I. A. Natchev, *Liebigs Ann. Chem.*, **1988**, 861.
5. (a) V. P. Kukhar, N. Y. Svistunova, V. A. Solodenko and V. A. Soloshonok, *Russian Chem. Rev.*, **1993**, *62*, 261. (b) B. Dhawan and D. Redmore, *Phosphorus Sulfur*, **1987**, 32, 119.
6. (a) K. M. Yager, C. M. Taylor and A. B. Smith, III, *J. Am. Chem. Soc.*, **1994**, *116*, 9377. (b) J. W. Huber and W. P Gilmore, *Tetrahedron Lett.*, **1979**, 3049. (c) I. Hoppe, U. Schollkopf, M. Nieger and E. Egert, *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1067. (d) R. Huber, A. Knierzinger, J. P. Obrecht and A. Vasella, *Hev. Chim. Acta*, **1985**, *68*, 1730. (e) T. Oshikawa and M. Yamashita, *Bull. Chem. Soc. Jpn.*, **1989**, *62*, 3177. (f) S. Shatzmiller, B. Z. Dolitzky, R. Meirovich, R. Neidlein and C. Weik, *Liebigs Ann. Chem.*, **1991**, 161. (g) S. Laschat and H. Kunz, *Synthesis*, **1992**, 90. (h) A. Bongini, R. Camerini, S. Hofman and M. Panunzio, *Tetrahedron Lett.*, **1994**, *35*, 8045.(i) R. Hamilton, B. Walker And B. J. Walker, *Tetrahedron Lett.*, **1995**, 36, 4451
7. (a) P. A. Bartlett and K. L. Mclaren, *Phosphorus Sulfur*, **1987**, *33*, 1. (b) S. Schollkopf and R. Schultze, *Liebigs Ann. Chem.*, **1987**, 45. (c) J. P. Genet, J. Uziel, A. M. Touzin and S. Juge, *Synthesis*, **1990**, 41. (d) C. Maury, J. Royer and H. P. Husson, *Tetrahedron Lett., 1992*, 6127. (e) G. Cabella, G. Jommi, R. Pagliarin, G. Sello and M. Sisti, *ibid.*, **1995**, 1817.
8. (a) S. Hanessian and Y. L. Bennani, *Tetrahedron Lett.*, **1990**, 6465. (b) A. Vasella and R. Voeffray, *Helv. Chim. Acta.*, **1982**, *65*, 1953.
9. (a) S. E. Denmark, N. Chatani and S. V. Pansare, *Tetrahedron*, **1992**, 48, 2191. (b) S. Hanessian and Y. L. Bennani, *Synthesis*, **1994**, 1272.
10. U. Schollkopf, I. Hoppe and A. Thiele, *Liebigs Ann. Chem.*, **1985**, 555.
11. (a) R. Graf, *Angew. Chem. Int. Ed. Engl.*, **1968**, *7*, 172. (b) P. Kocovsky, *Tetrahedron Lett.*, **1986**, *27*, 5521.
12. D. A. Evans and J. R. Gage, *Org. Synth.*, **1989**, *68*, 77.
13. (a) W. Oppolzer, C. Chapuis and G. Bernardinelli, *Tetrahedron Lett.*, **1984**, *25*, 5885. (b) W. Oppolzer, M. J. Kelly and G. Bernadinelli, *ibid.*, **1984**, *25*, 5889.
14. (a) H. Hiemstra and W. N. Speckamp, in *Comprehensive Organic Synthesis*, Ed. C. H. Heathcock, Pergamon, **1991**, vol. 2. pp. 1047-1082. (b) K. E. Harding, L. T. Lie, D. G. Farrer, M. T. Coleman and S. K. Tansey, *Synth. Commun.*, **1991**, *21*, 1409.
15. (a) C. Yuan, G. Wang and S. Chen, *Synthesis*, **1990**, 522. (b) A typical experimental procedure is as follows. To a mixture of a chiral carbamate (3 mmol), diethyl phosphite (4 mmol) and acetyl choride (5 ml) at 0 °C under Ar, was slowly added an aldehyde (5 mmol) over 10 min. The mixture was stirred for 30 min at this temperature and for 1 h at rt. Volatile components were removed under reduced pressure, and the oily residue was dissolved in ethyl acetate. The organic phase was extensively washed with sat. $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to give the crude product, which was purified on silica gel.
16. (a) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **1973**, *95*, 512. (b) D. E. Ward and C. K. Rhee, *Tetrahedron Lett.*, **1991**, *32*, 7165.
17. (a) W. Oppolzer, *Tetrahedron*, **1987**, *43*, 1969. (b) Y. Hamamoto, T. Nakada and H. Nemoto, *J. Am. Chem. Soc.*, **1992**, *114*, 121.
18. X-ray crystal structure of **4a** also revealed the (s)-configuration for the newly generated chiral center.
19. All new compounds reported have been fully characterized by IR, ^{1}H-, ^{13}C- and ^{31}P-nmr spectroscpy and mass spectrometry.

(*Received in Japan* 9 *October* 1995)