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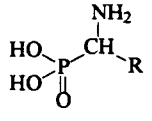
Asymmetric addition of dialkyl phosphite and diamido phosphite anions to chiral, enantiopure sulfinimines: a new, convenient route to enantiomeric α-aminophosphonic acids

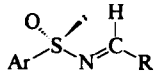
Marian Mikołajczyk,* Piotr Łyżwa and Józef Drabowicz
Centre of Molecular and Macromolecular Studies, Department of Organic Sulfur Compounds, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

Abstract: Lithium or sodium dialkyl phosphites and diamido phosphites **3** undergo addition to (+)-(S)-benzylidene-p-toluenesulfinamide **2** affording N-sulfinyl-α-aminophosphonates **4** in a diastereoisomeric ratio from 63:37 to 94:6. The major diastereoisomers formed in addition of lithium dimethyl phosphite **3a** and lithium bis-diethylamido phosphite **3e** to (+)-(S)-**2** were separated and converted into enantiopure (+)-(R)- and (−)-(S)-α-aminobenzyl phosphonic acids **5**, respectively. © 1997 Published by Elsevier Science Ltd. All rights reserved.

α-Aminophosphonic acids **1**, the phosphonic acid analogues of α-amino carboxylic acids, are attracting increasing interest. This is mainly due to the wide spectrum of biological activity exhibited by α-aminophosphonic acids or their peptide conjugates.[1] Many natural or synthetic α-aminophosphonic acids show pharmacological properties, behave as enzyme inhibitors, are growth regulators in plants and function as potent antimicrobial agents.[2] Since the bioactivity of these compounds is known to be strongly dependent on the chirality at the stereogenic α-carbon atom, a number of asymmetric syntheses have been devised during the past two decades.[3,4] Among them, the asymmetric addition of dialkyl or trialkyl phosphites to chiral imines or imine derivatives proved to be a very useful approach. Searching for a simple, general and efficient method for the synthesis of enantiomerically pure α-aminophosphonic acids **1** we turned our attention to enantiopure sulfinimines **2** as chiral auxiliaries.[5]



1



2

In addition to their ready availability[6] they contain an arylsulfinyl moiety as a powerful stereodirecting group inducing high diastereoselectivity and an activated carbon–nitrogen double bond prone to attack by nucleophilic reagents. In fact, we have recently described a highly efficient asymmetric synthesis of β-aminophosphonic acids via addition of α-phosphonate carbanions to enantiopure sulfinimines **2**.[7] We now extend our work in this area by reporting the asymmetric synthesis of α-aminophosphonic acids based on the stereoselective addition of dialkyl or diamido phosphite **3** anions to (+)-(S)-benzylidene-p-toluenesulfinamide **2** (Ar=p-Tol).[8]

* Corresponding author. Email: marmikol@bilbo.cbmm.lodz.pl

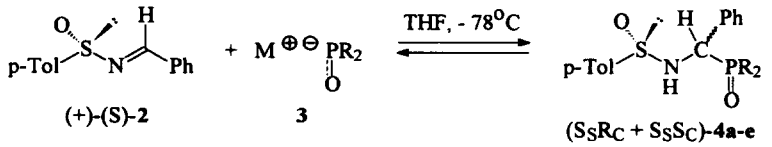
Table 1. Asymmetric addition of lithium and sodium phosphites **3** to (+)-(S)-sulfinimine **2**

Entry	3-M⁺	Ratio of reagents 3-H/MHMDS/2 [mmol]	Reaction time [h]	Adduct 4 dr [%] / δ_P [ppm]
1	**3a**-Na	2 : 2 : 1[a]	2	88.5 : 11.5 / 23.65 : 24.5
2	**3a**-Li	2 : 2 : 1[a]	2	94 : 6
3	**3b**-Li	2 : 2 : 1[b]	2	86 : 14 / 21.32 : 22.05
4	**3b**-Li	2 : 2 : 1[a]	2	90 : 10
5	**3c**-Li	2 : 2 : 1[a]	2	74 : 26 / 19.64 : 20.40
6	**3d**-Li	2 : 2 : 1	7.5	37 : 63 / 32.28 : 33.13
7	**3e**-Na	2 : 2 : 1[b,c]	1	31 : 69 / 31.37 : 32.40
8	**3e**-Li	2 : 2 : 1[b,c]	1	10 : 90
9	**3e**-Li	2 : 2 : 1[a]	7.5	21 : 79
10	**3e**-Li	1 : 1 : 2[a]	7.5	14.5 : 85.5

[a]Reaction components were dissolved in 15 ml of THF.

[b]Reaction components were dissolved in 8 ml of THF.

[c]The adducts **4** were isolated in lower yield (ca. 20-30%).

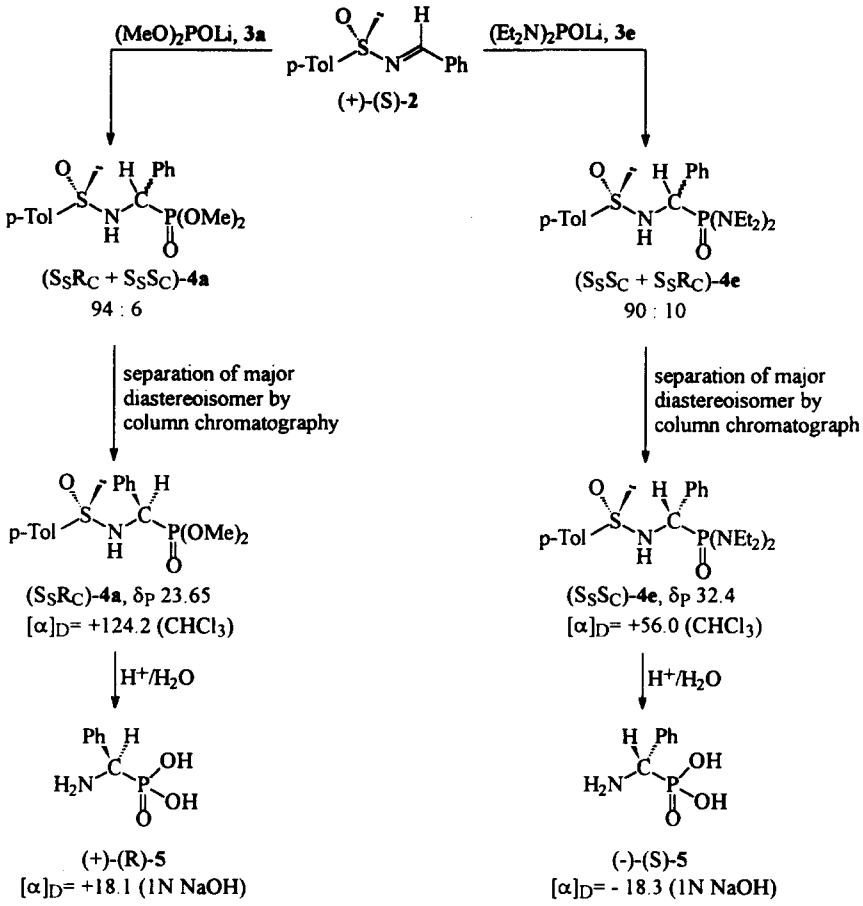


(+)-(S)-**2** **3** (SSRC + SSSC)-**4a-e**

a, R=MeO
b, R=EtO
c, R=iPrO
d, R=Me_2N
e, R=Et_2N

Thus, the lithium or sodium salts of dialkyl and diamido phosphites **3a–e** (generated from the corresponding phosphites and lithium or sodium hexamethyldisilazane, MHMDS, in THF) were added at −78°C to a THF solution of the (+)-(S)-sulfinimine **2**. After quenching the reaction mixture at this temperature with ammonium chloride and extraction with ether, the diastereoisomeric adducts **4** obtained in 70–90% yield were purified and analyzed. It should be emphasized that the room temperature addition of **3** to (+)-(S)-**2** is not effective due to reversibility of the reaction which at this temperature is shifted towards the starting reagents. Therefore, the diastereoselectivity of the addition was additionally investigated as a function of some reaction conditions. The results of the experiments performed are summarized in Table 1.

An inspection of the results in Table 1 reveals three important features of the reaction investigated: (a) the use of lithium phosphites **3** enhances the diastereoselectivity of the addition (entries 1 and 2 and 7 and 8); (b) the same effect is observed when the reaction is carried out in a more dilute solution (entries 2 and 3) and (c) the signals of the major diastereoisomers of the adduct **4a–c** occur in the ^{31}P-NMR spectra at higher field while the signals of the major diastereoisomers of **4d–e** lie at lower field. The latter observation was a strong indication that the stereochemical outcome of the addition of dialkyl phosphites **3a–c** and diamido phosphites **3d–e** to (+)-(S)-sulfinimine **2** may be contrasting. This was found to be the case. The experiments shown in Scheme 1 demonstrate how both enantiopure forms of α-aminobenzylphosphonic acid **5** can be prepared from (+)-(S)-**2**.



Scheme 1.

Since the absolute configuration of the enantiomeric phosphonic acids **5** is known[9] and during the deprotection of the amino function and phosphonate ester moiety the bonds around the stereogenic α-carbon atom are not broken, it is possible to assign the (S_SR_C)- and (S_SS_C)-configuration to the major diastereoisomers formed in the reaction of (+)-(S)-**2** with the phosphite **3a** and amido phosphite **3e**, respectively. It is interesting to point out that the synthesis of the enantiopure α-aminophosphonic acids **5** shown above represents a rare example of preparing both enantiomers using the same chiral auxiliary.

Experiments to rationalize the contrasting steric course of the addition of dialkyl phosphites and diamido phosphites to (+)-(S)-sulfinimine **2** as well as study on the scope of this new asymmetric synthesis of α-aminophosphonic acids **1** are under way.

References

1. P. Kafarski and P. Mastalerz, in *Beiträge zur Wirkstofforschung*, ed. P. Oehme, H. Löwe and E. Gores, J. Axt, Inst. f. Wirkstofforschung, Berlin, 1984, Vol. 21.
2. For a comprehensive review on the biological activity of aminophosphonic acids **1** see: P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon*, **1991,** *63,* 193.
3. For comprehensive reviews, see: B. Dhawan and D. Redmore, *Phosphorus and Sulfur*, **1987,** *32,* 119; V. P. Kukhar, V. A. Soloshonok and V. A. Solodenko, *Phosphorus, Sulfur and Silicon*, **1994,** *92,* 239.

4. For recent examples of asymmetric synthesis of α-aminophosphonic acids **1**, see: K. M. Yager, C. M. Taylor and A. B. Smith III, *J. Am. Chem. Soc.*, **1994,** *116,* 9377; H. Sasai, S. Arai, Y. Tahara and M. Shibasaki, *J. Org. Chem.*, **1995,** *60,* 6656; R. Hamilton, B. Walker and B. J. Walker, *Tetrahedron Lett.*, **1995,** *36,* 4451; A. Heisler, C. Rabiller and G. Hägele, *Phosphorus, Sulfur and Silicon*, **1995,** *101,* 273.
5. For recent applications of chiral sulfinimines in asymmetric synthesis, see: M. Mikołajczyk, J. Drabowicz and P. Kiełbasiński, *Chiral Sulfur Reagents: Applications in Asymmetric and Stereoselective Synthesis*, CRC Press, Boca Raton, 1997, pp. 195–233.
6. F. A. Davis, R. E. Reddy, J. M. Szewczyk and P. S. Portonowo, *Tetrahedron Lett.*, **1993,** *34,* 6229.
7. M. Mikołajczyk, P. Łyżwa, J. Drabowicz, M. W. Wieczorek and J. Błaszczyk, *Chem. Commun.*, **1996,** 1503.
8. After completion of our results we become aware of a poster presented by I. M. Lafebvre and S. A. Evans, Jr, at the ESOC-X in Basel where the asymmetric addition of sodium and lithium diethyl phosphite to (+)-(S)-**2** was shown.
9. T. Głowiak, W. Sawka-Dobrowolska, J. Kowalik, P. Mastalerz, M. Soroka and J. Zoń, *Tetrahedron Lett.*, **1977,** 3965.

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