Heteroatom Chemistry
Volume 20, Number 7, 2009

Addition of Di-(trimethylsilyl)phosphite to *N*,*N*′-Dialkyl Terephthalic Schiff Bases: Synthesis of 1,4-Phenylene-bis-(aminomethyl)-Phosphonic Acids

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Received 5 October 2009; revised 7 December 2009

ABSTRACT: *The addition of di-(trimethylsilyl)-phosphite to N,N′-terephthalylidene-alkyl-(or aryl-)-amines resulted in 1,4-phenylene-bis-(N-alkylaminomethyl)-phosphonic acids in moderate yields. The stereochemical behavior of such reactions was studied, and NMR studies demonstrated that, for several examples, this reaction led to the exclusive formation of only one diastereomeric form. The investigation of the chiral salt of the acid identified the pair of enantiomers.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 20:431–435, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20569

INTRODUCTION

The addition of hypophosphorous acid to terephthalic Schiff bases was stereoselective in a majority of cases. The addition of hypophosphorous acid to achiral *N*-alkyl terephthalic imines has been reported [1,2] to be diastereoselective to 100% and lead to a meso-form, whereas the reaction performed on *N*-aryl imines has been noted to depend on the nature of a substituent to an aromatic ring [2]. Similar results have been reported for the addition of dialkyl phosphites to achiral *N*-alkyl and *N*-aryl terephthalic Schiff bases [1,3–7].

These 1,4-phenylene-bis-(*N*-alkylaminomethyl)-phosphonic derivatives have been found to have coordination abilities toward Cu(II) ions [8] or diaminophosphonate peptide receptor for lysine and arginine [9]. So, investigations of these compounds and their synthesis deal with not only their mechanism but also their applications.

That is why, we have adopted a methodology for the preparation of nonprotected aminophosphonic acids [10] and applied it with case to 1, 4-phenylene-bis-(*N*-alkylaminomethyl)-phosphonic derivatives. To our knowledge, it is the first example of the preparation of 1,4-phenylene-bis-(*N*-alkylaminomethyl)-phosphonic acids via the addition of di(trimethylsilyl)phosphite to the azomethine bond of terephthalic Schiff bases.

RESULTS AND DISCUSSION

We have chosen several model amines **1a–g** and prepared their imines **2a–g** with terephthalic aldehyde. Imines **2a–g** were prepared following the modification of commonly known procedure by the condensation of corresponding amines **1a–g** with terephthalic aldehyde in methanol at room temperature. Schiff bases **2a–g** were obtained in almost quantitative yields [2,6,7] (Scheme 1).

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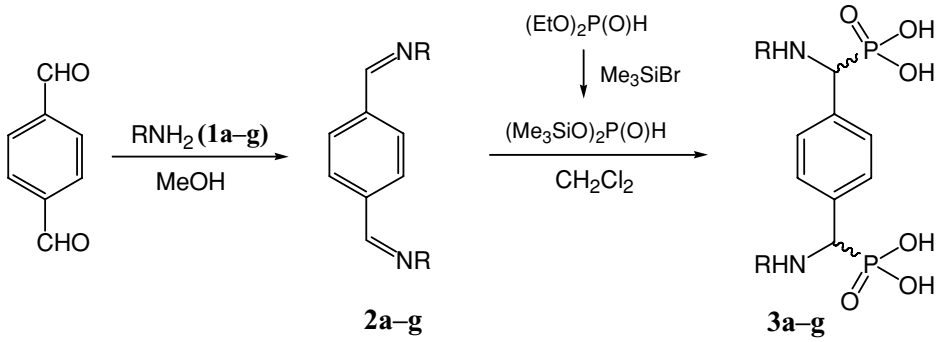
Contract grant sponsor: University of Łódź.
Contract grant number: 505/0683.



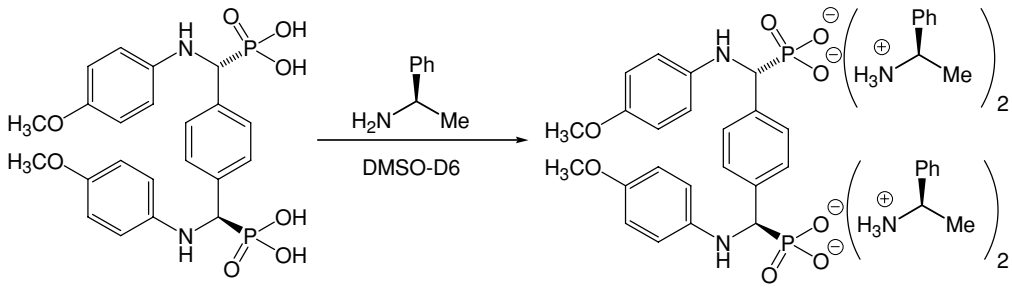
a: R = CH_2Ph; **b**: R = CH_2Fur; **c**: R = $C(CH_3)_3$; **d**: R = *p*-$CH_3C_6H_4$; **e**: R = *p*-$CH_3OC_6H_4$; **f**: R = *m*-$CH_3C_6H_4$; **g**: R = *m*-$CH_3OC_6H_4$

SCHEME 1

1,4-Phenylene-bis-(*N*-alkylaminomethyl)-phosphonic acids **3a–g** were prepared using the method of Boduszek [10]. Diethyl phosphite was reacted with bromotrimethylsilane in dry dichloromethane. In situ formed di(trimethylsilyl) phosphite then was reacted with terephthalic Schiff bases **2a–g** in dry dichloromethane, and in the end the reaction was stopped by methanolysis (Scheme 1). Acids **3a–g** were obtained as powder solids with moderate yields approximately 65%, which was expected, as Barycki and coworkers [1] suggested much lower conversion rate for addition to two azomethine groups. Acids **3a–g** were purified by dissolution in 10% aqueous NaOH followed by precipitation by acidification with 1 M HCl and gave appropriate results of spectroscopic and elemental analysis. Nevertheless, 1,4-phenylene-bis-(*N*-(*m*-methoxyphenyl)aminomethylphosphonic acid) (**3g**) decomposed in the above-described conditions. Therefore, its purification was very troublesome and its identity was confirmed only by the NMR spectroscopy and mass spectrometry measurements of the crude product without purification. It may be surprising that the crude product has a very sharp melting point, but results of their elemental analysis were not within the accepted range.

The ^1H and ^{31}P NMR spectroscopy demonstrated that all investigated *N*-alkyl substituted acids **3a–c** occurred exclusively as one of two possible diastereoisomeric forms. The same situation has been noticed in a case of *N*-aryl substituted acids **3d** and **3e**, which also exclusively occurred as one diastereoisomeric form. The *N*-aryl-substituted acids **3f–g** occurred as the mixture of two diastereomeric forms, in a 10:1 ratio for **3f** and 3:2 for **3g**.

The following experiment was performed to establish that which diastereomeric form of acids **3a–e** occurred as a sole product (Scheme 2). 1,4-Phenylene-bis-(*N*-(*p*-methoxyphenyl)-aminomethylphosphonic acid) (**3e**) was dissolved in deuterated DMSO, and the stoichiometric amount of (*R*)-α-methylbenzylamine was added to form the ammonium salt of the phosphonic acid (**4e**). Although the appearance of two sets of ^1H and ^{13}C NMR signals and two ^{31}P NMR signals of the formed salt is expected theoretically in both cases of the



3e
and the (*S,S*) enantiomer

4e
and the (*S,S,R*) isomer

SCHEME 2

meso form and the pair of enantiomers, we expected the occurrence of one set of ^{1}H and ^{13}C NMR signals and one ^{31}P NMR signal of the formed salt in the case of the meso form as it has been demonstrated previously in [2,6,7].

The formed salt **4e** gave two ^{31}P NMR signals and two sets of ^{1}H and ^{13}C NMR key signals, i.e. the P—C—H doublet as well as the C—P bond doublet. The optical rotation of the formed salt **4e** after the crystallization from acetone ($+6.07^{\circ}$, $c = 0.016$) differed significantly from the optical rotation of the purified salt **4e** before crystallization ($+10.89^{\circ}$, $c = 0.016$). Simultaneously, we observed the decrease in the peak height of the signal at 12.68. The ratio became from 1:1 to 3:2. This allowed us to suggest that the exclusive diastereoisomeric form occurring in the case of acids **3a–e** is most probably a pair of enantiomers.

So, contrary to previously published cases of addition to achiral terephthalic Schiff bases (i.e., additions of dialkyl phosphites, hypophosphorous acid) [2,6,7], the addition of di(trimethylsilyl)phosphite led to the formation of the enantiomeric pair.

Our explanation of this effect is the following and is concordant with analogous explanations of similar cases, which we have published previously [2,67]. Barycki et al. [1] suggested a two-step mechanism of this type reaction, the addition of a nucleophile to the first azomethine bond to form the imino-aminophosphonate derivative **5** and then to the other. Considering it, it is possible that two imino-aminophosphonate molecules **5** form an intermediate dimer **6**, inside which the coordination of di(trimethylsilyl) phosphite molecules occurs, which attacks from the defined sides leading to two enantiomers of a di(aminophosphonic) acid **3** (Scheme 3). In this scheme, formation of the *S*,*S* enantiomer is depicted.

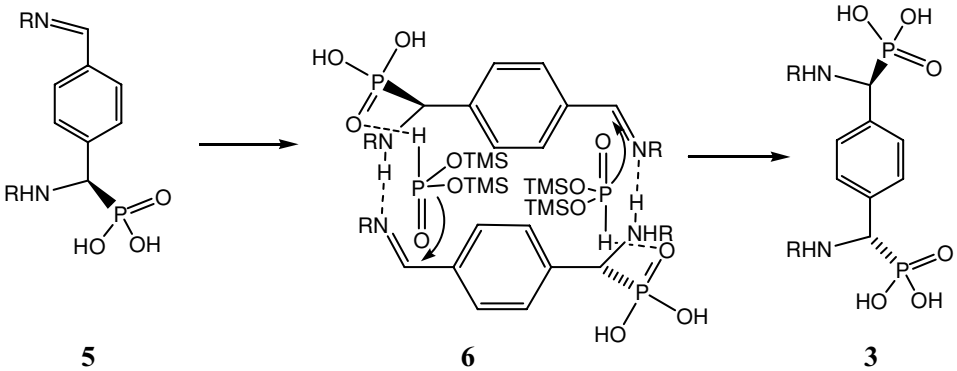
The results discussed above are surprisingly contrary to previously reported observations [1–7]. The addition of either dialkyl phosphites [1–6] or hypophosphorous acid [1,2] or described above addition of di(trimethylsilyl) phosphite led to the similar diastereoselectivity but the other diastereoisomeric form occurred. We feel that the addition of any phosphorus nucleophile to *N*-alkyl (or *N*-alkylaryl) terephthalic Schiff bases leads to the exclusive formation of one diastereomeric form and in some cases it is a meso-form and in others a pair of enantiomers, but it is diastereoselective to 100% [1–7]. Contrary to this, the addition of a phosphorus nucleophile to *N*-aryl terephthalic Schiff bases is not so well stereochemically defined—its stereochemistry depends greatly on a phosphorus nucleophile and the nature of *N*-aryl substituent. Generally, more electron-donating character *N*-aryl groups have higher diastereoselectivity, as the possibility of the formation of the intermediate **6** increases [7]. This problem, however, will be investigated in various aromatic dialdehydes.

EXPERIMENTAL

All solvents (POCh, Poland) were routinely distilled and dried prior to use. Amines, diethyl phosphite ,and terephthalic aldehyde (Aldrich) were used as received. NMR spectra were recorded on a Varian Gemini 200 BB apparatus operating at 200 MHz (^{1}H NMR), 50 MHz (^{13}C NMR), and 81 MHz (^{31}P NMR). Elemental analyses were carried out at the Centre for Molecular and Macromolecular Science of the Polish Academy of Science in Łódź, Poland.

*1,4-Phenylene-bis-(aminomethylphosphonic Acids) (**3a–g**)*

General Procedure. Diethyl phosphite (10 mmol) was dissolved in dry dichloromethane, and to this solution bromotrimethylsilane (42 mmol,



SCHEME 3

5.6 mL) was added dropwise for 15 min. The mixture was stirred for 1 h at room temperature. Then, a solution of an appropriate Schiff base (5 mmol) in dry dichloromethane was added, and the mixture was refluxed for 4 h. Then, the solution was evaporated in vacuo, and the residue was dissolved in dry methanol. It was stirred for 30–45 min until precipitation of a solid, which was filtered off and collected. In the case, if the solid did not precipitated, 10–20 mL of propylene oxide was added and the mixture was refrigerated for 3–7 days. Then the solid was filtered off and collected. Products were purified by dissolution in 10% aqueous NaOH followed by precipitation by acidification with 1 M HCl.

1,4-Phenylene-bis-(N-benzylaminomethylphosphonic Acid) **3a**. Yield = 92% (2.2 g); mp 242–244°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.27 (s, C_6H_4, 4H); 7.21 (m, PhH, 10 H); 3.61 (d, $^2J_{PH}$ = 16.5 Hz, 2H); 3.57 (d, J = 12.4 Hz, $C\underline{H_A}H_B$, 2H); 3.43 (d, J = 12.4 Hz, $CH_A\underline{H_B}$, 2H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 15.13. Elemental analysis: Calcd for $C_{22}H_{26}N_2O_6P_2{\cdot}2H_2O$: C, 51.57; H, 5.90; N, 5.47. Found: C, 51.89; H, 5.12; N, 5.51.

1,4-Phenylene-bis-(N-furfurylaminomethylphosphonic Acid) **3b**. Yield = 79% (1.80 g); mp: 190–193°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.25 (m, CH^5_{fur}, 2H); 7.14 (s, C_6H_4, 4H); 6.17 (dd, J = 1.8 and 3.2 Hz, H^4_{fur}, 2H); 6.00 (d, J = 3.2, H^3_{fur}, 2H); 3.49 (d, J = 13.9 Hz, $C\underline{H_A}H_B$, 2H); 3.42 (d, J = 13.9 Hz, $CH_A\underline{H_B}$, 2H); 3.61 (d, $^2J_{PH}$ = 24.1 Hz, 2H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 15.09. Elemental analysis: Calcd for $C_{18}H_{22}N_2O_8P_2{}^1/_2H_2O$: C, 46.46; H, 4.98; N, 6.02. Found: C, 46.19; H, 5.01; N, 5.91.

1,4-Phenylene-bis-(N-t-butylaminomethylphosphonic Acid) **3c**. Yield = 80% (1.63 g); mp: 214–216°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.27 (s, C_6H_4, 4H); 3.62 (d, $^2J_{PH}$ = 19.7, PCH, 2H); 0.64 (s, $C(CH_3)_3$, 18H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 16.64. Elemental analysis: Calcd for $C_{16}H_{30}N_2O_6P_2{\cdot}3H_2O$: C, 41.56; H, 7.85; N, 6.06. Found: C, 41.92; H, 7.94; N, 5.52.

1,4-Phenylene-bis-(N-(p-methylphenyl)aminomethylphosphonic Acid) **3d**. Yield = 93% (2.23 g); mp: 183–185°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.11 (s, C_6H_4, 4H); 6.72 (d, J = 7.7 Hz, Part of AA′XX′ system, 4H); 6.37 (d, J = 7.7 Hz, Part of AA′XX′ system, 4H); 4.19 (d, $^2J_{PH}$ = 20.4 Hz, PCH, 2H); 1.93 (s, CH_3, 6H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 14.76. Elemental analysis: Calcd for $C_{22}H_{26}N_2O_6P_2{\cdot}H_2O$: C, 53.44; H, 5.71; N, 5.67;. Found: C, 53.83; H, 5.85; N, 5.48.

1,4-Phenylene-bis-(N-(p-methoxyphenyl)aminomethylphosphonic Acid) **3e**. Yield = 95% (2.40 g); mp: 186–188°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.18 (s, C_6H_4, 4H); 6.56 (d, J = 9.1 Hz, Part of AA′XX′ system, 4H); 6.48 (d, J = 9.1 Hz, Part of AA′XX′ system, 4H); 4.22 (d, $^2J_{PH}$ = 20.3 Hz, PCH, 2H); 3.48 (s, OCH_3, 6H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 14.76. Elemental analysis: Calcd for $C_{22}H_{26}N_2O_8P_2{\cdot}2H_2O$: C, 48.54; H, 5.55; N, 5.14. Found: C, 48.95; H, 5.45; N, 5.04.

1,4-Phenylene-bis-(N-(m-methylphenyl)aminomethylphosphonic Acid) **3f**. Y = 32% (0.77 g); mp: 160–162°C. ^{1}H NMR (DMSO-D6, 200 MHz): δ 7.35 (s, C_6H_4, 4H); 6.84 (dd, J = 7.9 and 7.2 Hz, *m*-C_6H_4, 2H); 6.48 (s, *m*-C_6H_4, 2H); 6.41 (d, J = 7.9 Hz, *m*-C_6H_4, 2H); 6.29 (d, J = 7.2 Hz, *m*-C_6H_4, 2H); 4.57 (d, $^2J_{PH}$ = 23.2 Hz, PCH, 2H); 2.09 (s, CH_3, 6H). ^{31}P NMR (DMSO-D6, 81 MHz): δ 17.20; 17.10 (10:1). Elemental analysis: Calcd for $C_{22}H_{26}N_2O_6P_2 \cdot {}^3/_2H_2O$: C, 52.49; H, 5.81; N, 5.56. Found: C, 52.65; H, 6.10; N, 5.22.

1,4-Phenylene-bis-(N-(m-methoxyphenyl)aminomethylphosphonic Acid) **3g**. Yield = 46% (1.17 g); mp: 236–238°C. ^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.18 (s, C_6H_4, 4H); 6.84 (dd, J = 8.0 and 8.2 Hz, *m*-C_6H_4, 2H); 6.15 (m, *m*-C_6H_4, 2×2H); 6.05 (m, *m*-C_6H_4, 2H); 4.25 (d, $^2J_{PH}$ = 20.2 Hz, PCH, 2H); 3.42 (s, OCH_3, 6H). ^{31}P NMR (NaOD/D_2O, 81 MHz): δ 14.45; 14.39 (3:2). EI-MS: m/z = 508 [M^+]; 346 [$M^+ - (PO_3H_2)_2$].

*1,4-Phenylene-bis-(N-(p-Methoxyphenyl)aminomethylphosphonic Acid) di-(R)-α-Methyl-benzylammonium Salt (***4e***)*

1,4-Phenylene-bis-(*N*-(*p*-methoxyphenyl)aminomethylphosphonic acid) (**3e**) (0.95 g, 5 mmol) was dissolved in acetone, and (*R*)-α-methylbenzylamine (2.42 g, 20 mmol) was added during vigorous stirring. The mixture was stirred at room temperature for 24 h; the precipitated solid was filtered off, dried, and carried out NMR study. Before crystallization $[\alpha]_{20}$ = +10.89° (c = 0.016) after $[\alpha\chi]_{20}$ = +6.07° (c = 0.016).

^{1}H NMR (DMSO-D_6, 200 MHz): δ 7.44 (m, ArH, 4H); 7.31 (m, ArH, 6H); 7.12 (s, C_6H_4, 4H); 6.56 (d, J = 8.9 Hz, part of AA′XX′ system, 4H); 6.48 (d, J = 8.9 Hz, part of AA′XX′ system, 4H); 4.15 and 4.11 (2d, $^2J_{PH}$ = 21.6 Hz, PCH, 2H); 4.04 (q, J = 5.1 Hz, $\underline{CH}CH_3$, 2H); 3.58 (s, OCH_3, 6H); 1.39 (d,

J = 5.1 Hz, CH$\underline{CH_3}$, 6H). ^{31}P NMR (DMSO-D_6, 81 MHz): δ 13.60, 12.68. ^{13}C NMR (DMSO-D_6, 50 MHz): δ 50.85 (C_{ipso}), 143.10 (d, $^2J_{PH}$ = 12.7 Hz, C_{ipso}), 140.57 (C_{ipso}), 139.18 (C_{ipso}), 128.85 (C_{meta}), 128.31 (C_{meta}), 128.64 (C_{para}), 127.26 (C_{ortho}), 127.04 (C_{ortho}), 122.84 ($C_{ortho+meta}$), 58.89 and 58.81 (d, $^1J_{PH}$ = 132.0 Hz, CP), 55.47 (OCH_3), 50.18 ($\underline{CH}CH_3$), 21.26 ($CH\underline{CH_3}$).

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