ISSN 1070-4280, Russian Journal of Organic Chemistry, 2014, Vol. 50, No. 4, pp. 481–483. © Pleiades Publishing, Ltd., 2014.
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Dithiophosphorylation of Racemic and Enantiomerically Pure 1-Phenylethanamines

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Received February 3, 2014

Abstract—*N*,*N*′-Bis[(*RS*)-, (*S*)-, and (*R*)-1-phenylethyl]phosphorodiamidodithioic acids were synthesized by reactions of racemic and enantiomerically pure 1-phenylethanamines with tetraphosphorus decasulfide.

DOI: 10.1134/S1070428014040058

Natural and synthetic chiral organic compounds containing hydroxy and amino groups are used to synthesize organophosphorus derivatives possessing asymmetric centers in O- and N-substituents [1]. The synthesis of optically active phosphorus dithio acids and their salts and esters have received less attention. Among these compounds, the most accessible are those containing asymmetric carbon atoms in O-, N-, and S-substituents on the four-coordinate phosphorus atom. By contrast, organophosphorus compounds with asymmetric phosphorus atoms are difficult to obtain. We believe that studies in the field of reactions of synthetic chiral alcohols, amines, and thiols with tetraphosphorus decasulfide could lead to the preparation of new optically active dithiophosphoric, amidodithiophosphoric, and tetrathiophosphoric acids and their derivatives. We have recently synthesized *O*,*O*-bis(1-phenylethyl)dithiophosphoric acid as a mixture of stereoisomers by reaction of racemic 1-phenylethanol with tetraphosphorus decasulfide [2].

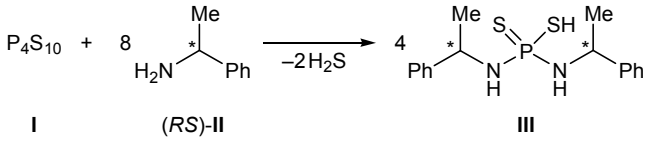
Reactions of amines with tetraphosphorus decasulfide and 1,3,2λ^5,4λ^5-dithiadiphosphetane 2,4-disulfides give different products whose structure is determined by the amine nature, reactant ratio, and reaction conditions. Aniline reacted with tetraphosphorus decasulfide at a molar ratio of 1:12 to produce phosphoric acid trianilide [3]. Thiophosphoric acid amides, diamides, and triamides were obtained by reactions of secondary amines with tetraphosphorus decasulfide [3]. It was presumed that primary amines react with tetraphosphorus decasulfide to form diamidodithiophosphoric acid ammonium salts [3]. According to [4], reactions of secondary and primary amines with Lawesson's reagent in diethyl ether or chloroform at 25°C lead to the formation of ammonium phosphonamidodithioates. However, the products obtained in [4] were characterized by ^{31}P signals in the region δ_P 75–87 ppm (chloroform), though ammonium salts derived from dithiophosphoric and dithiophosphonic acids are generally characterized by ^{31}P chemical shifts ranging from δ_P 105 to 115 ppm [5].

Reactions of secondary and primary amines with Lawesson's reagent under drastic conditions yield N,N′-substituted (4-methoxyphenyl)phosphonothioic diamides (δ_P 51–65 ppm) which, in our opinion, are secondary reaction products [4]. Products isolated in the reactions of Lawesson's reagent with piperazine, thiomorpholine, 4-methylpiperazine, pyridine, pyridazine, pyrimidine, pyrazine, 1*H*-pyrrole, 1*H*-pyrazole, 1*H*-imidazole, and isopropylamine displayed ^{31}P signals in the region δ_P 72–88 ppm [6, 7], which is not consistent with the structure of ammonium phosphonamidodithioates. By contrast, Karakus [8] recently showed that reactions of primary chiral amines with 2,4-diferrocenyl-1,3,2λ^5,4λ^5-dithiadiphosphetane 2,4-disulfide on heating in toluene produced optically active N-substituted phosphonamidodithioates whose ^{31}P signals were observed at δ_P 67–72 ppm (DMSO), i.e., in the region typical of phosphonamidodithioic acids rather than their ammonium salts.

Taking into account the data of [8], we anticipated that proper selection of the conditions for reactions of

primary amines with tetraphosphorus decasulfide could ensure the formation of phosphorodiamidodithioic acids as final products. Reactions of chiral amines with tetraphosphorus decasulfide were not reported previously. However, from the viewpoint of fundamental chemistry of organoelement compounds, the synthesis of optically active phosphorus dithio acids via reaction of tetraphosphorus decasulfide with primary amines containing an asymmetric carbon atom in the N-substituent seems to be important. For this purpose, we initially examined the reaction of racemic 1-phenylethanamine with P_4S_{10} (**I**). The reaction of **I** with (*RS*)-1-phenylethanamine (**II**) was carried out in benzene for 1.5 h at 35°C. As a result, we isolated crystalline *N*,*N*′-bis[(*RS*)-1-phenylethyl]phosphorodiamidodithioic acid (**III**) as a mixture of diastereoisomers (Scheme 1).

Scheme 1.

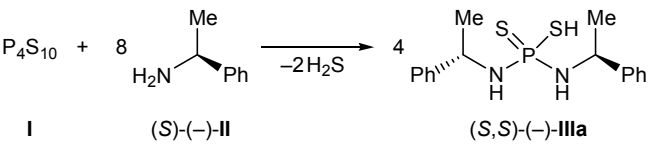


I (*RS*)-**II** **III**

GLC analysis of the product showed two peaks with retention times of 8.13 and 10.26 min at a ratio of 1:1. The $^{31}P–\{^1H\}$ NMR spectrum of **III** (benzene) contained a broadened signal at δ_P 79.54 ppm, whose position is close to the range typical of amidodithiophosphates (δ_P 67–72 ppm) [8]. In the IR spectrum of **III** we observed two broadened bands at 3666 and 3398 cm^{-1}, which may be assigned to stretching vibrations of free and associated NH groups [9]. Weak IR absorption bands at 2558 and 2478 cm^{-1} correspond to stretching vibrations of free and associated SH groups. Thus, no ammonium phosphorodiamidodithioate was formed in the reaction of phosphorus sulfide **I** with racemic amine **II**.

Likewise, sulfide **I** reacted with (*S*)-(–)-1-phenylethanamine [(*S*)-(–)-**II**] in benzene at 20°C (3 h) to afford crystalline (–)-*N*,*N*′-bis[(*S*)-1-phenylethyl]phosphorodiamidodithioic acid (**IIIa**) (Scheme 2). The product was optically active, $[\alpha]_D^{20}$ = –6° (*c* = 0.7, $CHCl_3$), and it displayed a sharp singlet at δ_P 79.6 ppm in the $^{31}P–\{^1H\}$ NMR spectrum (benzene).

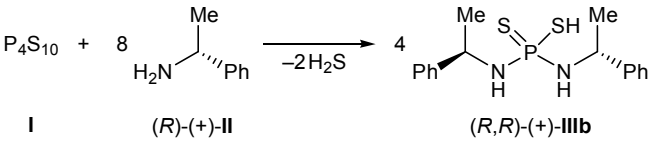
Scheme 2.



I (*S*)-(–)-**II** (*S*,*S*)-(–)-**IIIa**

(+)-*N*,*N*′-Bis[(*R*)-1-phenylethyl]phosphorodiamidodithioic acid (**IIIb**), $[\alpha]_D^{20}$ = +8° (*c* = 0.3, $CHCl_3$) was synthesized in a similar way from (*R*)-(+)-1-phenylethanamine (*R*)-(+)-(**II**) (Scheme 3). Its $^{31}P–\{^1H\}$ NMR spectrum (benzene) contained a singlet at δ_P 80.1 ppm; its position coincided within the experimental error with those observed for diastereoisomer mixture **III** and enantiomer **IIIa**. The NH stretching vibration band in the IR spectrum of **IIIb** was located at 3276 cm^{-1}.

Scheme 3.



I (*R*)-(+)-**II** (*R*,*R*)-(+)-**IIIb**

In summary, we were the first to synthesize diamidodithiophosphoric acids possessing asymmetric centers in the substituents on the nitrogen atoms by reaction of tetraphosphorus decasulfide with racemic and enantiomerically pure 1-phenylethanamines.

EXPERIMENTAL

The IR spectra (400–4000 cm^{-1}) were recorded on a Bruker Vector 22 spectrometer with Fourier transform from samples dispersed in mineral oil. The ^1H NMR spectra were measured on Bruker Avance-400 (400 MHz) and Bruker Avance-600 (600 MHz) spectrometers from solutions in $CDCl_3$. The ^{31}P NMR spectra were recorded on a Bruker Avance-400 instrument at 161.98 MHz using 85% H_3PO_4 as external reference. The mass spectra (electron impact, 70 eV, and chemical ionization) were obtained on a Thermo Electron DFS GC/MS system.

***N*,*N*′-Bis[(*RS*)-1-phenylethyl]phosphorodiamidodithioic acid (III).** Racemic amine **II**, 0.4 g (2.8 mmol), was added under stirring at 20°C in a stream of dry argon to a suspension of 0.6 g (1.4 mmol) of phosphorus sulfide **I** in 10 mL of anhydrous benzene. The mixture was stirred for 1.5 h at 35°C, kept for 4 days at 20°C, and filtered. The filtrate was evaporated under reduced pressure for 1 h at 40°C (0.5 mm) and for 1 h at 0.02 mm. Yield 1.1 g (61%). IR spectrum, ν, cm^{-1}: 3666 w (N–H, free), 3398 w.br (N–H, assoc.), 3037 w (C–H_{arom}), 2558 w (S–H, free), 2478 w ((S–H, assoc.), 1586 m, 1550 m, 1496 m (C=C_{arom}), 1314 w (δC–H), 604 m.br (P=S), 537 m (P–S). ^1H NMR spectrum, δ, ppm: 1.67 d and 1.68 d (3H each, CH_3, $^3J_{HH}$ = 5.9 Hz), 1.86 m (1H, SH),

4.39 m (2H, CH), 7.34–7.48 m (5H, C_6H_5), 8.66 m (1H, NH). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 304 [*M* – S]$^+$ (2), 259.8 [*M* – Ph]$^+$ (3). Found, %: C 57.40; H 6.44; N 8.05; P 8.89; S 19.38. $C_{16}H_{21}N_2PS_2$. Calculated, %: C 57.12; H 6.29; N 8.33; P 9.21; S 19.06. *M* 336.46.

(–)-*N*,*N*′-Bis[(*S*)-1-phenylethyl]phosphorodiamidodithioic acid (IIIa) was synthesized in a similar way from enantiomer (*S*)-(–)-**II** and P_4S_{10}. The product was isolated from the filtrate by precipitation with 30 mL of anhydrous petroleum ether (bp 70–100°C). Yield 92%, mp 110–112°C, $[\alpha]_D^{20}$ = –6° (*c* = 0.7, $CHCl_3$). Found, %: C 57.47; H 6.35; N 8.55; P 8.91; S 19.42. $C_{16}H_{21}N_2PS_2$. Calculated, %: C 57.12; H 6.29; N 8.33; P 9.21; S 19.06.

(+)-*N*,*N*′-Bis[(*R*)-1-phenylethyl]phosphorodiamidodithioic acid (IIIb) was synthesized in a similar way from enantiomer (*R*)-(+)-**II** and P_4S_{10}. Yield 67%, mp 108–110°C, $[\alpha]_D^{20}$ = +8° (*c* = 0.3, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3581 w (N–H, free), 3276 w (N–H, assoc.), 3098 w, 3076 w, 3038 w (C–H_{arom}), 2469 w (S–H)], 1591 m, 1560 sh (C=C_{arom}), 628 m (P=S), 537 m (P–S). Found, %: C 57.28; H 5.90; N 8.09; P 9.17; S 19.36. $C_{16}H_{21}N_2PS_2$. Calculated, %: C 57.12; H 6.29; N 8.33; P 9.21; S 19.06.

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 11-03-00264-a, 14-03-00897-a).

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