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Synthesis of enantiopure 1,3,4-thiazaphospholes

Lyudmila K. Kibardina, Mikhail A. Pudovik, Vladimir A. Alfonsov* and Olga N. Kataeva

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 8432 75 5322; e-mail: alfonsov@iopc.knc.ru

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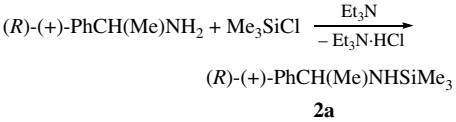
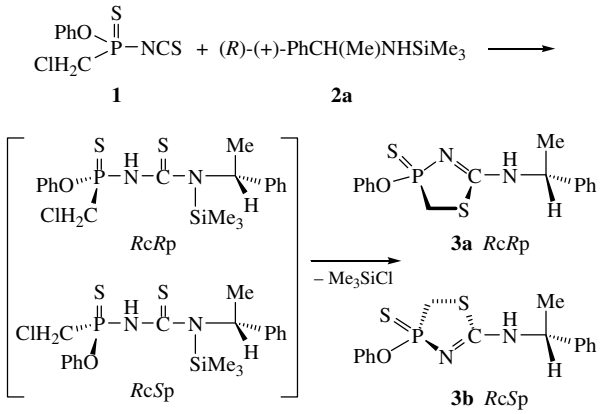
Racemic and (*R*)-(+)-*N*-trimethylsilyl-(1-phenyl)ethylamines stereoselectively react with *O*-phenylchloromethylisothiocyanatothiophosphonate to give a diastereomeric mixture of separable 1,3,4-thiazaphospholes; racemic thiazaphosphole crystallises as a conglomerate.

Enantiopure organophosphorus compounds are of interest as chiral drugs and ligands for the design of homogeneous or heterogeneous catalysts.[1,2] A small number of non-racemic compounds with phosphorus being a stereogenic centre have been reported.[1,2] Recently, we studied the reaction of chiral racemic *O*-phenylchloromethylisothiocyanatothiophosphonate **1** with chiral (*S*)-(–)- and (*R*)-(+)-(1-phenyl)ethylamine in the presence of triethylamine.[3] We found that this reaction proceeds under very mild conditions with good stereoselectivity and give 4-thioxo-1,3,4-thiazaphospholes with the chiral phosphorus atom. The first step of this reaction is stereocontrolled and includes amine addition to the isothiocyanate group with the formation of phosphorylated thiourea. The subsequent intramolecular nucleophilic replacement of the chlorine atom in the chloromethyl group by the sulfur atom of the thiourea fragment takes place, the chiral centre on the phosphorus atom being preserved. The stereoselectivity of this reaction is sufficient for the isolation of a predominant diastereomer; however, there are some complications such as the use of a solvent and a base and the removal of the precipitate that hampers the isolation of hydrolytically labile products. To avoid the above difficulties, we used silylated (1-phenyl)ethylamine, both racemic **2** and non-racemic **2a** in the reaction. Moreover, the bulky trimethylsilyl group could increase the stereoselectivity of this reaction. Racemic silylamine **2** was synthesised according to a published procedure.[4] (*R*)-(+)-*N*-Trimethylsilyl-(1-phenyl)ethylamine **2a** was synthesised by the interaction of (*R*)-(+)-(1-phenyl)ethylamine with trimethylchlorosilane in the presence of triethylamine (Scheme 1).†



Scheme 1

The reaction of isothiocyanate **1** with silylamine **2** proceeds easily in a diethyl ether solution at room temperature and results in the formation of a diastereomeric pair (δ_P 120.09 and 119.85 ppm) in a 24:76 ratio. Consequently, the diastereoselectivity is approximately the same,[3] but the separation of reaction products is more convenient because amine hydrochloride is absent from the reaction mixture.



Scheme 2

To obtain the major diastereomer in an enantiopure form, we studied the reaction of isothiocyanate **1** with silylamine **2a** (Scheme 2) taken in different ratios. The best result was obtained at the ratio **1**:**2a** = 1:0.7. This reaction easily proceeds under the same conditions and results in the formation of a mixture of **3a** and **3b** (23:77) with the chemical shifts δ_P of 120.05 and 119.77 ppm, respectively. Diastereomer **3b** crystallised from a reaction mixture after 24 h, its angle of the specific rotation was $[\alpha]_D^{20}$ +240.5.† Earlier, the structure of **3b** and its antipode obtained by a reaction with free amine[3] was studied by X-ray single crystal diffraction. The determination of the unit cell and the space group of **3b** showed that crystallographic parameters are consistent with those reported previously[3] within the limits of experimental errors (Figure 1), which is enough to identify **3b**.‡

Note that the reaction with a silylated amine in place of a free amine is more convenient and gives no by-products. The addition of a crystal of **3b** as a seed into the reaction mixture

† NMR spectra were measured on a Bruker MSL-400 spectrometer, ^{1}H, ^{13}C and ^{31}P at 400.13, 100.62 and 162.98 MHz, respectively.

2a: yield 52%, bp 82 °C (12 Torr), n_D^{20} 1.4918, $[\alpha]_D^{20}$ +36.2° (*c* 1.4, C_6H_6). ^{1}H NMR ($CDCl_3$) δ: 0.10 (s, 9H, Me_3Si), 1.44 (d, 3H, MeC, $^3J_{HH}$ 7.1 Hz), 4.17 (m, 1H, CH), 7.36 (m, 5H, Ph).

3b: yield 30%, mp 161.5–163 °C, $[\alpha]_D^{20}$ +240.5° (*c* 0.87, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 1.54 (d, 3H, MeC, $^3J_{HH}$ 7.0 Hz), 3.49 (dd, 1H, PCH_A, $^2J_{HP}$ 3.6 Hz, $^2J_{HH}$ 13.3 Hz), 3.81 (dd, 1H, PCH_B, $^2J_{HP}$ = $^2J_{HH}$ = = 13.3 Hz), 5.23 (dq, 1H, CHN, $^3J_{HH}$ = $^3J_{HP}$ = 7.0 Hz), 6.79–7.40 (m, 10H, 2Ph), 8.28 (s, 1H, NH). ^{13}C NMR [$(CD_3)_2CO$] δ: 22.37 (Me), 35.18 (d, CH_2, $^1J_{PC}$ 56.88 Hz, $^1J_{CH}$ 144.27 Hz), 55.35 (CH), 122.34 (C^o_{PhC}, $^1J_{CH}$ 162.3 Hz), 125.23 (C^o_{PhOP}, $^1J_{CH}$ 159.53 Hz), 126.87 (C^p_{PhC}, $^1J_{CH}$ 160.91 Hz), 127.96 (C^p_{PhOP}, $^1J_{CH}$ 159.53 Hz), 129.23 (C^m_{PhC}, $^1J_{CH}$ 159.53 Hz), 129.89 (C^m_{PhOP}, $^1J_{CH}$ 160.91 Hz), 144.24 (C^i_{PhC}), 151.74 (d, C^i_{PhOP}, $^2J_{PC}$ 9.71 Hz), 167.61 (N=C). ^{31}P NMR [$(CD_3)_2CO$] δ: 120.67. IR, ν/cm^{-1}: 685 (P=S), 1210 (POPh), 1570 (C=N), 1590 (Ph), 3275 (NH). Found (%): C, 55.47; H, 4.85; N, 8.02; P, 9.32, S, 18.23. Calc. for $C_{16}H_{17}N_2OPS_2$ (%): C, 55.14; H, 4.93; N, 8.04; P, 8.82; S, 18.41.

‡ X-ray data were obtained with an Enraf Nonius CAD4 diffractometer: a = 5.684(5), b = 15.009(10) and c = 10.492(10) Å, β = 105.1(1)°, V = = 865.2(12) Å^3, space group $P2_1$, Z = 2.

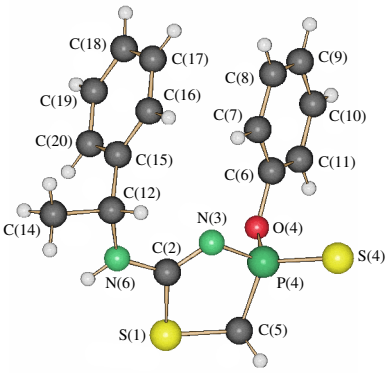


Figure 1 Molecular geometry of **3b**.

obtained from **1** and racemic **2** resulted in *Rc*S*p* thiazaphosphole in 30% yield. This result allows us to conclude that the enantiomeric pair (*Rc*S*p*, *Sc*R*p*) of the basic diastereomer crystallises as a conglomerate.

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