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Thermal rearrangement of bis(hydroxymethyl)phosphines as a way to *P*-chiral phosphine oxides

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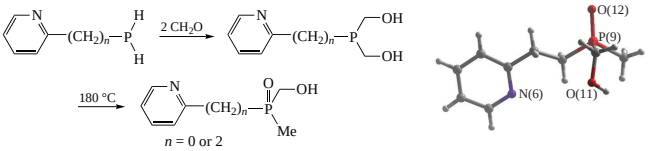
Bis(hydroxymethyl)(2-pyridyl)- and bis(hydroxymethyl)-[(2-pyridyl)ethyl]phosphines on heating to 180 °C undergo rearrangement leading to racemic *P*-chiral tertiary *P*-methyl-*P*-(hydroxymethyl)-containing phosphine oxides. The spontaneous self-resolution of these enantiomer mixtures during the crystallization was demonstrated.



Keywords: chiral phosphine oxides, P-chirality, rearrangement, bis(hydroxymethyl)phosphines, primary phosphines.

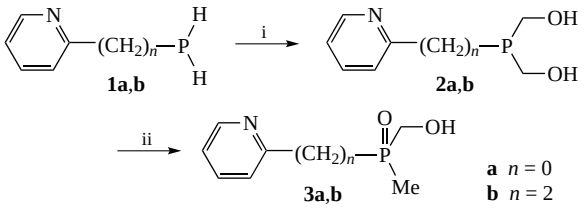
Chiral phosphorus compounds carrying additional functional groups find application in organocatalysis, materials fabrication or drug development.[1,2] The formation of asymmetric P–C bonds promoted by transition metals[3–5] or inorganic bases[6,7] is one of the main strategies for the preparation of chiral phosphorus compounds[8–10] with chiral centers at phosphorus and/or carbon atoms.[11–15] In the syntheses of *P*-stereogenic phosphine oxides, secondary phosphine oxides suitable for functionalization are utilized as the starting materials. Consequently, for the synthesis of tertiary chiral phosphine oxides the corresponding secondary phosphine oxides should be required.[16–23]

In late 1970s, Valetdinov[24] and Frank[25] independently discovered the rearrangement of tris(hydroxymethyl)phosphines and bis(hydroxyethyl)ethylphosphine to phosphine oxides under the heating at 180–190 °C. This thermal rearrangement occurred due to high lability of the hydroxymethyl group, so on moving to bis(hydroxyalkyl)phosphines one can access new chiral functionalized tertiary phosphine oxides. Despite of this, the rearrangement still did not find a broad attention. In the pioneering work of Valetdinov,[24] this reaction was discussed as a property of α-hydroxyethylphosphine but not as a methodology to the synthesis of chiral phosphine oxides. To date, thermal rearrangement of hydroxymethylphosphines has been studied scarcely. Previously,[26–29] we obtained primary phosphines bearing pyridyl group which played an important role as basic, donor and chromphore center. In those studies bis(hydroxymethyl)phosphines were formed as intermediate adducts.

Herein, we present the straightforward one-pot synthesis of chiral phosphine oxides with *P*-stereogenic centers by the reaction of primary phosphines with paraformaldehyde and the following intermolecular Valetdinov–Frank rearrangement. The reaction of primary pyridyl- or pyridylethyl-containing phosphines **1a**,**b** with paraformaldehyde at 110–120 °C led to bis(hydroxymethyl)phosphines **2a**,**b** (Scheme 1).[26,30,31] The subsequent solvent-free heating of the reaction at 180 °C afforded phosphine oxides **3a**,**b** as racemic mixtures (Scheme 1). These compounds appeared as viscous oils soluble in ethanol, ethyl acetate, diethyl ether, chloroform, dichloromethane, but insoluble in hexane, benzene and toluene.

The ^{31}P signal of phosphine oxides **3a**,**b** ($CDCl_3$) is detected at 34.5 and 48.5 ppm, respectively. Their ^{1}H NMR spectra contained well resolved signals for pyridyl, hydroxymethyl and methyl groups. Protons of ethylene spacer of compound **3b** resonated as four multiples at the 2.1–2.5 and 3.1–3.4 ppm ranges, which is indicative of their nonequivalence.

The crystallization of compound **3b** from a 10 : 1 mixture of toluene and ethanol gave the crystals whose XRD analysis finally confirmed the formation of chiral phosphine oxide.†



Scheme 1 *Reagents and conditions*: i, $(CH_2O)_x$ (2 equiv.), 120 °C, up to homogenization; ii, 180 °C, 4 h.

† *Crystal data for* $C_9H_{14}NO_2P$. M = 199.18 g mol^{-1}, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 5.4755(2), b = 7.7897(3) and c = 23.7035(8) Å, V = 1011.01(6) Å^3, Z = 4, T = 100.00(10) K, μ(CuKα) = 2.168 mm^{-1}, d_{calc} = 1.309 g cm^{-3}, 4618 reflections measured (7.46° ⩽ 2θ ⩽ 152.626°), 1999 unique (R_{int} = 0.0443, R_{sigma} = 0.0523) which were used in all calculations. The final R_1 was 0.0653 [$I > 2\sigma(I)$] and wR_2 was 0.2080 (all data). Data set for single crystal of **2** was collected on a Rigaku XtaLab Synergy S instrument with a HyPix detector and a PhotonJet microfocus X-ray tube using CuKα (1.54184 Å) radiation at room temperature. Images were indexed and integrated using the CrysAlisPro data reduction package. Data were corrected for systematic errors and absorption using the ABSPACK module. The GRAL module was used for analysis of systematic absences and space group determination. The structure was solved by direct methods using

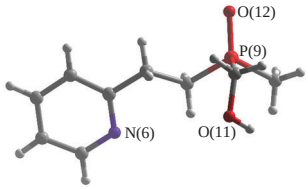
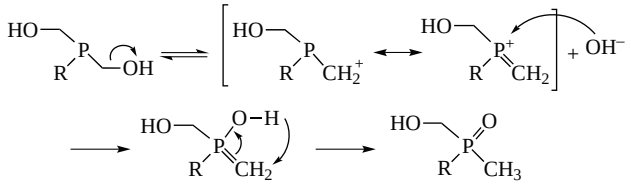


Figure 1 Molecular structure of single crystal **3b** established by XRD analysis.



Scheme 2

According to the XRD data (Figure 1), the single crystal **3b** belonged to the chiral space group $P2_12_12_1$ and represented only (*R*)-isomer. Since the solution of compound **3b** did not rotate the plane-polarized light, we assumed that deracemization leading to crystals of (*R*)- and (*S*)-isomers occurred during crystallization. The molecules in crystal have a compact organization caused by the net of the H-bonds from hydroxyl group and oxygen of P=O moiety. Possibly, these numerous H-bonding allowed us to obtain the phosphine oxide as a crystalline sample.

The thermal rearrangement possibly started due to the elimination of hydroxy group and formation of methylenephosphonium ion (Scheme 2). Such a mechanism was suggested by Frank for tris(hydroxymethyl)phosphines.[25] It is noteworthy that analogous mechanism was also supposed by Swor[32] for the reactions of hydroxymethylphosphines with amines. According to Frank's and Swor's works it is possible to suppose that after thermal elimination of hydroxy group and formation of methylenephosphonium ion, the liberated hydroxyl anion would react with phosphonium center with following formation of phosphine oxide as the most stable compound.

In summary, the thermal rearrangement of bis(hydroxymethyl)pyridyl- and bis(hydroxymethyl)(pyridylethyl)-phosphines is a convenient way to the synthesis of chiral phosphine oxides. This rearrangement may be expanded for the wider scope of phosphines with various substituents at phosphorus atoms. The crystallization of herein obtained phosphine oxides leads to spontaneous resolution of their enantiomers.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.017.

SHELXT[33] and refined by the full-matrix least-squares on F^2 using SHELXL.[34] Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were inserted at the calculated positions and refined as riding atoms.

CCDC 2166143 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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