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Effect of Isopropyl Group on Phosphorylation of Phenols with Phosphorous Amides

E. E. Nifant'ev, S. V. Suvorkin, E. N. Rasadkina, O. V. Selyutina, and A. V. Shishin[†]

Moscow State Pedagogical University, Moscow, Russia

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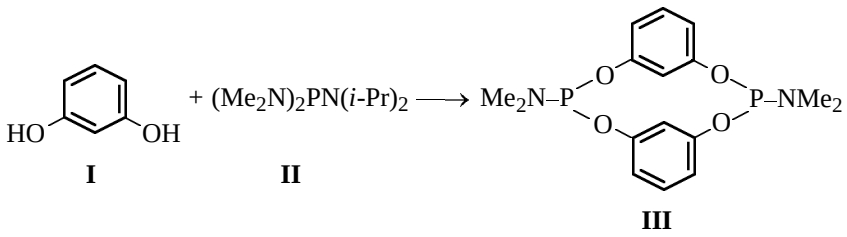
Abstract — Reaction of resorcinol with phosphorous triamides containing various aliphatic radicals was studied. The preferential cleavage from phosphorus of the diisopropylamino group compared with the less bulky dimethylamino group was observed for the first time. It was shown that resorcinol is easily phosphorylated under mild conditions independent of the nature of substituent on nitrogen, but sterically hindered bulky radicals on nitrogen slow down phenolysis not only of the first, but also of the second amido group.

Phosporylation of alcohols and phenols with dialkylamides of trivalent phosphorus acids has been widely studied [1]. Much emphasis in these works has been put on the effect of the nature of substituents on phosphorus on the reaction progress. At the same time, the effect of the size and other properties of alkyl substituents on nitrogen on the dynamics of such reactions has not been considered.

In the previous works [2, 3], we used hexamethyl- and hexaethylphosphorous triamides as phosphorylating agents for preparing phosphorus-containing macroheterocycles on the basis of aromatic diols. As a rule, the obtained compounds were viscous oils, which complicated their isolation and investigation. We proposed that introduction of more bulky radicals, such as isopropyl or piperidyl, to the nitrogen atom of the amido group would diminish the amount of by-products and improve crystallization of the target compounds.

This work was begun with investigation of the reaction of resorcinol (**I**) with the equivalent amount of unsymmetrical phosphorous triamide **II** containing two dimethylamino and one diisopropylamino group. We proposed that the reactions would involve initial substitution of the less bulky and more reactive dimethylamido groups. But it occured that at room temperature phosphorylation of resorcinol begins with substitution of the heavier diisopropylamino group to form product **III** which was previously obtained in [4].



I **II** **III**

This conclusion was made on the basis of spectral data. The ^{31}P NMR spectrum of the obtained compound contained one singlet with δ_P 139.9 ppm, characteristic of cyclic phosphoramidites containing a dimethylamino group. The ^{1}H NMR spectrum contained, together with aromatic proton signals, a doublet at 2.73 ppm assignable to the dimethylamino group.

Since the use of unsymmetrical triamide **II** did not lead to the expected results, we tried as phosphorylating agents symmetrical phosphorous amides, such as phosphorous tris(diisopropylamide) and tripiperidide (**IV, V**).

It was shown that phosphorous amides **IV, V** readily and successfully react with resorcinol. The reactions are complete at room temperature within one

[†] Deceased.

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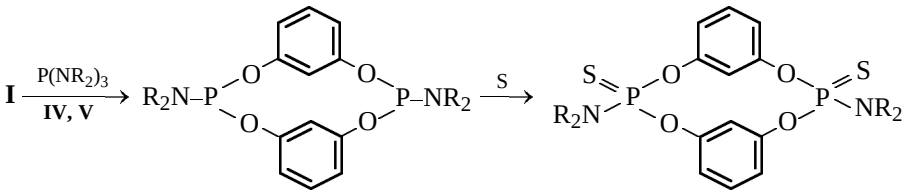
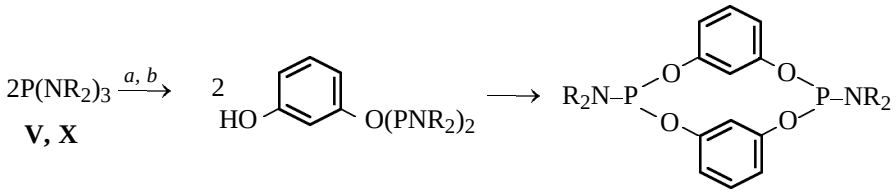
day and give cyclic phosphoramidites **VI, VII** in high yields. Hence, the new phosphorous triamides proved to be effective phosphorylating agents. The resulting phosphorus-containing macrocycles **VI, VII** are oils. Their ^{31}P NMR spectra contain single singlets at δ_P 142.3 and 135.8 ppm, respectively. The ^{1}H NMR spectra of these compounds agree with the proposed structures. For a more complete identification, cyclic phosphoramidites **VI, VII** were converted to the corresponding phosphoramidothioates **VIII, IX**.



VI, VII **VIII, IX**

R = *i*-Pr (**IV, VI, VIII**),  (**V, VII, IX**).

With the purpose of a more detailed investigation of the effect of the size of substituent in the phosphoramidite moiety on the rate of phenolysis of phosphoramidites we performed comparative analysis of the rates of reactions of phosphorous tris(dimethylamide) and tripiperidide with resorcinol by means of ^{31}P NMR spectroscopy. The reactions were carried out in dioxane, since, as we showed previously [2, 5], phenolysis of phosphorous triamides in dioxane proceeds rather slowly. For this reason, we could more effectively trace the reaction progress.



XI, XII **XIII, XIV**

R = Me (**X, XI, XIII**),  (**V, XII, XIV**).

Here *a* stands for the reaction with triamide **X** and *b* stands for the reaction with triamide **V**. δ_P, ppm: 116.5 (**V**), 122.2 (**X**), 135.0 (**XI**), 126.7 (**XII**), 139.2 (**XIII**), and 135.7 (**XIV**).

It was shown that in the first minutes of the reaction the rate of substitution of the first amido group is slightly higher in reaction *b*. Then the amount of monophosphorylated resorcinol in reaction *a* increases 2.5 times, and in reaction *b* only 1.3 times. After 1 day, the amount of cyclic phosphoroamidite in reaction *a* reaches 78%, while in reaction *b*, only 30%. After 3 days, reaction *a* is practically complete, while the amount of phosphoramidite **XIV** in reaction *b* reaches 55% only. Hence we showed that sterically hindered bulky radicals on nitrogen slow down phenolysis not only of the first, but also the second amido group, but in such solvents as diethyl ether and acetonitrile this difference is insignificant.

To conclude, cyclophosphorylation of resorcinol proceeds easily and successfully under mild condi-

tions independent of the nature of substituent on nitrogen. This opens up a synthetic approach to macroheterocyclic compounds with various phosphamide groups.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker WH-250 (250 MHz) spectrometer against internal TMS. The ^{31}P NMR spectra were obtained on a Bruker-80 SY (32.4 MHz) spectrometer against 85% phosphoric acid. Column chromatography was carried out on Silica gel L 100/250, and TLC, on Silufol plates, eluents 3:1 benzene–dioxane 3:1 (A), 34:1 benzene–hexane (B), and 3:1 chloroform–methanol (C), development by calcination and by treatment with 1% aqueous $AgNO_3$. Phosphorous tripiperidide (**V**) was prepared according to [6].

***N,N*-Diisopropyl-*N*',*N*',*N*'',*N*''-tetramethylphosphorous triamide (II).** To a solution of 13.75 g of phosphorus trichloride in 500 ml of hexane, a mixture of 10.1 g of diisopropylamine and 10.1 g of triethylamine was added with stirring and cooling to 0°C. The reaction progress was controlled by ^{31}P NMR spectroscopy. After the reaction was complete, dry dimethylamine was passed through the resulting solution for 1 h, and then the reaction mixture was left to stand at room temperature for a day. The precipitate that formed was filtered off, and the solvent was removed under reduced pressure. The residue was distilled in a vacuum [64–65°C (3 mm)]. Yield 18.83 g (86%), n_D^{20} 1.4724. ^{1}H NMR spectrum, δ, ppm: 0.74 d (12H, CH_3–*i*-Pr, $^3J_{HH}$ 5.9 Hz), 2.41 d (12H, N–CH_3, $^3J_{HP}$ 12.79 Hz), 3.15 m (2H, CH). δ_P 106.4 ppm. Found, %: C 54.71; H 11.85, P 14.18. $C_{10}H_{26}N_3P$. Calculated, %: C 54.79, H 11.87, P 14.15.

Hexaisopropylphosphorous triamide (IV). To a solution of 0.2 g of phosphorus trichloride in 50 ml of benzene, a mixture of 0.45 g of diisopropylamine and 0.44 g of triethylamine in 40 ml of benzene was added with stirring and cooling to 0°C. The reaction mixture was kept at room temperature for a day, the precipitate that formed was filtered off, and the solvent was removed at reduced pressure. Phosphorous triamide **IV** was isolated pure by vacuum distillation (150°C, 1×10^{-4} mm). Yield 0.2 g (42%), mp 140–144°C, R_f 0.36 (A), 0.30 (B), 0.97 (C). ^{1}H NMR spectrum, δ, ppm: 1.24 d, 1.27 d (18H, CH_3, $^3J_{HH}$ 6.12 Hz), 3.68 m (3H, CH, $^3J_{HH}$ 6.37 Hz). δ_P 130.1 ppm, s. Calculated, %: C 65.21; H 12.77; P 9.34. $C_{18}H_{42}N_3P$. Found, %: C 65.12; H 12.74; P 9.33.

Cyclic bis(*O,O*-*m*-phenylene dialkylphosphoramidothioates) VIII, IX. To a solution of 1 mmol of resorcinol (**I**) in 9 ml of diethyl ether, 1.8 mmol of hexaalkylphosphorous triamide **IV, V** was added with vigorous stirring at room temperature. The reaction mixture was kept at room temperature for a day, and the solvent was removed in a vacuum. Compound **VI**: R_f 0.9 (A), 0.83 (B), and 0.74 (C); δ_P 142.3 ppm. Compound **V**: R_f 0.62 (A), 0.7 (B), and 0.95 (C); δ_P 135.83 ppm. The reaction product was dissolved in 3 ml of benzene, and 2.97 mmol of sulfur was added. The reaction mixture was kept at room temperature for a day. The solvent was removed in a vacuum, and compounds **VIII, IX** were isolated by column chromatography, eluent 10:1 benzene–dioxane. After removal of the solvents in a vacuum, an oilish residue was kept in a vacuum for 3 h [30°C (1 mm)].

3,7-Diisopropylamino-2,4,6,8-tetraoxa-3λ^5,7λ^5-diphospha-1,5(1,3)-dibenzenacyclooctaphane 3,7-disulfide (VIII). Yield 65%, R_f 0.42 (A), 0.3 (B), 0.92 (C). ^{1}H NMR spectrum, δ, ppm: 1.33 br.s (24H, CH_3), 3.62 m (4H, CH), 6.46 br.s, 6.78 m, 7.18 m (8H, CH arom.). δ_P 60.0 ppm, s. Calculated, %: C 53.07, H 6.63, P 11.42. $C_{24}H_{36}N_2O_4P_2S_2$. Found, %: C 53.13; H 6.69; P 11.25.

3,7-Dipiperidino-2,4,6,8-tetraoxa-3λ^5,7λ^5-diphospha-1,5(1,3)-dibenzenacyclooctaphane 3,7-disulfide (IX). Yield 67%, R_f 0.24 (A), 0.03 (B), 0.77 (C). ^{1}H NMR spectrum, δ, ppm: 1.54 s (12H, $CH_2 \cdot CH_2CH_2$), 3.39 s (8H, NCH_2), 6.38, 6.66, 6.79, 7.13 br.s (8H, CH arom.). δ_P 63.34 ppm. Calculated, %: C 51.70; H 5.48; P 12.14. $C_{22}H_{28}N_2O_4P_2S_2$. Found, %: C 51.46; H 5.40; P 12.04.

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