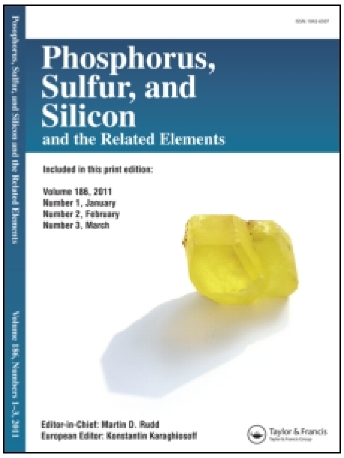

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PHOSPHORYLATION OF BENZANILIDES BY PHOSPHORIC ANHYDRIDE

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PHOSPHORYLATION OF BENZANILIDES BY PHOSPHORIC ANHYDRIDE

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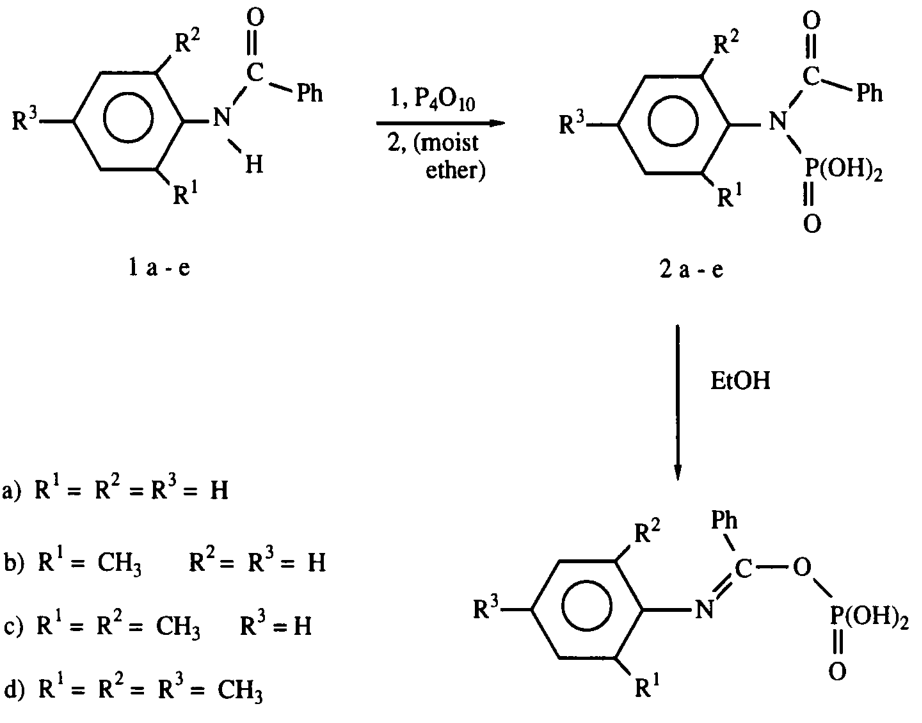
Phosphoric anhydride reacts with benzanilides (**1a–e**) to give N-phosphorylated amides (**2a–e**) which readily rearrange to give O-phosphorylated products (**3a–e**) as a mixture of E and Z isomers.

Key words: Phosphorylation of benzanilides; (N-aryl-*N*-benzoyl)aminophosphonamidic acids; (N-arylphenyliminomethyl)phosphoric acids.

Phosphorylation is a widely studied reaction primarily due to its key use in the synthesis of biologically active phosphates. Phosphorylated compounds are also used as flame retardant, sequestering agents, extractants, surfactants, and as various additives. The acid chlorides are usually considered as the most powerful phosphorylating reagents and are used for the synthesis of monoesters, $ROP(O)(OH)_2$, symmetrical diesters, $(RO)_2P(O)OH$ and also triesters.[2a,3] On the other hand, phosphoramidites and phosphoramidates are used for the synthesis of unsymmetrical diesters $ROP(O)(OR')OH$.[4] The reactivity of the latter reagents may be enhanced through the use of the corresponding phospholanes.[5] Pyrophosphoric diesters have been used in some limited cases.[2b] New reagents and more versatile methods are keenly sought.

It has been postulated that phosphoric anhydride is formed in a free state in volcanic magma,[6] and that it was probably responsible for the formation of the initial organic phosphates required for the evolution of life on this planet, and indeed, recent studies have shown that phosphoric anhydride (P_4O_{10}) can react with a wide range of nucleophiles.[7]

In this report we show that phosphoric anhydride reacts readily with benzanilides, and indeed, reacts faster than phosphoryl trichloride, to give high yields of phosphorylated products. The reactions gave, initially, N-phosphorylated products indicating that the anhydride is a relatively "soft" electrophile and the corresponding O-phosphorylated products were obtained by a facile rearrangement of the N-phosphorylated benzanilides. The benzanilides (**1a–e**) in trichloromethane reacted readily with two equivalents of phosphoric anhydride (based on its phosphorylating potential) to give the N-phosphorylated products (**2a–e**) in yields of 65 to 95%.[8] The dimethyl and trimethyl substituted anilides were the most reactive, a spontaneous and slightly exothermic reaction occurring. The other anilides required heating in trichloromethane under reflux for twenty minutes before the reaction started. Although the phosphoric anhydride was insoluble, the products dissolved in the hot media. The products were isolated by removal of the solvent and trituration of the residue with moist ether causing selective hydrolysis of the residual phosphoric anhydride P—O—P bonds.



1 a - e

2 a - e

3 a - e

a) $R^1 = R^2 = R^3 = H$

b) $R^1 = CH_3$ $R^2 = R^3 = H$

c) $R^1 = R^2 = CH_3$ $R^3 = H$

d) $R^1 = R^2 = R^3 = CH_3$

e) $R^1 = R^2 = CH(CH_3)_2$ $R^3 = H$

The infra-red spectra of each initially formed product showed the absence of the NH group and presence of an amide group—the latter being confirmed by a ^{13}C n.m.r. signal in the region 168–176 ppm. The ^{31}P n.m.r. spectrum contained a signal in the region −10 to −12 ppm.

The O-phosphorylated products (**3a–e**)[9] were obtained by rearrangement of the initial products by the action of a polar solvent such as alcohol. The ^{31}P n.m.r. spectrum contained either one broadened signal or (more usually) two signals in the region 2 to −2 ppm. In the ^{13}C n.m.r. spectrum the amide carbonyl signal at ca 170 had been replaced by a new signal (quaternary carbon) in the region 135–143 which is attributed to the N═C—O—P group. The amide region of the infra-red spectrum was markedly changed and in addition to a band at 1250 cm^{-1} due to the phosphoryl group, two strong bands also appear in the region 1050–1000 cm^{-1} which are assigned to the C—O—P groups of E and Z isomers. The presence of two isomers was confirmed by the n.m.r. spectra. Thus the ^{31}P n.m.r. spectra of the O-phosphorylated product (**3c**) derived from 2,6-dimethylaniline and the product (**3d**) derived from 2,4,6-trimethylaniline gave two signals near zero in their ^{31}P n.m.r. spectra and their ^{1}H and ^{13}C n.m.r. spectra contained two sets of signals for the ortho orientated methyl groups. The ratio of the two isomers were approximately 1:0.5 and 1:0.8, respectively—these ratios remaining constant across a wide range of solvents (acetone, ethanol, methanol, DMSO).

The O-phosphorylated benzanilides are hydrolytically stable and the approach enables the synthesis of unusual monoesters of phosphoric acid, the E-isomer having some interesting chelation potential from the imine nitrogen and the phosphoric acid group.

EXPERIMENTAL

The phosphorylation procedure involved heating a heterogeneous mixture of the appropriate benzanilide (1; 0.02 mol) and phosphoric anhydride (P_4O_{10}; 0.01 mol) in trichloromethane (25 ml; distilled from phosphoric anhydride). The reaction was complete when a yellow or pink colour had fully developed leaving a small amount of unreacted anhydride. After evaporation of the solvent, a sticky residue was obtained which was triturated repeatedly with diethyl ether until the (N-aryl-*N*-benzoyl)-aminophosphoramidic acid (**2**) was obtained as a yellow or pink powder. Treatment with ethanol for 10 to 15 min gave the (N-aryl-phenyliminomethyl) phosphoric acids (**3**) as yellow crystals.

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8. All products had infra-red, ^1H, ^{13}C and ^{31}P n.m.r. spectra in accordance with their structures. The O-phosphorylated products also gave satisfactory C, H, N and P elemental analyses.
9. Only the E geometric isomers of the O-phosphorylated products (**3a–e**) are shown in the diagram.