Nucleophilic Oxidation with Bis[diphenylphosphinyl] Peroxide: Direct Preparation of *O*-Phosphinylated Aminating Reagents

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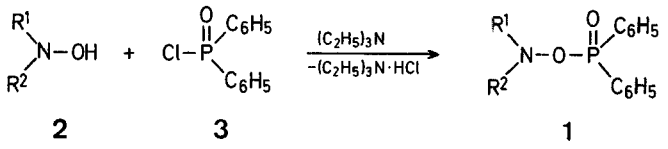
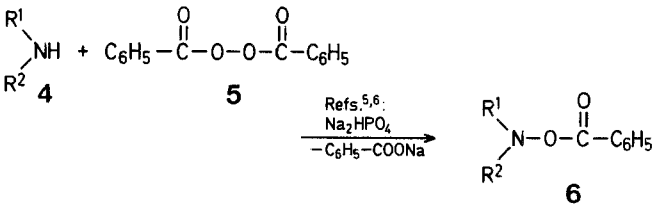
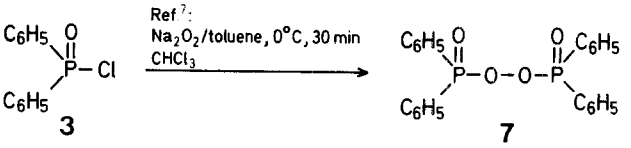
In connection with studies on electrophilic amination with *O*-diphenylphosphinylhydroxylamine derivatives **1**[1-4], we needed *N,N*-dialkylhydroxylamines **2**, which on treatment with chlorodiphenylphosphine oxide (**3**) would give the expected reagents **1**.



The oxidation of secondary amines to *N,N*-dialkylhydroxylamines is a common synthetic transformation for which no generally reliable methodology exists. The most widely used method for preparing such hydroxylamines is the direct oxidation of secondary amines **4** with dibenzoyl peroxide (**5**), and subsequent treatment of the *O*-benzoylated *N,N*-dialkylhydroxylamines **6** formed with sodium methoxide[5,6].



In 1965, the preparation of bis[diphenylphosphinyl] peroxide (**7**), by the reaction of chloridiphenylphosphine oxide (**3**) with sodium peroxide at ~0°C in 65–70% yield, was reported[7].



It was found that **7** rearranged at room temperature in most solvents to give an unsymmetrical anhydride **8**. Furthermore, in the presence of stoichiometric amounts of pyridine (or quinoline), **7** rearranged to the symmetrical anhydride **9**

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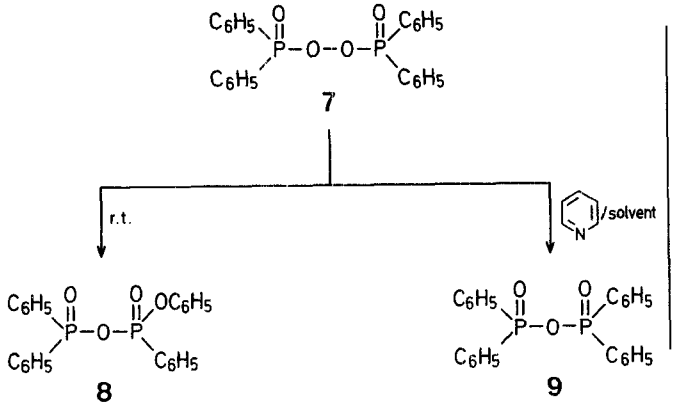
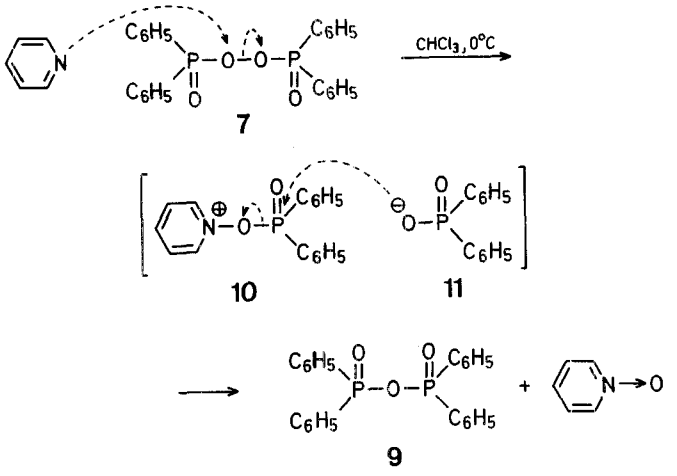
with an unexplained loss of a peroxo oxygen atom[7]. As the pyridine was recovered unchanged, it was supposed that the solvent used was oxidized, but unequivocal evidence for this hypothesis was found.



These considerations led us to reinvestigate the mechanism of this reaction by ^{31}P-N.M.R. spectroscopy. We observed that the reaction of **7** with one equivalent of pyridine at room temperature gave two new phosphinylated species, *O*-diphenylphosphinylpyridine *N*-oxide [**10**; ^{31}P-N.M.R. ($CDCl_3$): $\delta = -30$ ppm] and a diphenylphosphinate counterion [**11**; ^{31}P-N.M.R. ($CDCl_3$): $\delta = -12$ ppm] that slowly rearranged to give, as the only phosphorus-containing compound, the symmetrical anhydride **9** [^{31}P-N.M.R. ($CDCl_3$): $\delta = -28$ ppm] and pyridine *N*-oxide[8].



On the basis of this very likely mechanism for the decomposition of **7** in the presence of amines, it was of interest to attempt the direct synthesis of the aminating reagents **1** by reacting the appropriate secondary amine with **7**. We have now found that the reaction at −40 °C in alcohol-free chloroform of two equivalents of secondary amines **4a–f** with **7** [^{31}P-N.M.R. ($CDCl_3$): $\delta = -43$ ppm] proceeded through a nucleophilic displacement at the peroxide O–O linkage and led to the formation of the corresponding diphenylphosphinate dialkylammonium salts **12** and the expected *N,N*-dialkyl *O*-diphenylphosphinylhydroxylamines **1a–f** (Table).

Table. *N,N*-Dialkyl-*O*-diphenylphosphinylhydroxylamines **1a–f** and Free Hydroxylamines **2a–e** prepared

Product No.	Yield[a] [%]	m.p. [°C][b] or b.p. [°C]/torr[c]	Molecular Formula[d] or Lit. Data	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	^{31}P-N.M.R. ($CDCl_3$/80% H_3PO_4) δ [ppm]
1a	97	65–67°	$C_{16}H_{20}NO_2P$ (289.3)	0.98 (t, 6H, J = 7.0 Hz, CH_2CH_3); 2.98 (q, 4H, J = 7.0 Hz, CH_2CH_3); 7.15–8.0 (m, 10H$_{arom}$)	−32.3
1b	80	oil[e]	$C_{18}H_{24}NO_2P$ (317.4)	1.02 [d, 12H, J = 6.75 Hz, $CH(CH_3)_2$]; 3.32 [hept., 2H, J = 6.75 Hz, $CH(CH_3)_2$]; 7.28–8.09 (m, 10H$_{arom}$)	−32.8
1c	77	58–60°	$C_{20}H_{28}NO_2P$ (345.4)	0.82 (dist. t, 6H, $CH_2CH_2CH_2CH_3$); 1.02–1.72 (m, 8H, $CH_2CH_2CH_2CH_3$); 2.96 (t, 4H, J = 6.75 Hz, $CH_2CH_2CH_2CH_3$); 7.29–8.15 (m, 10H$_{arom}$)	−31.7
1d	88	oil[e]	$C_{20}H_{28}NO_2P$ (345.4)	0.90 [d, 12H, J = 6.75 Hz, $CH_2CH(CH_3)_2$]; 1.80 [m, 2H, $CH_2CH(CH_3)_2$]; 2.70 [d, 4H, J = 6.75 Hz, $CH_2CH(CH_3)_2$]; 7.2–8.2 (m, 10H$_{arom}$)	−30.8
1e	81	77–78°	$C_{24}H_{32}NO_2P$ (397.5)	0.82–2.02 [m, 20H, $-(CH_2)_5-$]; 2.90 (m, 2H, N—CH<); 7.22–8.1 (m, 10H$_{arom}$)	−32.2
1f[e]	70	–	$C_{26}H_{24}NO_2P$ (413.5)	4.15 (s, 4H, $CH_2C_6H_5$); 7.25, 7.15–8.0 (s, m, 20H$_{arom}$)	−33.5
2a	41[f]	–	71–73°[11] (·HCl)	1.22 (t, 6H, J = 7.2 Hz, CH_2CH_3); 3.7 (q, 4H, J = 7.2 Hz, CH_2CH_3); 5.1 (br. s, 1H, OH)	
2b	83	–	143–145°[12] (·HCl)	1.08 [d, 12H, J = 6 Hz, $CH(CH_3)_2$]; 3.09 [hept., 2H, J = 6 Hz, $CH(CH_3)_2$]; 5.37 (br. s, 1H, OH)	

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Table. (Continued)

Product No.	Yield[a] [%]	m.p. [°C][b] or b.p. [°C]/torr[c]	Molecular Formula[d] or Lit. Data	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	^{31}P-N.M.R. ($CDCl_3$/80% H_3PO_4) δ [ppm]
2c	96	–	52–54°/12 (free)	0.93 (dist. t, 6H, $CH_2CH_2CH_2CH_3$); 1.16–1.97 (m, 8H, $CH_2CH_2CH_2CH_3$); 3.72 (t, 4H, J = 7.5 Hz, $CH_2CH_2CH_2CH_3$); 5.04 (br. s, 1H, OH)	
2d	92	57–59° (free)	$C_8H_{19}NO$ (145.2)	0.86 [d, 12H, J = 6.75 Hz, $CH_2CH(CH_3)_2$]; 1.62 [m, 2H, $CH_2CH(CH_3)_2$]; 2.45 [d, 4H, J = 6.75 Hz, $CH_2CH(CH_3)_2$]; 5.22 (br. s, 1H, OH)	
2e	85	222–224° (·HCl)	$C_{12}H_{23}NO$ (197.3)	0.87–2.1 [m, 20H, —$(CH_2)_5$—]; 2.72 (m, 2H, N—CH<); 4.22 (br. s, 1H, OH)	

[a] Yields are based on reagent **7** for products **1** and on **1** for products **2**.

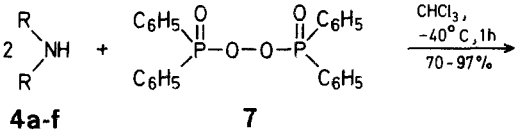
[b] Melting points of hydrochlorides are given for compounds **2a**, **2b** and **2e**. Melting points of compounds **2c** and **2d** are those of free hydroxylamine derivatives.

[c] Compounds **1** are very sensitive towards heat. Decomposition occurred before boiling point had been reached for **1a,b**, and **1d**, probably due to the generation of nitrenium ion.

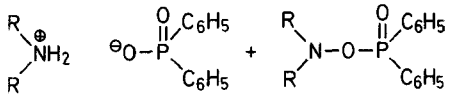
[d] Satisfactory microanalyses obtained: C ±0.22, H ±0.05, N ±0.05, P ±0.20.

[e] Product **1f** could be obtained only by work-up at < −10 °C. *N,N*-Dibenzylhydroxylamine **(2f)** could not be obtained in this way, while its *O*-diphenylphosphinylated precursor **1f** rearranged thermally and/or by a base-catalysed process to give *N*-benzylidenebenzaldehyde[10].

[f] The poor yield is due to the use of ether as solvent for extraction. Free *N,N*-diethylhydroxylamine **(2a)** is known to distill out with ether vapour[9]. The yield might be improved by using chloroform instead of ether for extraction.



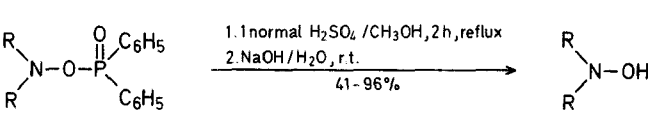
4a-f **7**



12 **1a-f**

1,4	R	1,4	R
a	C_2H_5–	e	
b	*i*-C_3H_7–		
c	*n*-C_4H_9–	f	
d	*i*-C_3H_7–CH_2–		

To our knowledge, this is the first example of a direct preparation of *O*-phosphinylated aminating reagents, that could only be obtained otherwise via the two-step procedure[5] and subsequent *O*-substitution by chlorodiphenylphosphine oxide. Free *N,N*-dialkylhydroxylamines **2a–e** could be obtained in good yields by acidic hydrolysis of the compounds **1a–e**.



1a-e **2a-e**

Bis[diphenylphosphinyl] Peroxide (7):
This is prepared as mentioned in Ref.[7]. The compound is purified by dissolution in alcohol-free chloroform and reprecipitation with hexane at < 10 °C. The product **7** is dried at reduced pressure at 0 °C/0.01 torr; yield: 71%; m.p. 87 °C (Lit.[7], m.p. 88–89 °C). Reagent **7** can be stored at − 80 °C for several months without noticeable decomposition.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 7.2–8.3 ppm.

^{31}P-N.M.R. ($CDCl_3$/80% H_3PO_4): δ = − 43 ppm

***N,N*-Dialkyl-*O*-diphenylphosphinylhydroxylamines (1a–f); General Procedure:**
To a well stirred solution of (**7**; 8.68 g, 20 mmol) in alcohol-free chloroform (100 ml) is added dropwise at − 40 °C a solution of the appropriate secondary amine **4** (40 mmol) in alcohol-free chloroform (20 ml). Stirring is continued at − 40 °C for 1 h and the mixture is allowed to warm to room temperature (except for **1f**). The solvent is removed under reduced pressure (without external heating) and the residue is taken up in cold hexane (100 ml), upon which the amine phosphinate separates. Salts **12** and the unsymmetrical anhydride **8**, produced from thermal decomposition of **7** are separated by filtration at 0 °C and discarded. The filtrate is evaporated to dryness and the residue containing the expected *O*-phosphinylated hydroxylamine **1** and the unreacted amine **4** is separated on a silica gel column using ethyl acetate/hexane (3/1) as eluent (Table).

***N,N*-Dialkylhydroxylamines 2a–e; General Procedure:**
Compound **1** (10 mmol) is refluxed with 1 normal aqueous methanolic sulfuric acid [100 ml, water: methanol, 2 : 1 (v/v)] for 2 h. The diphenylphosphinic acid precipitated on cooling is filtered and the filtrate is basified to pH 10 with 38% aqueous sodium hydroxide. The product is extracted with chloroform (4 × 50 ml), the combined organic phase is dried with sodium sulfate and evaporated to dryness to give pure dialkylhydroxylamines **2a–e** as amorphous solids that need not be recrystallized for further purposes. The hydrochlorides are obtained by bubbling gaseous hydrogen chloride through an ether solution of **2** (Table).

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