A Facile One-Pot Synthesis of 3-Dialkoxyphosphoryl- and 3-[Alkoxy(phenyl)phosphoryl]-1-hydroxyindoles

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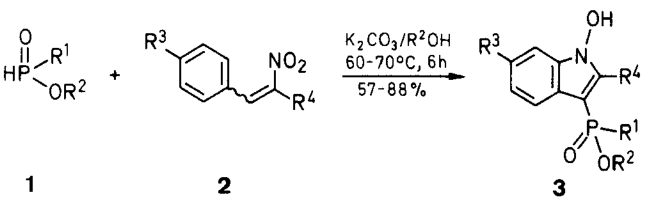
The one-pot reaction of dialkyl phosphites or alkyl phenylphosphonites with equimolecular amounts of 1-aryl-2-nitro-1-alkenes in an alcohol in the presence of solid potassium carbonate give the title compounds, i.e., 1-hydroxyindole-3-phosphonic or -3-phosphinic esters, respectively, in 57–88 % yield.

Since the isolation of 1-hydroxyindole derivatives from plants and microorganisms,[1–12] intense efforts have been focused on their synthesis.[13–18] However, only few reports deal with the synthesis of phosphorus-containing indole derivatives. A mixture of 1-acetyl-2,5-dimethyl-3-(diphenylphosphinyl)indole and 1-acetyl-5-methyl-2-(diphenylphosphinylmethyl)indole has been obtained from *N*-acetyl-*N*-(4-methylphenyl)hydroxylamine and (diphenylphosphinyl)allene, via Michael addition and Cope-rearrangement.[19] 3-Phosphoryl-substituted 1-hydroxyindoles were synthesized by the reaction of nitrostyrenes with *in situ* formed dialkyl trimethylsilyl phosphites under carefully controlled reaction conditions,[20] but a large excess of reagents and long reaction time are required.

We now report a simple and practical synthesis of 3-dialkoxyphosphoryl- (**3a–e**) and 3-[alkoxy(phenyl)-phosphoryl]-1-hydroxyindoles (**3f,g**) by the one-pot reaction of dialkyl phosphites or alkyl phenylphosphonites **1** with equimolecular amounts of 1-aryl-2-nitro-alkenes **2** in an alcohol in the presence of solid potassium carbonate.



1 **2** **3**

3	R¹	R²	R³	R⁴
a	OEt	Et	H	Me
b	OEt	Et	Me	Me
c	OPr-*i*	*i*-Pr	H	Me
d	OPr-*i*	*i*-Pr	Me	Me
e	OPr-*i*	*i*-Pr	Me	Et
f	Ph	*i*-Pr	H	Me
g	Ph	*i*-Pr	Me	Me

The alcohol used as solvent should correspond to the alkoxy group of **1** to avoid transesterification. The reaction is complete within 6 h at 60–70 °C, compounds **3** being obtained in 57–88 % yields. The structure of the products was established by microanalyses, IR, and ^1H-NMR spectrometry (Table).

Product **3a** was converted into the corresponding 1-methoxyindole by reaction with methyl iodide under the conditions given in Lit.[16]

Table. 3-Dialkoxyphosphoryl- and 3-[Alkoxy(phenyl)phosphoryl]-1-hydroxyindoles **3** Prepared

Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c] or Lit. mp (°C)	IR (KCl) ν (cm^{-1})	^{1}H-NMR (CCl$_4$/TMS) δ, J (Hz)
3a	82	104–105	99–101[20]	3100, 1510, 1200, 1050 (br)	1.02 (t, 6H, J = 7, 2OCH$_2$C$\underline{H}_3$), 1.96 (s, 3H, CH$_3$), 3.67 (qd, 4H, J = 7, 10, 2OCH$_2$), 7.2 (m, 4H$_{arom}$), 10.5 (s, 1H, OH)
3b	82	108–109	$C_{14}H_{20}NO_4P$ (297.3)	3050, 1500, 1210, 1030 (br)	1.10 (t, 6H, J = 7, 2OCH$_2$C$\underline{H}_3$), 1.96 (s, 3H, CH$_3$), 2.38 (s, 3H, CH$_3$), 3.75 (qd, 4H, J = 7, 10, 2OCH$_2$), 7.0 (m, 3H$_{arom}$), 11.8 (s, 1H, OH)
3c	87	112–113	$C_{15}H_{22}NO_4P$ (311.3)	3050, 1520, 1200, 1010	1.2 [m, 12H, 2OCH(C$\underline{H}_3$)$_2$], 2.20 (s, 3H, CH$_3$), 4.38 (m, 2H, 2OCH), 7.2 (m, 4H$_{arom}$), 10.5 (s, 1H, OH)
3d	88	110–111	$C_{16}H_{24}NO_4P$ (325.4)	3100, 1520, 1200, 1010	1.1 [m, 12H, 2OCH(C$\underline{H}_3$)$_2$], 2.05 (s, 3H, CH$_3$), 2.37 (s, 3H, CH$_3$), 4.3 (m, 2H, 2OCH), 7.0 (m, 3H$_{arom}$), 11.1 (s, 1H, OH)
3e	78	133–134	$C_{17}H_{26}NO_4P$ (339.4)	3050, 1510, 1210, 1010	1.1 [m, 15H, 2OCH(C$\underline{H}_3$)$_2$ + CH$_2$C$\underline{H}_3$], 2.40 (s, 3H, CH$_3$), 2.75 (m, 2H, CH$_2$), 4.30 (m, 2H, 2OCH), 7.0 (m, 3H$_{arom}$), 11.15 (s, 1H, OH)
3f	60	172–173	$C_{18}H_{20}NO_3P$ (329.3)	3050, 1510, 1190, 1025, 990	1.3 (m, 9H, 3CH$_3$), 4.5 (m, 1H, OCH), 7.4 (m, 9H$_{arom}$), 11.3 (br s, 1H, OH)
3g	57	190–191	$C_{19}H_{22}NO_3P$ (343.4)	3050, 1510, 1200, 1030, 990	1.25 (m, 9H, 3CH$_3$), 2.40 (s, 3H, CH$_3$), 4.4 (m, 1H, OCH), 7.3 (m, 8H$_{arom}$), 11.0 (br s, 1H, OH)

[a] Yield of isolated pure product.

[b] Uncorrected.

[c] Satisfactory microanalyses: C ±0.19, H ±0.25, N ±0.14, P ±0.17.

Diethyl phosphite was purchased from Fluka Chemical Co. Diisopropyl phosphite was prepared according to Lit.[21] Isopropyl phenylphosphonite was synthesized according to Lit.[22] 1-Aryl-2-nitroalkenes were prepared from the nitroalkanes and benzaldehydes under the conditions given in Lit.[23] Solvents were dried by standard methods. Potassium carbonate was of commercial grade. IR spectra were recorded on a Shimadzu 440 Infrared spectrophotometer, ^{1}H-NMR spectra on a Varian EM360L (60 MHz) spectrometer.

3-Dialkoxyphosphoryl- and 3-[Alkoxy(phenyl)phosphoryl]-1-hydroxyindoles 3; General Procedure:

A mixture of the dialkyl phosphite or alkyl phenylphosphonite **1** (15 mmol), 1-aryl-2-nitroalkene **2** (15 mmol), and K_2CO_3 (5.53 g, 40 mmol) in the alcohol R^2–OH (60 mL) is vigorously stirred at 60–70 °C for 6 h. The mixture is then cooled and filtered, and the filtrate is evaporated under reduced pressure. The residue is dissolved in EtOAc (40 mL) and this solution is neutralized with 1 N aq HCl (12–15 mL). The organic phase is separated, dried (Na_2SO_4), and evaporated. The remaining product is purified by column chromatography on silica gel using EtOAc/petroleum ether (1 : 1) as eluent, and recrystallized from EtOAc (Table).

3-(Diethoxyphosphoryl)-1-methoxy-2-methylindole:

A stirred solution of **3a** (0.284 g, 1 mmol) and MeI (1.4 g, 10 mmol) in MeOH (10 mL) was treated with 2 N NaOH (5 mL), and stirring is continued for 10 h at r.t. Then, H_2O (20 mL) and CH_2Cl_2 (20 mL) are added, the organic layer is separated, and the water layer is extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts are washed with H_2O (15 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product is chromatographed on a silica gel column using EtOAc/petroleum ether (1 : 1) as eluent; yield: 0.27 g (91 %); yellow oil.

		C	H	N	P
$C_{14}H_{20}NO_4P$	calc.	56.56	6.78	4.71	10.42
(297.3)	found	56.76	6.92	4.69	10.40

IR (film): ν = 1530, 1455, 1390, 1330, 1245, 1225, 1050, 1025 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 1.30 (t, 6H, J = 7 Hz, 2OCH$_2$C$\underline{H}_3$), 2.72 (s, 3H, CH$_3$), 4.06 (m, 7H, OCH$_3$ + OCH$_2$), 7.2 (m, 4H$_{arom}$).

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(1) Gmelin, R.; Virtanen, A.I. *Acta Chem. Scand.* **1962**, *16*, 1378.

(2) Morimoto, H.; Oshio, H. *Liebigs Ann. Chem.* **1965**, *682*, 212.

(3) Morimoto, H.; Matsumoto, N. *Liebigs Ann. Chem.* **1966**, *692*, 194.

(4) Jones, S.R.; Lamberton, J.A.; Occolowitz, J.L. *Aust. J. Chem.* **1967**, *20*, 1737.

(5) Nomoto, M.; Tamura, S. *Agric. Biol. Chem.* **1970**, *34*, 1590.

(6) Nagel, D.W.; Pachler, K.G.R.; Steyn, P.S.; Wessels, P.L.; Gafner, G.; Kruger, G.J. *J. Chem. Soc., Chem. Commun.* **1974**, 1021.

(7) Nagel, D.W.; Pachler, K.G.R.; Steyn, P.S.; Vleggaar, R.; Wessels, P.L. *Tetrahedron* **1976**, *32*, 2625.

(8) Wagner, H.; Nestler, T. *Tetrahedron Lett.* **1978**, 2777.

(9) Konda, Y.; Onda, M.; Hirano, A.; Omura, S. *Chem. Pharm. Bull.* **1980**, *28*, 2987.

(10) Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1983**, *31*, 3198.

(11) Kawai, K.; Nozawa, K.; Nakajima, M.; Iitaka, Y. *Chem. Pharm. Bull.* **1984**, *32*, 94.

(12) Kinoshita, T.; Tatara, S.; Sankawa, U. *Chem. Pharm. Bull.* **1985**, *33*, 1770.

(13) Acheson, R.M., in: *New Trends in Heterocyclic Chemistry*, Mitra, R.B., Ayyangar, N.R., Gogte, V.N.; Acheson, R.M.; Cromwell, N. (eds.), Elsevier, New York, 1979, p. 1.

(14) Acheson, R.M.; Littewood, D.M.; Rosenberg, H.E. *J. Chem. Soc., Chem. Commun.* **1974**, 671.

(15) Acheson, R.M.; Hunt, P.G.; Littewood, D.M.; Murrer, B.A.; Rosenberg, H.E. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1117.

(16) Somei, M.; Inoue, S.; Tokutake, S.; Yamada, F.; Kaneko, C. *Chem. Pharm. Bull.* **1981**, *29*, 726.

(17) Acheson, R.M.; Aldridge, G.N.; Choi, M.C.K.; Nwankwo, J.O.; Ruscoe, M.A.; Wallis, J.D. *J. Chem. Res., Synop.* **1984**, 101.

(18) Somei, M.; Kawasaki, T. *Heterocycles* **1989**, *29*, 1251.

(19) Blechert, S. *Helv. Chim. Acta* **1985**, *68*, 1835.

(20) Li, Y.; Wang, G.; Zhang, D.; Miao, F.; Liu, X.; Cao, J.; Guo, H. *Sci. Sin., Ser. B* **1989**, *32*, 522.

(21) McCombie, H.; Saunders, B.C.; Stacey, G.J. *J. Chem. Soc.* **1945**, 380.

(22) Pudovik, A.N.; Yarmukhametova, D.Kh. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1952**, 902.

(23) Hass, H.B.; Susie, A.G.; Heider, R.L. *J. Org. Chem.* **1950**, *15*, 8.