A Facile Synthesis of 2-Phosphoryl-Substituted 3-Hydroxyindole Derivatives

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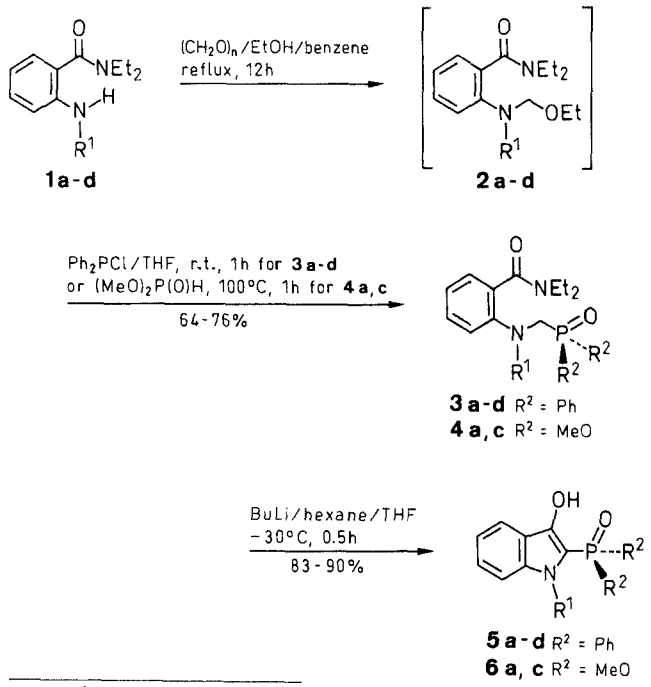
A variety of 1-substituted 2-diphenylphosphinoyl-3-hydroxy-1*H*-indoles **5a–d** and 2-dimethoxyphosphoryl-3-hydroxy-1*H*-indoles **6a,c** have been efficiently prepared by base-induced intramolecular cyclization of the appropriate Horner–Wittig and Wadsworth–Emmons reagents, 2-[(diphenylphosphinoyl)methylamino]-*N,N*-diethylbenzamides **3a–d** and 2-[(dimethoxyphosphoryl)methylamino]-*N,N*-diethylbenzamides **4a,c**, respectively.

Indoles and their derivatives have attracted a great deal of interest since they represent the common building block of a large variety of alkaloids and biologically active compounds.[1–3] Consequently the methods of synthesis of these heterobicyclic compounds are still the object of considerable attention and the elaboration of the indole framework from non-indolic starting materials represents a permanent challenge for organic chemists. Paradoxically, in spite of extensive work in this field, only few reports deal with the synthesis of phosphorus-containing indole derivatives. The presence of 1-acetyl-2,5-dimethyl-3-(diphenylphosphinyl)indole has been detected in the reaction mixture obtained from *N*-hydroxy-*N*-(4-methylphenyl)acetamide and (diphenylphosphinyl)allene, via Michael-addition and Cope rearrangement.[4] Recently, 3-phosphoryl-substituted 1-hydroxyindoles were synthesized by the reaction of nitrostyrenes with dialkyl trimethylsilyl phosphites[5] or alkyl phenylphosphonites.[6]

In this paper we report an efficient and simple synthesis of the previously unattainable 1-substituted 2-diphenylphosphinoyl-, **5a–d**, and 2-dimethoxyphosphoryl-3-hydroxyindoles, **6a,c**, from the readily accessible Horner–Wittig and Wadsworth–Emmons reagents **3a–d** and **4a,c**, respectively (Scheme 1). These heteroaromatic compounds cannot be obtained by direct functionalization of the parent model, the *N*-substituted 1*H*-indol-3(2*H*)-ones,[7] since the recent methodologies devised for the synthesis of the hardly accessible 2-monosubstituted indol-3(2*H*)-ones are restricted to alkyl groups.[8] On the other hand metalation of *N*-substituted 1*H*-indol-3(2*H*)-ones followed by treatment with chlorodiphenylphosphine or dimethyl phosphorochloridate would invariably lead to the *O*-phosphorylated heteroaromatic derivatives.[9]

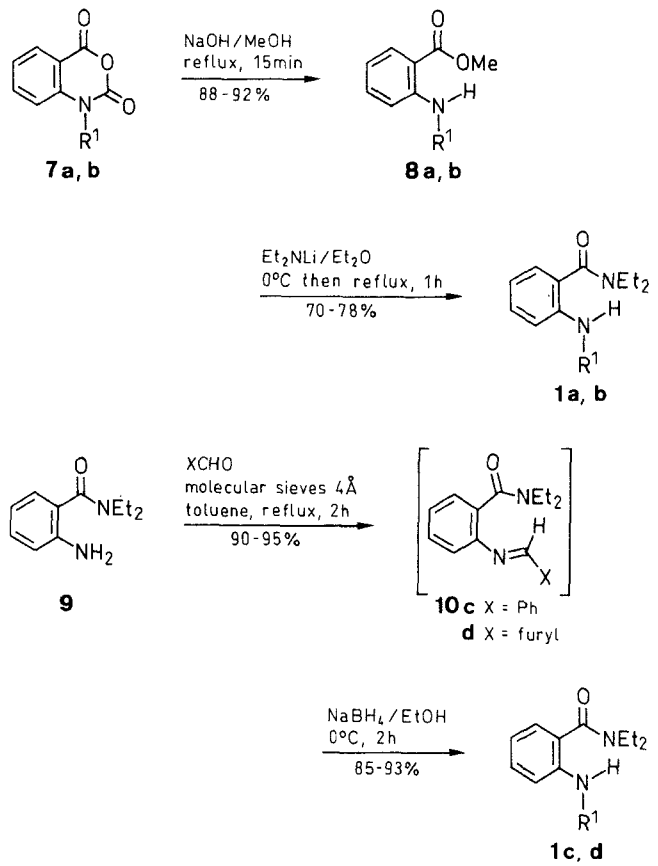
Our strategy consists of inducing the intramolecular cyclization of the lithiated 2-[(diphenylphosphinoyl)-methyl amino]- **3a–d**, and 2-[(dimethoxyphosphoryl)-methylamino]-*N,N*-diethylbenzamide derivatives **4a,c**, respectively (Scheme 1, Table 1).

These compounds are readily accessible from the appropriate 2-amino-*N,N*-diethylbenzamide derivatives **1a–d** via the *O,N*-acetals **2a–d**. Initially the secondary aromatic amines **1a–d** were synthesized following two different procedures. The *N*-methyl and *N*-allyl derivatives **1a,b** were obtained by treatment with lithium diethylamide[10] of the corresponding methyl carboxylates **8a,b** resulting from the ring opening of the *N*-methyl and *N*-allylisatoic anhydride, **7a,b** respectively, under basic conditions (Scheme 2).[11] The 2-benzylamino- **(1c)** and *N,N*-diethyl-2-furfurylaminobenzamide **(1d)** were conveniently prepared by reduction with sodium borohydride of the imines **10c,d** obtained by condensation of 2-amino-*N,N*-diethylbenzamide (*N,N*-diethylanthranilamide) **(9)** with the appropriate aldehyde (Scheme 2, X = phenyl or



1-6	R^1	1-6	R^1
a	Me	c	Bn
b	allyl	d	furfuryl

Scheme 1



Scheme 2

2-furyl). The 2-(ethoxymethylamino)-*N,N*-diethylbenzamide derivatives **2a–d** were readily obtained via a Mannich reaction starting from the secondary aromatic amines **1a–d**, ethanol and paraformaldehyde.[12,13] The desired products **3a–d** and **4a,c** were finally obtained by an Arbuzov reaction of the *O,N*-acetals **2a–d** with chlorodiphenylphosphine[14] or dimethyl phosphite[15] (Scheme 1, Table 1).

Deprotonation of the diphenylphosphine oxides **3a–d** and of the dimethyl phosphonates **4a,c** was effected with butyllithium at −30 °C in tetrahydrofuran. The completion of the intramolecular cyclization reaction was indicated by the disappearance of the deep-red color of the lithiated anion of **3a–d** and **4a,c**. The results of a representative series of products obtained by this sequence of reactions are presented in Table 2 where it may be seen that this simple procedure affords excellent yields of 1-substituted 2-diphenylphosphinoyl-, **5a–d**, and -2-dimethoxyphosphoryl-3-hydroxyindoles **6a,c**, respectively. This chemical behaviour is then unsensitive to the nature of the phosphoryl substituent in contrast to the results observed for the enamine synthesis with rather similar systems.[14,16]

In conclusion, the procedure described here represents a convenient, simple and general method for the preparation of 1-substituted 3-hydroxy-2-phosphorylindoles and can be undoubtedly extended onto other similar systems. These annelation reactions that give rise to **5a–d** and **6a,c** are actually the result of the remarkable reactivity of the phosphoryl-stabilized carbanions of the Horner–Wittig and Wadsworth–Emmons reagents, **3a–d** and **4a,c**, respectively, a property mainly used thusfar for enamine synthesis.[17] They also take advantage of the great sensitivity of the vicinal *N,N*-diethylcarboxamido group with respect to intramolecular nucleophilic attack, a precedented phenomenon.[10,18,19]

Methyl 2-(methylamino)benzoate **(8a)** and methyl 2-(allylamino)benzoate **(8b)** were synthesized by basic treatment[20,21] of the commercial *N*-methylisatoic anhydride **(7a)** and of the corresponding *N*-allyl derivative **7b** obtained by reacting the sodium salt of isatoic anhydride with allyl bromide according to a standard procedure.[11] The amides **1a,b** were readily and quantitatively accessible from the benzoates **8a,b** by treatment with $LiEt_2N$ in Et_2O as already reported for the unsubstituted model.[10]

2-(Benzylamino)-*N,N*-diethylbenzamide (1c) or *N,N*-Diethyl-2-(furfurylamino)benzamide (1d):

A solution of 2-amino-*N,N*-diethylbenzamide **(9)**[10] (1.92 g, 10 mmol), benzaldehyde (for **1c**) or furfuraldehyde (for **1d**) (11 mmol) in toluene (100 mL) was refluxed in the presence of molecular sieves 4Å for 2 h. After cooling, the mixture was filtered on Celite and evaporated in vacuo to dryness. The crude imine **10c,d** thus obtained was dissolved in abs. MeOH (50 mL) and carefully treated with $NaBH_4$ (760 mg, 20 mmol) under N_2 in an ice-cooled flask. The mixture was stirred for an additional h. H_2O (50 mL) was added and the product was extracted with CH_2Cl_2 (3 × 50 mL) which was then dried ($MgSO_4$). Evaporation of the solvent furnished an oily product which slowly solidified on standing.

Except for **1b**, compounds **1a,c,d** were recrystallized from toluene/hexane. Yields reported in Table 1 were evaluated from the starting compounds **7a,b** (for **1a,b**) and **9** (for **1c,d**).

2-(Ethoxymethylamino)-*N,N*-diethylbenzamide Derivatives 2a–d; General Procedure:

A solution of the monosubstituted 2-amino-*N,N*-diethylbenzamides **1a–d** (30 mmol), $(CH_2O)_n$ (1.35 g), EtOH (20 mL) in benzene

Table 1. Data of Starting Compounds **1**, **3**, **4** Prepared

Product	Yield (%)	mp (°C)[a]	Molecular Formula[b] or Lit. mp (°C)	^{1}H NMR ($CDCl_3$/TMS)[c,d] δ, J (Hz)	MS (70 eV)[e] m/z (%)
1a	68	58–59	51[22]	1.20 (t, 6H, J = 7.2, CH_3), 2.90 (d, 3H, J = 5, CH_3N), 3.45 (q, 4H, J = 7.2, CH_2), 4.70 (br s, 1H, NH), 6.40–6.80 (m, 2H, H_{arom}), 7.25–8.00 (m, 2H, H_{arom})	206 (M^+, 33), 134 (100), 120 (55), 72 (83)
1b	64	oil	$C_{14}H_{20}N_2O$ (232.3)	1.20 (t, 6H, J = 7.2, CH_3), 3.45 (q, 4H, J = 7.2, CH_2), 3.75 (d, 2H, J = 4.8, CH_2N), 4.90 (br s, 1H, NH), 5.00–5.20 (m, 2H, H_2C=), 5.65–6.20 (m, 1H, HC=), 6.50–6.80 (m, 2H, H_{arom}), 7.00–7.40 (m, 2H, H_{arom})	232 (M^+, 80), 159 (100), 130 (66), 72 (55)
1c	88	68–69	$C_{18}H_{22}N_2O$ (282.4)	1.20 (t, 6H, J = 7.2, CH_3), 3.45 (q, 4H, J = 7.2, CH_2), 4.35 (d, 2H, J = 5.5, CH_2Ph), 5.20 (br s, 1H, NH), 6.50–6.80 (m, 2H, H_{arom}), 7.00–7.40 (m, 7H, H_{arom})	282 (M^+, 35), 208 (32), 180 (100), 74 (85)
1d	76	40–41	$C_{16}H_{20}N_2O_2$ (272.3)	1.20 (t, 6H, J = 7.2, CH_3), 3.40 (q, 4H, J = 7.2, CH_2), 4.3 (d, 2H, J = 5.2, CH_2), 5.11 (br s, 1H, NH), 6.10–6.30 (m, 2H, H_{furan}), 6.50–7.40 (m, 3H, $H_{furan+arom}$)	272 (M^+, 53), 198 (21), 170 (82), 74 (100)
3a	76	123–124	$C_{25}H_{29}N_2O_2P$ (420.5)	0.82, 1.09 (2t, together 6H, J = 7.2, CH_3), 2.75, 3.0, 3.25, 3.58 (4dq, together 4H, J = 7.2, 13.1, CH_2), 3.05 (s, 3H, CH_3N), 3.91 (dd, 1H, J = 7.0, 15.0, CH_2P), 4.37 (d, 1H, J = 15.0, CH_2P), 6.48–8.01 (m, 14H, H_{arom})	420 (M^+, 2), 219 (27), 201 (78), 86 (100)
3b	71	112–113	$C_{27}H_{31}N_2O_2P$ (446.5)	0.91, 1.09 (2t, together 6H, J = 7.2, CH_3), 2.85, 3.01, 3.27, 3.74 (4dq, together 4H, J = 7.2, 13.5, CH_2), 3.89 (dd, 1H, J = 6.9, 14.7, CH_2P), 4.00, 4.41 (2dd, 2H, J = 6.2, 12.5, CH_2N), 4.56 (d, 1H, J = 14.7, CH_2P), 5.15 (dd, 1H, J = 1.5, 10.4, H_2C=), 5.31 (dd, 1H, J = 1.5, 17.2, H_2C=), 5.69 (m, 1H, HC=), 6.71–7.96 (m, 14H, H_{arom})	446 (M^+, 2), 245 (100), 201 (31)
3c	66	177–178	$C_{31}H_{33}N_2O_2P$ (496.6)	0.88, 1.19 (2t, together 6H, J = 7.2, CH_3), 2.79, 2.92, 3.21, 3.86 (4dq, together 4H, J = 7.2, 13.1, CH_2), 3.71 (dd, 1H, J = 7.2, 15.0, CH_2P), 4.59 (d, 1H, J = 15.0, CH_2P), 4.42, 5.13 (dd, 2H, J = 13.1, CH_2N), 6.75–7.91 (m, 19H, H_{arom})	496 (M^+, 2), 295 (18), 201 (32), 91 (100)
3d	64	169–170	$C_{29}H_{31}N_2O_3P$ (486.6)	0.83, 1.10 (2t, together 6H, J = 7.2, CH_3), 2.77, 2.95, 3.22, 3.80 (4dq, together 4H, J = 7.2, 13.4, CH_2), 3.70 (dd, 1H, J = 7.0, 14.8, CH_2P), 4.58 (d, 1H, J = 15.0, CH_2P), 4.34, 5.05 (dd, 2H, J = 13.0, CH_2N), 5.25 (d, 1H, J = 3.2, H_{furan}), 5.91 (dd, 1H, J = 1.9, 2.9, H_{furan}), 7.05–8.02 (m, 15H, $H_{furan+arom}$)	486 (M^+, 3), 285 (13), 201 (22), 81 (100)
4a	68	45–46	$C_{15}H_{25}N_2O_4P$ (382.6)	0.96, 1.20 (2t, together 6H, J = 7.3, CH_3), 2.77, 3.03, 3.27, 3.60 (4dq, together 4H, J = 7.3, 13.2, CH_2), 2.95 (s, 3H, CH_3N), 3.50, 3.68 (2s, together 6H, CH_3O), 3.37 (dd, 1H, J = 14.5, 16.3, CH_2P), 3.83 (d, 1H, J = 14.5, CH_2P), 6.60–7.44 (m, 4H, H_{arom})	328 (M^+, 3), 219 (7), 110 (100), 109 (38)
4c	70	61–62	$C_{21}H_{29}N_2O_4P$ (404.5)	1.02, 1.27 (2t, together 6H, J = 7.3, CH_3), 2.81, 2.96, 3.25, 3.79 (4dq, together 4H, J = 7.3, 13.2, CH_2), 3.43 (dd, 1H, J = 14.9, 16.5, CH_2P), 4.03 (d, 1H, J = 14.9, CH_2P), 4.34, 5.05 (dd, 2H, J = 12.9, CH_2N), 6.51–7.33 (m, 9H, H_{arom})	404 (M^+, 2), 313 (5), 295 (10), 109 (22), 91 (100)

[a] Uncorrected.
[b] Satisfactory microanalyses obtained: C ± 0.37, H ± 0.38, N ± 0.31, O ± 0.20, P ± 0.36.
[c] IR (KBR): ν_{NH} = 3380, ν_{CONH} = 1620 cm^{-1} for **1**; ν_{CO} = 1620, ν_{PO} = 1180 cm^{-1} for **3**; ν_{PO} = 1250 cm^{-1} for **4**.
[d] Recorded on a Bruker WP 80 for **1** and on a Bruker AM 400 WB for **3**, **4**.
[e] Obtained on a Riber 10-10 spectrometer.

(50 mL) was refluxed for 12 h. The solvent and the reagents were eliminated by evaporation in vacuo (5.10^{-2} Torr). Due to the instability of the *O,N*-acetals **2a–d** and to their slow decomposition during chromatographic treatments, they may be used without further purification for the next step.

2-[(Diphenylphosphinoyl)methylamino]-*N,N*-diethylbenzamide Derivatives 3a–d; General Procedure:

Ph_2PCl (2.43 g, 11 mmol) dissolved in THF (10 mL) was added in an atmosphere of dry N_2 to a solution of the crude *O,N*-acetals **2a–d** (10 mmol) in THF (20 mL) at such a rate that the temperature did not rise above 30 °C. The solution was then stirred for an additional 0.5 h, K_2CO_3 (2.5 g) was added and stirring was maintained for a further 15 min. The mixture was filtered on Celite and then poured on petroleum ether (300 mL) with vigorous stirring. After a night in the refrigerator, the organic layer was removed by decantation and the light-yellow oily residue was dissolved in CH_2Cl_2 (100 mL), dried ($MgSO_4$) and finally purified by column chromatography on silica gel using acetone/hexane (1:1) as eluent. Compounds **3a–d** were recrystallized from toluene/hexane. Yields reported in Table 1 are evaluated after recrystallization.

2-[(Dimethoxyphosphoryl)methylamino]-*N,N*-diethylbenzamide Derivatives 4a,c; General Procedure:

A mixture of the *O,N*-acetals **2a,c** (10 mmol), freshly distilled $(MeO)_2P(O)H$ (1.2 g, 11 mmol) was heated at 100 °C, with stirring under dry N_2 in a Claisen apparatus. EtOH which was formed during the reaction was distilled off and the crude product obtained after elimination of the excess $(MeO)_2P(O)H$ in vacuo was treated as described above for **3a–d**.

1-Substituted-2-Diphenylphosphinoyl-, 5a–d, and 2-Dimethoxyphosphoryl-3-hydroxy-1*H*-indoles and 6a,c; General Procedure:

In an atmosphere of dry N_2, a solution of BuLi in hexane (1.6 M, 3.4 mL, 5.5 mmol) was slowly added to a solution of compounds

Table 2. 2-Phosphoryl-Substituted 3-Hydroxyindoles **5**, **6** Prepared

Product	Yield (%)	mp (°C)[a]	Molecular Formula[b]	^{1}H NMR ($CDCl_3$/TMS)[c, d] δ, J (Hz)	MS (70 eV)[e] m/z (%)
5a	90	228–229	$C_{21}H_{18}NO_2P$ (347.4)	3.25 (s, 3H, CH_3N), 7.0–8.05 (m, 14H, H_{arom}), 10.00 (br s, 1H, OH)	347 (M^+, 49), 201 (36), 185 (37), 183 (33), 146 (31), 77 (100)
5b	88	180–181	$C_{23}H_{20}NO_2P$ (373.4)	4.30 (dd, 2H, J = 1.9, 3.1, CH_2N), 4.50, 4.70 (2m, 2H, H_2C=), 5.00 (m, 1H, HC=), 6.80–8.00 (m, 14H, H_{arom}), 10.10 (br s, 1H, OH)	373 (M^+, 49), 201 (98), 185 (100), 183 (94), 172 (43)
5c	87	175–176	$C_{27}H_{22}NO_2P$ (423.5)	5.00 (s, 2H, CH_2N), 6.70–8.00 (m, 14H, H_{arom}), 10.00 (br s, 1H, OH)	423 (M^+, 8), 332 (10), 222 (14), 201 (19), 185 (39), 183 (38), 91 (100)
5d	85	189–190	$C_{25}H_{20}NO_3P$ (413.4)	5.00 (s, 2H, CH_2N), 5.20–5.90 (m, 2H, H_{furan}), 7.05–8.00 (m, 15H, $H_{furan+arom}$), 10.00 (br s, 1H, OH)	413 (M^+, 18), 322 (29), 212 (19), 201 (31), 185 (86), 183 (65), 81 (100)
6a	87	109–110	$C_{11}H_{14}NO_4P$ (255.2)	3.25 (s, 3H, CH_3N), 3.70, 3.90 (2s, together 6H, CH_3O), 6.80–7.45 (m, 4H, H_{arom}), 8.40 (br s, 1H, OH)	255 (M^+, 100), 146 (32)
6c	86	82–83	$C_{17}H_{18}NO_4P$ (331.3)	3.70, 3.90 (2s, together 6H, CH_3O), 5.00 (s, 2H, CH_2N), 6.75–7.40 (m, 9H, H_{arom}), 8.50 (br s, 1H, OH)	331 (M^+, 15), 240 (28), 228 (25), 91 (100)

[a] Uncorrected.
[b] Satisfactory microanalysis obtained: C ±0.39, H ±0.33, N ±0.39, O ±0.36, P ±0.34.
[c] IR (KBr): ν_{OH} = 3400, ν_{PO} = 1180 cm^{-1}.
[d] Recorded on a Bruker WP 80.
[e] Obtained on a Riber 10-10 spectrometer.

3a–d or **4a,c** (5 mmol) in THF (20 mL) at −30 °C. The initially deep-red colored solution was stirred for 0.5 h at the same temperature and the mixture was quenched with sat. aq NH_4Cl (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated in vacuo to yield the condensed heterocycles **5a–d** and **6a,c** in almost quantitative yields. The compounds **5a–d** and **6a,c** were triturated with Et_2O, filtered and finally recrystallized from toluene/hexane. The yields reported in Table 2 were evaluated after recrystallization.

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