An Expeditious Synthesis of 3-Alkyl-, Aryl- and Heteroaryl-indoles by way of an Intramolecular Horner–Wittig Reaction

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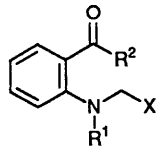
A variety of 3-alkyl-, aryl- and heteroaryl-indoles have been efficiently prepared by base-induced intramolecular cyclization of suitable aromatic *o*-acyl substituted Horner–Wittig reagents.

The importance of the indole ring system,[1] reflected in the numerous methods devised for its synthesis,[2,3] has particular relevance in alkaloid and natural product chemistry,[4,5] where many 3-substituted indoles function either as biochemical intermediates or as natural drugs.[1a]

Elaboration of the indole skeleton generally takes place when either a monosubstituted or an *ortho*-disubstituted benzene precursor undergoes intramolecular ring closure.[6] Bischler, Fischer and Madelung indole syntheses, based on such principles,[1a] are long-established methods which have been recently extended and significantly improved.[7,8] The Wittig reaction, which represents a method of choice for the inter and intramolecular creation of carbon–carbon double bonds has also been successfully applied to the preparation of diversely substituted indoles from *o*-acylaminobenzyltriphenylphosphonium salts.[9]

Although the introduction of new and simple methodologies to form α-nitrogen carbon–carbon double bonds is of considerable interest, few reported synthetic strategies have involved intramolecular attack of an α-amino carbanion on a vicinal carbonyl moiety in suitable *o*-amino ketones **1**. This may



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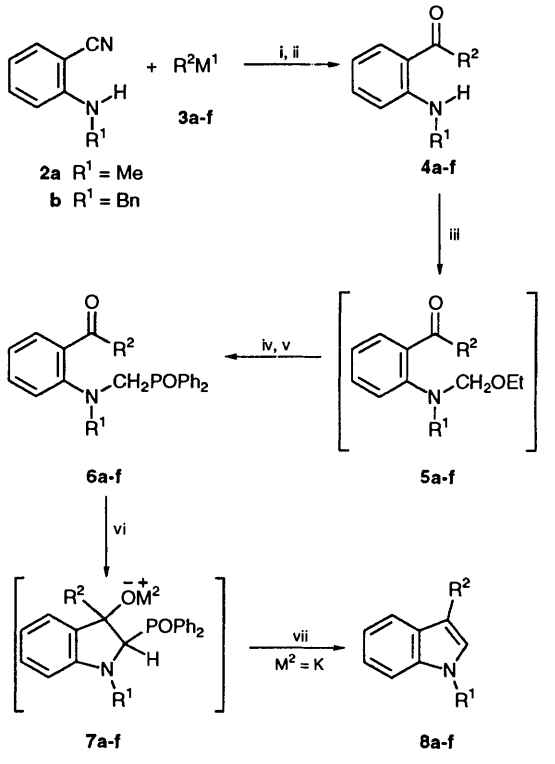
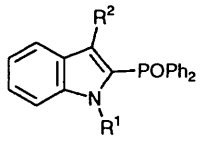
be because the generation of α-metalloamines is difficult,[10] although several recently developed procedures have solved this problem.[11] In 1972, C. D. Jones reported a new indole synthesis involving base-catalysed aldol condensation of the sulfonamides of *o*-aminocarbonyl compounds of structure **1** (R^1 = SO_2Ph; X = CN, COAr and CO_2R).[12] Application of the same methodology to *o*-aminocarbonylbenzophenones **1** (R^1 = COPh, X = Ph, vinyl) also provided a route to a variety of 3-phenylindoles,[13] although the compounds so prepared were invariably substituted at all three positions of the azole ring.

Here, we report an efficient and simple method for the elaboration of *N*-substituted indoles which, being tolerant of a variety of substituents, gives 3-alkyl, 3-aryl and 3-heteroaryl indoles in reasonable yields.

Our strategy is based upon the base-induced intramolecular cyclization of aromatic Horner–Wittig reagents **6a–f** *o*-substituted with suitable acyl groups. The Horner–Wittig reagents **6a–f** are readily accessible according to the general method outlined in Scheme 1. Initially, *N*-methyl- and *N*-benzylanthranilonitrile **2a**, **b**, respectively, were treated with the appropriate Grignard reagent **3a**, **b** or aliphatic, aromatic and heteroaromatic lithium derivatives **3c–f** to provide the 2-acylanilines **4a–f**. Conversion of these amino ketones into the diphenylphosphine oxides **6a–f** was accomplished in a one-pot reaction by the following three-step sequence:[14] (i) formation of the mixed *O*,*N*-acetals **5a–f** by way of the conventional Mannich reaction of the amines **4a–f** and paraformaldehyde in ethanol, (ii) removal of the solvent and incorporation of the diphenylphosphinoyl group by an Arbusov reaction of the intermediate *O*,*N*-acetals with chlorodiphenylphosphine in tetrahydrofuran (THF) and (iii) addition of solid potassium carbonate to complete the reaction and give the HCl-free



3-8	R^1	R^2	M^1
a	Bn	Et	MgBr
b	Me	Pr^i	MgCl
c	Me	Bu^s	Li
d	Me	Ph	Li
e	Me	2-Thienyl	Li
f	Me	2-Furyl	Li



9a,c

Scheme 1 *Reagents and conditions:* i, THF or Et_2O, 0 °C; ii, HCl H_2O; iii, $(CH_2O)_n$, EtOH, toluene, reflux; iv, Ph_2PCl, THF, room temp.; v, K_2CO_3; vi, KHMDS, THF, −10 °C; vii, room temp., HCl, H_2O

products **6a–f**. This reaction sequence is applicable to all the alkyl, aryl and heteroaryl amino ketones examined.

Deprotonation of the Horner–Wittig reagents **6a–f** was effected with potassium bis(trimethylsilyl)amide[15] (KHMDS) in THF at −10 °C (Scheme 1). Stirring of the reaction mixture for a few hours completed the Horner–Wittig reaction as indicated by the presence of potassium diphenylphosphinate. The results of a representative series of products obtained by this method are presented in Scheme 1. This simple procedure affords good yields of the 3-alkyl-, aryl- and heteroaryl-indole derivatives **8a–f**.

The use of KHMDS as the base allows formation of the annelation products **8a–f** under very mild and optimal conditions. Indeed, intramolecular attack of the phosphoryl-stabilized carbanion at the carbonyl function of the vicinal acyl substituent gives the adduct **7** (M^2 = K, Scheme 1). The presence of the weakly bound potassium counterion in **7** favours the elimination reaction[16] and hence readily gives the new α-nitrogen carbon–carbon double bond. Dramatically different behaviour is observed by using a lithiated base such as lithium diisopropylamide (LDA). In this case, the annelation reaction is not accompanied by the spontaneous elimination of lithium diphenylphosphinate from the adducts **7** (M^2 = Li, Scheme 1). Work-up of the reaction mixture preferentially provides the dehydration products as exemplified by the formation of 2-phosphorylated indole derivatives **9a, c** (Scheme 1) from the corresponding Horner–Wittig reagents **6a, c**.[17]

To summarize, the procedure described here represents a conceptually and experimentally simple new approach to the indole skeleton. The easy incorporation of alkyl, aryl and heteroaryl substituents at the 3 position of the heterocyclic nucleus demonstrates the great versatility of the process.

Experimental

^{1}H NMR spectra were recorded on Bruker AM 300 or AC 400 spectrometers and were run on samples dissolved in $CDCl_3$. Mass spectral analyses were performed on a Ribermag 10-10 mass spectrometer. For flash column chromatography, Merck silica gel 60 (230–400 mesh ASTM) was used. THF and Et_2O were freshly distilled from sodium–benzophenone under argon (Ar). Dry glassware for moisture-sensitive reactions was obtained by oven-drying and assembly under Ar. An inert atmosphere was obtained with a stream of Ar and glassware equipped with rubber septa; reagent transfer was performed by syringe or cannula techniques. Elemental analyses were determined by the CNRS microanalysis centre.

General Procedure for the Synthesis of Amino Ketones **4a–f**.—*N*-Benzylanthranilonitrile **2b** was prepared by reduction with $NaBH_4$ in ethanol of the imine obtained by condensation of anthranilonitrile with benzaldehyde.[17]

For the syntheses of compounds **4a–d**, commercial solutions of **3a** (3 mol dm^{-3} in Et_2O), **3b** (2 mol dm^{-3} in THF) and **3c** (1.4 mol dm^{-3} in cyclohexane) were used. For the preparation of **4e, f**, solutions of 2-thienyl-[18] and 2-furyl-lithium[19] in Et_2O were prepared according to the reported procedures.

A solution of R^2M^1 **3** (78 mmol) in the appropriate solvent was added dropwise, at 0 °C with stirring under Ar, to a solution of the amine **2a, b** (78 mmol) in Et_2O (for the synthesis of **4a–d**) or in THF (for **4e, f**). The reaction mixture was stirred for an additional 5 h and warmed to room temperature. After recooling to 0 °C with an ice-bath, it was carefully quenched by addition of dilute HCl (10%; 60 cm^3). The mixture was warmed to room temperature, stirred for 0.5 h, and then recooled to 0 °C when solid NaOH (10 g) was carefully added to it. The aqueous layer was extracted twice with Et_2O (2 × 50 cm^3) and the combined ethereal extracts were washed with brine, dried and evaporated. The crude amino ketones were purified by distillation **4b, c** or by flash column chromatography using EtOAc–hexane (25:75) as eluent.

o-(*Benzylamino*)*phenyl ethyl ketone* **4a**. (11.35 g, 61%) (Found: C, 80.1; H, 7.2; N, 5.8. $C_{16}H_{17}NO$ requires C, 80.3; H, 7.15; N, 5.85%); $\delta_H(CDCl_3)$ 0.95 (3 H, t, *J* 7.2), 2.56 (2 H, q, *J* 7.2), 4.45 (2 H, s), 6.66 (2 H, m), 7.35 (6 H, m), 7.65 (1 H, m) and 9.35 (1 H, s); *m/z* 239 (M^+, 26%) and 91 (100).

o-(*Methylamino*)*phenyl isopropyl ketone* **4b**. (8.95 g, 65%) (Found: C, 74.55; H, 8.15; N, 8.05. $C_{11}H_{15}NO$ requires C, 74.55; H, 8.55; N, 7.9%); $\delta_H(CDCl_3)$ 1.20 (6 H, d, *J* 6.9), 2.90 (3 H, d, *J* 3.3), 3.60 (1 H, m), 6.55 (1 H, m), 6.70 (1 H, d, *J* 8.1), 7.38 (1 H, m), 7.80 (1 H, d, *J* 7.9) and 8.90 (1 H, s); *m/z* 177 (M^+, 52%) and 134 (100).

o-(*Methylamino*)*phenyl* sec-*butyl ketone* **4c**. (10.15 g, 65%) (Found: C, 75.45; H, 8.75; N, 7.3. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.95; N, 7.3%); $\delta_H(CDCl_3)$ 0.70 (3 H, t, *J* 7.4), 1.16 (3 H, d, *J* 6.9), 1.20 (2 H, m), 1.60 (1 H, m), 3.00 (3 H, d, *J* 3.4), 6.64 (2 H, m), 7.26 (1 H, m), 7.81 (1 H, m) and 8.95 (1 H, s); *m/z* 191 (M^+, 21%), 134 (38) and 48 (100).

o-(*Methylamino*)*phenyl phenyl ketone* **4d**. (14.15 g, 86%), m.p. 66–67 °C (lit.,[20] 66–67 °C); $\delta_H(CDCl_3)$ 2.95 (3 H, s), 6.50 (1 H, t, *J* 9.0), 6.75 (1 H, d, *J* 8.5), 7.40 (5 H, m), 7.55 (2 H, m) and 8.55 (1 H, s); *m/z* 211 (M^+, 100%).

o-(*Methylamino*)*phenyl* 2-*thienyl ketone* **4e**. (14.05 g, 83%) (Found: C, 66.45; H, 5.4; N, 6.35. $C_{12}H_{11}NOS$ requires C, 66.35; H, 5.1; N, 6.45%); $\delta_H(CDCl_3)$ 2.90 (3 H, s), 6.60 (1 H, t, *J* 8.1), 6.70 (1 H, d, *J* 9.2), 7.02 (1 H, dd, *J* 5.0 and 3.6), 7.15 (1 H, dd, *J* 3.6 and 1.1), 7.31 (2 H, m) and 7.41 (1 H, dd, *J* 5.0 and 1.1); *m/z* 216 (M^+ − H, 30%) and 215 (100).

o-(*Methylamino*)*phenyl* 2-*furyl ketone* **4f**. (12.7 g, 81%) (Found: C, 71.55; H, 5.7; N, 7.0. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 6.95%); $\delta_H(CDCl_3)$ 2.90 (3 H, s), 6.48 (1 H, dd, *J* 3.6 and 1.7), 6.57 (1 H, dd, *J* 3.6 and 0.8), 6.68 (1 H, m), 6.74 (1 H, dt, *J* 7.2 and 1.9), 7.31 (1 H, dt, *J* 8.4 and 2.4), 7.50 (1 H, dd, *J* 1.7 and 0.8) and 7.55 (1 H, m); *m/z* 200 (M^+ − H, 39%), 199 (46) and 183 (100).

General Procedure for the Synthesis of Horner–Wittig Reagents **6a–f**.—A stirred solution of **4a–f** (30 mmol), paraformaldehyde (1.4 g), ethanol (20 cm^3) and toluene (50 cm^3) was refluxed overnight. Owing to their instability, the resulting *O,N*-acetals **5a–f** obtained after removal of the solvents and the excess of paraformaldehyde were used directly in the next step. The crude products were dissolved in THF (25 cm^3) and Ph_2PCl (7.2 g, 5.35 cm^3, 30 mmol) was slowly added by way of a syringe under Ar at a temperature < 20 °C. The reaction mixture was stirred at room temperature for 1 h, after which solid K_2CO_3 (5 g) was added to it and stirring continued for 15 min. The reaction mixture was filtered on Celite® and then poured into hexane (500 cm^3) with vigorous stirring. The mixture was kept in the refrigerator overnight after which the solution was decanted and the oily residue was dissolved in CH_2Cl_2 and the solution dried (Na_2SO_4). After evaporation of the solvent, purification of the product was effected by way of flash chromatography using acetone–light petroleum (1:1) as eluent. The solvents were removed on a rotary vacuum evaporator (water aspirator; 35 °C) and then under high vacuum (5 × 10^{-3} Torr) for several hours. The products **6a–f** were generally obtained as a yellowish emulsion or foam. ^{1}H NMR, TLC, EI mass spectral analysis and elemental analysis indicated that **6a–f** were of high purity and could be used directly in the subsequent Horner–Wittig reaction. If required, they might be purified by recrystallization from hexane–toluene.

o-[*Diphenylphosphinoylmethyl*(*benzyl*)*amino*]*phenyl ethyl ketone* **6a**. (6.12 g, 45%) (Found: C, 76.7; H, 6.2; N, 3.1. $C_{29}H_{28}NO_2P$ requires C, 76.8; H, 6.2; N, 3.1%); $\delta_H(CDCl_3)$ 0.90 (3 H, t, *J* 7.2), 2.55 (2 H, q, *J* 7.2), 3.85 (2 H, d, *J* 4.0), 4.55 (2 H, s),

6.85 (2 H, m), 7.10 (7 H, m), 7.32 (6 H, m) and 7.60 (4 H, m); *m/z* 453 (M^+, 1%), 252 (63) and 91 (100).

o-[*Diphenylphosphinoylmethyl(methyl)amino*]*phenyl isopropyl ketone* **6b**. (5.52 g, 47%) (Found: C, 73.6; H, 6.6; N, 3.55. $C_{24}H_{26}NO_2P$ requires C, 73.65; H, 6.65; N, 3.6%); $\delta_H(CDCl_3)$ 0.65 (6 H, d, *J* 6.7), 2.90 (3 H, s), 3.10 (1 H, m), 3.90 (2 H, d, *J* 4.0), 6.85 (1 H, m), 6.95 (1 H, d, *J* 8.0), 7.05 (1 H, d, *J* 8.0), 7.15 (1 H, m), 7.36 (6 H, m) and 7.62 (4 H, m); *m/z* 391 (M^+, 1%), 190 (75) and 91 (100).

o-[*Diphenylphosphinoylmethyl(methyl)amino*]*phenyl* sec-*butyl ketone* **6c**. (5.23 g, 43%), m.p. 110–111 °C (Found: C, 73.95; H, 6.8; N, 3.3. $C_{25}H_{28}NO_2P$ requires C, 74.0; H, 6.9; N, 3.45%); $\delta_H(CDCl_3)$ 0.68 (3 H, t, *J* 4.7), 0.76 (3 H, d, *J* 6.9), 1.15 (2 H, m), 1.48 (1 H, m), 3.00 (3 H, s), 3.95 (2 H, d, *J* 4.0), 6.85 (2 H, m), 7.17 (2 H, m), 7.42 (6 H, m) and 7.70 (4 H, m); *m/z* 405 (M^+, 8%), 205 (100), 183 (61), 174 (52) and 91 (93).

o-[*Diphenylphosphinoylmethyl(methyl)amino*]*phenyl phenyl ketone* **6d**. (7.65 g, 60%), m.p. 184–185 °C (Found: C, 76.25; H, 5.6; N, 3.0. $C_{27}H_{24}NO_2P$ requires C, 76.25; H, 5.65; N, 3.3%); $\delta_H(CDCl_3)$ 2.95 (3 H, s), 3.85 (2 H, d, *J* 4.0), 6.87 (2 H, m), 7.17 (2 H, m) and 7.48 (15 H, m); *m/z* 425 (M^+, 1%), 224 (100) and 91 (58).

o-[*Diphenylphosphinoylmethyl(methyl)amino*]*phenyl* 2-*thienyl ketone* **6e**. (7.10 g, 55%) (Found: C, 69.5; H, 5.15; N, 3.15. $C_{25}H_{22}NO_2PS$ requires C, 69.6; H, 5.1; N, 3.25); $\delta_H(CDCl_3)$ 2.80 (3 H, s), 3.95 (2 H, d, *J* 4.0), 7.12 (1 H, dd, *J* 5.0 and 3.8), 7.22 (1 H, m), 7.25 (1 H, m), 7.33 (6 H, m), 7.40 (3 H, m) and 7.60 (5 H, m); *m/z* 431 (M^+, 1%), 230 (100) and 97 (61).

o-[*Diphenylphosphinoylmethyl(methyl)amino*]*phenyl* 2-*furyl ketone* **6f**. (7.10 g, 57%) (Found: C, 71.95; H, 5.6; N, 3.3. $C_{25}H_{22}NO_3P$ requires C, 72.3; H, 5.3; N, 3.35%); $\delta_H(CDCl_3)$ 2.95 (3 H, s), 3.95 (2 H, d, *J* 4.0), 6.46 (1 H, dd, *J* 3.7 and 1.7), 6.88 (1 H, dd, *J* 3.7 and 0.8), 6.92 (2 H, m), 7.21 (2 H, m), 7.34 (4 H, m), 7.42 (2 H, m), 7.60 (1 H, dd, *J* 1.7 and 0.8) and 7.66 (4 H, m); *m/z* 415 (M^+, 1%), 217 (100), 214 (75) and 199 (62).

General Procedure for the Synthesis of 3-*Substituted Indole Derivatives* **8a–f**.—KH (35% suspension in oil; 103 mg, 0.9 mmol) was washed twice with hexane before the introduction under Ar of dry THF (6 cm^3). Hexamethyldisilazane (145 mg, 0.9 mmol) was slowly added at room temperature to the mixture which was then stirred for 1 h. The solution of KHMDS was then cooled to −10 °C and a solution of **6a–f** (0.82 mmol) in THF (2 cm^3) was added dropwise by way of a syringe to it. The mixture was then warmed to room temperature and stirred for 6 h. After this several drops of dilute HCl (10%), water (10 cm^3) and Et_2O (20 cm^3) were added to it. The organic layer was separated, rinsed with brine, dried ($MgSO_4$) and concentrated to dryness. The crude product was finally purified by flash chromatography using EtOAc–hexane (2:3) as eluent.

1-*Benzyl*-3-*ethylindole* **8a**. (112 mg, 58%), m.p. 37–38 °C (lit.,[21] 37.5–38.5 °C); $\delta_H(CDCl_3)$ 1.70 (3 H, t, *J* 7.1), 3.15 (2 H, q, *J* 7.1), 5.60 (2 H, s), 7.20 (1 H, s), 7.48 (4 H, m), 7.63 (4 H, m) and 7.90 (1 H, d, *J* 7.5); *m/z* 235 (M^+, 28%), 220 (32) and 91 (100).

3-*Isopropyl*-1-*methylindole* **8b**. (74 mg, 52%) (Found: C, 82.9; H, 8.6; N, 8.0. $C_{12}H_{15}N$ requires C, 83.2; H, 8.75; N, 8.1%); δ_H[22]$(CDCl_3)$ 1.40 (6 H, d, *J* 6.8), 3.30 (1 H, m), 3.80 (3 H, s), 6.90 (1 H, s), 7.15 (1 H, m), 7.30 (2 H, m) and 7.70 (1 H, d, *J* 7.9); *m/z* 173 (M^+, 34%), 158 (100) and 143 (13).

1-*Methyl*-3-(1-*methylpropyl*)*indole* **8c**. (89 mg, 58%) (Found: C, 83.25; H, 9.15; N, 7.55. $C_{13}H_{17}N$ requires C, 83.4; H, 9.15; N, 7.5%); $\delta_H(CDCl_3)$ 0.90 (3 H, t, *J* 7.4), 1.40 (3 H, d, *J* 7.0), 1.67 (1 H, m), 3.00 (1 H, m), 3.75 (3 H, s), 6.80 (1 H, s), 7.10 (1 H, t, *J* 7.6), 7.28 (2 H, m) and 7.55 (1 H, d, *J* 7.6); *m/z* 187 (M^+, 21%) and 158 (100).

1-*Methyl*-3-*phenylindole* **8d**. (93 mg, 55%), m.p. 65–66 °C (lit.,[23] 65–66 °C); $\delta_H(CDCl_3)$ 3.85 (3 H, s), 7.25 (1 H, s), 7.37 (4 H, m), 7.55 (2 H, m), 7.77 (2 H, m) and 8.07 (1 H, d, *J* 8.1); *m/z* 207 (M^+, 100%).

1-*Methyl*-3-(2-*thienyl*)*indole* **8e**. (115 mg, 66%) (Found: C, 73.0; H, 5.5; N, 6.5. $C_{13}H_{11}NS$ requires C, 73.2; H, 5.2; N, 6.6%); $\delta_H(CDCl_3)$ 3.80 (3 H, s), 7.12 (1 H, dd, *J* 4.9 and 3.7), 7.20–7.30 (4 H, m), 7.34 (2 H, m) and 8.00 (1 H, d, *J* 7.3); *m/z* 213 (M^+, 100%).

3-(2-*Furyl*)-1-*methylindole* **8f**. (97 mg, 60%) (Found: C, 78.95; H, 5.65; N, 7.0. $C_{13}H_{11}NO$ requires C, 79.15; H, 5.6; N, 7.1%); $\delta_H(CDCl_3)$ 3.80 (3 H, s), 6.53 (2 H, m), 7.30 (3 H, m), 7.38 (1 H, s), 7.46 (1 H, dd, *J* 1.6 and 0.8) and 8.00 (1 H, d, *J* 7.8); *m/z* 197 (M^+, 100%) and 168 (65).

General Procedure for the Synthesis of 2-*Diphenylphosphinoyl* 3-*Substituted Indole Derivatives* **9a, c**.—A solution of butyllithium (1.6 mol dm^{-3} in hexanes; 3.5 cm^3, 5.5 mmol) was added slowly to a mixture of anhydrous THF (10 cm^3) and diisopropylamine (560 mg, 0.78 cm^3, 5.5 mmol) in a flask under a stream of Ar at −78 °C. The mixture was kept at 0 °C for 1 h after which a solution of each of compounds **6a, c** (5 mmol) in anhydrous THF (10 cm^3) was added dropwise to it at −78 °C. The solution was stirred for 0.5 h at this temperature after which it was warmed to room temperature and then quenched with water (30 cm^3). The aqueous layer was extracted twice with CH_2Cl_2 (50 cm^3) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the phosphorylated indoles **9a, c**. Trituration of the oily products with Et_2O furnished solid products which were finally purified by recrystallization from hexane–toluene.

1-*Benzyl*-2-*diphenylphosphinoyl*-3-*ethylindole* **9a**. (242 mg, 68%), m.p. 54–55 °C (Found: C, 79.65; H, 5.95; N, 3.0. $C_{29}H_{26}NOP$ requires C, 80.0; H, 6.0; N, 3.2%); $\delta_H(CDCl_3)$ 0.80 (3 H, d, *J* 7.2), 2.28 (2 H, q, *J* 7.2), 5.78 (2 H, s) and 6.80–7.70 (19 H, m); *m/z* 435 (M^+, 20%), 344 (100), 201 (37) and 91 (79).

2-*Diphenylphosphinoyl*-1-*methyl*-3-(1-*methylpropyl*)*indole* **9c**. (222 mg, 70%), m.p. 107–108 °C (Found: C, 77.7; H, 6.5; N, 3.5. $C_{25}H_{26}NOP$ requires C, 77.5; H, 6.75; N, 3.6%); $\delta_H(CDCl_3)$ 0.53 (3 H, t, *J* 7.2), 1.11 (3 H, d, *J* 7.0), 1.60 (2 H, m), 2.12 (1 H, m), 3.76 (3 H, s) and 6.90–7.80 (14 H, m); *m/z* 387 (M^+, 12%), 358 (23), 204 (100), 201 (60) and 183 (13).

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