Indolization by Phosphorus Trichloride of Functionalized Ketone Arylhydrazones: Synthesis of Pharmacological Interesting Indoles

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The synthesis of indoles starting from phosphorus trichloride and arylhydrazones either functionalized in the ketone entity or *N*-substituted is reported. The reaction, carried out at room temperature, allows several substituents on the ketone framework of the hydrazone (*e.g.* ether, alkoxycarbonyl, halogeno, dialkylamino, olefinic, and phosphonic). Under optimum conditions high product yields were obtained. Evidence for the proposed mechanism is also reported.

Indoles are of importance both in natural product chemistry and pharmacology and because of this there is interest in new routes for their synthesis, particularly where compounds bearing several functionalized groups are formed.

Recently, we discovered[1] that phosphorus trichloride is an efficient activator in the cyclization of arylhydrazones to indoles. Although at first sight this reaction could be considered to be a modification of the Fischer[2] indolization procedure, it shows a number of important and novel features. For example a stoicheiometric amount of PCl_3 must be used for all reactions, and these must always be carried out at room temperature. The reaction tolerates a wide variety of substituents on the phenyl ring and the direction of cyclization is predictable both with unsymmetrical ketones and with a *meta*-substituent on the phenyl entity of the arylhydrazones. Finally, we have reported[3] recently a mechanism in which phosphorus adducts, diazaphosphole derivatives, are intermediates and in which the last stage is a Wittig-like elimination of Cl_2PNH_2.

Here we study the possibility of obtaining indoles starting from *N*-substituted phenylhydrazones and functionalized ketones which are generally used in the synthesis of indoles of biological interest. The results for several functionalized ketones are reported in Table 1.

Once again, this reaction shows both considerable versatility and wide applicability, the mild conditions employed ensuring high yields of indoles bearing amino-, alkoxy-, chloro-, alkoxycarbonyl-, phosphonic-, and olefinic-functions.

It is noteworthy that the two isomeric ketones 4-methoxyphenylacetone and 4-methoxypropiophenone give the two corresponding and isomeric indoles (entries 1 and 2) without transposition of the groups; this result differs from that obtained with the Fischer reaction. These indoles were identified from their u.v. spectra. It is reported,[4] in fact, that u.v. spectra of 2-alkyl-3-arylindoles are different from those of the corresponding 3-alkyl-2-arylindoles, the $\lambda_{max.}$ for the first being at $\approx$280 nm and, the second at $\approx$300 nm. Because these indoles show anti-inflammatory properties[5] it is important that they should be obtained without by-products which are difficult to eliminate.

Indoles bearing a side chain containing a double bond or a halogen atom are readily available with our synthesis (entries 4 and 5). Since such compounds easily polymerize or decompose in the light or when heated Fischer indolization of the corresponding hydrazones gives them in lower yields. It is noteworthy that these products are not obtained *via* the Fischer synthesis.[6,7] α,β-Unsaturated ketone phenylhydrazones give 4,5-di-hydropyrazoles spontaneously before the addition of PCl_3.

Indoles with phosphonic groups which are plant-growth regulators,[8] may be synthesized by our route (see entry 6, a previously unknown indole of this class).

Methyl 5-methoxy-2-methylindol-3-ylacetate (entry 7), a key intermediate in the synthesis of the pharmacologically interesting compound indomethacin, represents a class of compounds inaccessible from their respective keto esters *via* the classical Fischer synthesis, because of competing hydrolysis or trans-esterification processes.[9] Under our mild conditions, the reaction suffers none of these drawbacks, each indolylacetate being obtained from the corresponding levulinate. The well-known analgesic and anti-inflammatory[10] *N*,*N*-diethyl-2-methyltriptamine (entry 8) is also easily prepared by means of our procedure.

Table 1. Indoles from the reaction of substituted ketone arylhydrazones with PCl_3

Entry	Indole	Yield (%)
1	3-(4-Methoxyphenyl)-2-methyl	90
2	2-(4-Methoxyphenyl)-3-methyl	87
3	2-Methyl-3-phenoxy	90
4	3-Allyl-2-methyl	44
5	3-(2-Chloroethyl)-5-methoxy-2-methyl	65
6	3-Butyl-2-dimethylphosphonatomethyl	90
7	5-Methoxy-3-methoxycarbonylmethyl-2-methyl	85
8	3-(2-Diethylaminoethyl)-2-methyl	70

Table 2. Results of the reaction of *N*-phenyl-*N*-substituted ketone hydrazones with PCl_3 at room temperature in dichloromethane

Entry	Indole	Yield (%)	Reaction time (min)
1	1-Methyl-2,3-diphenyl	85[a]	30
2	1-Benzyl-2,3-diphenyl	77[a]	40
3	1-Isopropyl-2,3-diphenyl	65[a]	60
4	2-Methyl-1,3-diphenyl	71[b]	900
5	1-Benzoyl-2,3-diphenyl	23[a]	1 440

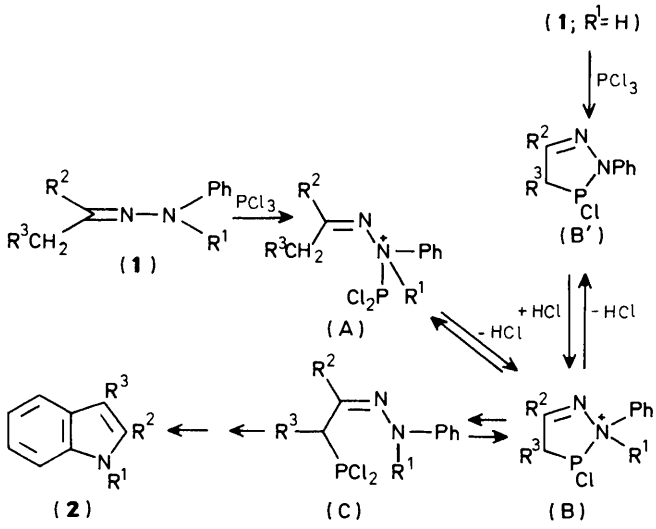
[a] The corresponding *N*-unsubstituted indole (2,3-diphenylindole) was obtained in 75% yield in *ca.* 30 min. [b] The corresponding *N*-unsubstituted indole (3-phenyl-2-methylindole) was obtained in 86% yield in *ca.* 30 min.

Finally, we turned our attention to the synthesis of *N*-substituted phenylhydrazones. In Table 2 are collected the synthesized indoles. All products were obtained in good to high yields except for the benzoyl derivative (entry 5, Table 2). From these reactions, further evidence was gained of the validity of our proposed mechanism.[3] Thus a comparison of *N*-substituted and *N*-unsubstituted hydrazones shows that with electron-donating substituents, the reaction is faster and proceeds with high yields, while with electron-withdrawing or steric hindered ones the reaction is slower and the yield decreases.

These results support our earlier proposal[3] of nucleophilic attack by nitrogen on phosphorus (intermediate [A]). Subsequently, with *N*-unsubstituted hydrazones, this inter-

mediate gives a diazaphosphole intermediate such as [B'] which with addition of HCl gives an ionic form such as [B]. In contrast, with *N*-substituted hydrazones this ionic form [B] is formed immediately and , as a consequence, subsequent rig-opening of the latter to give [C] becomes easier than with *N*-unsubstituted hydrazones.

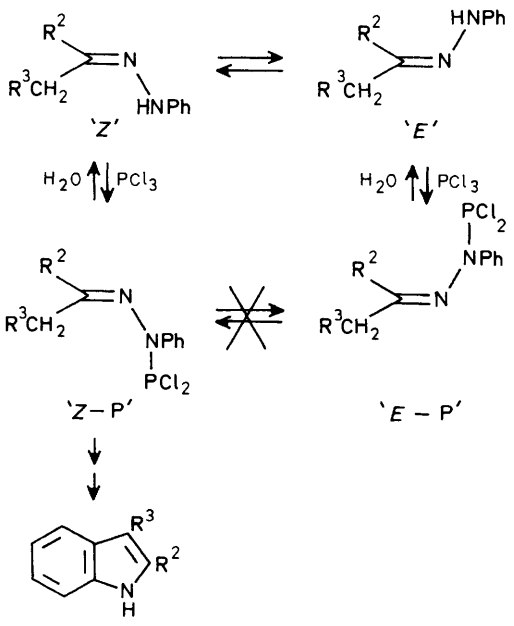
In several cases, we observed disappearance of the two hydrazone isomers by t.l.c. and n.m.r. analysis at different reaction times, further evidence for the formation of a diazaphosphole intermediate such as [B] (Scheme 1; R = H).



Scheme 1.

Initially, only the isomer of suitable configuration to give this intermediate is able to react, the other having first to isomerize. Finally, in the absence of an *E vs. Z* equilibrium, the 'unsuitable' isomer should be recovered unchanged at the end of the reaction. In fact, with 2-(4-methoxyphenyl)-3-methylindole and of *N,N*-diethyl-2-methyltryptamine t.l.c. analysis showed the predominance of one of the starting hydrazones together with the corresponding indole; longer reaction times failed to increase the conversion into the indole. Then, quenching and stirring of the CH_2Cl_2 reaction mixture for several minutes regenerated the starting hydrazone presumably from its phosphorus adduct (*E*-P) and successively its equilibration (Scheme 2).

Consequently, if this reaction mixture is treated again, after drying, with PCl_3, more indole can be obtained.



Scheme 2.

Experimental

^{1}H N.m.r. spectra were recorded at 60 MHz with a Varian EM-360-L instrument. Chemical shifts were given in p.p.m. from tetramethylsilane as internal standard. Mass spectra were recorded with a Jeol JMS-D 100 spectrometer. I.r. spectra were recorded on a Perkin-Elmer 983 spectrophotometer. U.v. spectra were recorded on a Perkin-Elmer 402 spectrophotometer. Commercial ketones, hydrazines, and phosphorus trichloride were used without any purification. *N*-Substituted *N*-phenylhydrazines were synthesized from the corresponding halogen derivative and phenylhydrazine with a phase-transfer catalyst.[11]

Reaction of Phenylhydrazones with PCl_3*: General Procedure.*—Phosphorus trichloride (5.5 mmol) was added at room temperature to a dichloromethane solution of the hydrazone (5 mmol). At the end of the reaction, the mixture was poured into saturated aqueous $NaHCO_3$. The organic layer was separated, washed with water, and dried (Na_2SO_4) and the indole was separated by distillation, crystallization, or column chromatography.

3-(4-*Methoxyphenyl*)-2-*methylindole.* The reaction went to completion in 4 h and the indole, purified by passage through a short silica gel column [light petroleum–diethyl ether (2:1) as eluant], was obtained in 90% yield; m.p. 126—127 °C (lit.,[12] m.p. 127 °C); R_F 0.27; δ_H(60 MHz, $CDCl_3$) 2.49 (s, 3 H, Me), 3.90 (s, 3 H, Me), and 6.97—7.87 (m, 9 H, ArH + NH); $\lambda_{max.}$(EtOH) 227 (ε 34 200 dm^3 mol^{-1} cm^{-1}) and 270 nm (18 500).[4]

2-(4-*Methoxyphenyl*)-3-*methylindole.* The reaction went to completion in 6 h and the indole, purified by passage through a short silica gel column [light petroleum–diethyl ether (2:1) as eluant], was obtained in 30% yield; m.p. 125—127 °C (lit.,[13] m.p. 127 °C); R_F 0.35; δ_H(60 MHz, $CDCl_3$) 2.40 (s, 3 H, Me), 3.80 (s, 3 H, Me), 6.78—7.72 (m, 8 H, ArH), and 7.82 (s, 1 H, NH); $\lambda_{max.}$(EtOH) 245 (ε 22 000 dm^3 mol^{-1} cm^{-1}) and 307 nm (24 100).[4]

Although t.l.c.-analysis of the course of the reaction showed disappearance of one of the two hydrazones, both were detected (t.l.c. and ^{1}H n.m.r.) after work-up. Further, although when the reaction mixture was allowed to stand for several days at room temperature, no yield increase was observed, if the CH_2Cl_2 solution was shaken for several minutes with water, dried, treated again, with PCl_3 and the procedure repeated the indole yield was increased to 87%.

2-*Methyl*-3-*phenoxyindole.* The reaction went to completion in 18 h and the indole purified by passage through a short silica gel column [light petroleum–diethyl ether (2:1) as eluant] was obtained in 90% yield; m.p. 134—135 °C; R_F 0.31; δ_H(60 MHz, $CDCl_3$) 2.27 (s, 3 H, Me), 6.78—7.50 (m, 9 H, ArH), and 7.79 (s, 1 H, NH); $\nu_{max.}$(CCl_4) 3 500 (NH) and 1 225 cm^{-1} (ArOC); *m/z* 223 (M^+), 146, 94, and 77 (Found: C, 80.9; H, 5.9; N, 6.2. $C_{15}H_{13}NO$ requires C, 80.7; H, 5.9; N, 6.3%).

3-*Allyl*-2-*methylindole.* The reaction went to completion in 24 h and the indole, purified by passage through a short silica gel column [light petroleum–diethyl ether (1:1) as eluant] and obtained in 44% yield was identified by comparison of its physical data with literature values.[6] The yield decreased to 20% if the product was purified by distillation (b.p. 111 °C at 0.5 Torr).

3-(2-*Chloroethyl*)-5-*methoxy*-2-*methylindole*. The reaction went to completion in 18 h and the indole, purified by passage through a short silica gel column [light petroleum–diethyl ether (4:1) as eluant] was obtained in 90% yield;[7] m.p. 90 °C; R_F 0.15; δ_H(60 MHz, $CDCl_3$) 2.28 (s, 3 H, Me), 2.90—3.75 (m, 4 H, CH_2CH_2), 3.85 (s, 3 H, OMe), 6.65—7.24 (m, 3 H, ArH), and 7.85 (s, 1 H, NH); *m/z* 223—225 (M^+), 174, 84, and 77 (Found: C, 64.2; H, 6.3; Cl, 16.0; N, 6.2%. $C_{12}H_{14}ClNO$ requires C, 64.4; H, 6.3; Cl, 15.9; N, 6.3%).

3-*Butylindol*-2-*ylmethyldimethylphosphonate*. The reaction went to completion in 24 h and the indole, purified by passage through a short silica gel column [benzene–ethyl acetate (1:1) as eluant] was obtained in 90% yield; b.p. 175 °C at 0.25 Torr (decomp. > 190 °C); R_F 0.17; δ_H(60 MHz, $CDCl_3$) 0.62—2.00 (m, 7 H, Pr), 2.50—3.00 (m, 2 H, CH_2), 3.33 (d, 2 H, CH_2P, $J_{CH,P}$ 22.0 Hz), 3.70 (d, 6 H, OMe, $J_{CH,P}$ 11.0 Hz), 6.90—7.80 (m, 4 H, ArH), and 9.12 (s, 1 H, NH); $\nu_{max.}$(CCl_4) 3 400 (NH), 1 270 (P=O), and 1 040 cm^{-1} (O–P); *m/z* 295 (M^+), 252, 143, 109, 79, and 77 (Found: C, 60.8; H, 7.6; N, 4.7; P, 10.4. $C_{15}H_{22}NO_3P$ requires C, 61.0; H, 7.5; N, 4.7; P, 10.5%).

Methyl 5-*methoxy*-2-*methylindol*-3-*ylacetate*. The reaction went to completion in 12 h and the indole, purified by passage through a short silica gel column [light petroleum–diethyl ether (20:15) as eluant] was obtained in 85% yield; m.p. 78—80 °C (lit.,[14] m.p. 79—81 °C); R_F 0.16; δ_H(60 MHz, $CDCl_3$) 2.21 (s, 3 H, Me), 3.70 (s, 5 H, CH_2 + OMe), 3.88 (s, 3 H, OMe), 6.60—7.20 (m, 4 H, ArH), and 9.12 (s, 1 H, NH).

N,N-*Diethyl*-2-*methyltryptamine*. The reaction went to completion in 48 h and after repetition of the treatment described for 2-(4-methoxyphenyl)-3-methylindole, the indole, purified by passage through a short silica gel column [light petroleum–diethyl ether (2:1) as eluant] was obtained in 70% yield; m.p. 207—209 °C (lit.,[8] m.p. 207—208 °C); R_F 0.18; δ_H(60 MHz, $CDCl_3$) 1.07 (t, 6 H, Me, *J* 7.0 Hz), 2.28 (s, 3 H, Me), 2.33—3.12 (m, 8 H, 4 CH_2), 6.60—7.70 (m, 4 H, ArH), and 8.65 (s, 1 H, NH).

1-*Methyl*-2,3-*diphenylindole*. The reaction went to completion in *ca.* 30 min and the indole, purified by crystallization from light petroleum, was obtained in 85% yield and identified by comparison of its physical data with literature values.[15]

1-*Benzyl*-2,3-*diphenylindole*. The reaction went to completion in *ca.* 40 min and the indole, purified by crystallization from diethyl ether, was obtained in 77% yield; m.p. 133—134 °C; R_F 0.55 [diethyl ether–light petroleum (2:13)]; δ_H(60 MHz, $CDCl_3$) 5.30 (s, 2 H, CH_2) and 6.90—8.00 (m, 19 H, ArH) (Found: C, 90.1; H, 6.0; N, 3.9. $C_{27}H_{21}N$ requires C, 90.2; H, 5.9; N, 3.9%).

1-*Isopropyl*-2,3-*diphenylindole*. The reaction went to completion in *ca.* 60 min and the indole purified by chromatography of the reaction mixture on a silica gel column [diethyl ether–light petroleum (2:13) as eluant], was obtained in 65% yield; m.p. 122—124 °C; R_F 0.52; δ_H(60 MHz, $CDCl_3$) 1.57 (d, 6 H, Me, *J* 8.0 Hz), 4.55 (m, 1 H, CH), and 7.00—7.90 (m, 14 H, ArH) (Found: C, 88.8; H, 6.7; N, 4.5%. $C_{23}H_{21}N$ requires C, 88.7; H, 6.8; N, 4.5%).

2-*Methyl*-1,3-*diphenylindole*. The reaction went to completion in *ca.* 15 h and required an excess of PCl_3 (2:1). The indole, purified by crystallization from diethyl ether, was obtained in 71% yield; m.p. 92—95 °C; R_F 0.54 [cyclohexane–ethyl acetate (5:1)]; δ_H(60 MHz, $CDCl_3$) 2.30 (s, 3 H, Me) and 7.00—7.80 (m, 14 H, ArH) (Found: C, 88.9; H, 6.2; N, 4.9. $C_{21}H_{17}N$ requires C, 89.0; H, 6.1; N, 4.9%).

1-*Benzoyl*-2,3-*diphenylindole*. The reaction went to completion in *ca.* 24 h and the indole, purified by chromatography on a silica gel column [light petroleum–diethyl ether (5:1)] was obtained in 23% yield and identified by comparison with literature data.[16]

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