Regioselective Indolization of Unsymmetrical Phenylhydrazones by Reaction, at Room Temperature, with PCl_3

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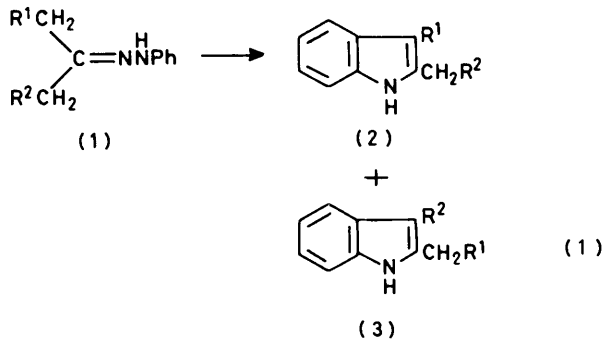
Unsymmetrical ketone phenylhydrazones (1) ($R^1 \neq R^2$) react with PCl_3, at room temperature to give predominantly one, (2), of the two possible 2,3-disubstituted indoles in good to excellent overall yield. When the R^1 and R^2 groups are very different (R^1 = Ph or Me; R^2 = alkyl or H) the reaction is highly regioselective leading to exclusive or prevalent formation of the corresponding 3-R^1 indoles (2), whereas when R^1 and R^2 are very similar (R^1, R^2 = alkyl chains) the regioselectivity is decreased and the indole having the shorter chain in the 3-position predominates, but only slightly.

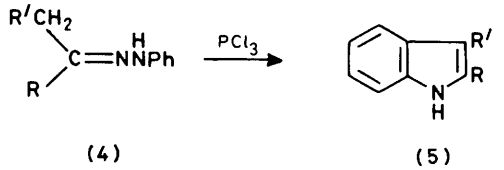
Inspection of the results enables the direction of indolization to be predicted and the positions of the substituents in the 2,3-disubstituted indoles to be assigned with certainty, features not inherent in the classical Fischer indolization.

In a recent communication,[1] we reported a new method for the synthesis of 2,3-disubstituted indoles by the reaction at room temperature of ketone arylhydrazones with PCl_3. Here, we describe the results of this indolization reaction when unsymmetrical acyclic arylhydrazones of type (1) are used. Arylhydrazones (1) can conceivably lead to the two indoles (2) and (3) on Fischer indolization or its classical modifications[2] [equation (1)].



(1)

a; R^1 = Ph, R^2 = Me
b; R^1 = Ph, R^2 = Et
c; R^1 = Me, R^2 = Et
d; R^1 = Me, R^2 = Bu^n
e; R^1 = Et, R^2 = Pr^n
f; R^1 = Me, R^2 = Pr^i
g; R^1 = Me, R^2 = H



(2)

The ease of cyclization and often the success or failure of a Fischer indolization depends to a large degree upon the choice of catalyst, reaction conditions, and the type of carbonyl component in the hydrazone. Different combinations of these varied considerably. No one catalyst or set of conditions can be chosen as best for all arylhydrazones or even for those which are closely related. At the present time only an empirical approach to the choice of the best combination of catalyst, solvent, and reaction temperature in the Fischer indolization can be made. In addition, the direction of indolization, which does not appear to have been very thoroughly investigated, seems to be guided by steric effects and considerations of the stabilization of the enehydrazine form,[2b] as well as by the choice of overall reaction conditions. Moreover, migration of substituents from the 3- to the 2-position can occur in several of the 2,3-substituted indoles during this indolization reaction.[3] Consequently a prediction of the direction of cyclization in the classical Fischer indolization is not possible.

As we reported previously[1] the reaction between arylhydrazones such as (4) and PCl_3 gave 2,3-disubstituted indoles (5) in good yields (70—90%) after a few minutes at room temperature [equation (2)]. This reaction could be considered at first sight to be a modification of the Fischer indolization, but it shows some important features which are not inherent in the classical Fischer indolization: (*a*) PCl_3 cannot be considered as a catalyst but is an activator because a stocheiometric amount is necessary to obtain good yields of the indoles. In fact, PCl_3 reacts immediately with the hydrazone which disappears from the reaction mixture.

(*b*) PCl_3 can be used for all ketone arylhydrazones such as (4) with good results.

(*c*) The reaction is always carried out at room temperature and consequently side reactions are minimized.

(*d*) In the reaction with PCl_3 it is possible to place specific groups in the 2- and 3-positions: no transposition of substituents between the 2- and the 3-position is observed.

For these reasons, which contrast with classical Fischer routes, the reaction with PCl_3 of type (1) unsymmetrical arylhydrazones should give only one of the two possible indoles, and it might be possible to predict the direction of indolization. In Table 1 are reported the results of this reaction in comparison with the corresponding Fischer reaction. The indoles, obtained in good yields, were isolated by standard techniques and their structures were assigned essentially by ^1H n.m.r. spectroscopy (see Table 2) and confirmed by comparison with authentic samples. Table 1 shows that, in several cases, the reaction at room temperature of the hydrazone (1) with PCl_3 is highly regioselective, giving exclusively or prevalently only one of the two possible indoles. In particular, from 1-phenylbutan-2-one phenylhydrazone (1a) we obtained 2-ethyl-3-phenylindole (2a) in good yield (61%) with small amounts (10%) of 2-benzyl-3-methylindole (3a). In contrast, the corresponding Fischer reaction is reported to give only the latter indole. From 1-phenylpentan-2-one phenylhydrazone (1b) and hexan-3-one phenylhydrazone (1c) we obtained exclusively 3-phenyl-2-n-propylindole (2b) and 3-methyl-2-n-propylindole (2c), respectively. The corresponding Fischer routes (EtOH, HCl) give a mixture of the two

Table 1. Reaction of phenylhydrazones (1) with PCl_3 to give indoles (2) and/or (3)

Hydrazone	Yield of indoles (%)		Fischer route, (2) : (3)	Ref.
(1a)	(2a) 61	(3a) 10	0 : 52	*a*
(1b)	(2b) 65		47 : 15	*b*
(1c)	(2c) 61		*c*	*d*, *b*
(1d)	(2d) 55	(3d) 16	*c*	*b*
(1e)	(2e) 41	(3e) 36	*c*	*b*
(1f)	(2f) 58		51 : 0	*e*, *b*
(1g)	(2g) 74		48 : 0	*f*

[a] E. F. J. Janetzky and P. E. Verkade, *Recl. Trav. Chim. Pays-Bas*, 1945, **64**, 129. [b] Fischer route (EtOH, HCl) carried out at refluxing temperature in our laboratory. [c] Complex mixture. [d] A. E. Arbuzov and I. A. Zaitzev, *Trans. Butlerov Inst. Chem. Tech. Kazan.*, N.1, 33, 1934 (*Chem. Abstr.*, 1935, **29**, 4006). [e] Ng. Ph. Buu-Hoi and R. Royer, *Recl. Trav. Chim. Pays-Bas*, 1947, **66**, 305. [f] A. H. Jackson and P. Smith, *Tetrahedron*, 1968, **24**, 2227.

possible isomers. The phenylhydrazones of butan-2-one and octan-3-one give 2,3-dimethylindole (2g) (74%) and a mixture of 3-methyl-2-n-pentylindole (2d) (55%) and 2-ethyl-3-n-butylindole (3d) (16%), respectively. The reaction of octan-4-one phenylhydrazone with PCl_3 gives a mixture of 3-ethyl-2-n-butylindole (2e) (41%) and 2,3-di-n-propylindole (3e) (36%).

In these cases the corresponding Fischer routes give similar results in the ratios of indoles but the reaction mixture is more complex showing many spots on t.l.c., perhaps owing to collateral reactions. The tabulated examples demonstrate that the degree of regioselectivity of this reaction depends on the nature of the R^1 and R^2 groups in the phenylhydrazones (1). In particular when R^1 is a phenyl or a methyl group and R^2 is an alkyl group we predominantly [*cf.* Table 1, (1a) and (1d)] or exclusively [(1b), (1c), and (1f)] obtained the corresponding 3-phenyl- or 3-methyl-indoles, respectively. When R^1 and R^2 are two different alkyl chains the reaction gives a mixture of isomers (2) and (3) in which the indole bearing the shorter chain slightly predominates. When R^1 is methyl and R^2 is hydrogen the exclusive formation of 2,3-dimethylindole is observed. It is thus clear that the direction of this indolization reaction will depend upon electronic and steric effects inherent in the two different methylene groups, and the one which will react with PCl_3 will be the more acidic one or, for groups of similar acidity, the one which has the smaller steric hindrance. Thus, for these reasons, a prediction of the direction of cyclization is possible in this indolization reaction. Moreover, the fact that in our reaction no exchange of substituents between the 2- and 3-positions was observed, at variance with the Fischer reaction, means that the positions of the substituents in the 2,3-disubstituted indoles can be assigned with certainty.

Experimental

The indoles were fully characterized by i.r., u.v., ^1H n.m.r., and mass spectroscopy and by comparison with authentic samples. The yields are based on starting ketones and on isolated products. ^1H N.m.r. spectra were recorded on a Varian EM 360L spectrometer with $CDCl_3$ as a solvent and tetramethylsilane as internal standard. M.p.s are uncorrected. The analytical samples of oily indoles were obtained by bulb-to-bulb distillation, and b.p.s given are the oven temperatures. Microanalyses were performed on the pure isomers as well as on mixtures of isomers. The results obtained were practically identical. Column chromatography was performed with Merck silica gel of particle size 0.05—0.2 mm. Commercial PCl_3 was used without further purification. Light petroleum refers to the fraction with boiling range 40—60 °C and ether to diethyl ether throughout. All solvents were dried and distilled before use.

Table 2. ^1H N.m.r. data [a] ($CDCl_3$) of indoles (2) and (3)

Compound	
(2a)	1.27 (t, 3 H, Me, *J* 7.0), 2.83 (q, 2 H, CH_2, *J* 7.0), 7.08, 7.71 (m, 9 H, aromatic), 7.93 (br, 1 H, NH)
(3a)	2.30 (s, 3 H, Me), 4.05 (s, 2 H, CH_2), 6.95—8.05 (m, 10 H, aromatic + NH)
(2b)	0.80 (br t, 3 H, Me), 1.40 (m, 2 H, CH_2), 2.60 (br t, 2 H, CH_2), 6.85—7.90 (m, 10 H, aromatic + NH)
(3b)	1.30 (t, 3 H, Me, *J* 7.0), 2.84 (q, 2 H, CH_2, *J* 7.0), 4.13 (s, 2 H, CH_2), 6.80—8.10 (m, 10 H, aromatic + NH)
(2c)	0.91 (br t, 3 H, Me), 1.55 (m, 2 H, CH_2), 2.20 (s, 3 H, Me), 2.62 (br t, 2 H, CH_2), 6.75—7.90 (m, 5 H, aromatic + NH)
(2d)	0.90 (br t, 3 H, Me), 1.35 [m, 6 H, $(CH_2)_3$], 2.58 (br t, 2 H, CH_2), 6.90—7.80 (m, 5 H, aromatic + NH)
(3d)	0.72—1.95 [m, 10 H, $(CH_2)_3CH_3$ and Me], 2.68 (q, 2 H, CH_2, *J* 7.0), 6.95—7.85 (m, 5 H, aromatic + NH)
(2e)	0.70—1.95 [m, 10 H, $(CH_2)_2CH_3$ and Me], 2.70 (q, 2 H, CH_2, *J* 7.0), 2.70 (t, 2 H, CH_2, *J* 7.0), 6.95—7.90 (m, 5 H, aromatic + NH)
(3e)	0.98 (br t, 6 H, 2 Me), 1.20—2.00 (m, 4 H, 2 CH_2), 2.68 (br t, 4 H, 2 CH_2), 6.80—7.85 (m, 5 H, aromatic + NH)
(2f)	0.82 (d, 6 H, 2 Me, *J* 7.0), 1.78 (m, 1 H, CH), 2.20 (s, 3 H, Me), 2.38 (d, 2 H, CH_2, *J* 7.0), 6.75—7.80 (m, 5 H, aromatic + NH)
(2g)	2.20 (s, 3 H, Me), 2.29 (s, 3 H, Me), 6.90—7.80 (m, 5 H, aromatic + NH)

[a] Chemical shifts in p.p.m. from Me_4Si; *J* values in Hz.

Phenylhydrazones.—These were obtained by heating the respective ketone and phenylhydrazine together in equivalent amounts at 95 °C for *ca.* 1 h or in benzene solution at reflux temperature for *ca.* 2 h. The products were dried (Na_2SO_4) in benzene and, after removal of the solvent, were used immediately.

2-Ethyl-3-phenylindole (2a).—To a solution of 1-phenylbutan-2-one phenylhydrazone (1a) (2 g, 8 mmol) in dry benzene (80 ml) was added a small excess of PCl_3 (1 ml, 11 mmol) and the mixture was allowed to react for *ca.* 1 h at room temperature. The course of the reaction was followed by t.l.c. and the immediate disappearance of (1a) was noted. After the end of the reaction the benzene solution was neutralized with saturated sodium hydrogen carbonate solution, washed with water, dried (Na_2SO_4) and evaporated. The mixture was chromatographed on a silica-gel column using as eluant light petroleum–ether (4 : 1). 2-Ethyl-3-phenylindole (2a)[4] (R_F 0.30) (61%) was obtained as a yellow oil (b.p. 175–180 °C, 1 Torr) which crystallized after distillation as white needles, m.p. 73—75 °C (picrate m.p. 135 °C).[4] A small amount (10%) of 2-benzyl-3-methylindole (3a) (R_F 0.44), m.p. 94—95 °C (picrate m.p. 140—142 °C) was also isolated. ^1H N.m.r. data of all the indoles are summarized in Table 2. It is reported (ref. *a*, Table 1) that Fischer reaction ($CuCl_2$ at 200—220 °C) gave only (3a) in 52% yield. In contrast, we have

observed that the treatment of (1a) under reflux for 3 h with ethanolic hydrogen chloride afforded a complex mixture of products (2a) and (3a).

3-*Phenyl*-2-*n*-*propylindole* (2b).—This was prepared in a similar manner from 1-phenylpentan-2-one phenylhydrazone (1b) and PCl_3 in equimolar amounts at room temperature for *ca.* 1 h. Elution with light petroleum–ether (4 : 1) gave *compound* (2b) (R_F 0.58) (65%), m.p. 65—67 °C (b.p. 160—165 °C/0.1 Torr), *m/z* 235 (M^+) (Found: C, 86.7; H, 7.3; N, 5.8. $C_{17}H_{17}N$ requires C, 86.77; H, 7.28; N, 5.96%).

No appreciable formation of isomer (3b) was observed, even after a longer reaction time. In contrast, treatment under reflux for 3 h of the phenylhydrazone (1b) with ethanolic hydrogen chloride (Fischer route) afforded a mixture of isomers (2b) and (3b) in the ratio *ca.* 4 : 1. Elution with light petroleum–ether (4 : 1) gave pure product (3b) (15%), R_F 0.62, as dark oil (b.p. 150—155 °C/0.1 Torr); *m/z* 235 (M^+).

3-*Methyl*-2-*n*-*propylindole* (2c).—This was prepared in a similar manner to the above indoles but using methylene dichloride instead of benzene as solvent. Hexan-3-one phenylhydrazone (1c) afforded, after *ca.* 3 h at room temperature, product (2c)[5] (R_F 0.52) as a pale yellow oil (61%) (b.p. 170—172 °C/1 Torr); *m/z* 173 (M^+). No formation of 2,3-diethylindole (3c)[6] was observed.

3-*Methyl*-2-*n*-*pentyl*- (2d) *and* 2-*Ethyl*-3-*n*-*butyl*-*indoles* (3d).—In a similar manner as described above the reaction between octan-3-one phenylhydrazone (1d) and PCl_3 gave a mixture of indoles (2d) and (3d) in 55 and 16% yield, respectively. The mixture was eluted with light petroleum–ether–benzene (20 : 2 : 1) giving *compound* (2d) as a pale yellow oil which darkened rapidly on exposure to air [R_F 0.30; b.p. 150–155 °C 1 Torr; *m/z* 201 (M^+)], and its *isomer* (3d) as a brown oil [R_F 0.18; b.p. 160—165 °C/1.5 Torr; *m/z* 201 (M^+)] (Found: C, 83.5; H, 9.5; N, 6.9. $C_{14}H_{19}N$ requires C, 83.52; H, 9.51; N, 6.95%).

3-*Ethyl*-2-*n*-*butyl*- (2e) *and* 2,3-*Di*-*n*-*propyl*-*indoles* (3e).—In a similar fashion the reaction between octan-4-one phenylhydrazone (1e) and PCl_3 in methylene dichloride solution gave, after *ca.* 3 h at room temperature, a mixture of indoles (2e) and (3e) in 41 and 36% yield, respectively. Elution with light petroleum–ether–benzene (20 : 2 : 1) gave *product* (2e) [R_F 0.30; b.p. 150—155 °C 0.5 Torr; *m/z* 201 (M^+)] and its *isomer* (3e) [R_F 0.14; b.p. 140—150 °C/0.4 Torr; *m/z* 201 (M^+)] as pale yellow oils (Found: C, 83.6; H, 9.6; N, 6.9. $C_{14}H_{19}N$ requires C, 83.52; H, 9.51; N, 6.95%).

The aliphatic regions of the ^1H n.m.r. spectra (see Table 2) of compounds (2e), (3e), (2d), and (3d) were complex and insufficiently well resolved to analyse, but inspection and comparison of these spectra permitted an easy assignment of indole structures. In particular, compounds (2e) and (3d), having almost identical ^1H n.m.r. spectra but different R_F values on t.l.c., will be effectively positional isomers.

2-*Isobutyl*-3-*methylindole* (2f).—This was prepared in a similar manner from 5-methylhexan-3-one phenylhydrazone (1f) and PCl_3 in equimolar amounts at room temperature for *ca.* 2 h. Elution of the reaction mixture with light petroleum–ether (4 : 1) gave product (2f) (58%) as a pale yellow oil [R_F 0.23; b.p. 145—146 °C/3 Torr; *m/z* 187 (M^+)].

No appreciable formation of the isomer (3f) was observed.

2,3-*Dimethylindole* (2g).—In a similar manner the reaction between butan-2-one phenylhydrazone (1g) and PCl_3 in methylene dichloride solution afforded the product (2g) (74%) after 4 h at room temperature. The indole was isolated from the reaction mixture by crystallization from ether or by column chromatography with light petroleum–ether (4 : 1) as eluant; R_F 0.29, m.p. 105—106 °C.

Acknowledgements

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