Tetrahedron Vol. 41, No. 20, pp. 4615 to 4620, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

SUBSTITUENT INFLUENCE ON THE INDOLIZATION WITH PCl_3 OF SOME o,m,p-SUBSTITUTED PHENYLHYDRAZONES

Graziano Baccolini*, and Emanuela Marotta

Istituto Chimica Organica, Università, Viale Risorgimento 4,
40136 Bologna, Italy

(*Received in UK* 14 *May* 1985)

Abstract - The indolization of deoxybenzoin o,m,p (Me, MeO, Cl), p-NO_2 and m-EtO-phenylhydrazones (1) by the above reaction has been examined. All the reactions are carried out at room temperature and high yields of the corresponding indoles (2) are obtained even when $-NO_2$ substituent is present. In this case longer reaction time is necessary. Alkoxyphenylhydrazones give the corresponding indoles (2) in high yields without showing collateral reactions which indeed are present in several Fischer routes on these derivatives. m-Substituted phenylhydrazones (1) give a mixture of 4- and 6-substituted indoles in which the 6-isomer is always prevalent, a feature not inherent in the Fischer reactions. The regioselectivity is enhanced by the substituent steric hindrance increasing. The reaction can be also carried out at 0°C with a further improvement of its regioselectivity.

The purpose of our recent research[1,2,3] is the development and generality of a new synthetic method which involves the indolization at room temperature of ketone arylhydrazones by the action of PCl_3.

This reaction could be considered at first sight to be a modification of the Fischer indolization but, as we reported previously,[3] it shows some important features which are not inherent in the classical Fischer indolization or in its modifications. a) The reaction is always carried out at room temperature, b) PCl_3 is an activator which can be used for all ketone arylhydrazones with no appreciable change in the yields,[1,2] c) the reaction is highly regioselective[3] when unsymmetrical ketones are used and a prediction of the direction of cyclization is possible.

Now we wish to study the influence of aryl substituents (X) (Me, MeO, EtO, Cl, NO_2) of phenylhydrazones (1) on the indolization with PCl_3 in comparison with the Fischer routes.

It should be noted that in the Fischer indolization[4] the results obtained with these different substituents are not always comparable because the product yield and the isomer ratio was found to depend on the catalyst employed. In addition it has been found[5] that Fischer indolization of many o-methoxyphenylhydrazones under various conditions gave a variety of unexpected indole products together with the

expected methoxyindole. Moreover, it was found[6] that in several cases o-substituents also promoted side reactions and then the ultimate yield of indoles in such abnormal Fischer indolizations is therefore often low.

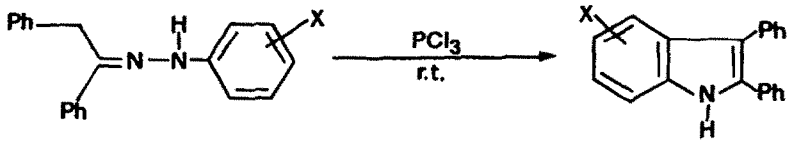
In connection with these observations we have carried out our reaction with phenylhydrazones (1) to investigate if in our mild conditions of indolization side reactions are minimized and if the reaction is regioselective when m-substituted phenylhydrazones are used.

In Table 1 are reported the results obtained with our procedure in comparison with the corresponding reported better Fischer routes. All the reactions are carried out at room temperature. The reaction does not appear to be very solvent dependent. However, of the various solvent used, we have found methylene chloride to be the most convenient. Indoles (2) were isolated by standard techniques and their structure were assigned essentially by ^{1}H n.m.r., mass spectroscopy and confirmed by comparison with authentic samples. In particular, the assignment of isomers 6-(Cl,MeO,EtO) and 4-(Cl,MeO,EtO) isomer was confirmed by their ^{1}H n.m.r. spectra carried out at 300 MHz (see Table 2). High yields of indoles were obtained in each case in contrast with the reported Fischer reactions in which different catalyst and drastic reaction conditions are necessary for obtaining high yields of products. For example, the reaction of deoxybenzoin m-tolylhydrazone with acetic acid and boron trifluoride gave,[7a] under reflux, (**2d**) in about 31%, while the same reaction gave (**2c**) and (**2d**) in 87% yield if carried out with anhydrous zinc chloride at 230°C (see Table 1 ref. d).

Table 1. Indolization of phenylhydrazones (1) with PCl_3 to give indoles (2)

X in (1)	X in (2) (isomers ratio)	Yield (%)	Fischer[a]	Ref.
p-Me	5-Me (**2a**)	85	82	b
o-Me	7-Me (**2b**)	72	65	c
m-Me	4-Me (**2c**):6-Me (**2d**) (2 : 3)	80	87	d
p-OMe	5-OMe (**2e**)	71	60	b
o-OMe	7-OMe (**2f**)	70	40	c
m-OMe	4-OMe (**2g**):6-OMe (**2h**) (1 : 3)	65	32	b
p-Cl	5-Cl (**2i**)	91	90	b
o-Cl	7-Cl (**2l**)	71	51	d
m-Cl	4-Cl (**2m**):6-Cl (**2n**) (2 : 3)	58	37	b
p-NO_2	5-NO_2(**2o**)	58	50	b
m-OEt	4-OEt (**2p**):6-OEt (**2q**) (1:4) or (1:5)[e]	81	45	c

[a] The selected routes were carried out under different conditions. [b] D.W. Ockenden and K. Schofield, J.Chem.Soc., 1957, 3175. [c] Fischer route (EtOH, HCl) carried out at refluxing temperature in our laboratory. [d] M.W.G. Coldham, J.W. Lewis, and S.G.P. Plant, J.Chem.Soc., 1954, 4528. [e] Reaction carried out at 0°C for about 5 h.



(1) (2)

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

Compound	
(2a)	2.45 (s,3H,CH_3), 7.00-8.00 (m,13H, aromatic) 8.12 (bs,1H,NH)
(2b)	2.53 (s,3H,CH_3), 6.70-8.40 (m,13H, aromatic) 8.60 (bs,1H,NH)
(2c)	2.15 (s,3H,CH_3), 6.90-7.80 (m,13H, aromatic) 8.27 (bs,1H,NH)
(2d)	2.50 (s,3H,CH_3), 6.90-7.80 (m,13H, aromatic) 8.10 (bs,1H,NH)
(2e)	3.87 (s,3H,OCH_3), 6.80-7.80 (m,13H, aromatic)
(2f)	4.00 (s,3H,OCH_3), 6.60-7.90 (m,13H, aromatic) 8.60 (bs,1H,NH)
(2g)[b]	3.75 (s,3H,CH_3O), 6.62 (dd,1H,H_5,$J_{5,6}$8.0,$J_{5,7}$1.5), 7.12 (dd,1H,H_7 $J_{7,6}$8.0, $J_{7,5}$1.5), 7.20 (t,1H,H_6, $J_{6,5}$8.0); 7.25-7.60 (m,10H, aromatic), 8.34 (bs,1H,NH)
(2h)[b]	3.86 (s,3H,CH_3O), 6.81 (dd,1H,H_5,$J_{4,5}$8.5,$J_{5,7}$2.0, 6.90 (d,1H,H_7, $J_{5,7}$2.0), 7.20-7.64 (m,11H, aromatic), 8.14 (bs,1H,NH)
(2i)	7.05-7.50 (m,12H, aromatic), 7.65 (bs,1H,H_4), 8.20 (bs,1H,NH)
(2l)	6.85-7.60 (m,13H, aromatic), 8.40 (bs,1H,NH)
(2m)[b]	7.09 (dd,1H,$H_5J_{5,7}$1.5, $J_{5,6}$7.5), 7.14 (t,1H,H_6, $J_{6,5}$7.5), 7.30-7.54 (m,11H, aromatic), 8.40 (bs,1H,NH)
(2n)[b]	7.11 (dd,1H,H_5,$J_{4,5}$8.5,$J_{5,6}$2.0) 7.24-7.44 (m,11H, aromatic), 7.55 (d,1H,H_4,$J_{4,5}$8.5) 8.18 (bs,1H,NH)
(2o)	7.30-8.35 (m,12H, aromatic), 8.75 (d,1H,H_4,$J_{4,6}$2.0), 8.90 (bs,1H, NH)
(2p)[b]	1.08 (t,3H,CH_3,J 7.0), 3.90 (q,2H,CH_2,J 7.0), 6.48 (dd,1H,H_5,$J_{5,6}$ 8.0, $J_{5,7}$ 1.5), 7.00 (dd,1H,H_7,$J_{7,6}$ 8.0, $J_{7,5}$ 1.5), 7.10 (t,1H, H_6,$J_{6,5}$ 8.0), 7.16-7.60 (m,10H, aromatic), 8.16 (bs,1H,NH)
(2q)[b]	1.40 (t,3H,CH_3,J 7.0), 4.04 (q,2H,CH_2,J 7.0), 6.80 (dd,1H,H_5,$J_{4,5}$ 9.0,$J_{5,7}$ 2.0), 6.84 (d,1H,H_7,$J_{5,7}$ 2.0), 7.20-7.50 (m,11H, aromatic) 8.22 (bs,1H,NH).

[a] Chemical shifts in p.p.m. from Me_4Si; J values in Hz. [b] Spectra recorded at 300 MHz

However, it should be noted that p-nitrophenylhydrazone (1) was indolized much more slowly than all the other hydrazones (1), even when a large excess of PCl_3 was used. The time necessary for the reaction to be complete was about few minutes for Me-, MeO- and EtO-substituents, two hours for Cl-substituent and five days for NO_2-substituent. Even if the reaction time for NO_2-derivative is longer than the corrisponding Fischer route[7a] (3 h) our method offers the advantage to be applicable to the preparation of indole derivatives with functionality which would be sensitive to elevated temperatures.

As can be seen from comparison of the data in Table 1, one of the most remarkable advantages of our reaction over the Fischer cyclization is the high yield obtained from alkoxyphenylhydrazones, particularly o-methoxyphenylhydrazones. This is due to the fact that collateral reactions are minimized in our reaction in contrast to the Fischer indolization of o-methoxyphenylhydrazones in which, under various conditions, a variety of unexpected indole products were formed together with the normally expected substituted indole.[5]

Additionally, our reaction results to be regioselective when m-substituted phenylhydrazones are used.

In contrast, the Fischer indolization of m-substituted phenylhydrazones gives ambiguous results in the ratio of 6- and 4-substituted indoles.[4,7] In particular, using boron trifluoride etherate as reagent, deoxybenzoin m-tolylhydrazone gave[7a] a small yield of 6-methyl-2,3-diphenylindole, m-methoxyphenylhydrazone gave a small yield of 6- (or 4)-isomer as an uncharacterized product, while the m-chloro-phenylhydrazone gave a fair yield of 4-chloro isomer. In the Fischer reaction the explanation of these different proportions of isomers was attributed to different electron-donating effects of the substituents but was also found to depend on the catalyst employed and then on the overall reaction conditions.[8]

We have found that indolization with PCl_3 of m-substituted phenylhydrazones (**1**) gave a mixture of 6- and 4-isomers in which the 6-isomer was always prevalent. When the substituents were Me and Cl the ratio was about 3:2, when the substituent was MeO the ratio was 3:1 and when the substituent was EtO the ratio was 4:1. In our cases which identical reaction conditions are used we think that steric effects play an important role in determining the prevalence of the 6-isomer over the 4-isomer even when there are different electronic effects. In fact this prevalence is higher the EtO-derivative than in the other derivatives. The fact that 6-isomer is always prevalent can be used for an easy, immediate assignment of the two isomers before using spectroscopic or alternative analyses. In addition we have found than our reaction can be also carried out at 0°C with conseguent increasing of the regioselectivity: in this condition the ratio between 6- and 4-EtO-isomer became 5:1.

In conclusion, our procedure for obtaining 2,3-substituted indoles is a general method which tolerates several substituents on the aromatic ring of phenylhydrazones giving always at room temperature the corresponding indole in good yields; when m-substituted phenylhydrazones are used the reaction is also regioselective and it affords a mild condition synthesis of certain indoles such as 5- and 7-methoxyindoles, which are of importance in natural product chemistry.

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. ^1H n.m.r. spectra were recorded on a Varian EM 360L spectrometer and a Bruker C.X.P. 300 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. Column chromatography was performed with Merck silica gel of particle size 0.05-0.2 mm. Commercial PCl_3 was used without further purification.

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

2,3-Diphenyl-5-methylindole (2a).- To a solution of deoxybenzoin p-tolylhydrazone (**1a**) (3 g, 10 mmol) in dry CH_2Cl_2 (200 ml) was added a small excess of PCl_3 (1,1 ml, 12 mmol) and the mixture was allowed to react for ca. 15 min at room temperature. The course of the reaction was followed by t.l.c., the immediate disappearance of (**1a**) and the concomitant appearance of (**2a**) was noted. The reaction mixture 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) and after crystallization from n-hexane 2,3-diphenyl-5-methylindole was obtained in 80% yield. [R_F 0.38; m.p. 151-152°C] (lit.[7a] m.p. 150-151°C).
^1H N.m.r. data of all the indoles (2) are summarized in Table 2.

2,3-Diphenyl-7-methylindole (**2b**).- This was prepared in a similar manner from deoxybenzoin o-tolylhydrazone and a small excess of PCl_3 at room temperature for ca. 15 minutes. Elution with light petroleum-ether (4:1) gave compound (**2b**) [(R_F 0.34) (72%), m.p. 128-129°C, m/z 283 (M^+)] (lit.[8] m.p. 128-129°C).

2,3-Diphenyl-4-methyl- (**2c**) and 2,3-Diphenyl-6-methylindoles (**2d**). The reaction between deoxybenzoin m-tolylhydrazone and a small excess of PCl_3 gave after ca. 15 minutes at room temperature (**2c**) and (**2d**) (80% overall yield) in a ratio of 2:3. Elution with light petroleum-ether-benzene (30:1:1) gave product (**2d**) as pale yellow glass [R_F 0.10; b.p. 150-160°C 0.1 Torr; m.p. 68-75°C; m/z 283 (M^+)] (lit.[7a] b.p. 240-260°C 7 Torr; m.p. 70-80°C) and its isomer (**2c**) as brown syrup [R_F 0.07; b.p. 170-180°C 0.1 Torr; m/z 283 (M^+)] (lit.[7a] dark oil, lit.[7c] m.p. 134-135°C).[10] The ratio of isomers was determined by integration of methyl peaks in the ^1H n.m.r. spectra of reaction mixture.

2,3-Diphenyl-5-methoxyindole (**2e**).- This was prepared from deoxybenzoin p-methoxyphenylhydrazone and PCl_3 at room temperature for ca. 10 minutes. Elution of the reaction mixture with light petroleum-ether (4:1) gave pure indole (**2e**) as white crystals (71%) [R_F 0.18; m.p. 154- 156°C] (lit.[7a] 155-156°C).

2,3-Diphenyl-7-methoxyindole (**2f**).- As above the reaction between deoxybenzoin o-methoxyphenylhydrazone and PCl_3 gave (**2f**) after ca. 10 minutes at room temperature. After chromatographic separation using the same eluant the indole (**2f**) (70%) was obtained as white crystals from light petroleum [R_F 0.27, m.p. 150-152°C; m/z 299 (M^+)] (lit.[11] m.p. not available).

2,3-Diphenyl-4-methoxy- (**2g**) and 2,3-diphenyl-6-methoxyindole (**2h**).- The reaction between deoxybenzoin m-methoxyphenylhydrazone and PCl_3 in equimolar amounts gave, after ca. 30 minutes at room temperature, a mixture of (**2g**) and (**2h**), (65%) in a ratio of about 1:3. Elution with light petroleum-ether (4:1) gave product (**2g**) as a yellow gum which crystallised from light petroleum [R_F 0.23, m.p. 138-140°C] (lit.[7b] m.p. 146-147°C; m.p.[7b] 136-140°C) and its isomer (**2h**) as white crystals [R_F 0.11, m.p. 203-204°C] (lit.[7b] m.p. 203°C).

5-Chloro-2,3-diphenylindole (**2i**).- This was prepared from deoxybenzoin p-chlorophenylhydrazone and PCl_3 at room temperature for about 2 h. Elution of the reaction mixture with light petroleum-ether (6:1) gave product (**2i**), (91%) as white crystals [R_F 0.12, m.p. 126-128°C, m/z (303 (M^+)] (lit.[7a] m.p. 128-130°C).

7-Chloro-2,3-diphenylindole (**2l**).- In a similar manner the reaction between deoxybenzoin o-chlorophenylhydrazone and PCl_3 afforded the product (**2l**) (71%) after 2 h at room temperature. The indole was isolated from the reaction mixture by column chromatography with light petroleum-ether (6:1) as eluant [R_F 0.37, m.p. 95-96°C; m/z 303 (M^+)] (lit.[7c] m.p. 96-97°C).

4-Chloro- (**2m**) and 6-chloro-2,3-diphenylindoles (**2n**).- In a similar fashion the reaction between deoxybenzoin m-chlorophenylhydrazone and PCl_3 in methylene dichloride solution gave, after ca. 2 h at room temperature, a mixture of indoles (**2m**) and (**2n**) in a ratio of 2:3. Elution with light petroleum-ether (6:1) gave

product (**2m**) |R_F 0.13, m.p. 165-166°C; m/z 303 (M^+)| (lit.[7a] m.p. 165-167°C) and its isomer (**2n**) |R_F 0.20, m.p. 102-105°C; m/z 303 (M^+)| (Found: C, 79.2; H, 4.7; N, 4.6. $C_{20}H_{14}NCl$ requires C, 79.2; H, 4.6; N, 4.6%).

2,3-Diphenyl-5-nitroindole (**2o**).- The reaction between deoxybenzoin p-nitrophenylhydrazones (2g, 6 mmol) in dry CH_2Cl_2 (200 ml) and a large excess of PCl_3 (1.5 ml, 18 mmol) gave, after 5 days at room temperature, the product (**2o**) (58%).[3] The reaction mixture was eluted with light petroleum-ether (2:1) giving compound (**2o**) as yellow crystals |R_F 0.13, m.p. 195-198°C| (lit.[7a] m.p. 198-200°C).

4-Ethoxy- (**2p**) and 6-Ethoxy-2,3-diphenylindoles (**2q**). In a similar fashion deoxybenzoin m-ethoxyphenylhydrazone and PCl_3 in equimolar amounts gave after ca 30 minutes, a mixture of (**2p**) and (**2q**) (81%) in a ratio of about 1:4. Elution with light petroleum-ether (3:1) gave product (**2p**) as white crystals |R_F 0.31, m.p. 160-162°C| and its isomer (**2q**) as white crystals |R_F 0.20, m.p. 162-164°C; m/z 313 (M^+)|. (Found: C, 84.4; H, 6.1; N, 4.4. $C_{22}H_{19}NO$ requires C, 84.3; H, 6.1; N, 4.4%).
When the reaction was carried out at 0°C the time necessary for going to completion was about 5 h and the ratio between (**2p**) and (**2q**) became 1:5.
The aromatic regions of the ^1H n.m.r. spectra of compounds (**2g**), (**2h**), (**2m**), (**2n**), (**2p**), (**2q**) were very complex but, when these spectra were recorded at 300 MHz, a careful examination of the peaks due to H_4, H_5, H_6, H_7 protons permitted to distinguish between 4- and 6-isomer (See Table 2). In particular, compound (**2h**) showed a peak at 6.90 δ as a doublet ($J_{5,7}$=2 Hz) which can easy attributed to H_7 of 6-isomer; while compound (**2g**) showed a peak at 7.12δas a doublet of doublet ($J_{7,6}$=8 Hz, $J_{5,7}$=1.5 Hz) which can be assigned to H_7 of 4-isomer. The assignment of all the other protons were in agreement with these structures. Similar assignments were given to the couples of isomers (**2m**), (**2n**) and (**2p**), (**2q**).

Acknowledgements

We thank the Highfield ^1H n.m.r. service of C.N.R. (Bologna) for running the ^1H n.m.r. spectra and Mr. Dante Macciantelli for useful discussions. Thanks are also due to C.N.R. for financial support.

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