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# ROLE OF PHOSPHORUS ADDUCTS IN THE INDOLIZATION REACTION BETWEEN ARYLHYDRAZONES AND PHOSPHORUS TRICHLORIDE

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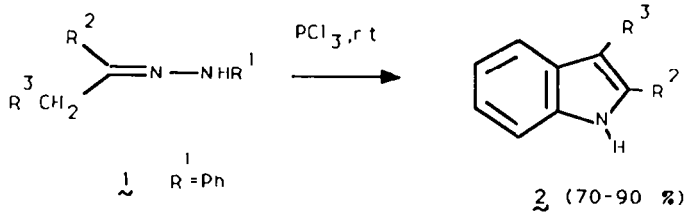
**Abstract.** The reaction between arylhydrazones and $PCl_3$ can give both diazaphospholes and indoles, via a common hypothetical diazaphospholine intermediate. The product ratio depends on the reaction conditions. In particular when a solvent which dissolves the phosphorus adducts is employed, indole is the almost exclusive reaction product. A mechanism is suggested for the whole indolization reaction. It involves an acid promoted cleavage of the P-N bond of the diazaphospholine to give intermediates similar to those of the accepted Fischer indolization mechanism, where the dichlorophosphino group, substituting a hydrogen atom should have an important role in promoting of the loss of the amino group in the last stage of the reaction, via a "Wittig-like" elimination of $Cl_2PNH_2$.

Recently we reported a general method[1] for the synthesis of 2,3-disubstituted indoles 2 by reaction of ketone arylhydrazones 1 with phosphorus trichloride, at room temperature (see Scheme 1).

SCHEME 1




1 R = Ph

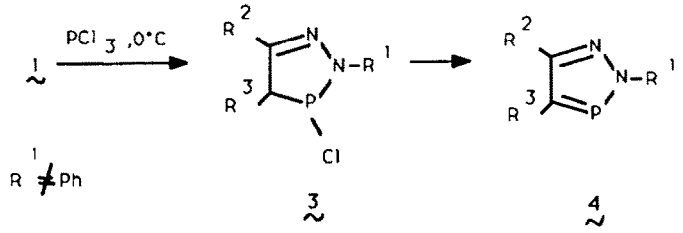
2 (70-90 %)

On the other hand, it is known[2] that the reaction of alkylhydrazones 1, ($R^1 \neq Ph$) with phosphorus trichloride leads to the diazaphosphole 4. It is reported[3] that the diazaphospholine 3 or its ionic form is an intermediate in this reaction and in some specific cases it was isolated.[2a] (see Scheme 2)

It is reported[2] too, that it is very difficult to obtain diazaphosphole 4 starting from phenylhydrazones.

At first sight, this reaction could appear in contrast with our results, but, actually, it is useful to give an explanation of the indolization with $PCl_3$. Very likely, in fact, the difficult in obtaining 2-phenyl-1,2,3-diazaphosphole might be due to the formation of indoles also under the reported conditions (e.g. $Et_2O$,

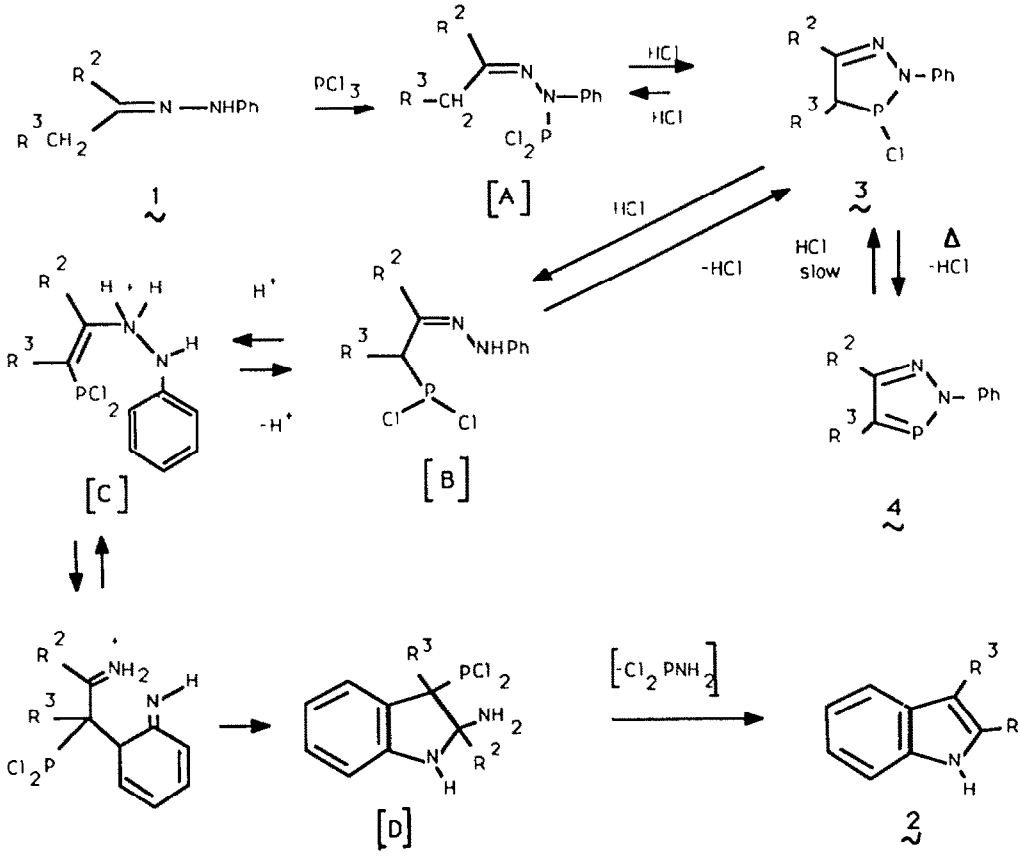
SCHEME 2



0°C).

In this paper we wish to propose a possible mechanism to explain both indole and diazaphosphole formation, based on a common intermediate which should be the diazaphospholine 3.

SCHEME 3



The hypothesized mechanism is depicted in Scheme 3 and can be summarized as follows: the reaction presumably proceeds by double nucleophilic attack on phosphorus to give the dihydrodiazaphosphole 3 with elimination of two moles of hydrogen chloride.

Subsequently this compound could evolve in two different ways:

i) it could give the diazaphosphole 4, as previously reported;[2]

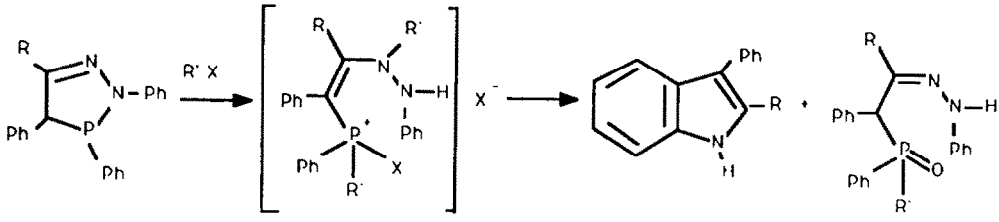
ii) it could lead to indole 2 with a pathway which consists essentially in a ring-opening step, followed by a pathway similar to the generally accepted Fischer indolization mechanism.[4]

Some of our results, in part reported previously, may support the hypothetical mechanism.

Since, the nucleophilicity of the anilino-nitrogen is clearly greater than that of the carbon, we speculate at first a displacement of a chlorine of the $PCl_3$ by this nitrogen atom. On the other hand, it is noteworthy that the indolization rate depends on steric effects inherent in the methylene groups in the α-position of the C=N double bond (i.e. the rate is faster when these groups have a small steric hindrance).[1b] This effect can be a support to the necessity of the formation of a C-P bond. The necessity of a ring closure has been also suggested by the formation of indole in the reaction of phenylhydrazones with $PCl_5$[1a] and $PhPCl_2$. By way of contrast, no indole formation was observed in the reaction with $Ph_2PCl$,[5] where only one mole of HCl can be eliminated and consequently dihydrodiazaphosphole such as 3 cannot be formed.

Once formed, the diazaphospholine 3[6] can be opened by the hydrogen chloride present in the reaction mixture. We have previously found that compounds related to 3 can easily undergo a ring-opening process in a feeble acidic medium.[7] In addition, we observed previously[8] the formation of substituted indole 6 as the major product and of ring-opened compound 7 as by product from the reaction of 2,3,4-triphenyl-5-R-1,2,3-diazaphospholine 5 with alkyl halides (see Scheme 4).

SCHEME 4



5 6 (40 %) 7 (15 %)

As a consequence of the above results, we have hypothesized now the formation of a ring opened intermediate such as [B] (see Scheme 3).

The HCl plays a fundamental role in promoting this step. When freshly distilled $PCl_3$ is used, hydrogen chloride is absent at the beginning of the reaction. Only after several minutes does it reach a suitable concentration to promote the ring-opening step and consequently the whole reaction is slower. On the other hand, the use of crude $PCl_3$ makes the process faster, since the adventitious HCl is enough to open the intermediate 3. Obviously, the presence of $PCl_3$ is essential. In fact, when the reaction is carried out under our conditions ($CH_2Cl_2$, r.t.) exclusively in the presence of a large excess of HCl, no indole formation was observed.

The presence of a $PCl_2$-group bonded to the carbon enhances the acidity of the α-hydrogen, favouring the enehydrazine tautomer [C] with respect to [B].

Supporting evidence of a Fischer-like mechanism from [C] to [D] (Scheme 3) comes from the effect of substituents in the phenyl ring.[1c]

Finally, we have explored the possibility to have experimental evidences on

the formation of some of the above hypothesized intermediates carrying out the reaction of butan-2-one phenylhydrazone (**1a**, $R^2$=$R^3$=Me) with $PCl_3$. In fact, this reaction is reported to give a mixture of the two isomeric diazaphospholes **4a** ($R^2$=$R^3$=Me) and **4b** ($R^2$=Et,$R^3$=H)[9] when the hydrazone is allowed to react with three moles of $PCl_3$ in $Et_2O$ at 0°C. On the other hand, under our experimental conditions ($CH_2Cl_2$, room temperature, one mole of $PCl_3$), 2,3-dimethylindole is obtained in 74% yield.[1b]

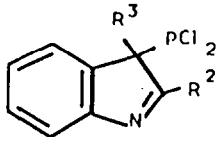
Repeating the first reaction, we observed by g.l.c.-m.s. analysis also the formation of indole **2a** (30-60% yield) together with the expected diazaphospholes **4a** and **4b**. It should be noted that repeating the reaction several times, very variable yields and relative ratios were obtained. In adddition following the reaction by t.l.c., $^{31}P$ and $^{1}H$-n.m.r. analyses we found that compounds **4a** and **4b** are not present in the reaction mixture but we observed them only after distillation or heating the crude of the reaction. Very likely, the diazaphospholes are present in the mixture in their hydrochloride form ("phosphenium chloride").[6,2b]

Moreover, adding $CH_2Cl_2$ to this reaction mixture several hours after the mixing of the reactants, a high increase in indole **2a** despite of **4a** and **4b** formation was observed at 0°C, too. Presumably, an increase of the solubility of phosphorus adducts occurs favouring a different course of the reaction.

Finally, bubbling HCl in a $CH_2Cl_2$ solution of **4a**, it was converted very slowly to indole **2a**; on the other hand, under the same conditions, no indole formation was observed with the isomer **4b**, in agreement with our previous results.[1b] The absence of an alkyl group ($R^3$=H) in the enehydrazine tautomer [C] can be responsible of a slower enolization and the inductive effect of an alkyl group eases the new C-C bond formation in the indolization. This effect is also observed in the Fischer reaction.[3]

Monitoring by g.l.c.-m.s. analysis the reaction of **1a** with $PCl_3$ under our conditions, we were able to observe the disappearance of hydrazone **1a**, and the concomitant formation of diazaphospholes **4a** and **4b** together with indole **2a**.

Subsequently, an increase of **2a** and a decrease of **4a** and **4b** was detected together with two new compounds, the fragmentation pattern of which is consistent with the following structures: $Cl_2PNH_2$ and 2,3-dimethyl-3-dichlorophosphino-3H-indole (**8**).




**8**

Finally, after several hours we observed only the presence of **2a** and small amounts ( 10%) of **4b**. After aqueous quenching of the crude of the reaction we noted the disappearance of **4b** and the reappearance of small amounts of starting hydrazones **1a**.

It should be outlined that the presence of diazaphospholes **4a** and **4b** were not detected by $^{31}P$ and $^{1}H$-n.m.r. and t.l.c. analyses and these findings support the hypothesis of their formation only after heating from a precursor. In addition,

the peak attributed to the aminodichlorophosphine was observed only when the reaction and the sampling were carried out under a dry nitrogen atmosphere. The presence of this compound supports the formation of an intermediate such as |D| which gives **2a** via a "Wittig-like" elimination of $Cl_2PNH_2$. In our knowledge, this is the first example of such a type of elimination.

The presence of intermediate [D] is also supported by the formation of compound **8** which may arise by thermal elimination of ammonia from [D] in the gas-chromatograph injector. Attempts to isolate this compound from the reaction mixture were unsuccessful. According to our hypothesis, under our reaction conditions, intermediate [D] prefers to eliminate $Cl_2PNH_2$ instead of $NH_3$ giving indole **2a**. It was impossible to isolate compound **8**, even if the reaction was carried out at reflux. We exclude the formation of the 1-dichlorophosphino-2,3-dimethylindole rather than **8** on the basis of the following findings:

i) if compound **8** arises from indole **2a** by reaction with the slight excess of $PCl_3$, its concentration must increase increasing the indole one. On the contrary, compound **8** disappeared by prolonging reaction times.

ii) Submitting to g.l.c.-m.s. analysis under the same reaction and analytical conditions a mixture of $PCl_3$ and **2a**, compound **8** is revealed only in traces.

In our opinion, these results support clearly that the mechanism must involve dihydrodiazaphospholes **3** or their hydrochloride as common intermediates in both indole and diazaphosphole formation. These intermediates by heating (distillation or in the injector chambre) lead to diazaphospholes **4**. In a medium which dissolves all the possible phosphorus adducts in a good extent (e.g. $CH_2Cl_2$), compounds **3** can be in equilibrium with the ring-opened compounds |B| which lead to indoles **2** in an irreversible manner. The phosphorus moiety in this mechanism should have the important role of activator of the whole reaction and then it permits the indolization process under very mild conditions.

## EXPERIMENTAL

$^1$H-N.m.r. spectra were recorded with a Varian EM360L instrument. Chemical shift are given in p.p.m. from tetramethylsilane as internal standard. $^{31}$P-N.m.r. spectra were recorded with a Varian XL-100 instrument. Positive values indicate downfield shifts from an 85% aqueous $H_3PO_4$ as external standard. G.l.c.-m.s. analyses were carried out with an HP 5997O workstation formed by an HP-5890 gas-chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass-detector.

Reaction of butan-2-one phenylhydrazone **1a** with $PCl_3$ in $Et_2O$.

The reaction was carried out as previously reported.[9] In particular; a solution of **1a** (3.2 g) in 3 mL of anhydrous $Et_2O$ was added dropwise to a stirred solution of $PCl_3$ (5.2 mL) in 20 mL of $Et_2O$ during an hour, at 0°C. The reaction mixture was allowed to stand at 0°C overnight and then filtered. The ethereal solution was evaporated under reduced pressure and the residual was distilled under vacuum (102-5°C, 0.1 mm/Hg) to obtain a mixture of 5-ethyl-2-phenyl-2H-1,2,3-diazaphosphole (**4b**) and 4,5-dimethyl-2-phenyl-2H-1,2,3-diazaphosphole (**4a**). Small amounts of pure **4a** and **4b** were obtained after chromatography on silica gel (light petroleum: diethyl ether 4:1 as eluant). The t.l.c. and $^{31}$P-n.m.r. analyses of the reaction mixture before distillation does not reveal the presence of compound **4a** and **4b**.

**4a**: $R_f$=0.52, yellow oil, $^1$H-n.m.r. ($CDCl_3$) $\delta$ 2.20 (d, 3H, 5-$CH_3$, $J_{P-CH}$=14.0 Hz); 2.33 (d, 3H, 4-$CH_3$, $J_{P-CH}$=1.5 Hz); 7.00-8.10 (m, 5H, Ph); m/z = 190 ($M^+$); 175; 148; 122; 107; 86; 51; $^{31}$P-n.m.r. ($CDCl_3$) 219, p.p.m.

**4b**: $R_f$=0.60, yellow oil, $^1$H-n.m.r. ($CDCl_3$) $\delta$ 1.23 (t, 3H, $CH_3$, $J_{CH_3-CH_2}$ = 7.0 Hz); 2.85 (dq., 2H, $CH_2$, $J_{P-CH}$ = 1.0 Hz); 7.00-8.10 (m, 6H, Ph and H-4); m/z = 190 ($M^+$); 175; 161; 135; 122; 107; 77; 51; $^{31}$P-n.m.r. ($CDCl_3$) 226 p.p.m.

Most of the distillation residual was recognized as 2,3-dimethyl indole (**2a**) by comparison with authentic sample and by its mass spectrum: m/z = 145 ($M^+$); 144; 130; 115; 107; 77. Running out a series of experiment the yield in **2a** varied from 30 to 60%, the global yield in **4a+4b** from 60 to 20% and the **4a:4b** ratio from 3:2 to 2:3.

Reaction of butan-2-one phenylhydrazone **1a** with $PCl_3$ in $CH_2Cl_2$.

To a solution of **1a** (1.62 g) in $CH_2Cl_2$ was added a small excess of $PCl_3$ (1.0 mL) and the mixture was allowed to react at room temperature, adding if necessary further $CH_2Cl_2$ to ensure the lack of precipitates. The course of the reaction was followed by g.l.c.-m.s. analysis. The chromatogram showed the following results.

After few minutes the chromatogram showed: starting hydrazone **1a** (relative abundance 57%), m/z: 162 ($M^+$), 147, 133, 106, 93, 92, 77, 65, 42; indole **2a** (18%); **4a** (10%); **4b** (8%).

After about two hours the chromatogram showed: indole **2a** (54%); **4a** (18%); **4b** (13%); 8 (11%); m/z: 245-247-249 (6:4:1, $M^+$); 210-211; 144, 115, 103, 77.

Carrying out the reaction under nitrogen atmosphere, a further peak appeared that we attributed to $Cl_2PNH_2$ (2%): m/z: 117-119-121 (6:4:1, $M^+$); 82-84, 66 46. At the end of the reaction the chromatogram showed: **2a** (80%), **4b** (10%). After aqueous quenching diazaphosphole **4b** disappeared and starting hydrazone **1a** (7%) was detected again. After purification on silica-gel column indole **2a** was recovered in 74% yield.[4b]

Following the reaction course by t.l.c.-analysis we never observed the presence of **4a** and **4b** in the reaction mixture.

The same results were obtained running the reaction in a n.m.r.-tube in $CD_2Cl_2$. In particular $^1$H-n.m.r. revealed a doublet at 3.20 ppm with a coupling constant of 24.0 Hz typical of a P-C-H coupling in a diazaphospholine ring and $^{31}$P-n.m.r. analysis on the other hand revealed peaks only at 221,144,117 ppm.

Reaction of diazaphosphole **4a** and **4b** with HCl in $CH_2Cl_2$.

A sample of the ethereal slurry was dissolved in $CH_2Cl_2$ and allowed to stand at 0°C. After 7 hours the g.l.c. chromatogram revealed the presence of about 60% of **2a** and only traces of **4a** and **4b**.

In a $CH_2Cl_2$ solution of diazaphosphole **4a** (1 mmol) was bubbled HCl gas at room temperature. The t.l.c. and g.l.c. analyses showed the almost complete conversion of **4a** in indole **2a** after about 8 hours.

Under the same conditions and after the same period of time, diazaphosphole **4b** gave no appreciable indole formation.

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5. Indole formation was never observed even employing more drastic conditions and longer reaction times. Therefore, we can exclude that indole was not formed because of the lower electrophilicity of $Ph_2PCl$ with respect to $PCl_3$.
6. Diazaphospholine **3** should be in tautomeric equilibrium with the corresponding "phosphenium chloride" as reported by Schmidpeter.[2b]
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