Reactivity of 2*H*-1,2,3-Diazaphosphole Derivatives: Unexpected Formation of Indoles and a New Indolization Reaction

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2*H*-1,2,3-Diazaphosphole derivatives (1) react with alkyl halides to give the corresponding 2,3-disubstituted indoles (3) as the major products (30—40% yields). Small amounts (15—20%) of the ring-opened compounds (4) in the two diastereoisomeric *Z*-configurations are also obtained. During this reaction a *cis*-(1) ⇄ *trans*-(1) isomerization is also observed. Mechanistic explanations of these results have been described and a new general method has been developed for the synthesis of 2,3-disubstituted indoles from ketone arylhydrazones and PCl_3.

In a recent communication,[1] we described the first results of a new method for the synthesis of 2,3-disubstituted indoles from reaction, at room temperature, between ketone arylhydrazones and phosphorus trichloride. This synthesis was realized by observing the unexpected formation of indole derivatives from reaction of the diazaphosphole (1) with alkyl halides. Here, we describe the details [2] of this unexpected result and the mechanistic implication in connection with our consequent indolization reaction.[1] In addition we report in detail the relative experimental conditions of this simple method for the synthesis of 2,3-disubstituted indoles.

Results

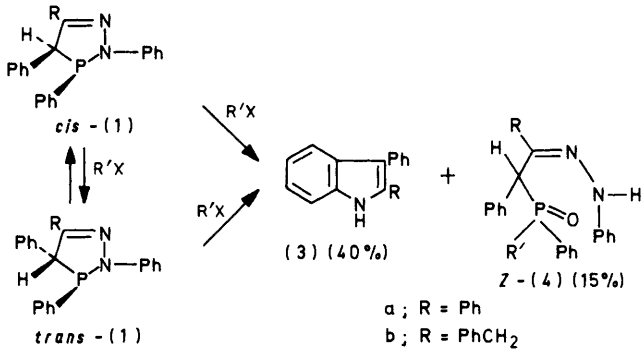
During attempts to prepare phosphonium salts from 2*H*-1,2,3-diazaphosphole derivatives (1a) [3] and (1b) we noted the unexpected formation of 2,3-diphenylindole (3a) and 2-benzyl-3-phenylindole (3b) as the major products. Thus, reaction of *cis*-(1a) or *cis*-(1b) † with an excess of alkyl halides (2) in benzene or acetonitrile under reflux for several hours furnished respectively the indoles (3a) in 40% yield or (3b) in 35% yield.

Small amounts (15—20%) of the corresponding ring-opened phosphine oxide *Z*-(4) as a mixture of the two isomers, *Z*-(4)′ and Z-(4)″ in a ratio of *ca.* 1 : 2, was obtained. This ratio, was dependent on the reaction conditions and the alkyl halides used. During these reactions a *cis*-(1) ⇄ *trans*-(1) isomerization was observed; under identical reaction conditions but in the absence of alkyl halide the interconversion was not observed. It is interesting to note that the isomeric phosphines (1) are not interconvertible in a variety of solvents ($CDCl_3$, CH_2Cl_2, C_6H_6) under basic or acidic conditions or even after many hours under reflux.

The overall reaction is shown in Scheme 1.

It is worth noting that the reaction of *trans*-(1) with R′X was noticeably slower (2 days for MeI, 10 days for EtBr).

All reactions were monitored by t.l.c. and the mixtures were separated by silica-gel chromatography; all the isolated ring-opened products were characterized essentially by ^1H n.m.r. spectroscopy (see Table 1). The ^1H n.m.r. data were also useful in determining the ratio of diastereoisomers *Z*-(4)′ and *Z*-(4)″. The NH proton resonance of compound *Z*-(4) is strongly intramolecularly bonded as indicated by its low-field resonance, and this indicates a *Z*-configuration about the C=N bond. The relative configurations of the two chiral centres in *Z*-(4)′ and *Z*-(4)″ as depicted in Scheme 2 are arbitrary and are tentatively assumed on the basis of the mechanism. We have reported [4] analogous assignments for related ring-opened compounds.



Scheme 1. *Reagents:* R′X = MeI or EtBr

Table 1. N.m.r. data [a] ($CDCl_3$) of compounds *Z*-(4)

Compd.	$\delta_{PR'}$	$J_{PR'}$	δ_{PCH}	J_{PCH}	δ_{NH}
Z-(4a)′ (R′ = Me)	1.80(d)	12.0	4.78	14.5	11.45
Z-(4a)″ (R′ = Me)	1.75(d)	12.0	4.70	13.0	11.70
Z-(4a)′ (R′ = Et)	0.80—2.45(m)		4.82	13.0	11.50
Z-(4a)″ (R′ = Et)	0.72—2.24(m)		4.70	12.8	11.70
Z-(4b)′ (R′ = Me)	1.45(d)	12.0	4.35	11.5	11.20
Z-(4b)″ (R′ = Me)	1.35(d)	12.0	4.25	10.5	11.30
Z-(4b)′ (R′ = Et)	0.50—2.15(m)		4.00	12.0	11.25
Z-(4b)″ (R′ = Et)	0.42—2.05(m)		3.95	11.0	11.60

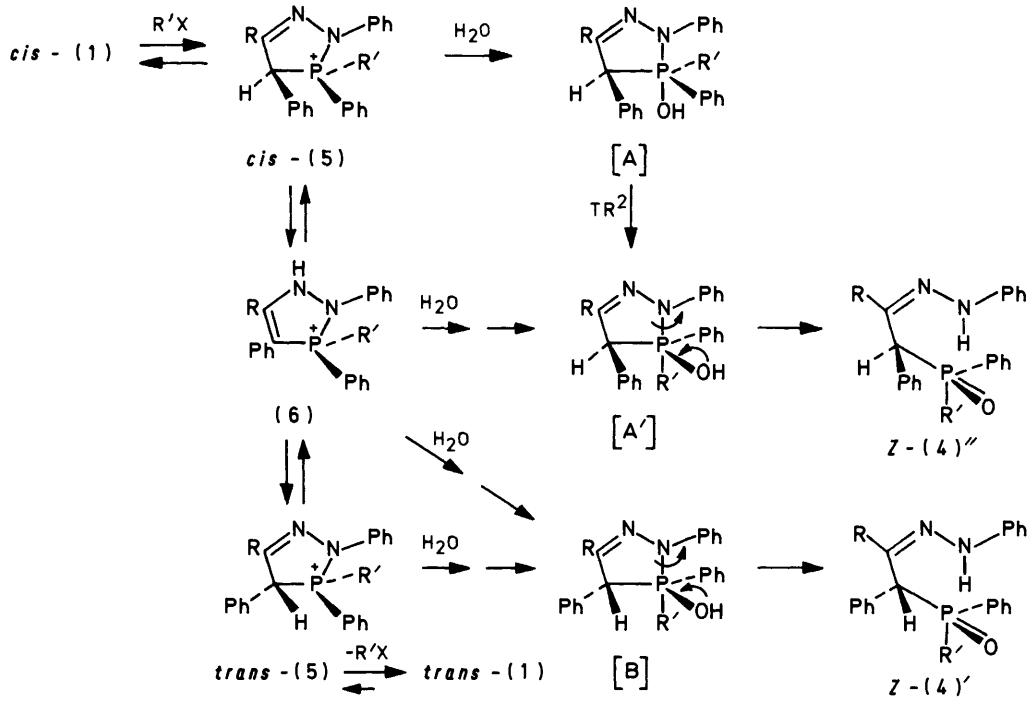
[a] Concentrations of 3—5 mol% were used; chemical shifts in p.p.m. from Me_4Si; *J* values in Hz.

Discussion

In Scheme 2 is depicted a possible mechanism which explains the formation of the two diastereoisomeric ring-opened compounds *Z*-(4)′ and *Z*-(4)″ and the *cis*-(1) ⇄ *trans*-(1) isomerization.

It is likely that the first stage of the reaction is the formation of the phosphonium salt *cis*-(5) (which could not be isolated); subsequently reaction of *cis*-(5) with traces of water gives the phosphorane intermediate such as [A] which may isomerize to [A′] either by a turnstile rotation process [5] or, an alternative equivalent, Berry pseudorotation.[6] The intermediate such as [A′] then, finally, collapses to the ring-opened product *Z*-(4)″. It is possible that *cis*-(5) can be in equilibrium with the cyclic enehydrazine form (6) which reacts with water to give,

† In the text prefixed *cis* and *trans* refer to the relationship between P-phenyl and C-phenyl groups.



Scheme 2

in a similar manner, [A'] or/and [B] and then the ring-opened products *Z*-(4)'' and *Z*-(4)' respectively. The relative amounts of these isomers can be explained by the different stability of their phosphorane intermediates such as [A'] and [B].

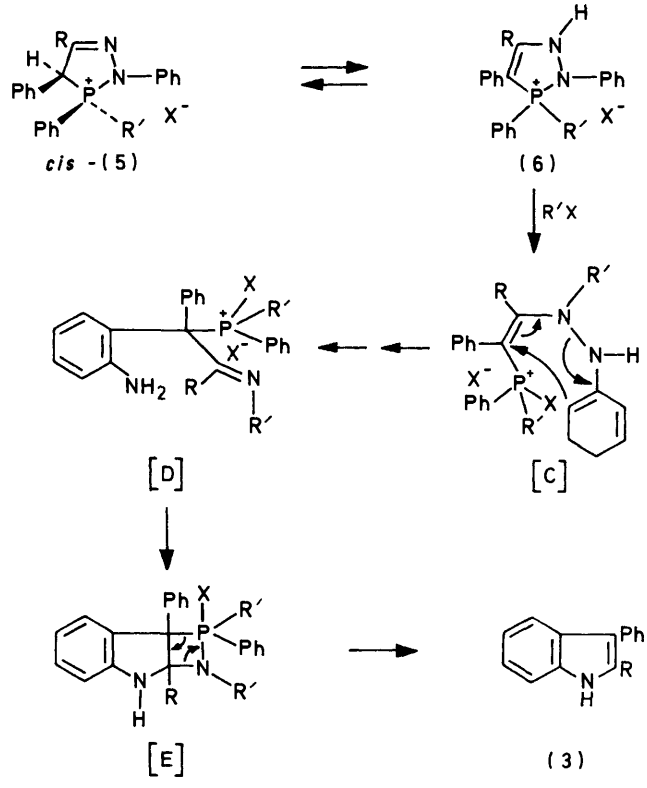
The cyclic enehydrazine (6) may be in equilibrium with the phosphonium salt *trans*-(5); elimination of R'X from *trans*-(5) gives *trans*-(1) and in this way the *cis*-(1) $\rightleftharpoons$ *trans*-(1) isomerization is rationalized. In addition, the proposed cyclic intermediates such as (5) or (6) are consistent with the exclusive formation of ring-opened compounds (4) with the *Z*-configuration about the C=N bond. Moreover, when the reaction is carried out in super-dry solvent only traces of the ring-opened compounds (4) were observed.

At present the mechanism suggested for the formation of (3) (see Scheme 3) can be considered only tentative. However, it is possible that the first stage of this indolization reaction may be the tautomerization of the phosphonium salt *cis*-(5) to its enehydrazine form (6). This equilibrium is very similar to the accepted Fischer indolization mechanism [7] but in our case the enehydrazine form (6) may be favoured over the hydrazono-form (5) by the presence of a phosphonium phosphorus atom. Conversion of (6) into the indole (3) may be explained by subsequent intermediates such as [C], [D], and [E] which are a simple consequence of the accepted Fischer mechanism.

The formation of the intermediate [C] may be presumably aided by addition of a further molecule of R'X to the enehydrazine form (6); this is in accord with the excess of alkyl halide used.

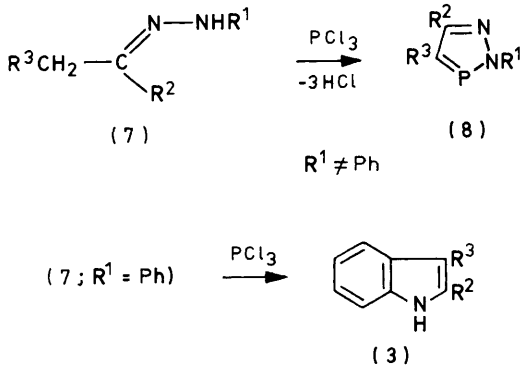
The difference between our hypothetical intermediates [C] and [D] and the corresponding Fischer intermediates consists in the substitution of an hydrogen atom by a phosphonium group which could have an important role in promoting the loss of a nitrogen atom during this indolization reaction: in the last stage an intermediate such as [E] may be invoked.

The rate-determining step of this reaction should be the formation of the phosphonium salt (5) which it is not possible to isolate. In fact, when the reaction was carried out in C_6D_6 solution in a sealed n.m.r. tube placed in a bath at 78 °C and



Scheme 3

monitored by ^1H n.m.r. spectroscopy, gradual disappearance of the methine proton doublet of (1b) was observed with a concomitant appearance of the benzyl signal of indole (3b). Moreover, the observation that *trans*-(1) is uniformly slower



during nucleophilic attack by phosphorus on the alkyl halide further suggests that the step *trans*-(1) ⟶ (5) is rate limiting.

In connection with our results, it is interesting to note that the reaction of alkylhydrazones (7) with phosphorus trichloride leads after elimination of hydrogen chloride to the corresponding 2*H*-1,2,3-diazaphosphole (8).[8]

However, we have found, as earlier reported,[8] that it is either impossible or difficult to obtain the corresponding 2*H*-1,2,3-diazaphospholes from reaction of *aryl*hydrazones with phosphorus trichloride. From these findings and the proposed mechanism we have realized that an easy indolization reaction could arise from a simple reaction between arylhydrazones and phosphorus trichloride. In fact, we have found that the reaction, at room temperature, between ketone phenylhydrazones (7; R^1 = Ph) and phosphorus trichloride give the corresponding indoles in high yields (70—90% yield).

The first results of this reaction have been reported in a previous communication [1] and Table 2 summarizes the indoles obtained up to date.

In conclusion we think that the unusual reactivity of our cyclic phosphines may probably lead to further insight into the accepted mechanism [9] for Fischer indole synthesis and the subsequent reaction could explain the lack of formation of the corresponding diazaphosphole (8) from reaction between arylhydrazones and phosphorus trichloride. In addition our indolization reaction gives further evidence of the role of the phosphorus atom in the activation of a reaction process.

Experimental

^{1}H N.m.r. spectra were recorded on a Varian EM 360L spectrometer with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. M.p.s are uncorrected. Column chromatography was performed with Merck silica gel of particle size 0.05—0.2 mm. Microanalyses were performed on mixtures of isomers as well as on pure isomers. The results obtained were practically identical. The indoles (3) were fully characterized by i.r., u.v., ^{1}H n.m.r., and mass spectroscopy and by comparison with authentic samples.

Reaction of (1a) *with Methyl Iodide.*—To a solution of the diazaphosphole *cis*-(1a) [3] (0.78 g, 2×10^{-3} mol) in benzene (70 ml) was added an excess of methyl iodide (0.3 ml) and the mixture was heated under reflux for *ca.* 24 h. The course of the reaction was followed by t.l.c. After a few hours the formation of 2,3-diphenylindole (3a), the concomitant isomerization of *cis*-(1a) into *trans*-(1a), and the appearance of ring-opened compounds Z-(4a)′ and Z-(4a)″ (R′ = Me) was observed. At the end of the reaction period the mixture was chromatographed on a silica-gel column: elution with n-hexane–ether (10 : 1) gave small amounts of *trans*-(1a) and 2,3-diphenylindole (3a) in 40% yield. The latter was crystallized from n-hexane and had m.p. 123 °C, *m/z* 269 (M^+), and was identified by comparison with authentic sample (see Table 2) (Found: C, 88.9; H, 5.5; N, 5.1. Calc. for $C_{20}H_{15}N$: C, 89.2; H, 5.6; N, 5.2). The ring-opened isomers *Z*-(4a)′ and *Z*-(4a)″ (R′ = Me) were obtained in 15% yield in a ratio of *ca.* 1 : 2 and were separated on a silica-gel column with benzene–ether (4 : 1) as eluant. Isomer *Z*-(4a)′, R_F 0.42, was crystallized from n-hexane and had m.p. 166 °C, *m/z* 424 (M^+); isomer *Z*-(4a)″, R_F 0.25, had m.p. 177 °C, *m/z* 424 (M^+) (Found: C, 76.5; H, 6.0; N, 6.5. Calc. for $C_{27}H_{25}N_2OP$: C, 76.4; H, 5.9; N, 6.6). ^{1}H N.m.r. data of these compounds are summarized in Table 1. Attempts to isolate the intermediate *cis*-(5a) or (6a) were not successful. In a similar manner the reaction between *trans*-(1a) and methyl iodide gave the same products (3a) (35% yield) and the corresponding *Z*-(4a)′ and *Z*-(4a)″ (15% yield). In this case the reaction was noticeably slower: 2 days in benzene solution at refluxing temperature.

Table 2. Reaction of phenylhydrazones (7; R′ = Ph) with PCl_3 to give the indoles (3)

R^3	R^2	Yield (%)	Ref.
Ph	Ph	75	*a*
Ph	$PhCH_2$	80	*b*
Me	Et	70	*c*
Me	Ph	75	*c*
$Me_2C{=}CHCH_2$	Me	90	*d*
Ph	Me	80	*e*
$PhCH_2$	Ph	90	*f*

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Reaction of (1a) *with Ethyl Bromide.*—To a solution of *cis*-(1a) (0.78 g, 2×10^{-3} mol) in acetonitrile (70 ml) was added an excess of ethyl bromide (0.4 ml); the reaction was then left under reflux for *ca.* 48 h, the course of the reaction being followed by t.l.c. After several hours, isomerization of *cis*-(1a) into *trans*-(1a) was observed with the concomitant formation of (3a) and the appearance of products *Z*-(4a) (R′ = Et). Chromatography on a silica-gel column (4 : 1 benzene–ether as eluant) afforded *trans*-(1a) in 20%, (3a) in 35%, and the corresponding isomers *Z*-(4a) in 20% yield. Isomer *Z*-(4a) (R′ = Et), R_F 0.50, had m.p. 158 °C (from n-hexane), *m/z* 438 (M^+); isomer *Z*-(4a)″ (R′ = Et), R_F 0.35, had m.p. 167 °C (from n-hexane) *m/z* 438 (M^+), and their ratio was *ca.* 1 : 2 (Found: C, 76.6; H, 6.3; N, 6.3. Calc. for $C_{28}H_{27}N_2OP$: C, 76.7; H, 6.2; N, 6.4).

When this reaction was repeated under the same conditions with *trans*-(1a) appreciable formation of (3a) and *Z*-(4a) was observed only after 10 days.

Reaction of (1b) *with Methyl Iodide.*—The addition of an excess of methyl iodide to a benzene solution of *cis*-(1b) gave after *ca.* 24 h under reflux the indole derivative (3b) in 35% yield and small amounts of the corresponding isomers *Z*-(4b) (15% yield). These products were separated by column chromatography using as eluant benzene–ether (4 : 1). The indole (3b), crystallized from n-hexane had m.p. 101 °C; ^{1}H n.m.r. ($CDCl_3$) 4.20 (2 H, s, CH_2), 6.8—7.8 (15 H, arom. and NH); *m/z* 283 (M^+) (Found: C, 88.9; H, 5.9; N, 5.0. Calc. for $C_{21}H_{17}N$: C, 89.0; H, 6.0; N, 5.0). The ring-opened product

Z-(4b)″ (R′ = Me), R_F 0.30, had m.p. 172 °C, *m/z* 438 (M^+) (Found: C, 76.8; H, 6.0; N, 6.3. Calc. for $C_{28}H_{27}N_2OP$: C, 76.7; H, 6.2; N, 6.4). The corresponding isomer *Z*-(4b)′, R_F 0.45, was not isolated in pure form. The ratio between *Z*-(4b)′ and *Z*-(4b)″ was *ca.* 1 : 4. This reaction was also repeated in C_6D_6 and it was examined periodically by ^1H n.m.r. spectroscopy. The signals at δ 3.80 (m) and 4.50 (s) due to the starting phosphine *cis*-(1b) were slowly replaced by a concomitant appearance of signals of indole (3b). No appreciable new absorptions due to phosphonium salts *cis*-(5b) or (6b) were detected during this reaction. In a similar fashion the reaction between *trans*-(1b) and methyl iodide gave the same products (3b) (35% yield) and the two products *Z*-(4b) (15% yield) which were identified by comparison with the corresponding products prepared above.

Reaction of (1b) *with Ethyl Bromide.*—In a similar manner the addition of an excess of ethyl bromide (0.4 ml) to an acetonitrile solution (70 ml) of *cis*-(1b) (0.81 g, 2×10^{-3} mol) gave after *ca.* 48 h under reflux the indole (3b) in 35% yield and the corresponding ring-opened products *Z*-(4b)′ and *Z*-(4b)″ (R′ = Et) in 15% yield in a ratio of *ca.* 1 : 3. Isomerization of *cis*-(1b) into *trans*-(1b) was also observed. The products were separated by column chromatography using as eluant benzene–ether (4 : 1). The indole (3b) was characterized by comparison with an authentic sample, the isomer *Z*-(4b)′ (R′ = Et), R_F 0.31, had m.p. 139 °C and *m/z* 452 (M^+). The reaction between *trans*-(1b) and ethyl bromide gave after 10 days the products (3b) and *Z*-(4b) (R′ = Et) in a ratio practically identical with that described above.

General Procedure of Indolization with PCl_3.—To a benzene solution of the ketone phenylhydrazone (7) was added an equimolar amount of PCl_3 and the mixture was stirred for a few minutes at room temperature. The course of reaction was followed by t.l.c. and after the end of the reaction a sodium hydrogencarbonate solution was added to the mixture. The organic layer was separated, washed several times with water, dried, and evaporated. The corresponding indole (3) was obtained in 70—90% yield by simple crystallization or by chromatographic purification.

Acknowledgements

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