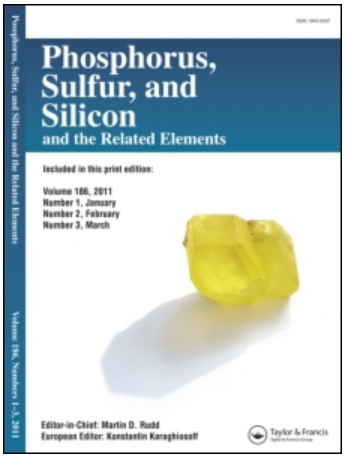

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

An Unusual Synthesis of Arylazo Substituted Azaphospha [5, 1-A] Quinolines by Reaction of N-Alkylarylazo Quinolinium Salts with Phosphorus Trichloride

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Online publication date: 27 October 2010

To cite this Article Sharma, Pratibha , Kumar, Ashok and Pandey, Priti(2003) 'An Unusual Synthesis of Arylazo Substituted Azaphospha [5, 1-A] Quinolines by Reaction of N-Alkylarylazo Quinolinium Salts with Phosphorus Trichloride', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 3, 583 — 594
To link to this Article: DOI: 10.1080/10426500307935
URL: http://dx.doi.org/10.1080/10426500307935

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:583–594

1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390170732

AN UNUSUAL SYNTHESIS OF ARYLAZO SUBSTITUTED AZAPHOSPHA [5, 1-A] QUINOLINES BY REACTION OF N-ALKYLARYLAZO QUINOLINIUM SALTS WITH PHOSPHORUS TRICHLORIDE

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(Received May 10, 2002; accepted August 12, 2002)

1,2-Dialkyl-3-arylazo quinolinium chloride ***1*** *having N-methylene group activated by the insertion of arylazo site react with phosphorus trichloride to give N-(dichloro phosphinomethylene) quinolinium ylide* ***2****. The site of the reaction is determined by the relative activation of 1- and 2-methylene groups, in the absence of sufficient activation of N-methylene group, reactions occur at the 2-methylene group to give dichloro phosphinylated anhydrobases 5 and 11.*

Keywords: 1-Alkyl-2-(dichlorophosphinomethylene) quinolinium anhydrobases; 2,4,6-trialkyl-3-arylazo quinolines; N-alkyl quinolinium halides; N-(dichloro phosphino methylene) quinolinium ylides

Anullated heterophospholes[1–6] constitute a special class of heterocyclic compound in which a phosphole ring is fused with an aromatic nucleus to generate a $4n+2\pi$ electron system. The synthesis of anullated heterophosphole manifests the mechanism for investigating the reaction of various substituted N-alkyl quinolinium salt with PCl_3 in presence of triethylamine to investigate the role of sufficiently activated N-methylene group, which undergoes cyclization and results in the formation of 1,3-azaphospholoquinolines. The literature[7] has shown that such attempts on N-alkyl quinoline could not be successful in revealing the desired product, however similar reaction sequence on N-alkyl isoquinolinium salts have been found to be fruitful and resulted in the formation of azaphospholo isoquinolines.

Our sincere thanks are due to Prof. R. K. Bansal, University of Rajasthan, Jaipur for many helpful suggestions.

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We sought to control the difficulty associated with quinoline nucleus and rectified the problem by inserting an arylazo grouping in the 3-position and thereby activating the nuclei to undergo anullation under optimal conditions. The developed methodology delineates the [4 + 1] cyclocondensation of 2-substituted cycloiminium salts with phosphorous trichloride in the presence of triethylamine.[8] It has been realized that if the N-methtylene group was not sufficiently activated, either the reaction stopped at the intermediate stage or only 1-dichlorophosphino substituted-2-phospholoquinolines could be generated. For example 1-benzyl-2-methyl quinoline bromide formed an intermediate which did not cyclize to give the corresponding azaphospholoquinolines under the given reaction conditions, whereas 2-methyl-1-(4-methoxy benzyl) quinolinium bromide under these conditions gave a very poor yield (~10%) of 1-unsubstituted 2-phosphaquinolines, though the corresponding 1-dichloro phosphino-2-phosphaquinolines could be generated quantitatively. It was inferred that 1-dichlorophosphino-2-phosphaquinoline was formed from the substitution of the initially formed 2-phosphaquinolines. Characterization of the isolated reaction intermediate as 1-(dichlorophosphinomethylene) quinolinium ylide gave the impression that the reaction always initiated at the N-methylene group.

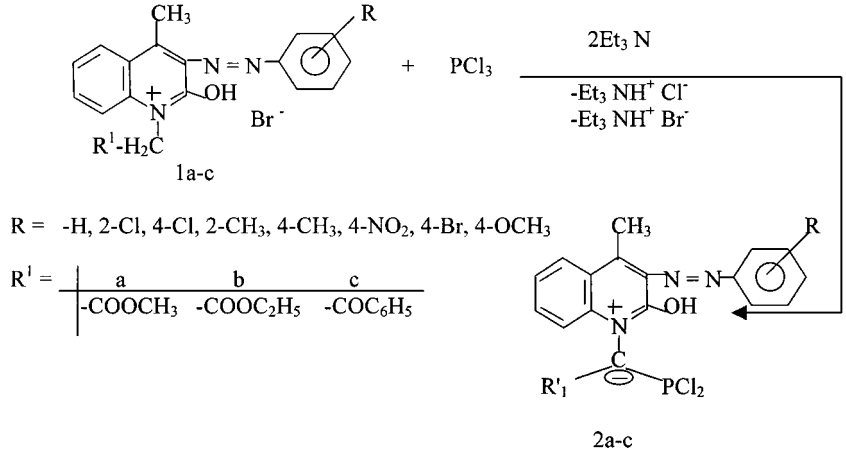
Buoyed from these encouraging results and keeping in view the analogy of Kröhnke's synthesis of indolizines[9] with our 2-phosphaquinolines an inspiration has been aroused to investigate the reaction of differently substituted N-quinolinium salts with phosphorus trichloride. It has been realized that cyclization to 2-phosphaquinolines occurs only if the N-methylene group is quite activated; the reaction may be initiated at either of the two terminal methylene groups depending on their relative activation.

RESULTS AND DISCUSSION

Reaction of 2-Nonalkyl Substituted 1,4-Dialkyl Quinolinium Bromides

Reaction of 2-hydroxy 1,4-dialkyl quinolinium bromide (**1**) ($R' = -COOCH_3$, $-COOC_2H_5$, $-COC_6H_5$) with phosphorus trichloride in the presence of triethylamine at room temperature gives 1-(dichloro phosphino methylene) quinolinium ylides (**2**) (Scheme 1).

1-Benzyl and 1-(4-methoxy benzyl) quinolinium bromides do not show any reactivity under these conditions. This indicates that in the



SCHEME 1

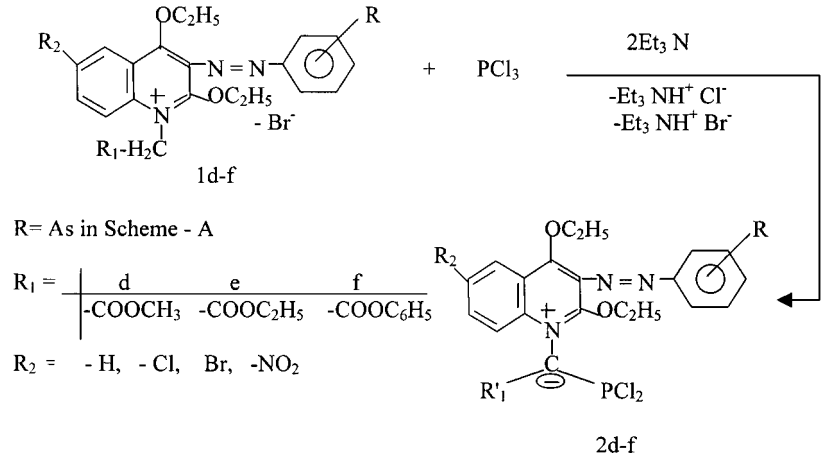
above reaction the quinolinium salt with an activated N-methylene group undergoes deprotonation in the presence of trioethylamine to generate the N-quinolinium ylide which reacts with phosphorus trichloride to form **2**. This analogy has been derived from the alkylation of N-pyridinium ylides.[10] Compounds **2a**,**b** are isolated in a pure state as orange crystalline solids. The **2c**, however could not be separated from the ammonium salt due to its insolubility in diethyl ether.

The structure of **2** has been ascertained on the basis of ^{31}P and ^{1}H NMR spectroscopic data (Table I). The ^{31}P-NMR chemical shift at $\delta \sim 152$ agrees well with those reported for dichloro phosphino derivatives.[11] The ylidic nature of **2** is supported by the absence of any ^{1}H-NMR signal in the range δ 6–7 characteristics for the proton on the ylidic carbon of N-quinolinium ylides.[12] Similar evidences have been obtained upon identical treatment on 1-alkyl-2-4-diethoxy-3-arylazoquinolinium halide (**1 d–f**) which gives (1-dichloro phosphinomethylene)-2,4-diethoxy derivative under similar reaction conditions **2d–f** (Scheme 2).

Reaction of 1,2,4–Trialkyl Quinolinium Halide

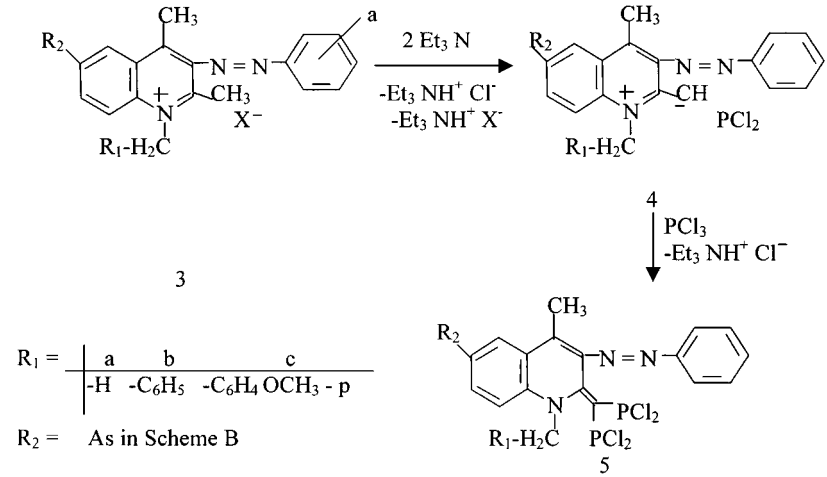
1-Alkyl-2, 4-dimethyl quinolinium halides (**3**) (R_1=H, C_6H_5, $C_6H_4OCH_3$–p) react with phosphorus trichloride (2 equv.) in presence of triethylamine (3 equn.) in benzene at room temperature to give 1-alkyl-2,-[bis(dichlorophosphino)methylene] 4-methyl-1,2-dihydro quinoline (**5**) (Scheme 3).

Compounds **5a**,**b** are orange amorphous solids, highly sensitive to moisture, and are soluble in common organic solvents. Its



SCHEME 2

characterization as the bis dichlorophosphino derivative is supported by elemental analysis and NMR spectroscopy (Table I). The ^{31}p-NMR signal at $\delta\sim146$ does not split under the proton coupled mode showing the absence of any proton on 2-methylene carbon. In the ^{13}C-NMR spectrum (Table II) of **5b**, the signal of 2-methylene carbon appears as a triplet at δ86.5 (^{1}Jpc = 75.6 Hz) indicating the presence of two dichlorophosphino moities on this carbon. The C-2 also gives a triplet at δ161.4 (^{2}Jpc = 15.1 Hz).



SCHEME 3

TABLE I Physical and Spectra Characteristics of Some Reaction Products

Compound	R_1	m.p.°C	Yield %	Molecular formula	^{1}H-NMR$_1$ δppm (J, H$_z$)
2a (R=H)	$COOCH_3$	151–152	65	$C_{21}H_{22}N_3O_4PCl_2$	3.50 (s, 3H, OCH_3) 1.1 (t, 6H, $CH_3 \times 2$) 4.1 (q, 4H, $CH_2 \times 2$) 6.65 (t, $^3J_{HH} = 7.5$, 2H; 3′-^{1}H, 5-H) 7.1 (t, $^3J_{HH} = 8.0$, 1H, 4-H) 7.30 (d, $^3J_{HH} = 7.4$, 2H; 2^1-H, 6^1-H) 7.50–8.10 (m, 4HH, Ar-H)
2b (R=H)	$COOC_2H_5$	126–127	62	$C_{22}H_{24}N_3O_4PCl_2$	0.95 (t, 6H, $CH_3 \times 2$), 3.95 (q, 4H, $OCH_2 \times 2$), 6.95 (d, $^3J_{HH} = 7.5$, 2H; 5H, 8H) 6.75 (t, $^3J_{HH} = 8.1$, 2H, 6H, 7H), 7.40 (t, $^3J_{HH} = 7.8$, 2H, 3^{1}H, 5H) 7.55 (t, $^3J_{HH} = 8.0$, 1H, 4^1-H). 7.85 (d, $^3J_{HH} =$ 7.5, 2H; 2′H, 6H).
2c (R=H)	COC_6H_5	115–116	55	$C_{27}H_{24}N_3O_3PCl_2$	1.0 (dt, 6H, $CH_3 \times 2$) 4.5 (q, 4H, $CH_2 \times 2$) 7.0–7.2 (t, $^3J_{HH} = 7.5$, 3H$_1$, 3′-H, 4′-H, 5′-H), 7.5–7.7 (d, $^3J_{HH} = 7.8$, 2H, 2^1-H, 6′-H) 7.9–8.2 (m, 9H; Ar'-H).
5a R_2=H	H	140–141	60	$C_{16}H_{15}N_3P_2Cl_4$	3.4 (s, 6H; $CH_3 \times 2$), 7.8 (d, ^{3} $J_{HH} = 6.6$, 2′-H, 6′-H), 6.95–7.2 (t, $^3J_{HH} = 7.1$, 3H, 3′-H, 4′=H, 5′-H) 7.32–7.40 (t, $^3J_{HH}$=7.8. 2H, 6-H, 7-H) 7.50–7.65 (d, $^3J_{HH} = 8.0$, 2H; 5-H, 8-H)
5b (R_2=H)	C_6H_5	161–162	62	$C_{22}H_{19}N_3P_2Cl_4$	2.4 (s, 3H, CH_3), 4.5 (s, 2H, CH_2) 7.30–7.95 (m, 14H; Ar-H)
11a	H	135–136	60	$C_{16}H_{20}N_3PCl_2$	2.4 (s, 6H, $CH_3 \times 2$), 7.4–8.1 (m, 14H; Ar-H)
14a	C_6H_5	110–111	55	$C_{24}H_{25}N_3O_2P_2Cl_4$	1.1 (t, 6H; $CH_3 \times 2$) 4.4 (q, 4H, $CH_2 \times 2$) 3.8 (S, 2H, —CH_2—) 6.75–7.15 (t, $^3J_{HH}$–7.0, 3H, 3′-H, 4′-H, 5′-H), 7.30 (s, 5H, Ar-H), 7.85 (s, aromatic —CH) 7.50–7.70 (d, $^3J_{HH} =$ 7.6, 2H; 7-H, 8-H)

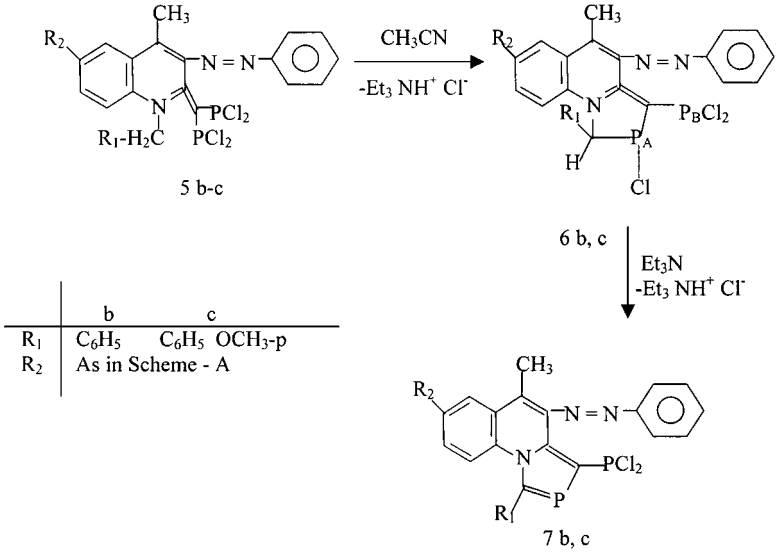
These results indicate that if the N-methylene group is not activated, deprotonation of the 2-methylene group is preferred as the resulting anhydrobase is stabilized by resonance.[7] The initially formed monodichlorophosphino derivative **4** could not be isolated even on using one equivalent of phosphorus trichloride under controlled condition. This shows that the methine proton of **4** is highly activated and undergoes instantaneous substitution by phosphorus trichloride.

The polarity of the solvent influences the progress of the above reaction. In nonpolar solvents such as benzene, toluene the reaction stops at stage **5**, whereas in polar solvents viz, acetonitrile, ethylacetate the initially formed bis(dichlorophosphino) methylene derivative **5** undergoes intra molecular cyclocondensation if R=C_6H_5 or $C_6H_4OCH_3$-p to form species (**6**) and finally 1-dichloro-phosphino-2-phospha (**5**, **1-a**) quinoline (**7**) (Scheme 4). The formation of species **6** is revealed by ^{31}P-NMR spectrum of the reaction mixture in which two doublets (δP_A = 25–40, δP_B = 140–170) corresponding to a characteristics AB spin system are observed.

Furthermore in the case where R=C_6H_5, the initially formed, **7b** undergoes disproportionation to form **9b** (Scheme 5) as revealed by

TABLE II ^{13}C-NMR Data of 5b ($CDCl_3$ + DMF d_6, J = H_z)

C-2	161.4	C-i	138.4
$^2J_{PC}$	15.1	$^2J_{CH}$	4.8
C-3	171.4	C—O	130.4
$^3J_{PC}$	6.1	$^1J_{CH}$	155.6
		$^2J_{CH}$	9.6
C-4	135.5	C—m	135.4
		$^1J_{CH}$	131.3
C-5	131.2	$^2J_{CH}$	10.6
$^1J_{CH}$	169.7		
$^2J_{CH}$	6.5	C—P	138.6
C-6	128.5	$^1J_{CH}$	148.5
$^1J_{CH}$	165.5	$^2J_{CH}$	7.9
$^2J_{CH}$	8.6		
C-7	126.1	2-C$<^{P}_{P}$	86.5
$^1J_{CH}$	148.6		
$^2J_{CH}$	6.4	$^1J_{PC}$	75.6
C-8	155.5		
$^1J_{CH}$	173.4		
$^2J_{CH}$	7.5	C—CH_3	15.8
C-9	139.1		
C-10	150.5	N—CH_2	60.2
		$^1J_{CH}$	155.5

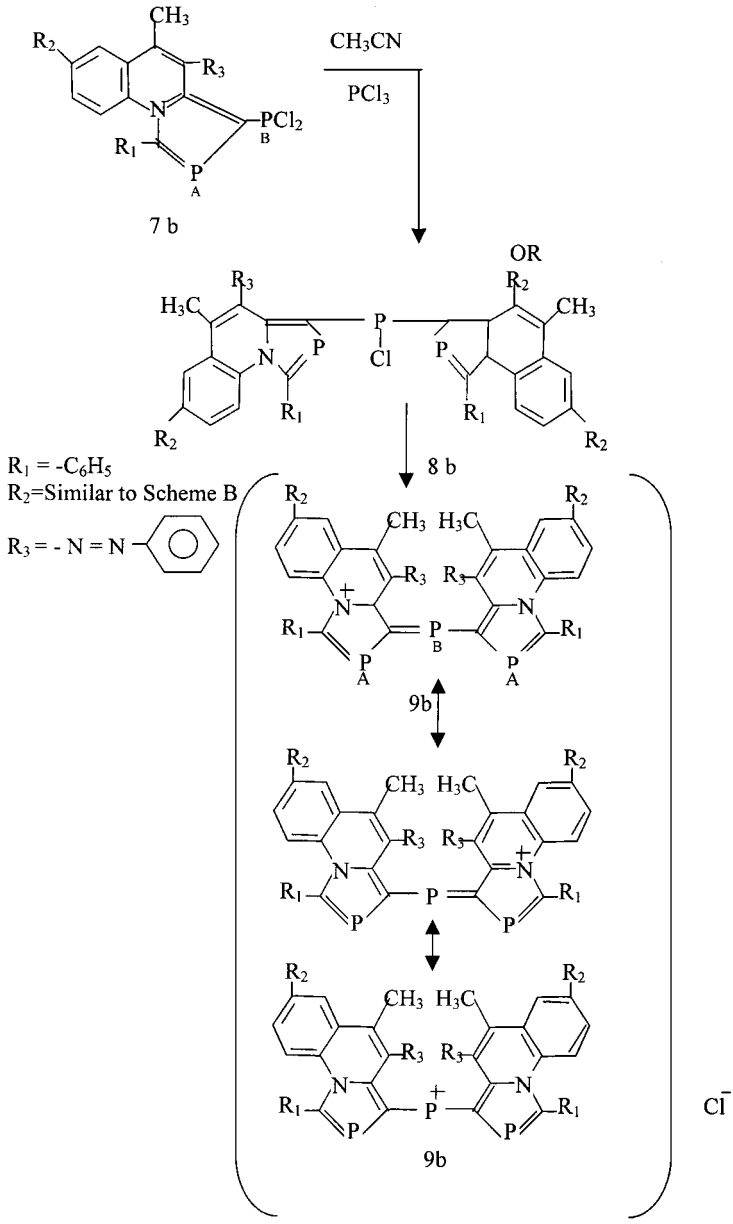


SCHEME 4

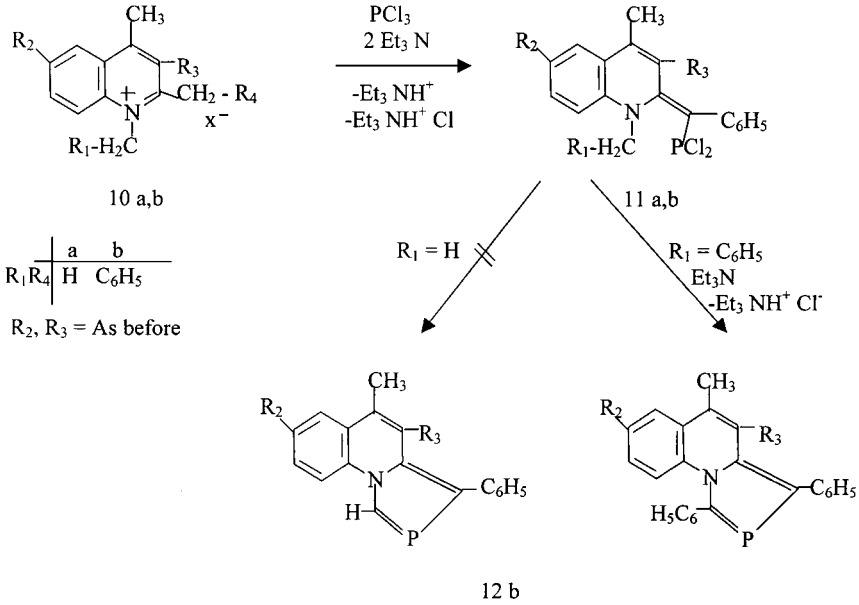
A_2B spin system in the ^{31}P-NMR spectrum. A highly downfield shift of P_A in **9b** ($\delta^{31}P = 315$, $^2Jpp = 32$ Hz) indicates the presence of cationic charge on the ring system. The ionic nature of **9b** is also supported by its insolubility in diethyl ether to which it could not be separated from the ammonium salt.

Furthermore, a reinvestigation of the synthesis of 1,3-diphenyl derivative from the cyclocondensation of 1,2-dibenzyl quinolinium bromide with phosphorus trichloride indicates that in this case the reaction also is initiated at the 2-methylene group. The reaction of 2-benzyl-1-methyl salt (**10b**) with phosphorus trichloride in presence of triethylamine in benzene, gives **11a** which does not cyclize on heating on carrying out the reaction in acetonitrile (Scheme 6). The structure of **11a** has been confirmed on the basis of ^{31}P and ^1H-NMR spectra (Table I). Likewise, 1,2-dibenzyl substituted compound forms **11b** in benzene, which does not cyclize to 2-phosphaquinoline under these conditions. However, if the reaction is carried out in acctonitrile the initially formed **11b** changes into 2-phosphaquinoline (**12b**) ($\delta^{31}P = 118.5$).

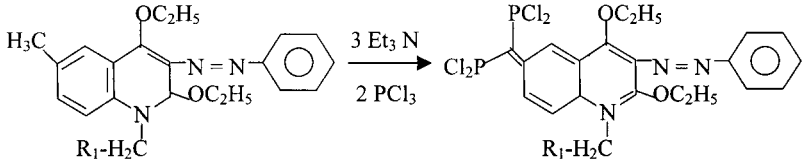
Typically 1-benzyl-3-arylazo-2,4-diethoxy-6-methyl-quinolinnium bromide (**13**) reacts with phosphorus trichloride (2 equv.) in presence of triethylamine (3 equv.) to give 1-benzyl-3-arylazo-2,4diethoxy-6-[bis(di



SCHEME 5



SCHEME 6



SCHEME 7

chloro phosphino) methylene] quinoline (**14**) (Scheme 7) as yellow crystalline compound.

EXPERIMENTAL

All the reported melting points were determined in an open capillary and are uncorrected. Solvents and reagents were distilled and dried by standard procedure before use. NMR Spectra were recorded on a Gemini

TABLE III ^{31}P-NMR Data of Some Synthesized Quinolines

Compound	δP_A	δP_B	$^2J_{PP}$ (Hz)	Solvent
2a	148.2			$CDCl_3$
4a	171.5	—	—	DMSO
5a	145.5	—	—	CH_3CN
6b	29.5	165.0	168.6	$CDCl_3$
6c	39.5	148.0	98.1	DMSO-d_6
7b	138.5	152.0	135.5	CH_3CN
7c	146.1	165.3	125.0	CH_3CN
9b	275.5	253.0	32.5	$CDCl_3$
11a	172.4			C_6H_6
11b	168.6			C_6H_6
12b	125.0			C_6H_6
14	156.5			C_6H_6

200 MHz (^{1}H and ^{31}P) and Bruker DR X 300 MHz (^{13}C) Spectrometers. Chemical shift are given with respect to 85% H_3PO_4(^{31}P) as external and TMS (^{1}H and ^{13}C) as internal standards.

2,4,6-Trialkyl-3 Arylazoquinoline 4-arylamino-3-arylazo butane-2-one[10,11] (0.032 M) or 3-arylamino-1,3-diethoxy-propanone (0.032 M) was added in portion to 25.0 ml of concentrated sulphuric acid contained in a 250 c.c. conical flask. The mixture was occasionally swirled to ensure thorough mixing. The reaction mixture was heated on the steam bath for 30 min, and then cooled to room temperature and slowly added to 250 ml of ice cold water in a 1 litre beaker. To the solution solid sodium carbonate was added until it became alkaline. The mixture was cooled down in an ice water bath until the quinoline solidifies. The product was filtered and washed with a little cold water. The purity of the quinoline thus obtained was ascertained after recrystallization from hot ethanol.

N-Alkyl Quinolinium Halide (1,3,10,13): General Procedure

To a solution of ethyl halide (0.1 M) in tetra hydrofuran or di ethyl ether (50.0 ml) an equimolar amount of pre synthesized quinoline or alkyl quinoline was added and reaction mixture was stirred for 24–48 h at room temperature. The precipitate was filtered, washed with di ethyl ether (25 ml), and dried in vacuum. The salt obtained in 75–80% yield were used without further purification.

1a (R=H) (% Found C 73; H 5.75; N 15.10 Calculated for C_{17} H_{16} N_3; C 73.09; H 5.80; N 15.19%).

1-(Dichlorophosphino Methylene) Quinolinium Ylide2): General Procedure

To a well stirred suspension of 1-alkyl quinolinium bromide(1) (0.01 M) in benzene (30 ml) at room temperature was added triethylamine (2.02 g, 0.02 M) followed by the addition of a solution of phosphorus trichloride (1.37 g, 0.01 M) in benzene (10 ml). The reaction was completed in 5–6 h as revealed by ^{31}P–NMR. The solvent was there after removed in vacuum and the residue was extracted with di ethyl ether (2×25 ml) The combined extracts were concentrated to about 25 ml and left in refrigerator overnight when yellowish to orange red crystals deposited, which were filtered and dried in vacuum. The **2c** and **2f**, however, could not be obtained in pure form due to its poor solubility in diethyl ether. A sample directly obtained from the benzene filtrate by removal of the solvent was found to contain traces of the ammonium salt.

2a (R=H) (% Found C 52.10; H 4.45; N 8.65; Calc, for C_{21} $H_{22}N_3O_4$, PCl_2; C 52.28; H 4.56; N 8.71%).

2b (R=H) (% Found C 2.95; H 4.82; N 8.42; Calc for C_{22} H_{24} N_3 O_4 PCl_2 C 53.03; H 4.86; N 8.50%).

1-Alkyl-2-[bis(dichloro phosphino)methylene] Guinoline [5] and 1-Alkyl–6-[bis-(dichlorophosphino) Methylene] Quinoline (14)

General Procedure

The above procedure was followed using pertinent alkyl quinolinium halide (0.01 M), triethylamine (3.03 gm, 0.03 M), and phosphorus tri chloride (2.74 gm, 0.02 M). The reaction mixture was directly filtered and on removing the solvent from the filtrate under vacuum an amorphous brown solid was obtained.

5a (R=H) (% Found: C 56.40; H 4.08; N 11.01 Calculated for C_{17} H_{15} N_3P_2Cl; C 56.8; H 4.17; N 11.6%).

14 (R=H) (% Found: C 82.8; H 6.37; N 10.7 Calculated for C_{27} H_{25} $N_3O_2P_2Cl_4$; C 82.9; H 6.40; N 10.76%).

1-Alkyl-2-(dichlorophosphino-phenyl Methylene)-1,2-dihydro Quinoline (11)

General Procedure

The above procedure was followed using 1-alkyl-2-benzyl quinolinium halide (0.01 M), triethylamine (2.02 g, 0.02 M), and phosphorus tri

chloride (1.37 gm, 0.01 M). The sample (**11a**) obtained from removing the solvent from benzene filtrate contained traces of the ammonium salt.

11a (R=H) (% Found: C 80.9; H 6.13; N 12.8 Calculated for C_{22} H_{20} N_3PCl_2; C 80.94; H 6.20; N 12.9%).

CONCLUSION

The reaction of differently substituted N-quinolinium salts with phosphorus trichloride has been investigated. It has been observed that cyclization to 2-phosphaquinolines takes place exclusively when N-methylene group is sufficiently activated. Furthermore, if N-methylene group is not sufficiently activated, reaction occurs at the 2-methylene group yielding dichloro phosphinylated an hydrobases **5** and **11**.

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