AN EFFICIENT SYNTHESIS OF 3-ALKYL-, 3-ALKENYL AND 3-ACETYLENETRIAZINE DERIVATIVES *via* PHOSPHORANYLIDENETRIAZINES

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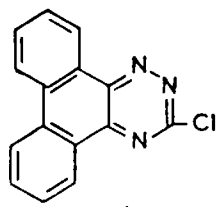
Abstract : The stable phosphoranylidene—1, 2, 4-triazines 12 and 15 were prepared in high yields and subjected to Wittig reaction, hydrolysis and pyrolysis whereas several triazine derivatives (alkyl, alkenyl and acetylenes) were isolated and identified.

Introduction

Numerous 1,2,4-triazine derivatives were evaluated for different biological activity (1-3). The most interesting aspects of these compounds are their antiphlogistic, cytostatic, antiviral and immunosuppressive properties (4,5).

In continuation of our previous investigation(6) pertaining to synthesis of organo-phosphorus compounds incorporating 1,2,4-triazine moiety with predicted pesticidal effects (6,7), we report here the synthesis of a series of stable phosphorus ylides derived from 3-chloro-phenanthro [9,10-e]-1,2,4-triazine 1 and 3-chloro-5,6-diphenyl-1,2,4-triazine 2 as accessible intermediates for preparing new 1,2,4-triazine-derivatives of therapeutical potencies.



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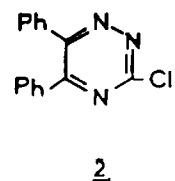

2

$Ph_3P=CHR$

3a , R = $COOCH_3$
3b , R = $COOC_2H_5$
3c , R = $COCH_3$

As a prelude to the current work, we reported (8,9) the action of Wittig reagents of

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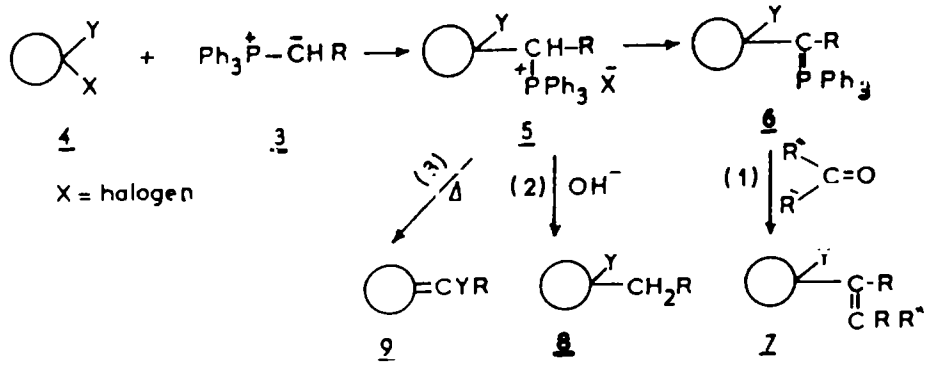
type 3 on several halo-substituted cyclic and acyclic substances. The reactions take place under mild conditions, and thus it has been possible on many occasions to intercept, yielding their respective phosphonium salts 5, otherwise their quite stable ylide-phosphoranes 6 were obtained. The produced phosphonium salts and their ylide form were further used as synthons for a series of secondary steps [reactions (1), (2) and (3)] to give a variety of derivatives as shown in scheme 1. We now apply this facile procedure

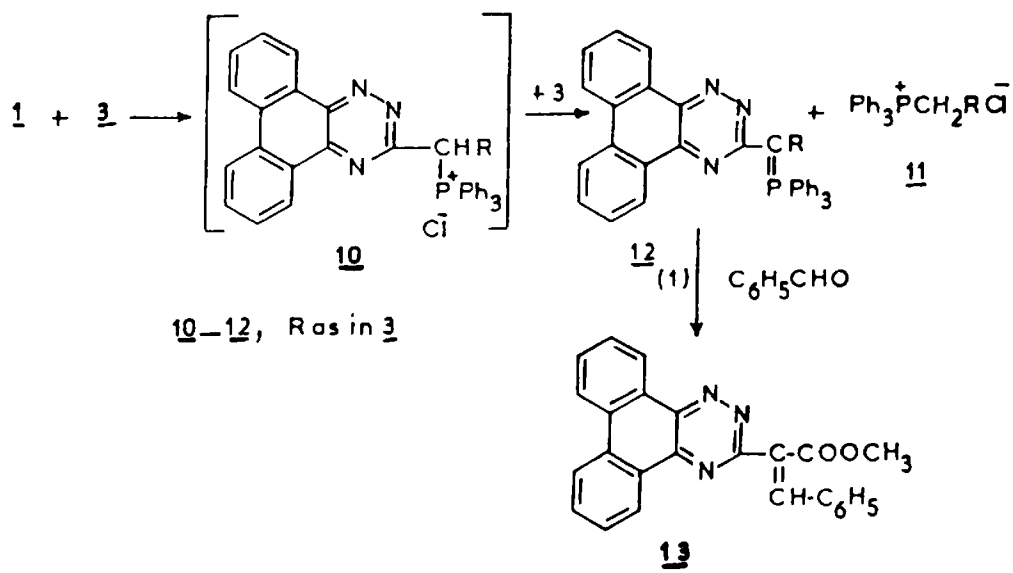


SCHEME 1

for the introduction of alkyl-, alkenyl- and acetylene groups at positions activated toward nucleophilic substitution reactions, utilizing halo-substituted triazines 1 and 2 as starting materials.

Results and Discussion

We now find that the reaction of 3-chlorotriazine 1 and methoxycarbonylmethylene-triphenylphosphorane 3a is completed by refluxing a toluene solution containing the



SCHEME 2

reactants 1 and an excess (> two molar equivalents) of 3a. The precipitated material was filtered off and proved to be methoxycarbonylmethylenetriphenylphosphonium chloride 11a. Evaporation of the filtrate *in vacuo* and crystallization of the residue from cyclohexane afforded yellow crystals 12a (> 85% yield), whose physical properties and spectroscopic data are collected in Tables 1 and 2. That this substance is an ylide phosphorane which is strongly supported by the ^{31}P NMR chemical shift, δ 24.6 ppm.

Table 1 Analytical data and physical properties of the products 12, 13, 15 and 16.

Compound[a,b]	Yield in (%)[c]	Mp (T/°C)	Mol. form (M.Wt)	Anal. Found/ (Calcd.) (%)				M⁺ m/z%
				C	H	N	P	
12a	87	179-181[c]	$C_{36}H_{26}N_3O_2P$	76.72	4.65	7.46	5.50	563
			(563.61)	76.56	4.53	7.34	5.37	
12b	85	182-184[c]	$C_{37}H_{28}N_3O_2P$	76.94	4.89	7.27	5.36	577
			(577.63)	76.85	4.77	7.14	5.21	
12c	78	177-179[d]	$C_{36}H_{26}N_3OP$	78.96	4.79	7.67	5.66	547
			(547.61)	78.83	4.66	7.61	5.53	
13	66[e]	153-155[d]	$C_{25}H_{17}N_3O_2$	76.71	4.38	10.74	–	391
			(391.43)	76.62	4.26	10.58	–	
15a	85	126-128[c]	$C_{36}H_{28}N_3O_2P$	76.44	4.99	7.43	5.48	565
			(565.62)	76.28	4.95	7.36	5.36	
15b	85	80-81[c]	$C_{37}H_{30}N_3O_2P$	76.67	5.22	7.25	5.34	579
			(579.65)	76.54	5.09	7.07	5.28	
15c	75	142-144[d]	$C_{36}H_{28}N_3OP$	78.67	5.13	7.65	5.64	549
			(549.62)	78.48	5.03	7.55	5.48	
16	80[e]	110-112[d]	$C_{36}H_{26}N_3O_2P$	76.32	4.87	10.68	–	393
			(393.45)	76.17	4.69	10.44		

a) All new products are coloured substances (yellow → brown).
b) IR spectra of 12a,b and 15a,b also showed bands around 1680 cm^{-1} (C=O), ester and ~ 1500 & 980 (C = P & Ar-P). Compounds 12c and 15c have signals at ~ 1540 cm^{-1} (C=O, acyl) and at ~1450 (C=P. in their IR spectra, while compounds 13 and 16 have absorption bands at ~ 1685 (C=O) and at ~1635 (C=C) in IR spectra.
Solvent of cryst. : c) Cyclohexane, d) Benzene-pet-ether (b.r. 40-60 °C). e) The yield is corresponding to the ylide.

It is also worth noting that the reaction products 11a and 12a are equally obtained, irrespective whether one or two mole equivalents of the Wittig reagent was used. Thus the initially produced phosphonium salt 10 is dehydrohalogenated by the starting phosphorane 3, it being a stronger base than chloride ion under the condition used (10), to give 11 and 12 (Scheme 2).

Similarly, the phosphoranes 12b,c accompanied by the appropriate Wittig salt 11b, c, were obtained by treating the halo-heterocycle 1 with > two equivalents of ethoxycarbonylmethylene-3b and acetonylidenetriphenylphosphorane 3c, respectively. No salt corresponding to 10 was isolated. The pertinent spectral data are presented in Tables 1 and 2.

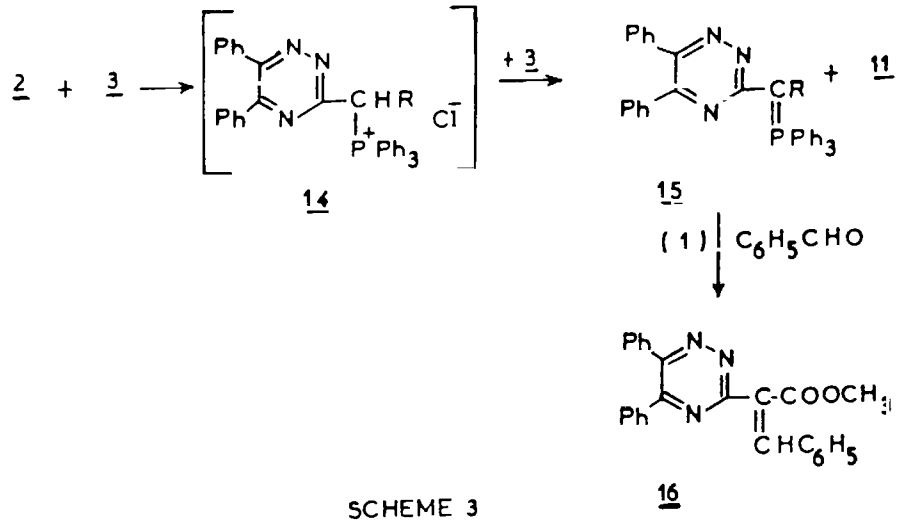
3-Chloro-5,6-diphenyl-1,2,4-triazine 2, which belongs to another important series of uncondensed triazine substrates, has been also allowed to react with > two molar equivalents of alkylidenephosphoranes 3a-c to give a mixture of the phosphorus ylides 15

Table 2 ^{1}H and ^{31}P NMR data[a] for 12, 13, 15, 16

Compound	^{1}H (δ ppm)[b,c]			δ ^{31}P, ppm
	C – CH_3	OCH_2/OCH_3	= CH	
12a		3.45(s,3H)		24.6
12b	0.62(t, 3H)	3.75(q,2H)		24.2
12c	1.40(s, 3H)		6.05(s,1H)	23.5
13		3.48(s,3H)	6.12	
15a		3.5(s,3H)		22.5
15b	0.85(t,3H)	3.85(q,2H)		21.3
15c	1.35(s,3H)			21.7
16		3.5(s,3H)	5.85(s,1H)	

[a]See experimental for details of NMR experiments.b) The solvent is $CDCl_3$. c) Aryl-hydrogen protons for : 12 and 13 lie in δ 7.3-7.9 ppm region, for 15 and 16 lie in δ 7.1-8.1 ppm region.

and the parallel Wittig salts 11. This mixture could be separated in the usual manner. No intermediate of 14 was isolated and 2 moles of 3 give only 1 mole of 15.

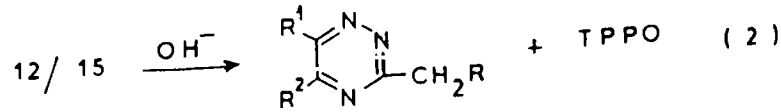


SCHEME 3

For conversion of 1 and 2 to alkenyl-substituted triazines, the product 12a or 15a (as representative examples) was refluxed in dry toluene solution containing an excess (about 3 equiv) of the appropriate aldehyde (e.g., benzaldehyde). The Wittig reaction occurred readily to give exocyclic olefins 13 and 16, respectively, (Reaction (1), Schemes 2 and 3).

For hydrolysis to alkyl-substituted triazines, sodium carbonate (1 equiv) in water or 10% NaOH (aq) was added to the phosphorus ylides 12 and 15. The reaction mixture was refluxed for ~3 h and then worked up by the convenient method (see experimental) to lead to the formation of 17 [reaction (2)]. Structure 17 is established from the elemental analysis

and spectral properties which are consistent with expectation (see experimental section).



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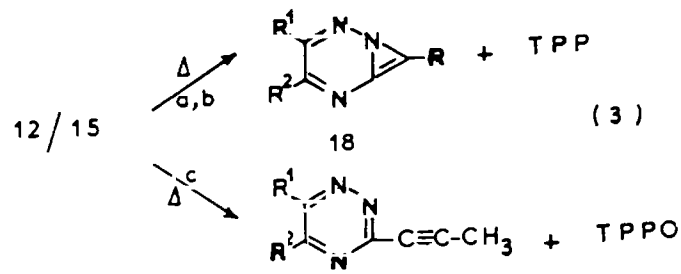
However, we have not succeeded in preparing the olefins 13 and 16 nor the alkyl-substituents 17 by carrying out reactions (1) and (2) on the original reaction - mixtures, as has been previously reported (8,9), which afforded a complicated mixture, can be difficult to separate in each case. Such a process is not efficient for our substrates.

Pyrolysis of 12 and 15 has also been investigated. Heating 12a,b and 15a,b under vacuum led to the formation of the azirines 18, accompanied by the elemination of triphenylphosphine as indicated below [reaction (3)]. However, some Wittig reaction



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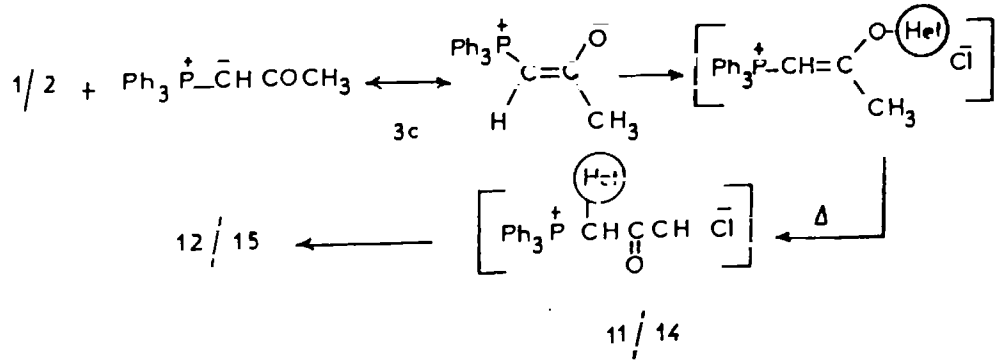
described in the literature (11) for preparation of azirines of type 18. Structure 18 is supported by the analytical data and the lack of the absorption bands due to the C=P present in the IR spectra of the parent compounds 12 and 15 at ~1455 cm^{-1}. The rest of the spectral data agree with the proposed structure.

Contrast to the behaviour of 12a,b and 15a,b, pyrolysis of 12c and 15c yielded the acetylenic derivatives 19 accompanied by triphenylphosphine oxide. Similar transformation occurred (12,13) and has been shown to constitute a general synthesis of acetylenes from phosphoranes of type ($Ph_3 P = CR^1.COR^2$) provided that neither R^1 nor R^2 is hydrogen and that R^1 or R^2 is alkyl, aryl or the equivalent (12-14). The structure ot the new acetylenes 19 is assignable from their analyses, IR, ^1H and ^{13}C NMR spectral data. The IR spectra showed the lack of the signal at ~1700 cm^{-1} due to the carbonyl group. The acetylene moiety was attested by the presence of an absorption bands at ~85 ppm (-C≡CR) and ~77 ppm (-C≡CR) in the ^{13}C NMR spectra.

Conclusion

As a consequence following from this work, we have shown that halotriazines react readily with phosphorus ylides to give new complex Wittig reagents which are of further synthetic use.

Although treatment of acylmethylenetriphenylphosphorane 3c with alkyl halide may result, in many occasions (15,16), in its O-alkylation due to the delocalization of the charge on the carbanion, it has been C-alkylated with halotriazenes. This behaviour is attributed to the drastic conditions (15,17) of the present reaction (Scheme 4).



SCHEME 4

Experimental

All melting points are uncorrected methoxycarbonylmethylene-, (18) ethoxycarbonylmethylene (18) and acetonylidenetriphenylphosphorane (15) were prepared according to established procedures. The IR spectra were measured in KBr, on Perkin-Elmer Infracord Spectrometer Model 157 (Grating). The ^{1}H NMR spectra were run on Varian Spectrometer at 90 MHz, using TMS as an internal reference. ^{31}P NMR Spectra were recorded with a Varian FT-80 Spectrometer (*vs.* 85% H_3PO_4). The mass spectra were performed at 70 eV on MS-50 Kratos (A.E.I.) Spectrometer.

Preparation of Phosphoranylidene-triazines 12 *and* 15*:* General procedure: 3-Chlorotriazine 1 or 2 (19) (0.01 mol) and ylide 3 (0.024 mol) were refluxed for 12-18 h (TLC) in dry toluene (50 ml). The material that precipitated after concentration and cooling was filtered off and proved to be the phosphonium salt of the respective phosphorus ylide 3. From the mother liquors of the above recrystallizations was isolated by evaporative distillation ~80-87% of the new phosphoranes 12 and 15 which recrystallized from the appropriate solvent. The crystals were filtered and air dried before melting point and spectral determinations were made. Consult Tables 1 and 2 for experimental details and spectroscopic data.

No reaction was observed, however, in a parallel experiment when the reactants (1 or 2 + 3a) were mixed at ambient temperature even after 48 h. Moreover, when the reaction was performed using equimolar amounts from reactants, the phosphoranes 12 or 15, the parallel Wittig salt and unchanged halocompound were obtained.

1. *Wittig Reaction of 12 and 15:* To a solution of toluene containing 12a (or 15a, 0.01 mol), benzaldehyde (0.03 mol) was added. The reaction was refluxed for 15-18 h (TLC) and the solvent evaporated. Extraction of the residual substance with hot petroleum ether (b.r. 60-80 °C), gave, on cooling, triphenylphosphine oxide. Crystallization of the residue from a suitable solvent afforded the olefinic products 13 and 16, respectively. The assignments for 13 and 16 are tabulated in Tables 1 and 2.

2. *Alkaline treatment of 12 and 15:*

a) **With sodium carbonate:** A mixture of 12a (or 15c, 1.0 g) and 50 ml of Na_2CO_3(15%, aq) was heated to reflux for 10 h. The mixture was cooled, diluted with water (5 ml) and extracted with chloroform. The residue obtained on removal of $CHCl_3$ was boiled with petroleum ether (b.r. 60-80 °C) to yield on concentration triphenylphosphine oxide. The insoluble material was recrystallized from the appropriate solvent to give the alkylated derivatives 17a (R^1 and R^2 = phenanthrene, R = $COOCH_3$) or 17b ($R^1 = R^2$ = phenyl, R = $COCH_3$), respectively.

17a, was obtained as yellow substance, 0.29 (55%) mp 172 °C (aqueous ethyl alcohol). Calcd. for $C_{18}H_{13}N_3O_2$ (303.32) : C 71.28, H 4.32, N 13.85. Found: C 71.16, H 4.21, N 13.71. IR cm^{-1} 1654 cm^{-1} (C=O, ester). ^1H NMR: δ 3.32 (2H, CH_2, s), 3.49 (3H, -OCH_3, s), 7.4 - 7.9 ppm (8H, aryl -H, m). MS: m/z = 303 (12%).

17b, was obtained as yellow substance, 0.27 g (50%) mp 152 °C (acetonitrile). Calcd. for : $C_{18}H_{15}N_3O$ (289.34): C 74.72, H 5.23, N 14.52. Found: C 74.65, H 5.18, N 14.26. IR : 1580 cm^{-1} (C=O, acyl). ^1H NMR : δ 1.4 (3H, CH_3, s), 3.3 (2H, CH_2, s), 7.3 - 8.1 ppm (10H, aryl -H, m). MS: m/z = 289 (15%).

b) **With sodium hydroxide:** The ylide adduct 12a (or 15c, 1.0 g) was refluxed in NaOH (15 ml, 10%) for 2 h, diluted with water to 25 ml, and cooled. After acidification with 10% HCl, the yellow precipitated material was filtered off and recrystallized from the appropriate solvent to give 17 (Mp, mixed mps and comparative IR spectra).

Remarkably, best yields of 17 were attained from method (b). Attempts to carry out reactions (1) and (2) on the product mixtures of the first experiment were unsuccessful. Thus when the produced complicated mixture was chromatographed on silica gel afforded very poor yields.

3. *Pyrolysis of 12 and 15:*

a) **Thermal decomposition of 12a,b and 15a,b:** The ylide adduct 12a,b (or 15a,b, 1.0 g) was heated (bath temp. 280 °C) for one hour under reduced pressure (5 mm/Hg) in a cold finger sublimator. The substance that sublimed was boiled in light petroleum. The colourless crystals that separated after concentration and cooling were collected and proved to be triphenylphosphine. The residue that left in the receiver was crystallized from CH_2Cl_2 - ether to give yellow crystals of 18.

18a (R^1 and R^2= phenanthrene, R= $COOCH_3$), 0.34 g (65%) mp 102-105 °C (pentane).

Calcd. for $C_{18}H_{11}N_3O_2$ (301.31) : C 71.28, H 4.32, N 13.85. Found: C 71.16, H 4.21, N 13.64. IR: 1715 (C=O), 1620 (C=C). ^{1}H NMR : δ 3.78 (3H, OCH_3, s), 7.3-7.9 (8H, aryl - **H**, m). MS: m/z = 301 (18%).

18b (R^1 and R^2= phenanthrene, R= $COOC_2H_5$), 0.4 g (72%) mp 108-110 °C (pentane). Calcd. for $C_{19}H_{13}N_3O_2$ (315.337). C 72.37, H 4.15, N 13.33. Found : C 72.24, H 4.02, N 13.26. IR, cm^{-1} : 1695 (C=O), 1622 (C=C). ^{1}H NMR : δ 0.8 (3H, CH_3, t), 4.0 (2H, OCH_2, q), 7.3-7.9 (8H, Ar-**H**, m). MS: m/z = 315 (16%).

18c (R^1= R^2= phenyl, R = $COOCH_3$), 0.3 g (58%) 68-70 °C (pentane). Calcd. for $C_{18}H_{13}N_3O2$ (303.32): C 71.28, H 4.32, N 13.85. Found: C 71.17, H 4.28, N 13.66. IR, cm^{-1} 1665 (C=O), 1622 (C=C). ^{1}H NMR : δ 3.65 (3H, OCH_3, s), 7.3-7.95 (10H, Ar-**H**, m). MS: m/z = 303 (8%).

18d (R^1 = R^2 = phenyl, R = $COOC_2H_5$), 48%, mp 60-62 °C (pentane). Calcd. for $C_{19}H_{15}N_3O_2$ (317.35): C 71.91, H 4.76, N 13.24. Found: C 71.83, H 4.49, N 13.02. IR, cm^{-1} : 1675 (C=O), 1615 (C=C). ^{1}H NMR : δ 0.9 (3H, CH_3, t), 3.85 (2H, OCH_2, q), 7.3-8.11 ppm (10H, Ar-**H**, m). MS: m/z = 317 (12%).

b) **Thermal decomposition of 12c and 15c:** The titled phosphorane (1.0 g) was heated for 1 h at 280°C/5 mm in a cold finger sublimator. The substance that sublimed was boiled in pentane. The yellow crystals that separated after concentration and cooling were collected and proved to be 19a and 19b, respectively.

19a (R^1= R^2= phenanthrene), 0.34 g (73.8%), mp. 64-66 °C. Calcd. for $C_{18}H_{11}N_3$ (269.31): C 80.28, H, 4.11, N 15.6. Found: C 80.15, H 4.06, N 15.45 IR: 2265 cm^{-1} (C≡C). ^{1}H NMR : δ 1.32 (3H, CH_3, s), 7.3-7.98 ppm (8H, Ar-**H**, m). ^{13}C NMR: δ 82.7 (C.CH_3), 77.5 ppm (C≡CR).

19b (R^1= R^2= phenyl), 0.3 g (68%), mp 46-48 °C. Calcd for $C_{18}H_{13}N_3$ (271.33): C 79.68, H 4.83, N 15.48. Found: C 79.62, H 4.77, N 15.36. IR: 2262 cm^{-1} (C≡C). ^{1}H NMR : δ 1.29 (3H, CH_3, s), 7.3-7.95 ppm (10H, Ar-**H**, m). ^{13}C NMR: δ 85.2 (C.CH_3), 75.8 ppm (C≡C.CH_3).

The residue left in the receiver was crystallized from ethanol to give triphenylphosphine oxide.

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