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SYNTHESIS OF STABLE PHOSPHORUS YLIDES VIA THREE COMPONENT REACTION OF TRIPHENYLPHOSPHINE, DIALKYL ACETYLENEDICARBOXYLATES AND 1- HYDROXY ISOQUINOLINE OR 4-HYDROXY QUINAZOLINE

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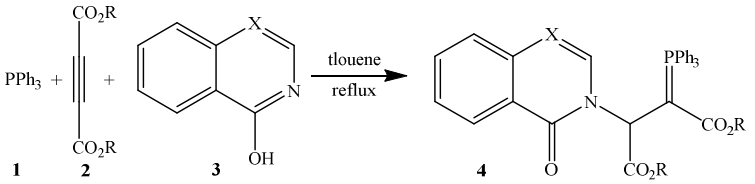
Abstract:
Stable phosphorus ylides are obtained in excellent yields from the 1:1:1 addition reaction between 1-hydroxy isoquinoline or 4-hydroxy quinazoline and dialkyl acetylenedicarboxylates in the presence of triphenylphosphine. These ylides exist in solution as a mixture of two geometric isomers.

Keywords: Triphenylphosphine; Acetylenic ester; phosphorus ylides; 1-hydroxy isoquinoline; 4-hydroxy quinazoline; Three Component Reaction.

Introduction

Phosphorus ylides are reactive compounds, which take part in many reactions of value in the synthesis of organic products [i-iv]. They are synthetic targets of interest, because of their value for a variety of industrial, biological and chemical synthetic uses [v, vi]. The α-keto stabilized ylides constitute an important class of hybrid ligands containing both phosphine and ylide functionalities, and can exist in ylidic and enolate forms. This versatility, has allowed the characterization of coordinated ylides in different bonding modes: C-coordinated (through the Ca atom), O-bonded (through the carbonyl O), P-bonded (through the P of the phosphine group), or even situations in which the same ylide shows a combination of bonding modes. Several methods of α-keto stabilized phosphorus ylides containing reaction between triphenyl phosphine, activated esters and OH, CH, and NH acids have been studied and reported [vii-xii]. In continuation of our interest in the application of triphenyl phosphine in MCRs [xii-xvii]
, we report herein an efficient synthesis of stable phosphorus ylides **4** from triphenyl phosphine **1**, dialkyl acetylenedicarboxylates **2**, and strong NH acids, such as 1-hydroxy isoquinoline and 4-hydroxy quinazoline.



1 2 3 4

2	R
a	Me
b	Et
c	*t*-Bu

3	X
a	C
b	N

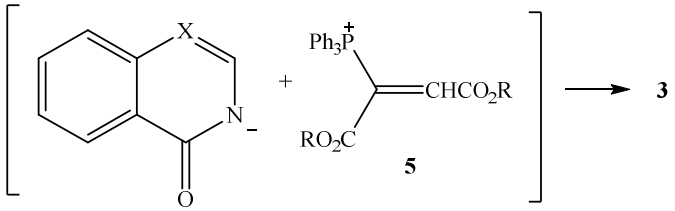
4	R	X	yield %
a	Me	C	93
b	Et	C	80
c	*t*-Bu	C	95
d	Me	N	82
e	Et	N	74
f	*t*-Bu	N	88

Scheme 1: Typical procedure for synthesis of compounds **4a-f**.

Results and discussion

The reaction of 1-hydroxy isoquinoline **3a** with dialkyl acetylenedicarboxylates **2** in the presence of triphenylphosphine proceeded spontaneously in toluene at reflux temperature and needed within 24 h to finish. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of stable phosphorus ylides (Scheme 1). No other products than **4** could be detected. The structures of compounds **4a**–**4f** were deduced from their elemental analyses and IR, ^{1}H, ^{13}C, and ^{31}P NMR spectra. The mass spectra of these stable ylides displayed molecular ion peaks at appropriate *m/z* values. Any initial fragmentation involves loss from, or complete loss of the side chains and scission of the heterocyclic ring system.

Mechanistically, it is conceivable that the reaction involves the initial formation of a zwitterionic intermediate between Ph_3P and the acetylenic compound and subsequent protonation of reactive 1:1 adduct followed by electrophilic attack of the nitrogen atom of the anion of the NH-acid to the vinylphosphonium cations **5** to generate ylides **4** (Scheme 2).

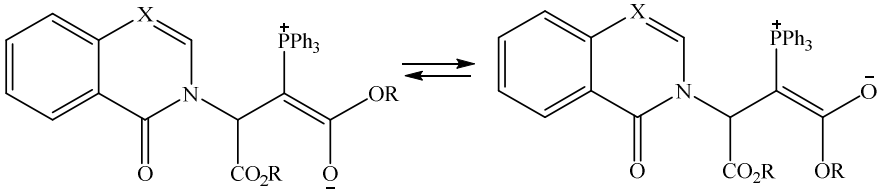


Scheme 2: A possible mechanism for preparation of **4**

^{1}H, ^{13}C, and ^{31}P NMR spectra of the ylides **4a**, **4b**, **4d** and **4e** are consisted with the presence of two diastereoisomers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and rotation about the partial double bond in the (*E*)-**4** and (*Z*)-**4** geometrical isomers (Scheme 2) is slow on the NMR time scale at room temperature. Selected ^{1}H, ^{13}C, and ^{31}P NMR chemical shifts and coupling constants in the major (M) and minor (m) geometrical isomers of compounds **4a**–**4f** are shown in Table 1. Only one geometrical isomer was observed for the di *tert*-butyl derivatives **4c** and **4f**, presumably, because of the bulky tertbutyl groups.

The ^{1}H NMR spectrum of **4a** in $CDCl_3$ at room temperature exhibits two sharp singlets for the CO_2CH_3 groups of (*E*) and (*Z*) isomers and two singlets for the OCH_3 groups along with two doublets for methine protons. A fairly complex multiplet was observed for aromatic protons of triphenylphosphine and 1-hydroxy isoquinoline at δ = 6.52–8.08 ppm.

Table 1: Selected ^{1}H, ^{13}C and ^{31}P NMR chemical shifts (δ /ppm) and coupling constants (J = Hz) for H, OR, CO_2R, C-2 and C-3 in the major (M) and minor (m) diastereomers of compounds **4a–4f**



(*Z*)-**4**; Major (*E*)-**4**; Minor

Cmpd	Isomer (%)	^{1}H NMR			^{13}C NMR		^{31}P NMR
		H ($^{3}J_{PH}$)	CO_2R	OR	C ($^{2}J_{pc}$)	C ($^{1}J_{pc}$)	
4a	M (57)	5.62 (17.8)	3.74	3.18	58.5 (17.4)	42.4 (124.3)	24.29
	m (36)	5.56 (19.5)	3.62	3.65	53.9 (16.9)	42.0 (124.0)	24.20
4b	M (62)	5.61 (18.0)	4.15	3.75	60.2 (17.8)	41.4 (125.0)	24.28
	m (18)	5.55 (20.0)	4.10	4.26	61.2 (15.8)	43.0 (127.5)	24.24
4c	M(95)	5.49 (18.5)	1.54	0.98	58.7 (18.8)	41.1 (125.5)	24.26
5a	M (47)	5.46 (19.0)	3.79	3.17	57.4 (17.8)	41.8 (134.0)	24.25
	M (43)	5.45 (17.4)	3.61	3.76	53.94 (16.5)	42.0 (134.2)	24.22
5b	M (59)	5.46 (18.1)	4.18	3.79	61.3 (17.1)	47.0 (125.8)	24.27
	M (15)	5.75 (17.8)	4.28	-	55.72 (17.6)	41.2 (124.6)	24.21
5c	M (88)	5.34 (18.3)	1.59	0.97	54.64 (17.5)	42.4 (133.8)	24.20

Experimental

General

Compounds **1**, **2** and Ph_3P were obtained from Fluka and were used without further purification. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz, respectively; δ in ppm. EI-MS (70 eV): Finni-gan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyser.

General Procedure for the Preparation of compound **4**

To a stirred solution of 0.52 g of Ph_3P (2 mmol) and 0.19 g **1** (2 mmol) in toluene (10 ml) was added drop wise a mixture of **2** (2 mmol) in toluene (2 ml) at room temperature over 5 min. The reaction mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure, and the viscous residue was purified by column chromatography (SiO2; hex-ane/AcOEt 1:1) to afford the pure adducts.

dimethyl 2-(1-oxoisoquinolin-2(1H)-yl)-3-(triphenyl-λ^{5}-phosphanylidene)succinate (4a)

Yellow Oil; yield: 1.02 g (93%); IR (KBr) υ: 1730 (C=O), 1644 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ/ppm: 3.18 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.62 (d, 1H, $^{3}J_{PH}$ =17.8, CH), 6.52 (d, 1H, $^{3}J_{HH}$ = 7.5 Hz, CH), 7.33-7.62 (m, 18H, Ar-*H*), 7.96 (d, 1H, $^{3}J_{HH}$ = 7.6 Hz, CH), 8.12 (d, 1H, $^{3}J_{HH}$ = 8.1 Hz, CH); ^{13}C NMR ($CDCl_3$) δ/ppm: 42.4 (d, $^{1}J_{PC}$ = 124.3 Hz, CH), 49.4 (OCH_3), 52.7 (OCH_3), 58.5 (d, $^{2}J_{PC}$ =17.4, CH), 105.0 (CH), 125.5 (CH), 125.8, (CH), 126.8 (d, $^{1}J_{PC}$ = 91.5 Hz, C_{ipso}), 127.8 (CH), 128.8 (d, $^{3}J_{PC}$ = 12.5 Hz, C_{meta}), 131.0 (CH), 131.6 (CH), 132.3 (d, $^{4}J_{PC}$ =

1.0 Hz, C_{para}), 133.4 (d, $^2J_{PC}$ = 9.7 Hz, C_{ortho}), 134.6 (C), 137.3 (C), 161.0 (C=O), 169.5 (d, $^3J_{PC}$ = 12.0 Hz, C=O), 170.1 (d, $^2J_{PC}$ = 12.7 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ/ppm: 24.29; MS *m/z*: 549 (M+, 12 %) and 287 (M^+-262). Anal. Calcd. for $C_{33}H_{28}NO_5P$: C 72.12, H 5.14, N 2.55; found: C 72.19, H 5.08, N 2.61.

diethyl 2-(1-oxoisoquinolin-2(1H)-yl)-3-(triphenyl-λ^5-phosphanylidene)succinate (4b)

Yellow Oil; yield: 0.92 g (80%). IR (KBr) υ: 1747 (C=O), 1651 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ/ppm: 0.48 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.26 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.75 (complex (AB)X_3 system, 2H, OCH_2), 4.15 (complex (AB)X_3 system, 2H, OCH_2), 5.61 (d, 1H, $^3J_{PH}$ = 18.0 Hz, CH), 6.52 (d, 1H, $^3J_{HH}$ = 7.5 Hz, CH), 7.33-7.67 (m, 18H, Ar-*H*), 7.99 (d, 1H, $^3J_{HH}$ = 7.5 Hz, CH), 8.12 (d, 1H, $^3J_{HH}$ = 8.1 Hz, CH); ^{13}C NMR ($CDCl_3$) δ/ppm: 13.9 (CH_3), 14.2 (CH_3), 41.4 (d, $^1J_{PC}$ =125.0 Hz, CH), 60.2 (d, $^2J_{PC}$ =17.8 Hz, CH), 61.3 (OCH_2), 61.9 (OCH_2), 105.1 (CH), 125.3 (CH), 125.7, (CH), 127.5 (d, $^1J_{PC}$ = 90.5 Hz, C_{ipso}), 127.5 (CH), 128.6 (d, $^3J_{PC}$ = 12.2 Hz, C_{meta}), 130.9 (CH), 131.3 (CH), 132.0 (d, $^4J_{PC}$ = 1.1 Hz, C_{para}), 133.5 (d, $^2J_{PC}$ = 9.8 Hz, C_{ortho}), 134.9 (C), 137.8 (C), 161.4 (C=O), 168.2 (d, $^3J_{PC}$ = 12.4 Hz, C=O), 171.3 (d, $^2J_{PC}$ = 13.1 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ/ppm: 24.28; MS *m/z*: 577 (M^+, 25 %) and 315 (M^+-262). Anal. Calcd. for $C_{35}H_{32}NO_5P$: C 72.78, H 5.58. N 2.42; found: C 72.86, H 5.50, N 2.49.

ditert-butyl 2-(1-oxoisoquinolin-2(1H)-yl)-3-(triphenyl-λ^5-phosphanylidene)succinate (4c)

Yellow Oil; yield: 1.20 g (95%). IR (KBr) υ: 1723 (C=O), 1651 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ/ppm: 0.98 (s, 9H, C*Me*$_3$), 1.54 (s, 9H, C*Me*$_3$), 5.49 (d, 1H, $^3J_{PH}$ = 18.5 Hz, CH), 6.52 (d, 1H, $^3J_{HH}$ = 7.5 Hz, CH), 7.29-7.65 (m, 18H, Ar-*H*), 8.03 (d, 1H, $^3J_{HH}$ = 7.5 Hz, CH), 8.08 (d, 1H, $^3J_{HH}$ = 8.0 Hz, CH); ^{13}C NMR ($CDCl_3$) δ/ppm: 28.2 (C*Me*$_3$), 28.4 (C*Me*$_3$), 41.1 (d, $^1J_{PC}$ = 125.5 Hz, P=C), 58.7 (d, $^2J_{PC}$ = 18.8 Hz, CH), 77.6 (*C*Me$_3$), 80.8 (*C*Me$_3$), 104.9 (CH), 125.4 (CH), 125.7 (CH), 126.9 (d, $^1J_{PC}$ = 91.6 Hz, C_{ipso}), 127.9 (CH), 128.6 (d, $^3J_{PC}$ = 12.1 Hz, C_{meta}), 131.3 (CH), 131.4 (CH), 132.0 (d, $^4J_{PC}$ = 2.9 Hz, C_{para}), 133.6 (d, $^2J_{PC}$ = 9.7 Hz, C_{ortho}), 134.6 (C), 137.4 (C), 160.8 (C=O), 169.5 (d, $^3J_{PC}$ = 12.7 Hz, C=O), 170.1 (d, $^2J_{PC}$ = 13.8 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ/ppm: 24.26; MS *m/z*: 633 (M^+, 47 %) and 371 (M^+-262). Anal. Calcd. for $C_{39}H_{40}NO_5P$: C 73.92, H 6.36, N 2.21; found: C 73.98, H 6.30, N 2.29.

dimethyl 2-(4-oxoquinazolin-3(4H)-yl)-3-(triphenyl-λ^5-phosphanylidene)succinate(4d)

Yellow Oil; yield: 0.90 g (82%); IR (KBr) υ: 1699 (C=O), 1666 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ/ppm: 3.17 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.48 (d, 1H, $^3J_{PH}$ =17.5, CH), 7.38-7.63 (m, 18H, Ar-*H*), 8.02 (d, 1H, $^3J_{HH}$ = 7.8 Hz, CH), 8.90 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ/ppm: 41.8 (d, $^1J_{PC}$ = 134.0 Hz, CH), 49.7 (OCH_3), 52.9 (OCH_3), 57.4 (d, $^2J_{PC}$ =17.8 Hz, CH), 121.5 (CH), 125.8 (CH), 126.4 (d, $^1J_{PC}$ = 90.5 Hz, C_{ipso}), 126.6 (CH), 128.5 (d, $^3J_{PC}$ = 12 Hz, C_{meta}), 132.0 (CH), 132.1 (d, $^4J_{PC}$ = 1.1 Hz, C_{para}), 133.6 (d, $^2J_{PC}$ = 9.6 Hz, C_{ortho}), 134.6 (C), 147.4, (CH), 148.9 (C), 160.2 (d, $^3J_{PC}$ = 23.6 Hz, C=O) 162.1 (C=O), 170.1 (d, $^2J_{PC}$ = 9.2 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ/ppm: 24.25; MS *m/z*: 550 (M+, 19 %) and 288 (M^+-262). Anal. Calcd. for $C_{32}H_{27}N_2O_5P$: C 69.81, H 4.94, N 5.09; found: C 69.89, H 4.86, N 5.01.

diethyl 2-(4-oxoquinazolin-3(4H)-yl)-3-(triphenyl-λ^5-phosphanylidene)succinate (4e)

Yellow Oil; yield: 0.85 g (74%). IR (KBr) υ: 1692 (C=O), 1663 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ/ppm: 0.52 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.29 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.79 (complex (AB)X_3 system, 2H, OCH_2), 4.18 (complex (AB)X_3 system, 2H, OCH_2), 5.46 (d, 1H, $^3J_{PH}$ = 18.1 Hz, CH), 7.40-7.67 (m, 18H, Ar-*H*), 8.09 (d, 1H, $^3J_{HH}$ = 7.8 Hz, CH), 8.93 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ/ppm: 14.1 (CH_3), 14.6 (CH_3), 47.0 (d, $^1J_{PC}$ =125.8 Hz, CH), 61.3 (d, $^2J_{PC}$ =17.1 Hz, CH), 61.6 (OCH_2), 62.4 (OCH_2), 121.1 (CH), 125.7 (CH), 126.5 (d, $^1J_{PC}$ = 91.6 Hz, C_{ipso}), 126.2 (CH), 128.6 (d, $^3J_{PC}$ = 12.5 Hz, C_{meta}), 131.6 (CH), 132.0 (d, $^4J_{PC}$ = 1.0 Hz, C_{para}), 133.2 (d, $^2J_{PC}$ = 9.3 Hz, C_{ortho}), 134.5 (C), 147.4, (CH), 148.1 (C), 160.3 (d, $^3J_{PC}$ = 20.0 Hz, C=O) 161.4 (C=O),

169.2 (d, $^{2}J_{PC}$ = 12.6 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ/ppm: 24.27; MS *m/z*: 578 (M^+, 15 %) and 316 (M^+-262). Anal. Calcd. for $C_{34}H_{31}N_2O_5P$: C 70.58, H 5.40, N 4.84; found: C 70.66, H 5.32, N 4.87.

ditert-butyl 2-(4-oxoquinazolin-3(4H)-yl)-3-(triphenyl-λ^5-phosphanylidene)succinate (4f)

Yellow Oil; yield: 1.1 g (88%). IR (KBr) υ: 1739 (C=O), 1672 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ/ppm: 0.97 (s, 9H, C*Me*$_3$), 1.59 (s, 9H, C*Me*$_3$), 5.34 (d, 1H, $^{3}J_{PH}$ = 18.3 Hz, CH), 7.35-7.74 (m, 18H, Ar-*H*), 8.00 (d, 1H, $^{3}J_{HH}$ = 7.8 Hz, CH), 8.96 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ/ppm: 28.0 (C*Me*$_3$), 28.1 (C*Me*$_3$), 42.4 (d, $^{1}J_{PC}$ = 133.8 Hz, CH), 54.6 (d, $^{2}J_{PC}$ = 17.5 Hz, P=C–*C*H), 77.6 (*C*Me$_3$), 80.8 (*C*Me$_3$), 121.6 (CH), 126.1 (CH), 126.3 (d, $^{1}J_{PC}$ = 91.9 Hz, C_{ipso}), 126.7 (CH), 128.8 (d, $^{3}J_{PC}$ = 12.2 Hz, C_{meta}), 132.0 (CH), 132.2 (d, $^{4}J_{PC}$ = 1.2 Hz, C_{para}), 133.5 (d, $^{2}J_{PC}$ = 9.8 Hz, C_{ortho}), 134.6 (C), 147.9, (CH), 148.2 (C), 160.0 (d, $^{3}J_{PC}$ = 20.5 Hz, C=O) 161.8 (C=O), 169.5 (d, $^{2}J_{PC}$ = 12.4 Hz, C=O); ^{31}P NMR ($CDCl_3$) δ/ppm: 24.20; MS *m/z*: 634 (M+, 36 %) and 372 (M^+-262). Anal. Calcd. for $C_{38}H_{39}N_2O_5P$: C 71.91, H 6.19, N 4.41; found: C 71.98, H 6.10, N 4.47.

Conclusion

In conclusion, the present method features the advantages that can be the reaction performed under neutral conditions and the starting materials and reagents can be mixed without any activation or modification. Phosphorus ylides **4a**–**4f** can be considered as potentially useful synthetic intermediates.

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