A FACILE APPROACH TO N-HETEROCYCLES. THE REACTIONS OF YLIDE PHOSPHORANES WITH HYDRAZONES

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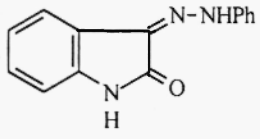
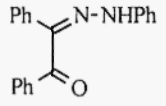
Abstract: The reactions of isatin-β-phenylhydrazone **1** and benzil monophenylhydrazone **2** with some ester- **3a,b** and keto ylides **3c** were studied in details, under different experimental conditions with the aim of evaluating the synthetic potential of this approach for the synthesis of N-heterocyclic systems. Structures of the new compounds were established on the basis of elemental and spectroscopic analyses.

Introduction

As a contribution to previous studies of phosphonium ylides for the synthesis of N-heterocyclic compounds (1), the reactivity of methoxy-, ethoxycarbonyl- and acetylmethylenetriphenylphosphorane **3a-c** toward isatin-β-phenylhydrazone **1** and benzil monophenylhydrazone **2** has now been investigated for the synthesis of the corresponding heteronitrogen cycles. Relatively little work has been reported (2,3) on the behaviour of this class of compounds, hydrazones, toward stabilized phosphorus ylides.



1



2

$Ph_3P=CHCOR$

3

a, R = OCH_3
b, R = OC_2H_5
c, R = CH_3

Results and Discussion

Treatment of hydrazone **1** with equimolar amounts of **3a** or **3b**, respectively, in boiling toluene (containing benzoic acid) for 60 h gave, after separation on column chromatography, red needles of spiro-ylide phosphorane structure **5** (~68%). The structure of compound **5** is elucidated by its analytical and spectral properties (Tables I and II).

It may be considered that ylide **5** is formed by an initial nucleophilic attack by an carbanion center in the ylide **3a,b** on the activated carbon-nitrogen double bond in **1** to give a resonance hybride like **4**, followed by intramolecular cyclization to afford **5** *via* the expulsion of an alcohol moiety in accordance with the mechanism, previously reported by Strandtmann *et al* (2,4) (Scheme 1).

TABLE I: Analytical Data, Physical Properties and IR spectra for the products **5**,**6**,**8**,**9**,**10**, **11**,**15** and **17**

Comp.	m.p. °C	Mol. Form. (M. wt)	Anal. Found (Calcd.)% C	H	N	M^+ m/z%	IR, ν cm^{-1} C=O ester	C=O ring	others
5[a,b]	308-10	$C_{34}H_{26}N_3O_2P$	75.71	4.83	7.84	539		1637	1436 (C=P)
		(539.586)	75.68	4.85	7.79	48			980 (Ar-P)
6[a]	245-47	$C_{16}H_{13}N_3O_2$	68.74	4.66	14.97	279		1641	
		(279.304)	68.80	4.69	15.05	39			
8a[a]	330-32	$C_{17}H_{15}N_3O_3$	66.09	4.82	13.49	309	1720		
		(309.331)	66.00	4.89	13.58	68			
8b[a]	344-46	$C_{18}H_{17}N_3O_3$	66.95	5.19	12.87	323	1714		
		(323.358)	66.86	5.30	12.99	25			
9a[a]	105-7	$C_{16}H_{15}N_3O$	72.34	5.75	15.95	265			1622 (C=C)
		(265.320)	72.43	5.69	15.84	100			1570(C=N)
9b[a]	119-21	$C_{17}H_{17}N_3O$	73.21	6.26	15.13	279			1618(C=C)
		(279.347)	73.09	6.13	15.04	100			1570(C=N)
10[a,c]	278-80	$C_{35}H_{30}N_3O_2P$	75.56	5.31	7.48	555	1735		1510(C=P),
		(555.629)	75.66	5.44	7.56	36	(acetyl)		980 (Ar-P)
11[a]	121-23	$C_{17}H_{17}N_3O_2$	69.04	5.68	14.27	295	1730		
		(295.347)	69.13	5.80	14.23	83	(acetyl)		
15	118-20	$C_{23}H_{18}N_2O$	81.59	5.41	8.31	338	1730		
		(338.413)	81.63	5.36	8.28	58	(acetyl)		
17	164-66	$C_{20}H_{17}NO$	83.62	5.91	4.83	287	1738		
		(287.364)	83.59	5.96	4.87	72	(acetyl)		

a) NH group lies in ν 3376-3355 cm^{-1} region and C=O (amide) lies in ν 1680-1700 cm^{-1} region b) Compound **5** has elemental analysis for P= 5.91 (5.74) c) Compound **10** has elemental analysis for P= 5.65 (5.58).

TABLE II: ^1H NMR (δ, ppm) data for products **5**,**6**,**8**,**9**,**10**,**11**,**15** and **17**

Comp.	C-CH_3/ N-CH_3/ N-CH_2	CH_2	OCH_3/ OCH_2	CH-NH	NH
5b[c]	-	-	-	-	8.62 (s, 1H)
					12.69 (s, 1H)
6	-	3.01& 3.03 (2d. 2x1H)	-	-	8.73 (s, 1H)
		J_{HH} = 6.8 Hz			12.51 (s, 1H)
8a[c]	-	2.11 (s, 2H)	3.78 (s, 3H)	-	12.65 (s, 1H)
8b	1.35 (t, 3H, J_{HH} = 6Hz)	2.34 (s, 2H)	4.01 (q, 2H, J_{HH} = 6 Hz)	-	12.68 (s, 1H)
9a[c]	1.18 (t, 3H, J_{HH} = 7 Hz)	2.54 (q, 2H, J_{HH} = 7 Hz)	-	-	12.55 (s, 1H)
9b	1.02 (t, 3H, J_{HH} = 6.5 Hz)	1.7 (sixtet. 2H),	-	-	12.54 (s, 1H)
	2.68 (t, 2H, J_{HH} = 6.5 Hz)	J_{HH} = 6.5 Hz			
10b[b,c]	2.55 (s, 3H)	-	-	4.25 (d, 1H)	12.32 (d, 1H)
				J_{HH} = 6.8 Hz	J_{HH} = 6.8 Hz
11	2.37 (s, 2H),	-	-	4.39 (d, 1H)	12.41 (d, 1H)
	2.85 (s,3H)			J_{HH} = 7 Hz	J_{HH} = 7 Hz
15[c]	2.68 (s, 3H)	-	-		
17[c]	2.43 (s, 3H),	-	-		
	2.8 (s, 3H)				

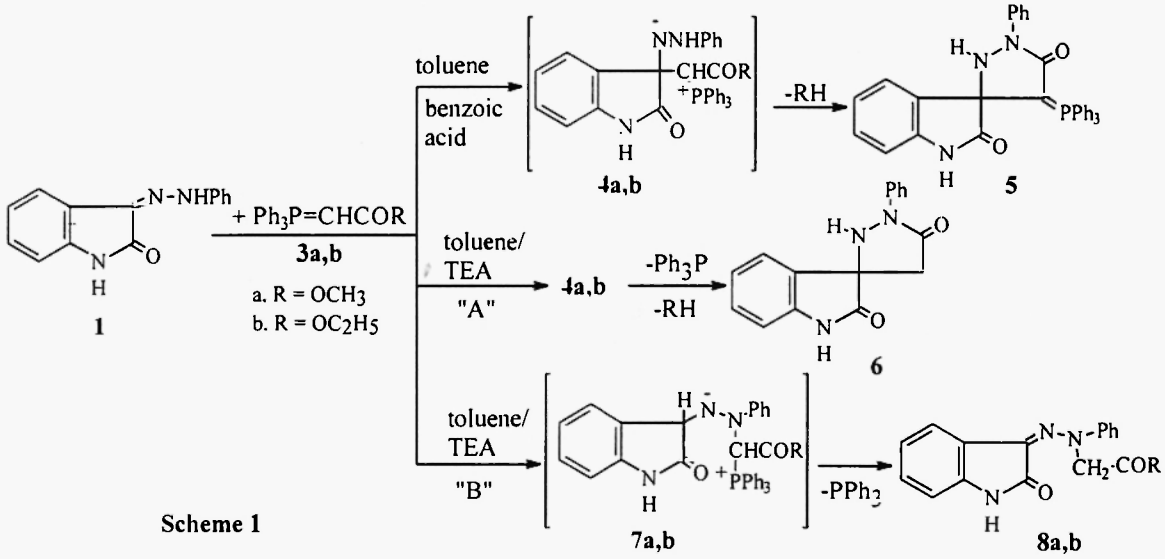
a) Aromatic hydrogen protons lie in δ 7.1-8.46 ppm region

b) ^{31}P NMR spectrum of compound **5** showed a singlet at δ_P = 24.8 ppm and for compound **10** a singlet at δp = 22.5 ppm.

c) ^{13}C NMR measurements for compounds: **5**, δ_C: 143.6 (d, $^1J_{CP}$ = 124.9 Hz, **C**=P), 170.5 & 173.2 ppm (2x d, J = ~8 Hz, 2 C=O); **8a**, δ_C: 28.4 (**CH_2**), 51.7 (**OCH_3**), 164.9 (**C**=O, ester), 170.5 (C=O, amide); **9a**, δ_C: 16.3 (**CH_3**), 44.2 (N-**CH_2**), 143.1 (=**C**-N), 172.5 ppm (**C**=O, amide); **10**, δ_C: 22.3 (C(O)**CH_3**), 47.4 (**CH**-NH), 131.7 (d, J = 97.5 Hz, **C**=P), 171.3 (**C**=O, amide), 189.2 ppm (**C**=O, acetyl); **15**, δ_C: 23.4 (C(O)**CH_3**, 190.3 ppm (**C**=O, acetyl); **17**, δ_C: 15.41 (**CH_3**), 22.5 (C(O)**CH_3**), 193.4 ppm (**C**=O, acetyl).

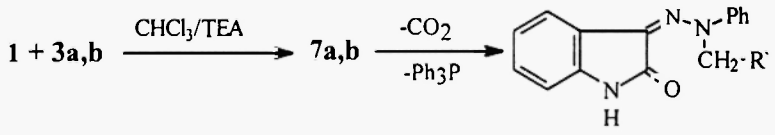
In order to study the base effect on the course of the Wittig reaction, reaction of **1** and **3a,b** was carried out in the presence of triethylamine (TEA). Chromatographic separation of the product mixture produced two yellow crystalline products **6** and **8a** or **8b**, respectively.

Structures **6** and **8** were based on the satisfactory analytical and spectral evidence (*cf.* Tables I and II). Formation of the pyrazolinone **6** can be rationalized in terms of the addition-elimination mechanism (2,5,6) (Scheme 1, A). Following an initial addition to generate **4**. Hofmann elimination of triphenylphosphine leads to the formation of the heterocyclic compound **6** accompanied by elimination of a molecule of the appropriate alcohol. Conversely, the formation of **8** is assumed to proceed through an initial attack of the carbanion center in **3a,b** on the active nitrogen atom in **1** to form the betaine **7a,b**, followed by intra Hofmann elimination of Ph_3P to afford **8a,b** (Scheme 1, B).



Scheme 1

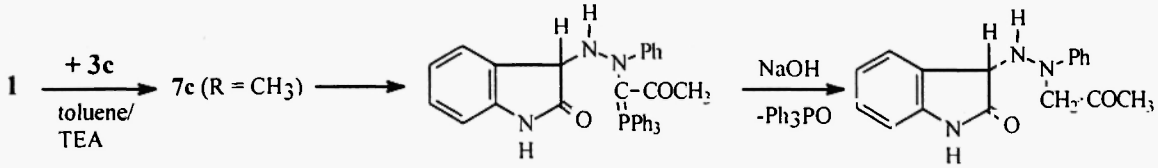
Repetition of the above reaction between the hydrazone **1** and **3a,b** in boiling chloroform containing TEA or benzoic acid for two days furnished compound **9a** or **9b**, respectively, (*cf.*, Tables I and II). It is suggested that **9** is arisen through the decarboxylation of the betaine **7a,b**. Decarboxylation process can be looked upon as being catalysed by the alkylidene phosphoranes acting as Lewis bases (7) (Scheme 2).



9a,b; a, R` = CH_3
b, R` = C_2H_5

Scheme 2

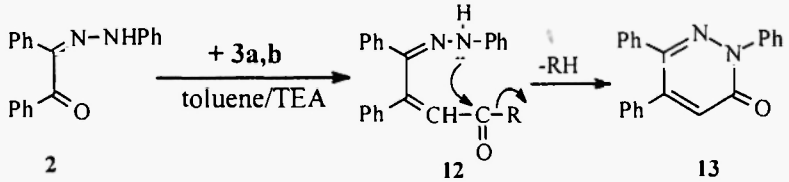
On allowing the hydrazone **1** to react with acetonylmethylenetriphenylphosphorane **3c** in refluxed toluene containing TEA for ~ 3 days (TLC), the new ylide **10** was obtained (Scheme 3), which crystallized directly from the product mixture in a pure form. Obviously, the betaine analogue **7c** (R = CH_3), thus produced is mainly stabilized *via* migration of the α-proton to the electron-rich center of the molecule (6). On treating **10** with 10% (aq.) sodium hydroxide, the expected product **11** was obtained.



10 **11**

Scheme 3

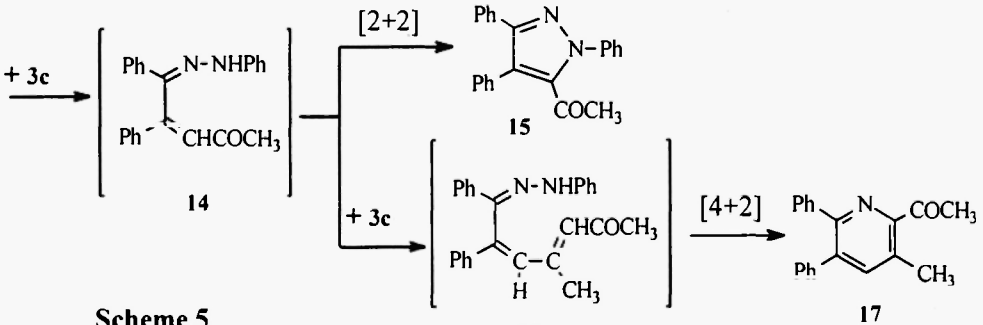
When benzil monophenylhydrazone **2** was treated with an equimolar amount of **3a** or **3b**, respectively, in boiling toluene containing (TEA or benzoic acid), the expected pyridazinone **13** (~81%) (2) was isolated and identified (Scheme 4). Compound **13** was previously obtained by the reaction of the hydrazone **2** with accumelene ylide (**8**).



2 **12** **13**

Scheme 4

Next, the behaviour of hydrazone **2** toward the ylide phosphorane **3c** was also investigated (Scheme 5). When **2** was caused to react with **3c** (2 equiv.) in the presence of (TEA or benzoic acid), in boiling toluene, the reaction afforded two compounds **15** and **17**. Obviously, compounds **15** and **17** are produced *via* the corresponding primary mono-olefinated intermediate **14**, which by [2+2] intramolecular cyclization affords the pyridazine derivative **15**. Further Wittig reaction of the acetonyl-carbonyl (4,6,9) of **14** with a second ylide species **3c** affords the intermediate **16**. However, the latter step can be followed by [4+2] intramolecular cyclization to give the pyridine derivative **17** accompanied by extrusion of ($PhNH_2$) species.



14 **15** **16** **17**

Scheme 5

In conclusion, the title reactions provide an easy synthetic route for the preparation not only for new ylides, similar to **5** and **10**, but also for spiro N-heterocycle derivatives in moderate yields. The manuscript, however, described the competition between two options available in **1** and **2** to be attacked by the stabilized ylides.

Experimental

Melting points are uncorrected. IR spectra were obtained with a Philips Infracord spectrophotometer model PU 9712 in KBr. ^{1}H-, ^{13}C-NMR spectra were recorded in $CDCl_3$ or [D_6] DMSO as solvents on a Jeol-270 MHz spectrometer. The ^{31}P-NMR spectra was taken with a Varian CFT-20 (*vs.* external 85% H_3PO_4).

I. Reaction of Isatin-β-phenylhydrazone **1** *with Ylides* **3a,b.** *General Procedure*:

I.a) In Toluene (benzoic acid): A suspension of hydrazone **1** (10) (1 g, 3.3 mole) and **3a** or **3b** (11) (3.8 mmol) in (50 ml) dry toluene (benzoic acid) was refluxed for 60 h. After evaporation of the solvent, the remainder was subjected to column chromatography on silica gel. Elution with hexane/chloroform (3:7 *v/v*) afforded red needles of **5** (1.54 g, 68%) from ethyl acetate, physical and spectral data of compound **5** are listed in Tables I and II.

I.b) In Toluene (TEA): The above reaction was repeated in boiling toluene containing triethylamine (TEA) using the same amounts. After usual work up, two compounds were obtained: a) yellow crystals (hexane/chloroform, 2:8 *v/v*) of **6;** b) pale yellow crystals (ethyl acetate) of **8a** (0.28 g, 22%) from $CHCl_3$ or **8b** (0.24 g, 18%) from ethyl acetate. Ph_3P was also obtained and identified by mp., mixed mps and comparative IR. Compound 6 was obtained from (**1+3a**) (0.42 g, 36%) from dichloromethane and obtained from (**1+3b**) in (0.37 g, 32%). Data for compounds **6** and **8a,b** are tabulated in Tables I and II.

I.c) In Chloroform: The same reaction was repeated in boiling chloroform (TEA or benzoic acid, best yield with TEA) for two days. After usual work up, yellow crystals (hexane/$CHCl_3$, 7:3 *v/v*) of **9a** (0.64 g, 57%) from cyclohexane or **9b** (0.61 g, 52%) from cyclohexane, respectively, were isolated (see Tables I and II). Ph_3P was also isolated and identified.

II. Reaction of Monohydrazone **1** *with* **3c**: A mixture of hydrazone **1** (1 g, 3.3 mmol) and acetonylmethylene-triphenylphosphorane **3c** (12) (1.2 g, 3.8 mmol) in toluene (TEA) was refluxed for ~3 days (TLC). The material that precipitated after concentration and cooling was filtered off and recrystallized from dichloromethane to give yellow solid (1.68 g, 72%) of the new phosphorane **10**. Physical properties and spectral data for **10** are given in Tables I and II.

Alkaline treatment of **10**: The ylide adduct **10** (1 g) was refluxed in NaOH (20 ml, 10%) for 2 h, diluted with water (30 ml), and cooled. After acidification with 10% HCl, the yellow precipitated material **11** was filtered off and recrystallized from cyclohexane (0.35 g, 66%). See Tables I and II for physical and spectral data. Ph_3PO was also obtained and identified by mp., mixed mps and comparative IR spectra.

III. Reaction of Benzil monophenylhydrazone **2** *with Ylides* **3a,b**: *General Procedure*: A mixture of **2** (13) (1.2 g, 4 mmol) and Wittig reagents **3a,b** (4.2 mmol) was refluxed in dry toluene (50 ml) containing TEA for ~ 2 days (TLC). The product mixture was separated by column chromatography on silica gel. Elution with hexane/$CHCl_3$ (8:2 *v/v*) afforded the pyridazinone derivative **13** as straw yellow crystals (1.05 g, 81%), mp. 243-45 °C. Lit. (8) 247 °C. Ph_3PO was also eluted and identified.

IV. Reaction of Hydrazone **2** *with Ylide* **3c**: A suspension of **2** (1.2 g, 4 mmol) and ylide **3c** (2.7 g, 8.5 mmol) in 50 ml toluene in the presence of (TEA) was heated under reflux for 65 h and then column chromatographed on silica gel (hexane/ethyl acetate). The fraction (8:2 *v/v*) yielded (0.29 g, 21%) of **15** as light yellow crystals from cyclohexane. Elution with (1:1 *v/v*) afforded yellow crystals of the pyridine derivative **17** (0.42 g, 37%) from dichloromethane. Ph_3PO was also eluted and proved. See Tables I and II for the data of **15** and **17**.

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