Chemistry Letters

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Advance Publication on the web September 23, 2017
doi:10.1246/cl.170758

Syntheses of 3-Oxo-λ^5-benzophospholes by an Intramolecular Cyclization of Phosphorus-ylide

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Three synthetic procedures have developed for a new class of phosphorus-ylide containing conjugate heterocycles, 3-oxo-λ^5-benzophospholes. The key to the heterocycle is unusual intramolecular acylation of phosphorus-ylide forming an endocyclic ylide. Several types of 2-substituted benzophospholes are synthesized, some of which showed a fluorescence.

Phosphorus-containing conjugate heterocycles have recently received much attention due to their characteristic properties.[1] In the previous paper,[2] we have reported a new class of phospholes as symmetrical bis-phosphole **1** (Figure 1), containing carbonyl-stabilized phosphorus ylide in the cycle. According to molecular orbital calculations at B3LYP/6-31G(d) level, the ylide-containing phosphole **2** is expected to show a characteristic property due to a narrow HOMO-LUMO gap and high lying HOMO, compared with phosphole and phosphole oxide (Figure 2). However, no general synthetic procedure for this type of ylide-containing phospholes **2** is disclosed; the only existing compound having this type of structure is bis-phosphole **1** despite recent active research on several types of phospholes.

Herein, we wish to report a new approach for monocyclic benz-annulated 3-oxo-λ^5-phospholes by a new intramolecular acylation of phosphorus-ylide (Scheme 1).

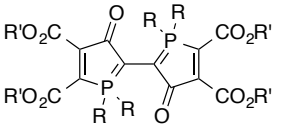


Figure 1. Bis-3-oxo-l^5-phosphole **1**.[2]

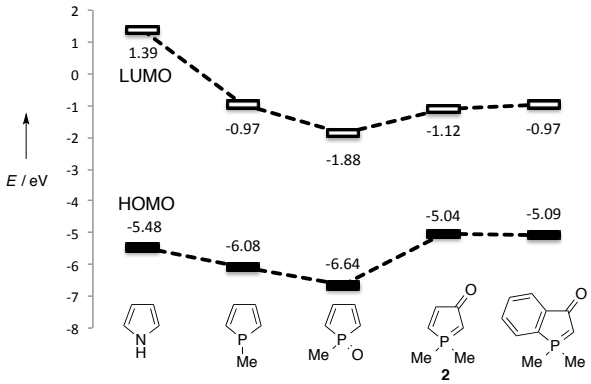
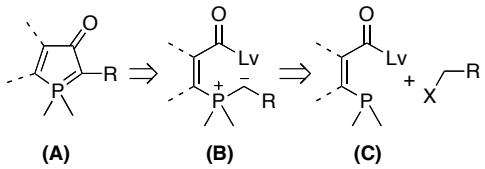


Figure 2. Comparison of the HOMO and LUMO energy levels among pyrrole, phospholes and the ylide-containing phospholes based on calculations at the B3LYP/6-31G(d) level.

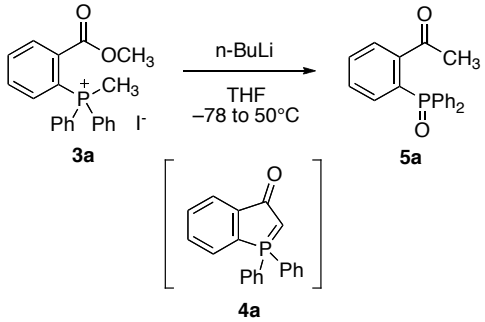


Scheme 1. Intramolecular ylide-acylation approach.

To construct an oxophosphole ring (A), we planned to apply an intramolecular acylation of a *cis*-β-phosphinylacryloyl compound (B) having an ylide; a leaving group (Lv) on the carbonyl carbon is essential.[3] The precursor (B) would be generated from the corresponding phosphonium salt that would be prepared from a cis-phosphanylacrylate (C) and haloalkane.

Methyl *ortho*-phosphinylbenzoate was chosen as a model substrate to test the plan without difficulties of stereocontrolled synthesis of *cis*-β-phosphinylacrylates. In addition, the resulted benz-annulated 3-oxo-λ^5-phosphole is also an attractive derivative of **2** (Figure 2). Though only limited examples have appeared for acylation of ylides with esters,[4-6] we expected that the ylide fixed near the carbonyl group would react with a methyl ester to form an endocyclic ylide.

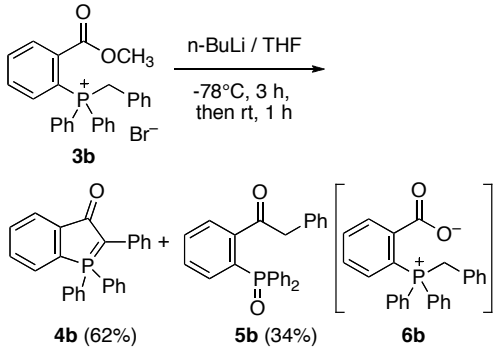
As an initial attempt, methylphosphonium salt **3a** was reacted under usual ylide-generating conditions,[7] followed by heating for cyclization (Scheme 2).



Scheme 2. An initial attempt of cyclization.

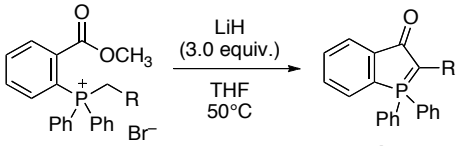
Unfortunately, 3-oxophosphole **4a** was not isolated; **5a** was obtained instead after aqueous workup, where the methyl group was actually transferred from the phosphorus to the carbonyl carbon. It is reasonable to assume that **5a** was formed through **4a** or an equivalent, and followed by hydrolysis resulted in a ring-opening.[8] Actually, phenyl-substituted **4b** was isolated from **3b** and *n*BuLi with considerable amount of ring-opened side product **5b** after aqueous workup (Scheme 3). Survey of a base revealed that

LiH is the best suited for this ylide-cyclization.[9] Use of an excess amount of LiH is essential; the methoxide formed during the initial cyclization may be insufficient to deprotonate from the intermediate cyclic phosphonium salt which is subsequently hydrolyzed to give the product **5a**. Since excess use of *n*BuLi causes unfavorable reaction with an ester, less nucleophilic LiH is suitable for this cyclization. 2-Aryl-3-oxo-λ^5-benzophospholes were obtained in fairly good yields, regardless of the nature of the substituent (Table 1).



Scheme 3. Formation of **4b** by using *n*-BuLi.

Table 1. Synthesis of 2-Aryl-3-oxobenzophosphole (method A).[a]



Entry	R	Time (h)	Product	Yield (%)[b]
1	Ph	19	**4b**	74[c]
2	*p*-CNC_6H_4	3.5	**4c**	83
3	*m*-CNC_6H_4	12	**4d**	60
4	*p*-$MeOC_6H_4$	5.5	**4e**	60
5	*m*-$MeOC_6H_4$	8	**4f**	78
6	*o*-$MeOC_6H_4$	6	**4g**	52
7	*p*-*t*BuC_6H_4	5	**4h**	72[c]
8	2-Pyridyl[d]	24	**4i**	82

a) **3** prepared in situ was used without purification. b) Isolated yields. c) NMR yield determined by ^{31}P NMR.[10] d) Hydrobromide was used with 4.0 equiv. of LiH.

Recrystallization of **4c** from EtOAc/*n*-Hexane gave a single crystal suitable for X-ray diffraction study (Figure 2).[11] The oxophosphole ring in **4c** is quite similar to that of **1**.[2]

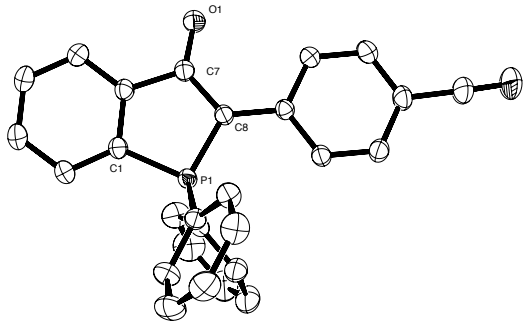
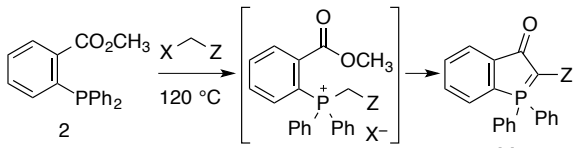


Figure 2. X-ray molecular structure of **4c**.[11] H atoms are omitted for clarity. Thermal ellipsoids are drawn at the 30% probability level. Selected bond lengths [Å] and angles [°]: P-C(1) 1.791(2), P-C(8) 1.741(2), C(7)-C(8) 1.431(3), C(7)-O 1.242(3), C(1)-P-C(8) 95.95(9), P- C(8)-C(7)-C(6) 5.7(2).

Next, we would prepare the salt from methyl *ortho*-phosphinylbenzoate and $BrCH_2CO_2Et$ at 120 °C. Surprisingly, cyclization proceeded during preparation of the salt even in the absence of a base (Table 2, entry 1). The yield was dramatically improved when the counter anion was changed from Br^- to Cl^- (entry 2). Heating at 120 °C in halides or in xylenes is required for the preferential cyclization over other side reactions like a nucleophilic de-methylation. Addition of a base is effective for milder conditions (entry 3). $ClCH_2CN$ and $ClCH_2COCH_3$ also gave the corresponding oxobenzophospholes in good yields (entries 4-6). The vicinity of the ylide and the ester is essential for this non-basic cyclization; aliphatic phosphanylester, $Ph_2PCH_2CH_2CO_2Et$, did not give the cyclic ylide in $ClCH_2CN$; only the corresponding phosphonium salt was formed even under the elevated temperature.

Table 2. Non-basic synthesis of **4** (method B).[a]



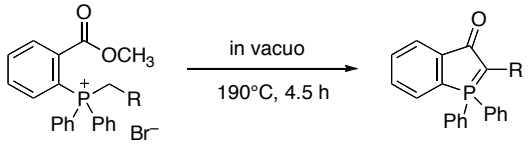
Entry	X	Z	Conditions	Product	Yield (%)[b]
1	Br	CO_2Et	120°C, 4.5 h	**4j**	7[c]
2	Cl	CO_2Et	120°C, 2.5 h	**4j**	78[c]
3	Cl	CO_2Et	80°C, 2 h[d]	**4j**	78[c]
4	Cl	$C(O)CH_3$	120°C, 3.5 h	**4k**	70
5	Cl	CN	120°C, 2 h	**4l**	100
6	Cl	CN	120°C, 1 h[e]	**4l**	80
7	Cl	Ph	120°C, 6 h	**4b**	-[f]

a) A halide (XCH_2Z) was used as a solvent. b) Isolated yields. c) NMR yield determined by ^{31}P NMR.[10] d) K_2CO_3 (2.0 equiv.) was added as a base. e) Xylenes were used as a solvent. Chloroacetonitrile (3 equiv.) was used as a halide. f) Benzylphosphonium benzoate **6b** was isolated instead of **4b**.

On the contrary, methyl *ortho*-phosphinylbenzoate in benzyl chloride did not afford **4b** under the same conditions

(entry 7), probably due to low acidity of α-proton to generate the ylide on heating. Indeed, heating at more elevated temperature in vacuo was found to be effective.[12] It is very curious that bromide is suitable in this case.[13] Several substrates with aryl, heteroaryl, and alkenyl substituents are successfully converted to the corresponding 3-oxobenzophospholes in good yields (Table 3). The results are comparable to those of method A, except the case of *p*-anisyl substrate (entry 5), where the electron-donating nature of the substituent inhibited the salt from generating the ylide at that temperature.

Table 3. Non-basic cyclization in vacuo (method C).[a]



3 **4**

Entry	R	Product	Yield (%)[b]	with LiH
1	Ph	**4b**	51 (80)[c]	74
2	2-Naphthyl	**4m**	81	-
3	*p*-CNC_6H_4	**4c**	90	83
4	*m*-CNC_6H_4	**4d**	80	60
5	*p*-$MeOC_6H_4$	**4e**	16	60
6	*p*-BrC_6H_4	**4n**	57 (80)[c]	-
7	*p*-*t*BuC_6H_4	**4h**	72	60
8	2-Pyridyl[d]	**4i**	54	82
9	*β*-(*E*)-Styryl	**4o**	53	-
10	*p*-CN-(*E*)-Styryl	**4p**	72	-

a) **3** was prepared in toluene and was used without purification after removal of the solvent. b) Isolated Yields. c) NMR yield determined by ^{31}P NMR was shown in parantheses.[10] d) Hydrobromide was used.

On the contrary to the previous bis-phosphole **1** (λmax = 680 nm), the benzophospholes **4** prepared here have absorbtion in shorter wavelength range (Table 4). Preliminary results of the obtained 3-oxo-λ^5-benzophospholes revealed that some of the products showed a faint fluorescence both in solution (Table 4) and solid phase. Unfortunately, the fluorescence was weak and its Φ_F was measured as 0.03 (**4l**).

Table 4. UV-Vis and fluorescence data of **4**.[a]

4	R	λmax (nm)	ε ($x10^3$ $cm^{-1}M^{-1}$)	λmax (FL, nm)
4b	Ph	345	12	-[b]
4c	*p*-CNC_6H_4	360	21	-[b]
4d	*m*-CNC_6H_4	342	11	-[b]
4e	*p*-$MeOC_6H_4$	343	4.8	-[b]
4f	*m*-$MeOC_6H_4$	345	9.5	-[b]
4g	*o*-$MeOC_6H_4$	350	9.8	-[b]
4h	*p*-*t*BuC_6H_4	346	8.0	-[b]
4i	2-Pyridyl	342	12	-[b]
4j	CO_2Et	338[c], 300	6.3 (301)	452[d]
4k	$C(O)CH_3$	344[c], 306	5.7 (301)	450[d]
4l	CN	346[c], 301	5.1 (301)	465[d]
4m	2-Naphthyl	361	15	-[b]
4n	*p*-BrC_6H_4	345	12	-[b]
4o	*β*-(*E*)-Styryl	377	15	-[b]
4p	*p*-CN-(*E*)-Styryl	408	25	-[b]

a) $CHCl_3$ solution. b) No fluorescence was observed. c) λ_{irr} = 333 nm.

In conclusion, we have developed three synthetic methods for 3-oxo-λ^5-benzophospholes, some of which showed a fluorescence property. Since this approach starts from two parts of the phosphole ring, the present methods opened the route toward wide variety of 3-oxo-λ^5-benzophospholes with tunable functionality. In addition, the stable ylidic structure of **4** allows alkylation and acylation of the carboxyl oxygen to form the phosphole-type structure with phosphonium salt and further structural conversion could be available. The further conversions are now under investigation.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

ACKNOWLEDGMENT This work was partly supported by Grant-in-Aid for Scientific Research (C) (20550046) and Ehime University COE incubation program. We also thank Advanced Research Support Center (ADRES), Ehime University for the measurements of NMR spectra and X-ray crystallographical analyses.

Dedicated to the late Professor Yoshihiko Ito on the occation of the 10th anniversary of his sudden death.

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8 This type of degradation of a phosphorane is known; see, Cooke, P., *J. Org. Chem*. **1973**, 38, 4082-4084.

9 Details of survey of a base are found in SI. **4a** could not be isolated even when LiH (3 equiv.) was used instead of *n*BuLi in Scheme 2; **5a** was formed as a main product instead.

10 Some of the products were difficult to separate from the phosphane oxide of the starting phosphine by a column chromatography.

11 Crystal data: **4c**: $C_{27}H_{18}NOP$; M = 403.39; monoclinic; space group $P2_1/n$ (No.14); a = 13.299(5), b = 11.774(5), c = 13.454(5); b = 96.221(6); V = 2094.3(14) Å^3; Z = 4; $m(Mo_{Ka})$ = 0.150 mm^{-1}; T = 288 K; 9932 reflections collected; R_{int} = 0.0251; $R(F)$ = 0.0525 for 3598 data with $I > 2s(I)$, $wR(F^2)$ = 0.1308 for all 4738 independent data. CCDC-759534 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Date Centre via www.ccdc.cam.ac.uk/data_request/cif.

12 In vacuo condition (*ca* 0.1 to 1 mmHg using a rotary oil pump) is necessary because the formed HBr and MeOH should be removed to complete the ylide formation under equilibrium. Heating under N_2 at 190°C gave ring-opened **5b** exclusively after aqueous workup, probably because the intermediate cyclic phosphonium salt was not converted to **4b** without removal of HBr.

13 **3b**·Cl gave the expected oxophosphole in 19% at 190°C; the main product was phosphonium benzoate **6b**.