# LETTERS

# Phosphorus-Containing Bis-allenes: Synthesis and Heterocyclization Reactions Mediated by Iodine or Copper Dibromide

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**(5)** Supporting Information

**ABSTRACT:** Bisphosphorylallenes were easily obtained in multigram scale from the Wittig-type rearrangement of bispropargyl alcohols. Unlike other conjugated bis-allenes, these reagents underwent a double cyclization mediated by iodine or copper dibromide leading to the formation of bis-1,2-oxaphospholenes.



C umulenes, and more specifically allenes, are versatile building blocks in organic synthesis, and their unique reactivity makes them particularly attractive reagents. Although their high reactivity may have impeded the development of efficient organic transformations, recent years have seen the emergence of mild processes allowing the selective modifications of allenes into valuable functional and/or cyclic derivatives.<sup>1</sup> These new methodologies have thus considerably extended the synthetic organic tool box, and allenes are even increasingly involved in cascade or tandem reactions, metal catalyzed organic transformations, and enantioselective reactions for the synthesis of natural product.<sup>2</sup>

Similar to Janus, allenyl derivatives bearing an electronwithdrawing group have two faces and typically behave as ambivalent reagents. For instance, allenyl phosphonates, -phosphinates, or -phoshine oxides that belong to this category present alkene functions having electrophilic and nucleophilic character.<sup>3</sup>

In contrast with monoallenes, bis-allenes remain more rarely used. They can be divided into conjugated and nonconjugated allenes.<sup>4</sup> Recently, their synthesis and reactivity have been reviewed by Hopf et al.,<sup>5</sup> and Alcaide et al. reported cyclization reactions of these atypical structures specifically for the synthesis of a fused heterocyclic pattern.<sup>6</sup> Although conjugated bis-allenes are not common, some studies based on their reactivity have already been explored. Most of the studies involved the intramolecular reactions between the two unsaturated allenyl systems. For example, the thermal cyclization of conjugated bis-allenes gave straightforwardly bismethylene cyclobutenes through a Cope-type rearrangement.<sup>7</sup> Typical reactions of conjugated bis-(phosphinylallenes) obtained from the thermal rearrangement of benzene-1,2-bis(propargyl alcohols) and chlorodiphenyl phosphines underwent intramolecular [2 + 2] cycloaddition leading to naphtho[*b*]cyclobutenes.<sup>8</sup>

The present work relates the synthesis of conjugated 1,2bis-phosphorylallenes<sup>9</sup> and explores their reactivity in a double heterocyclization process (Figure 1).



Figure 1. Double heterocyclization of bisphosphonylallenes.

1,2-Bisphosphorylallenes 2 were readily obtained in two steps from terminal propargyl alcohols. The first step involved the synthesis of diyne-diols 1 from Glaser–Hay coupling mediated by copper and nickel salts in the presence of air (Scheme 1).<sup>10</sup> The reactions proceeded smoothly and furnished both symmetrical and unsymmetrical diyne-diols 1 in 62–88% yields comparable with those of the literature. In

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the second step, diyne-diols 1a-1h were reacted with either diethyl chlorophosphite or chlorodiphenylphosphine to give the bis-allenylphosphonates 2a-2h and bis-allenylphosphine oxides 2i-j in multigram scales in yields up to 99% (Table 1).<sup>11</sup>

diyne diol	R <sup>1</sup>	<b>R</b> <sup>2</sup>	yield (%)ª	bis-allene	$\mathbb{R}^3$	yielo (%)
la	Me-	Me-	82	2a	OEt	82
1b	Et-	Et-	76	2b	OEt	92
1c	$\triangleright$	⊳	70	2c	OEt	-
1d	-(CH <sub>2</sub> ) <sub>4</sub> -	-(CH <sub>2</sub> ) <sub>4</sub> -	80	2d	OEt	44
1e	-(CH <sub>2</sub> ) <sub>5</sub> -	-(CH <sub>2</sub> ) <sub>5</sub> -	88	2e	OEt	99
1f	Ph-	Ph-	76	2f	OEt	83
1g	Ph-	Me-	62	2g	OEt	62
1h		OO	85	2h	OEt	61
	Me-	Me-		2i	Ph	82
	-(CH <sub>2</sub> ) <sub>5</sub> -	-(CH <sub>2</sub> ) <sub>5</sub> -		2j	Ph	71

The reactions readily proceeded at low temperature in the presence of triethylamine as a base to give first the trivalent phosphorus ester. The latter spontaneously rearranged as the temperature rose to room temperature. It can be noted that cyclopropyl diyne 1c failed to give the desired bis-allene 2c core cleanly. A complex mixture of phosphorus compounds was observed as the probable result of cyclopropyl ring opening. By contrast, the reaction worked well with cyclopentyl- and cyclohexyl diynes 1d and 1e. Even dibenzosuberenyl substituted diyne 1h afforded the expected bis-allene 2h in 61% isolated yield.

The reaction proceeded efficiently from dichlorophenylphosphine giving the bis-allenyl diphosphine dioxides 2i-j in 80% to 71% yields.

With the bis-allenylphosphonates 2a-h in hand, their behavior in electrophilic cyclization was studied. To the best of our knowledge, the reactions where two allenyl systems react independently are quite scarce in literature, particularly for conjugated bis(allenes).<sup>4–6</sup> Bisphosphonylallenes 2a-hwere subjected to electrophilic cyclization mediated by the addition of iodine in chloroform at 110 °C in a sealed tube.<sup>12</sup> It appeared that a double reaction occurred and two products were observed by <sup>31</sup>P NMR in almost equal proportions (two singlets in <sup>31</sup>P NMR). At this stage, the main hypothesis was that the reaction proceeded through the possible formation of bis(iodooxaphospholenes) **3** and oxaphosphinine dioxides **4** (Scheme 2). Nevertheless, the ambiguity was easily resolved





by deprotection of the ethyl phosphonic ester functions. Indeed, the cleavage of the ethyl group using trimethylsilyl bromide resulted in the formation of only one product, thereby confirming the presence of one type of heterocyclic linkage.<sup>13</sup> In terms of mechanism, the formation of bis(oxaphospholenes) **3** was suspected rather than oxaphosphinines **4**. Although both types of compounds could be formed, the formation of the six-membered ring compound **4** and the attack of the phosphoryl directly on the  $C_{sp}^2$  carbon of the iodonium intermediate **5** (red arrows) are clearly less favorable (Scheme 2). Therefore, the two singlets observed by <sup>31</sup>P NMR can readily be explained by the presence of two stereogenic phosphorus atoms illustrated by the  $C_2$ -symmetric and *meso*-bisoxaphospholenes **3** (Scheme 2).

The cyclization reaction was then extended to other bisallenes 2a-h, thus affording bisoxaphospholenes 3a, 3d, and 3e in 37% to 68% isolated yields. Unfortunately, the reaction of dibenzosuberenyl allene 2h failed to give cleanly the bisoxaphospholene core. In this case, it is plausible that a concurrent addition of iodine to the alkene moiety of the dibenzosuberenyl group preferentially took place during the reaction (Table 2).

Similarly, a cyclization mediated by cupric bromide originally developed by Ma et al. for the synthesis of bromo-oxaphospholenes has been studied.<sup>14</sup> These reactions were conducted in ethanol at 50  $^{\circ}$ C in the presence of an

Table 2. Diiodo- and Dibromobisoxaphospholenes 3 and 6

compd	$\mathbb{R}^1$	$\mathbb{R}^2$	Х	diastereomeric ratio <sup>a</sup>	yield (%) <sup>b</sup>		
3a	Me	Me	Ι	62/38	68		
3d	$(CH_{2})_{4}$	$(CH_2)_4$	Ι	53/47	37		
3e	$(CH_{2})_{5}$	$(CH_{2})_{5}$	Ι	53/47	60		
6a	Me	Me	Br	64/36	78		
6b	Et	Et	Br	92/8	63		
6d	$(CH_{2})_{4}$	$(CH_2)_4$	Br	64/36	53		
6e	$(CH_{2})_{5}$	$(CH_{2})_{5}$	Br	69/31	58		
6f	Ph	Ph	Br	100/0	49		
6g	Ph	Me	Br	93/7	42		
<sup><i>a</i></sup> Determined by <sup>31</sup> P NMR experiments. <sup><i>b</i></sup> Isolated yields.							

excess of CuBr<sub>2</sub>, and the formation of dibromo-bisoxaphospholenes 6a-b and 6d-g were observed and isolated in a range of 42-78% yield (Scheme 3 and Table 2).





The nature of the substituents  $R^1$  or  $R^2$  had a decisive influence on the diastereoselectivity of the reaction mediated by CuBr<sub>2</sub>. When  $R^1$  and  $R^2$  were methyl, cyclopentyl, or cyclohexyl groups, the reaction produced the bis 4-bromooxaphospholenes **6** with moderate diastereoselectivities, whereas phenyl or ethyl substituents furnished high diastereomeric ratios of 100/0 and 92/8, respectively. In the case of a phenyl group, a unique diastereoisomer **6f** was confirmed by the presence of one singlet in <sup>31</sup>P NMR and by the explicit <sup>1</sup>H and <sup>13</sup>C NMR spectra. Similarly, mixed derivative **6g** (Ph and Me substituents) was obtained in 93/7 diastereomeric ratio.

The presence of the oxaphospholene core was definitively confirmed by an X-ray diffraction experiment on dibromooxaphospholene **6f-OH** (Figure 3).<sup>15</sup> The compound **6f-OH** crystallized in an orthorhombic *Pcca* centro-symmetric space group. The packing diagram indicated that, at solid state, bisoxaphospholene **6f-OH** presented fixed conformational



Figure 3. X-ray representation of dibromo-bisoxaphospholene 6f-OH.

orientations of oxaphospholene rings. Steric or electronic repulsions appeared sufficient to ensure configurational stability in solid form. By contrast, in solution, no apparent diastereotopicity was observed in the  $^{13}$ C or  $^{1}$ H NMR of potential diastereotopic groups or for the other bisoxaphospholenes **3** and **6**.

Electrophilic cyclization was also attempted from bis-allenyl phosphine oxide 2i (Scheme 4). The purpose of this reaction

Scheme 4. Proposed Mechanism for the Reaction of Bisallene 2i with PTSA



was the synthesis of bis(benzophosphinene) dioxide 7 through an intramolecular  $S_EAr$  trapping of the tertiary carbocation 9. Both Lewis and Brönsted acid activations were attempted. However, no reaction was observed with Lewis acids such as boron trifluoride etherate, silver nitrate, bismuth trichloride, mercury acetate, or iron trifluoromethylsulfonate at temperatures ranging from room temperature to 100 °C. Even dry *para*-toluene sulfonic acid (PTSA) gave no reaction. By contrast, the presence of water drastically changed the nature of the expected product when PTSA was used in dichloromethane in a sealed tube, giving diphosphine dioxide 8 in 52% isolated yield.

In light of the structure of the final product 8, a plausible mechanism was proposed (Scheme 4). As expected, the first step is consistent with the formation of the tertiary carbocation 9. The lack of reactivity observed for the phenyl moiety prevented the Friedel–Crafts cyclization. Surprisingly, no reaction was observed with the second allenyl group. The carbocation is then trapped by water giving the alcohol 10. An oxa-Michael addition occurred through a Brönsted acid activation of the phosphoryl group leading to the diphosphine dioxide 8 after isomerization of the exocyclic alkene bond.

In conclusion, bisphosphonylallenes 2 were easily synthesized from diyne diols 1. The behavior of such reagents when they were engaged in polar cyclization using iodine or cupric bromide proved to be original compared to other conjugated bis-allenes. Specifically, the two allenyl systems reacted independently creating four bonds in a single step and giving bis(oxaphospholene) halides 3 and 6. Further, these original structures could be investigated for their reactivity and their unusual features, particularly for the formation of atropochiral bis(phosphonic acids).

## ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b00648.

Crystallographic data for **6f-OH** (CIF) Experimental details; NMR data (PDF)

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#### Notes

The authors declare no competing financial interest.

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(15) See the Supporting Information for details on X-ray analysis (CCDC 1530156 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre).