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A metal-free radical cascade reaction of phosphine oxides with 2-aryloxy phenylacetylenes to synthesize diphosphonyl xanthene derivatives†

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A radical cascade reaction of 2-aryloxy phenylacetylenes with phosphine oxides promoted by $K_2S_2O_8$ was developed, which provided diphosphonyl xanthenes as products. This reaction proceeds under transition metal-free and mild conditions with simple operation and good yields. The mechanistic study indicated that phosphine oxide was induced into a phosphonyl radical, and then the following double radical addition/cyclization with 2-aryloxy phenylacetylenes generated bisphosphonyl xanthenes.

Organophosphorous compounds exhibit valuable applications in organic synthesis,[1] materials chemistry,[2] and medicinal chemistry.[3] During the past years, great breakthroughs have been made in the development of efficient synthetic methods for the construction of organic monophosphorous compounds; however, facile methods for the preparation of diphosphonyl compounds are rare. Ananikov's group reported the nickel-catalyzed double addition of the P(O)–H bond with alkynes to prepare 1,2-bisphosphorylethanes.[4] Ogawa's group achieved the phosphinylphosphination of alkenes initiated by V-40.[5] Han and co-workers developed palladium-catalyzed dehydrogenative bisphosphorylation of alkynes with H-phosphonate.[6] The nucleophilic reaction of amides with phosphites promoted by Tf_2O provided α-amino bisphosphonates with high chemoselectivity.[7] The tandem reaction of P(O)–H with N-containing heterocycles such as 1,10-phenanthrolines,[8] quinolones,[9] and benzoxazoles[10] led to double hydrophosphonylated compounds (Fig. 1). The above reported methods mainly focus on the bisphosphonylation of simple alkenes, alkynes and limited nitrogen-containing heterocycles; hence, efficient and green methods for the synthesis of diverse diphosphonyl compounds are still highly desired.

Xanthene is a common structural scaffold with diverse biological activities, and widely exists in natural products.[11] The introduction of different substituents in position 9 of xanthenes has a strong influence on their chemical properties and biological applications; therefore, substantial attention has been devoted to modify the 9 position of xanthenes during the past decades. Different groups such as acylamino,[12] thio,[13] carbonyl,[14] heteroaryl,[15] monophosphonyl,[16] *etc*. are introduced at the 9 position *via* the direct coupling of xanthenes; however, diphosphonyl xanthene derivatives have not been reported. Alkynes are considered as important building blocks and have been widely used in the construction of heterocycles.[17] Meanwhile, the couplings of alkynes with phosphine oxides are commonly used for the preparation of organophosphorous compounds.[18] Herein, we developed a metal-free cascade reaction of 2-aryloxy phenylacetylenes with phosphine oxides initiated by $K_2S_2O_8$ leading to diphosphonyl xanthene derivatives.

Initially, the reaction of 2-phenoxyphenylacetylene **1a**, diphenylphosphine oxide **2a** and $(NH_4)_2S_2O_8$ in CH_3CN at 70 °C was studied, and a diphosphorylated product **3a** was obtained in 62% yield and its structure was confirmed by X-ray

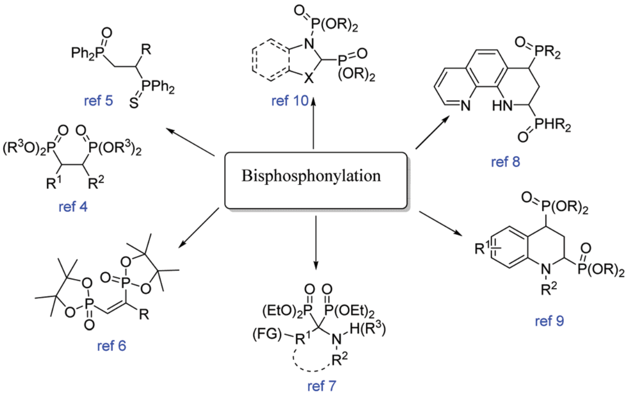

Fig. 1 The reported bisphosphonylations.

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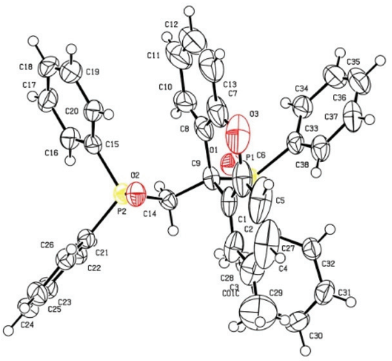

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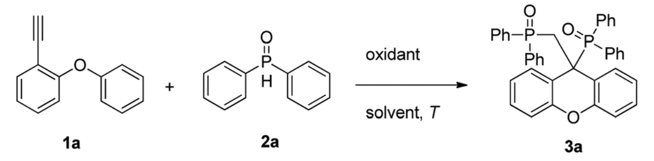
Fig. 2 The X-ray crystal structure of **3a**.

Table 1 Optimized conditions[a]

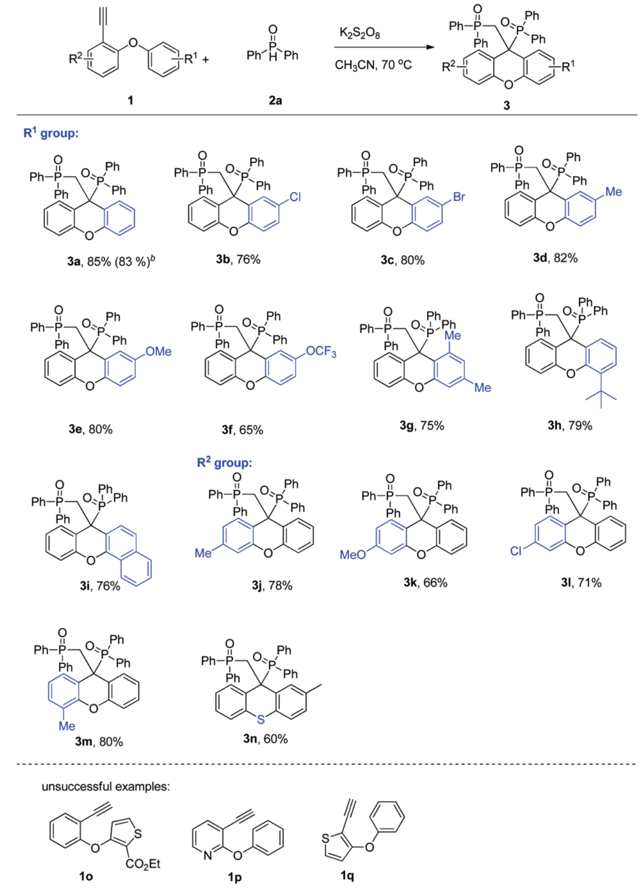


Entry	Oxidant	Solvent	T (°C)	Yield[b] (%)
1	$(NH_4)_2S_2O_8$	CH_3CN	70	62
2	$K_2S_2O_8$	CH_3CN	70	85
3	*t*-BuOO*t*-Bu	CH_3CN	70	20
4	$AgNO_3$	CH_3CN	70	0
5	$Mn(OAc)_3$	CH_3CN	70	0
6	$K_2S_2O_8$	1,4-Dioxane	70	52
7	$K_2S_2O_8$	EtOAc	70	Trace
8	$K_2S_2O_8$	Toluene	70	38
9	$K_2S_2O_8$	DCE	70	45
10	$K_2S_2O_8$	DMF	70	10
11	$K_2S_2O_8$	CH_3CN	80	83
12	$K_2S_2O_8$	CH_3CN	60	78
13[c]	$K_2S_2O_8$	CH_3CN	70	Trace
14[d]	$K_2S_2O_8$	CH_3CN	70	64
15[e]	$K_2S_2O_8$	CH_3CN	70	73

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol) and oxidant (0.5 mmol) in solvent (2.0 mL) were stirred under a nitrogen atmosphere at 70 °C for 7 h. [b] Yields of the isolated products. [c] The reaction was performed under an air atmosphere. [d] **2a** (0.8 mmol) was used. [e] $K_2S_2O_8$ (0.4 mmol) was used.

crystal structure analysis (Fig. 2). Then, the reaction conditions were further screened and the results are shown in Table 1. Oxidants such as $K_2S_2O_8$, *t*-BuOO*t*-Bu, $AgNO_3$ and $Mn(OAc)_3$ were investigated, and $K_2S_2O_8$ was proven as the best radical initiator which provided **3a** in 85% yield (entries 2–5, Table 1). Other solvents were unsuitable for this reaction and they led to a serious decrease of the yield (entries 6–10, Table 1). Higher and lower temperatures were unfavorable, affording **3a** in 83% and 78% yields, respectively (entries 11 and 12, Table 1). Only a trace amount of **3a** (entry 13, Table 1) was obtained under an air atmosphere. When smaller loadings of **2a** and $K_2S_2O_8$ were used, lower yields were obtained (entries 14 and 15, Table 1). Finally, the optimal conditions are as follows: 5.0 equivalents of **2a** and 2.5 equivalents of $K_2S_2O_8$ in CH_3CN at 70 °C under an air atmosphere.

With the optimal conditions in hand, the substrate scope of 2-aryloxy phenylacetylenes **1** was studied and the results are shown in Scheme 1. Firstly, different groups such as 4-Cl, 4-Br, 4-Me and 4-MeO were introduced into the R^1 position on the benzene ring, and **3b–3e** were obtained in 76–82% yields. 4-Trifluoromethoxy and 3,5-dimethyl slightly decreased the yields of the desired products, giving **3f** and **3g** in 65% and 75% yields, respectively. Introduction of 2-*tert*-butyl provided **3h** in 79% yield, indicating that steric hindrance does not have a significant impact on this reaction. When 1-(2-ethynylphenoxy)naphthalene was used, it reacted smoothly with **2a**, giving **3i** in 76% yield. In the moiety of the R^2 group, methyl, methoxy and chloro were tolerant, generating the corresponding products **3j–3m** in moderate yields. When oxygen was replaced, 2-(4-methylphenylthio) phenylacetylene reacted well with **1a**, providing **3n** in 60% yield. Unfortunately, heterocycle groups were not compatible with this reaction, and only generated a trace amount of the desired products. When **1o** and **1p** were used as substrates, the reactions were complicated and no main product could be isolated. The reaction of **1q** and **1a**

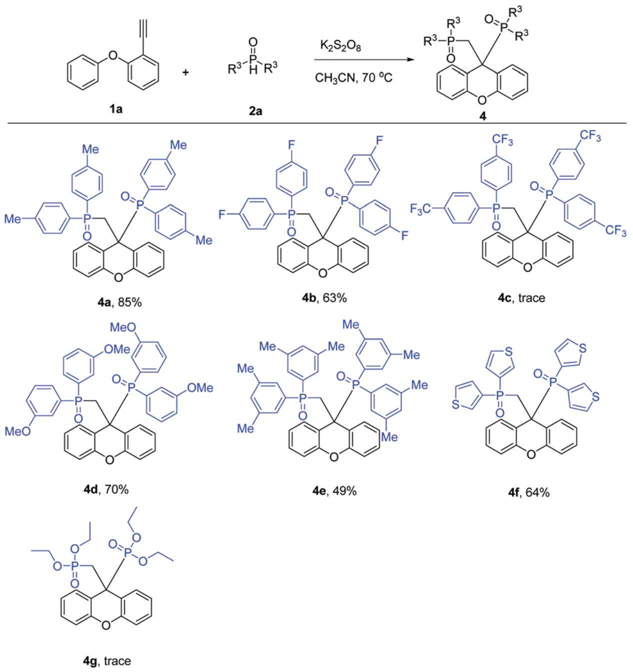


Scheme 1 The substrate scope of 2-aryloxy phenylacetylenes. Reaction conditions: **1** (0.2 mmol), **2a** (1.0 mmol) and $K_2S_2O_8$ (0.5 mmol) in CH_3CN (2.0 mL) were stirred under a nitrogen atmosphere at 70 °C for 7 h. [a]The reaction was carried out on a 1 mmol scale.

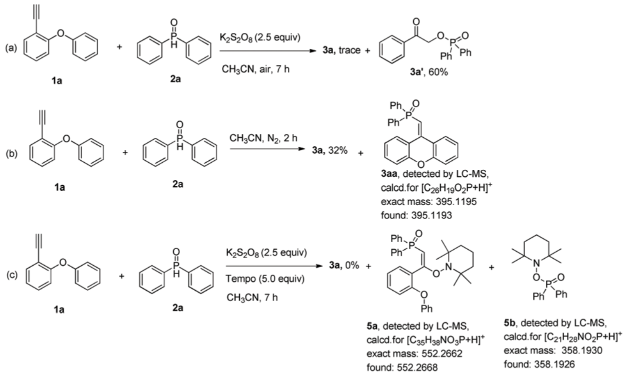
afforded 1-(3-phenoxythiophen-2-yl)ethenone as the main product (see the ESI†). We also studied the reaction of **1a** and **2a** on a 1 mmol scale, and to our delight, **3a** was obtained in 83% yield.

The scope of phosphine oxides was also explored as shown in Scheme 2. The benzene ring bearing 4-methyl and 4-fluoro produced the corresponding products **4a** and **4b** in 85% and 63% yields, respectively. However, 4-CF_3 was not tolerant and only a trace amount of **4c** was detected. 3-Methoxy and 3,5-dimethyl gave **4d** and **4e** in 70% and 49% yields, respectively. To our delight, thienyl was suitable, affording **4f** in 64% yield. However, diethyl phosphonate was not suitable, and only a trace amount of **4g** was observed.

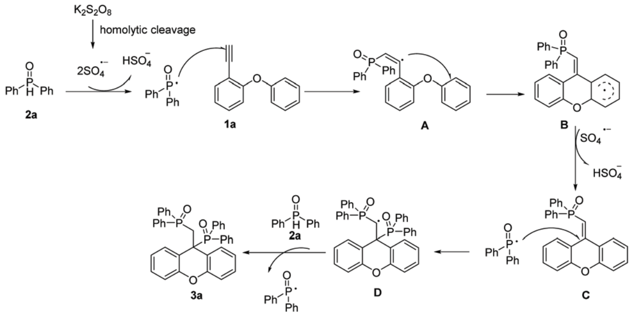
To investigate the possible pathway of this bisphosphonylation, several control experiments were conducted. Firstly, the reaction of **1a** and **2a** was carried out under an air atmosphere; **3a′** was isolated as the main product and only a trace amount of **3a** was observed (Scheme 3a). When the standard reaction was carried out for 2 h, **3a** was obtained in 32% yield with a trace amount of **3aa** detected by LC-MS (Scheme 3b). We speculated that **3aa** was the key intermediate; however, **3aa** readily reacted with **2a** to afford the final product **3a** which led to the low loading of **3aa** in the reaction solution. When the radical scavenger TEMPO was added, **3a** was completely inhibited, and the radical addition products **5a** and **5b** were detected by LC-MS, indicating that this reaction is probably initiated by a radical pathway (Scheme 3c).



Scheme 2 The substrate scope of phosphine oxides.Reaction conditions: **1a** (0.2 mmol), **2** (1.0 mmol) and $K_2S_2O_8$ (0.5 mmol) in CH_3CN (2.0 mL) were stirred under a nitrogen atmosphere at 70 °C for 7 h.



Scheme 3 Control experiments.



Scheme 4 The proposed possible mechanism.

Based on the control experiments, a possible reaction pathway was proposed (Scheme 4). At first, potassium persulfate underwent homolytic cleavage under heating conditions, providing a sulfate radical anion which abstracted a hydrogen from **2a** generating the diphenylphosphine oxide radical and HSO_4^-. After the coupling of the diphenylphosphine oxide radical with **1a**, a vinyl radical **A** was obtained which readily underwent intramolecular cyclization to give **B**. Subsequently, oxidation of **B** by the sulfate radical anion afforded intermediate **C**. **C** attacked by diphenylphosphine oxide radical gave an intermediate **D**. Finally, the hydrogen abstraction of **D** from **1a** generated the product **3a**.

Conclusions

In conclusion, we have developed a cascade reaction of 2-aryloxy phenylacetylenes with phosphine oxides promoted by $K_2S_2O_8$, producing diphosphonyl xanthenes in moderate to good yields. A possible reaction pathway involving the double addition/cyclization of a phosphonyl radical with 2-aryloxy phenylacetylenes was proposed. This reaction features metal-free conditions, simple operation and good yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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