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Disulfide Promoted C<C->P Bond Cleavage of Phosphoramide: <+>“P” Surrogates to Synthesize Phosphonates and Phosphinates

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C<C->P bond cleavage
Disulfide

Alkyl phosphonates
Phosphoramides
Phosphinates

A metal-free C<C->P bond cleavage reaction is described herein. Phosphoramides, a phosphine source, can react with alcohols to produce phosphonate and phosphinate derivatives in the presence of a disulfide. P<C->H_2, P-alkyl, and P,P-dialkyl phosphoramides can be used as substrates to obtain the corresponding pentavalent phosphine products.

<?><?><?>Dear Author, Table^^2 is missing (is listed in the text). <?><?><?>

Organophosphorus compounds are widely used in materials,[1] catalysis,[2] agriculture,[3] pharmaceuticals,[4] and modern organic syntheses.[5] One representative is phosphonate which has attracted significant attention in recent years.[6] The current strategy for synthesizing phosphonates mainly includes the classical Michaelis-Arbuzov reaction and Atherton-Todd reaction,[7] direct esterification of phosphoric acid,[8] phosphorylation of alcohols[9] and C<C->P coupling reaction.[10] These strategies often require pre-activated organic halides or pseudo halides as substrates.[11] The severe effects associated with the industrial preparation of organophosphorus compounds are well known.[12] Therefore, it is important to develop a new and environment-friendly method to synthesize phosphonates and phosphinates.

In the past few decades, the cleavage of C<C->P bond has emerged as an interesting topic of research.[13,14] The C<C->P bond cleavage is mostly realized through transition metal catalysis (Scheme^^1<schr1>A, a).[15] In addition, Davidson[16] has demonstrated the photocatalytic acyl C<C->P bond cleavage of acyl phosphine oxide under UV irradiation (Scheme^^1<xschr1>A, b). Recently, Wang and co-workers have reported the acyl phosphorus C<C->P bond cleavage using Pd or Ni catalysts (Scheme^^1<xschr1>A, **c**).[17]

Phosphinecarboxamide was initially reported by Goicoechea et al[18] and our group[19] recently. We reported the reaction of phosphinecarboxamide with nucleophiles in an addition-

elimination reaction, and the phosphorylation of the P<C->H bond.[20] We also observed the dephosphorization of phosphinecarboxamide (removal of PH_2) in these reactions. These phenomena drew our attention, and we speculated that these side reactions could be a new route for the synthesis of phosphine organic compounds (Scheme^^1<xschr1>B). C<C->P bond rupture and reconstruction has been an emerging topic because it provides an easy way to prepare value-added products from low-functionality molecule.[21] In this study, we developed an efficient method to cleave the C<C->P bond of phosphoramides for synthesizing phosphates and phosphinates.

Initially, reaction of phosphoramide **1^a** and 1,2-diphenyldisulfane was tested in ethanol in the presence of K_2CO_3. However, the desired product was not obtained, and all the starting materials were fully recovered. Interestingly, phosphoramide **1^b** reacted with EtOH gave the target product diethyl phosphite (**4^a**) in 23% yield under the same reaction conditions (Scheme^^2<schr2>).

Inspired by the above results, *P*-alkylated phosphinecarboxamide (**1^c**) with EtOH (**2^a**) was used as the model substrates to explore the optimal reaction conditions in the presence of disulfide **3^a** for 3^^h at room temperature (Table^^1<?><?>Table^^2 missing<?><?>). First, we investigated the effect of disulfide concentration on the yield of the reaction (entries^^**1--6**, Table^^1<tabr1>). No product was detected in the absence of disulfide (entry^^**1**). The product yield gradually increased with increasing amount of the disulfide compound. When 2.5 equivalent of disulfide was added, the product yield increased to 52% (entries^^**2--6**). Different types of bases were also examined (entries^^**7--13**). K_2CO_3 was found to be the most beneficial for this reaction, and yield of the target product (**4^b**) increased to 83% (entry^^**12**). Following this, various solvents were screened (entries^^**14--18**). When ethanol was replaced by equivalent amount of acetonitrile, **4^b** was isolated in 80% yield (entry^^**14**), suggesting that acetonitrile was also effective in this reaction.

Considering the generity and sustainability, ethanol was chosen as the optimal solvent for this reaction (entry^^**12**). Increasing the temperature inhibited the reaction (entries^^**19**--**20**). Particularly, it is worth mentioned that air was an essential component for this reaction. Under inert atmosphere, the product was obtained in only 10% yield (entry^^**21**). When **3^a** was replaced by thiophenol, **4^b** was obtained in a very low yield (10%, entry^^**22**). Moreover, the use of various disulfide such as 4-methyl disulfide (**3^b**) gave a good yield of **4^b** (entry^^**22**). Although thioester **5^a** or **5^b** is a byproduct of this reaction, it is a valuable and useful intermediate that has been widely used in organic synthesis.[22,23]

With the optimized reaction conditions in hand, substrates scope of the reaction was investigated. As show in scheme^^3<schr3>I, phenylpropyl and phenylbutyl substituted products **4^b** and **4^c** were obtained in excellent yields, and both of these are all useful and valuable pharmaceutical intermediates.[6,24,25] Notably, the more reactive benzyl substituted substrate gave product **4^d** in 64% yield, and the long-chain heptane substituted phosphanecarboxamide gave phosphate **4^e** in 68% yield.

To further increase the diversity of the functional groups on phosphorus in this C<C->P bond cleavage reaction, we prepared a series of P(III) substrates through the *P*-Michael addition reaction (Scheme^^4<schr4>). Such compounds are usually difficult to synthesize by the conventional methods. Thus, the method of establishing C<C->P bond is of great interest to organic researchers.[26] Although some advances have been made in this field,[27] the formation of C(sp^3)<C->P bond is still significantly challenging. Especially, the direct constructions of C(sp^3)<C->P bond and <C->PH_2 group have rarely been reported. The method developed in this study will provide a new alternative approach for the synthesis of organic P(III) compounds.

The phosphate products could be synthesized smoothly through the *P*-Michael addition reaction (Scheme^^3<xschr3>I). There is no obvious electronic effect of the

substituent group on the aromatic rings. Thus, similar yields were obtained for both electron-withdrawing (**4^j**, **4^m**) and electron-donating groups (**4^f**, **4^k**, **4^l**). The *o*-Methyl substituted aromatic product (**4^l**) was obtained in 68% yield, while naphthyl product (**4^n**) was obtained in 54% yield. For the unsubstituted aromatic ring, product **4^i** was obtained in 81% yield, which is comparable to the yields of phenylpropyl and phenylbutyl products (**4^b**, **4^c**).

It is worth emphasizing that the protocol works well for the synthesis of hypophosphonate compounds when *P*,*P*-difunctionalized phosphanecarboxamides are used as substrate (Scheme^^3<xschr3>II). For example, the desired products (**4^p**, **4^s**) were obtained in 86% and 80% yields. Notably, different alcohols (methanol, ethanol and propanol) could be used as the solvent, and all the reactions afforded the target products (**4^f--4^h**) in good yields. In addition, compounds **4^q** and **4^r** could be isolated in reasonably good yields (76% and 83% yields, respectively). Unfortunately, we found that phenol could not be used as a nucleophilic reagent to obtain the corresponding target product.

We next used **1Bl** as substrate to carry out the gram scale reaction (Scheme^^5<schr5>). We found **1Bl** could further undergo a gram-scale reaction to transform into phosphate ester **4^g**. Although this scale-up reaction required a longer reaction time (5^^h), and the product **4^g** was obtained in 71% yield.

In order to elucidate the reaction mechanism, several control experiments were conducted (Scheme^^6<schr6>). In the absence of alcohol, substrates **1Bl** and **1Bg** gave sole products: phosphoric acids (**7**) and (**8**) in good yields with and without disulfide **3^a** respectively. Products **7** and **8** did not react further with ethanol to give product (**4^g**) (Scheme^^6<xschr6>I, equations^^**1--4**). Therefore, compounds **7** and **8** were by-products, and not the intermediates of the reaction. It is evident from scheme^^6<xschr6>I**I** that oxidants such as air or O_2 played a crucial role in the generation of the desired product

(Scheme^^6<xschr6>I**I**, equation^^**1**). Furthermore, the reaction in the presence of a free radical inhibitor (2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)) gave the target product (**4^g**) in high yield (76%, Scheme^^6<xschr6>I**I**, equation^^**2**), suggesting that the reaction did not proceed through a free-radical process. Both disulfide and alcohol were indispensable in this transformation (Scheme^^6<xschr6>III, equations^^**1**--**2**). Unfortunately, we could not isolate any phosphorus product in the absence of ethanol except thioester **5^a** (84% yield).

Based on the above preliminary results and related literature reports,[28] a plausible reaction mechanism was proposed (Scheme^^7<schr7>). Initially, the reaction starting is promoted by disulfide (**3^a**) attacking substrate **1Bl** generating intermediate **S1** and thioester **5^a**. Then, intermediate **S1** is oxidized to **S2**, which reacts with EtOH to form intermediate **S3** (detected by **HRMS**). The **S3** reacts with **3^a** to form **S4** (detected by **HRMS**), which eventually undergoes nucleophilic substitution reaction with alcohol to form desired product **4^g** (path **a**). Alternatively, intermediate **S2** can be resulfurized to give the phosphonodithioate **S5**, which is subsequently esterized by EtOH to form **4^g** (path **b**). Since we estimated the molecular weight of the intermediates **S3** and **S4** in HRMS, we speculate that the reaction is more likely to proceed through path **a**. Furthermore, since P(III)<C->H was extremely sensitive to air and was easily oxidized, in the absence of a disulfide, substrate **1B** can be directly oxidized to phosphoric acid **7**.[28c,28f]

In summary, we have developed a successful method to capture PH_2(R) fragments generated from the C<C->P bond cleavage of a phosphoramide. A series of phosphonates and phosphinates were synthesized by this method. This method is operationally simple under mild conditions with high yields of products, broad substrate scope, and good practical applicability. More interestingly, even the byproduct of this reaction, thioester, is a valuable and useful intermediate in organic synthesis.

Experimental Section

General Procedure for the Synthesis of Phosphonates 4^b

To a solution of disulfide **3^a** (87.2^^mg, 2^^equiv.), and K_2CO_3 (55.2^^mg, 2^^equiv.) in EtOH (3.0^^mL) was added *N*-(4-methoxyphenyl)-1-(4-phenylbutyl)phosphanecarboxamide (**1^c**, 63^^mg, 0.2^^mmol) at room temperature and stirred for 3^^h. After the reaction reached completion, the reaction mixture was diluted with ethyl acetate (10^^mL). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel to give corresponding thioester 5a (petroleum ether:ethyl acetate=8:1) and phosphonates **4^b** (ethyl acetate).

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Table^^1 Optimization of reaction conditions.[a]

<forr1>

Entry	**1^c**:**3^** **a**	Base (equiv.)	Solvent	Yield (%)[c]	
				4^b	**5^a**

	(mmol)				
1	1:0	Cs_2CO_3 (1)	EtOH	0	0
2	1:0.5	Cs_2CO_3 (1)	EtOH	14	76
3	1:1	Cs_2CO_3 (1)	EtOH	20	78
4	1:1.5	Cs_2CO_3 (1)	EtOH	40	78
5	1:2	Cs_2CO_3 (1)	EtOH	50	80
6	1:2.5	Cs_2CO_3 (1)	EtOH	52	79
7	1:2	DBU (1)	EtOH	64	66
8	1:2	*t*-BuOK (1)	EtOH	trace	35
9	1:2	K_2CO_3 (1)	EtOH	70	83
10	1:2	Et_3N (1)	EtOH	62	71
11	1:2	K_2CO_3 (1)	EtOH	70	80
12	1:2	K_2CO_3 (2)	EtOH	83	83
13	1:2	Cs_2CO_3 (2)	EtOH	63	80
14[b]	1:2	K_2CO_3 (2)	CH_3CN	80	85
15[b]	1:2	K_2CO_3 (2)	DMSO	trace	trace
16[b]	1:2	K_2CO_3 (2)	Dioxane	32	53
17[b]	1:2	K_2CO_3 (2)	CH_2Cl_2	36	50
18[b]	1:2	K_2CO_3 (2)	Toluene	trace	trace
19[b,g]	1:2	K_2CO_3 (2)	MeCN	52	62
20[b,h]	1:2	K_2CO_3 (2)	MeCN	18	trace

21[d]	1:2	K_2CO_3 (2)	EtOH	10	84
22[e]	1:2	K_2CO_3 (2)	EtOH	10	12
23[f]	1:2	K_2CO_3 (2)	EtOH	76	80[i]

[a] Reaction conditions: A mixture of disulfide (0.4^^mmol) and K_2CO_3 (0.4^^mmol) in CH_3CN (3^^mL) was stirred under an air for 0.5^^h, then **1^c** (0.2^^mmol) was added. Stirring was continued at room temperature for 3^^h.
[b] 2 equivalents of ethanol was added.
[c] Isolated yields.
[d] Reaction under an argon atmosphere.
[e] **3^a** was replaced by thiophenol.
[f] 4-Methyl disulfide (**3^b**) was added to replace **3^a**.
[g] Reaction at 40^°C.
[h] Reaction at 80^°C.
[i] S-(*p*-tolyl) (4-methoxyphenyl)carbamothioate was obtained.

Scheme^^1 C<C->P bond cleavage to synthesize new organophosphorus compounds.

Scheme^^2 Disulfide-promoted alkyl phosphate formation.

Scheme^^3 Substrate scope for the synthesis of phosphonates/phosphinates.

Scheme^^4 Substrate scopes of the Michael addition reaction.

Scheme^^5 Gram-scale reaction to prepare single Michael addition product(**1Bl**) and phosphonates(**4^g**).

Scheme^^6 Control experiments.

Scheme^^7 Proposed mechanism.