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Copper(II)-catalyzed tandem cyclization for the synthesis of benzo[*d*][1,3]thiazin-2-yl phosphonates involving C–P and C–S bond formation†

Yang Liu, Shijie Yao, Chaoli Wang, Yahui Zhang and Wenyan Hao *

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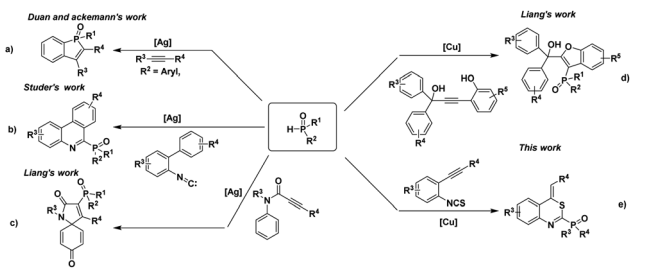
A copper(II)-catalyzed, high-efficiency and atom-economical synthesis of valuable organophosphorus compounds *via* tandem cyclization of *o*-alkynylphenyl isothiocyanates with phosphites is described. This protocol, having a good functional-group compatibility, provides a simple and direct pathway to organophosphorus heterocycles in good yields under mild conditions. The method could be efficiently scaled up to gram scale, thus providing a potential application of this cascade cyclization strategy in synthesis.

As the valuable precursors of many biologically active molecules,[1] organophosphorus compounds have wide applications in the field of materials science,[2] medicinal chemistry,[3] organic synthesis,[4] natural products,[5] and ligand chemistry.[6] For example, α-amino and α-hydroxy phosphonic acids have been found to act as antibiotics,[7] antitumor agents,[8] and enzyme inhibitors.[9] Therefore, the synthesis of these organophosphorus compounds is still appealing. The construction of a C(sp^2)–P bond on heterocycles is one of the most fundamental methods to synthesize the organophosphorus compounds. Through the efforts of many chemists, several extensively valuable methods have been established and developed.[10] For instance, the Duan group and the Ackermann group developed an Ag-mediated C–H/P–H functionalization method to construct a Csp^2–P bond by using arylphosphine oxides and internal alkynes as the substrates (Scheme 1a).[11] At the same time, Studer and co-workers reported a novel Ag-catalyzed radical cascade reaction for the synthesis of 6-phosphorylated phenanthridines from 2-isocyanobiphenyls and diphenylphosphine oxides (Scheme 1b).[12] Recently, Liang and co-workers also developed two cases of cascade functionalization of *N*-(*p*-methoxyaryl)-propiolamides and alkynol substrates with diphenylphosphine oxides to construct phosphorylated heterocycles (Scheme 1c and d).[13] Although various utilized methods for the construction of Csp^2–P bond on heterocycles have been established, the development of a new synthetic strategy from easily prepared starting materials is still a challenging task.

Recently, transition-metal-catalyzed cascade cyclization of *o*-alkynylphenyl isothiocyanates with various nucleophiles provides a new and powerful synthetic strategy to synthesize different heterocycles. *o*-Alkynylphenyl isothiocyanates have extensively been used as versatile organic synthons for the construction of different compounds such as indoles,[14] quinoline,[15] thiazine[16] due to its high reactivity and easy preparation. Encouraged by this fascinating research and our continuing interest in the transformation of *o*-alkynylphenyl isothiocyanates,[17] we herein report an efficient copper-catalyzed cyclization of *o*-alkynylphenyl isothiocyanates with phosphites for the synthesis of phosphorylated heterocycles and related derivatives (Scheme 1e).

According to the literature procedure,[14c,18] the starting *o*-alkynylphenyl isothiocyanates were prepared *via* the Sonogashira coupling of 2-iodoanilines with terminal alkynes,[19] followed by reacting with thiophosgene. At the outset, we used *o*-



Scheme 1 Synthesis of P-containing heterocycles through Csp^2–P bond formation. (a) Previous report through C–H/P–H functionalization. (b) Previous report through radical process. (c) and (d) Previous reports through cascade functionlization. (e) This work: copper-catalyzed cyclization of *o*-alkynylphenyl isothiocyanates with phosphites.

Key Laboratory of Functional Small Organic Molecules, Ministry of Education, College of Chemistry & Chemical Engineering, Jiangxi Normal University, 99 Ziyang Road, Nanchang, Jiangxi, 330022, P. R. China. E-mail: wenyanhao@jxnu.edu.cn

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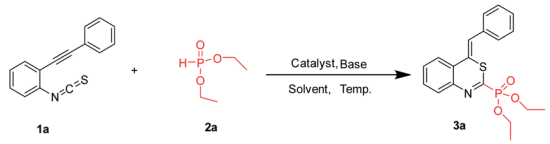
Table 1 Initial studies for the tandem reaction of *o*-alkynylphenyl isothiocyanate **1a** with phosphite **2a**[a]



Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	CuI	Cs_2CO_3	MeCN	25
2	CuBr	Cs_2CO_3	MeCN	35
3	CuCl	Cs_2CO_3	MeCN	39
4	$Cu(OTf)_2$	Cs_2CO_3	MeCN	20
5	$Cu(OAc)_2$	Cs_2CO_3	MeCN	15
6	CuO	Cs_2CO_3	MeCN	Trace
7	$CuCl_2$	Cs_2CO_3	MeCN	41
8	$CuBr_2$	Cs_2CO_3	MeCN	39
9	—	Cs_2CO_3	MeCN	Trace
10	$CuCl_2$	—	MeCN	NR
11	$CuCl_2$	K_3PO_4	MeCN	45
12	$CuCl_2$	*t*-BuOK	MeCN	28
13	$CuCl_2$	NaOH	MeCN	32
14	$CuCl_2$	Et_3N	MeCN	Trace
15	$CuCl_2$	DBU	MeCN	50
16	$CuCl_2$	DBU	DMF	31
17	$CuCl_2$	DBU	1,4-Dioxane	45
18	$CuCl_2$	DBU	THF	49
19	$CuCl_2$	DBU	Toluene	42
20	$CuCl_2$	DBU	DCM	60
21	$CuCl_2$	DBU	DCE	45
22[c]	$CuCl_2$	DBU	DCM	25
23[d]	$CuCl_2$	DBU	DCM	75
24[e]	$CuCl_2$	DBU	DCM	Trace

[a] Reaction was performed with **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (0.04 mmol), base (0.6 mmol), in solvent (2 mL) at 80 °C for 18 h. [b] Isolated yield based on *o*-phenylethynylphenyl isothiocyanate **1a**. [c] The temperature is 100 °C. [d] The temperature is 45 °C. [e] The temperature is 25 °C.

phenylethynylphenyl isothiocyanate **1a** and diethyl phosphonate **2** as the substrates in a model reaction to optimize the conditions, and the results are summarized in Table 1. Firstly, different copper salts (20 mol%) were screened in the presence of Cs_2CO_3 (2.0 equiv.) used as the base in MeCN (2 mL) at 80 °C for 18 h (Table 1, entries 1–8). $CuCl_2$ was the best choice, leading to the desired product **3a** in 41% yield. It is worth noting that trace amounts of the products were obtained in the absence of metal salts (Table 1, entry 9) and no product was obtained in the absence of base (Table 1, entry 10). These results indicated that the combination of a Lewis acid catalyst and a base is indispensable to afford the target product. Subsequently, we examined the base effect on the reaction (Table 1, entries 11–15). Lower yields were observed when other bases such as K_2CO_3, K_3PO_4, *t*-BuOK, NaOH, and Et_3N were employed, whereas DBU gave the best yield (Table 1, entry 15). We next examined the solvent effect (Table 1, entries 16–21). When DCM was employed as the solvent, the highest yield of 60% was obtained (Table 1, entry 20). Finally, we examined the effect of temperature on the reaction. When the reaction temperature was reduced to 45 °C, the reaction was completed with a yield of 75% (Table 1, entry 23). Increasing the reaction temperature to 100 °C or reducing the reaction temperature to 25 °C resulted in a diminished yield (Table 1, entries 22 and 24).

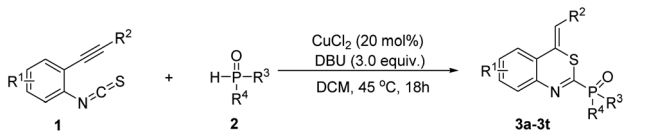
In order to further demonstrate the substrate scope, different *o*-alkynylphenyl isothiocyanates and phosphites were then explored; the results are summarized in Table 2. All reactions proceeded smoothly, leading to the desired 4*H*-benzo[*d*][1,3]thiazin-2-yl phosphonate in moderate to good yields. For example, the substituents on the R^2 position of substrates **1** showed obvious electronic effects on the reaction. Compared with the substrates **1** with an electron-rich aryl group such as *p*-$MeOC_6H_4$ and *p*-MeC_6H_4 at the R^2 position, the reaction of the R^2 group in the substrates **1** bearing an electron-deficient aryl, such as *p*-FC_6H_4, *p*-ClC_6H_4, and *p*-BrC_6H_4, could lead to the desired products (**3b–3d**) in lower yields. Surprisingly, no desired products were obtained when the R^2 group was an alkyl group, such as methyl, ethyl, *n*-butyl, *t*-butyl, and *n*-hexyl. However, when the R^2 group in the substrate **1** was the cyclopropyl group, the desired 4*H*-benzo[*d*][1,3]thiazin-2-yl phosphonate was obtained in 52% yield. Electronic properties and substitution position on the benzene ring of substrate **1** did not hamper the reaction process. With both of electron withdrawing groups, such as F-, Cl-, Br-, CF_3-, and electron-donating group Me- on the benzene ring, the reactions could afford desired products **3h–3o** in moderate to good yields. The other two substitution products **3p** and **3q** were also obtained successfully under standard conditions. Diphenylphosphine oxide was also a suitable substrate for this cyclization, by reacting with **1** under the standard conditions, the corresponding products (*Z*)-(4-benzylidene-4*H*-benzo[*d*][1,3]thiazin-2-yl)diphenylphosphine oxide **3s** and (*Z*)-(4-benzylidene-6-bromo-4*H*-benzo[*d*][1,3]thiazin-2-yl)diphenylphosphine oxide **3t** were obtained in 60% yield and 52% yield, respectively. The structure of **3t** was further confirmed using X-ray diffraction analysis (see Fig. S2 in the ESI†). Due to a kinetic effect according to Baldwin's rules and a smaller steric effect compared to the *E*-isomer, all products were uniformly formed as the *Z*-isomer.[20] It is worth mentioning that all these reactions could be efficiently scaled up to gram scale under the optimal conditions, providing a potential application in the synthesis industry.

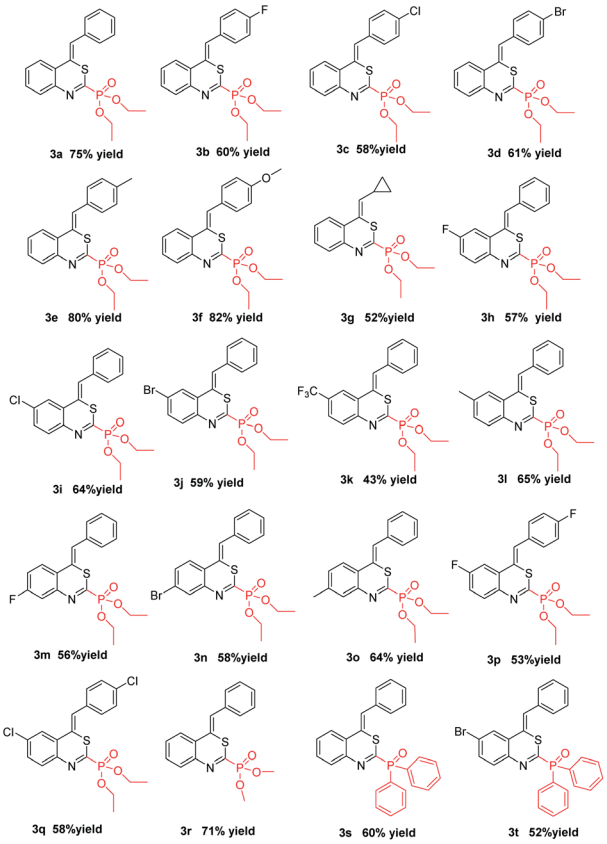
The structure of (*Z*)-(4-benzylidene-6-bromo-4*H*-benzo[*d*][1,3]thiazin-2-yl)diphenylphosphine oxide was corroborated by X-ray diffraction analysis of the crystal structure of **3t**, the ORTEP diagram of which is displayed in Fig. 1.

Next, we examined the reaction of 2-isothiocyanato-3-(phenylethynyl)pyridine with **2a** under the standard conditions (Scheme 2), the corresponding product diethyl (*Z*)-(4-benzylidene-4*H*-pyrido[2,3-*d*][1,3]thiazin-2-yl)phosphonate (**3u**) was obtained in 42% yield.

In order to insight into the reaction mechanism more clearly, two radical control experiments were carried out. The reaction proceeded smoothly by using the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) or butylated hydroxytoluene (BHT) probably suggesting that the reaction may not undergo a radical pathway (Scheme 3).

Table 2 Substrate scope of different *o*-alkynylphenyl isothiocyanates and phosphites[a,b]





[a] Reaction was performed with *o*-alkynylphenyl isothiocyanate **1** (0.2 mmol), phosphite or diphenylphosphine **2** (0.6 mmol), $CuCl_2$ (0.04 mmol), DBU (0.6 mmol) in DCM (2 mL) under 45 °C for 18 h. [b] Isolated yield based on *o*-alkynylphenyl isothiocyanate **1**.

Taking the experimental results into account, a possible mechanism was proposed, which is shown in Scheme 4. Firstly, in the presence of a base, isothiocyanate moiety in compound **1**

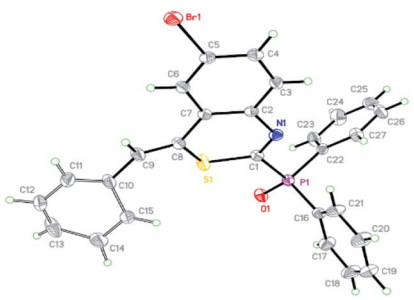
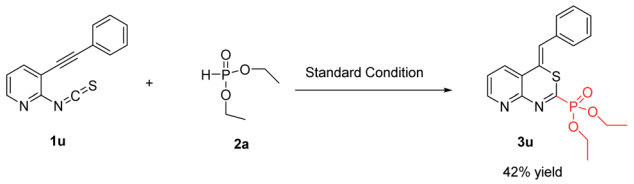
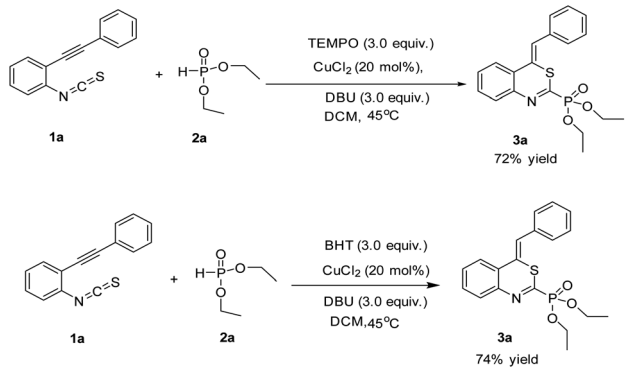


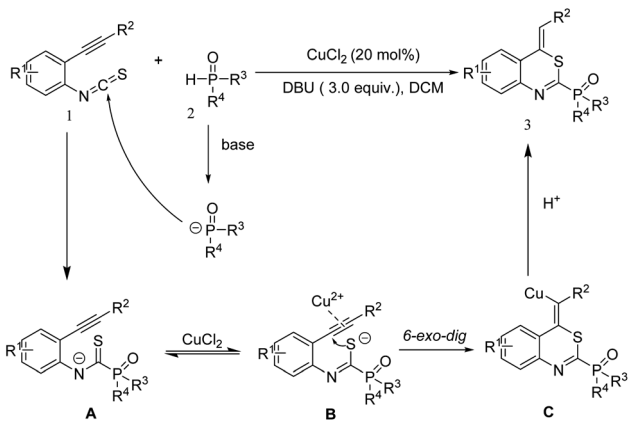
Fig. 1 Single-crystal X-ray diffraction structure of **3t**, the thermal ellipsoids are at the 30% probability level, the CCDC number is 2014442.†



Scheme 2 The reaction of 2-isothiocyanato-3-(phenylethynyl)pyridine with **2a**.



Scheme 3 Control experiments.



Scheme 4 Proposed mechanism.

was attacked by phosphite to produce the intermediate **A**. Intermediate **A** could then undergo isomerization to afford intermediate **B**. Next, the alkyne moiety of intermediate **B** was activated by the copper species which was then attacked by the sulfur anion through 6-*exo*-dig cyclization, leading to the intermediate **C**. Finally, intermediate **C** underwent protonolysis to give the target product **3**.

Conclusions

In summary, we have developed an efficient method for the synthesis of 4*H*-benzo[*d*][1,3]thiazin-2-yl phosphonates *via* the copper(II)-catalyzed tandem cyclization of *o*-alkynylphenyl isothiocyanates and phosphites. In this reaction, a series of

organophosphorus heterocycles could be synthesized in good yields involving C–P and C–S bond formation in one pot. This present cascade cyclization strategy represented an effective way to construct phosphorus-containing small molecular N,S-heterocycles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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