ChemPubSoc Europe

DOI: 10.1002/ejoc.201700022

EurJOC European Journal of Organic Chemistry

Communication

C–H Phosphorylation

$K_2S_2O_8$-Promoted Direct C–H Phosphorylation of (Benzo)thiazoles

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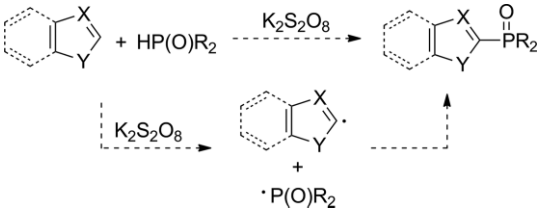
Abstract: The direct phosphorylation of (benzo)thiazoles with various H-phosphine oxides was realized by using $K_2S_2O_8$ as the oxidant. A series of 2-phosphoryl (benzo)thiazoles were obtained in moderate to good yields.

Introduction

Aromatic phosphorus compounds represent a class of ubiquitous molecules in biochemistry and catalysis.[1,2] The construction of these compounds through efficient C(sp^2)–P bond formation is of great importance in organic chemistry. Since the pioneering work of Hirao et al. in 1981,[3] plenty of synthetic procedures based on the transition-metal-catalyzed cross-coupling of aryl (pseudo)halides with H-phosphonates have been developed.[4] However, these methodologies are environmentally and economically less attractive owing to the need for prefunctionalization of Ar–H bonds and the use of a large amount of base. Recently, two straightforward routes for the direct phosphorylation of C(sp^2)–H bonds have received significant attention. The first route relies on palladium-, copper-, or rhodium-catalyzed C(sp^2)–H phosphorylation.[5] The groups of Yu and Murakami independently developed a route for the first pyridine-directed Pd^{II}-catalyzed C–H phosphorylation of aryl C–H bonds.[5b,5c] The second route relies on the radical phosphorylation of (hetero)arenes. Several metal salts, such as Mn(OAc)$_2$/Co(OAc)$_2$,[6] Mn(OAc)$_3$,[7] and peroxodisulfate/$AgNO_3$,[8] were reported to promote the phosphorylation of (hetero)arenes with dialkyl phosphonates.

2-Substituted benzothiazole derivatives are of particular interest in pharmaceutical chemistry and materials science. Recently, the direct C2 phosphorylation of benzothiazoles has attracted much attention from synthetic chemists.[5d,9] In 2012, Li and his co-workers reported the first Pd-catalyzed direct phosphonation of azoles with dialkyl phosphites.[5d] In 2014, Chen and Qu et al. found that the direct C2 phosphorylation of benzothiazoles could be realized by the reaction of benzothiazoles with dialkylphosphites and diphenylphosphine oxide by using di-*tert*-butyl peroxide (DTBP) as a radical initiator.[9a] Later, we developed a method for the $AgNO_3$-mediated direct phosphorylation of (benzo)thiazoles with various diaryl- and dialkylphosphine oxides.[9b] Recently, Wu et al. reported the first direct route for the C–H phosphorylation of thiazoles with diarylphosphine oxides catalyzed by visible light along with 5 mol-% eosin B.[9c] The phosphoryl radical generated from the reaction of diarylphosphine oxides and silver salts may be involved in the transformation. Recently, Yang and co-workers reported a transition-metal-free $K_2S_2O_8$-mediated oxidative arylphosphination of activated N-substituted-*N*-arylacrylamide derivatives.[10,11] The reaction of $HP(O)Ph_2$ with the sulfate radical anion derived from $K_2S_2O_8$ may lead to the formation of a phosphoryl radical. Encouraged by this work, we envisioned that the direct C–H phosphorylation of (benzo)thiazoles might be realized through a simple peroxodisulfate-promoted radical process (Scheme 1). Herein, we report on the realization of this hypothesis.



Scheme 1. C–H phosphorylation of (benzo)thiazoles.

Results and Discussion

Our research commenced with the reaction between benzothiazole (**1a**) and diphenylphosphine oxide (**2a**) in the presence of $K_2S_2O_8$ under an argon atmosphere (Table 1, entries 1–5). Phosphorylation product **3aa** was obtained in 65 % yield upon performing the reaction at 70 °C with the use of 2 equivalents of $K_2S_2O_8$ (Table 1, entry 1). Treatment of **1a** with **2a** in the presence of 1 and 3 equivalents of $K_2S_2O_8$ afforded **3aa** in lower yields (41 and 61 %, respectively; Table 1, entries 2 and 3). Performing the reaction at 50 and 90 °C provided desired product **3aa** in much lower yields (45 and 44 %, respectively; Table 1, entries 4 and 5). To our delight, conducting the reaction of **1a** with **2a** in air provided a much better yield of **3aa** (71 %; Table 1, entry 6). However, the reaction under an O_2 atmosphere gave **3aa** in only 31 % yield (Table 1, entry 7). Moreover, if

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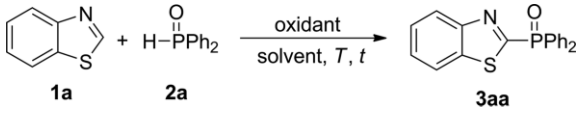
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201700022.

the reaction was performed for 12 or 36 h, the phosphorylation product was afforded in a much lower yield (Table 1, entries 8 and 9). Thereafter, other persulfate salts, including $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$, were examined, but they were less effective than $K_2S_2O_8$ (Table 1, entries 10 and 11). Various solvents such as MeCN, 1,2-dichloroethane (DCE), 1,4-dioxane, EtOAc, and DMSO were screened, and MeCN proved to be the best choice (Table 1, entries 12–15). Finally, the yield of isolated **3aa** was further increased by changing the purification process (Table 1, entry 16).

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

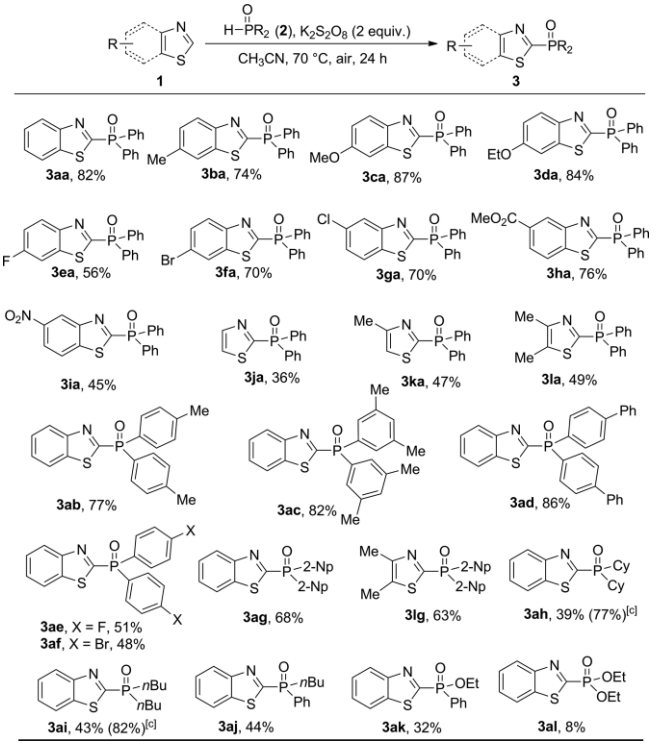


Entry	Oxidant (equiv.)	*T* [°C]	*t* [h]	Solvent	Yield[b] [%]
1[c]	$K_2S_2O_8$ (2)	70	24	MeCN	65
2[c]	$K_2S_2O_8$ (1)	70	24	MeCN	41
3[c]	$K_2S_2O_8$ (3)	70	24	MeCN	61
4[c]	$K_2S_2O_8$ (2)	50	24	MeCN	45
5[c]	$K_2S_2O_8$ (2)	90	24	MeCN	44
6	$K_2S_2O_8$ (2)	70	24	MeCN	71
7[d]	$K_2S_2O_8$ (2)	70	24	MeCN	31
8	$K_2S_2O_8$ (2)	70	12	MeCN	53
9	$K_2S_2O_8$ (2)	70	36	MeCN	64
10	$(NH_4)_2S_2O_8$ (2)	70	24	MeCN	33
11	$Na_2S_2O_8$ (2)	70	24	MeCN	35
12	$K_2S_2O_8$ (2)	70	24	DCE	36
13	$K_2S_2O_8$ (2)	70	24	1,4-dioxane	59
14	$K_2S_2O_8$ (2)	70	24	EtOAc	44
15	$K_2S_2O_8$ (2)	70	24	DMSO	61
16[e]	$K_2S_2O_8$ (2)	70	24	MeCN	82

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), oxidant (0.4 mmol), MeCN (1.5 mL), air. [b] Yield of isolated product. [c] Under an argon atmosphere. [d] Under an O_2 atmosphere. [e] At completion of reaction, instead of directly removing the solvent, the resulting mixture was washed with water and extracted with EtOAc before column chromatography.

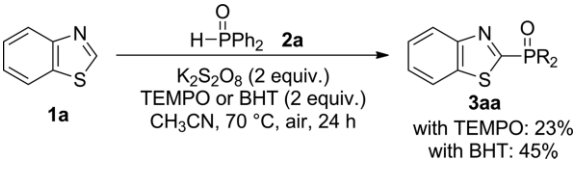
To test the generality of this chemistry, benzothiazoles and thiazoles with different substituents and various H-phosphine oxides were screened (Table 2). Different ring-substituted (–Me, –OMe, –OEt, –F, –Br, –Cl, $–CO_2Me$, $–NO_2$) benzothiazoles were suitable substrates for this reaction, although lower yields of the desired products were obtained for benzothiazoles containing electron-deficient substituents. Furthermore, thiazoles also reacted with diphenylphosphine oxide and gave corresponding 2-phosphorylation products **3ja**–**la** in moderate yields (36–49 %). Next, various H-phosphine oxides were examined. Diarylphosphine oxides containing electron-donating or electron-neutral groups (4-Me, 3,5-Me_2, and 4-Ph) on the phenyl ring were well tolerated and gave desired products **3ab**–**ad** in good yields (77–86 %). Furthermore, the reaction of benzothiazole (**1a**) with diarylphosphine oxides containing electron-withdrawing groups (4-F and 4-Br) proceeded smoothly and led to the formation of **3ae** and **3af** in lower yields (**3ae**, 51 %; **3af**, 48 %). Notably, di(naphthalen-2-yl)phosphine oxide also reacted with benzothiazole (**1a**) and 4,5-dimethylthiazole (**1l**) to afford corresponding products **3ag** and **3lg** in moderate yields (**3ag**, 68 %; **3lg**, 63 %). In addition, the reactions of alkylphosphine oxides, such as dicyclohexylphosphine oxide (**2h**), dibutylphosphine oxide (**2i**), and butyl(phenyl)phosphine oxide (**2j**), with benzothiazole (**1a**) were performed. Corresponding phosphorylation products **3ah**, **3ai**, and **3aj** were obtained in moderate yields (39–44 %). Upon adding 4 Å molecular sieves (100 mg) to the reactions, **3ah** and **3ai** were obtained in dramatically increased yields (77 and 82 %, respectively). However, both ethyl phenylphosphinate (**2k**) and diethyl phosphonate (**2l**) reacted with **1a** to form the corresponding products in much lower yields (**3ak**, 32 %; **3al**, 8 %).

Table 2. Substrate scope.[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), oxidant (0.4 mmol), MeCN (1.5 mL), air; Cy = cyclohexyl, 2-Np = 2-naphthyl. [b] Yield of isolated product. [c] 4 Å molecular sieves (100 mg).

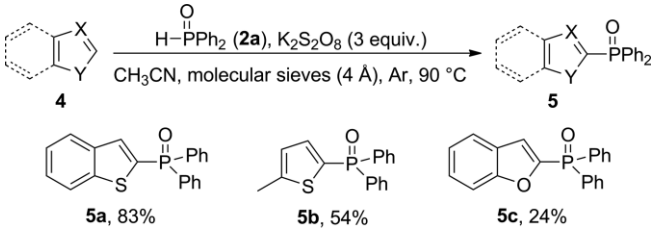
The reactions of **1a** with **2a** in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and butylated hydroxytoluene (BHT) as radical scavengers were performed to gain mechanistic insight into the C–H phosphorylation reaction [Equation (1)]. The yields of **3aa** decreased dramatically, which is consistent with a radical mechanism.



(1)

To explore the practical value of this $K_2S_2O_8$-mediated C–H phosphorylation process, the phosphorylation of other heterocycles such as benzothiophene, 2-methylthiophene, and benzofuran with $HP(O)Ph_2$ was examined (Scheme 2). The corre-

sponding phosphorylation products were obtained in good yields (**5a**, 83 %; **5b**, 54 %; **5c**, 24 %).



Scheme 2. C–H phosphorylation of several heterocycles.

Conclusions

In conclusion, we developed an efficient route for the $K_2S_2O_8$-mediated direct C–H phosphorylation of (benzo)thiazoles. This method is transition-metal free and provides straightforward access to various benzo[*d*]thiazol-2-yldiarylphosphine oxides. Further study on the reaction scope and applications of this method are still underway in our laboratory.

Experimental Section

General Procedure for the Phosphorylation of Benzothiazoles: In a 15 mL Schlenk tube, benzothiazole **1** (0.2 mmol), $R_2P(O)H$ **2** (0.6 mmol), and $K_2S_2O_8$ (0.4 mmol) were dissolved in MeCN (1.5 mL). The tube was sealed, and the mixture was stirred in air at 70 °C for 24 h. The resulting mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine. The organic layer was collected and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc, 5:1–1:1) to afford product **3**.

Acknowledgments

We are thankful for financial support from the National Natural Science Foundation of China (No. 21572188, 21302157) and Fundamental Research Funds for the Central Universities (No. 20720160049).

Keywords: Heterocycles · Oxidation · Phosphorylation · Radical reactions · Synthetic methods

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Received: January 8, 2017