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Three-Component Coupling Reaction in Water: A One-Pot Protocol for the Construction of P-S-C(sp³) and P-Se-C(sp³) Bonds

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ABSTRACT: A one-pot three-component coupling reaction of primary alkylhalides (or tosylates), elemental sulfur/selenium and P(O)-H compounds in water is developed, affording the valuable phosphorothioates or phosphoroselenoates including the P-chiral compounds with broad substrate scope and high efficiency. Moreover, this facile protocol also can be applicable for the gramscale preparation.

Introduction

The P-chalcogen derivatives are important and useful scaffolds in medicines¹, agricultural industry² and organic synthesis³. Among them, phosphorothioates have received considerable attention in the past decades due to their unique properties. The phosphorothioates were normally synthesized by coupling Hphosphonates with disulfides^{4,5a}, sulfonylhydrazides^{5b}, aryl sulfonyl chlorides^{5c,6} or thiols^{7,8}, catalyzed by transition metals, e.g., Cu^{5,7,9} and Pd¹⁰. However, these protocols have their own limitations, including narrow scope of substrates, foul-smelling materials and expensive metal catalysts. In addition, conventional strategies for the construction of P-S-C(sp³) bond often started with toxic and moisture sensitive phosphoryl chloride¹¹ [Scheme 1(a)], sodium reagents⁴ [Scheme 1(b)], RSX^{8a} [Scheme 1(c)] or phenylphosphinothioate salt¹² [Scheme 1(d)], which required a two-step workup procedure, further limiting their applications.

Even though some of the above reported procedures are efficient, to the best of our knowledge, there are still no reports on the synthesis of the P-chalcogen derivatives in aqueous solutions, i.e. water. Furthermore, the increased environmental requirements called for more efficient and organic solvent free procedures for chemical syntheses¹³. As a part of our continued activities in this area^{6,14}, herein we report a facile one-pot threecomponent coupling of P(O)-H compounds with elemental sulfur/selenium and primary alkylhalides (or tosylates) under relatively mild conditions in water [Scheme 1(e)].

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Reported two-step procedure to the construction of P-S-C(sp³) bond

ether

$$R^{1}$$
=(-)-Menthyl, R^{2} = alkyl; X = Br, I

e) This work $R^{1,H}_{2}$ R² R² R² + X + R³-Z $Et_{3}N$ R² H₂O, 50°C, 24 h R^1 , R^2 = aryl, O-aryl, O-alkyl; X = S₈, Se; R^3 = alkyl; Z = Cl, Br, I, OTs

Scheme 1. Synthesis of P-Chalcogen Derivatives

Results and Discussion

At the outset, compound 1a, (2-(4-bromobutyl)isoindoline-1,3dione), 2a, sulfur powder, and 3a, diphenylphosphine oxide, were chosen as model substrates to investigate the optimum reaction condition. The influence of the base, reaction time and reaction temperature were screened, which were summarized in Table 1. The desired P-S-C coupling product, 4a, was obtained in 31% yield when the reaction mixtures, 1a (0.5 mmol), 2a (0.5 mmol) and 3a (0.5 mmol), were stirred in neat water (0.75 mL) at 50 °C for 24 h (Table 1, entry 3). However, trace amount of 4a were examined by reducing reaction temperature and time (Table 1, entries 1 and 2). As expected, the yield of product 4a dramatically increased to 82% when the organic base, 1.0 equiv. of Et₃N, was added (Table 1, entry 4). Unfortunately, the P-S-C(sp³) bond transformation was not found to be accelerated by elevating the reaction temperature to 80 °C (80% yield, Table 1, entry 5). Moreover, an increase of the base amount results in a reduced yield (72%, 69% yields, Table 1, entries 6-7). No apparent improvement was observed when the usage amount of 2a, 3a was raised to 1.2 equiv. (84%, 78% yields, Table 1,

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	+ S ₈ + H Br	● ■P ^{Ph} =	Base H ₂ O, T	0 S ^P Pt
1a	2a	3a		4a
Entry	Base	T(°C)	t(h)	Yield (%) ^d
1 ^a	None	25	12	Trace
2 ^a	None	25	24	Trace
3 ^a	None	50	24	31
4 ^a	Et ₃ N(1.0eq.)	50	24	82
5 ^a	Et ₃ N(1.0eq.)	80	24	80
6 ^a	Et ₃ N(1.2eq.)	50	24	72
7 ^a	Et₃N(1.5eq.)	50	24	69
8 ^b	Et₃N(1.2eq.)	50	24	84
9 ^{<i>b</i>}	Et₃N(1.5eq.)	50	24	78
10 ^c	Et₃N(1.5eq.)	50	24	91
11 [°]	Na ₂ CO ₃ (1.5eq.)	50	24	54
12 ^c	K ₂ CO ₃ (1.5eq.)	50	24	73
13 ^c	DIPA(1.5eq.)	50	24	61
14 ^c	DIPEA(1.5eq.)	50	24	89
15 [°]	NaOH(1.5eq.)	50	24	54
16 ^c	<i>t</i> -BuOK(1.5eq.)	50	24	31
17 ^c	Et ₃ N(2eq.)	50	24	65
18 [°]	Et₃N(3eq.)	50	24	37

Table 1. Optimization of Reaction Condition

[a] The reactions were performed with (entries 1-7): **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), Base (0-1.5 eq. based on **1a**), H₂O (0.75 mL) in air. [b] Entries 8-9: **1a** (0.5 mmol), **2a** (0.6 mmol), **3a** (0.6 mmol), Base (1.2-1.5 eq. based on **1a**), H₂O (0.75 mL) in air. [c] Entries 10-18: **1a** (0.5 mmol), **2a** (0.75 mmol), **3a** (0.75 mmol), **3a** (0.75 mmol), Base (1.5-3 eq. based on **1a**), H₂O (0.75 mL) in air. ^{*a*}Isolated yields based on **1a**. (DIPA = Diisopropylamine, DIPEA = Diisopropylethylamine)

entries 8-9). The further study showed that this reaction was carried out most efficiently as the amount of the Et₃N, sulfur powder (**2a**) and P(O)-H compound (**3a**) were all increased to 1.5 equiv (91% yield, Table 1, entry 10). We then also investigated the influence of the base (Table 1, entries 10-16) and Et₃N was found to be superior to other bases, including Na₂CO₃, K₂CO₃, NaOH, *t*-BuOK, DIPA and DIPEA. Notably, increasing the amount of Et₃N led to a drastic reduction in reaction efficiency (Table 1, entries 17 and 18). Therefore, the optimum reaction condition was set as **1a** (0.5 mmol), **2a** (0.75 mmol), **3a** (0.75 mmol), and Et₃N (0.75 mmol) in 0.75 mL water at 50 °C for 24 h for the reaction scope investigations.

To explore the scope of the established protocol, a wide set of primary alkylhalides (or tosylates), 1, and four organophosphorus compounds containing P(O)-H, 3, were



Table 2. Base-Promoted Synthesis of Phosphorothioates in Water⁴

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), **3** (0.75 mmol), Et₃N (0.75 mmol), H₂O (0.75 mL) at 50°C for 24 h. Isolated yields based on 1. [b] for **4h**, **4i**: 1 (0.75 mmol), **2a** (0.75 mmol), **3** (0.5 mmol), Et₃N (0.75 mmol), H₂O (0.75 mL) at 50°C for 24 h. Isolated yields based on **3**.

examined under optimized reaction conditions. As illustrated in Table 2, the substrates bearing different leaving groups (iodide, bromide, chloride, tosylate) were readily reacted with sulfur powder and P(O)-H compounds to afford the corresponding phosphorothioates in moderate to excellent yields. Moreover, the P-S-C(sp³) bond was unambiguously confirmed by the X- ray crystallographic analysis of **4b** (Figure 1). Bis-coupling products can also be obtained from bis-substituted primary alkylbromides,

with yields in 71% and 49%, respectively (Table 2, 4I, 4m). Moreover, functional groups including carboxylic ester, hydroxyl, alkoxyl, bromide, chloride, alkynyl and alkenyl groups were tolerable under the current protocol, and afforded the corresponding products 4e-4k in 48-91% yields (Table 2, 4e-4k). Substituted primary alkylbromides with methoxy, alkenyl, and carboxylic ester groups could also react with DOPO (3b) and optically pure H-phosphinate ((R_P)-(-)-menthyl benzylphosphinate) (3c)¹⁵ to provide corresponding products in 65%, 56% and 59% yields (Table 2, 4r, 4s and 4x), respectively. It is worth noting that the R configuration of enantiomerically pure P-chiral phosphorothioates 4t-4x was confirmed by X-ray diffraction of 4w (Figure 1)¹². In contrasted to the classical Atherton-Todd reaction, the configuration at the phosphorus atom obtained by this approach is retentive, but not inversed¹⁶. However, less-effective reactions were also observed for Hphosphonates, 3d, which resulted in the corresponding products 4y and 4z in only 11% and 6% yields in water. To our delight, this method was not only suitable for small quantity synthesis, but also applicable for the gram-scale preparation. A gram scale preparation of compound 4a, S-(4-(1,3-dioxoisoindolin-2-yl)butyl) diphenylphosphinothioate, was obtained in 84% isolated yield (Table 2, 4a, 3.66 g), further demonstrating the practicality of the method.



Figure 1. Single-crystal X-ray structure of compound 4b (left) and (R_p)-4w (right) (ellipsoids at the 50% probability level). Some of the hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [deg]: 4b: P(1)-S(1) 2.0757(9), S(1)-C(23) 1.826(2), C(23)-S(1)-P(1) 99.68(7), C(22)-C(23)-S(1) 110.29(14); 4w: P(1)-S(1) 2.0865(12), S(1)-C(25) 1.828(4), C(25)-S(1)-P(1) 99.04(13), C(24)-C(25)-S(1) 111.0(2).

Encouraged by the successful and efficient construction of P-S-C(sp³) bond, we further extended the optimized reaction conditions to the construction of P-Se-C(sp³) bond. As collected in Table 3, the established protocol could also be applied to the synthesis of phosphoroselenoates by using selenium powder to instead of sulfur powder, generating the corresponding products 5 in moderate to good yields. The presence of the P-Se-C(sp³) was clearly identified by single-crystal X-ray diffraction (Figure 2, 5b). Different alkylhalides (or tosylates) were also examined using the established reaction protocol with similar reaction yields (Table 3, 5a, 5b, 5g and 5h), further corroborating the efficiency of this synthetic strategy. In addition, functional groups (Table 3, 5e, 5f) did not change the yields of the P-Se-C(sp³) coupling products significantly. As an application of the current method, a gram-scale reaction was also conducted and corresponding product 5d (Table 3, 5d, 2.41g) was obtained in







[a] Unless otherwise mentioned, the reactions were performed with **1a** (0.75 mmol), **2b** (0.6 mmol), **3** (0.5 mmol), Et₃N (0.75 mmol) at 50°C for 24 hours in 0.75 mL water. Isolated yields based on **3**.



Figure 2 Single-crystal X-ray structure of compound **5b** (left) and (R_p)-**5j** (right) (ellipsoids at the 50% probability level). Some of the hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [deg]: **5b**: Se(1)-C(23) 1.968(2), Se(1)-P(1) 2.2278(9), C(23)-Se(1)-P(1) 98.39(6), C(22)-C(23)-Se(1) 110.06(15); **5j**: Se(1)-C(25) 1.971(6), Se(1)-P(1) 2.2362(15), C(25)-Se(1)-P(1) 95.64 (18), C(24)-C(25)-Se(1) 111.0(4).

63% yield. Similarly, retentive configurations at the phosphorus atom were obtained from the P-chiral precursors **3c**, which was first confirmed by X-ray diffraction of **5j** (Figure 2). This observation further confirmed the formation of the chiral P-Se- $C(sp^3)$ bond in this protocol (Table 3, **5g-5j**).

Conclusions

In conclusion, a simple and efficient one-pot protocol for the construction of P-S-C or P-Se-C bond from elemental sulfur or selenium has been achieved under organic solvent-free and metal-free conditions. This methodology provided an alternative strategy to generate the valuable phosphorothioates or

phosphoroselenoates, including the P-chiral compounds. Moreover, it also works well for the large-scale preparation in water.

Experimental Section

Typical procedure for synthesis of phosphorothioates in water (A). Compound 1 (0.5 mmol), 2a (0.75 mmol), 3 (0.75 mmol), Et₃N (0.75 mmol) and H₂O (0.75 mL) were charged into a 20 mL glass tube without exclusion of air, and the reaction mixture was then stirred at 50 °C for 24 h. After completion of the reaction, the mixture was extracted with ethyl acetate (5.0 mL x 3). Then the organic phases were combined and dried with anhydrous MgSO₄, purified by silica gel column chromatography (ether/ethyl acetate as eluent) to afford the corresponding product **4** in yields listed in Table 2. The identity and purity of products were confirmed by ¹H, ¹³C, ³¹P, HRMS, and X-ray single crystal diffractometer spectroscopic analysis.

Typical procedure for synthesis of phosphoroselenoates in water (B). Compound 1 (0.75 mmol), 2b (0.6 mmol), 3 (0. 5 mmol), Et₃N (0.75 mmol) and H₂O (0.75 mL) were charged into a 20 mL glass tube without exclusion of air, and the reaction mixture was then stirred at 50 °C for 24 h. After completion of the reaction, the mixture was extracted with ethyl acetate (5.0 mL x 3). Then the organic phases were combined and dried with anhydrous MgSO₄, purified by silica gel column chromatography (ether/ethyl acetate as eluent) to afford the corresponding product **5** in yields listed in Table 3. The identity and purity of products were confirmed by ¹H, ¹³C, ³¹P, HRMS, and X-ray single crystal diffractometer spectroscopic analysis.

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Keywords: three-component coupling • P-chalcogen derivative • phosphorothioate • phosphoroselenoate

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A convenient and efficient one-pot protocol for the construction of P-S-C or P-Se-C bond from elemental sulfur or selenium has been developed in water, a series of valuable phosphorothioates or phosphoroselenoates including the P-chiral compounds were produced in good to excellent yields.

Organophosphorous chemistry

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