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A novel one-pot three-component tandem Michael/aldol/Horner–Wadsworth–Emmons (HWE) reaction of lithium alkylselenolates with 1-alkynylphosphine oxides and aldehydes: facile synthesis of selenium-substituted allenes†

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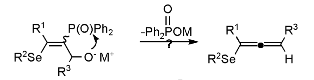
The one-pot tandem Michael/aldol/Horner–Wadsworth–Emmons (HWE) reaction of lithium alkylselenolates, 1-alkynylphosphine oxides and aldehydes in THF provides a new general access to selenium-substituted allenes with good to excellent yields.

The tandem reaction is of current interest because it offers a convenient and economical way to prepare desired organic molecules.[1] The Michael addition and the aldol reaction are acknowledged as useful tools for constructing complex organic molecules, and combining the two reactions in one pot has been a focus of organic chemistry.[2]

Allenes show unique reactivity in organic synthesis due to the presence of the cumulated C=C double bonds.[3] Many studies have been performed on their preparation and reactivity.[4,5] Heteroatom-substituted allenes have also received attention.[6] Selenium-substituted allenes are known as isolable compounds or reactive intermediates.[7] However, the difficulty in preparing this kind of compound has limited their application in organic synthesis. Thus, it is highly desirable to develop a convenient method to synthesize this kind of compound.

The selenolates are good nucleophiles for Michael addition reaction[8] and several selenolate anion-triggered Michael/aldol tandem reactions have been intensively studied.[9] Recently, our group has reported the stereoselective Michael/aldol tandem reaction of phenylselenomagnesium bromide with acetylenic sulfones and aldehydes to afford (*Z*)-β-phenylseleno-α-(*p*-tolylsulfonyl)allylic alcohols.[10] On the other hand, the Horner–Wadsworth–Emmons (HWE) reaction of β-phosphonato alkoxides is the most general procedure to construct the C=C double bond; the cumulated C=C double bonds of allenes can also be constructed by the HWE reaction of β-phosphonoallyl alcohols.[11] Thus, we envisaged that if the *p*-tolylsulfonyl group in the above tandem reaction is replaced by a phosphono group, the Michael/aldol intermediates, β-phosphonoallyl alkoxides, may undergo HWE olefination reaction leading to the selenium-substituted allenes as the final products (Scheme 1). Herein, we wish to report our preliminary results for the Michael/aldol/Horner–Wadsworth–Emmons (HWE) tandem reaction.

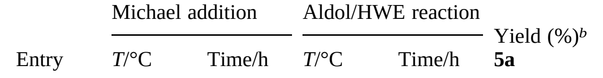
We first studied the reaction of $(n\text{-BuSe})_2$ with *n*-BuLi in solvents such as THF, ether and benzene. BuLi (1.5 M in hexane) was added to the solution of $(n\text{-BuSe})_2$ in the above solvents with stirring at rt. After 0.5 hour, the reaction mixtures were trapped with $PhCH_2Br$. The $n\text{-BuSeCH}_2Ph$ was formed in a yield of > 99%. This shows that the *n*-BuSeLi can be generated quantitatively from $(n\text{-BuSe})_2$ on treatment with *n*-BuLi in the above solvents. Then the Michael addition of *n*-BuSeLi with diphenyl-phenylethynylphosphine oxide (**1a**) in THF was investigated. When the mixture of *n*-BuSeLi and **1a** in THF was stirred for 2 hours at rt, only a complex mixture was obtained while 22% of **1a** was recovered and no Michael adduct was observed. This could be ascribed to the fact that the Michael adduct **4a** is a good nucleophile itself[12] which can further react with **1a**. To our surprise, when *p*-chlorobenzaldehyde (**3a**) was added to the mixture of *n*-BuSeLi and **1a** in THF one hour after the addition of **1a**, we got the allene **5a** in 38% yield (Table 1, entry 2). Shortening the time during the addition of **1a** and **3a** or dropping the reaction temperature of Michael addition can minimize the side reaction and improve the yield of **5a** dramatically (Table 1). When **3a** was added 0.5 hour after the addition of **1a** at 0 °C with stirring for a further hour at rt, the yield of **5a** was increased to 74% (Table 1, entry 4). It is noteworthy that no adduct of *n*-BuSeLi to *p*-chlorobenzaldehyde (**3a**) was detected during the reaction. This suggests that *n*-BuSeLi can react with **1a** selectively in the presence of **3a**. Thus we can carry out the tandem reaction by adding the **1a** and **3a** in one portion.



Scheme 1

In an effort to optimize this process by adding the **1a** and **3a** in one portion, a range of different reaction temperatures and solvents were investigated. The results are summarized in Table 2. From Table 2, it should be noted that reaction temperature and solvent were crucial for the success of the reaction. When the reaction was carried out at −25 °C, the HWE reaction could not proceed efficiently (entry 1). If the reaction temperature dropped to −40 °C, the HWE reaction did not occur at all, only the Michael/aldol adduct (**6a**) was obtained in 34% yield with recovered **1a** in the yield of 57% (entry 2). When **1a** and **3a** were added to the solution of *n*-BuSeLi in THF at −25 °C, the reaction was complete within 30 min to afford **5a** in the yield of 82% after warming the reaction mixture to rt in 20 min (entry 3). This indicates that the HWE reaction can proceed smoothly at rt. On the other hand, THF was proved to be the most efficient solvent for the preparation of selenium-substituted allene (entry 3). When the reaction was performed in benzene and diethyl ether, we obtained the Michael/aldol product (**6a**) exclusively in 63% and 51% yield, respectively (entries 4, 5).

Table 1 Two-step tandem reaction under various conditions [a]



	Michael addition		Aldol/HWE reaction		
Entry	*T*/°C	Time/h	*T*/°C	Time/h	Yield (%)[b] **5a**
1	rt	0.5	rt	1	63
2	rt	1	rt	1	38
3	rt	2	rt	1	16
4	0	0.5	rt	1	74

[a] The reaction was carried out using **1a** (1.0 mmol), **2** (1.0 mmol) and **3a** (1.0 mmol). [b] Isolated yield.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b304527g/

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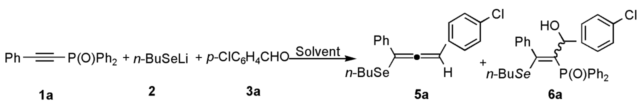
Table 2 One-pot tandem reaction under various conditions[a]



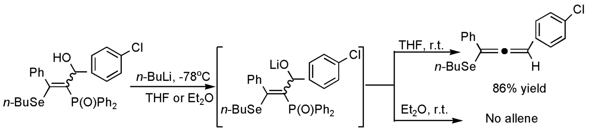
Entry	Solvent	*T*/°C	Time/h	Yield (%)[b] **5a**	**6a**	**1a**
1	THF	−25	5	29	36	28
2	THF	−40	5	—	34	57
3	THF	−25–rt	1	82	—	—
4	Et_2O	−25–rt	2	—	51	32
5	Benzene	rt	2	—	63	19

[a] The reaction was carried out using **1a** (1.0 mmol), **2** (1.0 mmol) and **3a** (1.0 mmol). [b] Isolated yield.

In order to confirm the Michael/aldol adduct as the reaction intermediate and the effect of the solvent, we transformed the Michael/aldol adduct (**6a**), β-phosphonoallyl alcohol, to lithium β-phosphonoallyl alkoxide by treating **6a** with *n*-BuLi at −78 °C in THF and in ether. When the solution of lithium β-phosphonoallyl alkoxide in THF was warmed to room temperature, it eliminated diphenylphosphinate spontaneously within 20 min to afford the selenium-substituted allene in 86% yield. However, no selenium-substituted allene was obtained and most of the material was recovered when the solution of lithium β-phosphonoallyl alkoxide in ether was stirred at rt for 1 hour and quenched with NH_4Cl saturated solution (Scheme 2).

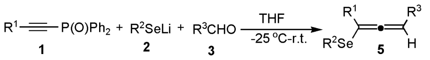
Further investigation showed that other lithium alkylselenolates such as *s*-BuSeLi, *i*-PrSeLi can also react with 1-alkynylphosphine oxides and aldehydes to give the selenium-substituted allenes smoothly in good yields. However, the reaction did not occur with the use of lithium phenylselenolate.

The present reaction conditions were compatible with the reaction of aromatic or aliphatic 1-alkynylphosphine oxides with other aromatic or aliphatic aldehydes or α,β-unsaturated aldehydes. The results are summarized in Table 3.



Scheme 2

Table 3 Synthesis of selenium-substituted allenes[a]



Entry	R^1	R^2	R^3	Time/ min	Product	Yield[b] (%)
1	C_6H_5	*n*-Bu	*p*-ClC_6H_4	30	**5a**	82
2	C_6H_5	*n*-Bu	C_6H_5	30	**5b**	80
3	C_6H_5	*n*-Bu	*p*-$CH_3OC_6H_4$	40	**5c**	87
4	C_6H_5	*n*-Bu	*p*-$(CH_3)_2NC_6H_4$	40	**5d**	83
5	C_6H_5	*n*-Bu	*n*-C_3H_7	60	**5e**	63
6	C_6H_5	*i*-Pr	*p*-$CH_3OC_6H_4$	40	**5f**	89
7	CH_3OCH_2	*n*-Bu	C_6H_5	25	**5g**	84
8	CH_3OCH_2	*n*-Bu	*p*-ClC_6H_4	25	**5h**	82
9	CH_3OCH_2	*n*-Bu	*p*-$CH_3OC_6H_4$	30	**5i**	86
10	CH_3OCH_2	*n*-Bu	*p*-$(CH_3)_2NC_6H_4$	30	**5j**	81
11	CH_3OCH_2	*s*-Bu	*p*-ClC_6H_4	25	**5k**[c]	82
12	CH_3OCH_2	*i*-Pr	*p*-ClC_6H_4	25	**5l**	85
13	CH_3OCH_2	*n*-Bu	$C_6H_5CH{=}CH$	40	**5m**	59
14	*n*-C_5H_{11}	*n*-Bu	C_6H_5	50	**5n**	77
15	*n*-C_5H_{11}	*n*-Bu	*p*-ClC_6H_4	50	**5o**	71
16	*n*-C_5H_{11}	*n*-Bu	*p*-$CH_3OC_6H_4$	50	**5p**	73

[a] The reaction was carried out by adding a solution of **1** (1.0 mmol) and **3** (1.0 mmol) in THF (4 ml) to a solution of **2** (1.0 mmol) in THF (6 ml) at −25 °C, then the reaction mixture was warmed to rt in 20 min and stirred for the time given in the Table at rt. The RSeLi was generated from $(RSe)_2$ on treatment with *n*-BuLi at rt. [b] Isolated yield of **5**. [c] **5k** d.r. = 1 : 1 (determined by 400 MHz ^{1}H NMR spectra).

As can be seen in Table 3, all the aromatic aldehydes give the selenium-substituted allenes in good yields. The aliphatic aldehydes and α,β-unsaturated aldehydes can also provide the selenium-substituted allenes in moderate yield (entries 5, 13). In the case of *s*-BuSeLi, an inseparable 1 : 1 ratio of diastereoisomers **5k** (determined by 400 MHz ^{1}H NMR spectra) was obtained (entry 11).

In summary, we have developed an efficient one-pot three-component Michael/aldol/Horner–Wadsworth–Emmons (HWE) tandem reaction of lithium alkylselenolates with 1-alkynylphosphine oxides and aldehydes, which provides a convenient synthesis of selenium-substituted allenes. This method possesses the advantages of readily available starting materials, easy manipulation, mild reaction conditions and good yields of products. Further application of selenium-substituted allenes in organic synthesis is now in progress in our laboratory.

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