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Facile synthesis of sulfur-substituted allenes by a three-component reaction

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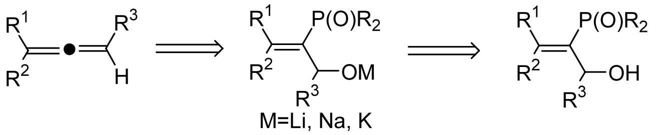
Abstract—The three-component reaction of lithium alkylthiolate, 1-alkynylphosphine oxide and aldehyde in THF affords sulfur-substituted allenes in good to excellent yield.

Allenes are interesting and important compounds in organic synthetic chemistry and a large number of studies have been reported on their reactivity and synthesis.[1,2] The sulfur-containing allenes have also received much attention.[3] For example, the Michael addition reaction of 1,2-allenic sulfoxides and 1,2-allenic sulfones has provided attractive routes to multifunctional alkenes,[4] and the cycloaddition reactions of 1,2-allenic sulfoxides and 1,2-allenic sulfones have led to elegant strategies for the synthesis of complex natural products.[5] However, the chemistry of the sulfur-substituted allenes and their analogues has been limited to some extent due to the difficulties of their preparation.[6] In this paper, we wish to report a facile synthesis of 1,3-disubstituted-(1-alkylthio)allenes by a three-component reaction.

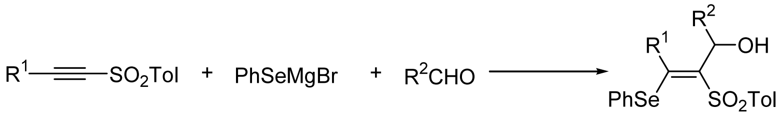


Scheme 1.

Horner–Wadsworth–Emmons (HWE) reaction[7] is one of the most efficient methods for the construction of C=C double bonds. The cumulated C=C double bonds of allene can also be synthesized by the HWE reaction of 2-phosphonoallyl alcohols (Scheme 1).[8]

A convenient synthesis of β-phenylseleno-α-(*p*-toylsulfonyl)allylic achohols by a three-component reaction of phenylselenomagnesium bromide with acetylenic sulfones and aldehydes has been reported recently by our group (Scheme 2).[9] If the *p*-toylsulfonyl group in the aforementioned reaction is replaced by a phosphono group, 2-phosphonoallyl alcohol will be generated easily. Furthermore, the reaction intermediates, 2-phosphonoallyl alkoxides may undergo HWE olefination reaction spontaneously, leading to allenes as final products. Thus, we envisage it would provide a facile synthesis of sulfur-substituted allenes by the three-component reaction of lithium alkylthiolate with 1-alkynylphosphine oxide and aldehyde.

Lithium butylthiolate, diphenyl-(phenylethynyl)phosphine oxide (**1a**) and *p*-chlorobenzaldehyde (**3a**) were



Scheme 2.

Keywords: sulfur-substituted allenes; three-component reaction; synthesis.

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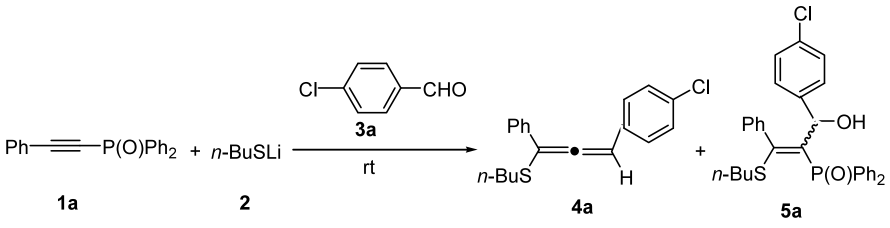


Scheme 3.

Table 1. Reaction under various conditions[a]

Entry	Solvent	Nucleophile	Time (h)	Yield (%)[b]	
				4a	**5a**
1	Et_2O	*n*-BuSLi	2	/	54
2	Benzene	*n*-BuSLi	1.5	/	61
3	THF	*n*-BuSLi	0.5	80	/
4	1,4-Dioxane	*n*-BuSLi	3	67	/
5	THF	*n*-BuSMgBr	5	/	/

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

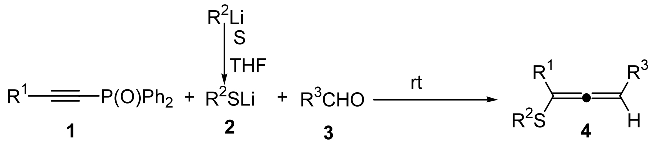
[b] Isolated yield.

chosen as model compounds to optimize the reaction conditions (Scheme 3). Lithium butylthiolate was prepared by the reaction of 1-butanethiol with *n*-butyllithium at room temperature.[10] Typical results are summarized in Table 1.

It is clear from Table 1 that THF is the most suitable solvent for the reaction. After **1a** and **3a** were added to a solution of lithium butylthiolate in THF, the mixture was stirred at room temperature until the completion of reaction (monitored by TLC). The sulfur-substituted allene was obtained in 80% yield (entry 3, Table 1). Dioxane was found to be less efficient than THF (entry 4, Table 1). On the other hand, when the reaction was performed in ether or benzene, only Michael/aldol adducts were obtained in 54 and 61% yields, respectively (entries 1 and 2, Table 1). The counter cation of the thiolate also has played an important role in the reaction. The reaction did not occur when the counter cation was magnesium.

In order to avoid the toxicity and the unpleasant odor of 1-butanethiol, *n*-BuSLi was prepared by reaction of *n*-butyllithium with sulfur powder in THF at room temperature and then was used for the above reaction. As a result, sulfur-substituted allene was isolated in 82% yield. It is noteworthy that the reaction could also give a satisfactory result by using *n*-BuSLi generated in

Table 2. Synthesis of the sulfur-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	**4a**	82
2	C_6H_5	*n*-Bu	*p*-$CH_3OC_6H_4$	20	**4b**	87
3	C_6H_5	*n*-Bu	C_3H_7	50	**4c**	61
4	C_6H_5	*i*-Pr	*p*-$CH_3OC_6H_4$	20	**4d**	83
5	CH_3OCH_2	*n*-Bu	*p*-$CH_3OC_6H_4$	30	**4e**	76
6	CH_3OCH_2	*n*-Bu	*p*-ClC_6H_4	25	**4f**	73
7	CH_3OCH_2	*n*-Bu	$C_6H_5CH{=}CH$	40	**4g**	63
8	CH_3OCH_2	*i*-Pr	*p*-ClC_6H_4	25	**4h**	80
9	CH_3OCH_2	*s*-Bu	*p*-ClC_6H_4	25	**4i**[c]	77
10	*n*-C_5H_{11}	*n*-Bu	*p*-$CH_3OC_6H_4$	40	**4j**	79
11	*n*-C_5H_{11}	*n*-Bu	*p*-$(CH_3)_2NC_6H_4$	40	**4k**	71

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

[b] Isolated yield.

[c] Two inseparable diastereoisomers **4i** in 1:1 ratio (determined by 400 MHz ^1H NMR spectroscopy) were obtained.

situ from the reaction of sulfur powder with *n*-butyllithium. Thus, lithium alkylthiolates generated via the reaction of sulfur with the corresponding alkyllithium were chosen for further investigation.

We have further investigated the reaction of other lithium alkylthiolates such as *s*-BuSLi, *i*-PrSLi in THF. They also reacted with 1-alkynylphosphine oxides and aldehydes smoothly to give allenes in good yields (entries 4, 8, 9, Table 2). On the contrary, the reaction did not take place when lithium phenylthiolate was employed.

The present reaction conditions were also applied to the reaction of aromatic or aliphatic 1-alkynylphosphine oxides with other aromatic, aliphatic aldehydes or α,β-unsaturated aldehydes, which afforded the sulfur-substituted allenes in good yields.[11] In the case of *s*-BuSLi, two inseparable diastereoisomers **4i** in 1:1 ratio (determined by 400 MHz ^{1}H NMR spectroscopy) were obtained (entry 9). The results are summarized in Table 2.

In summary, we have developed a convenient one-pot reaction for the synthesis of sulfur-substituted allenes. This method has the advantages of simple procedure, mild reaction conditions and high yields. Further application of sulfur-substituted allenes in organic synthesis is now in progress.

Acknowledgements

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11. *Typical experiment procedure*: A solution of aldehyde (1 mmol) and 1-alkynylphosphine oxide (1.0 mmol) in THF (4 mL) was syringed dropwise to the lithium alkylthiolate (1.0 mmol) solution at room temperature. The mixture was stirred at room temperature until the completion of reaction (monitored by TLC). Then the reaction mixture was quenched with saturated NH_4Cl (5 mL) and extracted with ether (3×10 mL). The organic phase was washed with saturated brine and dried over $MgSO_4$. After filtration and removal of the solvent in vacuum, flash chromatography of the crude product on silica gel using hexane as eluent afforded the products. Selected spectra data for 4e: a light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2H, $J=6.6$ Hz), 6.86 (d, 2H, $J=6.6$ Hz), 6.43 (t, 1H, $J=2.2$ Hz), 4.15 (d, 2H, $J=2.2$ Hz), 3.80 (s, 3H), 3.39 (s, 3H), 2.60–2.65 (m, 2H), 1.55–1.60 (m, 2H), 1.30–1.34 (m, 2H), 0.80 (t, 3H, $J=7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 159.6, 128.6, 126.9, 114.6, 105.3, 100.3, 73.7, 58.2, 55.7, 32.2, 31.7, 23.5, 13.9; IR (neat) cm^{-1} 2957, 1933, 1606, 1101; MS (EI): *m*/*z* 278 (2.57, M^+), 222 (14.5, M^+–*n*-Bu), 189 (100, M^+–*n*-BuS); Anal. calcd for $C_{16}H_{22}O_2S$: C, 69.03; H, 7.96. Found: C, 68.82; H, 8.10.