

## Alkynylation Reactions of *gem*-Difluorinated 3-Bromo-2-phenylthiopropene: Efficient Synthesis of *gem*-Difluorinated 2-Phenylthio-1,4-enynes

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Received November 16, 2010, Accepted December 8, 2010

**Key Words:** 3-Bromo-3,3-difluoro-2-phenylthio-1-propene, 3-Bromo-1,1-difluoro-2-phenylthio-1-propene, Alkynylation, 1,1-Difluorinated 1,4-enyne derivatives, 3,3-Difluorinated 1,4-enyne derivatives

Enynes represent a class of important synthetic intermediates and have been utilized as essential components in the synthesis of multifunctional molecules<sup>1</sup> and natural products.<sup>2</sup> However, most of papers related to enynes focused to the synthesis and application of 1,3-enynes, whereas chemistry of 1,4-enynes has attracted relatively less attention. In spite of various reports on the preparation of nonfluorinated 1,4-enynes,<sup>3</sup> there are only limited reports on the synthesis of fluorinated 1,4-enynes.<sup>4</sup> Fluorinated 1,4-enynes were prepared in good yields from the reaction of perfluorooctynyllithium reagent with  $\beta$ -perfluorinated enone<sup>4a</sup> or from lithium ethylpropionate with 2-fluoropropenal derivative.<sup>4c</sup> Reaction of alkynyllithium reagents with  $\beta$ -perfluoroalkylated enol phosphate provided polyfluorinated 1,4-enynes *via* allylic defluorination.<sup>4b</sup> Yamanaka *et al.* prepared 1,1,2-trifluoro-1,4-enyne derivative from the reaction of  $\beta$ -trifluoromethylated enamine with alkynylmagnesium bromide.<sup>4f</sup> 1,1-Difluorinated 1,4-enynes were synthesized from the reaction of 2,2-difluoroethynyllithium reagents with ynol derivatives at low temperature.<sup>4d,4e</sup> However, the previous methods have some drawbacks such as the use of unstable metal reagents and lack of generality. Herein, we wish to report the general and efficient preparation of *gem*-difluorinated 1,4-enyne derivatives having phenylthio group at 2-position *via* the simple allylic substitution reaction of *gem*-difluorinated 3-bromo-2-phenylthiopropene with alkynyllithium reagents. To our knowledge, the direct alkynylation of electrophilic *gem*-difluorinated 3-bromo-2-phenylthiopropene has not been reported.

Starting materials, 3-bromo-3,3-difluoro-2-phenylthiopropene (**1**) and 3-bromo-1,1-difluoro-2-phenylthiopropene (**2**), were obtained in 58% and 23% yield from the reaction of 1,1-

difluoro-2-phenylthiopropene with NBS in CH<sub>3</sub>CN at reflux temperature for 3 h.<sup>5</sup> The phenylthio group has remarkable effect in the nucleophilic addition reaction of olefin due to the ability of sulfur atom to stabilize the carbanion.<sup>6</sup> We then examined the reaction of **1** with phenylethynyllithium reagent under the different solvent and temperature. When **1** was reacted with phenylethynyllithium reagent (1.2 equiv) at room temperature for 1 h in THF, messy reaction mixture was obtained. The same reaction was performed at 0 °C to give the desired 1,1-difluorinated 1,4-enyne **3a** in 30% yield. The lower reaction temperature and longer reaction time resulted in the formation of **3a** in higher yield. The optimized reaction condition was achieved at -35 °C for 3 h, in which **3a** was obtained in 82% yield. The results of these reactions are summarized in Table 1. The favor of S<sub>N</sub>2' process in this reaction can be rationalized by the difficulty of direct S<sub>N</sub>2 reaction due to the repulsion between nucleophile and two fluorine atoms.

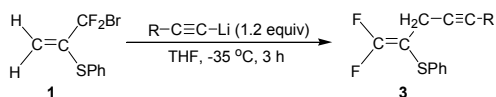
We attempted the reactions of **1** with a variety of alkyl-, aryl-, and silyl-substituted ethynyllithium reagents under the optimized reaction condition. When **1** was reacted with aryl-substituted ethynyllithium reagents having substituents on the benzene ring such as *p*-fluoro, *p*-chloro, *p*-methyl, *p*-methoxy, *m*-fluoro, *m*-methyl, and *o*-methoxy group, 1,1-difluorinated 1,4-enynes **3b-3h** were obtained in 50 - 80% yields. However, the reaction with 3,5-bis(trifluoromethyl)phenylethynyllithium reagent gave the desired product **3i** in only 15% yield, which indicates that electron-withdrawing group on benzene ring decreased the nucleophilicity of ethynyl anion. Reactions of **1** with alkyl-substituted ethynyllithium reagents such as pentyl, hexyl, heptyl and octyl group afforded the 1,4-enynes **3j-3m** in 82 - 94% yields. Similarly, treatment of **1** with trimethylsilyl- or triisopropylsilylethynyllithium reagent under the same reaction condition resulted in the formation of the corresponding 1,4-enynes **3n** and **3o** in 80% and 85% yields, respectively. Results of all of these reactions are summarized in Table 2.

We then examined the reaction of 3-bromo-1,1-difluoro-2-phenylthiopropene (**2**) with phenylethynyl-lithium reagent to check whether this reaction also provides 1,1-difluorinated 2-phenylthio-1,4-enyne **3a** or not because **2** has two electrophilic sites such as 1,1-difluorovinyl carbon and allylic carbon. Therefore, reaction of **2** with phenylethynyllithium reagent at -35 °C for 3 h in THF, afforded only 3,3-difluorinated 2-phenylthio-1,4-enyne **5a**, regioisomer of **3a**, in 75% yield. When the same reaction was performed at -60 °C for 3 h in THF, however, 1,1-difluorinated 2-phenylthio-1,4-enyne **3a** was obtained in 17% yield, along with **5a** in 58% yield (Table 3).

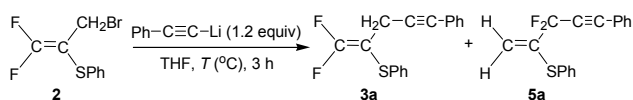
**Table 1.** Optimization for the reaction of **1** with phenylethynyllithium reagent

entry	Solvent	<i>T</i> (°C)	<i>t</i> (h)	Yield <sup>a</sup> (%)
1	THF	rt	1	- <sup>b</sup>
2	THF	0	1	30
3	THF	-25	2	42
4	THF	-35	2	56
5	THF	-35	3	82
6	THF	-70	3	NR <sup>c</sup>
7	ether	-35	3	67

<sup>a</sup>Isolated yield. <sup>b</sup>Messy reaction mixture was observed. <sup>c</sup>No reaction.

**Table 2.** Preparation of 1,1-difluorinated 2-phenylthio-1,4-enynes **3**

Compound	R	Yield <sup>a</sup> (%)
<b>3a</b>	C <sub>6</sub> H <sub>5</sub>	82
<b>3b</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	80
<b>3c</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	71
<b>3d</b>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	78
<b>3e</b>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	70
<b>3f</b>	<i>m</i> -FC <sub>6</sub> H <sub>4</sub>	75
<b>3g</b>	<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	69
<b>3h</b>	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	50
<b>3i</b>	3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	15
<b>3j</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub>	94
<b>3k</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	82
<b>3l</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub>	84
<b>3m</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	86
<b>3n</b>	(CH <sub>3</sub> ) <sub>3</sub> Si	80
<b>3o</b>	( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>3</sub> Si	85

<sup>a</sup>Isolated yield.**Table 3.** The reaction of **2** with phenylethyneyllithium reagent under the low temperature

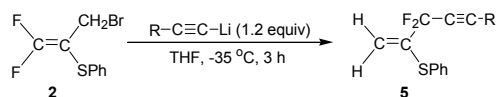
entry	T (°C)	Yield <sup>a</sup> (%)	
		<b>3a</b>	<b>5a</b>
1	0		<sup>b</sup>
2	-25	0	60
3	-35	0	75
4	-45	11	65
5	-60	17	58

<sup>a</sup>Isolated yield. <sup>b</sup>Messy reaction mixture was observed.

We prepared 3,3-difluorinated 2-phenylthio-1,4-enynes **5** in 45–75% yields from the reaction of **2** with alkyl-, aryl- and silyl-substituted ethynyllithium reagents under the same reaction condition (Table 4). Generally, fluorine atom attached to vinyl carbon activates the vinyl carbon toward the nucleophiles due to its high electronegativity effect.<sup>7</sup>

In conclusion, we have explored the preparation of *gem*-difluorinated 2-phenylthio-1,4-enynes *via* alkynylation reactions of *gem*-difluorinated 3-bromo-2-phenylthiopropene with alkyl-, aryl- and silyl-substituted ethynyllithium reagents at low temperature, in which reactions were proceeded *via* S<sub>N</sub>2' pathway.

A typical reaction procedure for the preparation of **3o** is as follows. A 15 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and argon tee connected to an argon source was charged with (triisopropylsilyl)acetylene (0.165 g, 0.905 mmol) and 4 mL THF. After the mixture was cooled to -35 °C, *n*-BuLi (2.0 M solution in hexane, 0.905 mmol) was added and then stirred for 1 h. 3-Bromo-3,3-difluoro-2-phenylthiopropene (0.200 g, 0.754 mmol) was added and then stirred at -35 °C for 3 h. The reaction mixture was extracted with diethyl ether (15 mL × 2), dried with anhydrous MgSO<sub>4</sub>, fil-

**Table 4.** Preparation of 3,3-difluorinated 2-phenylthio-1,4-enynes **5**

Compound	R	Yield <sup>a</sup> (%)
<b>5a</b>	C <sub>6</sub> H <sub>5</sub>	75
<b>5b</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	70
<b>5c</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	67
<b>5d</b>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	61
<b>5g</b>	<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	67
<b>5e</b>	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	45
<b>5f</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	73
<b>5g</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	71
<b>5h</b>	(CH <sub>3</sub> ) <sub>3</sub> Si	61
<b>5i</b>	( <i>i</i> -C <sub>3</sub> H <sub>7</sub> ) <sub>3</sub> Si	64

<sup>a</sup>Isolated yield.

tered, and concentrated under reduced pressure. Purification by silica gel column chromatography (*n*-Hexane) provided 0.235 g of **3o** in 85% yield. **3o**: oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39–7.37 (m, 2H), 7.33–7.28 (m, 2H), 7.26–7.22 (m, 1H), 3.19 (s, 2H), 1.09–1.02 (m, 21H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.8 (dd, *J* = 299, 288 Hz), 133.6, 129.3, 129.1, 127.7, 126.9, 124.2, 84.1 (dd, *J* = 24, 19 Hz), 82.8, 20.8, 18.6, 11.2; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, internal standard CFCl<sub>3</sub>) δ -79.57 (d, *J* = 20.3 Hz, 1F), -80.42 (d, *J* = 20.3 Hz, 1F); MS, *m/z* (relative intensity) 366 (M<sup>+</sup>, 3); Anal. Calcd for C<sub>20</sub>H<sub>28</sub>F<sub>2</sub>SSi: C, 65.53; H, 7.70. Found: C, 65.25; H, 7.63.

**Acknowledgments.** This work was supported by a grant from the Korea Sanhak Foundation (2010-68).

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