



# Mercuric acetate-mediated annulation of homopropargylic alcohols having thioether substituent. A general route for the synthesis of tetrasubstituted furans from propargylic dithioacetals

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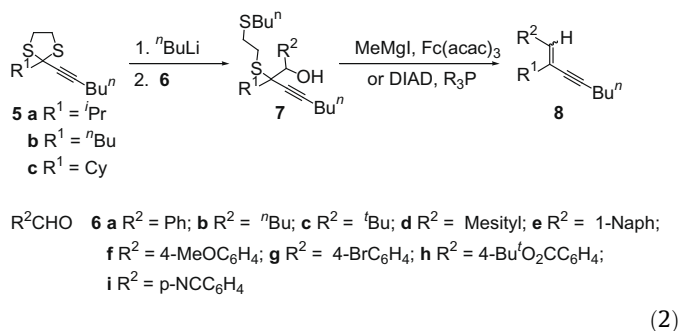
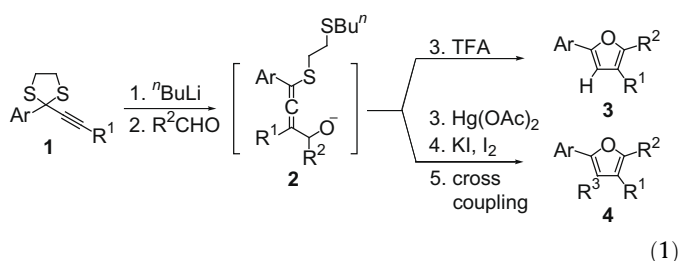
## ABSTRACT

Treatment of an alkyl-substituted propargylic dithioacetal with  $n\text{BuLi}$  followed by an aldehyde furnishes thio-substituted homopropargylic alcohol **7** which undergoes annulation in the presence of two equivalents of mercury acetate to give the corresponding mercurio-substituted furan **12**. Reaction of **12** with iodine gives iodofuran in moderate to good yield.

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There is an ever burgeoning interest in furan derivatives because they are widely found in natural products,<sup>1</sup> pharmaceuticals,<sup>2</sup> flavors,<sup>3</sup> and, more recently, materials applications.<sup>4</sup> Numerous annulation protocols are known for the constructions of this useful heterocycle.<sup>5–13</sup> In particular, cyclizations involving allenyl,<sup>6–8</sup> propargylic,<sup>7–9</sup> or homoallylic<sup>10</sup> substrates have provided versatile entries for the synthesis of polysubstituted furans. We recently found that aryl-substituted propargylic dithiolanes **1** can be regioselectively transformed into tri- and tetra-substituted furans **3** and **4** (Eq. 1).<sup>7,8</sup> The key to the success of this reaction lies on the regioselective formation of the allenyl methanol intermediate **2** which undergoes cyclization leading to furans. The process has been specifically useful for the synthesis of a range of alternating benzene-furan oligomers<sup>7,8</sup> and substituted allenes.<sup>14</sup> To our surprise, the regioselectivity is completely different when the propargylic dithioacetals contain only alkyl substituents (e.g., **5**). Thus, selective olefinations of such dithioacetals giving **8** were recently uncovered (Eq. 2).<sup>15</sup> In this regard, homopropargylic alcohol intermediates **7** are formed exclusively. Cyclizations of homopropargylic alcohols under various conditions are known to give the corresponding furan derivatives.<sup>11</sup> It is worthy to mention that the presence of an appropriate leaving group such as hydroxyl,<sup>11a,l-p</sup> alkoxy,<sup>11e</sup> or alkylidene group<sup>11i-k</sup> in homopropargylic alcohols appeared to be essential to facilitate such annulation procedure. As can be seen from Eq. 2, **7** contains a thioether substituent at the propargylic position which might be facilely eliminated under various conditions. It is therefore envisaged that annulation of homopropargylic alcohol **7** might provide a useful route for the synthesis of substituted furans with different regioselectivities as that described in Eq. 1. We now wish to report a selec-

tive synthesis of tetra-substituted furans from **5** having aliphatic substituents.



In the beginning of this research, a range of different conditions were employed to scrutinize the annulation conditions. As cyclization of **2** can readily be promoted by acids,<sup>7,8</sup> different kinds of Lewis acid conditions were employed. Whilst TFA is successful to mediate annulation of allenylmethanols, no reaction was found when **7a** was treated under the same conditions. Silver (I) has been

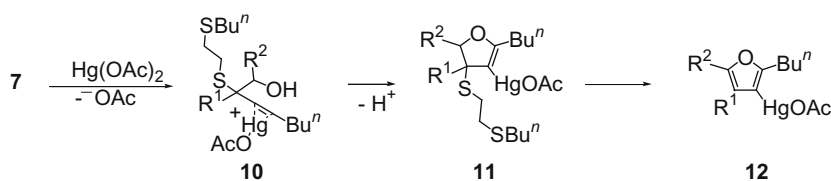
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**Table 1**  
Synthesis iodofurans **9** from propargylic dithioacetals **5** and aldehydes **6**

Entry	Substrate <b>5</b>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield of <b>7</b> (dr) <sup>a</sup>	Yield of <b>9</b>
1	<b>5a</b>	<sup>i</sup> Pr	<sup>n</sup> Bu	Ph	<b>a</b> 74(2.3/1)	<b>a</b> 67
2				<sup>n</sup> Bu	<b>c</b> 72 <sup>b</sup>	<b>c</b> 54
3				<sup>t</sup> Bu	<b>d</b> 54(4.4/1)	<b>d</b> 62
4				Mesityl	<b>e</b> 51(1.1/1)	<b>e</b> 80
5				1-Naphthyl	<b>f</b> 87(4.2/1)	<b>f</b> 54
6				<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>g</b> 80(6.4/1)	<b>g</b> 77
7				<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>h</b> 56(5.4/1)	<b>h</b> 47
8	<b>5b</b>	<sup>n</sup> Bu	<sup>n</sup> Bu	Ph	<b>i</b> 73(3.8/1)	<b>i</b> 46
9				<i>p</i> -Bu <sup>t</sup> O <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	<b>j</b> 37(1.7/1)	<b>j</b> 42
10				<i>p</i> -NC C <sub>6</sub> H <sub>4</sub>	<b>k</b> 83(1.6/1)	<b>k</b> 43
11	<b>5c</b>	<sup>c</sup> Hex	<sup>n</sup> Bu	Ph	<b>l</b> 69(4.8/1)	<b>l</b> 55

<sup>a</sup> Diastereomeric ratios (dr) were determined by <sup>1</sup>H NMR.

<sup>b</sup> Diastereomeric ratio was not determined.

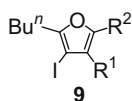


**Scheme 1.**

extensively employed for the annulation of alkynyl-substituted ethylene glycols<sup>11m</sup> or homopropargylic alcohols having vinylidene moiety to yield furans.<sup>11i,k</sup> However, treatment of **7a** under these conditions gave at most trace amount of the desired furans. Gold (III) catalyst<sup>7b,d–g</sup> was unable to promote the reaction of **7a**, and ICl<sup>8e,11n</sup> led to decomposition of the starting materials with no desired annulation product. We recently found the allenyl methanol derivatives **2** underwent ring closure reaction giving tetra-substituted furans **4** upon treatment with mercuric acetate followed by iodine.<sup>8e</sup> Since the mercuric species is very thiophilic, the sulfur moiety in **2** is readily eliminated. It is therefore envisaged that reaction of **7a** under similar conditions might also afford the corresponding tetrasubstituted furans **9** with different regioselectivities as those shown in Eq. 1.

Compound **7a** was treated with 2 equiv of mercuric acetate at room temperature for 12 h. The reaction mixture was then allowed to react with three equiv each of iodine and KI for 3 h to furnish the corresponding furan **9a** in 61% yield. The yield of **9a** was improved to 67% when the cyclization reaction time was 18 h.

Reactions of **5** with 1.1 equiv of BuLi in THF at –78 °C for 1 h followed by addition of 1 equiv of aldehyde **6** gave a diastereomeric mixture of homopropargylic alcohols **7**.<sup>16</sup> Compound **7** was treated with 2 equiv of mercuric acetate for 18 h and the mixture was allowed to react with 3 equiv each of iodine and KI to give **9** in moderate to good yield.<sup>17</sup> Representative results are outlined in Table 1. Although the mechanism for the annulation of **7** has not been established, oxymercuration at the triple bond may lead to **11** followed by elimination of the sulfur moiety to afford **12** (Scheme 1).



As can be seen from Table 1, methoxy, halogen, ester, or cyano groups on aldehyde **6** (entries 6, 7, 9, and 10) could be used and the corresponding furans **9** remained intact in both nucleophilic addition and ring closure steps. Even sterically hindered group

on dithiolane moiety (e.g., entry 11) or on aldehyde **6** (entries 4 and 5) was obtained in satisfactory yield. In order to assure the regioselective formation of homopropargylic alcohols **7**, R<sup>1</sup> and R<sup>2</sup> had to be aliphatic. In other words, when R<sup>1</sup> was an aryl group, **2** was the only product from the reaction. On the other hand, when R<sup>2</sup> was phenyl, a mixture of regioisomers **2** and **7** was obtained.

Although the origin of the regioselectivity of the nucleophilic addition of the anion derived from **5** to aldehyde **6** remained to be clarified, the overall reaction; however, does provide a convenient synthesis of substituted furans **9** from the corresponding alkyl-substituted propargylic dithioacetals **5**. The iodine substituent in **9** can be easily displaced by different kinds of coupling reactions.<sup>8e</sup> In addition, metal-halogen exchange process can also be used for further carbon–carbon bond formation.<sup>8e</sup> Tin hydride reduction of the carbon–iodine bond can lead to trisubstituted furans. The present results complement our previous works<sup>8</sup> for the synthesis of polysubstituted furans with different regioselectivities.

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## Supplementary data

Experimental details for the preparation of **5**, **7** and **9** and <sup>1</sup>H NMR spectra of **9**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.043.

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16. *Typical procedure for the preparation of homopropargylic alcohol 7*: At  $-78^{\circ}\text{C}$ , under  $\text{N}_2$  atmosphere, to a THF (50 mL) solution of **5a** (1.14 g, 5 mmol) was added  $^t\text{BuLi}$  (2.4 mL, 2.5 M in hexane, 6 mmol) dropwise and the mixture was stirred for 1 h. *p*-Anisaldehyde **6f** (0.61 mL, 5 mmol) in THF (10 mL) was then added dropwise and the mixture was gradually warmed to rt and stirred for 8 h, quenched with satd  $\text{NH}_4\text{Cl}$ , washed with brine, and extracted with ether. The organic layer was dried ( $\text{MgSO}_4$ ), filtered, and the filtrate was evaporated in vacuo to give the residue which was chromatographed on silica gel (hexane/ethyl acetate = 30/1) to give **7f** (dr ratio = 6.4/1) in 84% yield: major isomer:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  0.92 (t,  $J$  = 7.0 Hz, 3H), 0.94 (t,  $J$  = 7.0 Hz, 3H), 1.11 (d,  $J$  = 6.5 Hz, 6H), 1.34–1.47 (m, 4H), 1.48–1.58 (m, 4H), 1.84 (sept,  $J$  = 6.5 Hz, 1H), 2.29 (t,  $J$  = 7.0 Hz, 2H), 2.47 (t,  $J$  = 7.4 Hz, 2H), 2.51–2.72 (m, 4H), 3.04 (d,  $J$  = 6.0 Hz, 1H), 3.82 (s, 3H), 4.74 (d,  $J$  = 6.0 Hz, 1H), 6.82–6.88 (m, 2H), 7.42–7.47 (m, 2H); characteristic  $^1\text{H}$  NMR signals for the minor isomer:  $\delta$  3.90 (s, 3H), 4.78 (d,  $J$  = 4.8 Hz, 1H).
17. *Typical procedure for the preparation of 9*: A mixture of **7f** (167 mg, 0.5 mmol) and  $\text{Hg}(\text{OAc})_2$  (319 mg, 1.0 mmol) in THF (5 mL) was stirred at rt for 18 h. KI (249 mg, 1.5 mmol) and  $\text{I}_2$  (381 mg, 1.5 mmol) were then added and the mixture was further stirred for 3 h, quenched with satd  $\text{Na}_2\text{S}_2\text{O}_3$ , and extracted with ether. The organic layer was washed with 10%  $\text{Na}_2\text{S}_2\text{O}_3$ , dried ( $\text{MgSO}_4$ ), filtered, and the filtrate was evaporated in vacuo to give the residue which was chromatographed (hexane/chloroform = 30/1) on silica gel to give **9f** as a colorless liquid (153 mg, 77%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  0.97 (t,  $J$  = 7.2 Hz, 3H), 1.34 (d,  $J$  = 7.2 Hz, 6H), 1.36–1.48 (m, 2H), 1.62–1.72 (m, 2H), 2.72 (t,  $J$  = 7.6 Hz, 2H), 3.18 (sept,  $J$  = 7.2 Hz, 1H), 6.92–6.97 (m, 2H), 7.36–7.41 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.0, 21.6, 22.4, 26.2, 27.6, 30.3, 55.3, 65.8, 113.7, 124.1, 125.7, 129.0, 147.5, 155.3, 158.9; HRMS (FAB) calcd for  $\text{C}_{18}\text{H}_{23}\text{O}_2$ : 284.1674, found: 284.1674.