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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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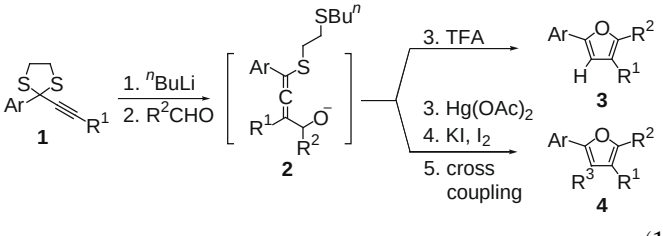
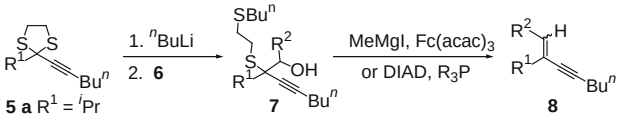
ABSTRACT

Treatment of an alkyl-substituted propargylic dithioacetal with ^{n}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.

There is an ever burgeoning interest in furan derivatives because they are widely found in natural products,[1] pharmaceuticals,[2] flavors,[3] and, more recently, materials applications.[4] Numerous annulation protocols are known for the constructions of this useful heterocycle.[5–13] In particular, cyclizations involving allenyl,[6–8] propargylic,[7–9] or homoallylic[10] 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).[7,8] 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[7,8] and substituted allenes.[14] 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).[15] 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.[11] It is worthy to mention that the presence of an appropriate leaving group such as hydroxyl,[11a,l-p] alkoxyl,[11e] or alkylidene group[11i-k] 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 selective synthesis of tetra-substituted furans from **5** having aliphatic substituents.



(1)



R^{2}CHO **6 a** R^2 = Ph; **b** R^2 = ^{n}Bu; **c** R^2 = ^{t}Bu; **d** R^2 = Mesityl; **e** R^2 = 1-Naph; **f** R^2 = 4-MeOC$_6$H$_4$; **g** R^2 = 4-BrC$_6$H$_4$; **h** R^2 = 4-Bu^{t}O$_2$CC$_6$H$_4$; **i** R^2 = p-NCC$_6$H$_4$

(2)

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,[7,8] 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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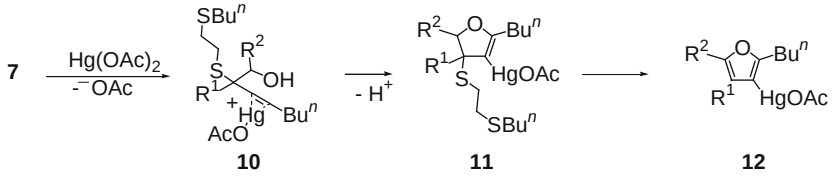
Table 1
Synthesis iodofurans **9** from propargylic dithioacetals **5** and aldehydes **6**

Entry	Substrate **5**	R^1	R^2	R^3	Yield of **7** (dr)[a]	Yield of **9**
1	**5a**	^{i}Pr	^{n}Bu	Ph	**a** 74(2.3/1)	**a** 67
2				^{n}Bu	**c** 72[b]	**c** 54
3				^{t}Bu	**d** 54(4.4/1)	**d** 62
4				Mesityl	**e** 51(1.1/1)	**e** 80
5				1-Naphthyl	**f** 87(4.2/1)	**f** 54
6				*p*-$MeOC_6H_4$	**g** 80(6.4/1)	**g** 77
7				*p*- BrC_6H_4	**h** 56(5.4/1)	**h** 47
8	**5b**	^{n}Bu	^{n}Bu	Ph	**i** 73(3.8/1)	**i** 46
9				*p*-$Bu^tO_2CC_6H_4$	**j** 37(1.7/1)	**j** 42
10				*p*-NC C_6H_4	**k** 83(1.6/1)	**k** 43
11	**5c**	^{c}Hex	^{n}Bu	Ph	**l** 69(4.8/1)	**l** 55

[a] Diastereomeric ratios (dr) were determined by ^{1}H NMR.
[b] Diastereomeric ratio was not determined.

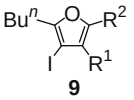


Scheme 1.

extensively employed for the annulation of alkynyl-substituted ethylene glycols[11m] or homopropargylic alcohols having vinylidene moiety to yield furans.[11i,k] However, treatment of **7a** under these conditions gave at most trace amount of the desired furans. Gold (III) catalyst[7b,d–g] was unable to promote the reaction of **7a,** and ICl[8e,11]n 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.[8e] Since the mercuric species is very thiophilic, the sulfur moiety in **2** is facilely 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**.[16] 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.[17] 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).



9

As can be see 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^1 and R^2 had to be aliphatic. In other words, when R^1 was an aryl group, **2** was the only product from the reaction. On the other hand, when R^2 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.[8e] In addition, metal-halogen exchange process can also be used for further carbon–carbon bond formation.[8e] Tin hydride reduction of the carbon–iodine bond can lead to trisubstituted furans. The present results complement our previous works[8] for the synthesis of polysubstituted furans with different regioselectivities.

Acknowledgment

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Supplementary data

Experimental details for the preparation of **5**, **7** and **9** and ^{1}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 °C, under N_2 atmosphere, to a THF (50 mL) solution of **5a** (1.14 g, 5 mmol) was added ^{n}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 NH_4Cl, washed with brine, and extracted with ether. The organic layer was dried ($MgSO_4$), 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}H NMR ($CDCl_3$, 400 MHz): δ 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}H NMR signals for the minor isomer: δ 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 $Hg(OAc)_2$ (319 mg, 1.0 mmol) in THF (5 mL) was stirred at rt for 18 h. KI (249 mg, 1.5 mmol) and I_2 (381 mg, 1.5 mmol) were then added and the mixture was further stirred for 3 h, quenched with satd $Na_2S_2O_3$, and extracted with ether. The organic layer was washed with 10% $Na_2S{\cdot}9H_2O$, dried ($MgSO_4$), 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}H NMR ($CDCl_3$, 400 MHz): δ 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}C NMR (100 MHz, $CDCl_3$): δ 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 $C_{18}H_{23}O_2I$: 398.0743, found: 398.0748.