A Convenient Synthesis of Tetrasubstituted Furans from Propargylic Dithioacetals

Jui-Chang Tseng, Jia-Hong Chen, Tien-Yau Luh*

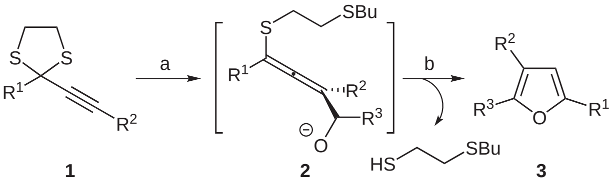
Department of Chemistry, National Taiwan University, Taipei 106, Taiwan
Fax +886(2)23644971; E-mail: tyluh@ntu.edu.tw

Received 29 November 2005

Abstract: A convenient procedure for the regioselective synthesis of tetrasubstituted furans from the corresponding propargylic dithioacetals is described. Treatment of propargylic dithioacetals with *n*-BuLi and an aldehyde followed by mercuric acetate promoted annulation and desulfurization affords the corresponding mercurio-substituted furans. Subsequent replacement of the mercury moiety with iodine yields the corresponding 2,4,5-trisubstituted 3-iodofurans. Transition-metal-catalyzed cross-coupling reactions of the iodofurans furnish a variety of tetrasubstituted furans.

Key words: annulation, tetrasubstituted furan, propargylic dithioacetal, mercuric acetate, transition-metal-catalyzed cross-coupling

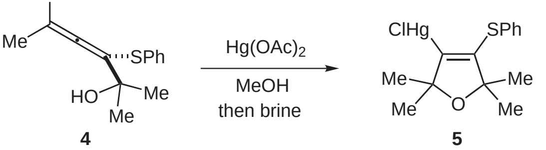
Polysubstituted furans are widely found in natural products,[1] important pharmaceuticals, and fragrance and flavor compounds,[2] and have been used as versatile intermediates in organic synthesis.[3] Facile approaches to the synthesis of polysubstituted furan derivatives from readily available starting materials involve derivatization of furans,[4] or cycloisomerization of alkyne- and allene-containing acyclic precursors.[4a,5,6]



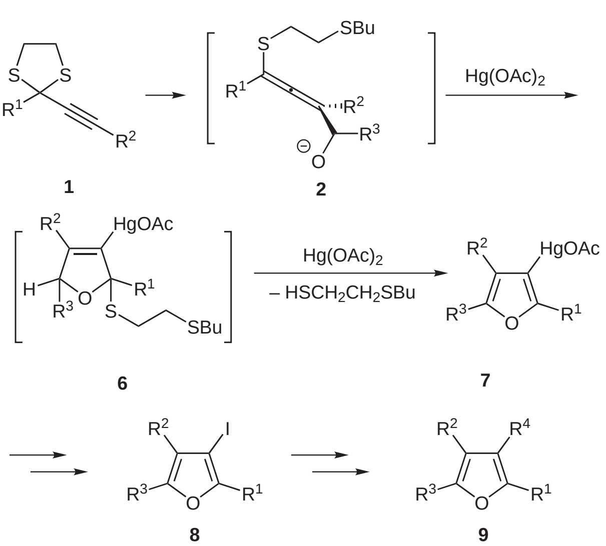
Scheme 1 One-pot furan synthesis from propargylic dithioacetal. *Reagents and conditions*: (a) i) *n*-BuLi, THF; ii) R^3CHO; (b) trifluoroacetic acid.

We recently reported a convenient procedure for the synthesis of 2,3,5-trisubstituted furans **3** from the corresponding propargylic dithioacetals **1** (Scheme 1).[7,8] A range of functional groups can survive under these conditions. In this reaction, the substituents on the furan ring are arisen regioselectively from the propargylic dithioacetal and the corresponding aldehyde, whereas the hydrogen at C-4 is from the treatment of trifluoroacetic acid in annulation step. This protocol provides a useful access for the preparation of a range of oligoaryls containing trisubstituted furan or pyrrole rings.[7,8a] It is noteworthy that furan-containing oligoaryls thus obtained have been shown to be efficient hole-transporting materials for electroluminescent applications.[8b]

$Hg(OAc)_2$ has been shown to promote the annulation of allenyl carbinol **4** to form 2,5-dihydrofuran **5** with a HgOAc substituent at C-3 (Equation 1).[9] It is well documented that carbon–mercury bonds can be displaced by a number of substituents under different conditions. We envisioned that $Hg(OAc)_2$ might serve as an alternative route for the annulation of allenyl-carbinol intermediate **2** obtained from the reaction of propargylic dithioacetal with *n*-BuLi and then an aldehyde. It is interesting to note that mercuric salts are known to be an active desulfurization agent,[10] the sulfur moiety in **2** may also be eliminated under such treatment so that furan skeleton might be obtained. We now wish to report a convenient procedure for the synthesis of a variety of tetrasubstituted furans from propargylic dithioacetals (Scheme 2).



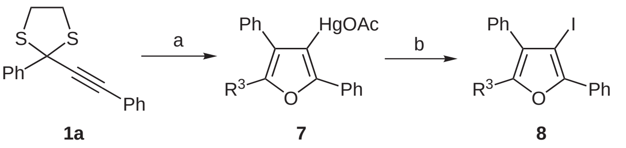
Equation 1 Cyclization of allenyl alcohol **4** by treatment with mercuric acetate.[9]



Scheme 2 Approaches to the synthesis of tetrasubstituted furan derived from propargylic dithioacetal.

SYNLETT 2006, No. 8, pp 1209–1212
Advanced online publication: 05.05.2006
DOI: 10.1055/s-2006-939686; Art ID: W31905ST

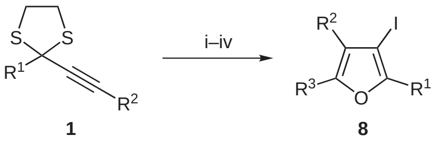
Aryl iodides are known to undergo transition-metal-catalyzed cross-coupling reactions.[11] We envisioned that **8** may also react in a variety of such coupling processes leading to carbon–carbon bond formation. Thus, treatment of **8a**–**f** with different aryl boronic acids in the presence of 5 mol% $Pd(PPh_3)_4$, 10 mol% *t*-Bu_3P using aqueous Na_2CO_3 as the base in refluxing toluene afforded the expected coupling products **9**–**14** in high yield (entries 1–6, Table 2). Iodofurans with either aryl substituent, ester moiety, or alkyl side chain works well under such Suzuki reaction conditions. In a similar manner, when phenylacetylene was employed, **8a**,**c**,**d** also gave the corresponding Sonogashira products **15**–**17** in good yield upon treatment with 5 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI and 10 mol% PPh_3 in the presence of Et_3N in DMF at 125 °C (entries 7–9).[12] Moreover, the Stille couplings of vinyltributylstannane with **8a** and **8d** were carried out using 5 mol% $PdCl_2(PPh_3)_2$ in DMF at 120 °C, and the desired coupling products **18** and **19** were isolated in good yield, respectively (entries 10 and 11). To our surprise, the Heck, Kumada, and Negishi couplings of **8a** produced the desired coupling adducts in moderate to low yield along with the formation of the reduced product, 2,3,5-triphenylfuran, in comparable yield (entries 12–14). When alkyl Grignard reagent was used for the cross-coupling with iodofuran **8a**, all attempts produced the reduced triphenylfuran exclusively by using $Ni(acac)_2$/dppf, $NiCl_2$dppf, $NiCl_2$dppp, $PdCl_2$dppf, or $PdCl_2$dppp as the catalyst. Attempts to use alkyl substituted 9-BBN for the Suzuki coupling reaction, a mixture of starting iodofuran **8a** and reduced 2,3,5-triphenylfuran were formed, whereas the desired coupling adduct was not detected. Alternatively, lithium–iodine exchange of 2,4,5-triphenyl-3-iodofuran followed by quenching with $ClCO_2Et$ or *n*-BuBr afforded the corresponding tetrasubstituted furan in good yield (entries 15 and 16).[13]



Scheme 3 Two-step synthesis of 3-mercurio- and 2,4,5-trisubstituted 3-iodofuran from propargylic dithioacetal. *Reagents and conditions*: (a) i) *n*-BuLi, THF, –78 °C, 50 min; ii) R^3CHO, THF, –78 °C, 30 min, –78 °C to r.t., 1 h; iii) $Hg(OAc)_2$, r.t., overnight (**7a**: R^3 = Ph, 84%; **7b**: R^3 = *p*-$MeO_2CC_6H_4$, 82%); (b) I_2, KI, CH_2Cl_2, r.t., 3 h (**8a**: R^3 = Ph, 96%; **8b**: R^3 = *p*-$MeO_2CC_6H_4$, 95%).

In the beginning, **1** was treated with *n*-BuLi at –78 °C followed by benzaldehyde to give the corresponding allenyl carbinol intermediate **2** which was allowed to react with two equivalents of $Hg(OAc)_2$ at room temperature overnight to afford the corresponding mercury compounds **7** in good yield. Further reactions of **7** with I_2/KI at room temperature for three hours gave the corresponding iodofuran **8** in excellent yield (Scheme 3). This reaction can also proceed in one pot to give **8** without isolation of the mercury intermediate **7**. Representative examples are shown in Table 1. Attempts of using I_2 or ICl to react with the allenyl carbinol intermediate **2** in a one-pot manner without

Table 1 One-Pot Synthesis of 2,4,5-Trisubstituted 3-Iodofurans from Propargylic Dithioacetals[a]



Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)[b]
1	**1a**	Ph	Ph	Ph	**8a**	78
2	**1a**	Ph	Ph	Ph	**8a**	90[c]
3	**1a**	Ph	Ph	Ph	**8a**	62[d]
4	**1a**	Ph	Ph	Ph	**8a**	54[d]
5	**1a**	Ph	Ph	*p*-C_6H_4-CO_2Me	**8b**	72
6	**1a**	Ph	Ph	*n*-Bu	**8c**	68
7	**1b**	Ph	CO_2Et	*n*-Bu	**8d**	68
8	**1c**	*p*-C_6H_4-CO_2Me	Ph	*p*-C_6H_4-CO_2Me	**8e**	63
9	**1d**	*n*-Bu	*n*-Bu	*i*-Pr	**8f**	56

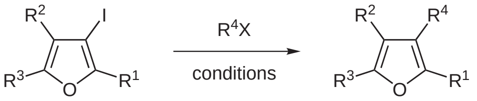
[a] *Reagents and conditions*: i) *n*-BuLi, THF, –78 °C, 50 min; ii) R^3CHO, THF, –78 °C, 30 min, –78 °C to r.t., 1 h; iii) $Hg(OAc)_2$, r.t., overnight; iv) I_2, KI, r.t., 3 h.

[b] Isolated yield of one-pot procedure.

[c] Work-up with additional washing with 20% Na_2S aq solution and subsequent filtration through a silica gel bed gave relative higher yield compared with the result of entry 1 in this table.

[d] *Reagents and conditions*: i) *n*-BuLi, THF, –78 °C, 50 min; ii) benzaldehyde, THF, –78 °C, 30 min, –78 °C to r.t., 1 h; iii) I_2 (entry 3) or ICl (entry 4), r.t., overnight.

Table 2 Synthesis of Tetrasubstituted Furan from 2,4,5-Trisubstituted 3-Iodofuran



Entry	Iodofuran	R^1	R^2	R^3	R^4	Product[a]	Conditions[b]	Yield (%)
1	**8a**	Ph	Ph	Ph	Ph	**9**	A	85
2	**8b**	Ph	Ph	p-$C_6H_4CO_2Me$	p-C_6H_4OMe	**10**	A	82
3	**8c**	Ph	Ph	*n*-Bu	p-C_6H_4OMe	**11**	A	82
4	**8d**	Ph	CO_2Et	*n*-Bu	p-C_6H_4OMe	**12**	A	80
5	**8e**	p-$C_6H_4CO_2Me$	Ph	p-$C_6H_4CO_2Me$	Ph	**13**	A	78
6	**8f**	*n*-Bu	*n*-Bu	*i*-Pr	p-C_6H_4OMe	**14**	A	80
7	**8a**	Ph	Ph	Ph	PhC≡C	**15**	B	78
8	**8c**	Ph	Ph	*n*-Bu	PhC≡C	**16**	B	76
9	**8d**	Ph	CO_2Et	*n*-Bu	PhC≡C	**17**	B	79
10	**8a**	Ph	Ph	Ph	$CH=CH_2$	**18**	C	82
11	**8d**	Ph	CO_2Et	*n*-Bu	$CH=CH_2$	**19**	C	76
12	**8a**	Ph	Ph	Ph	*trans*-$CH=CHCO_2Me$	**20**	D	55 (30)[c]
13	**8a**	Ph	Ph	Ph	Ph	**9**	E	45 (35)[c]
14	**8a**	Ph	Ph	Ph	Ph	**9**	F	20 (55)[c]
15	**8a**	Ph	Ph	Ph	CO_2Et	**21**	G	71
16	**8a**	Ph	Ph	Ph	*n*-Bu	**22**	H	68

[a] R^4 substituent of the corresponding tetrasubstituted furan comes from R^4X.

[b] Conditions: (A) Suzuki coupling: 1.5 equiv $R^4B(OH)_2$, 5 mol% $Pd(PPh_3)_4$, 10 mol% t-Bu_3P, 2 M $Na_2CO_{3\,(aq)}$, PhMe, reflux, 18 h; (B) Sonogashira coupling: 2 equiv PhC≡CH, 5 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI, 10 mol% PPh_3, Et_3N, DMF, 120 °C, 12 h; (C) Stille coupling: 2 equiv $CH_2=CHSnBu_3$, 5 mol% $PdCl_2(PPh_3)_2$, DMF, 120 °C, 12 h; (D) Heck coupling: 2 equiv $CH_2=CHCO_2Me$, 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, Et_3N, DMF, 120 °C, 12 h; (E) Kumada coupling: 3 equiv PhMgBr, 10 mol% $NiCl_2$dppp, PhMe, reflux, 18 h; (F) Negishi coupling: 3 equiv PhZnCl, 10 mol% $Pd(PPh_3)_4$, THF, reflux, 24 h; (G) i) 1.2 equiv *n*-BuLi, THF, –78 °C, 1 h; ii) 1.5 equiv $ClCO_2Et$, –70 °C to r.t., 2 h; (H) i) 1.2 equiv *n*-BuLi, THF, –78 °C, 1 h; ii) 1.5 equiv *n*-BuBr, –70 °C to r.t., 2 h.

[c] The reduced product 2,3,5-triphenylfuran was obtained as the side product and the yield is shown in parentheses.

the treatment of $Hg(OAc)_2$ also gave the corresponding iodofuran **8a** (entries 3 and 4, Table 1). However, the yield was relatively lower and sometimes produced the trisubstituted furan when utilizing the commercial available I_2 without purification by sublimation. Attempts to use a catalytic amount of $Hg(OAc)_2$ (e.g., 0.1 equiv) under similar conditions, the yield of **8a** was 9%. Presumably, the mercuric species would facilitate the desulfurization process leading to furan.

In conclusion, we have discovered a convenient and highly regioselective synthesis of tetrasubstituted furans from propargylic dithioacetals. The one-pot annulation procedure of propargylic dithioacetal furnished a variety of 2,4,5-trisubstituted 3-iodofurans, which undergo transition-metal-catalyzed cross-coupling reactions to give fully substituted furans. Substituents on furan ring can be aliphatic, aromatic, and functional groups such as esters or ethers. Further extensions of this reaction for the synthesis of related heteroaromatic rings are in progress.

Typical Experimental Procedure

A solution of 2.5 M *n*-BuLi in hexane (33.0 mmol) was introduced dropwise to a solution of propargylic dithioacetal **1** (30.0 mmol) in THF (200 mL), stirring under N_2 at –78 °C for 50 min. To this reaction mixture was added slowly a solution of aldehyde (33.0 mmol) in THF (30 mL) at this temperature. The mixture was stirred for 30 min at –78 °C, then gradually warmed up to r.t. and allowed to stir for 1 h. $Hg(OAc)_2$ (66.0 mmol) was then added and the slurry was stirred at rt overnight. I_2 (120.0 mmol) and KI (120.0 mmol) were then added and the mixture was further stirred at rt for 3 h. The mixture was quenched with 20% aqueous $Na_2S_2O_3$ (200 mL), then the organic layer was separated and washed with 20% aqueous $Na_2S_2O_3$ (200 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography to give pure iodofuran **8**.

Acknowledgment

This work is supported by the National Science Council of the Republic of China.

References and Notes

(1) (a) *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: New York, **1996**, Vol. 2. (b) *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katrizky, A. R.; Rees, C. W., Eds.; Pergamon: New York, **1984**. (c) *Natural Products Chemistry*; Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S., Eds.; Kodansha: Tokyo, **1974**, Vol. 1-3. (d) Shipman, M. *Contemp. Org. Synth.* **1995**, *2*, 1.

(2) (a) *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*; Eicher, T.; Hauptmann, S., Eds.; Wiley-VCH: Weinheim, **2003**. (b) *Common Fragrance and Flavor Materials*; Bauer, K.; Garbe, D., Eds.; VCH: Weinheim, **1985**. (c) Vernin, G. *The Chemistry of Heterocyclic Flavouring and Aroma Compounds*; Ellis Horwood: Chichester, **1982**.

(3) (a) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, **1995**, 231. (b) *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**. (c) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.

(4) For recent reviews, see: (a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955. (b) Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209.

(5) For recent reviews, see: (a) Brown, R. C. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 850. (b) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42.

(6) (a) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409; and references cited therein. (b) Liu, Y.; Song, F.; Cong, L. *J. Org. Chem.* **2005**, *70*, 6999. (c) Duan, X.-h.; Liu, X.-y.; Guo, L.-n.; Liao, M.-c.; Liu, W.-M.; Liang, Y.-m. *J. Org. Chem.* **2005**, *70*, 6980. (d) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2280. (e) Ma, S.; Zhang, J.; Lu, L. *Chem. Eur. J.* **2003**, *9*, 2447; and references cited therein. (f) Yavari, I.; Anary-Abbasinejad, M.; Alizadeh, A. *Tetrahedron Lett.* **2002**, *43*, 4503. (g) Aurrecoechea, J. M.; Pérez, E. *Tetrahedron Lett.* **2001**, *42*, 3839. (h) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117. (i) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687. (j) Iwasawa, N.; Ochiai, T.; Maeyama, K. *J. Org. Chem.* **1998**, *63*, 3164. (k) MaGee, D. I.; Leach, J. D. *Tetrahedron Lett.* **1997**, *38*, 8129. (l) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

(7) For a recent review, see: Luh, T.-Y.; Lee, C.-F. *Eur. J. Org. Chem.* **2005**, 3875.

(8) (a) Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-H.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992. (b) Zhang, L.-Z.; Chen, C.-W.; Lee, C.-F.; Wu, C.-C.; Luh, T.-Y. *Chem. Commun.* **2002**, 2336. (c) Lee, C.-F.; Liu, C.-Y.; Song, H.-C.; Luo, S.-J.; Tseng, J.-C.; Tso, H.-H.; Luh, T.-Y. *Chem. Commun.* **2002**, 2824. (d) Liu, C.-Y.; Luh, T.-Y. *Org. Lett.* **2002**, *4*, 4305. (e) Tseng, J.-C.; Lin, H.-C.; Huang, S.-L.; Lin, C.-L.; Jin, B.-Y.; Chen, C.-Y.; Yu, J.-K.; Chou, P.-T.; Luh, T.-Y. *Org. Lett.* **2003**, *5*, 4381.

(9) Bridges, A. J.; Thomas, R. D. *J. Chem. Soc., Chem. Commun.* **1984**, 694.

(10) (a) Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743. (b) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15.

(11) (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **2004**, 2nd ed. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**.

(12) *Application of Transition Metal Catalysts in Organic Synthesis*; Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D., Eds.; Springer-Verlag: Berlin/Heidelberg, **1999**.

(13) Tanabe, Y.; Wakimura, K.-i.; Nishii, Y.; Muroya, Y. *Synthesis* **1996**, 388.