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Multicomponent Type II Anion Relay Chemistry (ARC): One-Pot Syntheses of 2,3-Disubstituted Furans and Thiophenes

Nelmi O. Devarie-Baez,[†] Won-Suk Kim,[‡] Amos B. Smith III.,*[,‡] and Ming Xian*[,†]

Department of Chemistry, Washington State University, Pullman, Washington 99164, and Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

mxian@wsu.edu; smithab@sas.upenn.edu

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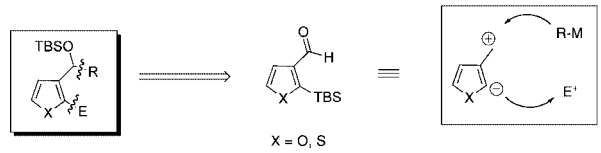
ABSTRACT



Effective, one-pot syntheses of 2,3-disubstituted furans and thiophenes, exploiting 2-*tert*-butyldimethylsilyl-3-formylfuran and -thiophene as the respective bifunctional linchpins, have been developed. The synthetic protocol involves multicomponent type II Anion Relay Chemistry (ARC) mediated by a solvent-controlled C(sp^2)→O 1,4-Brook rearrangement. Simple organolithiums and α-disubstituted ester enolates prove effective as the initiating nucleophiles.

Functionalized furans and thiophenes comprise important synthetic targets given their application in natural product total synthesis, drug discovery, and materials science.[1,2] Thus, methods to assemble quickly such diverse substituted heterocycles are of considerable importance. Although a few one-step strategies have been recently reported,[3] most methods to access polysubstituted furans and thiophenes rely upon multiple-step manipulations to install each substituent sequentially.[4] Given the potential utility of multicomponent Anion Relay Chemistry (ARC),[5] we anticipated that this tactic would constitute an effective protocol to access such

[†] Washington State University.
[‡] University of Pennsylvania.

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(2) (a) Bohlmann, F.; Zdero, C. In *Thiophenes and Its Derivatives*; Gronowitz, S., Ed.; The Chemistry of Heterocyclic Compounds, Vol. 44; John Wiley & Sons: New York, 1985; Part 1, p 261. (b) Press, J. B. In *Thiophenes and Its Derivatives*; Gronowitz, S., Ed.; The Chemistry of Heterocyclic Compounds, Vol. 44; John Wiley & Sons: New York, 1991; Part 4, p 397. (c) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (d) Schopf, G.; Komehl, G. In *Advances in Polymer Sciences: Polythiophenes—Electrically Conductive Polymers*; Abel, A., Ed.; Springer-Verlag: Berlin, 1997; Vol. 129, p 1.

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(4) For selected reviews, see the following. For furans: (a) Luh, T. *Pure Appl. Chem.* **2005**, *77*, 1213. (b) Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209. (c) 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. (d) Wong, H. N. C. *Pure Appl. Chem.* **1996**, *68*, 335. For thiophenes: (e) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583. (f) Guernion, N. J. L.; Hayes, W. *Curr. Org. Chem.* **2004**, *8*, 637. (g) Weissberger, A.; Taylor, E. C. In *Thiophenes and Its Derivatives*; Gronowitz, S., Ed.; The Chemistry of Heterocyclic Compounds, Vol. 44; John Wiley: New York, 1985; Part 1, p 1.

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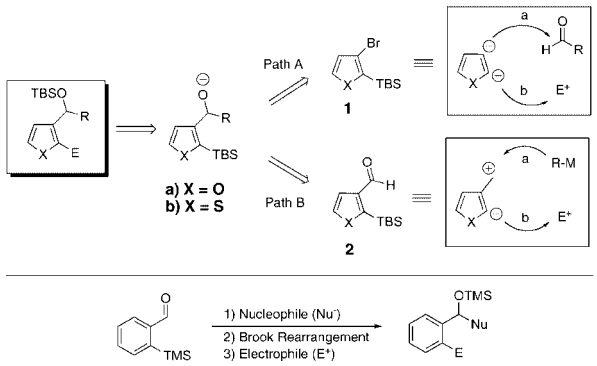
heterocycles. Precedent for this approach derives from our recent one-pot ARC constructions of both 2,3-disubstituted thiophenes exploiting 3-bromo-2-silylthiophene **(1b)**[6] and ortho-disubstituted benzene derivatives employing *o*-trialkylsilylbenzaldehyde (Scheme 1).[7]

Scheme 1



We reasoned that the same 2-trialkylsilyl-3-alkoxy modular anion derived from **1**, generated via lithiation and reaction with an aldehyde or ketone (Scheme 1, path A), could also arise upon addition of various nucleophiles to 2-trialkylsilyl-3-formylfurans (**2a**) and -thiophenes (**2b**) (path B). From the perspective of synthetic planning, it is important to recognize that these linchpins (**1** and **2**) are fundamentally different; linchpin **1** comprises a dianion synthon, while **2** entails a synthon possessing an electrophilic and nucleophilic site. Recognition of this difference, also apparent in linchpins **3**[5a] and **4**,[5d] foreshadows significant additional chemical versatility of the multicomponent type II ARC tactic (Figure 1).

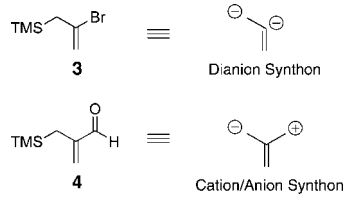
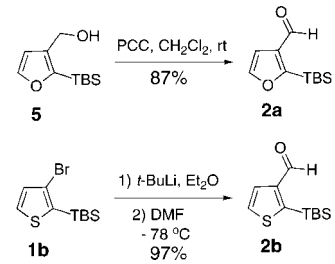


Figure 1. Linchpin synthon.

With these considerations in mind, we report here the use of organolithiums and lithium enolates derived from α-disubstituted esters as nucleophiles to generate, in a single flask, a series of 2,3-disubstituted furans and thiophenes via the multicomponent type II ARC tactic.

The requisite linchpins 2-TBS-3-formylfuran (**2a)** and -thiophene (**2b)** are readily prepared in excellent yield (Scheme 2): linchpin **2a** via PCC oxidation[8] of 2-TBS-3-(hydroxymethyl)furan **5**[9] and linchpin **2b** via formylation of

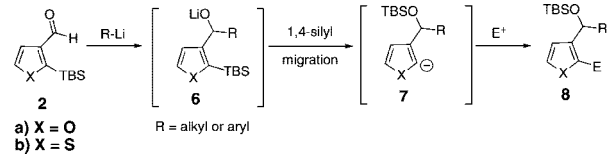
Scheme 2



2-TBS-3-bromothiophene (**1b**),[6] involving *tert*-butyllithium metalation followed by reaction with DMF.

Based on our earlier studies,[6,7] we reasoned that the reaction of **2a** or **2b** with alkyllithium would form alkoxide intermediate **6** (Scheme 3), which upon addition of either

Scheme 3



DMPU or HMPA would trigger a C(sp^2)→O 1,4-silyl migration to furnish carbanion **7**, which in turn could be captured by various electrophiles to provide disubstituted furans and thiophenes (cf., **8**). Earlier studies by Keay and co-workers[9] demonstrated the viability of C(sp^2)→O 1,4-silyl migration with a series of silylfuran and -thiophene substrates when sodium or potassium bases were used. However, no attempts to extend these reactions to a solvent-controlled multicomponent union have been reported.

We began with linchpin **2a** employing the solvent conditions of DMPU and THF (1:4), which were previously effective at triggering 1,4-silyl migration when applied to 3-bromo-2-silylthiophene (**1b**; Scheme 1, path A).[6] Surprisingly, silyl migration proved problematic, furnishing only

(5) Anion relay chemistry (ARC) involves the migration of a negative charge within a molecular system (i.e., through bond or through space, the latter employing a transfer agent such as a trisubstituted silyl group). Two types of through-space ARC have been identified. In type I ARC, the anion after initial migration returns to the site of origin, whereas in type II ARC, the anion is relayed to a new remote site. For an account on the evolution of type I and type II anion relay chemistry, see ref 5e. For earlier examples of anion relay chemistry developed by Smith and co-workers, see refs 5a−d. (a) Smith, A. B., III.; Duffey, M. O. *Synlett* **2004**, 1363. (b) Smith, A. B., III.; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66. (c) Smith, A. B., III.; Xian, M.; Kim, W.-S.; Kim, D.-S. *J. Am. Chem. Soc.* **2006**, *128*, 12368. (d) Smith, A. B., III.; Kim, D.-S.; Xian, M. *Org. Lett.* **2007**, *9*, 3307. (e) Smith, A. B., III.; Wuest, W. M. *Chem. Commun.* **2008**, 5883.

(6) Devarie-Baez, N. O.; Shuhler, B. J.; Wang, H.; Xian, M. *Org. Lett.* **2007**, *9*, 4655.

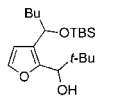
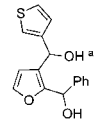
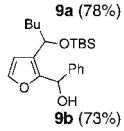
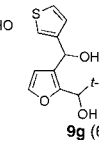
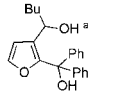
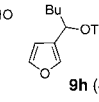
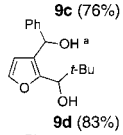
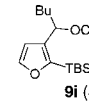
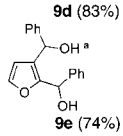
(7) Smith, A. B., III.; Kim, W.-S.; Wuest, W. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7082.

(8) Corey, E. J.; Suggs, W. *Tetrahedron Lett.* **1975**, *16*, 2647.

(9) (a) Bures, E.; Spinazze, P. G.; Beese, G.; Hunt, I. R.; Rogers, C.; Keay, B. A. *J. Org. Chem.* **1997**, *62*, 8741. (b) Spinazze, P. G.; Keay, B. A. *Tetrahedron Lett.* **1989**, *30*, 1765.

trace amounts of the desired product. However, when the electrophile was added in a mixture of HMPA and Et_2O (1:2) to the alkoxy anion initially derived at −78 °C, the desired 1,4-Brook process ensued to furnish 2,3-disubstituted furans in moderate to good yield. A series organolithium reagents (i.e., *n*-BuLi, PhLi, and 3-thienyllithium) served to initiate the multicomponent ARC reaction (Table 1). Aldehydes and ketones proved effective electrophiles for the type II ARC process, providing the 2,3-disubstituted furans (**9a**−**g**) in yields ranging from 62 to 83%. When isobutyraldehyde was employed as the electrophile, the Brook rearrangement took place to afford **9h** without capture of the aldehyde (entry 8). Presumably, the basicity of the C(2) furan anion in the presence of HMPA, the latter known to increase the basicity of organolithium agents,[10] leads to aldehyde deprotonation faster than reaction with the carbonyl group. Also of interest, use of reactive alkyl halides such as methyl iodide furnished only oxygen alkylation **9i** (entry 9).

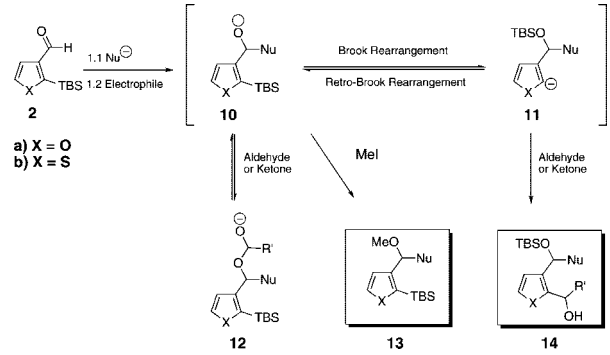
Table 1. One-Pot Synthesis of 2,3-Disubstituted Furans from 2-TBS-3-formylfuran **2a***

Entry	R-M	E	Product(yield)	Entry	R-M	E	Product(yield)
1	*n*-BuLi	*t*-Bu-CHO	 **9a** (78%)	6		Ph-CHO	 **9f** (62%)
2	*n*-BuLi	Ph-CHO	 **9b** (73%)	7		*t*-Bu-CHO	 **9g** (65%)
3	*n*-BuLi	$(Ph)_2CO$	 **9c** (76%)	8	*n*-BuLi	*i*-Pr-CHO	 **9h** (82%)
4	Ph-Li	*t*-Bu-CHO	 **9d** (83%)	9	*n*-BuLi	MeI	 **9i** (85%)
5	Ph-Li	Ph-CHO	 **9e** (74%)				

* Conditions: (step 1) **2a** (1.0 equiv), nucleophile (1.1 eq.uiv), Et_2O, −78 °C, 30 min; (step 2) HMPA/Et_2O = (1/1), electrophile (1.5 equiv), −78 °C to rt, 3 h. [a] TBS group was removed by TBAF in THF for 30 min to facilitate purification.

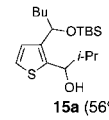
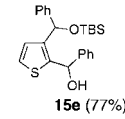
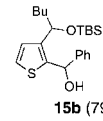
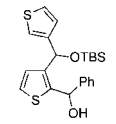
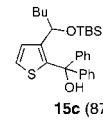
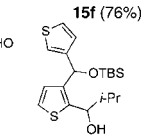
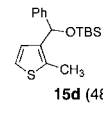
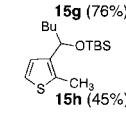
Brook and retro-Brook rearrangements are known to be reversible processes proceeding via a pentacoordinate silicon intermediate (Scheme 4).[11] Given that such an equilibrium exists between alkoxide **10** and the Brook-rearranged organolithium **11**, product formation would be based on the relative rate of the 1,4-Brook/retro-Brook rearrangement in conjunction with the stability of two anions (oxy anion vs carbanion). When MeI was employed as an electrophile, the result of irreversible *O*-methylation **13** is faster than Brook rearrangement in this system. On the other hand, when either an aldehyde or ketone was used, **14** was obtained. In essence, **12** serves as a reservoir of the carbonyl electrophile.

Scheme 4



Encouraged by the viability of the type II ARC process employing 2-TBS-3-formylfuran **2a**, we turned to the use of 2-TBS-3-formylthiophene **2b** as the bifunctional linchpin (Table 2). In this case, when DMPU and THF (1:4)[6] were employed as the solvent system, **2b** provided the 2,3-disubstituted thiophenes in moderate to good yield. Aldehydes, nonenolizable ketones, and in this case methyl iodide proved competent as electrophiles for the 1,4-Brook rearranged anion, with isolated yields of **15a**−**h** ranging from 45 to 87%. Unlike the reaction with **2a**, enolizable aldehydes (cf. isobutyraldehyde) furnished **15a** and **15g** in moderate yield (entries 1 and 7), presumably due to the decreased

Table 2. One-Pot Synthesis of 2,3-Disubstituted Thiophenes from 2-TBS-3-formylthiophene **2b***

Entry	R-M	E	Product(yield)	Entry	R-M	E	Product(yield)
1	*n*-BuLi	*i*-Pr-CHO	 **15a** (56%)	5	Ph-Li	Ph-CHO	 **15e** (77%)
2	*n*-BuLi	Ph-CHO	 **15b** (79%)	6		Ph-CHO	 **15f** (76%)
3	*n*-BuLi	$(Ph)_2CO$	 **15c** (87%)	7		*i*-Pr-CHO	 **15g** (76%)
4	Ph-Li	MeI	 **15d** (48%)	8	*n*-BuLi	MeI	 **15h** (45%)

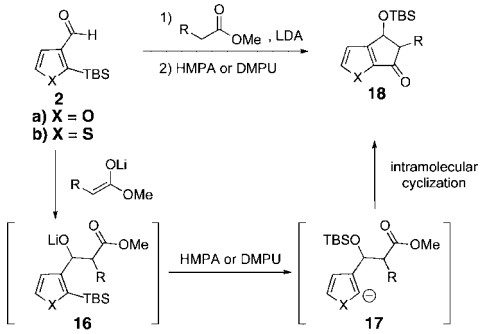
* Conditions: (step 1) **2b** (1.0 equiv), nucleophile (1.1 equiv), THF, −78 °C, 30 min; (step 2) DMPU/THF = (1/1), electrophile (1.5 equiv), −78 °C to rt, 3 h. [a] We also obtained *O*-methylation product (**15 i**) in 41%.

(10) Clayden, J.; Yasin, S. A. *New J. Chem.* **2002**, *26*, 191.

basicity of the thiophene anion. Interestingly, use of HMPA was not an effective agent to trigger the 1,4-Brook process with **2b**.[6]

We next turned to the possibility of using ester enolates as the initiating nucleophile in the ARC process (Scheme 5). We reasoned that intramolecular capture after silyl

Scheme 5

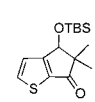
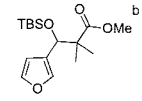
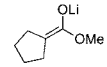
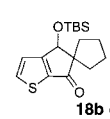
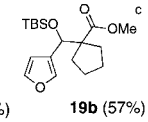
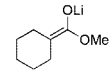
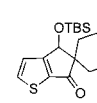
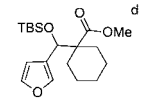
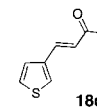


migration might occur to form 5-membered cyclic products (cf., **18**).

As illustrated in Table 3, enolates derived from a series of methyl esters, generated upon treatment with LDA, were reacted with linchpins **2a** and **2b**. After initial generation of the intermediate **16**, addition of either HMPA or DMPU triggered the C(sp^2)→O 1,4-Brook rearrangement. In the case of the thiophene linchpin (**2b**), cyclization occurred. Good to excellent yields of **18a**−**c** (entries 1−3) were obtained when esters possessing α-disubstitution were used. However, only trace amounts of cyclized products were observed when enolates derived from α-unsubstituted esters were employed as the initiating nucleophiles (entry 4). Again, acidic protons present on the initially derived adducts are presumably sufficiently acidic to be protonated by the intermediate carbanion. In the case of the enolate derived from isopropyl acetate, *β*-elimination product **18d** was isolated in moderate yield. Also of interest, when 2-TBS-3-formylfuran **2a** was used as the linchpin, 1,4-Brook-rearranged products (**19a**−**c**) not having undergone intramolecular cyclization were obtained as the major product (entries 1−3). The latter results presumably derived either from the reactivity (i.e., geometry) and/or basicity differences of the C(2) anion of the furan and thiophene.[12]

In summary, a multicomponent one-pot synthesis of 2,3-disubstituted furans and thiophenes exploiting type II anion

Table 3. Synthesis of 3- and 2,3-Disubstituted Furans and Thiophenes from **2a** and **2b** Employing Ester Enolates

Entry	Enolate	Product(yield)	
1		 **18a** (69%)	 **19a** (52%)
2		 **18b** (88%)	 **19b** (57%)
3		 **18c** (73%)	 **19c** (52%)
4		 **18d** (65%)	

[a] Conditions A: (step 1) **2b** (1.0 equiv), ester enolate (1.1 equiv), THF, −78 °C, 25 min; (step 2) DMPU, −78 °C to rt, 19 h. [b] Conditions B: (step 1) **2a** (1.0 equiv), ester enolate (1.2 equiv), Et_2O, −78 °C, 30 min; (step 2) HMPA, −78 °C to rt, 19 h. [c] Conditions C: same as conditions A except for the amount of DMPU. [d] Conditions D: (step 1) silyl enol ether (1.36 equiv), MeLi (1.28 equiv), Et_2O, rt, 1 h; (step 2) **2a** (1.0 equiv), Et_2O, −78 °C, 30 min; (step 3) HMPA, −78 °C to rt, 19 h.

relay chemistry (ARC) has been developed employing 2-TBS-3-formylfuran and -thiophene as the bifunctional linchpins. Central to this process is a solvent-mediated C(sp^2)→O 1,4-Brook rearrangement. As such, this study foreshadows the use of other nucleophiles (cf., organozincates, organocuprates, etc.) as well as the use of cross-coupling reactions as recently demonstrated with *o*-TMS benzaldehyde,[7] to access a wide variety of diverse polyfunctionalized heterocycles. Progress toward this end will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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