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Solvent-Controlled C^{sp2}→O Silyl Migration: The "One-Pot" Synthesis of 2,3-Disubsituted Thiophenes

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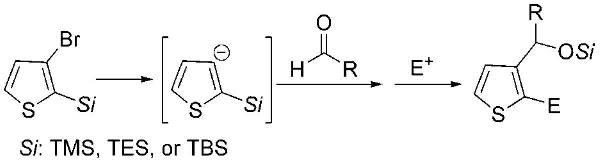
ABSTRACT



An effective "one-pot" synthesis of disubstituted thiophene derivatives employing 3-bromo-2-silyl thiophenes has been developed. A solvent-controlled [1,4] C^{sp2}→O silyl migration was involved as the key step in this process.

Substituted thiophenes are of interest in drug discovery and material science.[1] Although a number of methods have been developed for their syntheses,[2] current methods to prepare multisubstituted thiophenes still rely on multistep manipulations to install substituents one by one, which is inefficient and time-consuming. A "one-step" strategy to install multiple substituents on a thiophene ring is still a challenging goal.[3] We envisioned that the silyl group on a thiophene ring could serve as a carbanion precursor if triggered by the anionic C→O silyl migration to precipitate tandem C−C bond formations. Hence, multisubstituted thiophenes could be prepared from silylthiophenes in a "one-pot" fashion.

Anionic C→O silyl migration[4] is a mild way to generate synthetically useful carbanions, and significant progress has been made in the utility of this migration in tandem reactions.[5] These tandem reactions usually involve the silyl migration from an sp^3 carbon to oxygen.[6] In contrast, there has been very limited synthetic application of silyl migration from an sp^2 carbon to oxygen. Takeda reported the copper(I)−alkoxide promoted C→O silyl migration of vinylsilanes and subsequent reaction of the resulting vinylcopper species.[7] Moser investigated the addition of organolithium species to an *o*-trimethylsilylbenzaldehyde−$Cr(CO)_3$ complex and the reactions of aryl anions generated by silyl migration.[8] Herein, we report that silylthiophenes can be used to carry out silyl-migration mediated tandem reactions to introduce multiple

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[1] (a) Bhlmann, F.; Zedero, 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 1, p 397. (c) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (d) Schopf, G.; Komehl, G. In *Advances in Polymer Science: Polythiophenes-Electrically Conductive Polymers*; Abel, A., Ed.; Springer-Verlag: Berlin, Heidelberg, New York, 1997; Vol. 129.

[2] For selected reviews, see: (a) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun*. **2006**, 583. (b) Guernion, N. J. L.; Hayes, W. *Curr. Org. Chem*. **2004**, *8*, 637. (c) Weissberger, A.; Taylor, E. C. In *Thiophenes and Its Derivatives*; Gronowitz, S., Ed.; The Chemistry of Heterocyclic Compounds, Vol. 44; John Wiley & Sons: New York, 1985; Part 1, pp 1.

[3] For selected examples, see: (a) Mitsudo, K.; Thansandote, P.; Wilhelm, T.; Mariampillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939. (b) Ye, X. S.; Li, W. K.; Wong, H. N. C. *J. Am. Chem. Soc.* **1996**, *118*, 2511. (c) Fattuoni, C.; Usai, M.; Cabiddu, M. G.; Cadoni, E.; De Montis, S.; Cabiddu, S. *Synthesis* **2006**, 3855.

[4] Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

[5] For reviews, see: (a) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065. (b) Schaumann, E.; Kirschining, A. *Synlett* **2007**, 177.

[6] For selected examples: (a) Fischer, M. R.; Kirschning, A.; Michel, T.; Schaumann, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 217. (b) Smith, A. B., III; Kim, D.-S.; Xian, M. *Org. Lett.* **2007**, *9*, 3307. (c) Tietze, L. F.; Geissler, H.; Gewart, J. A.; Jakobi, U. *Synlett* **1994**, 511. (d) Nakai, Y.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2007**, *72*, 1379. (e) Kirschning, A.; Kujat, C. Luiken, S.; Schaumann, E. *Eur. J. Org. Chem.* **2007**, 2387. (f) Jones, P. F.; Lappert, M. F.; Szary, A. C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2272. (g) Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189.

[7] Tsubouchi, A.; Onishi, K.; Takeda, T. *J. Am. Chem. Soc.* **2006**, *128*, 14268 and references therein.

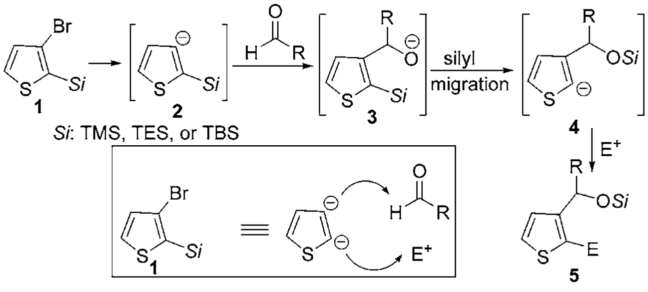
[8] (a) Moser, W. H.; Endsley, K. E.; Colyer, J. T. *Org. Lett.* **2000**, *2*, 717. (b) Moser, W. H.; Zhang, J.; Lecher, C. S.; Frazier, T. L.; Pink, M. *Org. Lett.* **2002**, *4*, 1981.

10.1021/ol702149c CCC: $37.00

substitutents on a thiophene ring in “one-pot”. To the best of our knowledge, this is the first synthetic application of the solvent-controlled $C^{sp2}\rightarrow O$ silyl migration.

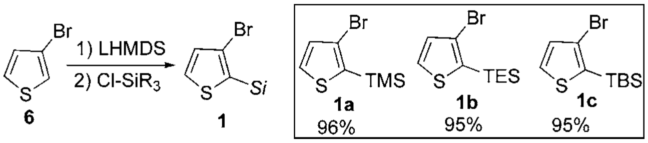
The silylthiophenes employed in our study were 3-bromo-2-silyl-thiophenes **1**. Our design is described in Scheme 1: the carbanion **2** generated from **1** via metal−bromine exchange will react with an aldehyde to provide alkoxide **3**, which in turn will undergo a [1,4] $C^{sp2}\rightarrow O$ silyl migration to result in a new carbanion **4**. Finally, **4** will be trapped by electrophiles to furnish disubsituted thiophene **5**. As such, 3-bromo-2-silyl-thiophenes **1** could serve as 2,3-thienyldianion equivalents for the assembly of two different subsitutents on the thiophene ring in one step.

Scheme 1



3-Bromo-2-silyl-thiophene substrates were prepared from 3-bromothiophene **6** via 2-lithiation and subseqent quenching with chlorosilanes (Scheme 2). In order to study the effect of silyl subsitutents on each step of the tandem reaction, three silyl variants, **1a**, **1b**, and **1c**, were prepared in almost quantitive yield.

Scheme 2



The first step of the tandem reaction is the coupling reaction between **1** and aldehydes. Organolithiums and organomagnesiums have been used to promote the reactions of some 3-bromothiophenes with aldehydes to form 3-hydroxyalkylthiophenes.[9] We are particularly interested in using organolithiums in our design since lithium counterions can be transmetalated to other metals such as Mg, Zn, Cu, etc. Such process could either facilitate the silyl migration or expand the reaction scope of carbanions generated from the silyl migration. However, the silyl group at the 2-position has been reported to markedly increase the tendency toward ring-opening of the 2-silyl 3-thienyllithiums,[10] which may have caused a limitation in this coupling step. To our delight, after several attempts we were able to find a suitable condition for this step: when the 3-thienyllithium of **1** generated via lithium−bromine exchange was treated with 1.0 equiv of aldehydes in Et_2O at −78 °C, desired products **3a**−**3f** were obtained in very high yields (Scheme 3 and Table 1). No ring-opening product was observed. Silyl subsitutents and aldehyde varients had little effect on the yields of the coupling reaction. This set up a good base for the designed tandem reaction.

Scheme 3

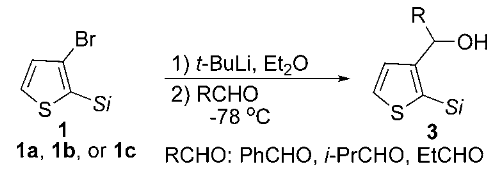
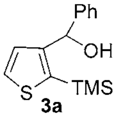
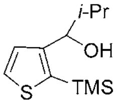
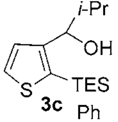
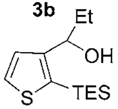
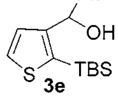
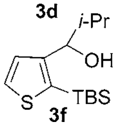


Table 1. Alkylation of 3-Bromo-2-silylthiophene with Aldehydes

Product	Yield	Product	Yield
 **3a**	90%	 **3b**	92%
 **3c**	91%	 **3d**	90%
 **3e**	93%	 **3f**	97%

With a series of 3-hydroxyalkyl-2-silylthiophenes (**3**) in hand, we next examined the $C^{sp2}\rightarrow O$ silyl migration and subsequent coupling reactions. In fact, Keay et al. did some pioneering work in this area.[11] They studied the silyl migration of several silylthiophene substrates and found the use of lithium bases resulted in the recovery of starting material. Silyl migration occurred only when sodium or potassium bases were used. However, they were not able to trap the carbanion formed by the migration with any electrophiles except protons. They concluded that any reactive species at the arene ring formed by silyl migration will be rapidly protonated during the reaction, which precluded further C−C bond formation.

The results of $C^{sp2}\rightarrow O$ silyl migration using our substrates are shown in Scheme 4 and Table 2. Compound **3e** was used to investigate the migration conditions. Similar to the Keay’s

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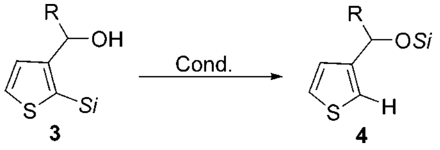
(9) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(10) Gronowitz, S.; Frejd, T.; Karlsson, O.; Lawitz, K.; Pedeja, P.; Petterson, K. *Chem. Scr.* **1981**, *18*, 192.

(11) (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.

Scheme 4

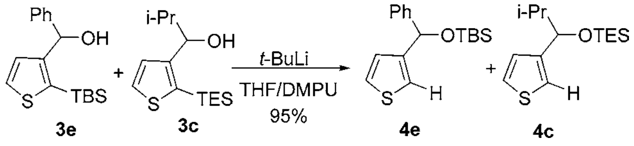


results, the [1,4] silyl migration proceeded nicely when NaHMDS and KHMDS were used as the base, whereas the migration completely stopped when a lithium base such as *t*-BuLi was used in a series of solvents: THF, Et_2O, and DME. Since we were particularly interested in using lithium base in the first step of the tandem reaction, we tested a series of solvent additives to explore the solvent-controlled conditions for the migration. The addition of TMEDA, HMPA, or crown ether to the reaction mixture did not help the migration as only the starting material was recovered (entry 6) or a small amount of migration product was obtained (entries 7, 8). Surprisingly, when DMPU was added to the mixture, the silyl migration occurred smoothly at low temperature (−30−0 °C) and the desired migration product was obtained in almost quantative yield (entry 9). This condition was then applied to other substrates including **3b**, **3c**, **3d**, and **3f**. All gave excellent results (entries 10−13). To establish the mode of silyl migration under this condition, we carried out a crossover experiment, wherein an equimolar mixture of **3e** and **3c** was treated with *t*-BuLi in THF/DMPU solvent (Scheme 4). No crossover products were observed. Thus, the silyl migration occurred intramolecularly.

Table 2. Silyl Migration of 3-Hydroxyalkyl-2-silylthiophenes

Entry	SM	Base	Sol./Add.	% Yield of **4**
1	**3e**	NaHMDS	THF	98
2		KHMDS	THF	95
3		*t*-BuLi	THF	0
4		*t*-BuLi	Et_2O	0
5		*t*-BuLi	DME	0
6		*t*-BuLi	THF/TMEDA	0
7		*t*-BuLi	THF/HMPA	~20
8		*t*-BuLi	THF/12-crown-4	<10
9		*t*-BuLi	THF/DMPU	98
10	**3b**	*t*-BuLi	THF/DMPU	98
11	**3c**	*t*-BuLi	THF/DMPU	95
12	**3d**	*t*-BuLi	THF/DMPU	98
13	**3f**	*t*-BuLi	THF/DMPU	98

Crossover experiment



With these results in hand, we then examined the silyl migration−alkylation of **3** with a series of electrophiles (Scheme 5 and Table 3). As such, a solution of **3** in THF/DMPU was treated with *t*-BuLi at −30 °C, followed by the addition of electrophiles and warming to rt. In constrast to Keay's results,[11] the carbanion intermediates formed under our conditions were able to react with alkyl halides, aldehydes, and ketones to introduce substituents at the 2-position of the thiophene. As shown in Table 3, both

Scheme 5

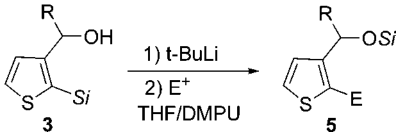


Table 3. Silyl Migration/Alkylations of 3-Hydroxyalkyl-2-silylthiophenes

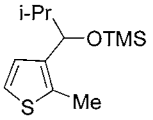
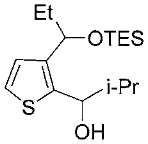
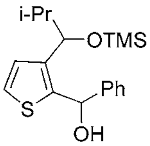
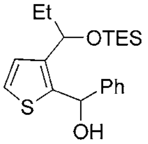
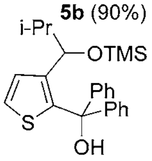
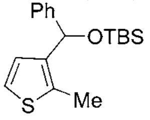
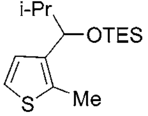
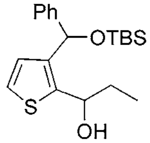
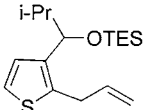
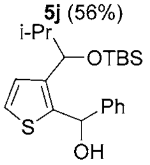
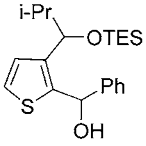
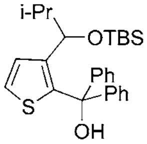
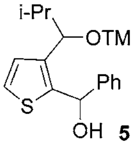
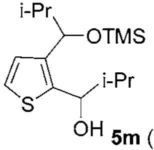
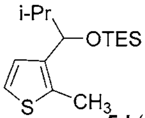
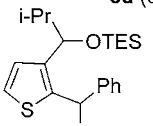
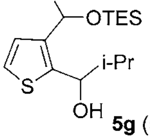
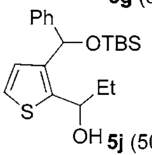
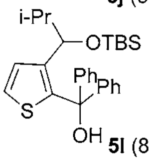
SM	E	Product (yield)	SM	E	Product (yield)
3b	MeI	 **5a** (67%)	**3d**	i-PrCHO	 **5g** (55%)
3b	PhCHO	 **5b** (90%)	**3d**	PhCHO	 **5h** (62%)
3b	$(Ph)_2CO$	 **5c** (77%)	**3e**	MeI	 **5i** (55%)
3c	MeI	 **5d** (56%)	**3e**	EtCHO	 **5j** (56%)
3c	AllylBr	 **5e** (36%)	**3f**	PhCHO	 **5k** (65%)
3c	PhCHO	 **5f** (84%)	**3f**	$(Ph)_2CO$	 **5l** (81%)

Table 4. "One-Pot" Synthesis of 2,3-Disubstituted Thiophenes

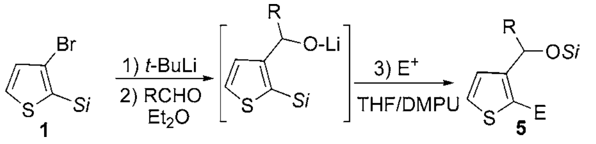
SM	RCHO	E	Product (yield)
1a	i-PrCHO	PhCHO	 **5b** (74%)
1a	i-PrCHO	i-PrCHO	 **5m** (60%)
1b	i-PrCHO	MeI	 **5d** (65%)
1b	i-PrCHO	PhCHO	 **5f** (75%)
1b	EtCHO	i-PrCHO	 **5g** (57%)
1c	PhCHO	EtCHO	 **5j** (50%)
1c	i-PrCHO	$(Ph)_2CO$	 **5l** (80%)

alkyl aldehydes and aryl aldehydes were good electrophiles to give the desired coupling products in good yields. Compounds **5b**, **5f**−**5h**, and **5j**,**5k** were obtained as an inseparable 1:1 mixture of diastereomers.

Nonenolizable ketones such as benzophenone are also good electrophiles for this reaction. However, alkyl ketones such as acetone and cyclohexanone only gave a trace amount of desired products (data not shown). Presumably, the carbanion protonation was faster than the addition to the ketone carbonyl groups in these cases. It is worth noting that the silyl subsitutents on the thiophene have little effect on the reaction, since TMS, TES, and TBS substrates all gave similar yields.

Encouraged by these results, we turned to the development of a one-flask three-component coupling protocol, employing 3-bromo-2-silyl-thiophenes **1**, aldehydes, and a series of electrophiles (Scheme 6 and Table 4). Optimal conditions entail Li−Br exchange of **1** in Et_2O at −78 °C for 30 min, followed by the addition of a solution of an aldehyde in Et_2O. Completion of the first alkylation was achieved in ca. 60 min at −78 to −20 °C (TLC). Addition of the second electrophile, premixed with THF/DMPU, completed the reaction sequence. In general, the yields of desired three-component coupling products are good (Table 4). Alkyl halides, aldehydes, and nonenolizable ketones served as suitable electrophiles in this reaction sequence.

Scheme 6



In summary, an effective one-pot synthesis of disubstituted thiophene derivatives employing 3-bromo-2-silyl thiophenes as 2,3-thienyldianion equivalents has been developed. A [1,4] $C^{sp2}{\rightarrow}O$ silyl migration was involved as the key step in this process. To the best of our knowledge, this is the first example of solvent-controlled $C^{sp2}{\rightarrow}O$ silyl migration. Given the potential to extend this tactic to other mono- or multisubstituted silyl thiophenes and other arylheterocycles, this "one-pot" strategy will greatly enhance our capability to synthesize polyfunctionalized heterocycles. Studies directed at these applications continue in our laboratory.

Acknowledgment. This work has been supported by the Washington State University.

Supporting Information Available: Synthetic procedures, spectroscopic data, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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