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Highly Regioselective Nucleophilic Carbon–Carbon Bond Formation on Furans and Thiophenes Initiated by Pummerer-Type Reaction

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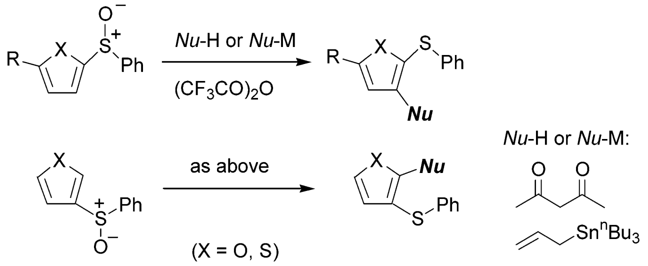
ABSTRACT



The reactions of (phenylsulfinyl)furans or -thiophenes with carbon nucleophiles in the presence of trifluoroacetic anhydride allowed the nucleophilic installation of carbon functional groups on the furan and thiophene nuclei with complete regioselectivity.

Furans and thiophenes serve as useful synthetic intermediates and building units for various compounds[1−3] as well as conductive molecules.[4] Therefore, the development of carbon−carbon bond-forming reactions of these compounds has received significant attention. The most popular methods are based on electrophilic reactions such as (i) the direct electrophilic substitution reactions of these nuclei[2,5] and (ii) the generation of metalated intermediates by either the halogen−metal exchange reaction or the directed metalation reaction followed by the reaction with carbon electrophiles.[3,6] The transition metal-catalyzed reactions of (halogenated) heteroaromatics have also been extensively employed recently.[7] On the other hand, direct nucleophilic substitution reactions on these heteroaromatic compounds have been limited to the specific combination of the substrates having powerful electron-withdrawing group(s), such as nitro or carbonyl groups, and highly reactive carbanions.[8,9]

Over the past several years, we have disclosed the preparation of benzofurans and indoles **III** via the aromatic Pummerer-type reaction[10] of *p*-sulfinyl-phenols and -anilines

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(1) For reviews, see: (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795−819. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109−118.

(2) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2003**, *44*, 7411−7415.

(3) (a) Apsel, B. Bender, J. A.; Escobar, M. Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1075−1077. (b) Krishna, U. M.; Srikanth, G. S. C.; Trivedi, G. K.; Deodhar, K. D. *Synlett* **2003**, 2383−2385. (c) de la Torre, M. C.; García, I.; Sierra, M. A. *J. Org. Chem.* **2003**, *68*, 6611−6618.

(4) For a recent review, see: McCullough, R. D. *Adv. Mater.* **1998**, *10*, 93−116.

(5) For an example, see: Roberts-Bleming, S. J.; Davies, G. L.; Kalaji, M.; Murphy, P. J.; Celli, A. M.; Donati, D.; Ponticelli, F. *J. Org. Chem.* **2003**, *68*, 7115−7118.

(6) For an example, see: Ponomarenko, S.; Kirchmeyer, S. *J. Mater. Chem.* **2003**, *13*, 197−202.

(7) For a review, see: Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1470. For examples, see: Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557−12565. Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301−304.

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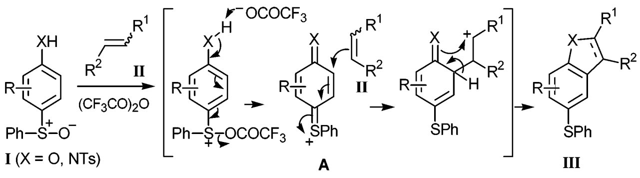
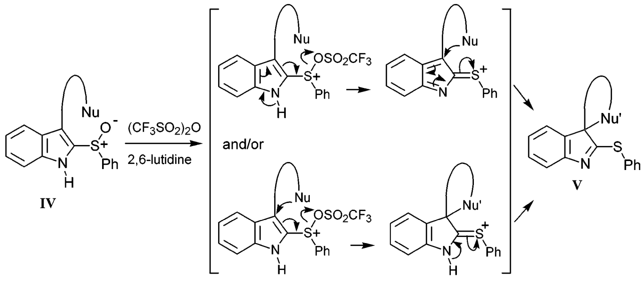
I. In these reactions, the treatment of **I** with trifluoroacetic anhydride caused the successive *O*-acylation and elimination of the acyloxy group, both of which were accelerated by the electron-donation of the *p*-hydroxyl or the *p*-amino group. The generated *p*-quinone sulfonium intermediates **A** allowed regioselective nucleophilic attack of the external olefins **II** followed by cyclization to give **III** (Scheme 1).[11]

Scheme 1



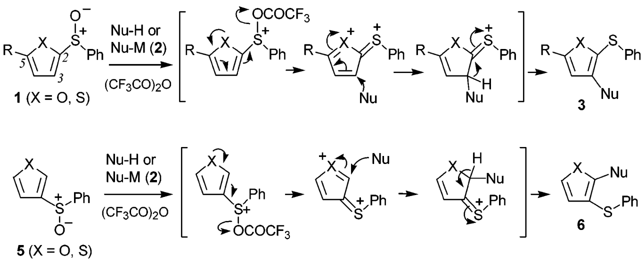
Similar intramolecular cyclizations using the Pummerer-type reaction of 2-sulfinylindoles **IV** having a nucleophilic alkyl chain at the C3-position have been reported to give spirooxindoles **V** (Scheme 2).[12]

Scheme 2



As an extension of these Pummerer-type reactions, we present here novel intermolecular nucleophilic carbon–carbon bond-forming reactions of the 2-sulfinyl-furans and -thiophenes **1** to give C3-substituted heteroaromatics **3**. Similarly, the 3-sulfinyl derivatives **5** afforded the C2-substituted products **6** with exclusive regioselectivity (Scheme 3).[13]

Scheme 3



We first investigated the reaction of 2-sulfinylfuran **1a** and acetylacetone **2a** as a typical example. The reaction of a mixture of these compounds with trifluoroacetic anhydride (2 equiv) in MeCN was immediately completed at room temperature to give the product **3a** (75% yield), in which the nucleophile was installed at the C3-position. The formation of other regioisomers was not observed upon ^{1}H NMR analysis. On the other hand, the use of other solvents such as toluene, CH_2Cl_2, $CHCl_3$, and acetone resulted in unsatisfactory yields of **3a** (up to 46% yield).

Similar reactions of the 2-sulfinylfurans (**1a**,**b**) or the thiophenes (**1c**–**e**) with carbon nucleophiles (**2a**,**b**) took place to afford the C3-substituted products (**3b**–**g**), each as a single regioisomer, in moderate to high yields (entries 2–8). Some features are noteworthy: First, the thiophene derivative **1c**, which has a higher degree of aromaticity than the furans,[14] also accepted the nucleophilic attack to give the C3-substituted products (**3d** and **3e**) in 78 and 86% yields, respectively (entries 4 and 6). Second, the thiophene **1d** having an electron-withdrawing group was less reactive when forming **3f** at 80 °C (entry 7), whereas the methylthiophene **1e** was a good substrate to give **3g** at 0 °C (entry 8). Third, some reactions at room-temperature suffered low yields of the products due to the formation of sulfides **4** as a side product (for example, entry 5), although the reaction mechanism for their generation has not yet been clarified. In such cases, similar reactions at 0 °C suppressed their formation to give the products in better yields (for example, entry 6).

In a like manner, the reactions of the 3-sulfinyl derivatives (**5a**,**b**) with **2a**,**b** took place to give the C2-substituted products (**6a**–**d**) in high yields with exclusive regioselectivity (entries 9–12).[15]

The sulfur functional group that remained in the products permitted the installation of a second carbon functional group

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(8) For examples, see: (a) Mąkosza, M.; Staliński, K. *Synthesis* **1998**, 1631–1634. (b) Lawrence, N. J.; Lamarche, O.; Thurrab, N. *Chem. Commun.* **1999**, 689–690. (c) Migaud, M. E.; Wilmouth, R. C.; Mills, G. I.; Wayne, G. J.; Risley, C.; Chambers, C.; Macdonald, S. J. F.; Schofield, C. J. *Chem. Commun.* **2002**, 1274–1275.

(9) For examples, see: (a) Moosa, B. A.; Abu Safieh, K. A.; El-Abadelah, M. M. *Heterocycles* **2002**, *57*, 1831–1840. (b) Iesce, M. R.; Graziano, M. L.; Cermola, F.; Montella, S.; Gioia, L. D. *Tetrahedron Lett.* **2003**, *44*, 5781–5784.

(10) (a) Kita, Y.; Takeda, Y.; Matsugi, M.; Iio, K.; Gotanda, K.; Murata, K.; Akai, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1529–1531. (b) Akai, S.; Takeda, Y.; Iio, K.; Takahashi, K.; Fukuda, N.; Kita, Y. *J. Org. Chem.* **1997**, *62*, 5526–5536.

(11) (a) Akai, S.; Morita, N.; Iio, K.; Nakamura, Y.; Kita, Y. *Org. Lett.* **2000**, *2*, 2279–2282. (b) Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y.; Iio, K.; Kita, Y. *Heterocycles* **2002**, *58*, 75–78.

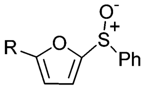
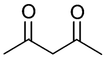
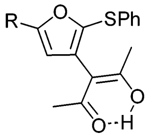
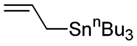
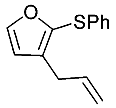
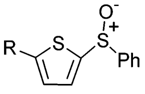
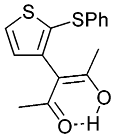
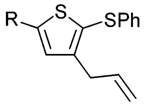
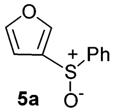
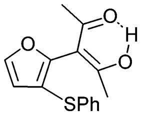
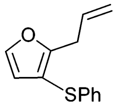
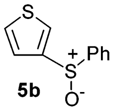
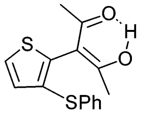
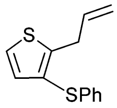
(12) (a) Feldman, K. S.; Vidulova, D. B. *Org. Lett.* **2004**, *6*, 1869–1871. (b) Feldman, K. S.; Vidulova, D. B. *Tetrahedron Lett.* **2004**, *45*, 5035–5037.

(13) Sulfoxides **1** and **5** were readily available by the oxidation of the corresponding sulfides, obtained by the lithiation at the C2-position of the furans and the thiophenes (for the 2-sulfinyl derivatives) or the bromo–lithium exchange reactions of commercial 3-bromofuran or 3-bromothiophene (for the 3-sulfinyl derivatives) followed by sulfanylation with $PhSSO_2Ph$.

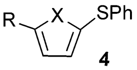
(14) Bird, C. W. *Tetrahedron* **1985**, *41*, 1409–1414.

(15) Strong electron donation of oxygen and sulfur in the furan and thiophene rings must accelerate the elimination of the acyloxy groups of the *O*-acylated sulfonium intermediates, respectively. In addition, the effect that the electron-donating group of the C-5 substituent (Me group, entry 8 in Table 1) accelerates the reaction, while the electron-withdrawing CO_2Me group deactivates it (entry 7), suggests the participation of the 6π-electrons of the heteroaromatics. Therefore, the aromatic Pummerer-type mechanism (Scheme 3) seems to be more plausible than the additive Pummerer mechanism,[12] although we cannot rule out the possibility of the latter one.

Table 1. Regioselective Nucleophilic Substitution on **1** or **5** with **2a**,**b**

entry	**1** or **5**	**2**	reaction conditions	**3** or **6**	yield (%)
1	 **1a** (R = H)	 **2a**	RT, 30 min	 **3a** (R = H)[a]	75
2	**1b** (R = Me)	**2a**	0 °C, 30 min	**3b** (R = Me)[a]	54
3	**1a**	 **2b**	0 ºC, 30 min	 **3c**	62
4	 **1c** (R = H)	**2a**	RT, 30 min	 **3d**[a]	78
5	**1c**	**2b**	RT, 30 min	 **3e** (R = H)	50[b]
6	**1c**	**2b**	0 ºC, 30 min	**3e** (R = H)	86[b]
7	**1d** (R = CO_2Me)	**2b**	80 °C, 2 h	**3f** (R = CO_2Me)	50[c]
8	**1e** (R = Me)	**2b**	0 ºC, 30 min	**3g** (R = Me)	63
9	 **5a**	**2a**	RT, 30 min	 **6a**[a]	80
10	**5a**	**2b**	0 ºC, 30 min	 **6b**	73
11	 **5b**	**2a**	RT, 30 min	 **6c**[a]	80
12	**5b**	**2b**	0 ºC, 30 min	 **6d**	96

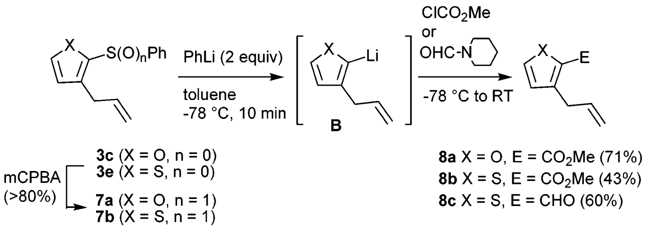
[a] Compound exists as the enol form. [b] Besides **3e**, the corresponding sulfide **4c** (X = S, R = H) was obtained in 30% (for entry 5) and <10% yield (for entry 6). [c] **1d** (50% yield) was recovered.


4

at the *ipso*-position. For instance, mCPBA oxidation of the furan **3c** gave the corresponding sulfoxide **7a**, which was treated with PhLi in toluene to generate the 2-lithiofuran **B** via the sulfur−lithium exchange reaction.[11a] Quenching this nucleophilic intermediate with $ClCO_2Me$ provided the furan-2-carboxylate **8a** in 71% yield. This type of reaction is also effective on the thiophenes; e.g., **7b**, prepared from **3e**, was converted to **8b** and **8c** in good yields (Scheme 4).

In conclusion, we have developed regioselective substitution reactions of furans and thiophenes via the Pummerer-type reaction. Our method features the nucleophilic substitutions under mild acidic conditions, in which even weak nucleophiles such as acetylacetone **2a** can be used. Complete regioselectivity was attained and found to be dependent on the position of the sulfinyl group. The iterative use of a single

Scheme 4



sulfinyl group for the introduction of two different carbon functional groups is another feature of this method. The extension of this method to other π-sufficient heteroaromatics and nucleophiles is now under study in our laboratory.

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Supporting Information Available: Experimental details and spectroscopic data for all products (**3**, **6**, and **8**). This material is available free of charge via the Internet at http://pubs.acs.org.

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