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Synthesis of Polycyclic Heterocycles via a One-Pot Ortho Alkylation/Direct Heteroarylation Sequence

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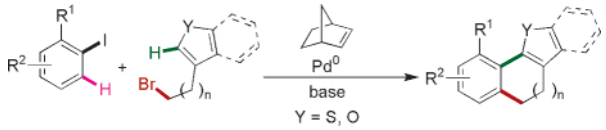
ABSTRACT



Polycyclic thiophenes and furans were synthesized using a one-pot ortho alkylation/direct heteroarylation reaction sequence. Under the optimized reaction conditions, aryl iodides were coupled with 3-(bromoalkyl)thiophenes or -furans, affording six- and seven-membered annulated ring products via formation of two C–C bonds from two aryl C–H bonds.

Catalytic aromatic C−H activation and direct arylation reactions have recently received significant attention as effective methods for the formation of C−C bonds.[1] Unlike traditional methods of aromatic C−C bond formation, these methods avoid the need for stoichiometric amounts of organometallic reagents, resulting in fewer reaction steps and reduced waste.

Our group has successfully combined these processes in a palladium-catalyzed, norbornene-mediated ortho alkylation/direct heteroarylation reaction of aryl iodides with nitrogen heterocycles.[2] Herein, we extend this methodology to include the direct arylation of thiophenes and furans,[3] forming two C−C bonds from two aromatic C−H bonds. In this coupling sequence, sulfur- and oxygen-containing polycyclic heterocycles are generated, some of which form the core of a family of retinoic acid acceptor antagonists for the treatment of leukemia and other carcinomas.[4]

An optimization of the reaction was carried out using aryl iodide **1a** and 3-(bromopropyl)thiophene (**2a**) and resulted in the conditions shown in Table 1. Under these conditions, seven-membered annulated ring product **3a** was obtained in 89% yield at 95 °C (entry 1). *N*-H acetyl (entry 2) and chloride (entry 3) substituents were also tolerated on the aromatic ring, affording **3b** and **3c** in 76% and 57% yield, respectively. Placing an inductively electron-withdrawing group para to the iodide (**1d**) afforded product **3d** in 56% yield (entry 4). Aryl iodides **1a**−**d** have electron-withdrawing

(1) Selected reviews: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253−1264. (b) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55−83. (c) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625−655. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1769. (e) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (f) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (g) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211−241. (h) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698−1712.

(2) (a) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148−13149. (b) Blaszykowski, C.; Aktoudianakis, V.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043−2045.

(3) For selected examples of direct arylation with thiophenes and furans (direct heteroarylation), see: (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951−1958. (b) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohrma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257−272. (c) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286−5287. (d) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074−5075. (e) Lavenot, L.; Gozzi, C.; Ilg, K.; Orlova, I.; Penalva, V.; Lemaire, M. *J. Organomet. Chem.* **1998**, *567*, 49−55. (f) Gozzi, C.; Lavenot, L.; Ilg, K.; Penalva, V.; Lemaire, M. *Tetrahedron Lett.* **1997**, *38*, 8867−8870. (g) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677−1680. (h) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301−304. (i) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467−473. (j) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5272−5275. (k) Fishwick, C. W. G.; Grigg, R.; Sridharan, V.; Virica, J. *Tetrahedron* **2003**, *59*, 4451−4468.

(4) Yoshimura, H.; Nagai, M.; Hibi, S.; Kikuchi, K.; Abe, S.; Hida, T.; Higashi, S.; Hishinuma, I.; Yamanaka, T. *J. Med. Chem.* **1995**, *38*, 3163−3173.

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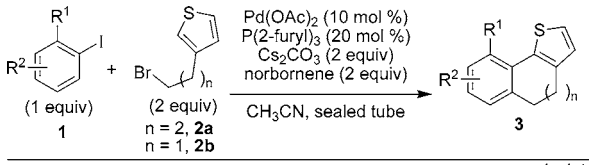
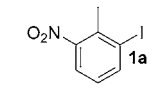
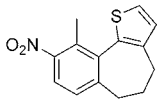
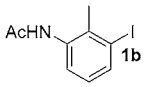
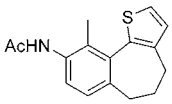
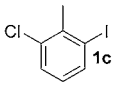
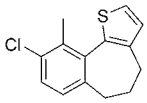
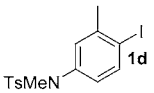
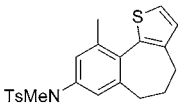
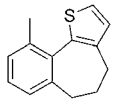
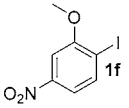
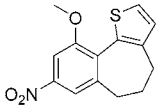
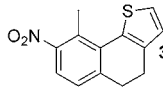
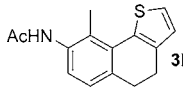
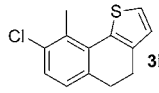
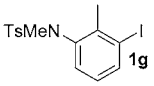
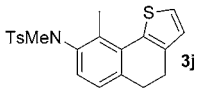
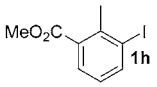
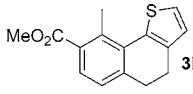
Table 1. Domino Coupling of 3-(Bromoalkyl)thiophene

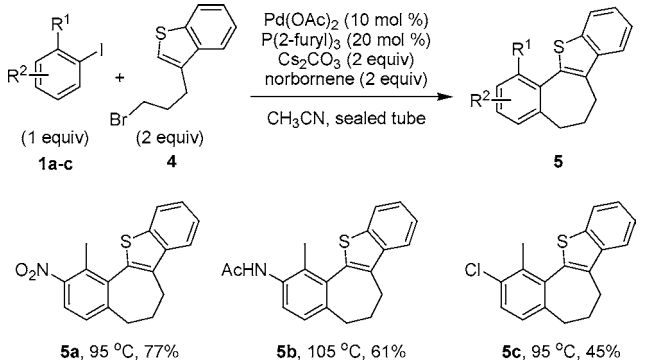


entry	Ar-I	R-Br	temp (°C)	product	isolated yield (%)
1	 1a	2a	95	 3a	89
2	 1b	2a	105	 3b	76
3	 1c	2a	95	 3c	57
4	 1d	2a	105	 3d	56
5	 1e	2a	85	 3e	19
6	 1f	2a	95	 3f	52
7	1a	2b	95	 3g	73
8	1b	2b	105	 3h	82
9	1c	2b	105	 3i	77
10	 1g	2b	105	 3j	66
11	 1h	2b	95	 3k	71

substituents, so to explore aryl iodides of different electronic character, 2-iodotoluene (**1e**, entry 5) was tried and afforded product **3e** in only 19% yield.[5] In addition, when more electron-rich aryl iodides were employed (containing methoxy or *N*,*N*-dialkylamino substituents), no desired product was obtained. These results support an electrophilic palladation mechanism for the direct heteroarylation step.[6] The presence of an electron-donating substituent on the aryl iodide could be counterbalanced with an electron-withdrawing group, as in entry 6, where product **3f** was obtained in 52% yield.[7,8] As a general trend, it was found that aryl iodides of greater electron density than **1a** required higher reaction temperatures for optimal yields. However, regardless of temperature, reactions with substrates **1a**−**f** were complete within 18 h.

Our next focus was the synthesis of six-membered ring annulated products using 3-(2-bromoethyl)thiophene (**2b**), which form the core of retinoic acid acceptor agonists when containing a *p*-benzoic acid substituent at the 4-thienyl position.[4] As with the seven-membered ring annulated products, a variety of functional groups were tolerated, including nitro, *N*-H acetyl, chloro, *N*-methyl-*N*-tosyl, and an aliphatic ester. Nitro-containing product **3g** was obtained in 73% yield (entry 7), which was noticeably lower than the yield for **3a**. However, yields for *N*-H acetyl (**3h**, 82%, entry 8) and chloro-containing aryl iodides (**3i**, 77%, entry 9) were higher than those for their seven-membered ring counterparts. Finally, products **3j** and **3k** were obtained in 66% and 71% yield, respectively. Product formation with **2b** was found to be faster than for reactions with **2a**, as reaction times were 12−15 h.

Scheme 1. Domino Coupling of 3-(3-Bromopropyl)benzothiophene



We next studied the annulation reaction with 3-(3-bromopropyl)benzothiophene (**4**) (Scheme 1). Benzothiophenes are medicinally interesting, as they form the core of the estrogen receptor modulator raloxifene (Evista)[9] and are often

(5) Yields were lower at elevated temperatures for this case.

(6) For examples supporting the electrophilic palladation pathway for direct heteroarylation, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057. (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159−1162. (c) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835−4837.

(7) It is not known if the yield is due solely to an electronic effect, as the *o*-methoxy group may also contribute to steric hindrance of the reactive center or may also undergo palladium-catalyzed reactions. See: Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023−1025.

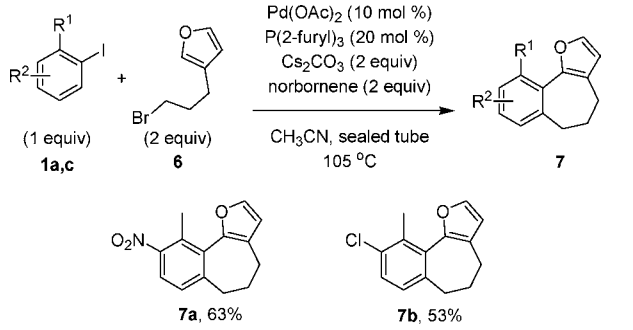
(8) An X-ray crystal structure unambiguously confirmed the structure of the product. See Supporting Information.

(9) Grese, T. A.; Cho, S.; Finley, D. R.; Godfrey, A. G.; Jones, C. D.; Lugar, C. W., III; Martin, M. J.; Matsumoto, K.; Pennington, L. D.; Winter, M. A.; Adrian, M. D.; Cole, H. W.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Short, L. L.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1997**, *40*, 146−167.

used as indole mimetics[10] for medicinal chemistry studies. In comparison to the coupling with **2a**, the yields were lower and reaction times were longer (18−24 h), presumably due to reduced nucleophilicity of benzothiophene vs thiophene; however, products **5a**−**c** were obtained in moderate to good yields.

Finally, we examined the coupling of aryl iodides with 3-(3-bromopropyl)furan (**6**) (Scheme 2). Nitro-containing

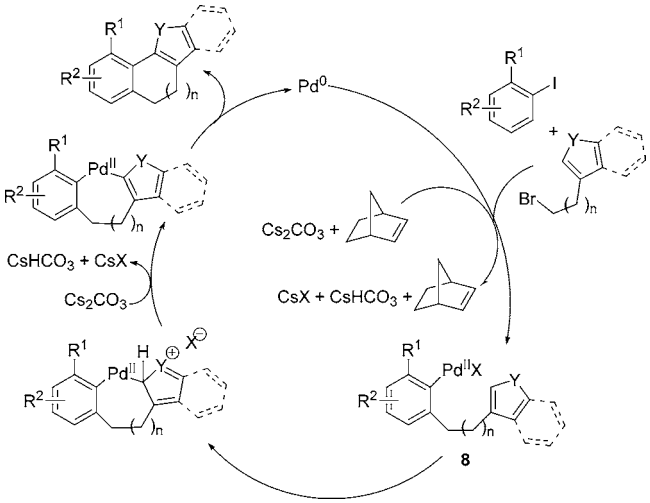
Scheme 2. Domino Coupling of 3-(3-Bromopropyl)furan



product **7a** was obtained in 63% yield, which was significantly lower than it's thiophene analogue (**3a**). However, the yield of chlorinated product **7b** (53%) was comparable to that of the thiophene **3c**. Reaction with **6** proceeds slowly, presumably due to the poor nucleophilicity of furan, as an increased reaction time (≥20 h) and higher temperatures (105 °C) were required.

The ortho alkylation step likely proceeds through a Pd(II)−Pd(IV) catalytic cycle[11] and generates heteroaryl-tethered arylpalladium(II) intermediate **8** (Scheme 3). Subsequent heteroaryl−aryl coupling of **8** via direct arylation affords the annulated product. Upon the basis of our previous research, we have found that the ortho alkylation reaction proceeds well with both electron-rich and electron-poor aryl iodides,[12] thus the differences in the observed yields may be due to an electronic effect on the direct heteroarylation step. The poor results obtained with electron-rich aryl iodides

Scheme 3. Proposed Reaction Mechanism



suggest that intramolecular direct heteroarylations of thiophenes and furans are promoted by an electron-deficient arylpalladium(II) halide. We propose that electron-rich aromatic systems stabilize Pd(II) species **8**, thus reducing it's electrophilicity and subsequent reactivity in the direct heteroarylation step. Conversely, electron-withdrawing groups destabilize **8**, resulting in a fast intramolecular electrophilic palladation followed by proton abstraction and reductive elimination to afford the desired products.

In summary, we have developed a method for the synthesis of polycyclic sulfur and oxygen-containing heterocycles through a one-pot palladium-catalyzed ortho alkylation/direct heteroarylation reaction sequence. The reaction works well with electron-deficient aryl iodides and poorly with electron-rich aryl iodides, providing insight into the mechanism of intramolecular direct heteroarylation with thiophenes and furans.

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

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(10) Selected examples: (a) Angeles, A. R.; Neagu, I.; Birzin, E. T.; Thornton, E. R.; Smith, A. B., III; Hirschmann, R. *Org. Lett.* **2005**, *7*, 1121−1124. (b) Moloney, G. P.; Garavelas, A.; Martin G. R.; Maxwell, M.; Glen, R. C. *Eur. J. Med. Chem.* **2004**, *39*, 305−321.

(11) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119−122. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336−4346. (c) Catellani, M. *Synlett* **2003**, 298−313.

(12) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127−8134.