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Regioselective Palladium-Catalyzed Arylation of 3-Carboalkoxy Furan and Thiophene

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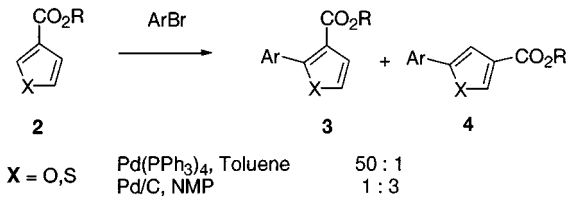
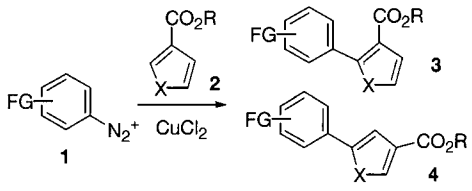
ABSTRACT



The regioselective palladium(0)-catalyzed arylation of 3-furoate and 3-thiophenecarboxylate esters with aryl bromides is described. Conditions were developed that allow for the selective synthesis of either 2-aryl or 5-aryl products.

In support of an ongoing medicinal chemistry program, an efficient, scalable synthesis of 2-aryl-3-carboxy-furans and thiophenes, **3**, was required. Previously, these intermediates were prepared by the copper(II)-catalyzed decomposition of aryl diazonium salts **1** in the presence of 3-carboalkoxy heterocycles **2**. However, this coupling reaction was found to be nonselective, affording a 1:1 mixture of 2-aryl- and 5-aryl-substituted products in moderate yield (Scheme 1).

Scheme 1



A more efficient synthesis of the desired 2-aryl-3-carboalkoxy furan and thiophene was desired that would allow ready access to large quantities of these intermediates. Other approaches that could be used to synthesize intermediates such as **3** include cross-coupling methods, for example, the Suzuki coupling of the 2-furan and 2-thiophene boronic acids with aryl halides,[1] the Stille coupling of the corresponding 2-stannylfurans,[2] or the coupling of trifuranylzincates.[3]

These methods, however, suffer from being multistep syntheses or requiring expensive starting materials. We were interested in developing a regioselective, direct arylation of the readily available 3-carboalkoxy furan and thiophene utilizing readily available aryl halides. Palladium-catalyzed arylations of furan and thiophene with aryl halides are well precedented.[4] We have also previously published work from our laboratories on the regioselective, palladium-catalyzed arylation of 2-furaldehyde in which the 5-aryl product is obtained exclusively.[5]

(1) Yang, Y.; Hornfeldt, A.; Gronowitz, S. *J. Heterocycl. Chem*. **1989**, *26*, 865.
(2) Gronowitz, S.; Timari, G. *J. Heterocycl. Chem*. **1990**, *27*, 1159.
(3) Gauthier, D. R., Jr.; Szumigala, R. H., Jr.; Dormer, P. G.; Armstrong, J. D.; Volante, R. P.; Reider, P. J. *Org. Lett*. **2001**, *4*, 375.
(4) (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocyles* **1990**, *31*, 1951. (b) Aoyagi, Y.; Inoue, A.; Koizumi, A.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257. (c) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc*. **2002**, *124*, 5286.

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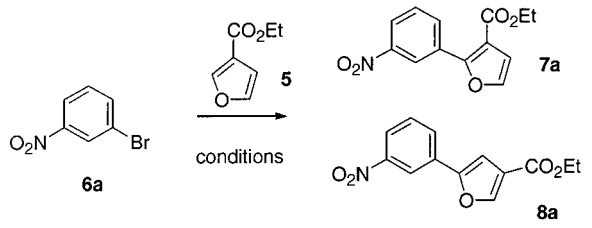
Thus, we decided to study the direct palladium-catalyzed arylation of 3-carboalkoxy furan and thiophene with aryl bromides. For our test reaction, we selected the coupling of ethyl 3-furoate (**5**) with 3-bromonitrobenzene (**6a**). In this first reaction, we screened three parameters (solvent, base, and catalyst) in a full factorial design[6] (total of 36 experiments, see Table 1) and measured the regioselectivity of the arylation by HPLC analysis.

Table 1. Screening Factors



solvent	catalyst (0.05 equiv)	base (1.5 equiv)
toluene	$Pd(PPh_3)_4$	KOAc
DMA	Pd/C	triethylamine
DMF	$Pd_2(dba)_3$	
NMP		
isobutyronitrile		
1,2-diethoxyethane		

Statistical analysis of the results of the 36 experiments indicated that solvent and catalyst were the most significant factors in controlling the regioselectivity of the reaction. The major factor controlling the regioselectivity of the arylation was found to be solvent polarity, with a good correlation observed between the dielectric constant of the solvent and the ratio of products (2-arylation vs 5-arylation). Less polar solvents favored the desired 2-aryl product **7a**, with toluene being the preferred solvent. The catalyst choice was also an important factor, with the phosphine-containing $Pd(PPh_3)_4$ being preferred over the "ligandless" palladium catalysts. It was also found that the use of potassium acetate as the base in the reaction is key to achieving a successful arylation since use of triethylamine resulted in very low conversion to the undesired 5-aryl product **8a**. The above trends are depicted graphically in Figure 1.

The preferred conditions found in the above reaction screen for the formation of the 2-aryl product (Method A) were the use of $Pd(PPh_3)_4$ as the catalyst and KOAc as the base in toluene at 110 °C. Indeed, it was found that with little modification, this reaction could be scaled to give an efficient process for the preparation of **7a**. On a preparative scale (50 g of aryl bromide), these optimum conditions (1.4 equiv of ethyl 3-furoate, 5 mol % $Pd(PPh_3)_4$, toluene reflux 24 h) afforded the 2-aryl product **7a** in 76% yield. Interestingly, this series of experiments also provided conditions that afforded the 5-aryl product **8a** as the major isomer. It was found that the use of the polar solvent NMP and ligandless palladium Pd/C (Method B) afforded a 3:1 mixture of the 5-aryl and 2-aryl isomers, respectively, in 69% yield.

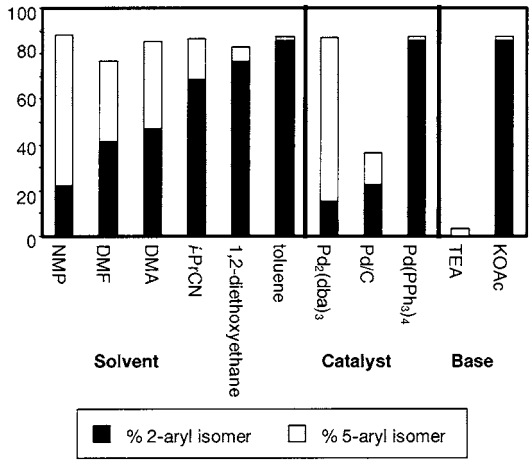
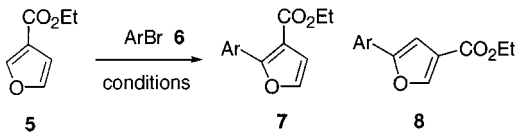


Figure 1. Conversion to arylation isomer (%). Results of the experiments that gave the highest conversion to the 2-aryl product for each factor are shown. The amounts of the 5-aryl isomer formed in these reactions are also shown.

Following the successful demonstration of the regioselective palladium-catalyzed arylation of ethyl 3-furoate with 3-bromonitrobenzene, we then proceeded to test the generality of the reaction with a number of aryl halides with both furan and thiophene substrates. The results of arylation of ethyl 3-furoate are shown in Table 2. Two major trends can be observed. First, it is evident from Table 2 that efficient arylation reactions require the use of aryl bromides substituted with electron-withdrawing groups. Attempted arylation

Table 2. Arylation of Ethyl 3-Furoate



entry	Ar (**6a**–**g**)	method[a]	product (yield)
1	(**6a**) 3-$NO_2C_6H_4$	A	**7a** (73%)
2	(**6a**) 3-$NO_2C_6H_4$	B	**8a** (42%)[b]
			7a (13%)
3	(**6b**) 3-CNC_6H_4	A	**7b** (60%)
4	(**6c**) 3-$MeO_2CC_6H_4$	A	**7c** (69%)
5	(**6d**) 4-$NO_2C_6H_4$	A	**7d** (59%)
6	(**6e**) 4-AcC_6H_4	A	**7e** (66%)
7	(**6f**) 3-$MeOC_6H_4$	A	
8	(**6f**) 3-$MeOC_6H_4$	B	**8f** (15%)
9	(**6g**) C_6H_5	A	

[a] Method A: $Pd(PPh_3)_4$, KOAc, toluene, 110 °C. Method B: Pd/C, KOAc, NMP, 110 °C. [b] Method B also afforded <5% of the 2,5-diarylated product.

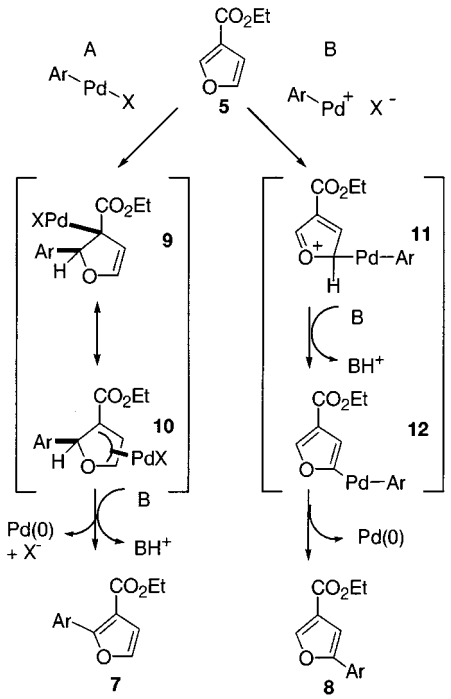
(5) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677.
(6) Federov, V. V. *Theory of Optimal Experiments*; Academic Press: New York, 1972.

of the furan with bromobenzene or 3-bromoanisole using Method A (entries 9 and 7) resulted in a complex mixture of products from which no product, or starting aryl bromide, could be isolated.[7] Arylation of the furan with 3-bromoanisole using Method B was slightly more successful, giving the 5-arylated product **8f** in 15% yield (entry 8). Interestingly, Ohta[4a] reported the need for electron-withdrawing groups on the aryl halide in the palladium-catalyzed arylation of the parent furan.

Second, it is clear that Method A [toluene, $Pd(PPh_3)_4$] consistently afforded the 2-aryl adduct in high selectivity, while Method B (NMP, Pd/C) yielded a less selective reaction favoring the 5-aryl adduct.

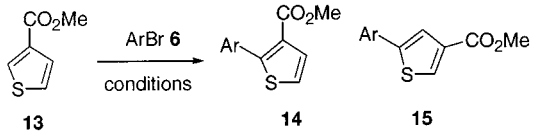
A possible explanation for the reversal of selectivity on going from Method A to Method B is a change in the reaction mechanism (Scheme 2).[8] The nonpolar solvent and phosphine ligands present in Method A are expected to stabilize the σ-bonded Pd(II) species favoring the Heck-type α,β-insertion reaction proximal to the electron-withdrawing group, therefore affording the Heck-type intermediate **9**, which leads to the 2-aryl product **7** after β-elimination. Conversely, the polar solvent and the absence of stabilizing phosphine ligands are likely to promote the ionization of the Pd−X σ-bond to form an electrophilic Pd(II) species. This species would be

Scheme 2



expected to react preferentially at the more electron-rich 5-position of the furan giving the cationic intermediate **11**, thus favoring the 5-aryl product **8** after proton abstraction and reductive elimination. Analogous cationic mechanisms have been used to explain the regioselectivity of the palladium-catalyzed arylation of azoles with aryl halides[9] as well as the intramolecular Heck coupling of a vinyl triflate with a benzofuran.[10] Further evidence of the electrophilic character of this reaction is the known susceptibility of the 5-position of 3-methylfuroate to electrophilic substitution, for example, bromination.[11]

Table 3. Thiophene Arylations



13 14 15

entry	Ar **6a**, **6g**	method[a]	product (yield)
1	(**6a**) 3-$NO_2C_6H_4$	A	**14a** (67%)
2	(**6a**) 3-$NO_2C_6H_4$	B	
3	(**6a**) 3-$NO_2C_6H_4$	C	**15a** (51%)
			14a (15%)
4	(**6g**) C_6H_5	A	**14g** (52%)

[a] Method A: $Pd(PPh_3)_4$, KOAc, toluene, 110 °C. Method B: Pd/C, KOAc, NMP, 110 °C. Method C: $Pd_2(dba)_3$, KOAc, NMP, 110 °C.

To examine the generality of this reaction further, we proceeded to study the palladium-catalyzed arylation of the corresponding thiophene. The results of the arylation of methyl-3-thiophenecarboxylate are shown in Table 3. The same reactivity trends as the furan case were observed. The nonpolar solvent and phosphine-bound palladium (Method A) afforded the 2-aryl thiophene **14** in high selectivity (entries 1 and 4). While the polar solvent and ligandless palladium catalyst afforded predominantly the 5-aryl adduct **15**, it should be noted that the use of Pd/C as the source of "ligandless palladium" (Method B) was not successful in the thiophene cases, presumably due to poisoning of the heterogeneous catalyst. However, this problem was overcome by switching to the "phosphine-less" homogeneous catalyst $Pd_2(dba)_3$ (Method C, see Table 3, entry 3). Another difference observed with the thiophene substrate is the higher reactivity of the thiophene over that of the furan to arylation with aryl bromides lacking electron-withdrawing groups. Where the attempted arylation of the furan with bromobenzene with Method A was unsuccessful and failed to give any detectable desired product (Table 2, entry 9), the analogous reaction with the thiophene afforded the 2-phenyl adduct **14g** in 52% yield (Table 3, entry 4).

To demonstrate the synthetic utility of the furan arylation described above, we applied the chemistry to the synthesis of the furo[3,2-c]quinolinone **16** as shown in Scheme 3. The furoquinolinone ring system is common in nature, particularly in alkaloids derived from Rutaceae species.[12] These alkaloids

(7) Use of the corresponding aryl iodides or aryl triflates did not lead to any improvement in these reactions, suggesting that the oxidative addition is not the rate-limiting step.

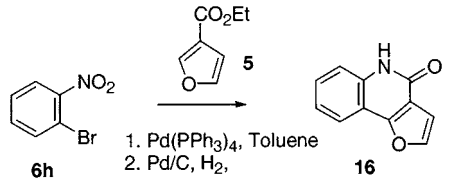
(8) For reviews of the mechanism of the Heck reaction, see: (a) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

(9) Pivsa-Art, S.; Tetsuya, S.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

(10) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569.

(11) Sornay, R.; Meunier, J. M.; Fournari, P. *Bull. Soc. Chim. Fr.* **1971**, 990.

Scheme 3



are also of considerable interest because of their reported biological activities, including antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, and antiarrhythmic.[13] A number of synthetic approaches to the furoquinolinone ring system have been reported;[13] however, we envisaged that the palladium-catalyzed arylation of ethyl 3-furoate described above would lead to a very rapid and efficient synthesis of this ring system. In practice, arylation of ethyl 3-furoate (**5**) with 1-bromo-2-nitrobenzene (**6h**) in the presence of $Pd(PPh_3)_4$ afforded 2-aryl furoate in 80% yield. Hydrogenation of the nitro group with Pd/C as the catalyst and subsequent cyclization occurred uneventfully to provide furo[3,2-c]quinolinone **16** in 75% yield. Thus, two sequential palladium-catalyzed reactions afforded the furoquinolinone in 60% overall yield.

In summary, we have developed a regioselective, palladium-catalyzed arylation of 3-carboxy furan and thiophene, and conditions have been developed that allow the selective formation of either the 2-aryl or 5-aryl isomers in good yields. This method was utilized in an efficient two-step synthesis of furo[3,2-c]quinolinone.

Acknowledgment. We thank Tom O'Connell for assistance with NMR spectroscopy.

Supporting Information Available: Experimental procedures and characterizations for compounds **7a**−**e**, **8a**, **8f**, **14a**, **14g**, **15a**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027266Q

(12) (a) Grundon, M. F. *Nat. Prod. Rep*. **1990**, *7*, 131. (b) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605.

(13) See: Lee, Y. R.; Kim, B. S.; Kweon, H. I. *Tetrahedron* **2000**, *56*, 3867 and references therein.