Palladium-Catalysed Direct Heteroarylations of Heteroaromatics Using Esters as Blocking Groups at C2 of Bromofuran and Bromothiophene Derivatives: A One-Step Access to Biheteroaryls

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Received: 23.04.2012; Accepted after revision: 26.06.2012

Abstract: Methyl 5-bromo-2-furoate and ethyl 5-bromothiophene-2-carboxylate have been found to be useful alternative reagents to 2-halofurans and 2-halothiophenes for the palladium-catalysed direct arylation of heteroaromatics. As their C5 is blocked by ester groups, the use of these substrates prevents the formation of dimers or oligomers, and therefore allows the formation of biheteroaryls in high yields. A very wide variety of heteroaromatics can be coupled with these two reagents. Moreover, with methyl 5-bromo-2-furoate, sequential catalytic C5 arylation, decarboxylation, catalytic C2-arylation reactions allowed the synthesis of 2,5-diarylated furan derivatives.

Key words: methyl 5-bromo-2-furoate, ethyl 5-bromothiophene-2-carboxylate, palladium, direct arylation, heteroaromatics, biheteroaryls

One of the most classical methods to prepare biheteroaryl derivatives is to employ an heteroaryl halide with an organometallic heteroaryl derivative using a palladium catalyst.[1] However, these reactions require the preliminary preparation of organometallic derivatives such as $HetArB(OR)_2$, HetArZnX, HetArMgX, or $HetArSnR_3$ which might be tricky in several cases due to the poor stability of some of these heteroaromatics. Moreover, these couplings provide either an organometallic or a salt (MX) as byproduct.

As several biheteroaryl derivatives such as thiabendazol, lificiguat, or preladenant have been found to present useful bioactivities (Figure 1), we assumed that the discovery of a simpler procedure for the preparation of a large variety of heteroarylated heteroarenes would provide a powerful tool for pharmaceutical researchers.

In recent years, the palladium-catalysed direct arylation of heteroaromatics with aryl halides proved to be an extremely powerful method for the synthesis of arylated heteroaromatics.[2–4] The palladium-catalysed direct heteroarylation at C2 of oxazole, thiazole, or imidazole derivatives with halothiophenes also proceed nicely in several cases.[5] With these reactants the reaction certainly

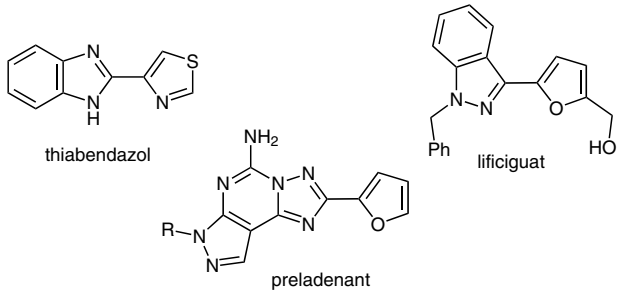

Figure 1

occurs via a base-assisted deprotonation of the azole derivatives followed by arylation.[6] On the other hand, the direct heteroarylation via 'concerted metallation deprotonation' mechanism, using halothiophenes or halofurans has attracted less attention.[7–11] The direct arylation with 5-substituted 2-halofurans or 2-halothiophenes generally gives the coupling products in quite good yields.[7–9] On the other hand, in the presence of unsubstituted 2-halothiophenes, the formation of dimers or oligomers is possible (Scheme 1, top).[10] This might explain the moderate yields obtained for the coupling of 2-bromothiophene with 1,2-dimethylimidazole (45%),[10a] or with 3,4-ethylenedioxythiophene (40%).[10c] To our knowledge, direct heteroarylations using unsubstituted 2-halofurans have not been described. This is certainly due to the limited access to 2-halofurans. Moreover, the low boiling point of 2-bromofuran (52 °C) makes its handling not very convenient.

To our knowledge, direct arylations using 5-bromo-2-furoate or 5-bromothiophene-2-carboxylate have not been reported. The use of these reactants, which are commercially available, would certainly avoid the formation of polyfurans or polythiophenes as side products. Moreover, methyl 5-bromofuroate display a much higher boiling point than 2-bromofuran (181 °C vs. 52 °C), allowing to perform the reaction in classical glassware instead of autoclaves. Finally, the functionalisation of such esters to introduce aryl, vinyl, alkyl, carbonyl, or even sulfide substituents should be possible.[12]

Here, we wish to report on the palladium-catalysed direct arylation of a set of heteroaromatics using esters as block-

SYNLETT 2012, 23, 2077–2082
Advanced online publication: 08.08.2012
DOI: 10.1055/s-0031-1290453; Art ID: ST-2012-D0352-L
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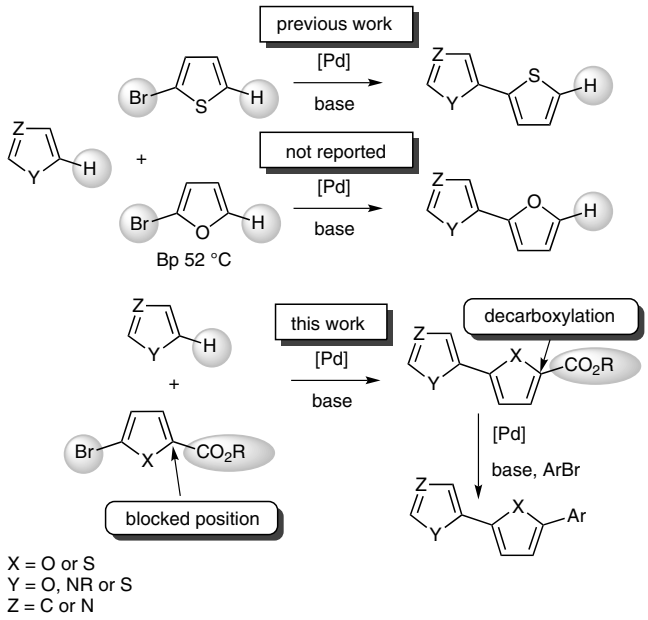
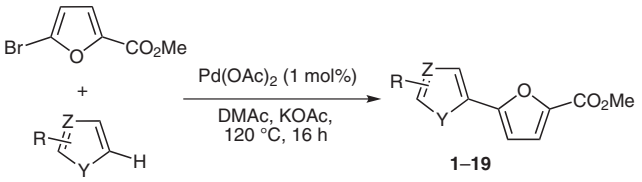


Scheme 1

ing groups in C5 position of 2-bromofuran and 2-bromothiophene derivatives.

First, we examined the reactivity of methyl 5-bromofuroate for the palladium-catalysed direct arylation of 2-isobutylthiazole using 1 mol% $Pd(OAc)_2$ as the catalyst, DMAc as the solvent, and KOAc as the base (Scheme 2, Table 1, entry 1). These conditions had been previously found operative for similar reactions.[4a,d] Using these conditions, a complete conversion of the bromofuran derivative was observed, and the desired coupling product **1** was isolated in 71% yield (Table 1, entry 1). Moreover, no significant amount of decarboxylated product was formed.[12] Then, we extended the scope of the heteroarylation of methyl 5-bromofuroate to a variety of thiophene derivatives. Thiophenes substituted at C2 by methyl, acetyl, protected acetyl, nitrile, or ester gave the C5-heteroarylated furans **2**–**6** in 75–83% yields (Table 1, entries 2–6). Several furan derivatives were also employed successfully to provide 2,2′-bifuranyl derivatives. For example, in the presence of methyl 2-methylfuran-3-carboxylate, the desired product **10** was produced in 84% yield (Table 1, entry 10). The monoarylation of 1-methylpyrrole or 1-phenylpyrrole was also successful, and led to **13** and **14** in 77% and 79% yields, respectively (Table 1, entries 13 and 14). For these two reactions, a larger excess of pyrrole derivative was employed in order to avoid the formation of diheteroarylation products. The heteroarylation at C4 of 3,5-dimethylisoxazole or 1,3,5-trimethylpyrazole gave **17** and **18** in 88% and 91% yields, respectively (Table 1, entries 17 and 18). Finally, a C2-substituted indole derivative was arylated at C3 to provide **19** in 81% yield (Table 1, entry 19).



Scheme 2

Table 1 Palladium-Catalysed Direct Arylation of Heteroarenes with Methyl 5-Bromofuroate (Scheme 2)[a,13]

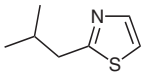
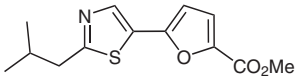
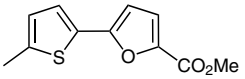
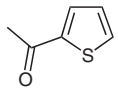
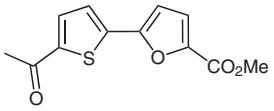
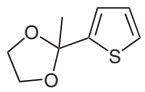
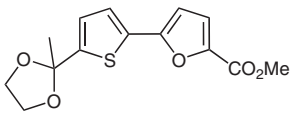
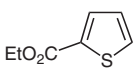
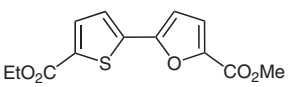
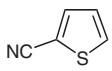
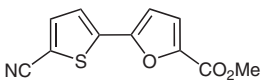
Entry	Heteroarene	Product	Yield (%)[b]
1		**1** 	71
2		**2** 	83
3		**3** 	81
4		**4** 	81
5		**5** 	76
6		**6** 	75

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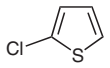
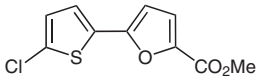
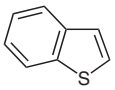
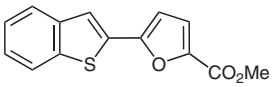
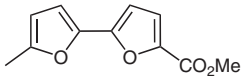
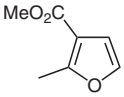
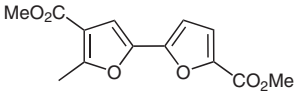
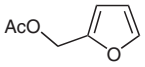
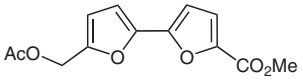
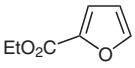
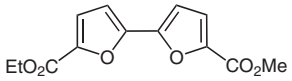
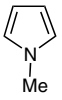
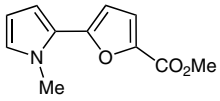
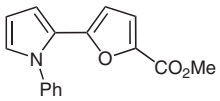
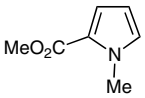
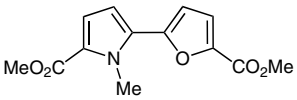
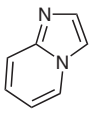
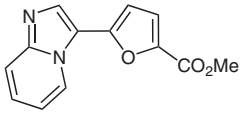
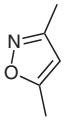
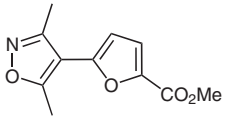
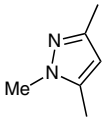
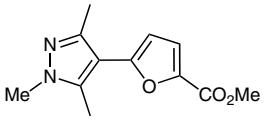
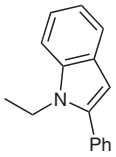
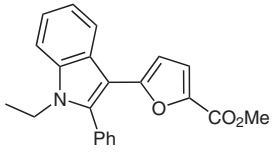
Table 1 Palladium-Catalysed Direct Arylation of Heteroarenes with Methyl 5-Bromofuroate (Scheme 2)[a,13] (continued)

Entry	Heteroarene	Product	Yield (%)[b]
7		**7** 	55
8		**8** 	63
9		**9** 	79
10		**10** 	84
11		**11** 	78
12		**12** 	71
13		**13** 	77[c]
14		**14** 	79[c]
15		**15** 	75
16		**16** 	90
17		**17** 	88
18		**18** 	91
19		**19** 	81

[a] Conditions: $Pd(OAc)_2$ (0.01 mmol), methyl 5-bromofuroate (1 mmol), heteroarene (2 mmol), KOAc (2 mmol), DMAc, 16 h, 120 °C.
[b] Isolated yields.
[c] Pyrrole derivative (4 mmol).

Then, we examined the reaction of methyl 5-bromofuroate with 2,2′-bithiophenyl (Scheme 3). Our objective was to obtain the monoarylated compound **20**. In the course of this reaction, the formation of 5,5′-diarylated 2,2′-bithiophenyl is also possible. However, from one equivalent of methyl 5-bromofuroate and 1.5 equivalents of 2,2′-bithiophenyl in the presence of 2 mol% catalyst, **20**

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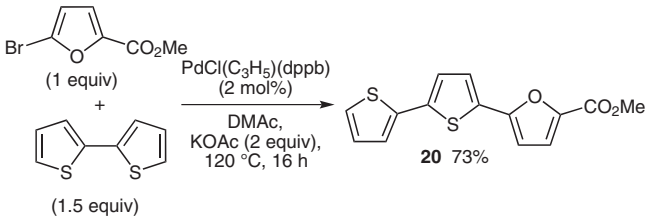
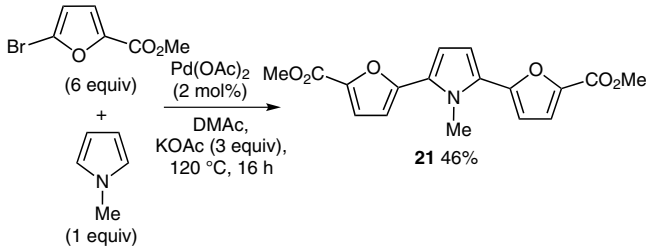
was obtained in 73% yield. Only traces of diarylated 2,2′-bithiophenyl were detected by GC–MS analysis.



Scheme 3

As carbons C2 and C5 of 1-methylpyrrole are much more reactive than positions C3 and C4,[4f] we could expect the formation of the 2,5-diheteroarylated pyrrole in the presence of an excess of methyl 5-bromofuroate as the coupling partner. Indeed, product **21** was obtained in 46% yield using 2 mol% $Pd(OAc)_2$ as the catalyst (Scheme 4).



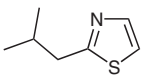
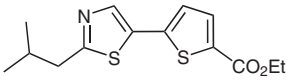
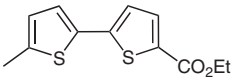
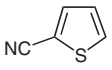
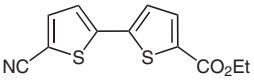
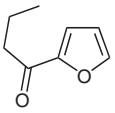
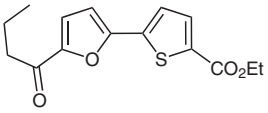
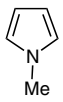
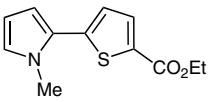
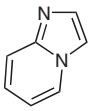
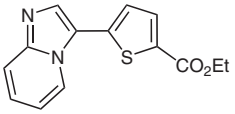
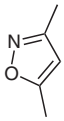
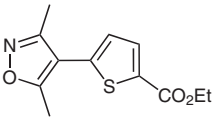
Scheme 4

Next, we studied the coupling of ethyl 5-bromothiophene-2-carboxylate with seven heteroarenes (Scheme 5, Table 2). The reaction with 2-isobutylthiazole gave **22** in a very high yield (Table 2, entry 1). Satisfactory results were also obtained with 2-methylthiophene and thiophene-2-carbonitrile. The desired 2,2′-bithiophenyl derivatives **23** and **24** were obtained in 78% and 61% yields, respectively. A moderate yield for **25** was obtained in the presence of 1-(furan-2-yl)butan-1-one, due to the formation of side products (Table 2, entry 4). Again, the use of a large excess of 1-methylpyrrole allowed the synthesis of the monoarylated pyrrole **26** in good yield (Table 2, entry 5). Finally, both imidazo[1,2-*a*]pyridine and 3,5-dimethylisoxazole were employed. In both cases, very high yields of the desired coupling products **27** and **28** were obtained (Table 2, entries 6 and 7). It should be noted that, in all cases, no significant decarboxylation of the thiophene derivatives occurred in the course of these reactions.

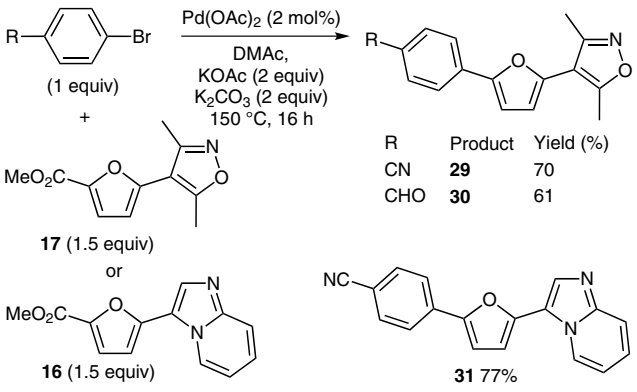
Finally, we examined the functionalisation of carbon C2 by decarboxylative coupling of some of our 5-heteroaryl-2-furoates.[12,14,15] We observed that the treatment of **17** by KOAc and K_2CO_3 as bases at 150 °C in the presence of 4-bromobenzonitrile or 4-bromobenzaldehyde gave the coupling products **29** and **30** in 70% and 61% yields, respectively. Using the same conditions, the reaction of **16** with 4-bromobenzonitrile led to **31** in 77% yield (Scheme 6).

Scheme 5

Table 2 Palladium-Catalysed Direct Arylation of Heteroarenes with Ethyl 5-Bromothiophene-2-carboxylate (Scheme 5)[a,13]

Entry	Heteroarene	Product	Yield (%)[b]
1		**22** 	92
2		**23** 	78
3		**24** 	61
4		**25** 	52
5		**26** 	75[c]
6		**27** 	87
7		**28** 	90

[a] Conditions: $Pd(OAc)_2$ (0.01 mmol), ethyl 5-bromothiophene-2-carboxylate (1 mmol), heteroarene (2 mmol), KOAc (2 mmol), DMAc, 16 h, 120 °C.
[b] Isolated yields.
[c] Pyrrole derivative (4 mmol).



Scheme 6

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In summary, we have demonstrated that the ester group can be advantageously employed as blocking group on some heteroaryl bromides in the course of the direct heteroarylation. Both methyl 5-bromofuroate and ethyl 5-bromothiophene-2-carboxylate, using 1 mol% $Pd(OAc)_2$ as the catalyst with KOAc as the base and DMAc as the solvent at 120 °C generally led to high yields of the biheteroaryl derivatives. Under these conditions, only traces of in situ decarboxylation products were observed. Methyl 5-bromofuroate represents an alternative reagent to 2-bromofuran which is not easily accessible and difficult to handle. In the presence of $KOAc/K_2CO_3$ as bases at 150 °C, the decarboxylation of this furoate is possible. This was demonstrated by its sequential catalytic C5 arylation, decarboxylation, and catalytic C2 arylation. This procedure is economically attractive as both methyl 5-bromofuroate and ethyl thiophene-2-carboxylate are commercially available. Another advantage is the reduction of number of steps to prepare these bi- or polyheteroaryls.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Typical Experiment for the Synthesis of Products 1–19 and 22–28**
The reaction of the heteroaryl bromide (1 mmol), heteroarene (2 mmol), and KOAc (0.196 g, 2 mmol) at 120 °C during 16 h in DMAc (4 mL) with $Pd(OAc)_2$ (2.24

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mg, 0.01 mmol), under argon affords the coupling product after evaporation of the solvent and purification on silica gel.

Methyl 5-(2-Isobutylthiazol-5-yl)-furan-2-carboxylate (1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1 H), 7.14 (d, *J* = 2.3 Hz, 1 H), 6.50 (d, *J* = 2.3 Hz, 1 H), 3.84 (s, 3 H), 2.81 (d, *J* = 7.7 Hz, 2 H), 2.10–2.00 (m, 1 H), 0.94 (d, *J* = 7.7 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 158.8, 150.3, 143.7, 139.8, 126.7, 119.9, 108.3, 52.0, 42.4, 29.8, 22.2. Anal. Calcd (%) for $C_{13}H_{15}NO_3S$ (265.33): C, 58.85; H, 5.70. Found: C, 58.99; H, 5.57.

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(15) **Typical Experiment for the Synthesis of Products 29–31**

The reaction of the heteroaryl bromide (1 mmol), heteroarene (1.5 mmol), KOAc (0.196 g, 2 mmol), and K_2CO_3 (0.276 g, 2 mmol) at 150 °C during 16 h in DMAc (4 mL) with $Pd(OAc)_2$ (4.48 mg, 0.02 mmol), under argon affords the coupling product after evaporation of the solvent and purification on silica gel.

4-[5-(3,5-Dimethylisoxazol-4-yl)-furan-2-yl]benzonitrile (29)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.2 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 2 H), 6.84 (d, *J* = 2.7 Hz, 1 H), 6.43 (d, *J* = 2.7 Hz, 1 H), 2.60 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 157.5, 151.1, 146.9, 134.2, 132.7, 123.7, 118.9, 110.4, 109.7, 109.0, 108.0, 12.7, 11.8. Anal. Calcd (%) for $C_{16}H_{12}N_2O_2$ (264.28): C, 72.72; H, 4.58. Found: C, 72.57; H, 4.40.

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