Synthesis of 2-(2-Arylethenyl)-5-arylfurans by Regioselective Palladium(0)-Catalyzed Coupling Reactions of 2-(2-Bromo-2-nitroethenyl)-5-bromofuran

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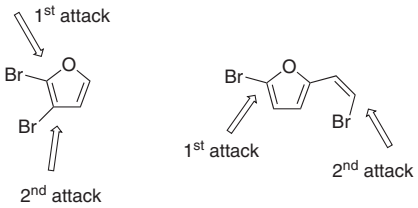
Abstract: The Suzuki reaction of 2-(2-bromo-2-nitroethenyl)-5-bromofuran, readily available from furfural, resulted in regioselective attack onto the furan moiety. The alkenyl moiety could be functionalized in a second Suzuki reaction.

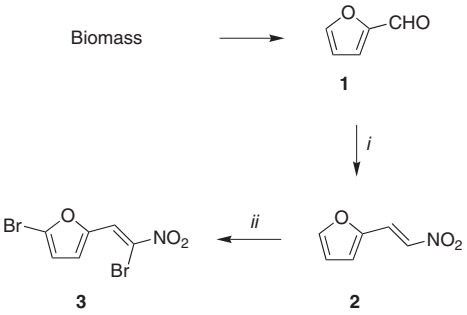
Key words: catalysis, furans, green chemistry, heterocycles, palladium, regioselectivity

Furans are of considerable pharmacological relevance and occur in a variety of natural products.[1,2] A number of synthetic approaches to furans have been reported.[2–9] Bach and coworkers reported an interesting approach to 2,3-disubstituted furans by regioselective palladium(0)-catalyzed coupling reactions of 2,3-dibromofurans.[10] The success of these transformations relies on the fact that the oxidative addition of the palladium(0) complex onto carbon atom C-2 of the furan is faster than onto C-3 (Scheme 1).[11] Herein, we wish to report what are, to the best of our knowledge, the first regioselective palladium(0)-catalyzed coupling reactions of 2-(2-bromoalkenyl)-5-bromofurans which contain both a furyl and an alkenyl bromide function (Scheme 1). These reactions should be of considerable interest, since the starting materials are readily available and the products are pharmacologically relevant and represent useful intermediates for further synthetic transformations (e.g. electrocyclic ring-closure reactions).[12]



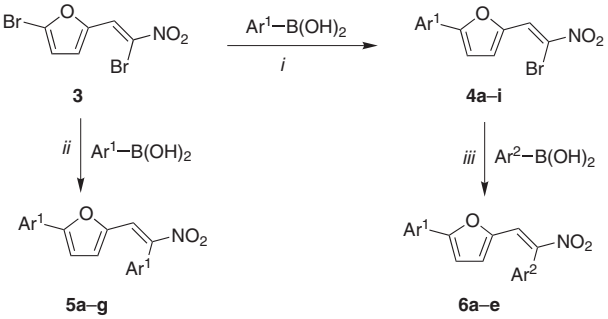
Scheme 1 Regioselectivity of palladium(0)-catalyzed coupling reactions.

As a starting point for our studies we chose (*Z*)-2-(2-bromo-2-nitroethenyl)-5-bromofuran (**3**) which is readily available by Henry reaction of furfural with nitromethane and subsequent bromination (Scheme 2).[13] It has been shown that compound **3** possesses interesting biological activity and its derivatization is, therefore, of considerable interest.[13e] Furfural represents an inexpensive, green starting material which is produced in large scale by acid-mediated hydrolysis of plant-derived polysaccharides (sustainable development).



Scheme 2 Synthesis of (*Z*)-2-(2-bromo-2-nitroethenyl)-5-bromofuran (**3**). *Reagents and conditions*: *i*, CH_3NO_2, NaOH, H_2O; *i*, 1) Br_2, AcOH; 2) pyridine.

The Suzuki reaction of **3** (1.2 equiv) with various boronic acids (1.0 equiv) resulted in regioselective coupling of the furan rather than the alkenyl moiety to give the 2-(2-bromo-2-nitroethenyl)-5-arylfurans **4a–i** (Scheme 3).[14] The reaction proceeded without *E*/*Z*-isomerization of the dou-



Scheme 3 Suzuki reactions of **3**. *Reagents and conditions*: *i*, **3** (1.2 equiv), $Ar^1B(OH)_2$ (1.0 equiv), $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (2.0 equiv), solvent (see Table 1); *ii*, **3** (1.0 equiv), $Ar^1B(OH)_2$ (2.0 equiv), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (4.0 equiv), solvent (see Table 2); *iii*, **4a–i** (1.0 equiv), $Ar^2B(OH)_2$ (1.0 equiv), $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (2.0 equiv), solvent (see Table 3).

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Table 1 Synthesis of 2-(2-Bromo-2-nitroethenyl)-5-arylfurans **4a–i**

Entry	**4**	Ar[1]	Solvent–H_2O (6:1)	Temp (°C)	Yield of **4** (%)[a]
1	**a**	Ph	Toluene	90	90
2	**a**	Ph	Toluene	20	76
3	**a**	Ph	THF	20	73
4	**a**	Ph	1,4-Dioxane[b]	90	70
5	**a**	Ph	1,4-Dioxane	90	78
6	**b**	4-(HO)C_6H_4	1,4-Dioxane	90	83
7	**b**	4-(MeO)C_6H_4	1,4-Dioxane	90	69
8	**b**	4-(MeO)C_6H_4	Toluene	90	38
9	**c**	4-(MeO)C_6H_4	1,4-Dioxane	90	64
10	**d**	3,5-$Me_2C_6H_3$	Toluene	90	93
11	**d**	3,5-$Me_2C_6H_3$	1,4-Dioxane	90	56
12	**e**	4-(EtO)C_6H_4	1,4-Dioxane	90	67
13	**f**	1-Naphthyl	1,4-Dioxane	90	52
14	**f**	1-Naphthyl	Toluene	90	75
15	**g**	3,4,5-$(MeO)_3C_6H_2$	1,4-Dioxane	90	77
16	**h**	2-Thienyl	1,4-Dioxane	90	87
17	**i**	4-MeC_6H_4	Toluene	90	84

[a] Isolated yields.
[b] Without addition of H_2O.

ble bond. The structure and configuration of the products was proved by spectroscopic methods and by X-ray crystal structure analyses. During the optimization, the stoichiometry, temperature, solvent, and the presence of water played an important role (Table 1). The reaction of **3** (1.0 equiv) with 2.0 equivalents of boronic acids resulted in double coupling and formation of the 2-(2-aryl-2-nitroethenyl)-5-arylfurans **5a–g** containing two identical aryl groups (Table 2). The Suzuki reaction of **4a** (1.0 equiv) with various arylboronic acids (1.0 equiv) allowed the synthesis of 2-(2-aryl-2-nitroethenyl)-5-phenylfurans **6a–e**, which contain two different aryl groups (Table 3). The formation of **5a–g** and **6a–e** proceeded, as expected for Suzuki reactions, without *E*/*Z*-isomerization of the double bond.

Table 2 Synthesis of 2-(2-Aryl-2-nitroethenyl)-5-arylfurans **5a–g**

5	Ar[1]	Solvent–H_2O (6:1)	Yield of **5** (%)[a]
a	Ph	Toluene	67
b	4-(MeO)C_6H_4	1,4-Dioxane	69
c	2-(MeO)C_6H_4	1,4-Dioxane	64
d	3,5-$Me_2C_6H_3$	1,4-Dioxane	86
e	4-(EtO)C_6H_4	Toluene	87
f	4-MeC_6H_4	Toluene	82
g	2-Thienyl	1,4-Dioxane	42

[a] Isolated yields (all reactions were carried out at 90 °C).

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Table 3 Synthesis of 2-(2-Aryl-2-nitroethenyl)-5-arylfurans **6a–e**

6	Ar[1]	Ar[2]	Solvent–H_2O (6:1)	Yield of **6** (%)[a]
a	Ph	1-Naphthyl	Toluene	63
b	Ph	3,5-$Me_2C_6H_3$	Toluene	74
c	Ph	4-MeC_6H_4	Toluene	79
d	Ph	4-(MeO)C_6H_4	1,4-Dioxane	75
e	Ph	2-Thienyl	Toluene	57

[a] Isolated yields (all reactions were carried out at 90 °C).

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(14) **General Procedure for the Synthesis of 2-(2-Bromo-2-nitroethenyl)-5-arylfurans 4a–i.**
To a toluene solution (3 mL) of **3** (0.356 g, 1.2 mmol) was added $Pd(PPh_3)_4$ (0.042 g, 3 mol%) at 20 °C. After stirring for 30 min, the arylboronic acid (1.0 mmol), K_3PO_4 (2.0 mmol) and H_2O (0.5 mL) were added. The mixture was stirred at 90 °C for 8 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite® pad. The solution was concentrated in vacuo and the residue was purified by column chromatography (silica gel, *n*-heptane–EtOAc = 20:1 to 5:1).
Synthesis of 2-[(*Z*)-2-bromo-2-nitrovinyl]-5-(4-ethoxyphenyl)furan (4e).
Starting with **3** (0.356 g, 1.2 mmol) and (4-ethoxyphenyl)boronic acid (1.0 mmol), **4e** was isolated (0.226 g, 67%) as a red solid; mp 127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, ^3J = 7.2 Hz, 3 H, CH_3), 4.05 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH_3), 6.76 (d, ^3J = 3.8 Hz, 1 H, furan), 6.92 (d, ^3J = 8.7 Hz, 2 H, Ar), 7.38 (d, ^3J = 3.8 Hz, 1 H, furan), 6.92 (d, ^3J = 8.7 Hz, 2 H, Ar), 8.53 (s, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (CH_2CH_3), 63.6 (OCH_2CH_3), 107.7 (CH), 115.1, 115.1, 126.8, 126.8 (CH, Ar), 124.2, 124.6 (CH, furan), 122.2, 123.9, 145.7, 159.9, 161.1 (C). IR (KBr): 3432 (m), 3050 (m), 2971 (w), 1603 (s), 1599 (s), 1467 (s), 1280 (s), 1235 (s), 1177 (s), 1035 (s), 964 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 339 (30) [M^+, ^{81}Br], 337 (31) [M^+, ^{79}Br], 258 (100), 227 (10), 212 (23), 184 (37), 183 (29), 155 (17), 131 (22), 77 (8), 69 (11). HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_{12}O_4NBr$ [M^+, ^{79}Br]: 336.9944; found: 336.9939. All products gave satisfactory spectroscopic data and correct elemental analyses and/or high-resolution mass data.