2,3-Disubstituted and 2,3,5-Trisubstituted Benzofurans by Regioselective Pd-Catalyzed Cross-coupling Reactions; a Short Synthesis of Eupomatenoid-15

Thorsten Bach,* Marc Bartels

Lehrstuhl für Organische Chemie I, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany
Fax +49(0)89/28913315; E-mail: thorsten.bach@ch.tum.de

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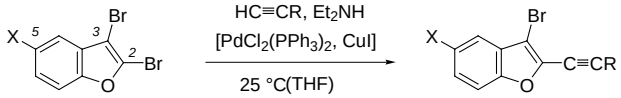
Abstract: 2,3-Dibromobenzofuran (**1**) and 2,3,5-tribromobenzofuran (**2**) undergo regioselective Sonogashira- and Negishi-type cross-coupling reactions at the 2-position. Subsequent substitution reactions at C-3 are possible for the cross-coupling products obtained from compound **1**. A regioselective functionalization of the 3,5-dibromobenzofurans derived from substrate **2** was achieved by an halogen-metal exchange which occurred selectively at the 3-position. In a conclusive reaction step cross-coupling reactions at C-5 were used to build up 2,3,5-trisubstituted benzofurans. As an example, the synthesis of eupomatenoid-15 (**8**) is described.

Key words: catalysis, cross-coupling, heterocycles, palladium, regioselectivity

Multi-substituted benzo[b]furan (benzofuran) rings are structural motifs found in many interesting biologically active compounds.[1] Synthetic efforts to access benzofurans have been centered both on ring closure reactions and on substitution reactions which occur at the preformed benzofuran nucleus.[2] Electrophilic aromatic substitution and metalation reactions are known to occur regioselectively at the 2-position.[2] The regioselectivity of reactions in which other atoms than hydrogen are substituted have been studied scarcely.[3,4] In connection with our studies on regioselective Pd-catalyzed cross-coupling reactions of five-membered furans[5] and thiazoles[6] we became interested in the analogous reactions of dibromo- and tribromo-substituted benzofurans. We now report our preliminary results in this area. It was found that an initial Pd-catalyzed cross-coupling occurs preferentially at the 2-position and that successive Pd- or Ni-catalyzed reactions at less reactive positions are possible. For the differentiation of the 3- vs. the 5-position a halogen-metal exchange at low temperature proved more selective than a Pd- or Ni-catalyzed process. The methodology was applied to a short synthesis of the naturally occurring 2-(4'-methoxyphenyl)-3-methyl-5-(*E*)-propenylbenzofuran (eupomatenoid-15).[7]

2,3-Dibromobenzofuran[4] (**1**) and 2,3,5-tribromobenzofuran[4,8] (**2**) are readily accessible starting materials which were used in our preliminary studies. If successful, consecutive cross-coupling reactions should lead to 2,3-disubstituted and 2,3,5-trisubstituted benzofurans. An all-carbon 2,3,5-trisubstitution pattern appeared particularly interesting as it is found in several biologically relevant benzofurans, e.g. in the lignans isolated from *Eupomatia laurina* and *Eupomatia bennettii* (eupomatenoids).[7,9,10] We were pleased to find that the Sonogashira-type cross-coupling[11] with both substrates **1** and **2** proceeded smoothly and with high regioselectivity (Scheme 1, Table). Modified conditions were used according to which a slight excess (1.5 equiv.) of diethylamine was employed in THF as the solvent.[12,13] Triethylamine was not suitable as a base in this procedure.



1 X = H **3**
2 X = Br **4**

Scheme 1

Table Regioselective Sonogashira Cross-coupling of Various Alkynes and Benzofurans **1** and **2**[13]

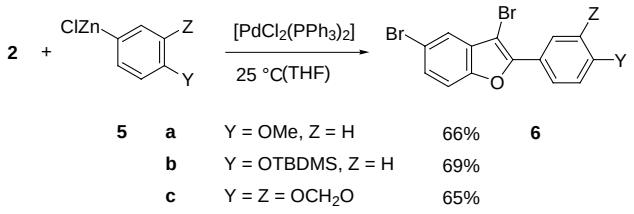
Entry	Substrate	X	R	Product	Yield[a] [%]
1	**1**	H	*t*-Bu	**3a**	78
2	**2**	Br	*t*-Bu	**4a**	78
3	**1**	H	Ph	**3b**	88
4	**2**	Br	Ph	**4b**	76
5	**1**	H	CH_2CH_2OH	**3c**	76
6	**2**	Br	CH_2CH_2OH	**4c**	91
7	**1**	H	CH_2OMe	**3d**	50
8	**2**	Br	CH_2OMe	**4d**	45
9	**1**	H	$SiMe_3$	**3e**	68
10	**1**	H	CH_2OH	**3f**	78

[a] Yield of isolated product after purification by flash chromatography

In general, the 2-substituted products **3** and **4** were the sole substitution products isolated. No regioisomers were observed. The comparably low yield in the reaction with propargyl methyl ether (entries 7 and 8) did not come as a surprise. This substrate had proved to be problematic in previous cross-coupling reactions.[5] Extensive hydro-debromination and homo coupling were observed.

In a second set of experiments, aryl zinc compounds were treated with benzofurans **1** and **2**. Negishi coupling[14] of these substrates proved equally regioselective. As an

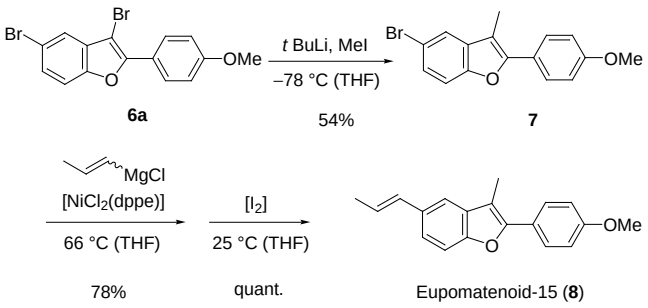
example, three reactions of the tribromo-substituted arene **2** are depicted in Scheme 2. The aryl zinc chloride **5** was prepared from the corresponding bromide by halogen-metal exchange (2.1. equiv. *tert*-BuLi, −78 °C, THF) and subsequent transmetalation (1 equiv. $ZnCl_2$, −78 °C → r.t., THF).



Scheme 2

Attempts to differentiate between the 3- and 5-position of 3,5-dibromobenzofurans **4** and **6** by a Pd-catalyzed cross-coupling remained unsuccessful so far. In reactions conducted with MeZnCl and benzofuran **6a** under more drastic condition we observed product mixtures. In the course of these studies conditions were discovered which allowed for a complete two-fold methyl-debromination of compound **6a** [6 equiv. MeZnCl, 0.1 equiv. $PdCl_2$(dppf), THF, reflux, 18 h]. In addition, methyl-debromination reactions of compounds **3** at the 3-position were achieved by cross-coupling with MeZnCl.

The halogen-metal exchange reaction[15] which can be carried out at much lower temperature than any cross-coupling was considered a viable alternative for the selective substitution of one bromine atom in compounds **6**. Indeed, treatment of benzofuran **6a** with *tert*-butyl lithium at −78 °C and subsequent quenching with water gave the hydrodebrominated products in a ratio of 4:1. The preferential position at which the bromine-lithium exchange had taken place was the 3-position and the major isomer consequently was the 2-aryl-5-bromobenzofuran. Quenching with methyl iodide was less selective presumably because an equilibration takes place prior to the methylation. Still, we succeeded in isolating the desired major product 3-methylbenzofuran **7** in 54% yield (Scheme 3). In order to convert this 5-bromobenzofuran into the natural product eupomatenoid-15 (**8**) a final substitution at the 5-position was required. Some optimization revealed that the Ni-catalyzed cross-coupling of propenyl magnesium chloride was a reliable and high-yielding method for the desired transformation. As the Grignard reagent we used was not stereochemically pure, a subsequent equilibration[10] was necessary to establish the correct *E*-configuration of the product. The total yield of eupomatenoid-15[16] starting from the readily available 2,3,5-tribromobenzofuran **2** amounted to 27%.



Scheme 3

Further studies are under way to prove the general applicability of this route for the synthesis of 2,3,5-trisubstituted benzofurans. In addition, we continue to study cross-coupling reactions which may lead to a differentiation of the 3- vs 5-position in compounds **6**. Results of these studies will be reported in due course.

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(13) Represenative procedure: 2,3-Dibromobenzofuran (2.0 mmol, 552 mg), copper iodide (0.2 mmol, 38 mg) and $PdCl_2(PPh_3)_2$ (0.1 mmol, 70 mg) were dissolved in 10 mL of THF. *N,N*-Diethylamine (3.0 mmol, 220 mg, 0.31 mL) was added to the stirred mixture at room temperature. A solution of *tert*-butylacetylene (3.0 mmol, 246 mg) in 5 mL of THF was then added within 1 h by syringe. The reaction mixture was stirred for another 17 h at ambient temperature. Diethylether (20 mL) was added and the solution was washed with 0.1% aqueous hydrochloric acid (3 × 10 mL) and once with brine (10 mL). The solvent was evaporated and the residue was purified by column chromatography (eluent: pentane). 432 mg of compound **3a** (78%) were obtained. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.32 (s, 9 H), 7.18-7.42 (m, 4 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.5 (s), 30.5 (q), 68.3 (s), 102.0 (d), 109.1 (s), 111.3 (d), 119.7 (d), 123.6 (d), 126.2 (d), 127.6 (s), 137.7 (s), 153.3 (s).

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(16) ^{1}H NMR ($CDCl_3$, 250 MHz) data of compound **8**: δ = 1.91 (dd, *J* = 6.4 Hz, *J* = 1.8 Hz, 3 H), 2.43 (s, 3 H), 3.87 (s, 3 H), 6.24 (dq, *J* = 15.9 Hz, *J* = 6.4 Hz, 1 H), 6.52 (dq, *J* = 15.9 Hz, *J* = 1.8 Hz; 1 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 7.28 (dd, *J* = 8.5 Hz, *J* = 1.5 Hz, 1 H), 7.37 (d, *J* = 8.5 Hz, 1 H), 7.44 (d, *J* = 1.5 Hz, 1 H), 7.74 (d, *J* = 8.8 Hz, 2 H).

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