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Synthesis of eupomatenoids by three consecutive transition metal-catalyzed cross-coupling reactions

Thorsten Bach* and Marc Bartels

Lehrstuhl für Organische Chemie I, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany

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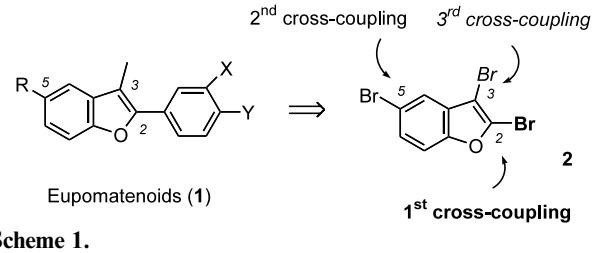
Abstract—Six different eupomatenoids (**1a–c**, **1f–h**) were prepared from 2,3,5-tribromobenzofuran (**2**) in a concise and high-yielding synthetic sequence. The overall yields vary between 29 and 60% over four to six steps. Key to the success of the syntheses is the high regioselectivity achieved in three Pd(0)- and Ni(0)-catalyzed cross-coupling reactions which were conducted consecutively. The order of substitution at the benzofuran nucleus is C-2, C-5 and C-3. © 2002 Elsevier Science Ltd. All rights reserved.

Multiply substituted benzofurans represent an interesting class of heterocycles which are intensively studied in connection with a variety of applications.[1] The benzofuran nucleus is a well known pharmacophore[2] which has been decorated with functional groups and other non-functional substituents by appropriate substitutions. Among the naturally occurring benzofurans, the eupomatenoids form a diversified class of neolignans.[3] They have been isolated originally from two plant species which belong to the archaic angiosperm family Eupomatiaceae. Structurally, the eupomatenoids (**1**) are characterized by a 2,3,5-substitution pattern with an aryl substituent in the 2-position, a methyl substituent in the 3-position and a C_3-substituent R in the 5-position (Scheme 1). Our synthetic approach[4] to these trisubstituted benzofurans is based on regioselective transition metal-catalyzed cross-coupling reactions[5] which we hoped to achieve on the easily available 2,3,5-tribromobenzofuran (**2**).[6]

In particular, we envisaged that three C–C-bond forming reactions could be consecutively conducted at the heterocyclic scaffold. To the best of our knowledge this extent of cross-coupling selectivity has not yet been achieved in heterocyclic chemistry. Based on previous results obtained with thiophenes,[5b,7] benzothiophenes,[8] furans,[5b,9] and benzofurans[10] a cross-coupling with a variety of aryl zinc reagents, however, appeared possible at the position C-2. For steric reasons a second cross-coupling was expected to occur at the more accessible position C-5 and a final cross-coupling at C-3 should conclude the sequence of events (Scheme 1). We now report that this strategy is indeed feasible and it paves the way to a general synthesis of eupomatenoids and other 2,3,5-trisubstituted benzofurans.



Scheme 1.

The key observation which finally led to the successful implementation of our strategy was made with benzofuran **3a** which has been previously synthesized from 2,3,5-tribromobenzofuran employing a regioselective cross-coupling reaction.[10] Careful experimentation revealed that the cross-coupling of Grignard reagents at C-5 is possible under Ni(0)-catalysis (Kumada cross-coupling). $NiCl_2$(dppe) [dppe = 1,2-bis(diphenylphosphino)-ethane] turned out to be the catalyst of choice.[11]

The required 1-propenyl group was successfully installed by this method (Scheme 2).[†] Benzofuran **4a**

* Corresponding author. Tel.: +49-89-28913330; fax: +49-89-28913315; e-mail: thorsten.bach@ch.tum.de

[†] Representative experimental procedure: 1.24 mL of a 0.5 M solution of 1-propenyl magnesium bromide in THF (0.62 mmol) were added to a solution of 200 mg (0.41 mmol) 3,5-dibromobenzofuran **3e** and 22.0 mg (0.04 mmol) 1,2-bis(diphenylphosphino)ethane nickel(II)-chloride in 5 mL of THF at rt. The reaction mixture was stirred for 18 h at rt and subsequently quenched with 7 mL of water. After extraction with ether the combined organic layers were washed with 10 mL of brine and dried over sodium sulfate. Filtration, evaporation and further purification by flash chromatography (silica gel, pentane) afforded 147 mg (0.33 mmol, 80%) of compound **4e** as a mixture of (*E*)- and (*Z*)-isomers.

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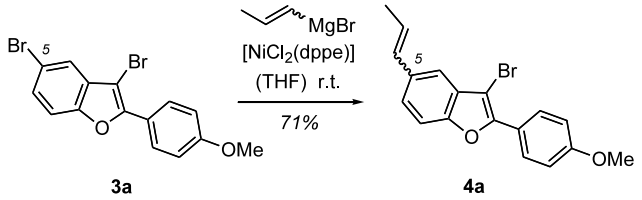


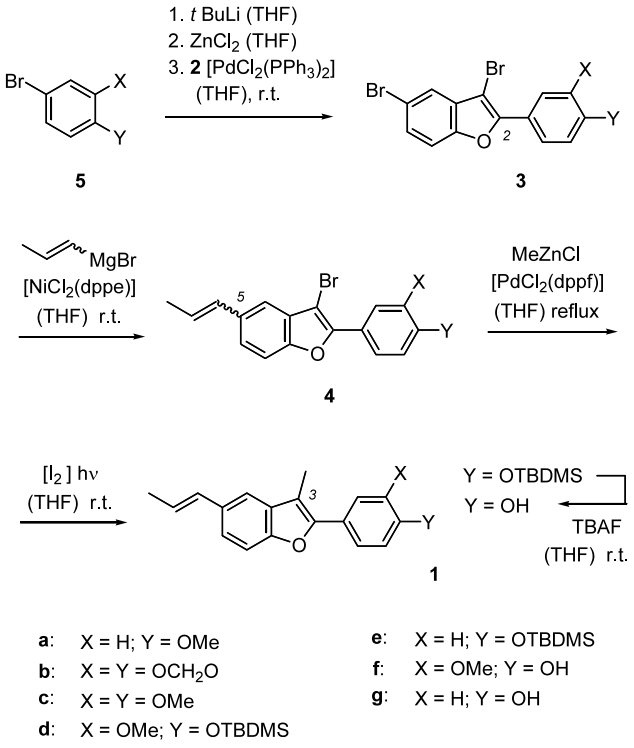
Scheme 2.

was obtained in 71% yield as a mixture of (*E*)/(*Z*)-diastereomers. Many alternative cross-coupling variants which we performed did not produce any cross-coupling products or proceeded unselectively. The position of the cross-coupling is clearly indicated by significant changes in the ^{13}C NMR data. The signal for the C-5 carbon atom which occurred at 116.5 ppm for compound **3a** is shifted to 133.2/133.8 ppm for the two diastereomers **4a**. The signal for carbon atom C-3 is not affected (**3a**: 91.0 ppm; **4a**: 92.2 ppm).

The methyl-debromination at the least reactive position C-3 was expected to be possible by a Negishi cross-coupling with $PdCl_2(dppf)$[12] [dppf = 1,2-bis(diphenylphosphino)ferrocene] as the catalyst. Indeed, this reaction worked nicely for compound **4a** (87% yield)‡ and enabled us to introduce the third substituent onto the benzofuran nucleus. Upon double bond equilibration with iodine,[4d] the (*E*)-configurated eupomatenoid-15 (**1a**) was obtained in a total yield of 46% starting from tribromobenzofuran **2** and commercially available bromide **5a** (Scheme 3, Table 1, entry 1). In an analogous fashion eupomatenoids-3 (**1b**) and -4 (**1c**) were prepared from the corresponding aryl bromides **5b**[13] and **5c** (Scheme 3, Table 1, entries 2 and 3).

Eupomatenoids-5 (**1f**) and -6 (**1g**) which are phenols require appropriate protection in the course of their synthesis. Initial attempts with the *i*-propyl group were hampered by the instability of the eupomatenoid double bond upon Lewis-acid promoted deprotection. The TBDMS group proved to be a reliable alternative.[14] It remained intact in the course of the cross-coupling reactions and was readily removed in a subsequent step. As starting compounds the bromides **5d**[15] and **5e** were

‡ Representative experimental procedure: 1.54 mL of a 0.5 M solution of zinc chloride in THF (0.77 mmol) were added to 0.55 mL of a 1.16 M solution of methyl lithium (0.64 mmol) in diethylether at −78°C and stirred for 10 min. The cooling bath was removed and the solution was warmed to rt. This solution was added to a mixture of 95 mg (0.21 mmol) 3-bromobenzofuran **4e** and 15 mg bis(diphenylphosphino)ferrocene palladium(II)-chloride (0.02 mmol) in 5 mL of THF which was then heated to reflux for 3 h. After cooling to rt 10 mL of water were added. After extraction with ether the combined organic layers were washed with brine (10 mL) and dried over sodium sulfate. Filtration, evaporation and further purification by flash chromatography (silica gel, pentane) afforded 61 mg (0.16 mmol, 77%) of compound **1e** as a mixture of (*E*)- and (*Z*)-isomers.

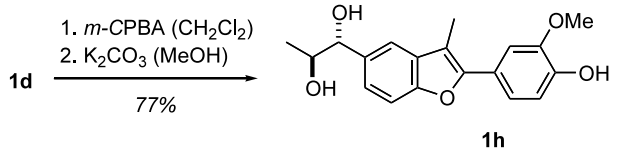


Scheme 3.

Table 1. Yields of the individual steps in the cross-coupling of 2,3,5-tribromobenzofuran (**2**) and organometallic reagents (cf. Scheme 3)

Entry	Bromide	Yield **3**[a] (%)	Yield **4**[a,b] (%)	Yield **1**[a,c] (%)
1	**5a**	75	71	87
2	**5b**	65	69	64
3	**5c**	75	86	93
4	**5d**	80	89	72
5	**5e**	88	80	77

[a] Yield of isolated product.
[b] For a typical procedure see footnote †.
[c] For a typical procedure see footnote ‡.



Scheme 4.

employed. The removal of the silyl group was induced by tetrabutylammonium fluoride (TBAF) in THF and proceeded quantitatively. By this means the target compounds **1f** and **1g** were obtained from the silyl ethers **1d** and **1e** (Scheme 3, Table 1, entries 4 and 5).

The 5-(1-propenyl)-substituted eupomatenoids **1a–e** represent useful starting materials for other eupo-

matenoids with a C_3-substituent at position C-5. As an example, we prepared the racemic *trans*-diol eupomatenoid-9 (**1h**) from intermediate **1d** (Scheme 4). In analogy to a known semi-synthetic procedure,[3b] the alkene was converted into the monoacylated diol by treatment with *m*-CPBA and concomitant ring opening by *m*-chlorobenzoic acid (89%). Upon cleavage of the *m*-chlorobenzoate with K_2CO_3 the silyl protective group was simultaneously removed (86%) and the desired product **1h** was obtained.

In summary, we have established a short and efficient synthesis of 2,3,5-trisubstituted benzofurans by three consecutive cross-coupling reactions. The applicability of the method was exemplified by the preparation of various naturally occurring eupomatenoids but it is expected to be also useful for the synthesis of other benzofurans.

Acknowledgements

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