



Multisubstituted benzo[*b*]furans through a copper- and/or palladium-catalyzed assembly and functionalization process



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ABSTRACT

Full details as well as the study of the scope, limitations, and further elaboration of a straightforward approach to the synthesis of 2,5,7-trisubstituted benzo[*b*]furans from 2-bromo- and 2-chloro-6-iodo-4-substituted phenols through a consecutive copper- and/or palladium-catalyzed assembly and functionalization process is described. Functionalization at the C(7) position is carried out by Suzuki–Miyaura cross-coupling, alkynylation, alkenylation, and C–N bond forming reactions. A one-pot protocol for the synthesis of 2,5,7-trisubstituted benzo[*b*]furans is also reported.

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1. Introduction

The development of methods for the construction of fused furan ring systems is of current interest.¹ This interest is stimulated by the identification of the benzofuran scaffold as a 'privileged structure' in medicinal chemistry.² Benzo[*b*]furans have been isolated from different medicinal plants and they were the subject of various investigations related to their therapeutic potential.³ Members of this class of compounds have shown biological activities ranging from anti-inflammatory, anti-arrhythmic, hemostatic, antifungal, and antimicrobial, to anti-viral, anti-tumor, and anti-oxidant activities and antagonists for the H₃ receptor and angiotensin II.⁴ Some of them are promising drugs against Parkinson's⁵ and Alzheimer's disease.⁶ Thus, these compounds are promising for discovery of new leads via pharmacophore modeling and QSAR analysis.⁷ A variety of methods have been developed to prepare specific structures characterized by given pharmacological qualities. A sulfated benzofuran library of 15 sulfated monomers and 13 sulfated dimers with different charged, polar, and hydrophobic substituents was studied as the first examples of potent, small allosteric inhibitors of thrombin.⁸ A novel series of 2,5,7-

trisubstituted benzofuran AChE inhibitors with significant inhibitory effects on Aβ aggregation was identified. The structure–activity relationships provide a suitable template whose key structural features will contribute by optimization to the inhibitory potency of the benzofuran derivatives against AChE.⁹ Usually, different types of substitution patterns in these heterocycles provide new opportunities for drug discoveries and a fine tuning of their physical properties for other applications in material science. Some benzofuran derivatives are attractive as organic materials, due to their optical and electronic properties.¹⁰ For their potential applications, development of novel synthetic strategies is in strong demand.

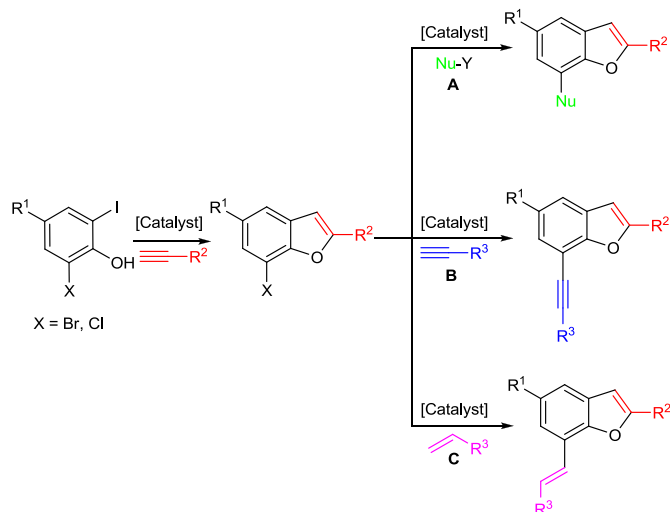
In recent years, transition metal-catalyzed reactions have played a remarkable role in this area.^{11–m} Particularly, palladium¹¹ and copper¹²-catalyzed reactions have been widely employed in the construction of the benzo[*b*]furan core providing functional group tolerance, simplified procedures, and improved yields.

However, procedures for the synthesis of 2,5,7-trisubstituted benzo[*b*]furans remain scarcely described in the literature^{9,13} and the development of simple and general methods for their preparation is a subject of great interest.

As part of our studies devoted to the construction of the benzo[*b*]furan skeleton through tandem Sonagashira coupling/5-*endo-dig* cyclization starting from alkynes and *o*-halophenols,¹⁴ we observed and previously communicated¹⁵ that readily available 2-bromo- and 2-chloro-6-iodo-4-substituted phenols can be used

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as suitable building blocks for the target 2,5,7-trisubstituted benzo[*b*]furans through a consecutive process that involves the assembly of the benzo[*b*]furan ring followed by the functionalization at the C(7) position via Suzuki–Miyaura cross-coupling and C–N bond forming reactions (Scheme 1A).

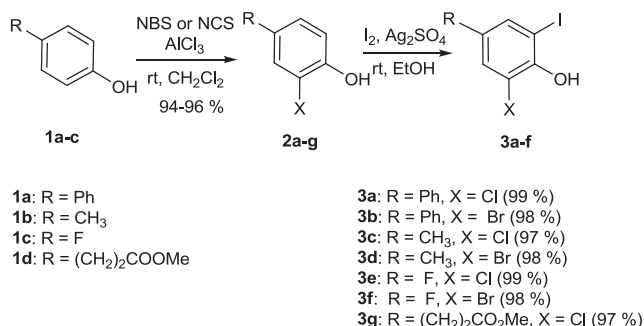


Scheme 1. Synthesis of 2,5,7-trisubstituted benzo[*b*]furans from 2-halo-6-iodo-4-substituted phenols.

Now, we wish to report full details of the results we have obtained as well as the study of the scope, limitations, and further elaboration of this approach (Scheme 1B,C) to highly functionalized benzo[*b*]furans. Moreover, a one-pot double-coupling procedure to afford a convergent synthesis of the target polysubstituted derivatives will be described.

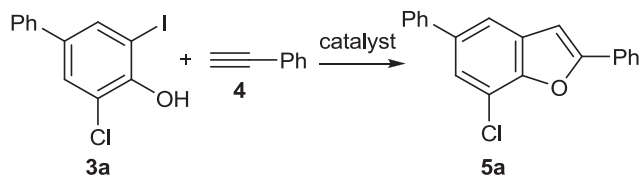
2. Results and discussion

The starting building blocks 2-bromo- and 2-chloro-6-iodo-4-substituted phenols **3a–g** were prepared in high yields from commercially available 4-substituted phenols **1a–d** according to the sequence outlined in Scheme 2.¹⁶



Scheme 2. Synthesis of 2-bromo- and 2-chloro-6-iodo-4-substituted phenols **3**.

Subsequent studies were directed toward searching for the best conditions for their conversion into the corresponding benzo[*b*]furan derivatives **5** by the reaction with terminal alkynes. 2-Chloro-6-iodo-4-phenylphenol **3a** and phenylacetylene **4** were selected as the model system (Scheme 3).



Scheme 3. Synthesis of 7-chloro-2,5-diphenylbenzo[*b*]furan **5a**.

Some results of our screening summarized in Table 1 show that benzo[*b*]furan formation was not observed by using PdCl₂(PPh₃)₂, CuI, and Et₂NH in DMF at room temperature (entry 1). Increasing the reaction temperature to 50 °C gave **5a** only in moderate yield (entry 2). A similar result was obtained with NH(Pr-*i*)₂ as the base

Table 1
Optimization of the reaction conditions for the synthesis of **5a** from **3a**^a

Entry	Catalytic system (equiv)	Solvent	Base	Temperature (°C)	Time (h)	Yield % of 5a ^b
1	PdCl ₂ (PPh ₃) ₂ (0.02)/CuI (0.04)	DMF	Et ₂ NH	rt	24	—
2	PdCl ₂ (PPh ₃) ₂ (0.02)/CuI (0.04)	DMF	Et ₂ NH	50	48	53
3	PdCl ₂ (PPh ₃) ₂ (0.02)/CuI (0.04)	DMF	NH(Pr- <i>i</i>) ₂	50	48	50
4	Pd ₂ (dba) ₃ (0.025), BF ₄ HP(Bu- <i>t</i>) ₃ (0.05)	DMSO	Cs ₂ CO ₃	60	48	68
5	Cu(phen)(PPh ₃) ₂]NO ₃ (0.10)	Toluene	K ₂ CO ₃	110	2	73
6	Cu(phen)(PPh ₃) ₂]NO ₃ (0.10)	Toluene	Cs ₂ CO ₃	110	2	74
7	Cu(phen)(PPh ₃) ₂]NO ₃ (0.10)	Toluene	K ₃ PO ₄	110	2	73
8	CuI (0.10)/L-proline (0.20)	Toluene	K ₃ PO ₄	120	1	75
9	CuI (0.10)/L-proline (0.20)	DMF	K ₂ CO ₃	120	1	68
10	CuI (0.10)/L-proline (0.20)	DMSO	K ₂ CO ₃	120	1	69
11	CuI (0.10)/L-proline (0.20)	1,4-Dioxane	K ₂ CO ₃	120	2	70
12	CuI (0.10)/L-proline (0.20)	1,4-Dioxane	K ₃ PO ₄	120	2	73
13	CuI (0.10)/L-proline (0.20)	1,4-Dioxane	Cs ₂ CO ₃	120	1	75

^a Reactions were carried out on a 2 mmol scale of **3a** using 6 mL of solvent, 1.5 equiv of phenylacetylene, and 2 equiv of base.

^b Yields refer to single run and are for pure isolated products.

(entry 3). Interestingly, **5a** was isolated in good yield when Pd₂(dba)₃ was used as the Pd(0) source in the presence of the bulky P(Bu-*t*)₃ ligand generated in situ from the robust BF₄HP(Bu-*t*)₃ salt¹⁷ under copper-free conditions (entry 4). Best results were observed by using copper catalysis. Recently, copper-catalyzed alkylation of aryl halides has gained a growing attention due to the lower toxicity and cost of copper catalysts. A number of ligands have been examined for this type of reaction.¹⁸ We initially used the Cu(I) complex Cu(phen)(PPh₃)₂]NO₃ developed by Venkataraman et al. and applied to the synthesis of 2-arylbenzo[*b*]furans.^{18j,19} Under their conditions **5a** was isolated in good yields (entries 5–7). Nevertheless, we subsequently found that similar results could be obtained by using the simpler CuI/L-proline combination developed by Ma et al. and successfully employed in the N-arylation of aryl bromides²⁰ and in the synthesis of 2-arylindoles from terminal alkynes and 2-bromoalkynyltrifluoroacetanilides.²¹ 1,4-Dioxane, toluene, and DMF were suitable solvents (entries 8–10) with this catalyst system and K₂CO₃ or K₃PO₄ or Cs₂CO₃ were effective as bases (entries 11–13).

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