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One-pot synthesis of 2,2′-bisbenzofurans using cuprous chloride as a catalyst

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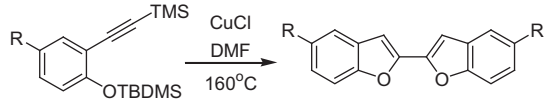
ABSTRACT

A variety of novel 5,5′-disubstituted-2,2′-bisbenzofuran derivatives were synthesized by treatment of 4-substituted-2-(2-trimethylsilylethynyl)phenyl *tert*-butyldimethylsilyl ether analogues with CuCl as a catalyst in 62–82% isolated yields. This novel strategy provides a straightforward and simple pathway for the preparation of 2,2′-bisbenzofuran derivatives of interest in life and material sciences.

Benzofuran and its derivatives have attracted considerable attention as synthetic targets due to their interesting properties.[1–3] However, their dimers are much less studied, although they are present in some molecules and natural products with biological activities, including the inhibition of propyl endopeptidase[4] and protein phosphatase 1B (PTP-1B),[5] antiprotozoal activities,[6] and antimicrobial effects.[7] Moreover, 2,2′-bis-(diphenylphosphino)-3,3′-bibenzo[*b*]furans have also been applied to diverse transition metal catalyzed asymmetric reactions.[8] Additionally, 3,3′-bis(arylbenzofurans) have been reported as substrates for the synthesis of benzonaphthofurans through photorearrangement reactions.[9] Yet, only few synthetic methodologies have been published for the construction of 2,2′-bisbenzofuran ring system in the literature; several new approaches have been disclosed in recent years.[10] Recently, Daugulis and co-workers reported a $CuCl_2$-catalyzed deprotonative dimerization of arenes to afford the 2,2′-bisbenzofuran in modest yield.[11] In 2010, Wegner and co-workers also discovered a novel pathway to access 3,3′-bisbenzofuran analogues via a gold-catalyzed domino cyclization–oxidative coupling reaction.[12] Generally, the generation processes of bisbenzofurans usually include the homocoupling of two benzofuran units which need to be activated prior to connection by metal-induced coupling reaction, such as modified Castro reaction,[13] copper-mediated palladium-promoted coupling,[14] or BuLi/$CuCl_2$ coupling.[15] Unfortunately these protocols in preparing dimeric benzofurans suffer from the use of expensive palladium or gold catalysts,[12] multisteps,[9] low isolated yields,[12] and harsh reaction conditions. Thus, the efficient and quick way to prepare 2,2′-bisbenzofurans from easily available starting material is a great challenge. Herein, we described a copper-mediated successive homocoupling/annulation reaction for the synthesis of 5,5′-disubstituted-2,2′-bisbenzofurans under a mild and efficient way with excellent regioselectivity (Eq. 1):



(1)

R = H, *i*-Pr, Et, Me, *t*-Bu, Cl, Br,

The synthesis of *tert*-butyldimethyl(2-((trimethylsilyl)ethynyl)phenoxy)silane **3a** starting from 2-iodophenol is presented in Scheme 1. Protection reaction of **1a** by TBDMSCl gained compound **2a** in 92% yield, followed by Sonogashira–Heck–Cassar (SHC) coupling reaction of **2a** with trimethylsilylacetylene using $Pd(PPh_3)_4$ as the catalyst that gave the precursor compound **3a** in 92% yield.

Our initial attempt for the oxidative dimerization/cyclization reaction of **3a** was treated with 10 mol % CuCl in DMF at room temperature for 24 h, and no desired product 2,2′-bisbenzofuran **4a** was observed (Table 1, entry 1). Upon heating the reaction mixture in refluxing DMF, expected product **4a** was afforded in 65% yield (entry 2).[16] To optimize the reaction conditions, we examined various reaction conditions for the tandem reaction of **3a** by employing different copper salts and solvents. The results are summarized in Table 1. Different copper-containing catalysts have been tested:

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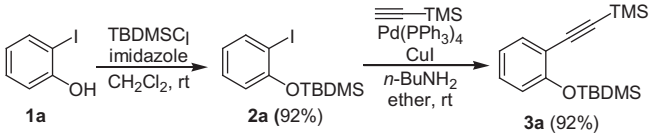


Scheme 1.

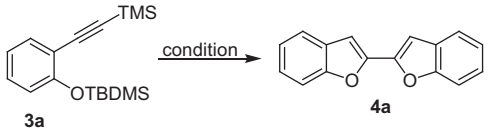
Cu(I) and Cu(II). CuCl was found to be superior to the others (entries 2–5). When we used CuI as the catalyst, the reaction accompanied with homocoupling reaction product **5** in 18% yield together with **4a** in 15% yield (Scheme 2). Further investigating the solvent effect, solvents, such as DMF, DMSO, CH_3CN, toluene, benzene, THF, and 1,4-dioxane, were used in this study (entries 2 and 6–11). We demonstrated that highly polar solvent DMF was the best reaction medium, providing **4a** in good yield (entry 2). Other solvents, such as DMSO, CH_3CN, toluene, benzene, THF, and 1,4-dioxane, showed no activity (entries 6–11). The chemical structure of the novel 2,2′-bisbenzofuran **4a** was characterized by spectroscopic analysis.[17] It should be noted that the sequential process proceeds in a regioselective manner.

With the optimum reaction conditions determined (entry 2), we turn our attention to test the generality of this sequential dehydrogenative homocoupling/annulation reaction. Other substrates **3b**–**g** bearing different substituents at the C-4 position of the phenyl ring have also been synthesized (Scheme 3) and subjected to the cascade reaction under the standard reaction conditions. The synthesis of *tert*-butyldimethyl(2-((trimethylsilyl)ethynyl)phenoxy)silane **3b**–**g** starting from 4-substituted iodophenols is outlined in Scheme 3. Iodination reactions of 4-substituted phenols by chloramines T and NaI gave compounds 4-substituted-2-iodophenols **1b**–**h** along with low yield minor products of 4-substituted-2,6-diiodophenol compounds **1b′**–**h′** as outlined in Scheme 4. Further protection reactions of **1b**–**h** by TBDMSCl produced compounds **2b**–**h** in 45–98% yields. Subsequent Sonogashira coupling reactions of **2b**–**g** afforded the substrates **3b**–**g** in 87–97% yields. However, the Sonogashira–Heck–Cassar (SHC) coupling reaction of **2h** gave unexpected monobenzofuran product, 5-nitro-2-trimethylsilylbenzofuran **6**, in 85% yield. This transformation involves a Sonogashira coupling reaction and a subsequent intramolecular heteroannulation process (Scheme 5). Treatment of **3b**–**g** in the presence of cuprous chloride induced these reactions, 5,5′-disubstituted-2,2′-bibenzofurans **4b**–**g** were obtained in modest to good yields. The results are presented in Scheme 6.

According to the preliminary research on the copper-catalyzed cyclization and oxidative coupling reaction[18] it may be reasonable to consider that this deprotonative dimerization/annulation reaction proceeds initial desilylation of the TMS group of the substrate **3a** in the presence of copper salt, leading to the formation of Cu-coordinated alkyne. Subsequently, Cu(I) acetylide intermediate homocouples to produce 1,3-butadiyne **5** via the Glaser–Hay alkyne dimerization, wherein the deprotection of the TBDMS group of **5** occurs, resulting in intramolecular 5-*endo*–*dig* cyclization of a copper complex to furnish product **4a**.

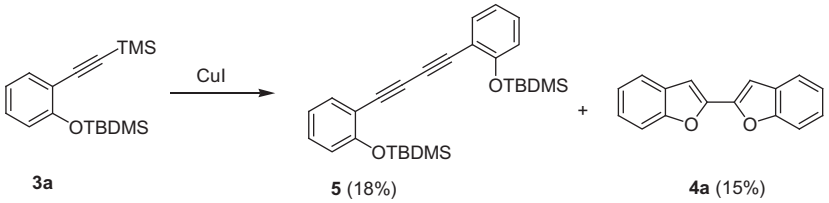
In conclusion, we have developed a CuCl-catalyzed tandem process to convert simple 4-substituted-2-(2-trimethylsilylethynyl)phenyl *tert*-butyldimethylsilyl ether analogues directly into novel 5,5′-disubstituted-2,2′-bisbenzofuran derivatives. The

Table 1
Copper-catalyzed sequential oxidative homocoupling/cyclization reactions under various conditions

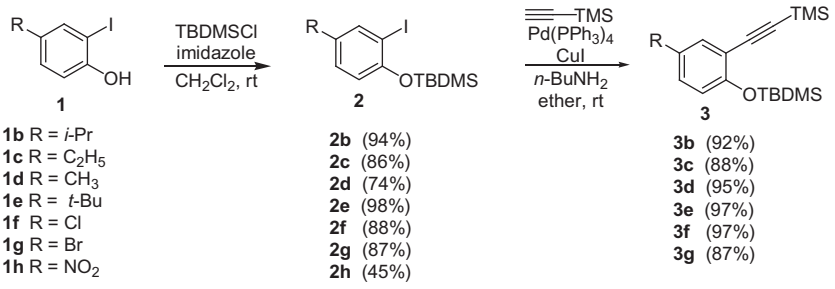


Entry	Additives (10 mol %)	Solvents	Temperature (°C)	Reaction time (h)	Products[a] (yield, %)
1	CuCl	DMF	rt	24	No reaction
2	CuCl	DMF	Reflux	24	65
3	$CuCl_2$[b]	DMF	Reflux	24	Decomposed
4	CuBr	DMF	Reflux	24	55
5	CuI[c]	DMF	Reflux	24	15
6	CuCl	DMSO	Reflux	24	Trace
7	CuCl	CH_3CN	Reflux	24	No reaction
8	CuCl	Toluene	Reflux	24	No reaction
9	CuCl	Benzene	Reflux	24	No reaction
10	CuCl	THF	Reflux	24	No reaction
11	CuCl	1,4-Dioxane	Reflux	24	No reaction

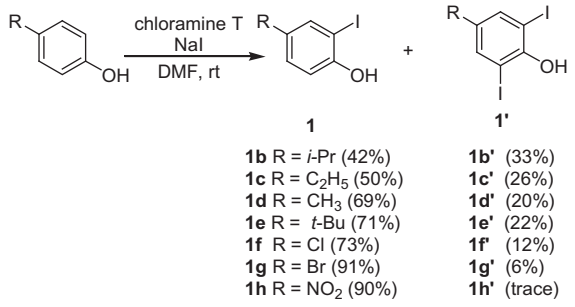
[a] Isolated yields.
[b] $CuCl_2$ (1.1 equiv).
[c] Reaction accompanied with homocoupling product.



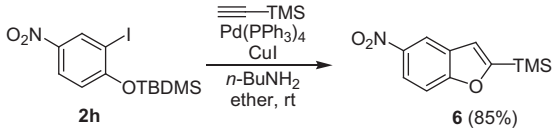
Scheme 2.



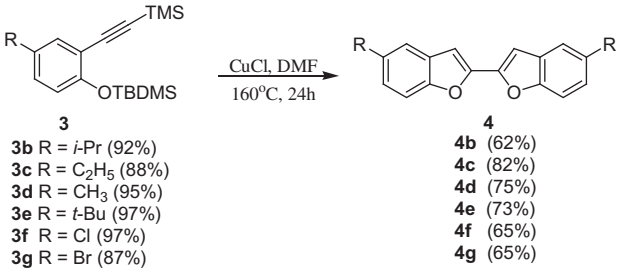
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

notable features of this cascade reaction are its mild reaction conditions, synthetic simplicity, excellent yields, high regioselectivity, and usage of less expensive CuCl as a catalyst. The application of this methodology to the preparation of pharmaceutical or material interest molecules, 2,2′-bisbenzofuran analogues, is currently under investigation.

Acknowledgment

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16. *General procedure for the preparation of 5,5′-disubstituted-2,2′-bisbenzofurans:* A slurry of the 4-substituted-2-(2-trimethylsilylethynyl)phenyl *tert*-butyldimethylsilyl ether **3a** (0.67 mmol) and CuCl (10 mol %) in dry DMF (10 mL) at 160 °C was stirred for 24 h. After cooling to room temperature, saturated $NaCl_{(aq)}$ solution was added to the reaction mixture, and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_{4(s)}$. After filtration and removal of the solvent, the residue was purified by flash chromatography to give the product **4a** (65%).
17. *Compound **4a** (65%) as a white solid:* mp = 193–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dq, 2H, J = 7.6, 0.8 Hz), 7.56 (dd, 2H, J = 8.0, 0.8 Hz), 7. 36 (td, 2H, J = 7.2, 1.2 Hz), 7. 29 (td, 2H, J = 7.6, 1.2 Hz), 7.17 (d, J = 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 147.7, 128.5, 125.1, 123.3, 121.4, 111.3, 103.7; EI(MS) m/z (rel. intensity) 234 (M^+, 100), 178 (11), 176 (25); HRMS (ESI-TOF) Calcd for $C_{16}H_{10}O_2$, 234.0681, Found: 234.0686; Anal. Calcd for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found: C, 81.79; H, 4.98.
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