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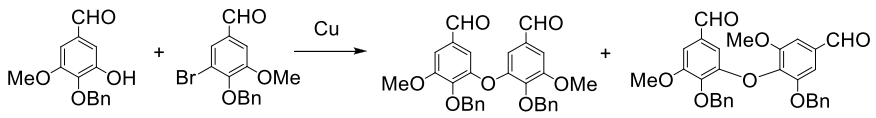

Unexpected copper mediated benzyl O→O migration during an Ullmann ether coupling

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Abstract

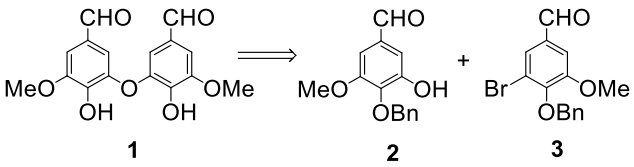
The synthesis of a highly functionalized phenolic diaryl ether 5,5'-oxybis(4-hydroxy-3-methoxybenzaldehyde) (**1**) potentially interesting as new scaffold for drug design, has been carried out using Ullmann coupling conditions. An unusual benzyl migration in *o*-benzyloxyphenol moiety occurred during this reaction leading to an unexpected compound identified as 4-(benzyloxy)-3-(2-(benzyloxy)-4-formyl-6-methoxyphenoxy)-5-methoxy benzaldehyde (**7**). A rationale for this migration process is proposed.

Keywords:

Diaryl ether, Ullmann condensation, Benzyl migration, Phenol dimers.

The diaryl ether moiety is found in a number of natural or synthetic products as well as in biologically important molecules that exhibits pharmacologically outstanding activities, such as anticancer, antifungal, antibiotic and antithrombotic.[1] In a previous report concerning

our search of new antiatherogenic molecules originating from natural sources, we highlighted the antioxidant and cytoprotective properties of functionalized diaryl phenols derived from vanillin.[2] In continuation of our work, we focused on the preparation of diaryl ether scaffold **1** (Scheme 1). We report herein our efforts to synthesize this target compound and an unexpected benzylic migration observed during the key Ullmann condensation step.



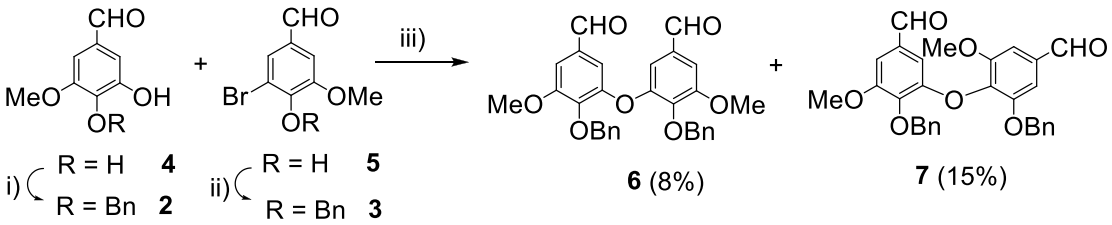
Scheme 1. Retrosynthesis of 5,5'-oxybis(4-hydroxy-3-methoxybenzaldehyde) (**1**).

Various methods have been developed for the preparation of diaryl ethers.[3] The most popular ones are the palladium-catalyzed[4] and the copper-mediated[5] coupling of a phenol and an aryl halide. However, synthetic access to highly functionalized symmetric diaryl ether is rather scarce in the literature. The synthesis of symmetric diaryl ether **1** was initially envisioned by starting from *O*-benzyl 3-hydroxyvanillin (**2**) and *O*-benzyl 3-bromovanillin (**3**) (Scheme 1).

Regioselective benzylation of commercial 3-hydroxyvanillin (**4**) (BnCl, $NaHCO_3$, NaI, DMF, 40°C, 16h)[7] afforded 4-benzyloxy-3-hydroxy-5-methoxybenzaldehyde **2** in 86% yield. *O*-benzyl-3-bromovanillin **3** was readily prepared in 97% yield following a reported protocol[6] starting from commercially available 3-bromovanillin (**5**) (Scheme2). With these starting materials in hand, we next turned our attention to the coupling reaction focusing on copper-mediated conditions. The first attempts were carried out under the modified catalytic Ullmann conditions. Unfortunately, screening of various reactions conditions (Cu(I) salt, base, ligand, solvent, temperature, reaction time)[8] did not afford the targeted diaryl ether **6**. Only starting materials were recovered along with O-benzylvanillin resulting from the debromination of compound **3**. Noteworthy, no such copper-catalyzed coupling reactions have ever been reported with such polysubstituted partners. To investigate the behaviour of the two reactants independently, we first applied the usual Buchwald[9] coupling conditions (CuI (20 mol %), picolinic acid (40 mol %), K_3PO_4 (2 equiv.), DMSO, 100°C, 24h) to phenol **2** with various poorly functionalized aryl halides: iodobenzene, 4-bromobenzaldehyde and 4-iodo-1-trifluoromethylbenzene. The resulting diaryl ethers were obtained with moderate to high yields (respectively 30%, 50% and 99% yield). On the other hand, coupling assay of the

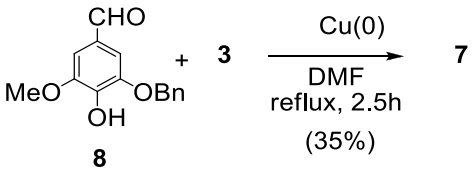
polyfunctionalized aryl bromide **3** with the phenol (C_6H_5OH) under the same conditions did not afford the expected diaryl ether. Starting materials were recovered in mixture with debrominated *O*-benzylvanillin, suggesting that **3** is not reactive for coupling process under copper-catalyzed conditions.

These unsuccessful results prompted us to examine the Ullmann condensation using super-stoichiometric amount of copper metal (5 equiv.) as recently reported by Abe *et al.*[10] for polysubstituted phenols and aryl bromides. The coupling reaction between compounds **2** and **3** was conducted in presence of 3 equivalents of bromide derivative in refluxing DMF for 2.5h (Scheme 2). To our delight, careful HPLC separation allowed us to obtain symmetric diaryl ether **6** for the first time under these conditions albeit in poor yield (8%). Surprisingly, an isomer of **6** was isolated as the major coupling product (15% yield). The structure of this compound was assumed to be the non-symmetric diaryl ether **7** based on spectroscopic analyses.



Scheme 2. Reaction conditions : i) $PhCH_2Cl$, $NaHCO_3$, NaI, DMF, 40°C, 16h (86%) ; ii) $PhCH_2Br$, K_2CO_3, DMF, 80°C, 4h (97%) ; iii) Cu(0), DMF, reflux, 2.5h.

We reasoned that compound **7** was likely the result of the coupling of phenol **8** with **3** (Scheme 3). To confirm this hypothesis, we prepared **8** in three steps according to a reported procedure.[11] As expected, reaction of **3** and **8** under Abe's conditions (Cu(0), DMF, reflux) afforded the non-symetric diaryl ether **7** in a 35% modest yield, along with *O*-benzylvanillin. This result allowed us to secure the structure of compound **7** obtained during the coupling of phenol **2** with aryl bromide **3**.



Scheme 3. Direct synthesis of non-symmetric diaryl ether **7**.

Noteworthy, all Ullmann condensations undertaken led to *O*-benzylvanillin formation due the efficient reductive dehalogenation side reaction[12] of aryl bromide **3**. This reaction rapidly consumes this starting material, so that improved yields could not be obtained by increasing the excess of **3** (4 equiv.) nor the reaction time.

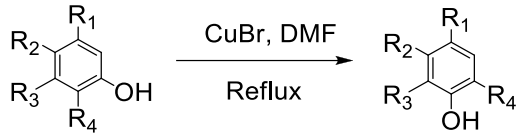
This result also confirmed that phenol **8** was formed during the Ullmann condensation step. This formation may stem from a 4,3 *O*→*O* migration of the benzyl group of phenol **2**. To the best of our knowledge, no such migration has ever been reported. Only rearrangements of benzyl aryl ethers into diarylmethanes under thermal or acidic conditions have been described.[13]

To further understand this intriguing benzyl migration, we undertook complementary experimental investigations. All the following results rely on ^{1}H NMR data.

Firstly, we pointed out the key role of the benzyl group in this rearrangement process : when 3-hydroxy-4,5-dimethoxybenzaldehyde[14] was used as reactant, no methyl migration product was observed.

When phenol **2** was heated in the presence of Cu(0) in DMF, the rearrangement did not occur (**2** was fully recovered) suggesting that other copper intermediates (copper bromides) are formed during the coupling reaction in the presence of aryl bromide **3a**. The current knowledge of the mechanism of the Ullmann condensation that implicates Cu(I) or Cu(II) species[5] led us to wonder about the nature of the oxidative state of copper involved in this rearrangement. To shed some light on this question, phenol **2** was first treated with $CuBr_2$ (0.5 equiv.) in refluxing DMF for 2.5h, resulting in no transformation. Then, **2** was allowed to react in the presence of CuBr under the same reaction conditions, leading to 25% conversion into **8**, suggesting that Cu(I) rather than Cu(II) plays a major role in this benzyl migration (Table 1, entry 1). Moreover, high temperature is required as no conversion was observed in DMF at room temperature.

Table 1. Benzyl migration rate of *O*-benzyloxyphenol derivatives



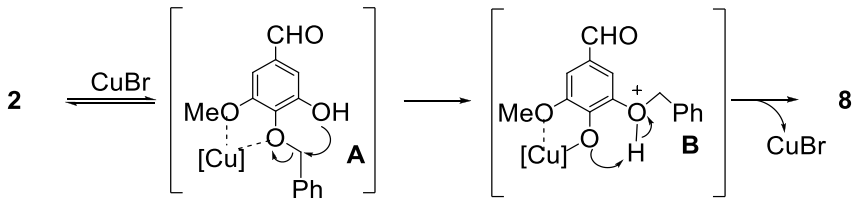
Entry	Reactant	R_1	R_2	R_3	R_4	Equiv. CuBr	Reaction time	Conversion rate*
1	**2**	CHO	H	OMe	OBn	0.5	2.5 h	25%
2	**2**	CHO	H	OMe	OBn	0.1	2.5 h	25%
3	**2**	CHO	H	OMe	OBn	0.5	7.5 h	40%
4	**9**	CHO	H	H	OBn	0.5	2.5 h	10%
5	**10**	H	H	OMe	OBn	0.5	2.5 h	0%
6	**11**	CN	H	OMe	OBn	0.5	2.5 h	20%
7	**12**	CHO	OBn	H	H	0.5	2.5 h	0%

*as estimated by ^{1}H NMR

In additional experiments, the reaction conditions were screened (Table 1). The same conversion rate (25%) was obtained when using 0.5 or 0.1 equivalent (Table 1, entries 1 and 2) of CuBr indicating that a catalytic process is implicated. The conversion rate grows up to 40% with increasing reaction time to 7.5h (Table 1, entry 3). Noteworthy, longer reaction times (15h or 22h) or switch DMF to DMSO as the solvent led to major degradation by-products formation. Other phenol derivatives were studied to ascertain the influence of different substituents. To investigate the effect of the 5-OMe group, 4-benzyloxy-3-hydroxybenzaldehyde (**9**) was prepared[7] and reacted with CuBr (0.5 equiv.) under the same experimental conditions as above. Only 10% conversion of the starting material into the expected migrated product was observed by ^{1}H NMR (Table 1, entry 4). Concerning the influence of the carbonyl moiety, 2-benzyloxy-3-methoxyphenol[15] (**10**) was initially submitted to the same reaction conditions, and was recovered unchanged (Table 1, entry 5). Moreover, when 4-benzyloxy-3-hydroxy-5-methoxybenzonitrile (**11**), readily prepared[16] in one pot starting from aldehyde **2** was used, the corresponding migration product[17] with 20% conversion rate (Table 1, entry 6) was obtained. These results highlighted the key role of the

carbonyl or other electron-withdrawing group on the benzyl migration and the cooperative effect of the 5-OMe substituent. Furthermore, the reaction was carried out on benzaldehyde derivative **12** obtained by regioselective benzylation of commercially available 2,5-dihydroxybenzaldehyde.[18] No migration of the benzyl group from the *O*-ortho to the *O*-meta position was detected indicating that this process requires vicinal reacting centers (Table 1, entry 7). Finally, we checked that reverse benzyl migration reaction of phenol **8** into **2** did not occur as anticipated according to the sole coupling product **7** obtained when **8** was reacted with aryl bromide **3** (Scheme 3).

With these results in hand, there is no obvious mechanism that would account for such reorganization. Nevertheless, we postulate a plausible mechanism for this reaction. The absence of detection of *o*-quinone or catechol products and the required vicinity of the reaction centers suggest that an intramolecular process is implicated. Indeed, as depicted in Scheme 4, copper bromide would activate compound **2** to generate a copper(I) complex **A**.[19] At this stage, the *O*-benzyl bond is weakened by the synergic effect of the para electron-withdrawing substituent and the copper(I), allowing the nucleophilic attack of the ortho hydroxy group leading to intermediate **B**. Subsequent proton exchange would afford product **8** and regenerated CuBr.



Scheme 4. Proposed mechanism for the benzyl migration process.

Finally, keeping in mind our initial aim to synthesize the phenolic diaryl ether **1**, debenzylation of protected derivative **6** was efficiently carried out using BCl_3 (6 equiv.) in the presence of pentamethylbenzene (6 equiv.) in CH_2Cl_2[20] in 90% yield.

In summary, we have shown that reaction of 4-benzyloxy-3-hydroxy-5-methoxybenzaldehyde **2** with *O*-benzyl-bromovanilline **3** in the presence of Cu(0) in DMF furnishes the rearranged diarylether **7** *via* a copper(I) mediated benzyl *O*→*O* migration. This copper (I) mediated benzyl migration may proceed through a copper activated intermediate as mentioned in the proposed mechanism. The phenolic diaryl ether target **1** was obtained in

global poor yield pushing us to envision an alternative strategy under development in the Laboratory.

Aknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data for compounds **2**, 4-(benzyloxy)-3-methoxy-5-phenoxybenzaldehyde, 4-(benzyloxy)-3-(4-formylphenoxy)-5-methoxybenzaldehyde, 4-(benzyloxy)-3-methoxy-5-(4-trifluoromethyl)phenoxy)-benzaldehyde, **6**, **7**, **11**, 3-(benzyloxy)-4-hydroxy-5-methoxybenzonitrile, **1** and copies of ^{1}H and ^{13}C NMR spectra of **6**, **7** and **1**) associated with this article can be found, in the online version, at.

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