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Synthetically Useful Brønsted Acid-Promoted Arylbenzyl Ether → *o*-Benzylphenol Rearrangements[1]

Frederick A. Luzzio* and Juan Chen

Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, Kentucky 40292

faluzz01@gwise.louisville.edu

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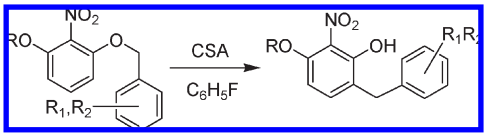
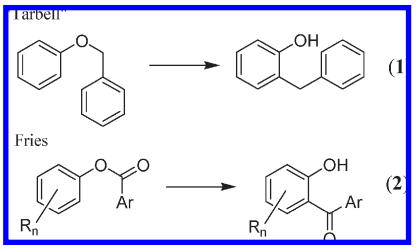


Camphorsulfonic acid in warm fluorobenzene facilitates the *ortho* rearrangement of (alkoxy-substituted) benzyl ethers of 1-(*O*-methyl)-2-nitroresorcinols to the corresponding *o*-(alkoxy-substituted) arylmethylnitrophenols. The substrate phenolic ethers are prepared by ultrasound-promoted arylmethylation of the appropriate 1-alkoxy-substituted 2-nitroresorcinol.

Due to their unique positional selectivity, *o*-aryl rearrangements significantly expand the synthetic latitude of aromatic substitution reactions involving carbon−carbon bonds. Tarbell and co-workers studied the acid-mediated *ortho* rearrangement of benzyl phenyl ether to 2-benzylphenol (eq 1) in depth during the 1950s with respect to product distribution and catalyst type.[2,3] Although studies of the so-called "Tarbell reaction" by a number of groups have continued to persist, the studies have been confined to only benzyl phenyl ether—with the more recent reports focusing on the mediating catalyst[3a−3d] or conditions.[4] Interestingly, the benzyl phenyl ether rearrangement has not been investigated with respect to scope and substrate generality and thus has garnered far less interest and synthetic utility than its archetypal cousin, the Fries rearrangement (eq 2).[5]



For such transformations to be synthetically useful, the substrates should bear a range of substituent atoms so that further synthetic elaboration is enabled. As expected, the aryl benzoyl ester Fries rearrangement was recently employed to deliver a range of benzophenone-derived experimental anti-inflammatory agents with single substitution on the phenolic (nonmigrating) ring and multiple substitution on the benzoyl (migrating) ring.[6] We began to develop the *o*-benzyl rearrangement as an effective route to scaffold units and pharmacophores having the diphenylmethane core structure.[7,8] Hence, we prepared rearrangement substrates with a diversity of substitution on *both* the phenolic and migrating aromatic rings. When substituents are specifically positioned, the rearrangement has the potential to deliver products of 1,2,3 and 1,2,3,4 substitution on the phenolic aromatic ring through the *o*-benzyl rearrangement. For substrates with at least one alkoxy substituent (at position 1 or 4) on the migrating arylmethyl unit or the nonmigrating (phenolic) unit, further bond formation through deprotection/ether formation is possible. The preparation of aromatic compounds with the 1,2,3,4-substitution patterns, specifically with the 1- or 4- substituent being a carbon, is very problematic with the use of conventional Friedel−Crafts chemistry due to the *para*-directing effect of activating substituents. The desired "in-line" 1,2,3 and 1,2,3,4 substitution patterns are usually accomplished with directed *o*-metalation chemistry or transition-metal coupling reactions when a carbon−carbon bond is desired at the terminus of the

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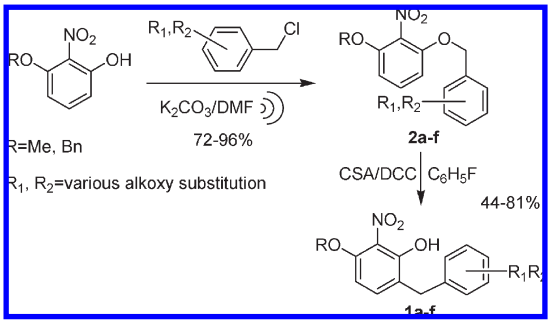
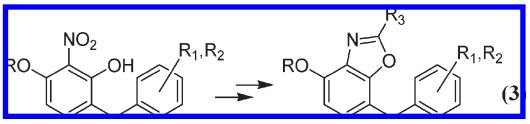
SCHEME 1. Preparation of Substituted Benzylic Nitroresorcinolic Ethers and Their Rearrangement to *o*-Arylmethyl Phenols



substitution pattern. While the "aroyl" Fries rearrangement has been proven to accommodate up to three substituents on the migrating ring, the substituents on the nonmigrating phenolic ring have been limited to one. Furthermore, when a diarylmethane rather than a diaryl ketone is the desired product, the *o*-benzyl rearrangement would surpass the analogous Fries transformation since the required one- or two-step carbonyl → methylene conversion is now bypassed.

Our interest in the rearrangement reaction originally stemmed from studies in which *ortho* rearrangement products formed to an appreciable extent during the preparation of PMB ethers of ring-activated phenols.[9] During a separate study, the formation of an *ortho*-selective carbon−carbon bond was of interest to us in preparing intermediates to 2-substituted 7-arylmethylbenzoxazoles and 2-substituted 7-aminobenzoxazoles (eq 3),[10−12] thereby making such a rearrangement worthy of study and optimization.



Accordingly, our initial experiments focused on rearrangements of the benzylaryl ether framework having electron-releasing substituents on the migrating ring and both electron-releasing (alkoxy) and electron-withdrawing (nitro) substituents on the phenolic ring (Scheme 1). In contrast to previous studies which utilized mainly Lewis acid-promoted rearrangement of benzylphenyl ether itself, we examined rearrangements of a variety of substrates using simple organic Brønsted acids in halogenated aromatic solvents without the use of high temperatures. Thus, so far, we have prepared a number of polysubstituted biarylmethanes **1a**−**f** (Table 1) in modest to fair yield which would prove difficult to prepare using Friedel−Crafts, *o*-metalation, or transition-metal coupling chemistries. Our scheme starts with the selection of the phenolic (nonmigrating) ring which possesses *ortho*-positioned N,O-substituents. One *ortho* oxygen bears the migrating benzyl group, while an additional *ortho* oxygen is protected for additional elaboration at a later stage. It was our intent that the benzylic ether oxygen which becomes the phenol group through benzyl migration and its *ortho* nitro group would later form a heterocycle. Hence, N,O heterocycle formation is possible through reduction of the nitro group to an amine followed by treatment with the requisite coreactants to form a 2-substituted aryl or aminobenzoxazole (vide supra).

The preparation of the benzylic ether rearrangement substrates **2a**−**f** (Table 1) was facilitated through our recently reported procedure for the protection of phenolic ethers with benzyl groups using ultrasound.[9a] 2-Nitroresorcinol monomethyl or monobenzyl ether was benzylated with a variety of substituted arylmethyl chlorides using *N*,*N*-dimethylformamide, potassium carbonate, and ultrasound, thereby affording the phenolic ether substrates **2a**−**f**. Our initial rearrangement experiments involved the selection of a suitable acid promotor for the conversion of substrate **2a** to nitrophenol **1a** (Table 1). First, we determined that the Lewis acids previously used in these rearrangements would be unsuitable since dealkylation would occur when applied to substrates bearing multiple alkylated phenolic hydroxyls. Hence, we opted to examine simple Brønsted acids which are inexpensive and easier to obtain commercially in high purity. In contrast to results with aluminum chloride or phosphotungstic acid,[3d] control reactions of benzyl phenyl ether and trifluoroacetic acid or camphorsulfonic acid (CSA) in fluoro- or chlorobenzene gave no rearrangement and quantitative recovery of starting material. The employment of trifluoroacetic acid (TFA) did promote the rearrangement of **2a** but with low yield of the nitrophenolic product **1a** due to competing cleavage to 4-methoxybenzyl alcohol.[9b,c] TFA was tested on **2a** in a range of solvents such as dichloromethane, nitromethane, fluorobenzene, chlorobenzene, benzene, toluene, and 1,4-dichlorobenzene but was considered too reactive. Fluorobenzene and chlorobenzene afforded the best results in terms of reducing the unwanted side reactions and maintaining a desirable reaction temperature. The optimal yield of the methyl ether **2a** was achieved with CSA which is near the lower end of the Hammett acidity (H_0) range for nonfluorinated sulfonic acids ($H_0 = -1.0$)[13] as opposed to TFA ($H_0 = -3.03$).[14]

The intramolecularity of the rearrangement has been previously investigated in the case of the isotopically labeled parent benzyl phenyl ether substrate.[15] With Lewis acid

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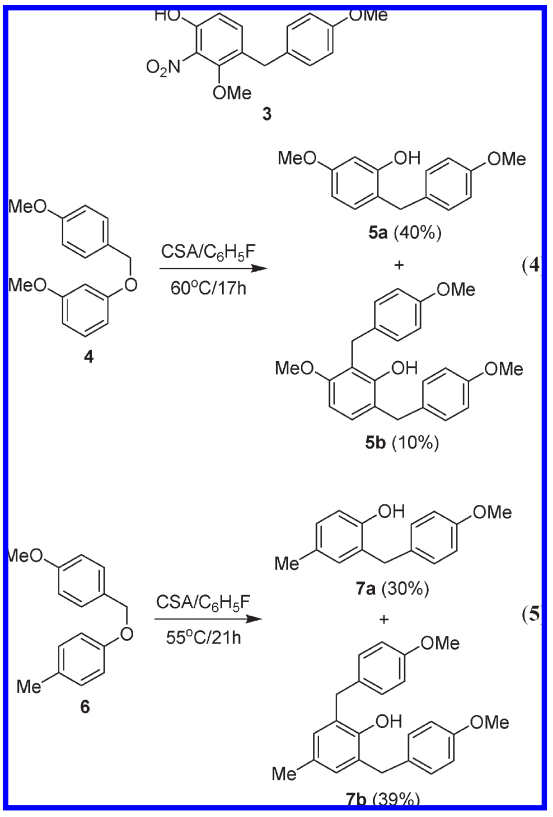
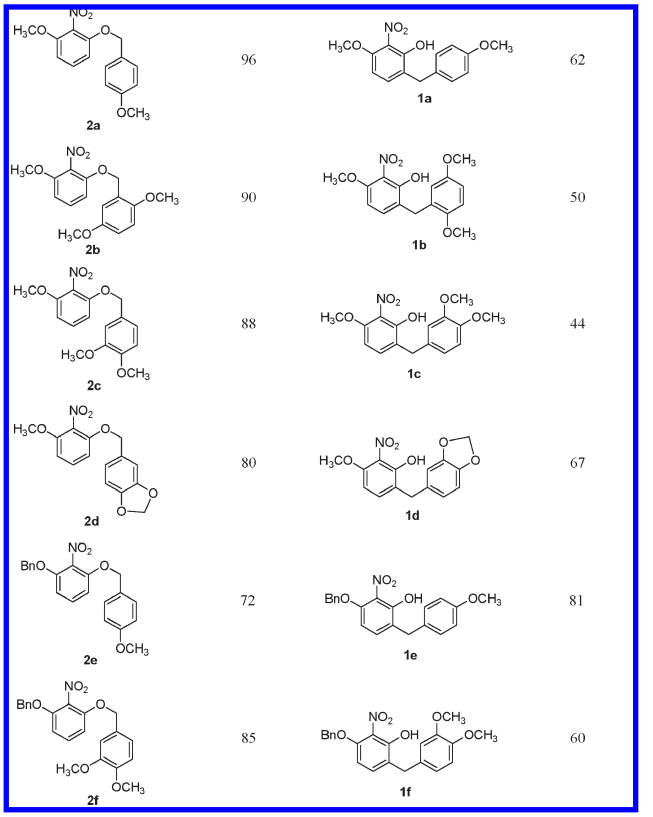
promotion, previous studies revealed that there were appreciable amounts of the *para*-isomer formed, thereby suggesting a competing pathway involving a solvent-associated benzylic cation. Accordingly, we wanted to identify the byproduct that might occur through any type of intermolecular pathway. Interestingly, substrate **2a** does give 10% of the *para* isomer of **1a**, 4-(4-methoxybenzyl)-3-methoxy-2-nitrophenol **3**, using camphorsulfonic acid in fluorobenzene (60 °C/44 h). Submission of substrates having electron-donating groups on the nonmigrating ring but with no nitro group gave markedly different results. Under standard conditions (CSA/C_6C_5F), 1-((3-methoxyphenoxy)methyl)-4-methoxybenzene **4** gave the *ortho* rearrangement product **5a** along with the disubstituted product 2,6-bis-(4-methoxybenzyl)-3-methoxyphenol **5b** (10%) (eq 4). Similarly, 1-(4-methoxybenzyloxy)-4-methylbenzene **6** gave the *ortho* product **7a** (30%) as well as a higher yield of bis-product **7b** (39%) (eq 5).



These results clearly indicate a competing intermolecular reaction although substrates which possessed the nitro groups on the nonmigrating ring gave no detectable disubstitution products under standard conditions. Substrate phenolic ether **2e** (Table 1) was designed with a benzyl protecting group so that, at a later stage, debenzylation would afford an intermediate with an open phenolic group for further synthetic elaboration. However, initial rearrangements of **2e** with CSA/fluorobenzene (75 °C/46 h) gave appreciable amounts of 4-methoxybenzyl alcohol through simple hydrolysis and low yields of the product **1e** (< 40%). When the reaction of **2e** was optimized, we found that, along with using anhydrous conditions, the hydrolysis reaction could be suppressed by the addition of dicyclohexylcarbodiimide (DCC, 1.3 equiv). The employment of any more DCC (> 1.3 equiv) or even the more soluble diisopropylcarbodiimide (DIC) in conjunction with

TABLE 1. Structures and Yields (%)[a] of Substrates 2a−f and Rearrangement Products 1a−f



[a] Isolated yields of chromatographically homogeneous compounds.

CSA would act as a "buffer" and completely suppress the desired rearrangement. In summary, Brønsted acids can mediate the *ortho* rearrangement of benzyl phenyl ethers having multiple substituents on both the migrating and nonmigrating rings. The presence of at least one electron-releasing group on the migrating ring allows the use of the relatively milder camphorsulfonic acid as the mediator. The 2-nitro-1,3-resorcinolic pattern on the nonmigrating ring tolerates the rearrangement well, allows for only monosubstitution, and may be semiprotected with benzyl groups for further synthetic utility. In terms of functionalized diarylmethane synthesis, the benzyl phenyl ether rearrangement of suitably substituted phenolic ether substrates should offer a reasonable alternative to the Fries rearrangement of aryl-substituted benzoyl phenyl esters. The nitrophenolic diarylmethane products are isolated in modest to good yield, and these intermediates may be further transformed to heterocycles such as 2-aminobenzoxazoles or 2-arylbenzoxazoles.

Experimental Section

Rearrangement of Benzylic Ethers 2a−f to Benzylphenols 1a−f, Typical Procedure: 6-(4-Methoxybenzyl)-3-methoxy-2-nitrophenol (1a). 1-((3-Methoxy)-2-nitrophenoxy)methyl-4-methoxybenzene (**2a**) (50.0 mg, 0.17 mmol) was dissolved in fluorobenzene (1 mL), and then camphorsulfonic acid (12.0 mg, 0.3eq) was added. The reaction mixture was then heated (oil bath) at 60 °C under nitrogen. The reaction progress was monitored by silica gel thin-layer chromatography (toluene/ethyl acetate, 9:1), which indicated the disappearance of starting material and the formation of the more mobile rearrangement product. At the end of the reaction

period (44 h), the fluorobenzene was removed by rotary evaporation under aspirator vacuum which left a crude yellow oily residue. The crude product was purified by flash column chromatography on silica gel (toluene/hexane, 1:1) to afford the rearrangement product **1a** (31.0 mg, 62%) as a yellow solid: mp 99−102 °C; R_f 0.30 (hexane/ethyl acetate, 2:1); FTIR (KBr, cm^{-1}) 3015, 2939, 2833, 1608, 1544, 1508, 1460, 1355, 1246, 1174, 1091, 1036, 799, 635; ^{1}H NMR (500 Hz, $CDCl_3$) 3.80 (s, 3H), 3.92 (s, 5H), 6.47 (d, 1H), 6.85 (d, 2H), 7.15 (d, 2H), 7.21 (d, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) 158.1, 154.2, 153.4, 136.1, 131.7, 129.8, 127.2, 123.2, 113.9, 103.0, 56.6, 55.2, 34.3; HRMS ($[M + Na]^+$) calcd for $C_{15}H_{15}NO_5$ ($[M + Na]^+$) 312.08424, found 312.08417.

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Supporting Information Available: Analytical and spectroscopic data for the rearrangement products **1a**−**f**, experimental procedures for the preparation of substrates **2a**−**f** and their associated analytical and spectroscopic data, and copies of the ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.