

Reductive Electrophilic Substitution of Pyrogallol Derivatives: Synthesis of 2,3-Disubstituted Phenols

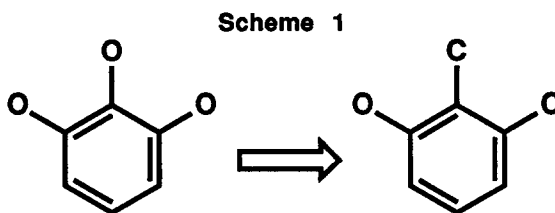
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Abstract: 1,2-Dimethoxy-3-methoxymethoxybenzene, **1**, was used as the starting material for the transformation of a 1,2,3-trioxybenzene into various 1-oxy-2,3-dicarbobenzenes, *via* regioselective reductive electrophilic substitution of the 2-methoxy group followed by Pd-catalyzed cross-coupling reaction.

Substituted phenols are a class of natural products endowed with interesting biological and pharmaceutical properties.¹ Their preparation requires the elaboration of efficient synthetic procedures for a highly regioselective substitution of the aromatic ring.

We wish to report on the transformation of 1,2,3-trioxy-substituted benzene derivatives into 1-oxy-2,3-dicarbo-substituted aromatics (Scheme 1); this conversion was achieved by connecting the regioselective reductive electrophilic substitution of the alkoxy group in the 2-position of ethers of 1,2,3-trioxybenzene² with the Pd-catalyzed cross-coupling reaction of organometallic reagents with aromatic triflates.³

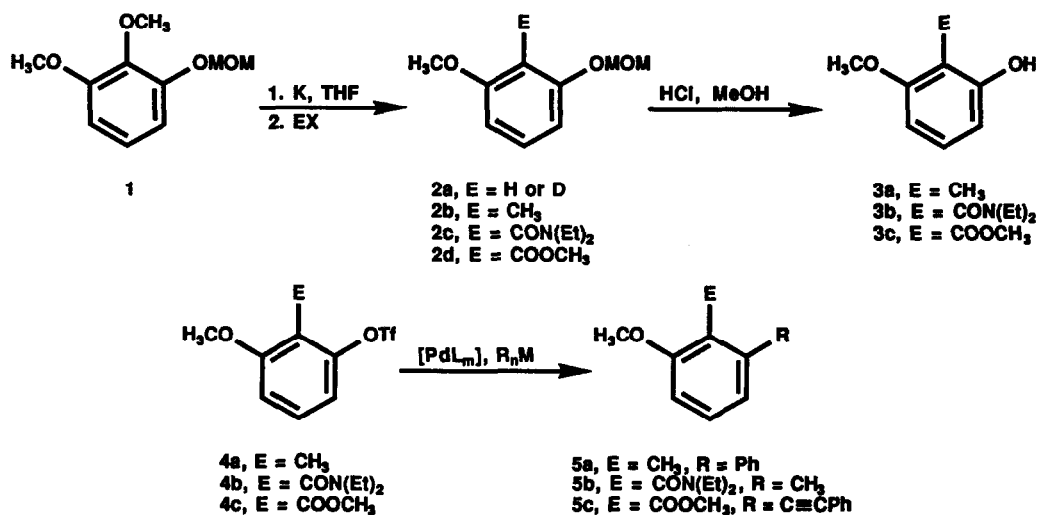


We have therefore investigated the reductive electrophilic substitution of 1,2-dimethoxy-3-methoxymethoxybenzene, **1**, with alkali metals in ethereal solvents, planning to complete the reaction sequence through successive selective hydrolysis of the methoxymethyl (MOM) group,^{4,5} transformation of the 2,3-disubstituted phenol thus obtained into the corresponding triflate, and cross-coupling reaction (Scheme 2).

After several attempts, the reductive demethoxylation in the 2-position of compound **1** was

accomplished under heterogeneous conditions by electron transfer from K metal in THF at room temperature. 1-Methoxy-3-methoxymethoxybenzene, **2a**,⁴ was obtained in 91% yield; no other products of dealkoxylation, such as 1-methoxy-2-methoxymethoxybenzene⁴ or 1,2-dimethoxybenzene, were detected in the reaction mixture, either by glc or ¹H-NMR (300 MHz) (estimated error <5%). Furthermore, almost quantitative formation of 2-methoxy-6-methoxymethoxyphenyl potassium was evidenced by D₂O quenching.⁶

Scheme 2



Trapping of this carbanion with various electrophiles was successful; under the above reaction conditions, 1-methoxy-2-methyl-3-methoxymethoxybenzene, **2b**, *N,N*-diethyl-2-methoxy-6-methoxymethoxybenzamide, **2c**, and methyl 2-methoxy-6-methoxymethoxybenzoate, **2d**, were obtained in satisfactory yields upon quenching of the reaction mixture with iodomethane, *N,N*-diethylcarbamoyl chloride, and methyl chloroformate, respectively (Table 1).

Table 1. Reductive Electrophilic Substitution of Compound **1**^a

electrophile ^b	T, °C	t, h	product, E =	yield, ^c %
D ₂ O	0	1	2a , D	> 90
CH ₃ I	0	1	2b , CH ₃	75
ClCONEt ₂	-40	2.5	2c , CONEt ₂	50 ^d
ClCOOCH ₃	-40	2.5	2d , COOCH ₃	66

^aThe carbanion was generated by the action of 3 equiv of K metal in THF at r. t. for 12-18 h. ^b3 equivalents of electrophile were added. ^cDetermined on products isolated by flash chromatography, unless otherwise indicated.

^dNot isolated; yield was calculated on the phenol, **3b**, after acid hydrolysis.

It is interesting to point out that this procedure allows the regioselective removal of the 2-methoxy group in the presence of a methoxymethoxy group. This is at variance with a previous report, stating that reductive cleavage of aryl-oxygen bonds is more easily obtained with methoxymethyl aryl ethers rather than with methyl aryl ethers.⁷

Acid hydrolysis (HCl 0.6 M in methanol, r.t., 1h) allowed the removal of the methoxymethyl group under mild reaction conditions; the subsequent reaction of phenols **3a-c** with trifluoromethanesulfonic anhydride in pyridine^{3a} afforded triflates **4a-c** in 70-80% yield.

To test the flexibility of the proposed methodology, triflates **4a-c** were allowed to react with different nucleophiles in the presence of a Pd catalyst. According to this procedure, 2-methyl-3-methoxybiphenyl, **5a**, *N,N*-diethyl-2-methoxy-6-methylbenzamide, **5b**, and 1-(2'-methylcarboxy-3'-methoxyphenyl)-2-phenylacetylene, **5c**, were obtained. Reaction conditions and yields are reported in Table 2.

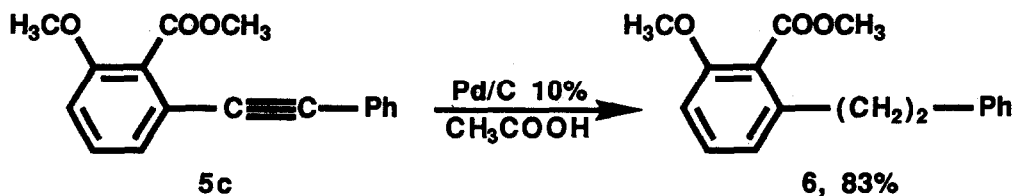
Table 2. Cross Coupling Reactions

substrate	catalyst (mol%)	R _n M (equiv)	solvent	t,h	T,°C	product (yield, %) ^a
4a	Pd(PPh ₃) ₄ (5)	PhB(OH) ₂ (2) ^b	DME	5	85	5a (80)
4b	PdCl ₂ (PPh ₃) ₂ (20)	Sn(CH ₃) ₄ (3) ^c	DMF	8	120	5b (49)
4c	PdCl ₂ (PPh ₃) ₂ (5)	PhC≡CH (1.5) ^d	DMF	16	90	5c (90)

^aDetermined on products isolated by flash chromatography. ^bIn the presence of 6.5 equiv of 2 M NaHCO₃ and of 3 equiv of LiCl. ^cIn two portions, according to ref. 3b, and in the presence of 8 equiv of LiCl and of 0.6 equiv of PPh₃. ^dIn the presence of 4.5 equiv of Et₃N.

The synthesis of compound **5b**, an intermediate in the synthesis of several isoquinolines,⁸ by the cross-coupling reaction of **4b** with Sn(CH₃)₄ deserves some comments. Indeed, while **4b** should be considered as an electron poor triflate, the cross-coupling conditions employed are characteristic of electron rich triflates.^{3b} However, under the reaction conditions usually employed for electron poor triflates^{3b} (small amount of catalyst, no phosphine added), decomposition of the catalyst was observed and the starting material was recovered unchanged.

Hydrogenation of **5c** at room temperature and ambient pressure over 10% Pd/C afforded 1-(2'-methylcarboxy-3'-methoxyphenyl)-2-phenylethane, **6**, in 83% yield. Compound **6** contains the whole carbon skeleton, as well as the correct pattern of 1,2,3-trisubstitution on a aromatic ring, of lunularic acid, a growth inhibitor found in *Lunularia cruciata*.^{9,10}



In conclusion, we have developed a versatile method for the regioselective synthesis of 1-oxy-2,3-dicarbobenzenes, starting from an easily accessible starting material. Further exploitation of this methodology is under investigation.

References and Notes

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- All compounds gave analytical and spectral (IR, NMR) data in accord with the assigned structures.

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