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THE REACTIONS OF UNACTIVATED ARYL HALIDES WITH SODIUM METHOXIDE IN HMPA

SYNTHESIS OF PHENOLS, ANISOLES, AND METHOXYPHENOLS

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Abstract—Sodium methoxide reacts with dichlorobenzenes in HMPA to give the chloroanisoles as a result of a S_NAr process. Excess MeONa then effects the demethylation of the ethers to give the chlorophenols via an S_N2 reaction. With tri- and tetrachlorobenzenes the initially formed chloroanisoles can be dealkylated to chlorophenols or can suffer further substitution to give the chlorodimethoxybenzenes; these react with excess MeONa to give the chloromethoxyphenols. The results obtained with the various isomers of the di-, tri-, and tetrachlorobenzenes are presented and discussed on the basis of the electronic effects of the substituents.

In recent papers we have shown that unactivated aryl halides easily react, in hexamethylphosphoramide, with sodium thiolates to give good yields of aryl alkyl sulphides.[1,2] Polychlorobenzenes react with excess thiolates to give poly(alkylthio)benzenes[1,3,4] in which all the Cl atoms have been substituted by an alkylthio group. These nucleophilic aromatic substitutions occur with the classical addition–elimination mechanism[1] and the alkylthio group activates the substitution of Cl by thiolate anions.[1] We have also shown that the alkylthio substituent activates the substitution of Cl by methoxide ions and this has been fruitfully employed to effect a very simple and efficient synthesis of methoxythioanisoles from dichlorobenzenes by means of two consecutive nucleophilic substitutions, first with sodium methanethiolate and then with sodium methoxide:[5]

$$C_6H_4Cl_2 \xrightarrow[HMPA]{MeSNa} C_6H_4ClSMe \xrightarrow[HMPA]{MeONa} C_6H_4(OMe)SMe.$$

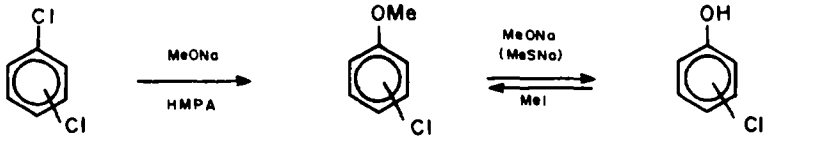
We now report that even the considerably less nucleophilic methoxide ions are capable of effecting nucleophilic aromatic substitutions on di-, tri-, and tetrachlorobenzenes, if the reactions are carried out in HMPA. In this case, however, the introduction of the first OMe group deactivates the molecule towards further aromatic substitutions. Thus, if excess MeONa is employed, a competitive reaction occurs, namely the nucleophilic aliphatic substitution at the OMe group which affords the corresponding phenols:

$$Ar(OMe)_2 \longleftarrow ArCl(OMe) + MeONa \longrightarrow ArCl(ONa) + Me_2O.$$

The relative importance of these two reactions depends on the nature of the chlorobenzene derivative employed. The results of the present investigations show that the reactions of methoxide ions with polychlorobenzenes can give good yields of chloroanisoles, chlorophenols, dimethoxychlorobenzenes and methoxychlorophenols.

RESULTS AND DISCUSSION

Shaw *et al.*[6] have shown that *o*- and *m*-dichlorobenzenes react with sodium methoxide (1.1 eqv), in HMPA, to give good yields of the corresponding chloroanisoles. We have now found that the reactions of *o*-, *m*- and *p*-dichlorobenzenes with excess MeONa (4 eqv), in HMPA at 120° for 2 hr, afford the chloroanisoles (**1–3**); these however were contaminated by the chlorophenols (**4–6**). These results indicate that the initially formed chloroanisoles further react with methoxide ions to suffer dealkylation as a result of a nucleophilic aliphatic substitution (Scheme 1) and not to give the products of displacement of the second Cl atom. The use of lower amounts of MeONa resulted in longer reaction times and in uncomplete transformation of the starting products. The composition of the reaction mixtures depends on the experimental conditions but complete transformation of



1 : *o*-
2 : *m*-
3 : *p*-

4 : *o*-(62%)
5 : *m*-(84%)
6 : *p*-(82%)

Scheme 1.

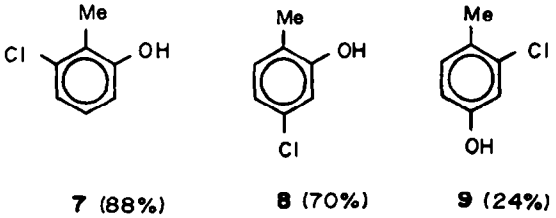
compounds (**1–3**) into (**4–6**) is not achieved even with prolonged reaction times and excess sodium methoxide. Once the starting products have been consumed the reaction mixtures consisting of the chloroanisoles and the chlorophenols can be directly used to obtain good yields of either of the two kinds of compounds. In fact, if a sodium alkanethiolate is added, compounds (**1–3**) are rapidly and completely dealkylated to the chlorophenols (**4–6**) with the yields indicated in parentheses in Scheme 1. It is noteworthy that even with strongly nucleophilic RSNa the substitution of Cl does not occur,[1] but the reaction takes place at the methyl C atom. The demethylation of aryl methyl ethers by thiolate ions is a well documented reaction[5,7] which occurs selectively also in the presence of a methylthio group.[8] On the contrary, if methyl iodide is added to the mixtures, compounds (**4–6**) are reconverted to the chloroanisoles (**1–3**) which can be isolated in yields similar to those of the chlorophenols (Scheme 1).

Similar results were obtained with the 2,6- and the 2,4-dichlorotoluenes. In this case the methoxyderivatives were not isolated but, after the reaction with MeONa, the reaction mixtures were directly treated with sodium isopropanethiolate to give the chlorocresoles (Scheme 2). From the reaction of the 2,6-dichlorotoluene compound (**7**) was obtained in 88% yield. In the case of the 2,4-dichlorotoluene the substitution process was not selective, but occurred preferentially at the 2 position; a mixture of the two isomers (**8** and **9**) was obtained with the yields indicated in parentheses in Scheme 2.

In a similar way, starting from 4-bromobiphenyl, α- and β-bromonaphthalene one can obtain 4-hydroxybiphenyl (75%), α- (64%) and β-naphthol (70%) or 4-methoxybiphenyl (78%), α- (68%) and β-methoxynaphthalene (74%). In the cases of the α- and β-naphthalene derivatives about 5–10% of the β- and α-derivatives were also produced indicating that an aryne mechanism may also be operating to a slight extent, as it was already observed in the reaction of α-chloronaphthalene.[6] With these three bromo derivatives traces of the dehalogenated compounds, biphenyl and naphthalene, were also isolated.

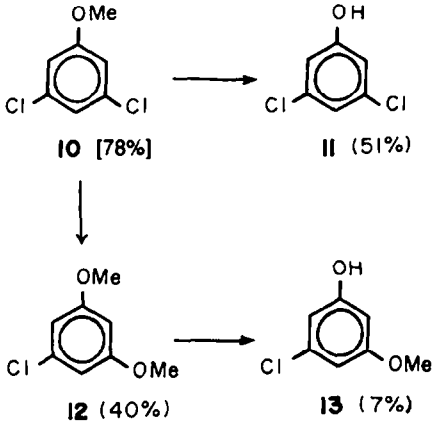
A more complicated picture emerges from the reactions of MeONa with tri- and tetrachlorobenzenes. In these cases in fact the first problem concerns the positional selectivity of the nucleophilic substitution. Furthermore, once the first OMe group has been introduced the further reaction with methoxide ions is not limited to the dealkylation of the ethereal function but the displacement of a second Cl atom is in competition. This process also presents problems of positional selectivity. In these cases the reaction mixtures could not be treated with an alkane thiolate because this does not effect only the demethylation reaction but it also gives rise to the substitution of the Cl atoms; in this way alkylthiochloroanisoles and their dealkylated products are formed giving a complex mixture of products. The mixtures from the reactions of the tri- and tetrachlorobenzenes were therefore either analysed directly or after treatment with methyl iodide.

In order to determine the positional selectivity of the substitution reaction the three isomeric tri- and tetrachlorobenzenes were treated with 1.5 equivalents of sodium methoxide in HMPA at 120° for 1 hr. Under these conditions the reactions gave only the products of monosubstitution; small amounts of phenols, if present, were reconverted to the OMe derivatives by adding methyl iodide. With the symmetrical 1,2,3-trichlorobenzene and 1,2,4,5-tetrachlorobenzene a single product was obviously obtained, namely compounds **10** and **21** (Schemes 3 and 6) in 78% and 66% yields respectively. A single product was also obtained from the 1,2,4-trichlorobenzene; interestingly this compound was that deriving from the displacement of the Cl atom from the 2 position, **14** (88%) (Scheme 4). This selectivity is not completely unexpected; in fact it can be expected that the balance of the electronic effects of the Cl atoms would favour the nucleophilic addition at the 2 position. For the same reason the reaction of the 1,2,4,6-tetrachlorobenzene occurred preferentially at the same position to give the 2,3,5-trichloroanisole, **27** (76%); substitution at the 1 position to give **25** (10%) (Scheme 7)



7 (88%) **8** (70%) **9** (24%)

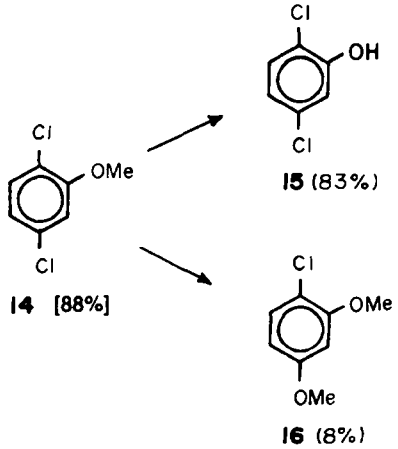
Scheme 2.



10 [78%] **11** (51%)

12 (40%) **13** (7%)

Scheme 3.



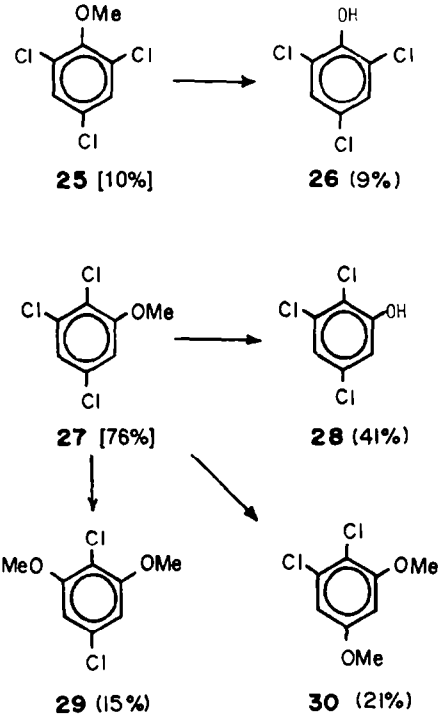
14 [88%] **15** (83%) **16** (8%)

Scheme 4.

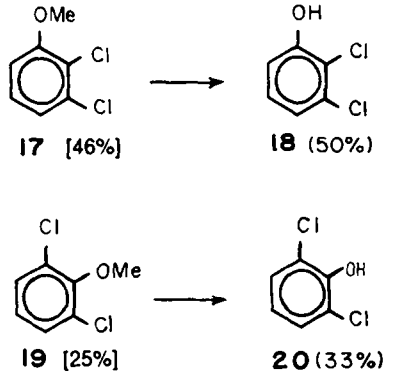
was considerably less important. With 1,2,3-trichlorobenzene and 1,2,3,4-tetrachlorobenzene the substitutions at the 1 and at the 2 positions were in competition; in the first case compounds **17** and **19** (Scheme 5) were formed in 46% and 25% yields respectively and in the second case compounds **31** and **33** (Scheme 8) were obtained in 52% and 32% yields. The yields of these chloroanisoles are reported in square brackets in the Schemes 3–8.

In a second type of experiments the tri- and tetrachlorobenzenes were allowed to react, in HMPA at 120°, with an excess of sodium methoxide (2 equivs for each Cl atom) until all the starting and the monosubstituted products were consumed (2–7 hr). Under these conditions the chloroanisoles (**10**, **14**, **17**, **19**, **21**, **25**, **27**, **31** and **33**) were completely transformed into the corresponding phenols and into the dimethoxy derivatives. The results of these experiments are reported in the Schemes 3–8. In some cases the dimethoxy derivatives were not isolated because they suffered dealkylation to give the corresponding methoxyphenols. The relative amount of these two kinds of compounds is a function of the amount of the sodium methoxide employed and of the reaction time and different results can therefore be obtained if the experimental conditions are changed. Thus, it can be expected that under more drastic conditions (higher temperatures, longer reaction times and larger excess of MeONa) all the dimethoxy derivatives can be transformed into the methoxyphenols; on the other hand, if the dimethoxy are the desired products, one can simply add methyl iodide to the mixtures before work up.

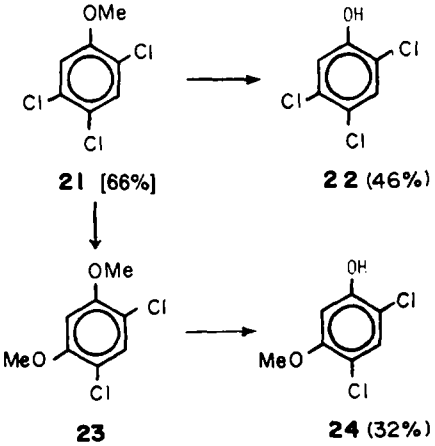
From the reaction of 1,3,5-trichlorobenzene a mixture of 3,5-dichlorophenol **11** (51%), 3-methoxy,5-chloroanisole **12** (40%) and 3-methoxy,5-chlorophenol **13** (7%) was obtained (Scheme 3); in this case therefore,



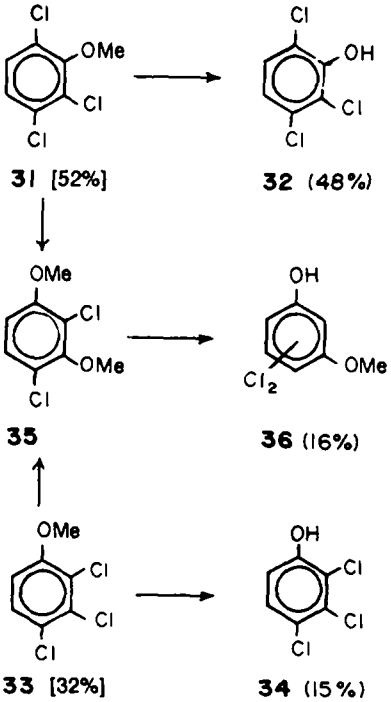
Scheme 7.



Scheme 5.



Scheme 6.



Scheme 8.

once the first methoxy group has been introduced to give **10**, the nucleophilic aromatic substitution of the second Cl atom and the dealkylation of the OMe group occur with comparable rates. On the contrary, in the case of the isomer **14**, derived from the 1,2,4-trichlorobenzene, the dealkylation reaction to give the 2,5-dichlorophenol **15** (83%) is greatly favoured in respect to the substitution; the displacement of the second Cl atom occurs selectively at the 4 position to give **16** (8%) (Scheme 4). From the 1,2,3-trichlorobenzene the only process observed is the dealkylation of **17** and **19** to give the 2,3-dichlorophenol **18** (50%) and 2,6-dichlorophenol **20** (33%) respectively (Scheme 5).

The introduction of a further Cl atom makes the molecules much more reactive towards the second nucleophilic substitution. Thus, with the exception of the 2,4,6-trichloroanisole (**25**) which gives rise exclusively to the corresponding phenol **26** (9%) (Scheme 7), all the trichloroanisoles deriving from the three isomeric tetrachlorobenzenes give rise to both dealkylation and nucleophilic aromatic substitution. The 2,4,5-trichloroanisole (**21**) affords a mixture of the phenol **22** (46%) and of the 2,4-dichloro,5-methoxyphenol **24** (32%) (Scheme 6). Similarly, 2,3,5-trichloroanisole **27** gives the phenol **28** (41%) and a mixture of the two dimethoxy derivatives **29** (15%) and **30** (21%) (Scheme 7). Finally, from the reaction of the 1,2,3,4-tetrachlorobenzene a mixture of 2,3,6-trichlorophenol **32** (48%) deriving from **31** and of 2,3,4-trichlorophenol **34** deriving from **33** was obtained; also formed in this reaction was the compound **36** (16%) which originates from the dealkylation of **35** and which can have the structure of the 2,6-dichloro,3-methoxyphenol or of the 2,4-dichloro,3-methoxyphenol. Compound **35** can be formed by **33** as well as from **31**; this latter reaction however should occur to a limited extent in view of the large amount of the phenol **32** obtained.

The whole of the results described above demonstrate that the substitution of the second Cl atom is mainly governed by the electronic effect of the OMe group; this reaction involves selectively only the Cl atoms which are *meta* to the OMe substituent, i.e. those nuclear positions which are made more positive by the electron-attracting inductive effect of the MeO group. This would explain why **19** and **25** give only the dealkylation process and can also justify the observed different reactivity of **10** in respect to **14** and **17**; in these two latter compounds in fact the substitution is made difficult by the presence of a Cl atom in the *para* or in the *ortho* positions.

The structural assignment of the reaction products could be easily effected by proton NMR spectroscopy. In the case of the dimethoxy derivatives the positions occupied by the two OMe groups were also established chemically; for this purpose compounds **13**, **24** and **36** were reconverted to **12**, **23** and **35** by treatment with methyl iodide. All the dimethoxy compounds reacted with excess sodium in HMPA to give the product of reduction of all the Cl atoms present in the molecule and of monodealkylation; in every case the product obtained was the *m*-methoxyphenol. This clearly demonstrates that the two methoxy groups are in *meta* in all the compounds investigated.

$$\mathbf{12, 16, 23, 29, 30, 35} \xrightarrow[\text{HMPA}]{\text{Na}} m\text{-}C_6H_4(OMe)OH$$

The reaction with sodium has been previously employed for similar purposes, in the case of some halogeno poly(alkylthio)benzenes.[3,4] In these compounds we observed that, not only all the Cl atoms were replaced by H, but also all the alkylthio groups present in the molecule were dealkylated to afford poly(mercapto)benzenes. It is interesting that in the reaction of excess sodium with the chlorodimethoxy compounds reported above the reaction does not proceed after the dealkylation of the first alkoxy group. This different behaviour between the ethers and the thioethers is also confirmed by other examples[8] which are presently under investigation and it is very likely due to the fact that the reduction of the two types of compounds proceeds with different mechanisms.[9]

EXPERIMENTAL

Commercial HMPA and polychlorobenzenes were used without further purification. Sodium methanethiolate, isopropanethiolate and methoxide were prepared as described in previous works.[3-5] Reaction products were identified by comparison of their physical and spectral properties with those reported in the literature and by proton NMR spectra. NMR spectra were recorded, in $CDCl_3$ solutions, on a 90 MHz Varian EM 390 instrument.

Reactions of polychlorobenzenes with sodium methoxide

General procedure. To a stirred soln of the chloro derivative (0.01 mol) in HMPA (30 ml), kept under N_2 at 120°, NaOMe (2 equivs for each Cl atom present in the molecule of the chloro derivative or 1.5 equivs) (*Cf.* Results and Discussion) was added. The progress of the reaction was monitored by TLC on silica gel using a mixture of light petroleum and ethyl ether (95:5) as eluant. The reaction times are reported in the Results and Discussion. In the cases of the mono- and dihalogeno derivatives the mixtures were treated with sodium methanethiolate or isopropanethiolate (2 equivs) and kept at 120° for 1 hr, cooled and poured into dilute HCl. This procedure was employed for the synthesis of the phenols. For the preparation of the OMe derivatives the mixtures were cooled to room temp and treated with MeI (1.5 equivs); after stirring for 1 hr the mixtures were poured into dilute HCl. This procedure was employed also for the synthesis of the monomethoxy derivatives of the tri- and tetrachlorobenzenes. The reactions of 4-bromobiphenyl, α- and β-bromonaphthalene were similarly carried out according to these two procedures. The final mixtures of the reactions of the tri- and tetrachlorobenzenes with excess NaOMe were instead directly poured into dilute HCl.

In every case the mixtures were then extracted with ether; the organic layer was washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel using a mixture of light petroleum and ethyl ether (95:5) as eluant. The reaction yields are reported in parentheses in the Schemes 1–8.

Compounds **1–6**, **10–13**, **17–20**, **22**, **26**, **28** and **31–34** are commercial products and their NMR spectra are reported in the Aldrich Library of NMR spectra. The physical and the NMR data of all the remaining compounds are reported below.

2-*Methyl*,3-*chlorophenol* (**7**), m.p. 84–6° (Lit.[10] m.p. 86°), δ 6.9–6.6 (m, 3H), 4.85 br (s, 1H), 2.3 (s, 3H).

2-*Methyl*,5-*chlorophenol* (**8**), m.p. 75–76° (Lit.[11] m.p. 74–5°). δ 6.95 (d, 1H, J = 7.8 Hz), 6.75 (dd, 1H, J = 7.8 and 1.8 Hz), 6.65 (d, 1H, J = 1.8 Hz), 5.35 br (s, 1H), 2.15 (s, 3H).

3-*Chloro*, 4-*methylphenol* (**9**), m.p. 55–6° (Lit.[12] m.p. 54°). δ 7.0 (d, 1H, J = 8.4 Hz), 6.8 (d, 1H, J = 2.5 Hz), 6.6 (dd, 1H, J = 8.4 and 2.5 Hz), 5.5 br (s, 1H), 2.25 (s, 3H).

2,5-*Dichloroanisole* (**14**), Oil (Lit.[13] m.p. 24°). δ 7.2 (d, 1H, J = 8.4 Hz), 6.9 (d, 1H, J = 2.4 Hz), 6.65 (dd, 1H, J = 8.4 and 2.4 Hz), 3.75 (s, 3H).

2, 5-*Dichlorophenol* (**15**), m.p. 60–1° (Lit.[13] m.p. 59°). δ 7.1 (d, 1H, J = 8.4 Hz), 6.95 (d, 1H, J = 2.4 Hz), 6.8 (dd, 1H, J = 8.4 and 2.4 Hz), 5.55 br (s, 1H).

2,4-*Dimethoxychlorobenzene* (**16**), Oil (Lit.[14] b.p. 135–

7°/18 mm). δ 7.2 (d, 1H, J = 8.4 Hz), 6.45 (d, 1H, J = 2.7 Hz), 6.4 (dd, 1H, J = 8.4 and 2.7 Hz), 3.85 (s, 3H), 3.75 (s, 3H).

2,4,5-*Trichloroanisole* (**21**), m.p. 74–5° (Lit.[15] m.p. 70°). δ 7.45 (s, 1H), 7.0 (s, 1H), 3.85 (s, 3H).

2,4-*Dichloro*,5-*methoxyanisole* (**23**), m.p. 118–119° (Lit.[16] m.p. 118°). δ 7.25 (s, 1H), 6.45 (s, 1H), 3.8 (s, 6H).

2,4-*Dichloro*, 5-*methoxyphenol* (**24**), Oil (Lit.[17] b.p. 82–5°/0.4 mm). δ 7.2 (s, 1H), 6.55 (s, 1H), 5.2 br (s, 1H), 3.8 (s, 3H).

2, 4, 6-*Trichloroanisole* (**25**), m.p. 58–9° (Lit.[18] m.p. 60°). δ 6.9 (s, 2H), 3.75 (s, 3H).

2,3,5-*Trichloroanisole* (**27**), m.p. 84–5° (Lit.[19] m.p. 84°). δ 7.05 (d, 1H, J = 2.1 Hz), 6.75 (d, 1H, J = 2.1 Hz), 3.85 (s, 3H).

2,5-*Dichloro*,3-*methoxyanisole* (**29**), m.p. 101–3°. δ 6.6 (s, 1H), 3.9 (s, 3H).

2,3-*Dichloro*,5-*methoxyanisole* (**30**), m.p. 58–9°. δ 6.55 (d, 1H, J = 3 Hz), 6.35 (d, 1H, J = 3 Hz), 3.85 (s, 3H), 3.75 (s, 3H).

2,6-*Dichloro*,3-*methoxyanisole* (**35**), Oil. δ 7.2 (d, 1H, J = 9 Hz), 6.6 (d, 1H, J = 9 Hz), 3.95 (s, 3H), 3.9 (s, 3H).

2,6-*Dichloro*,3-*methoxyphenol* or 2,4-*dichloro*,3-*methoxyphenol* (**36**), Oil. δ 7.1 (d, 1H, J = 9 Hz), 6.4 (d, 1H, J = 9 Hz), 5.9 br (s, 1H), 3.85 (s, 3H). Acetate, m.p. 78–80°. δ 7.2 (d, 1H, J = 9 Hz), 6.7 (d, 1H, J = 9 Hz), 3.85 (s, 3H), 2.35 (s, 3H).

Reactions of the chlorodimethoxy derivatives with sodium. To a stirred soln of the dichlorodimethoxy derivative (**12**, **16**, **23**, **29**, **30**, **35**) in HMPA, under N_2 at 120°, small pieces of Na(10 equivs) were added. The progress of the reaction was monitored by tlc; after about 2–3 hr the starting products were completely consumed and the mixtures were poured into dil HCl and worked up in the usual way. In every case the only product obtained was the *m*-methoxyphenol, identical to an authentic sample.

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