A NEW METHOD FOR THE SELECTIVE ORTHO-FORMYLATION OF PHENOLS

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In connection with our previous work on the synthesis of some phenolic mould metabolites (1) and the researches in progress on the reactivity of phenoxymagnesium halides (2,3) ArOMgX, (I) (4), we have investigated their behaviour towards orthoformic esters. We found that on heating the halides (I) with an excess of ethylorthoformate the corresponding ortho-hydroxyaldehydes are formed without any detectable amount of the para-isomer. This reaction offers therefore a valuable practical method for the selective orthoformylation of phenols.

A typical procedure is as follows : 0.1 mole of o-cresol was added at room temperature to the equivalent amount of EtMgBr in ether; when the evolution of ethane had ceased, 20-30 ml of ethylorthoformate was added, and the ether distilled at ordinary pressure allowing the temperature to rise to 100°C. At this point the reaction mixture was decomposed with aqueous 10% hydrochloric acid and then extracted with ether. Steam distillation of the oil left after removal of the solvent gave 2-hydroxy-3-methylbenzaldehyde in 42 % yield (calculated on the weight of the pure 2,4-dinitrophenylhydrazone, m.p. 251-252°); no 4-hydroxy-3-methylbenzaldehyde could be detected in the residue of the steam distillation.

The results obtained with different phenols and phenolethers are presented in Table I.

Table I

Starting material	Product	Yield %(5) (as DNP)
Phenol	2-Hydroxy-benzaldehyde	7
o-Cresol	2-Hydroxy-3-methyl-	42
m-Cresol	2-Hydroxy-4-methyl-	22
p-Cresol	2-Hydroxy-5-methyl-	30
2,5-Xylenol	2-Hydroxy-3,6-dimethyl-	55
3,4-Xylenol	2-Hydroxy-4,5-dimethyl-	25
3,5-Xylenol	2-Hydroxy-4,6-dimethyl-	35
p-tert.Butylphenol	2-Hydroxy-5-tert.butyl-	15
2-Methyl-4-tert. butylphenol	2-Hydroxy-3-methyl-5-tert.butyl-	37
Thymol	2-Hydroxy-3-isopropyl-6-methyl-	45
Carvacrol	2-Hydroxy-3-methyl-6-isopropyl-	4.5
o-Methoxyphenol	2-Hydroxy-3-methoxy-	-
m-Methoxyphenol	2-Hydroxy-4-methoxy-	18
p-Methoxyphenol	2-Hydroxy- 5-methoxy-	12
o-Chlorophenol	2-Hydroxy-3-chloro-	1.5
p-Chlorophenol	2-Hydroxy-5-chloro-	4.5

The reaction proved to be highly specific for the orthoformylation of phenols and in this regard differs from the methods already known(6); no p-hydroxy isomer could be found in the reaction mixture in all the cases investigated, and ortho-disubstituted phenols such as 2,6-xylenol were recovered unaffected.

Phenols containing electron-attracting substituents do not react indipendently from the position of the substituent in respect to the hydroxyl; thus, negative results have been obtained with the magnesium derivatives of o-, m- and p-carbomethoxy- and nitro-phenols, and very poor yields are given by chlorophenols. Alkyl substituents facilitate the process, but steric factors clearly affect its general course. Ortho alkylphenols are more reactive than their meta and para isomers; moreover, for 2,5-dialkylphenols, the yield decreases dramatically when a bulky substituent is present in 5-position as in the case of carvacrol.

The formation of inter- or intramolecular complexes concerning the phenoxymagnesium compounds plays also an important role, as shown by the behaviour of the three isomeric methoxyphenole. The reaction is inhibited in aprotic solvents only when they possess a high complexing and/or solvating power on the cation(7); accordingly, phenoxy- and p-methylphenoxymagnesium bromide do not react in pyridine or dioxane at 100° with ethylformate, but they behave normally in benzene and xylene solution. In an experiment performed in a protic solvent (phenoxymagnesium bromide in a large excess of phenol) in the usual conditions, no reaction occurred.

REFERENCES

1. C. Cardani and G. Casnati, Gazz. Chim. It. 87, 43 (1957); C. Cardani, G. Casnati, F. Piozzi and B. Cavalleri, Gazz. Chim. It. 88, 487 (1958).
2. About the reactivity of the phenoxymagnesium halides see H. Gilman and F. Schulz, Rec. trav. chim. 47, 752 (1928).
3. Some examples of Kolbe's reaction for phenoxymagnesium halides were reported by B. Oddo, Gazz. Chim. It. 41, 255 (1911).
4. It is possible that equilibria of type :

$$2\ ArOMgBr \rightleftharpoons (ArO)_2Mg \cdot MgBr_2$$

or similar may occur in the conditions in which the reaction is carried out; the phenoxyderivative actually involved in the process might therefore possess a structure different from (I).
5. Some unchanged phenol is always present in the reaction mixture; actual yields on the reacted phenol are therefore somewhat higher. Gas chromatographic analysis of the crude reaction product showed that no other substance, besides the o-hydroxylaldehyde and the phenol, was present.
6. The Duff reaction is also highly selective, but frequently, besides the expected o-hydroxyaldehydes, o,p-dialdehydes are formed which may in some cases become the only reaction product. See Note 1.
7. N. Kornblum, P.J. Berrigan and N.J. Le Noble, J. Am. Chem. Soc. 85, 1141 (1963).