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# HYDROGEN BONDING IN ORGANIC SYNTHESIS IV:
# A SIMPLE, HIGH-YIELD METHOD FOR THE METHYLENATION OF CATECHOLS

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The methylenedioxy group is of special interest in chemistry because it occurs in many natural products[1] and has been suggested as a protecting group in catechols[2]. However, attempts to carry out the methylenation of catechols have generally afforded low yields of products though many attempts at improvement have been made.

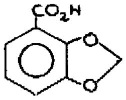
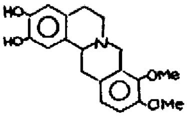
Bonthrone and Cornforth have shown[3] that the use of a dipolar aprotic solvent such as dimethylsulphoxide may considerably enhance the rate of reaction and the product yield although this method sufferred from the somewhat tedious procedure of slow addition of a mixture of solid sodium hydroxide and the catechol under a nitrogen atmosphere. Since then, a number of workers have reported the high-yield methylenation of several substituted catechols using dimethylsulphoxide or N,N-dimethylformamide as solvent in the presence of a bronze[4], nickel oxide[5] or cupric oxide[6] catalyst. More recently, Bashall and Collins have shown[7] that high yields of methylenated catechols may be obtained in the absence of a dipolar aprotic solvent by using a phase transfer catalyst under reflux conditions, although this process still required the use of strong base and the method of slow addition of the reactants under a nitrogen atmosphere during a period of some 3 hours.

We now wish to report a simple method for the high-yield methylenation of catechols which requires neither the use of strong base nor any special precautions such as a nitrogen atmosphere or controlled addition of reagents. The reaction of a catechol with dihalogenomethane in D.M.F. in the presence of an excess of potassium or caesium fluoride provides a high yield of the corresponding methylenedioxy compound in a relatively short period of time.

In a recent communication[8] we reported a number of rapid and high-yield H-bond assisted condensations between halogenoalkanes and aromatics capable of acting as H-bond electron acceptors with fluoride. *We believe that these reactions and those described here are* accelerated by the formation of an H-bond between the fluoride anion and the aromatic molecule which directs electrons from the electron-rich fluoride anion to the organic part of the complex.

We have shown, by observing the large shift in the electron acceptor stretching band in the I.R., that 1,2-dihydroxyaromatics are capable of behaving as H-bond electron acceptor sites and producing strong H-bonds ($\Delta H^\circ$ = 62 kJ mol$^{-1}$ [9]) with fluoride.

The various methylenations that were attempted[10] are shown along with recovered yields and extent of intermolecular reaction[3] in the table. Products were identified by routine analysis and by comparison with authentic samples.

| Reactant | Product | Recovered Yield (%) | Reaction Time (h) | Degree of Intermolecular Reaction* (%) |
|---|---|---|---|---|
| 1. Catechol/KF/CH$_2$Br$_2$ | Benzo-1,3-dioxole | 84 | 1 | >10 |
| 2. Catechol/CsF/CH$_2$Br$_2$ | Benzo-1,3-dioxole | 86 | 0.5 | 8 |
| 3. Catechol/CsF/CH$_2$Cl$_2$ | Benzo-1,3-dioxole | 98 | 1.5 | trace |
| 4. 2,3-Dihydroxynaphthalene/KF/CH$_2$Br$_2$ | Naphtho[2,3-d][1,3]dioxole | 70 | 1.2 | >20 |
| 5. 2,3-Dihydroxynaphthalene/CsF/CH$_2$Br$_2$ | Naphtho[2,3-d][1,3]dioxole | 88 | 0.5 | <10 |
| 6. 2,3-Dihydroxynaphthalene/CsF/CH$_2$Cl$_2$ | Naphtho[2,3-d][1,3]dioxole | 98 | 1.5 | trace |
| 7. 3-Methylcatechol/KF/CH$_2$Br$_2$ | 3-Methyl-benzo-1,3-dioxole | 81 | 1 | -- |
| 8. 3,4-Dihydroxybenzaldehyde/KF/CH$_2$Br$_2$ | Piperonal | 90 | 1.2 | -- |
| 9. 2,3-Dihydroxybenzoic acid†/KF/CH$_2$Br$_2$ |  | 82 | 1.2 | -- |
| 10.  | dl-Canadine | 78 | 1.5 | -- |

* Determined by recovery of residue from separation.

† This methylenation reaction was carried out using the ethyl ester

On shaking anhydrous caesium fluoride (7.6 g, 0.05 mol.) with a solution of catechol (1.1 g, 0.01 mol.) in anhydrous D.M.F. (30 g), the mixture became warm and the I.R. of the mixture showed a new strong broad band at ca 2500 cm$^{-1}$ due to $\nu_s(\text{O-H}\ldots\bar{\text{F}})$ which represents a shift $\Delta\nu_s(\text{OH})$ of some 1100 cm$^{-1}$ indicative of a strong H-bond. Dichloromethane (0.935 g, 0.011 mol.[11]) was added to the cooled solution and the mixture heated at 110-120°C for 1.5 h (100% reaction by $^1$H N.M.R. analysis). The cooled reaction mixture was then separated by ether extraction followed by washing the ethereal extracts with water (to remove D.M.F.) and with cold dilute alkali. Drying and evaporation followed by extraction of the pure product with hot pentane or by steam-distillation afforded benzo-1,3-dioxole (1.19 g, 0.0098 mol., 98%). Analysis of the residue showed only a trace (<1%) of dimer (m/e 244).

To date, the ionizing base for catechols has always been an alkoxide, alkali hydroxide or carbonate. Our method offers an alternative route to methylenations involving the use of an alkali metal fluoride and D.M.F. via an H-bonding mechanism. The method is fast, efficient, provides high recoverable yields and avoids strongly basic conditions. Furthermore, it would seem that by using caesium fluoride and dichloromethane, intermolecular condensations may be kept to a minimum. These results offer further striking evidence for the potential general significance of the method of H-bond assisted reactions to synthetic chemistry.

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References

1. F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963.
2. J. F. McOmie, "Protective Groups in Organic Chemistry", Plenum, London, 1973.
3. W. Bonthrone and J. W. Cornforth, J. Chem. Soc. [C], 1969, 1202.
4. H. Fujita and M. Yamashita, Bull. Chem. Soc. Japan, 1973, 46, 355.
5. H. Fujita and M. Yamashita, Yukui Gosei Kagako Kyokai Shi, 1973, 31, 932.
6. I. R. C. Bick and R. A. Russell, Aust. J. Chem., 1969, 22, 1563.
7. A. P. Bashall and J. F. Collins, Tet. Lett., 1975, 40, 3489.
8. J. H. Clark and J. M. Miller, Chem. Commun., 1976, 229.
9. J. H. Clark and J. M. Miller, J. Amer. Chem. Soc., submitted for publication.

10. We have attempted to extend this reaction procedure to the preparation of the polycyclic compounds hydrastine and bicuculline using the corresponding di- and tetrahydroxy compounds as starting materials. To date, our reactions have only provided break-down products although reaction monitoring by thin layer chromatography and by $^1$H N.M.R. analysis has revealed the presence of the desired products during the course of the reactions. We believe that by carefully controlling the conditions of these reactions it may be possible to prepare reasonable quantities of these materials. Work is continuing in this direction.

11. A 10 mole% excess of dihalogenomethane was used in all the reactions described to allow for minor dehydrohalogenation processes which may occur in the presence of fluoride/ D.M.F.