

Hydrogen Bonding in Organic Synthesis; Enhanced Reactivity of Aromatic Compounds Capable of Hydrogen Bonding to Fluoride

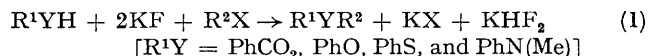
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Summary Reactions of halogenoalkanes with mixtures of potassium fluoride and a number of simple aromatic compounds capable of behaving as hydrogen-bond electron-acceptors give high yields of products in a short time; the reactions are thought to involve the transfer of electrons from fluoride to the aromatic molecule *via* the hydrogen bond.

RECENT studies on fluoride-carboxylic acid systems have revealed the presence of very strong H-bonds formed between the fluoride anion and the acid hydroxy-proton.¹ These systems have been shown to be only mild fluorinating agents but strong acyloxylating agents.² We have found that mixtures of KF and a number of aromatic compounds capable of acting as H-bond electron acceptors† rapidly react with halogenoalkanes with more or less complete

conversion of the halogen into water-soluble halide, producing the organic condensation [reaction (1)].



The reactions are usually more rapid and provide higher recoverable yields than standard methods for the preparation of the various condensation products (see Table). The reactions involving KF are probably 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.

Liquid phenol (2 mol. equiv.) and anhydrous KF (1 mol. equiv.) were shaken together at room temperature. The mixture became hot as the KF dissolved and the i.r.

TABLE

Preparation of various organic condensation products by H-bond assisted reactions and comparison with standard procedure

Desired products ^a	Starting materials	Time/h	Temp./°C	Yield/%
PhCO ₂ [CH ₂] ₄ O ₂ CPh	PhCO ₂ H-KF-Cl[CH ₂] ₄ Cl	1.5	130	90
MeCH(O ₂ CPh)CO ₂ H ^b	PhCO ₂ KF-MeCH(Cl)CO ₂ H	0.5	130	90
PhO[CH ₂] ₄ OPh ^c	PhOH-KF-Br[CH ₂] ₄ Br	0.5	130	93
MeCH(OPh)CO ₂ H ^d	PhOH-KF-MeCH(Cl)CO ₂ H	0.1	130	95
PhS[CH ₂] ₄ SPh	PhSH-KF-Cl[CH ₂] ₄ Cl	4	120	92
MeCH(SPh)Et ^e	PhSH-KF-MeCH(I)Et	8	120	92
PhN(Me)[CH ₂] ₄ N(Me)Ph ^f	PhN(Me)H-KF-Cl[CH ₂] ₄ Cl	1	130	20
PhN[CH ₂] ₃ CH ₂		1	130	36
PhNMe ₂		1	130	37
PhN(Me)[CH ₂] ₂ N(Me)Ph ^g	PhN(Me)H-KF-Cl[CH ₂] ₂ Cl	1	110	37

^a In none of these reactions was any fluoroalkane found. Standard procedures: ^b Starting materials: PhCO₂H-MeCH(Cl)CO₂H; 6 h; 130 °C; 20% yield; this work. ^c PhOH-NaOH-Cl[CH₂]₄Cl; 1 h; 150 °C; 49% yield; ref. 5. ^d See text for comparison with preparation of MeCH(OC₆H₄R)CO₂H. ^e PhSNa-MeCH(Br)Et; 24 h; 120 °C; 45% yield; ref. 6. ^f For preparation of PhN(Me)-[CH₂]₅N(Me)Ph (nearest literature equivalent) PhN(Me)H-Na₂CO₃-Br[CH₂]₅Br; 24 h; 105 °C; 22% yield, ref. 4. ^g PhN(Me)H-Na₂CO₃-Br[CH₂]₂Br; 24 h; 105 °C; 83% yield; ref. 7.

† We prefer the use of the more general terms *electron* donor and acceptor rather than *hydrogen* donor and acceptor in accordance with their usage in 'Hydrogen Bonding by C-H Groups,' by R. D. Green, Wiley, New York, 1974.

spectrum showed a $\Delta\nu_s$ (OH) of *ca.* 1000 cm^{-1} indicative of a very strong H-bond. Heating the mixture with 2-chloropropanoic acid (0.4 mol. equiv.) at 130 °C for 5 min followed by extraction with ether and treatment with HCO_3^- to remove the product as its sodium salt gave on acidification 2-phenoxypropanoic acid (\pm) (m.p. 113 °C, 95%). This compares with yields of *ca.* 30% of ring-substituted 2-phenoxypropanoic acids of the type $\text{MeCH}(\text{OC}_6\text{H}_4\text{R})\text{CO}_2\text{H}$ obtained by treatment of activated phenols $\text{RC}_6\text{H}_4\text{OH}$ with $\text{MeCH}(\text{Cl})\text{CO}_2\text{Na}$ during 8 h.³

Similarly rapid and efficient reactions occurred on heating 1,4-dibromobutane or 1,4-dichlorobutane with mixtures of KF and phenol, KF and benzoic acid, and KF and benzene-thiol producing 1,4-diphenoxybutane, 1,4-dibenzoxybutane, and 1,4-bis(phenylthio)butane. Heating 1,4-dihalogenobutane with a mixture of KF and *N*-methylaniline produced *NN'*-dimethyl-*NN'*-diphenyltetramethylenediamine, *NN*-dimethylaniline, and *N*-phenylpyrrolidine in a molar ratio of *ca.* 1 : 2 : 2. The predominance of the latter two products

is probably due to preferred cyclisation as was suggested in an earlier attempt to prepare compounds of the type $\text{PhN}(\text{Me})[\text{CH}_2]_n(\text{Me})\text{Ph}$.⁴ In all these reactions, the avoidance of a solvent and the overall efficiency facilitates separation procedures and helps to afford high recoverable yields. The inorganic components may be removed in the aqueous extract and any excess of changed aromatic compound may be readily removed by chemical methods or by distillation.

The reactions that were attempted are summarised and, where possible, compared to standard preparations, in the Table. In all these systems the solubility of KF in the aromatic solvent (a melt in the case of benzoic acid) was sufficient to reveal, by virtue of observed shifts in ν_s (YH) and δ (YH), the formation of an H-bond of the type $\text{RYH} \cdots \text{F}^-$.

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