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METAL FLUORIDES AS BASE FOR THE "TEMPLATED" SYNTHESIS OF CROWN ETHERS

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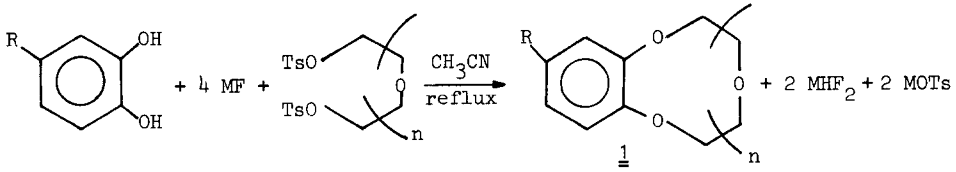
In a number of reactions weakly solvated ("naked") fluoride anions have been used as a base, either in catalytic or in stoichiometric amounts[1-3]. The basic character of the fluoride anions in these reactions are related to the formation of strong hydrogen bonds with, rather than to complete deprotonation of, the acid[2,4]. Recently Clark and Miller[5] reported the synthesis of aryl ethers by reaction of phenol with alkylhalides in the presence of two equivalents of potassium fluoride.

In connection with our work on crown ethers we have investigated the possibility of using metal fluorides as the base for the synthesis of such ethers. Crown ethers are now used for many purposes such as the generation of nucleophiles[3], the selective complexation of cations[6] and the resolution of chiral amines[7], but unfortunately only a few methods are available for their synthesis[8]. Hitherto most crown ethers have been obtained by substitution of in situ generated α, ω- dialkoxides for the halogens in α,ω-dihalides. The bases normally used in such reactions are alkali metal hydroxides, potassium tert-butoxide, sodium hydride and butyllithium.

We have now found that good yields of crown ethers are obtained when aromatic diols, e.g. catechol, and polyethylene glycol ditosylates are reacted in the presence of excess ($\geqslant 4$ equivalents) of solid metal fluorides (M = K, Rb or Cs) in dry acetonitrile at reflux temperature. Our results, presented in Table I, show not only that these fluorides are sufficiently strong bases to generate a good nucleophile for the formation of an ether bond, but also that the cations play an important role in the cyclization step. They act as a template ion, as can be concluded from the result of a comparative experiment with tetrabutylammonium fluoride. The yield of benzo-18-crown-6 in the latter reaction was less than 5 %, whereas the yield obtained with the metal fluorides ranged from 52 to 67 %. The rate of the substitution reaction proved to depend on the type of fluoride ($Cs^+ > Rb^+ \geqslant K^+ \gg Na^+ \sim Li^+$), a phenomenon that is probably related to the different solubilities of the salts[11]. It should be noted that the yields of the crown ethers obtained are higher with cesium and rubidium fluoride than with potassium fluoride, even in the case of benzo-15-crown-5 and benzo-18-crown-6. This seems to be in contrast with the accepted picture of the template cation ideally fitting into the cavity of the crown ether that is formed[8,9]. There are no data about the template effect, on the yield of crown ethers, of alkali metal cations larger than potassium. However, Piepers and Kellogg[12] recently reported high yields of macrocyclic bis-lactones from the reaction of the dicesium salts of aromatic dicarboxylates with α,ω-dibromides derived from polyethylene glycols. The same reaction applied to bis-phenolic compounds gave high yields of the corresponding crown ethers[13]. It was found that in these reactions cesium cannot be replaced by other alkali metal cations.

TABLE I

REACTIONS OF CATECHOL WITH POLYETHYLENE GLYCOL DITOSYLATES IN THE PRESENCE OF METAL FLUORIDES (MF)[a)]



n (R = H)	MF	Reaction time[b)] (h)	Yield (isolated) (%)	Ref.[c)]
3	KF	140	39	9
3	CsF	21	61	
4	KF	69	52	9
4	RbF	65	67	
4	CsF	17	60	
4	$(nBu)_4NF$	19	5	
5	KF	142	28	
5	CsF	21	65	
6	CsF	24	59	
7	CsF	24	44	10

a) With lithium and sodium fluoride no conversion of the ditosylate was achieved, even after 140 hours.

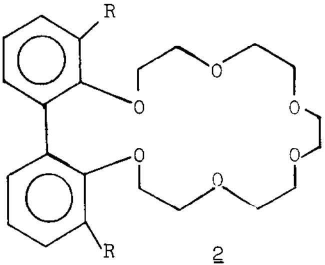
b) Reactions were run till complete conversion of the ditosylate (PMR spectroscopic evidence).

c) Crown ethers were identified either by comparison with authentic samples (n = 3, 4, 7) or by PMR/^{13}C NMR spectroscopy and mass spectrometry (n = 5, 6).

Several substituted catechols (R = CHO, $COCH_3$, $COOC_2H_5$, CH_2OH) gave good yields of crown ethers (1) without any side reaction of the substituents (Table II). Other aromatic diols such as 2,2'-dihydroxy-1,1'-binaphthyl also reacted with pentaethylene glycol ditosylate in the presence of cesium fluoride to give the 20-crown-6 compounds, but the yields were lower (23-47 %).

TABLE II

SYNTHESIS OF CROWN ETHERS 1 - 3 FROM AROMATIC DIOLS AND PENTAETHYLENE GLYCOL DITOSYLATE WITH CESIUM FLUORIDE IN ACETONITRITE



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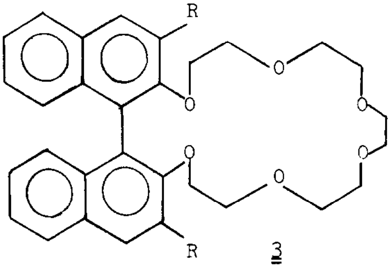

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Crown ether	R	Reaction time, h	Yield, %	Ref.
1, n = 4	CH_3CO	23	52	14
1, n = 4	CHO	23	57	15
1, n = 4	CH_2OH	19	47	a
1, n = 4	$COOC_2H_5$	16	68	b
2	H	40	23	16
2	$CH_2CH = CH_2$	27	47	
3 (-)-S-	H	24	29c	16

a) Prepared independently (for identification purposes) by reduction of 1 (R = $COOC_2H_5$) with lithium aluminium hydride

b) Prepared independently by reaction of 1 (R = CH_3CO) with hypochloride followed by esterification of the acid 1 (R = COOH)

c) $[\alpha]_D = 77.1$ (m.p. 70-71 °C)

We found that this method of crown ether synthesis depends greatly on the acidity of the diol reactant. For instance, similar reactions of polyethylene glycols with α,ω-ditosylates only yielded the corresponding α,ω-difluorides. In this case the fluoride anion reacts as a nucleophile rather than as a base, a type of reaction which metal fluorides are known to display in weakly solvating solvents such as acetonitrile[3]. The same result was obtained when benzoin was reacted with pentaethylene glycol ditosylate in the presence of cesium fluoride[17].

The use of metal fluorides instead of aqueous bases is advantageous in those cases where the substrate has a base-sensitive substituent, such as an ester or aldehyde group.

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