NEW ANHYDROUS FLUORINATING SYSTEMS: THE COMBINATION OF CROWN-ETHERS AND CESIUM FLUORIDE. A RELATIVE RATE STUDY.

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Abstract: New, anhydrous fluorinating systems are presented. 18-Crown-6 or dibenzo-24-crown-8 act as solid-liquid phase transfer catalysts with cesium fluoride. A catalytic amount of these crown ethers with CsF increased the rate of fluorodestannylation of trialkyltin mercaptides (used as a good fluoride probe) by a factor of 5-7. In addition, alkyl bromides, such as benzyl bromide, reacted in a similar way. Kinetic evidence for "sandwich" or "edge" complexes with the cesium cation and 18-crown-6 is presented.

Although numerous fluorinating agents have been developed since 1970, only a few of them are effective enough to be used in a totally anhydrous medium. This lack of a simple, practical and anhydrous SN2 type fluorinating agent appears to be mainly caused by strong hydrogen bonding of the fluoride ion with water.

Recent work by Clark and Ichihara has focussed on calcium fluoride-supported alkali metal fluoride (including cesium fluoride) in order to enhance fluorinations. While developing our fluorodestannylation procedure we have made a systematic study of several fluoride sources. We found that cesium fluoride is not very efficient as a destannylation agent. In a similar fashion, we found that addition of a catalytic amount of 18-crown-6 (0.20 eq.) or dibenzo-24-crown-8 (0.20 eq.) resulted in a significant increase in reaction rate at room temperature for the generation of sulfide from bis(tributyltin) sulfide (1). Although these are not well known reagents, we demonstrated in a previous publication that organotin sulfides (including 1), act as excellent probes to assign the relative nucleophilicity of the fluorinating agent. While the idea of using 18-crown-6 with metal fluorides (NaF, KF) is not new, this simple crown-ether with cesium fluoride appears not to have been investigated.

\[ \text{Bu}_3\text{Sn-S-SnBu}_3 \]

1
Indeed, it is expected that the large diameter of cesium (3.34 Å, revised version\textsuperscript{9}) makes it impossible to fit perfectly in the cavity of 18-crown-6 (2.6–3.2 Å, revised version\textsuperscript{4} to form a flat 1:1 complex as described by Pedersen in 1967\textsuperscript{9}. Later, he found that some 2:1 or 3:2 complexes are possible with cesium\textsuperscript{8}. Recently, Kellogg\textsuperscript{7} demonstrated by using \textsuperscript{133}Cs NMR that some 1:1 and higher complexes with 18-crown-6 were indeed possible (although not shown with CsF). In our case, it is also possible that cesium fluoride and 18-crown-6 complex together to make a "sandwich" or a "club-sandwich" complex as proposed by Pedersen\textsuperscript{8} or a 1:1 "edge" complex. Thus, this fluorodestannylation constitutes evidence of the existence of these sandwich or edge complexes\textsuperscript{10}.

In Figure 1, the rate of fluorodestannylation of benzyl(tributyltin) sulfide (2) with cesium fluoride with or without 18-crown-6 is displayed. Using the initial rate method\textsuperscript{11}, the reaction rate increased by a factor of five at room temperature when using 18-crown-6 (Eq. 1).

\[
\text{CsF} \\
\text{Bu}_3\text{Sn-S-CH}_2\text{Ph} + \text{CH}_3(\text{CH}_2)_5\text{Br} \rightarrow \text{PhCH}_2\text{S(CH}_2)_5\text{CH}_3 + \text{Bu}_3\text{Sn-F} + \text{CsBr} \quad (\text{Eq. 1})
\]

![Figure 1: Rate Effect of Crown Ethers on Equation 1.](image)

In addition, we investigated the same reaction with dibenzo-24-crown-8 as catalyst (0.20 eq.). We obtained a rate increase of seven, roughly equivalent as with 18-crown-6 (factor of 5). From this, we conclude that "sandwich" or "edge" complexes have a similar efficiency as with a "usual" and flat 1:1 guest/host ratio complex (Fig. 2). Furthermore, the low solubility of cesium fluoride in acetonitrile\textsuperscript{12} suggests that 18-crown-6 and dibenzo-24-crown-8 act as solid-liquid phase transfer catalysts (PTC)\textsuperscript{13}. An evaluation of the nucleophilicity of these fluorinating systems thus give this qualitative order: TBAF "anhydrous"\textsuperscript{2} > CsF,24-crown-8 \sim CsF,(18-crown-6)\textsubscript{4} > KF,18-crown-6.
Figure 2

These fluorinating systems demonstrate a useful approach towards an anhydrous fluorinating source. Indeed, 18-crown-6 can be dried in acetonitrile according to Gokel and Cram\textsuperscript{14} and dibenzo-24-crown-8 is much less hygroscopic than the former.\textsuperscript{15} Also, it should be pointed out that these catalysts are used in catalytic amounts, hence the water associated with their presence should be negligible when dried. To confirm this, we never observed a significant amount of thiol in these fluorodestannylation reactions.\textsuperscript{5}

As previously mentioned, the recent reports\textsuperscript{4} on the fluorination of benzyl bromide and other organic substrates indicated a rate enhancement by the use of CsF or KF supported on CaF\textsubscript{2}. We carried out experiments to see if fluorinations would be increased by the use of CsF with 18C6. The result is displayed in Figure 3. There is an approximate rate enhancement of a factor of five for the production of benzyl fluoride from benzyl bromide. Thus, this system of CsF with crown ethers has applicability for the destannylation/alkylation reaction as well as a classic fluorination procedure.

Figure 3

Finally, these kinetic enhancements with the complexation of CsF and crown-ethers could certainly modify to some extent, pioneering works with this reagent in macrocyclic lactone ring closure reactions\textsuperscript{16} and macrocyclic sulfide formation (including cyclophanes and related compounds).\textsuperscript{17}

Acknowledgements

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References

1. These include: fluorophosphoranes, tetraalkylammonium fluorides, 18-crown-6 and sodium or potassium fluoride, fluorinated resins, dialkylaminoaluminotrifluorides (DAST), tri(dialkylamino) sulfur (trimethylsilyl) trifluorides (TASF) and pyridinium hydrogen fluorides.


3. An H-bond is estimated to be 100 kJ/mol (24 kcal/mol) with potassium fluoride in acetic acid, A good summary is given by J. H. Clark, *Chem. Rev.*, 80, 431 (1980).


11. J. Casado, M. López-Quintela and M. Lorenzo-Barral, *J. Chem. Educ.*, 63, 450 (1986); we carried out a $^1$H NMR rate study (200 MHz) following the proton signals for C$_6$H$_5$CH$_2$S-SnBu$_3$ using (C$_6$H$_5$CH$_2$)$_2$S as standard.


14. A hot solution of 18-crown-6 (5.00 g) in 10.5 ml of dried acetonitrile (reflux over CaH$_2$) followed by cooling resulted in an acetonitrile complex. After cooling at -78°C, the solid was collected in a Schlenk tube under Argon. The complexed acetonitrile was removed while heating slightly (55°C) under high vacuum; no significant hydroxyl absorption were recorded by infrared: G. W. Gokel and D. J. Cram, *J. Org. Chem.*, 39, 2445 (1974).

15. CsF was dried for 1-2 days in a drying pistol under high vacuum (0.01 mm Hg) and flame-dried prior to use. Crown-ethers were obtained from the Aldrich Chemical Company and kept under argon. Hexyl iodide was purchased from Aldrich and tributyltin benzoate were prepared according to J. J. Talley and A. M. Colley: *J. Organomet. Chem.*, 215, C38-C40 (1981). The catalytic amount of crown-ether used was 0.2 mol/eq of halide/tin compound (typically ca. 0.8 mmol of each in 2 mL of CD$_2$CN) but good results are also obtained with a smaller amount. The reaction rates with dried or undried 18C6 (with CsF) were similar. The fluorinations were carried out in acetonitrile using a 1.7/1.0 ratio of F$^\cdot$/halide; the reactions were carried out at R.T. or 80°C. A $^1$H NMR (200 MHz) rate study was done in every case.


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