Fluoride Ion as a Base in Organic Synthesis

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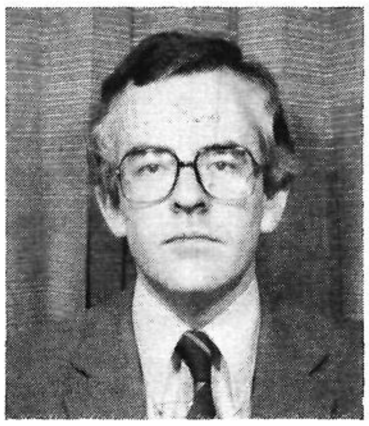
I. Introduction.

The increasing popularity of ionic fluorides as bases has prompted this review of such uses of these reagents in organic synthesis. The reactions are presented in a systematic manner, and although there is no attempt to include all examples, one or several of each type of reaction are given and an effort has been made to include reference to all of those reports which, in detailing reaction applications or discussing the role of the reagent, have helped to achieve a better understanding of the scope and utility of these interesting reagents.

The potential ability of the fluoride anion to act as a base might be predicted on considering the strength of the H–F bond (~569 kJ mol^{-1}; cf. H–Cl, ~432 kJ mol^{-1}; H–O, ~428 kJ mol^{-1}; H–N, ~314 kJ mol^{-1}). On this basis, nucleophilic attack by fluoride toward other nucleii, including silicon (E(Si–F) = 540 ± 13 kJ mol^{-1}) and phosphorus (E(P–F) = 439 ± 96 kJ mol^{-1}) as well as carbon (E(C–F) = 536 ± 21 kJ mol^{-1}), might also be expected to be of possible synthetic value. Corey and others have used fluoride attack on silicon centers as a simple and efficient means of removing silyl protecting groups[1] and, more recently, Ogilvie has carried out similar experiments at phosphorus centers.[2] Attack by fluoride at carbon centers is, of course, the basis of perhaps the best known area of fluoride ion chemistry—the synthesis of organofluorine compounds.[3] Miller has shown[4] that the fluoride ion shows a high order of nucleophilic attack toward unsaturated fluorinated carbon centers to give fluorocarbanions which are responsible for many interesting and useful fluorocarbon rearrangements, and this has resulted in an additional growth area in fluoride ion chemistry.[5] These subjects are beyond the scope of this review.



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The range of typically base-assisted reactions that are promoted by fluorides is large enough for the reader to find precedent for many reactions of interest, but interest will be enhanced if he is mindful of certain conclusions which emerge from the wealth of data available. The base strength of an ionic fluoride is dependent on the solvent in which it is dissolved, on the amount of water that is present, and on the countercation. These contributing factors help to explain the inconsistencies of reported basicities of fluorides. Thus many early reports based on the use of alkali metal fluorides dissolved in protic solvents such as alcohols or diols consider fluorides to be behaving as weak bases whereas aprotic solvent solutions of the very hygroscopic tetraalkylammonium fluorides have been reported to be between trialkylamines and alkoxides on the basis of Michael addition experiments,[6] ~10^3 more efficient than alkoxides on the basis of dehydrohalogenation experiments,[7] and comparable to organomagnesium or even organolithium reagents on the basis of their ability to generate carbanions from such weak carbon acids as Me_2SO, MeCN, $MeNO_2$, and fluorene.[8] This subject is amplified in sections IIB and IIC.

While the question of the relative basicity of fluorides may remain a matter for speculation, there is no doubting the enormous potential scope of the reagents as bases. Most ionic fluorides are easy to prepare and use and are stable over long periods of time. They are hygroscopic, but they do not react

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with water and may therefore be recovered from aqueous solution by conventional techniques. They react under essentially neutral conditions and are therefore often associated with "clean" reactions where side reactions are kept to a minimum. Workup procedures are generally simple and efficient since the fluorides or other inorganic products may be removed and recovered by precipitation or aqueous washing. The variable basicity of fluorides may also be considered as contributing to their popularity.

The first example of the basic behavior of ionic fluorides can be traced back to 1948 when Nesmeyanov reported the fluoride-catalyzed decarboxylation of some carboxylic acids.[9] For many years fluorides were rarely exploited in organic synthesis other than in the organofluorine field, and many of the early reports of fluorides behaving as bases were based on accidental discoveries usually resulting from attempts to introduce fluorine into organic molecules by halogen exchange. The recent growth of interest in their role as bases justifies this review which covers the literature through 1979. We are not aware of any previous comprehensive review on this subject.

Abbreviations used in the manuscript are the following:

acac	2,4-pentanedione
AcOH	acetic acid
BTMAF	benzyltrimethylammonium fluoride
Bu	butyl
Bzl	benzyl
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
DMA	dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
Et	ethyl
H bond	hydrogen bond
HMPA	hexamethylphosphoramide
Me	methyl
Ph	phenyl
Pr	propyl
i-Pr	isopropyl
TBAF	tetra-*n*-butylammonium fluoride
TEAF	tetraethylammonium fluoride
THF	tetrahydrofuran
TMAF	tetramethylammonium fluoride
Ts	tosyl

II. The Reagent

A. Preparation and Purification

A variety of ionic fluorides are commercially available and of these, the alkali metal fluorides KF and CsF and the tetraalkylammonium fluorides TBAF, TEAF, and BTMAF have attracted the most attention as basic reagents.

The alkali metal fluorides heavier than NaF are hygroscopic, the hygroscopicity roughly increasing with molecular weight. They are occasionally supplied in hydrated forms, although most manufacturers claim that their products are anhydrous and in a highly pure form. It is usually desirable to remove any water present, and this may be readily accomplished by heating the salt in a vacuum oven, or some similar arrangement, to over 100 °C for a period of several hours or to constant weight. All of these salts are stable to very high temperatures. Thereafter, it is advisable to handle the very hygroscopic RbF and CsF in a drybox or in a polyethylene glovebox kept inflated with dry nitrogen. Reasonably rapid manipulation (i.e., transfer to the reaction solvent) is sufficient precaution with the other alkali metal fluorides. While all of these fluorides may be stored indefinitely, it is advisable that they also be dried immediately prior to use.

A number of tetraalkylammonium fluorides have recently come on the market, but their present cost is somewhat prohibitive and they may be easily and less expensively prepared by one of the following methods: (1) by neutralization (pH 7–8) of the hydroxide (usually supplied as a 20 or 40% aqueous solution) with dilute hydrofluoric acid;[6,10] (2) by passing an aqueous solution of the bromide (several tetraalkylammonium bromides are commerically available) through an ion-exchange resin such as Amberlite IRA 410, previously converted to the fluoride form via the hydroxide form by treatment with aqueous NaOH, water (excess), and dilute hydrofluoric acid in that order;[11,12] (3) by treatment of the bromide with silver fluoride in aqueous solution.[13] The last method is probably too expensive unless the silver is efficiently recovered.

While aqueous solutions of tetraalkylammonium fluorides may be easily and efficiently prepared, subsequent removal of water presents considerable difficulties. It seems that complete removal of water from those salts heavier than TMAF, without introducing an alternative protic material,[14] is virtually impossible.[14,15] The bulk of water can, however, be removed by gentle warming (30–40 °C) of the aqueous solutions in vacuo ($\sim$0.5 mm) for about 24 h. Tetraalkylammonium fluorides heavier than TMAF may be assumed to start to decompose at temperatures in excess of 80 °C. Once again, it is advisable to use the reagents immediately after drying although the "dried" reagents may be kept in vacuo over P_2O_5 for a few days without appreciable loss in activity. The only satisfactory method for complete removal of water relies on the presence of another protic material (which can compete with the water for the H-bond electron-donor fluoride ion), either as the solvent during preparation (e.g., treating the chloride with KF in MeOH)[16] or during subsequent manipulation (i.e., conversion of the fluoride to a nonaqueous solvate such as TBAF·Hacac).[17]

Recently, several new sources of the fluoride ion have been suggested, and of these, the fluoride forms of ion-exchange resins, especially those suitable for nonaqueous solvent work such as Dowex MSA-1 macroporous resin and Amberlyst A-26 and A-27 macroreticular resins,[12] tetraalkylammonium fluoride[19] or KF[20,21] impregnated on suitable inert supports such as silica, alumina, or Celite, and the in situ source of TBAF, tetra-*n*-butylammonium chloride–KF·$2H_2O$–MeCN,[22] would seem to be the most promising.

Aqueous or nonaqueous solutions of ionic fluorides are likely to etch glassware, particularly after long periods of contact. This is presumably due to the formation of small amounts of HF. The extent of this etching (i.e., the amount of HF produced in solution) is very dependent on the system; for example, a water-free solution of KF–AcOH only etches glass very slowly whereas KF–AcOH–H_2O systems may actually be used to prepare KHF_2[18] and manipulation of such solutions in Teflon apparatus is advisable. In the overwhelming majority of circumstances, however, etching is not a serious problem, and ordinary glassware may be used with impunity.

B. Selection of the Fluoride and of the Solvent

Once it has been decided to attempt a fluoride ion promoted reaction, the chemist must decide which particular fluoride–solvent combination is best suited to his needs. Until the last 10 years or so, fluoride ion promoted reactions were almost entirely carried out by using KF; however, the advent of the various other types of ionic fluorides mentioned earlier as well as the possibility of using a KF–crown ether complex does present the chemist with a difficult choice. The correct choice of solvent is also important because of the variable basicity and solubility shown by ionic fluorides as well as the possibility of solvent participation in subsequent reactions. Certain conclusions may be drawn from the literature which should help to alleviate these problems.

The alkali metal fluorides are appreciably soluble in only a few solvents. KF, RbF, and CsF are soluble in the lighter carboxylic acids[23,24] and diols,[25] some fluorinated alcohols,[26] formamide and *N*-methylformamide,[27] HF, and water. None of these solvent systems are suitable as all-purpose fluoride ion sources. The fluorides are solubilized by strong H bonding between the anion and the solvent, and this has the effect of lowering the nucleophilicity of the anion while at the same time enhancing the nucleophilicity of the solvent. Thus KF-carboxylic acid systems are very useful sources of the carboxylate anion but are of much less value in reactions not involving the solvent as a reactant.[28] The advent of polar aprotic solvents has gone some way to alleviate the problem of fluoride ion solvation and solvent interference, but the solubility of alkali metal fluorides in these solvents is very low (e.g., a saturated solution of KF in Me_2SO at 25 °C contains 8 mg of fluoride/100 g of solvent),[29] and reaction involving the solvent has been known to occur under prolonged reflux conditions.

Most reported examples of alkali metal fluoride promoted reactions nowadays involve KF or CsF, the latter usually being regarded as the most active[30,31] although the former is less hygroscopic and appreciably less expensive. Reactions involving KF or CsF in aprotic media may be considered to involve a significant amount of reaction at the surface of the undissolved fluoride,[31] and reactions should always be well stirred. The experimental evidence available clearly points to their being less active than their tetraalkylammonium counterparts,[14,15,32] but they continue to find widespread application especially where high reaction temperatures and/or stoichiometric amounts of fluoride are required. Solutions of KF or CsF in protic solvents such as 1,2-ethanediol may be considered useful as weakly basic homogeneous media in reactions where solvent interference is not a potential problem.

The addition of an excess (with respect to the KF) of 18-crown-6 to KF-benzene or KF-MeCN systems improves the fluoride solubility by at least a factor of 10, which may have the effect of a dramatic improvement in the reaction efficiency of the fluoride both as a base[33-35] and as a nucleophile toward carbon in halogen-exchange reactions.[33] Crown ethers are, however, expensive and very toxic, and their application to reactions requiring stoichiometric amounts of fluoride is not practicable. The KF-(18-crown-6)-MeCN (or benzene) basic reagent is possibly less active than a well-dried tetraalkylammonium fluoride-polar aprotic solvent system,[32] but the former has often been shown to be an effective basic *catalyst* especially in Michael reactions.[36] The best solvents for KF-(18-crown-6) promoted reactions would seem to be MeCN or benzene. The reactivity of KF systems involving good cation solvating solvents such as DMF is not significantly enhanced by the addition of 18-crown-6 despite the apparent increase in the KF solubility.[34]

Tetraalkylammonium fluorides, of which TBAF, TEAF, BTMAF, and to a lesser extent TMAF have received the most attention, are soluble in polar aprotic solvents although their hygroscopicity is such that on dissolution the fluoride will almost certainly be accompanied by varying amounts of water or some other protic material.[14] The amount of protic material present will have a profound influence on the effective basicity of the fluoride solution, and this may hinder reaction[11] or may actually be used to deliberately moderate a reaction.[37] If only traces of protic material are present, then the basicity of the solution is such that the fluoride may be capable of abstracting a proton from such weakly acidic solvents as Me_2SO or MeCN.[8]

The solubility of TEAF in acetone was recognized as early as 1932,[38] and many polar aprotic solvents (of which DMF, MeCN, THF, and Me_2SO are the most popular) have been successfully employed as solvents in tetraalkylammonium fluoride promoted reactions.

The greatest drawbacks in using tetraalkylammonium fluorides are their hygroscopicity and low thermal stability. If small amounts of water can be tolerated in a reaction system, then they are probably the best choice for most, but not necessarily all,[39] reactions carried out at <100 °C.

The fluoride form of some ion-exchange resins suitable for work in aprotic media are probably less expensive and easier to handle than their tetraalkylammonium counterparts although they seem to be less efficient and also suffer from low thermal stability.[12] THF is reported as being the best solvent for those reactions which proceed smoothly at or near room temperature (e.g., Michael additions) whereas DMF is preferred for those reactions requiring higher temperatures (e.g., ortho alkylations).[12] In view of the enormous potential of utilizing a reagent that may be easily regenerated and reused with little loss in efficiency,[12] further work on their properties and applications would seem worthwhile.

More detailed studies on supported fluoride (tetraalkylammonium or alkali metal fluoride impregnated on support materials such as alumina, silica, and Celite) reagents should also be encouraged since preliminary investigations have been very promising.[19-21] Supported TBAF is effectively nonhygroscopic presumably because of anion-surface hydroxyl H bonding; unfortunately it would seem to be less efficient than the unsupported fluoride.[19] KF supported on alumina, however, would seem to be more efficient at promoting alkylations than unsupported KF.[21]

Table I summarizes the advantages and disadvantages of the most popular sources of the fluoride ion in synthesis.

C. Role of the Fluoride

There is considerable spectroscopic and nonspectroscopic evidence to suggest that the fluoride ion is capable of forming strong H bonds to a variety of H-bond electron-acceptor (protic) compounds.[31,40-42] KF, for example, dissolves in acetic acid with considerable evolution of heat,[23] and calorimetric,[43] spectroscopic[40] and theoretical[44] studies suggest an H-bond enthalpy in excess of 100 kJ mol^{-1}.

H bonding must play a role in the basic behavior of any anion, and it seems reasonable to assume that H bonding will be particularly important in baselike reactions of the fluoride anion. Clark and Miller have shown that an increase in the reactivity of carboxylic acids, phenols, amines, and thiols on complexing with ionic fluorides is accompanied by a large shift in the stretching frequency of the O-H, N-H, or S-H bonds which is indicative of H bonding.[31] Kinetic studies on fluoride-promoted reactions have also confirmed the occurrence of H-bonded intermediates.[45]

The formation of an H bond between a fluoride anion and an organic compound will result in the transfer of electron density from the anion to the organic, thus enhancing the nucleophilicity of the organic while at the same time reducing the nucleophilicity of the fluoride. This premise has been used to explain a variety of fluoride-promoted reactions,[12,14,28,31,35,46-50] and we may assume that it plays a significant role in the majority of reactions described here.

The H-bonding ability of fluorides may also be utilized in less direct ways; for example, Ogilvie has shown that when faced with two possible reaction centers, fluoride will preferentially attack at the one closest to a hydroxyl group.[37]

We are now in a position to understand why the presence of water may have such a profound effect on the basic behavior of the fluoride anion.[8,11,15,51] In the absence of a more powerful H-bond electron acceptor, water will solvate and effectively mask the fluoride anion. Rozhkov looked at this problem from a thermodynamical standpoint and suggested that the damaging effect of even small amounts of water on fluoride basicity may be explained on the basis of the dramatic variation of up to 20 p*K* units in the ionization constant of HF on passing from aqueous to aprotic solvents.[6]

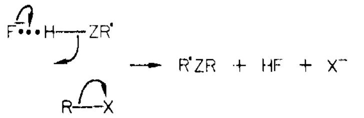
TABLE I

fluoride	commercially available	advantages	disadvantages
KF	yes	inexpensive; easily dried; easy to handle; high thermal stability	very low solubility in all but a few protic solvents; reactions usually require heating
CsF	yes	fairly easily dried; high thermal stability; more soluble and more reactive than KF	expensive; hygroscopic; low solubility in all but a few protic solvents
KF-(18-crown-6)	yes[a]	more soluble in aprotic solvents and more reactive than KF alone	expensive; toxic; solubility remains low
TBAF, TEAF, BTMAF	yes	soluble in polar aprotic solvents; potentially the most reactive of the fluorides; basicity may be controlled by addition of a protic such as water	very hygroscopic; low thermal stability
fluoride resins	no	inexpensive; easily prepared; regeneration and reuse may be possible	insoluble; low thermal stability; little information available
TBAF–silica	no	easily prepared; may be dried; less hygroscopic and more thermally stable than TBAF alone	lower reactivity than TBAF; large amount of reagent required in reactions especially if noncatalytic; little information available
KF-alumina (etc.)	no	easily prepared: inexpensive; more reactive than KF?	large amount of reagent required in reactions especially if noncatalytic; little information available

[a] Not as the complex.

Fluorides differ from conventional bases in many respects; for example, while they resemble many other strong bases in having an affinity for water, they do not actually react with water. It has been suggested that the role of a fluoride in typically base-assisted reactions should be differentiated from that of a simple proton acceptor.[28] There is no evidence to suggest that significant amounts of proton transfer occur in solutions of KF in carboxylic acids,[24,40,43,44] for example, although it has been shown that a mixture of KF and highly acidic organics such as some nitro ketones produces a double salt composed of KHF_2 and the nitroketonate.[52]

The function of a base, such as a metal hydride, in nucleophilic substitution reactions is to generate the protic anion as the reactant nucleophile; the fluoride–protic H-bonded complex may, at least partly, play the role of the reactant nucleophile (eq 1). This concept may help to explain why a fluoride–protic complex may actually appear to be a more effective reagent than the salt of the protic.



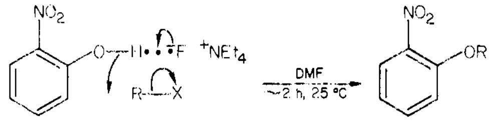
(1)

For example, the H-bond energy of the biformate anion, although large in comparison to most H-bond energies, is less than that of $[RCO_2\cdots H\cdots F]^-$,[50] and it might therefore be expected that this would manifest itself in differences in the chemical reactivity of the two species. The use of potassium acetate-acetic acid in place of potassium fluoride-acetic acid in the esterification of simple alkyl halides appears to bear this out (see section IVA).[50,53] The calculated Mulliken charges on the hydroxy oxygen atoms reflect this difference in reactivity, being −0.4 e in formic acid, −0.6 e in the formate anion, −0.6 e in the biformate anion, and −0.7 e in the formic acid-fluoride complex.[50]

III. Alkylations and Arylations

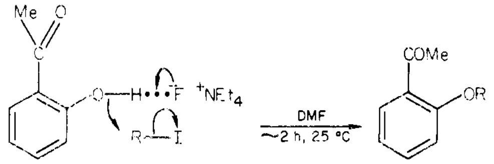
A. Phenols, Catechols, and Alcohols

The most thorough investigation of the fluoride ion promoted alkylation of phenols was carried out by Miller and co-workers[54] who studied the effect of various substituents on the reactions of phenols with alkyl halides in the presence of TEAF in DMF to produce alkyl phenyl ethers. Yields were generally good and compared favorably with those obtained by classical and more recent methods. Only in the case of 2,6-di-*tert*-butylphenol was there evidence for the occurrence of any side products—C-alkylation and phenol oxidation products being detected as well as the O-alkylated product. The most interesting results in this report[54] came from the study of the reactions of 2- and 4-nitrophenols and 2-hydroxyacetophenone where, because of resonance stabilization in the nitrophenoxide anions and intramolecular H bonding in the latter phenol, conventional base promoted O-alkylation may often prove to be less than satisfactory. TEAF was found to react rapidly with these phenols in the presence of alkyl halide to produce good yields of the respective alkyl phenyl ethers, presumably because of H-bonded complex anion attack (rather than phenoxide anion attack) on the alkyl halide and fluoride ion disruption of the intramolecular H bond, respectively (eq 2 and 3).



(2)

RX = MeI, EtI, BzlCl (72–83%)



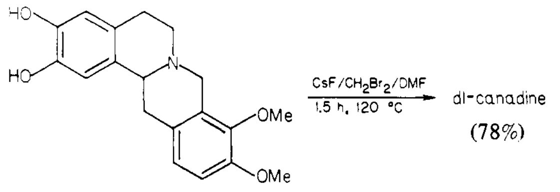
(3)

R = Me, Et (78–85%)

Phenol alkylation has proved to be a popular choice for testing the efficiency of various sources of fluoride. Apart from TEAF–DMF, KF (no solvent),[31,49] the fluoride form of Amberlyst A-26 and Dowex MSA-1 resins with DMF or THF,[12] KF on Celite with MeCN, THF, or DMF,[20] and KF on various supports with MeCN[21] have been employed. In the last of these reports,[21] Yamawaki and Ando tested the effectiveness of various inorganic solids as supports of KF for promoting the O-alkylation of phenol with methyl iodide and found alumina to be the most effective support material, the KF–alumina reagent giving up to 96% product by GLPC after 4 h at room temperature.

TEAF or KF–alumina would seem to be the reagents of choice since other methods fail to give good yields, require above ambient temperatures, or require prolonged periods of reaction.

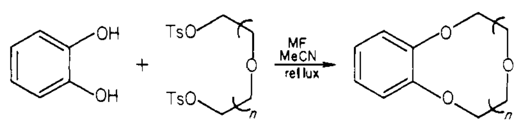
The methylenedioxy group is of special interest in chemistry because it occurs in many natural products and has been suggested as a protecting group in catechols. Classical methods for the methylenation of catechols usually afford low yields, and among the many attempts to improve the efficiency of such reactions, the reported alkali metal fluoride—DMF method[48] is one of the most promising. Catechol itself, along with 2,3-dihydroxynaphthalene, 3-methylcatechol, 3,4-dihydroxybenzaldehyde, 2,3-dihydroxybenzoic acid (run as the ethyl ester), and **1** give good yields of the methylenedioxy products on reaction with CH_2Cl_2 or CH_2Br_2 and KF or CsF in DMF (eq 4).[48] Cesium fluoride was found to be a particularly effective reagent for this type of reaction. The degree of intermolecular reaction was usually tolerably low.[48]



(4)

1

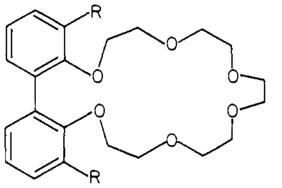
The synthetic utility of crown ethers is now well established. Unfortunately, only a few methods are available for their synthesis. In a recent note, Reinhoudt and co-workers described the use of metal fluorides as bases for the "templated synthesis" of crown ethers (eq 5).[39] For example, when n = 3, and M = Cs, the authors claimed 61% of isolated product after 21 h. It would seem that not only are the metal fluorides (M = K, Rb, or Cs) sufficiently strong bases to generate a good nucleophile for the formation of the ether bond but also that the cation plays an important role in the cyclization step. The cation appears to act as a template ion, as demonstrated by the relatively low yield (5%) obtained on replacing MF by TBAF.



(5)

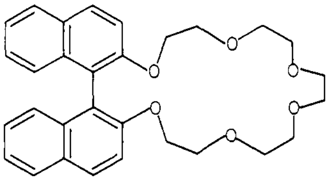
This is a rare example of a base-assisted reaction where a tetraalkylammonium fluoride is clearly inferior to its alkali metal counterparts.

Reaction 5 has been successfully applied to the synthesis of other crown ethers such as the 20-crown-6 compounds **2** and **3**.[39]



R = H or $CH_2CH{=}CH_2$

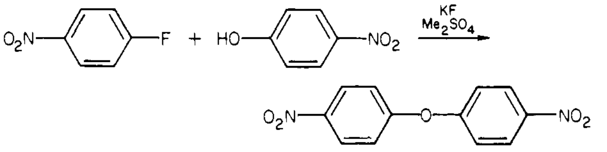
2



3

There is a paucity of literature information on fluoride-promoted arylations, and the reports available are largely limited to reactions involving replacement of aromatic fluorines or highly activated chlorines.

Yakobson and co-workers have reported the CsF-assisted reaction of 2,4-dinitrofluorobenzene with tertiary alcohols to produce the aryl alkyl ethers,[55] and Sokolenko has shown that KF, CsF, or even KHF_2 will promote the methanolysis of 2,4,6-trinitrochlorobenzene.[46] Detailed kinetic studies on the latter showed that the fluoride promotion could be explained by F^-···HOMe H bonding enhancing the nucleophilicity of the alcohol.[46] These reports may be of curiosity value, but they are of little synthetic value since the reactions of phenols and alkyl halides described earlier provide simple and efficient fluoride-promoted routes to a wide variety of alkyl aryl ethers. The same cannot be said of Ishikawa's report on the reaction of 4-fluoronitrobenzene with 4-hydroxynitrobenzene in KF–dimethyl sulfate (eq 6) since this is a rare example of a fairly mild conditions route to aryl aryl ethers.[56]

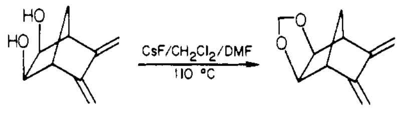


(6)

B. Aliphatic Diols

One of the first examples of a fluoride-promoted O-alkylation was reported in 1957 by Kitano and Fukui who observed that treating n-hexyl bromide with 1,2-propanediol, 1,3-propanediol, or 1,4-butanediol in the presence of KF at temperatures close to 200 °C produced the hydroxy ether as well as hexyl fluoride and n-hexene.[57] In the case of 1,3-propanediol, the O-alkylated diol was the major product.

More recently, Chollet and co-workers produced good yields of 1,3-dioxolanes by treating 1,2-cycloalkanediols (hydroxy groups in the cis-eclipsed conformation) with CH_2Cl_2–DMF containing an excess of CsF.[58] This method can be successfully applied to sensitive diols such as 5,6-dimethylidene-*exo*,-*exo*-2,3-norbornanediol (**4**)[56] (eq 7).

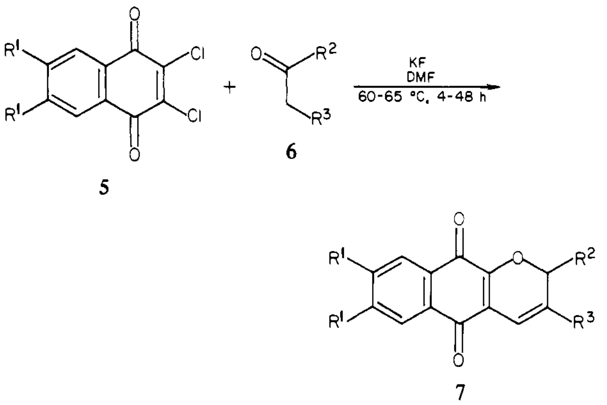


(7)

4

C. Ketones (Including Dicarbonyl Compounds)

Kuo and co-workers recently reported the one-step synthesis of naphtho[2,3-*b*]furan-4,9-diones (**7**) directly from 2,3-dichloro-1,4-naphthoquinone (**5**) and an active methylene compound (**6**) in DMF in the presence of an excess of KF (eq 8).[59]



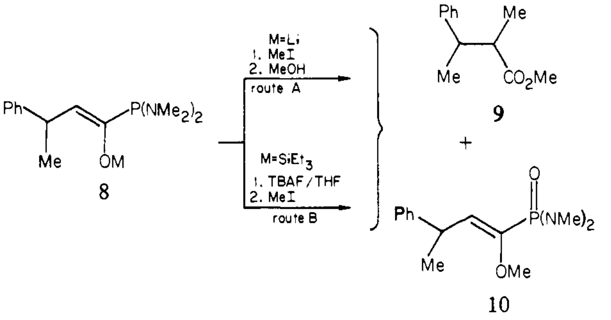
(8)

R^1 = H, R^2 = Ph, R^3 = CN; R^1 = H, R^2 = Me, R^3 = COMe;
R^1 = H, R^2 = Ph, R^3 = COPh; R^1 = H, R^2 = Me, R^3 = COPh;
R^1 = H, R^2 = Me, R^3 = CO_2Et; R^1 = Me, R^2 = Ph, R^3 = COPh

Product yields of 32–97% were claimed.[59] This method represents a considerable improvement over previous methods for the synthesis of **7**. The reaction presumably requires initial fluoride-promoted enolization of **6**.[14]

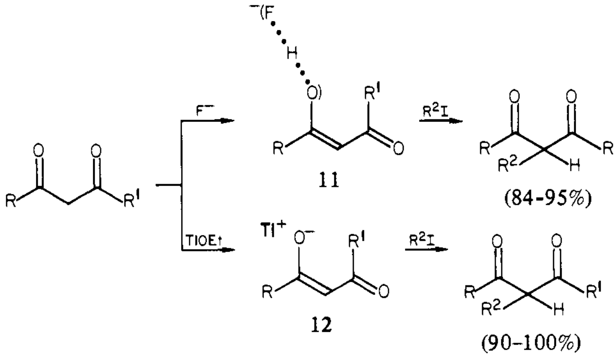
Evans and his co-workers used TBAF in an effort to help alleviate the problem of competing O-alkylation in the attempted regiospecific alkylation of the enolate **8**.[60] The authors noted an improvement in the C:O alkylation ratio, **9**:**10**, from 17:83 (route A) to 57:43 (route B) (eq 9).

Improvements in the regiospecificity of the alkylation of various β-dicarbonyl compounds on employing fluorides in place



(9)

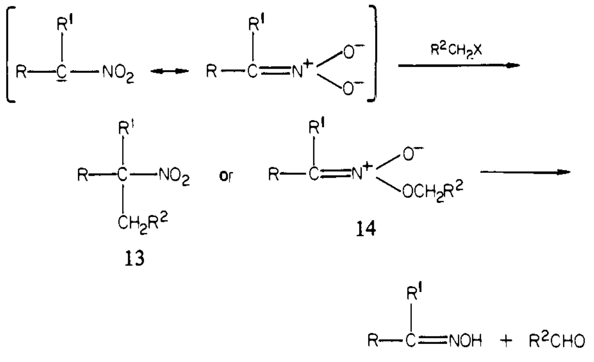
of more conventional bases have also been reported.[12,17,19,20,22,61,62] Attempts to C-alkylate β-dicarbonyl compounds often result in the concurrent formation of the O-alkylated product as well as products from competing Claisen condensation, β-dicarbonyl cleavage, and coupling of the air-oxidized salts of both starting material and its monoalkylation product. Reactions of a variety of β-dicarbonyl compounds with alkyl iodides in the presence of TBAF, TEAF, or BTMAF ($CHCl_3$ or DMF as solvent) were usually found to produce high yields of the mono-C-alkylated products under mild conditions.[17,62] For a series of alkyl iodides up to R = butyl, only the nonprimary butyl iodides failed to give satisfactory results. The success of the fluoride-promoted method may be attributed to shielding of the oxygen atom of the β-dicarbonyl compound **11**—an explanation which is comparable to that put forward for the exclusive C-alkylation of thallium enolates (**12**),[63] although the latter method requires more vigorous reaction conditions than the fluoride method.



Other reported examples of fluoride-promoted mono-C-alkylations of β-dicarbonyl compounds include the reaction of KF-Celite with 2,4-pentanedione-MeI in MeCN (room temperature, 16 h, 96% product by GLPC),[20] the reaction of $KF\cdot 2H_2O$-*n*-Bu_4NCl with β-diketones and MeI in MeCN (25 °C, 9 h, 93–94% isolated product),[22] the reaction of the fluoride forms of Dowex MSA-1 or Amberlyst A-26 or A-27 resins with 2,4-pentanedione-MeI in DMF or THF (the best product yield reported, 70%, came from the reaction using the Amberlyst A-27 resin for 24 h at 20 °C; the correct choice of resin and of solvent is critical—for example, Dowex MSA-1 gave no detectable product on reaction in THF),[12] and the reaction of TBAF-silica with 1,3-diphenylpropane-1,3-dione-EtI in THF (20 °C, 6 h, 55% isolated product).[19] The only reported C-alkylation of β-dicarbonyl compounds using KF itself that we are aware of described the reaction of several malonic esters with BzlCl in EtOH in the presence of KF and potassium carbonate.[61] Typically, these reactions required reflux conditions to provide moderate (ca. 60%) product yields.

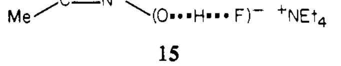
D. Alkylation of Nitro Compounds

The anion derived from an aliphatic nitro compound is ambident, and subsequent alkylation will yield the stable carbon alkylation product **13** or a mixture of carbonyl compound and an oxime derived from decomposition of the unstable O-alkylation product **14** (eq 10).



(10)

Reactions of the salts of nitro compounds with aliphatic, allylic, and benzylic halides usually produce carbonyl compounds, although instances are known in which the result is carbon alkylation. Clark and co-workers recently reported their results of a study on the reaction of the TEAF-2-nitropropane monosolvate (**15**) with benzyl halides over molecular sieves.[64]

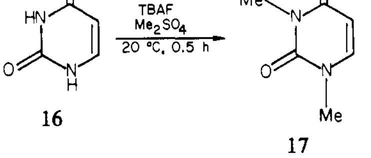


15

They found that the products were carbonyl compounds (with $PhCH_2X$ and Ph_2CHX, X = Cl, Br, or I; and *m*-$NO_2C_6H_4CH_2Cl$), C-alkylated 2-nitropropanes (with *p*-$NO_2C_6H_4CH_2Cl$), or mixtures of both (with *p*-$NO_2C_6H_4CH_2X$, X = Br or I; and *o*-$NO_2C_6H_4CH_2Cl$). The authors claimed that where product mixtures occurred, the proportion of the C-alkylated product seemed to be somewhat higher than in those reactions involving 2-nitropropane salts—an observation entirely in line with the results reported for the fluoride-promoted alkylation of β-dicarbonyl compound described in section IIIC.

E. Nucleic Acids and Their Components

In a series of recent articles, Ogilvie and co-workers have demonstrated that fluoride in the form of TBAF in THF has a marked effect on the rate of alkylation of nucleic acids and their components.[65–67] Alkylating agents used in these studies included alkyl halides, trialkyl phosphates, dialkyl sulfates, and alkyl methanesulfonates. For example, reaction of uracil (**16**) with dimethyl sulfate in THF containing an excess of TBAF at room temperature for 30 min yielded 99% of 1,3-dimethyluracil (**17**) (eq 11).[67] The amount of TBAF used is important since reducing this to equal that of the alkylating agent produced 1-methyluracil (18%), 3-methyluracil (7%), and 1,3-dimethyluracil (57%). Furthermore, if TBAF is omitted or replaced by *n*-Bu_4NBr, no reaction occurred.

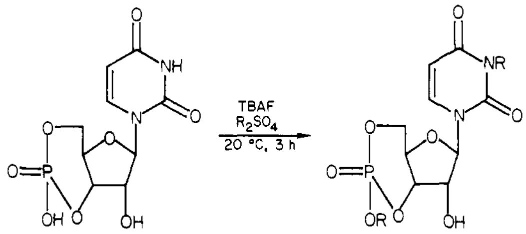


(11)

The dialkyl sulfate-TBAF alkylation system has also proved effective in converting uridine 3′,5′-phosphate (**18**) into its triester in very good yields (84–90%) (eq 12).[65]

F. Hydroxylamines, Amines, and Imides

The use of the KF or CsF adduct of the hydroxylamine, $(CF_3)_2NOH$ (as well as its alkali metal or mercury(II) salt), to

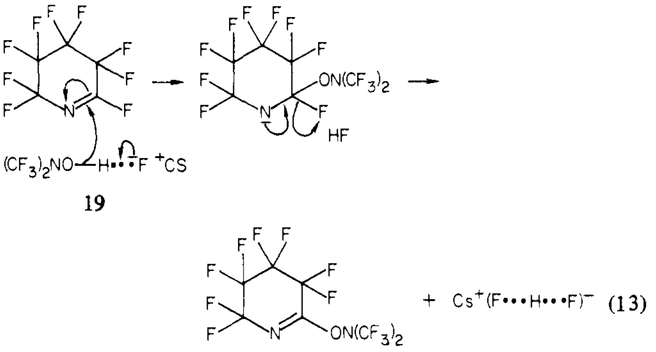


(12)

18

R = Me or Et

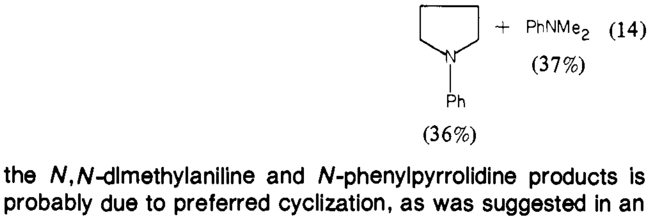
introduce the $(CF_3)_2NO$ group into organic, organometallic, or inorganic molecules via halogen exchange has been well exemplified.[88] Banks and co-workers have shown that this method may be extended to perfluoro imines and in particular to the displacement of fluorine from such compounds by *N*,*N*-bis(trifluoromethyl)hydroxylamine–CsF (**19**) (eq 13).[47] The authors suggested a mechanism involving H bonding as shown.



19

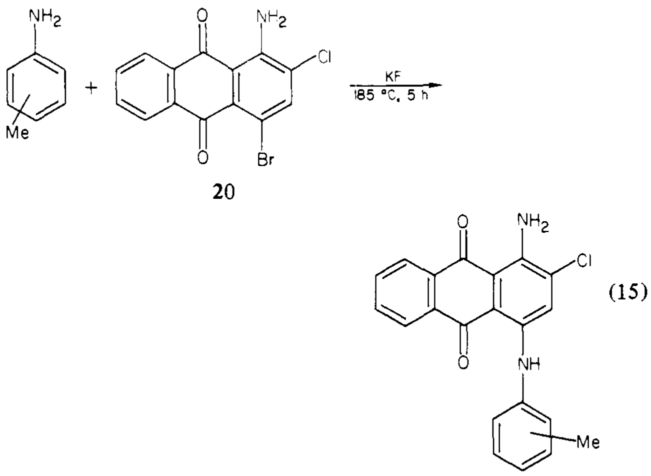
(13)

The N-alkylation of amines may be readily accomplished by using an alkyl halide in the presence of an excess of fluoride, and this method would seem to be superior to most other methods involving conventional bases as sodium carbonate, sodium hydroxide, potassium hydroxide, or zinc chloride.[31] Surprisingly, there has been relatively little work done in this field, and published reports are limited to the reactions of aniline[20,31] *N*-alkylanilines,[31,49] pyrrolidine,[31] and piperidine[20,31] in the presence of KF (no solvent)[31,49] or KF–Celite–MeCN;[20] yields are usually good (47–94%). KF–Celite appears to be the reagent of choice since reactions may often be carried out at room temperature, although long periods of time are often required. For example, reaction of aniline with *n*-butyl iodide in the presence of a slight excess of KF–Celite in MeCN for 137 h at room temperature gave, after work-up, 80% of *N*-butylaniline and 6% of *N*,*N*′-dibutylaniline.[20] The use of dihaloalkanes as the alkylating agents may result in mixtures of products. For example, reaction of *N*-methylaniline with 1,4-dichlorobutane and an excess of KF gave, after 1 h at 130 °C, a mixture of three products (eq 14).[31] The predominance of the *N*,*N*-dimethylaniline and *N*-phenylpyrrolidine products is probably due to preferred cyclization, as was suggested in an earlier attempt to prepare compounds of the type PhN(Me)-$(CH_2)_n$N(Me)Ph.[69]



(14)

The fluoride-assisted acylation of amines has attracted some interest among research workers. Yakobson, having successfully carried out the CsF-assisted arylation of alcohols,[55] extended his studies to include the alkali metal fluoride assisted arylation of amines.[70] The reaction of diphenylamine with iodobenzene at 200 °C in the presence of copper(II) oxide and an alkali metal fluoride gave triphenylamine in a yield that was dependent on the identity of the alkali metal fluoride cation. Thus, after 24 h, the following yields of triphenylamine were obtained: 52% (CsF), 14% (KF), ~0% (NaF or LiF).[70] The same article also reports the selective replacement of the 4-bromine in 1-amino-2-chloro-4-bromoanthraquinone (**20**) using methylaniline–KF as the reactant nucleophile (eq 15).[70]

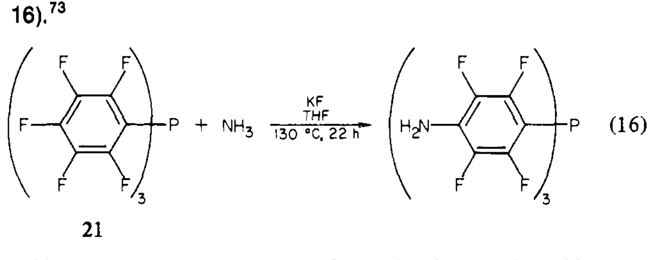


20

(15)

The more reactive halo-2,4-dinitrobenzenes react with primary or secondary aromatic amines in the presence of KF–DMF to produce the tertiary aromatic amines under somewhat less harsh conditions.[71,72]

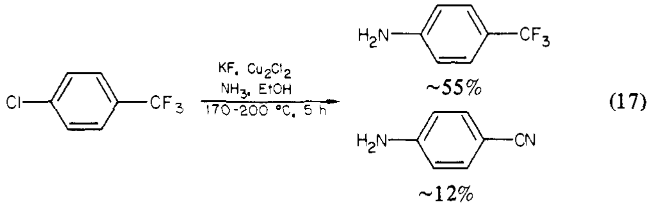
Hanna and Miller provided an excellent illustration of enhanced nucleophilicity due to H bonding to fluoride in their studies on nucleophilic substitution in tris(pentafluorophenyl)phosphine (**21**).[73] The authors observed considerable improvements in the product yields and/or reaction times on adding KF to reaction systems involving aniline or *N*,*N*-dimethylhydrazine as the reactant nucleophiles. Some representative results from their studies are given in Table II. Reaction of the phosphine with anhydrous ammonia in THF in a sealed bomb was also accomplished with the aid of KF, giving 50% of tris(4-amino-2,3,5,6-tetrafluorophenyl)phosphine (eq 16).[73]



21

(16)

Nonaqueous ammonolysis of *p*-chlorobenzotrifluoride may also be promoted by KF in combination with Cu_2Cl_2 (eq 17).[74]



(17)

The effect of the fluoride is to improve the conversion up to fivefold and is thought to be due to transitory formation of the very reactive *p*-fluorobenzotrifluoride and to the increased nucleophilicity of the NH_3 by H bonding to the fluoride. The major yield loss is conversion of the benzotrifluoride to 4-cyanoaniline

TABLE II. Reaction of Tris(pentafluorophenyl)phosphine with Aniline and *N*,*N*-Dimethylhydrazine[73]

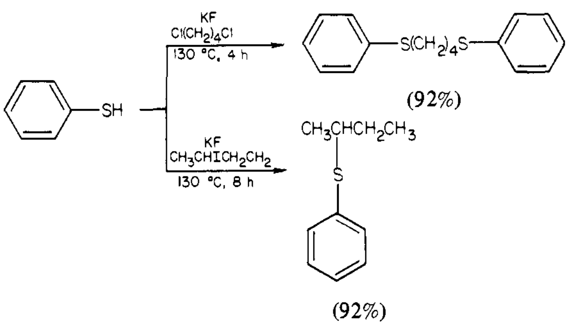
reactants	time, h (temp, °C)	substitution product, %		
		mono	di	tri
$(C_6F_5)_3P/PhNH_2/EtOH$	2 (86)	80	20	
$(C_6F_5)_3P/PhNH_2/EtOH$	71 (86)	10	80	10
$(C_6F_5)_3P/PhNH_2$	6 (180)	10	88	2
$(C_6F_5)_3P/PhNH_2/KF$	3 (180)		90	
$(C_6F_5)_3P/Me_2NNH_2$	7 (reflux)	?	?	40
$(C_6F_5)_3P/Me_2NNH_2/KF$	1.5 (reflux)			71[a]

[a] Plus an unstated amount of the symmetrical dimethylhydrazine isomer.

which is catalyzed by Cu_2Cl_2 and promoted by KF and is likely to occur by a mechanism involving ammonolysis of the CF_3 substituent to give $H_2NC_6H_4CF_2NH_2$ followed by elimination of HF.[74]

G. Thiols

Clark and Miller successfully carried out the S-alkylation of benzenethiol with 1,4-dichlorobutane and with 2-iodobutane in the presence of an excess of KF (eq 18).[31] The yield obtained in the latter reaction (92%) may be compared to that obtained (45%) after reacting PhSNa with 2-bromobutane for 24 h at 110–120 °C.[75] More recently, Ando and Yamawaki have shown that replacing KF by KF-Celite-MeCN affords similar reactions at room temperature with no apparent loss in efficiency[20]—the reported 100% S-alkylation (by GLPC) of benzenethiol by MeI after only 0.5 h at room temperature is a particularly spectacular demonstration of the improved reactivity of the fluoride on impregnation onto Celite.



(18)

In conclusion, fluorides have been successfully employed to promote a variety of C-, N-, O-, and S-alkylations and several N- and O-arylations. The reaction efficiencies are often superior to those employing more conventional bases such as metal hydroxides. Tetraalkylammonium fluorides or alkali metal fluorides impregnated on a suitable support material would seem to be the most effective reagents.

IV. Esterifications

A. Formation of Esters

The results reported in this section concern the fluoride-promoted esterification of carboxylic acids, usually by their reaction with alkyl halides. This method of esterification is particularly useful since KF (as well as RbF and CsF) is very soluble in liquid carboxylic acids[23] so that reactions may often be carried out by using the reactant acid as the bulk solvent.

Although the bulk of work in this field has been carried out within the last 5 years, Kim discovered, as early as 1963, that on attempting to fluorinate chlorocarboxylic acids by their reaction with KF, partial dimerization of the acid occurred.[76] Clark and Emsley used ^1H NMR to follow the progress of the reaction of monochloroacetic acid with KF at 150 °C.[28] This showed the disappearance of $ClCH_2CO_2H$ and the emergence of (chloroacetoxy)acetic acid and later the formation of higher polymers, several of which were isolated (eq 19). The reaction

$$ClCH_2CO_2H \xrightarrow[150\ °C]{KF} ClCH_2CO_2(CH_2CO_2)_nCH_2CO_2H \quad (19)$$

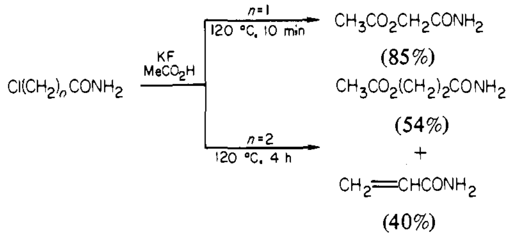
(n = 0, 1, 2, and 3 were isolated)

of monochloroacetic acid with KF in acetic acid, on the other hand, produced acetoxyacetic acid, there being no evidence for the formation of any chloroacetoxy product. 2-Chloropropanoic acid behaved similarly in KF-$MeCO_2H$, producing 2-acetoxypropanoic acid (eq 20). Heavier chlorocarboxylic acids gave

$$MeCHClCO_2H + KF\text{-}MeCO_2H \rightarrow MeCH(O_2CMe)CO_2H + KCl \quad (20)$$

mostly elimination products on reaction with KF-$MeCO_2H$ (see section VIA).[26]

The reactions of chloroacetamide and 3-chloropropionamide with KF-$MeCO_2H$ were also studied and found to give acetoxyacetamide as the sole product and 3-acetoxypropionamide plus the elimination product, acrylamide, respectively (eq 21).[26]



(21)

It is interesting to note that reaction of KF with chloroacetamide either in the absence of a solvent[26] or in an aprotic solvent such as xylene[77] or, more surprisingly, in glycols[77,78] results in essentially quantitative formation of fluoroacetamide. These observations serve to demonstrate the importance of the solvent in fluoride-promoted reactions.

Heating carboxylic acids and simple alkyl halides under reflux does not produce esters. The use of metal and quaternary ammonium carboxylates is necessary to effect carboxylation, probably because the use of these salts permits higher reaction temperatures.[79] The employment of KF in reactions of carboxylic acids and alkyl halides will give good yields of esters, free from byproducts.[28,31,49,50,53] Some useful general conclusions about fluoride-promoted esterifications which may be drawn from the literature are the following:

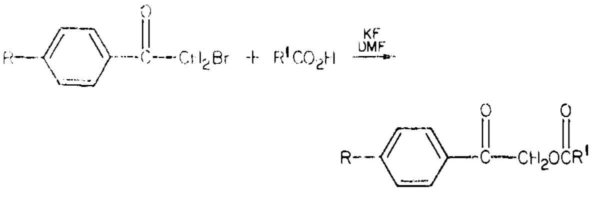
(1) The carboxylic acid–fluoride combination achieves esterification in much higher yields than can be produced by the use of metal carboxylates.[31,49,50,53] This is to be expected on the basis of the calculated Mulliken charges for free carboxylate and carboxylic acid fluoride (see section IIC).[50]

(2) In reactions involving solid acids, polar aprotic solvents such as DMF may be used, but protic solvents such as MeOH dramatically lower reactivity and may cause unwanted side reactions.[31]

(3) In reactions using the reactant acid as the bulk solvent, the lighter acids usually react much faster.[53] This may reflect the slight decrease in H-bond strength on increasing the molecular weight of the acid in $[F\cdots HOCOR]^-$ complexes.[80]

(4) The usual order of reactivity of the alkyl halides in fluoride-assisted reactions is iodide > bromide > chloride.[31,53]

The successful development of the fluoride-carboxylic acid-alkyl halide method for preparing esters has prompted some workers to apply the method to specific problems in ester synthesis. The synthesis of phenacyl esters has many uses in organic chemistry. They have been used as protecting groups and as a means of characterizing acids. Treatment of α-bromoacetophenone[81] as well as substituted α-bromoacetophenones[62] with carboxylic acid in KF-DMF has been shown to result in quantitative formation of the phenacyl ester (eq 22).



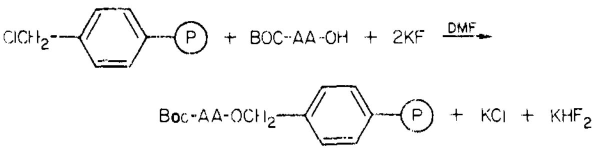
(22)

(91-99%)

R = H, Br, or Ph; R^1 = Me, Et, Me_3C, Ph, 2-$MeOC_6H_4$, 4-*t*-BuC_6H_4, or 2,4,6-$(Me)_3C_6H_2$

Reactions were usually complete in about 10 min at room temperature which would seem to make them the most attractive route to phenacyl esters. Several interesting points came out of these investigations.[81,62] (1) A mixture of KF with an aromatic or low molecular weight aliphatic carboxylic acid in DMF often becomes warm on shaking, presumably as a result of the formation of the very strong $[F\cdots HOCOR]^-$ H bond. This internal heat may well be sufficient to drive the reaction to completion since addition of the reactants in a manner that allows dissipation of the heat before the alkyl halide is added results in considerably longer periods of time being required for the reaction to go to completion. (2) Replacing KF by CsF reduces the time of reaction. (3) Traces of water in the reaction mixture have little effect on the reaction rate.

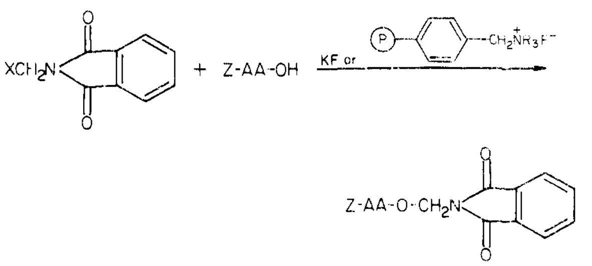
Two of the most important advantages of the KF-promoted phenacyl ester synthesis are that it requires neither the potassium salt of the carboxylic acid to be prepared in advance nor the use of an expensive crown ether, and these advantages were recognized by Horiki and co-workers as being relevant to the synthesis of Merrifield resin esters of N-protected amino acids.[63] These esters are considered to be key intermediates for solid-phase peptide syntheses. The reaction scheme employed is shown in eq 23.[83] Reactions of various Boc-amino acids at 50 °C for 24 h afforded the desired esters in almost quantitative yields.[83] The protecting Boc group was shown to be unharmed in these derivatizations.



(23)

P = polystyrene backbone; Boc-AA-OH = *tert*-butoxycarbonylamino acid

In a subsequent study,[84] Horiki successfully synthesized the phthalimidomethyl esters of N-protected amino acids (which can be used as protective groups in peptide chemistry) using KF-DMF or a strongly basic anion exchange resin (Amberlyst A-26) containing fluoride ion as a counter ion in THF (eq 23a). Isolated ester yields were in excess of 60%, being slightly higher in reactions employing the resin than in those using KF.



(23a)

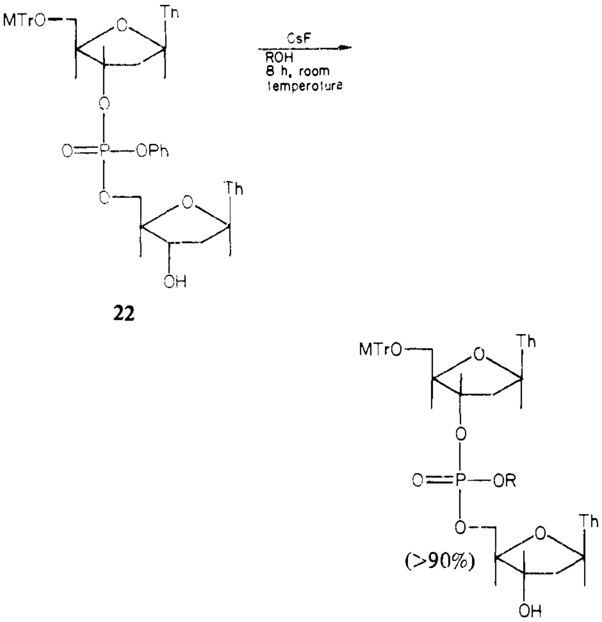
Reported fluoride-assisted esterifications not involving an alkyl halide as the reactant electrophile are few in number and of little interest here.[51,85]

B. Transesterifications

Triesters of phosphoric acid have important uses ranging from plasticizers to key intermediates in nucleotide synthesis. Ogilvie and Beaucage observed that triphenyl phosphate is rapidly and quantitatively converted into trialkyl phosphates when dissolved in anhydrous alcohols containing an excess (10 mol equiv) of CsF (eq 24).[86] CsF could be replaced by TBAF (THF as the bulk solvent) with little change in the overall reaction efficiency. In an attempt to demonstrate the particular value of this reaction in nucleotide chemistry, the authors converted **22** to **23** in quantitative yields (eq 25).[86]

$$(PhO)_3PO \xrightarrow[\text{8 h, rom temperature}]{\text{CsF, ROH}} (RO)_3PO + 3PhOH \qquad (24)$$

R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu and *n*-C_5H_{11}



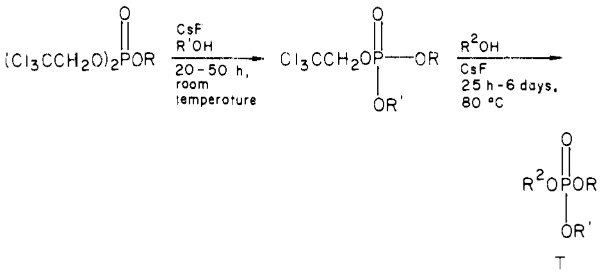
22

23

(25)

R = Cl_3CCH_2, Et, or Me; Th = thymine; MTr = monomethoxytrityl

Although the displacement of ordinary alkyl groups does not occur under these conditions, the trichloroethyl group may be displaced, and this has been utilized in the synthesis of mixed trialkyl phosphate in high yields (eq 26).[87] The reactions occur equally well when TBAF is used in place of CsF; however, the reactions do not occur in the absence of fluoride.

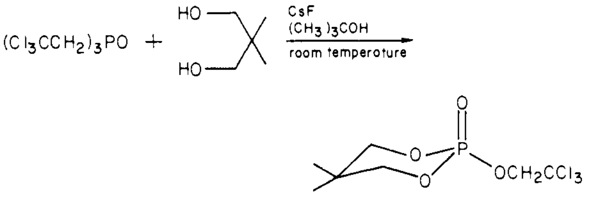


$$(Cl_3CCH_2O)_2P(O)OR \xrightarrow[\text{20-50 h, room temperature}]{\text{CsF, R'OH}} Cl_3CCH_2OP(O)(OR')OR \xrightarrow[\text{25 h-6 days, 80 °C}]{\text{R}^2\text{OH, CsF}} R^2OP(O)(OR')OR \qquad (26)$$

R = Me, R' = Et, R^2 = *i*-Pr; R = Et, R' = *n*-Pr, R^2 = *n*-C_8H_{17}

Cyclic phosphates may also be prepared by this method (eq 27).[87]

More recently, fluoride (TBAF or CsF) has been used to successfully exchange phenyl and trichloroethyl groups for methyl, ethyl, and butyl groups in nucleotide triesters.[2]



(27)

(98%)

The mechanism of these transesterifications may involve the intermediate formation of phosphofluoridates and elimination of either phenoxide or trichloroethoxide.[2] Alternatively, it is possible that fluoride ion through strong hydrogen bonding to the alcohols sufficiently increases the nucleophilicity of oxygen that the alcohol displaces the phenol or trichloroethanol groups directly.[2] In either case, reaction should be encouraged by the production of a more powerful electron acceptor compound (Cl_3CCH_2OH or PhOH) capable of forming stronger H bonds to fluoride than the reactant alcohol itself. This would help to explain the observed inertness to substitution of ordinary alkyl groups. While we are not aware of any detailed studies on the relative H-bonding abilities of alcohols or phenols toward fluoride, it seems reasonable to assume that the more acidic alcohols would be the more powerful H-bond electron acceptors. The order of acidities of a series of protic compounds is usually a good indication of the order of fluoride-protic H-bond strengths.[31]

In conclusion, fluorides have proved to be effective reagents for promoting the esterification of acids using alkyl halides and for transesterifications of phosphate triesters. The majority of reported examples have involved alkali metal fluorides and in particular KF. Liquid carboxylic acid-KF and solid carboxylic acid-KF-DMF would seem to be the reagents of choice for carboxylic acid-alkyl halide esterifications, while alcoholic solutions of CsF are excellent transesterification reagents.

V. Intermolecular Condensations

A. Michael

The nucleophilic addition of an enolate or analogous anion to the carbon-carbon double bond of an α,β-unsaturated ketone, aldehyde, nitrile, or carboxylic acid derivative is a process known as the Michael reaction. The reaction constitutes a method for the alkylation of active methylene compounds and as such has found widespread use in organic synthesis. Various bases including metal alkoxides, metal and quaternary ammonium hydroxides, and metal hydrides as well as ionic fluorides have been employed to generate the enolate anion.

There are numerous reports in the literature relating the use of fluorides as the bases in Michael reactions. Most of the common sources of fluoride described earlier have been tried, and although KF has probably received the most attention, it is interesting to note that other ionic fluorides, and quaternary ammonium fluorides in particular, have become increasingly popular choices in Michael reactions. Since the base employed in Michael reactions is regenerated, only catalytic amounts are required, and this alleviates possible drawbacks such as limited solubility of the catalyst. The most frequently cited advantages of the fluoride method for Michael reactions are the following: (i) special preparation of a strong base, which is frequently required for the reactions of weak carbon acids, is not required; (ii) separation of the catalyst is easy; (iii) reactions can sometimes be accomplished when other strong bases are inert.

The remainder of this section is devoted to examples of fluoride-catalyzed Michael reactions involving nitro compounds, nitriles, esters, thiols, and diketones as the donors.

Ostaszynski and co-workers used KF as the catalyst for the Michael addition of nitromethane to chalcone (benzylideneacetophenone) (eq 28).[88] The same authors also described

$$CH_3NO_2 + PhCH{=}CHCOPh \xrightarrow[6\text{ h, }60\ ^\circ C]{\text{KF, EtOH}} PhCOCH_2CH(Ph)CH(NO_2)CH(Ph)CH_2COPh \quad (28)$$

the use of RbF as the catalyst in similar reactions.[88] The choice of ethanol as the reaction solvent might seem an unusual one in view of its known ability to mask the fluoride ion by specific solvation, but in a subsequent study, Iasuda and Kambe found that the yield of 1-cyano-3-nitropropane resulting from the reaction of nitromethane with acrylonitrile in the presence of KF (eq 29)[89] increased with the solvating ability of the solvent:

$$CH_3NO_2 + CH_2{=}CHCN \xrightarrow[2\text{h, reflux}]{\text{KF}} O_2N(CH_2)_3CN\ (63\%) \quad (29)$$

95% EtOH > 50% aqueous EtOH > Me_2CHOH > Me_3COH > dioxane-water (9:1). Indeed, the use of dioxane itself as the reaction solvent gave no detectable product under the same conditions. Presumably, the solubility of KF, which is certainly greater in the more protic solvents, is the most important factor here. The same authors also noted that 0.1 mol of the KF/mol of nitromethane was necessary to optimize the product yield.[89] It is interesting to note that no bis- or triscyanoethylated products were obtained in these reactions even in the presence of an excess of acrylonitrile.[89] The KF-catalyzed Michael additions of nitromethane to methyl acrylate, methyl methacrylate, methyl crotonate, dimethyl fumarate, and methyl cinnamate were also described, although mixtures of 1:1 and 1:2 adducts were sometimes reported on using a 1:1 molar ratio of donor/acceptor.[89]

Patterson and Barnes extended the KF-catalyzed method to the reactions of a series of nitroalkanes with acrylamide and acrylonitrile using ethanol as the bulk solvent.[90] They reported that KF catalysis usually gave better yields, simpler reaction conditions, and easier product mixture workup than KOH or liquid ammonia catalysis.

In the case of ethyl nitroacetate and *gem*-dinitroalkanes, the KF-, RbF-, or CsF-catalyzed Michael reactions first produce double salts composed of MHF_2 and the salt of the nitro compound.[52] On reaction with acceptors, the salts decomposed to yield normal products. For example, ethyl nitroacetate reacted with acrylonitrile in the presence of KF to give ethyl 3-cyano-1-nitropropanecarboxylate (eq 30).[52] Nitro ketones with a nitromethyl group gave a similar but more complicated reaction in alcoholic media. The condensation products were derived from reaction of the acceptors with nitromethane and not with the original nitro ketones. The mechanism shown in eq 31[52] was proposed

$$\underset{0.033\text{ mol}}{O_2NCH_2CO_2Et} + \underset{0.06\text{ mol}}{CH_2{=}CHCN} \xrightarrow[6\text{ h, }60\text{–}65\ ^\circ C]{\text{KF (0.034 mol)}} \underset{(75\%)}{NO_2CH(CH_2CH_2CN)CO_2Et} \quad (30)$$

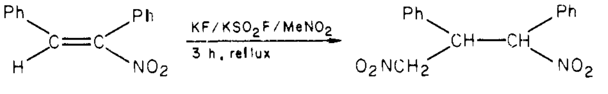
$$O_2NCH_2COR + 2KF \rightarrow K^{+-}O_2N{=}CHCOR + KHF_2$$

$$K^{+-}O_2N{=}CHCOR + R'OH \rightarrow [K^{+-}O_2N{=}CH]^- + RCO_2R' + H^+$$

$$[K^{+-}O_2N{=}CH]^- + H^+ \rightarrow K^{+-}O_2NCH_2$$

$$K^{+-}O_2NCH_2 + 3CH_2{=}CHCO_2Me + KHF_2 \rightarrow O_2NC(CH_2CH_2CO_2Me)_3 + 2KF \quad (31)$$

A more recent example of a KF-catalyzed Michael addition involving nitromethane was provided by Hoz and co-workers who in attempting to add fluoride ion from $KF-KSO_2F$ to the nitroalkene **24** in nitromethane produced the solvent adduct 1,3-dinitro-1,2-diphenylpropane (**25**) (eq 32).[91]



24 25 (22%) (32)

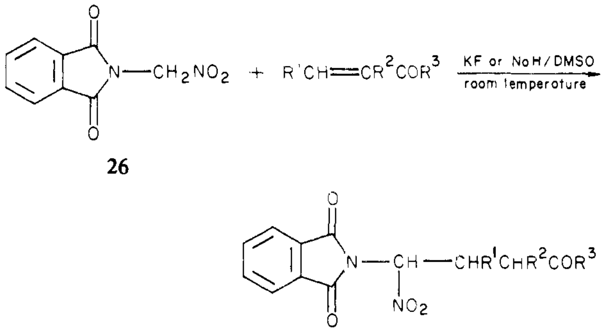
Despite the catalytic role of fluoride in Michael reactions, it seems likely that the KF-promoted reactions are hampered by the low solubility of this fluoride in most organic solvents. The presence of a crown ether such as 18-crown-6 will enhance the KF solubility in acetonitrile or benzene. Belsky described the KF-18-crown-6-catalyzed Michael addition of nitromethane to chalcone and acrylonitrile (eq 33 and 34).[36]

$$\underset{(0.1\ \text{mol})}{MeNO_2} + \underset{(5\ \text{mmol})}{1\ PhCH{=}CHCOPh} \xrightarrow[61\ °C,\ 1.5\ h]{\text{MeCN/KF (1 mmol)},\ \text{18-crown-6 (0.03 mmol)}} \underset{(94\%)}{O_2NCH_2CH(Ph)CH_2COPh} \quad (33)$$

$$MeNO_2 + \underset{(3\ \text{mol equiv})}{CH_2{=}CHCN} \xrightarrow[2.5\ h,\ 81\ °C]{\text{KF/18-crown-6/MeCN}} \underset{(72\%)}{O_2NC(CH_2CH_2CN)_3} \quad (34)$$

It is interesting to note that when Patterson and Barnes attempted the last reaction (eq 34) using KF-EtOH, they obtained 69% of the same product but only after a considerably longer period of time.[90]

The oximes or diphenylimidazolidines of the synthetically important 1,4-keto aldehydes have been prepared via Michael addition of *N*-(nitromethyl)phthalimide (**26**) to unhindered α,β-unsaturated ketones and esters followed by removal of the phthalimido moiety with hydroxylamine or 1,2-dianilinoethane. The Michael addition step was accomplished by using the "nonnucleophilic bases" NaH or KF in DMSO (eq 35).[92] α,β-Unsaturated ketones gave the best adducts when the anion of **26** was generated with NaH, whereas the best results for α,β-unsaturated esters were obtained by using KF as the catalyst.



26 (35)

(e.g., R$'$ = Ph, R^2 = H, R^3 = Me)

Among the more impressive examples of fluoride-catalyzed Michael additions involving nitroalkanes were those using TEAF-Me_2CHNO_2 as described by Clark and co-workers (eq 36).[64] The solvent used was THF, DMF, or $CHCl_3$. The fluoride-catalyzed reactions were shown to be clearly superior to those previously described with basic resins, phosphine, or hydrides as the catalysts.[64]

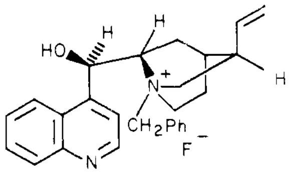
$$Me_2CHNO_2 + R^1CH{=}CHCOR^2 \xrightarrow[2\text{–}4\ h,\ 25\ °C]{\text{TEAF}} \underset{(78\text{–}95\%)}{Me_2C(NO_2)CHR^1CH_2COR^2} \quad (36)$$

$R^1 = H, R^2 = Me; R^1 = H, R^2 = OMe; R^1 = H, R^2 = OEt; R^1 = R^2 = Ph$

TBAF-silica has also been shown to be an effective catalyst for the Michael addition of nitromethane or 2-nitropropane to chalcone.[19] Reasonable yields were obtained after 3-6 h at room temperature or 1 h at 60 °C. The recovered catalyst could be reused in the same reaction with little loss in efficiency. Silica itself gave no detectable product under the same reaction conditions.[19]

Tetra-*n*-butylammonium chloride-KF-H_2O may also be used for the Michael addition of nitromethane to chalcone—the reported efficiency of the method (94% recovered after 0.5 h at 25 °C, MeCN as solvent) is excellent.[22] Replacing the chloride-KF-H_2O reagent (which acts as a source of solubilized fluoride) by KF-H_2O or KF alone resulted in a dramatic loss in reaction efficiency.

The success of such fluoride-catalyzed Michael reactions as those described here prompted Wynberg and co-workers to investigate the influence of fluoride ion on the asymmetric induction in the Michael addition of nitromethane to chalcone.[93] The authors compared the use of free chiral amines as the basic catalyst with chiral amminium fluorides such as the *N*-benzyl fluoride of quinine (**27**). With chiral amines as catalyst, no reaction was observed in aprotic solvents whereas the reaction proceeded well in MeOH with low (~1%) asymmetric induction. When an amminium fluoride was employed as the basic catalyst, reaction occurred readily in aprotic solvents and the extent of asymmetric induction reached a value of ~20%. The authors concluded that chiral amminium fluorides as basic catalysts in the Michael reaction may lead to an important extension in the field of catalytic asymmetric synthesis.[93]



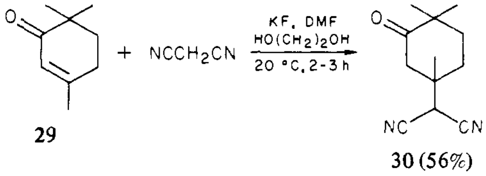
27

We are now in a position to make a better judgment of the early observation of Kambe and Yasuda that increasing the solvating ability of the solvent improves the Michael reaction catalytic efficiency of KF.[89] It is now clear that one must not only consider the effect of increasing the fluoride solubility but also the effect of masking the ion by solvation and that a reasonable order for the relative catalytic efficiencies of some of the more common sources of fluoride is KF (aprotic media) < KF (protic media) < KF-crown ether (aprotic media) < R_4NF (aprotic media).

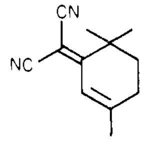
Nitriles have also been popular choices as the donors in fluoride-catalyzed Michael additions. Cyano esters such as **28** are particularly good donors and readily react with α,β-unsaturated aliphatic ketones,[94] esters[94] (e.g., eq 37) and nitriles.[95,96]

$$Me_2C{=}CHCO_2Me + \underset{\mathbf{28}}{NCCH_2CO_2Et} \xrightarrow[11\ h,\ reflux]{\text{KF, EtOH}} MeCO_2CH_2CMe_2CH(CN)CO_2Et \quad (37)$$

ApSimon and co-workers have shown that α,β-unsaturated ketones where the carbonyl group is hindered react with malonitrile in the presence of KF to give Michael products. Thus the cyclic α,β-unsaturated ketone **29** gives the Michael adduct **30**[96] (eq 38). This reaction occurred only very slowly in the absence of the diol, presumably because of reduced KF solubility. Prolonged reaction periods resulted in reduced yields of **30** and an increase in the yield of the Knoevenagel product (**31**).



29 30 (56%) (38)



31

α,β-Unsaturated ketones possessing unencumbered carbonyls tend to give the Knoevenagel adduct as the major or exclusive product (see section VB).[98]

More recent examples of fluoride-catalyzed Michael additions involving nitriles as donors have usually utilized the more soluble tetraalkylammonium fluorides or KF-crown ether complexes. Hoz and co-workers have described the use of TEAF as the basic catalyst for the Michael addition of acetonitrile (in excess) to 1,1-diphenyl-2-nitroethane (eq 39).[91]

$$F^- + MeCN \rightleftharpoons {}^-CH_2CN + HF$$

$$ {}^-CH_2CN + Ph_2C{=}CHNO_2 \xrightarrow{H^+} Ph_2C(CH_2CN)CH_2NO_2 \text{ (after 2 h at room temperature)} \quad (39)$$

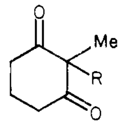
(45%)

Efficient KF-18-crown-6-promoted Michael reactions involving nitriles as the donors have also been reported (eq 40 and 41).[36]

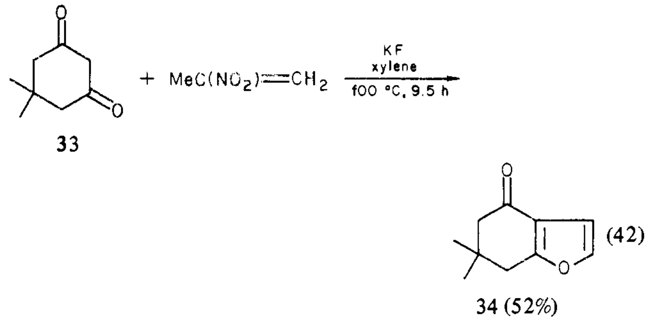
$$EtCO_2CH_2CN + \underset{(2\ \text{mol equiv})}{PhCH{=}CHCOPh} \xrightarrow{KF/18\text{-crown-6}} \underset{(83\%)}{EtCO_2C(CN)(CHPhCH_2COPh)_2} \quad (40)$$

$$CH_2(CN)_2 + \underset{(2\ \text{mol equiv})}{CH_2{=}CHCN} \xrightarrow{KF/18\text{-crown-6}} (CN)_2C(CH_2CH_2CN)_2 \quad (41)$$

β-Dicarbonyl compounds such as 2,4-pentanedione and ethyl acetoacetate react with various Michael acceptors in the presence of KF,[97,98] although few recent examples of these reactions are available and one can only assume that reaction efficiencies would be improved by using a tetraalkylammonium fluoride or a KF-crown ether complex in place of KF. One interesting recent example of this type of reaction was reported by Yoshikoshi and co-workers.[99] 2-Methylcyclohexane-1,3-dione (**32a**) and nitroethylene (2 mol equiv) gave the adduct **32b** in 62% yield on heating with KF (1.2 mol equiv) in xylene at 100 °C for 2 h, whereas other bases such as sodium hydride failed to catalyze the reaction. Reaction of **32a** with 2-nitropropene under similar conditions gave a mixture of the expected product **32c** and the triketone **32d**. Longer reaction periods (~25 h) resulted in an almost quantitative yield (92%) of the transformed product **32d**. 1,3-Diketones with no C(2)-alkyl substituent such as dimedone (**33**) gave 2-methyl-4-acylfurans such as **34** on treatment with 2-nitropropene-KF-xylene (eq 42).[99] These interesting nitro transformations were subsequently explained[64] as being due to the fluoride-promoted Nef transformations of the nitro compounds. The ring closure of the triketone is comparable to the reported fluoride-catalyzed cyclization of diketones.[14] The mechanism in eq 43 for the formation of **34** is proposed to illustrate these suggestions.

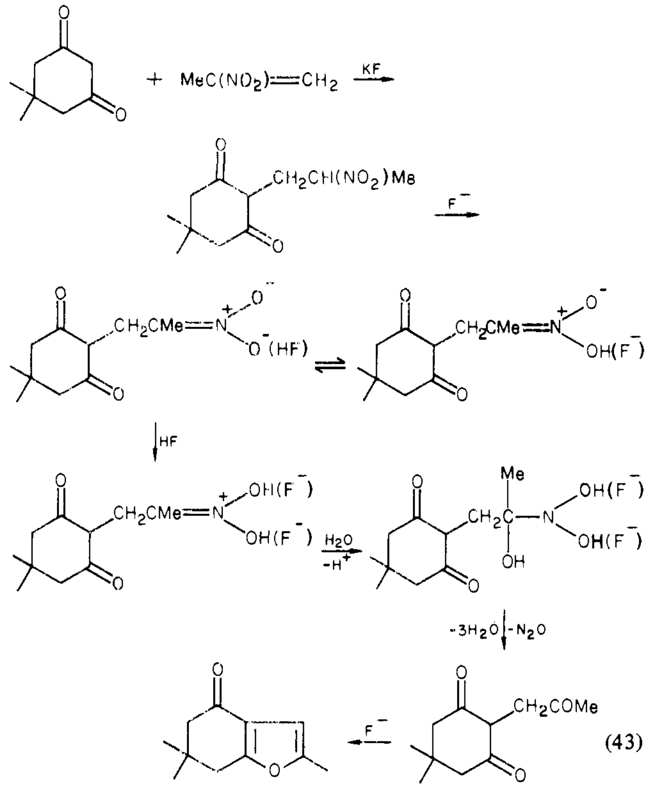


32a, R = H
b, R = $(CH_2)_2NO_2$
c, R = $CH_2CH(NO_2)Me$
d, R = CH_2COMe

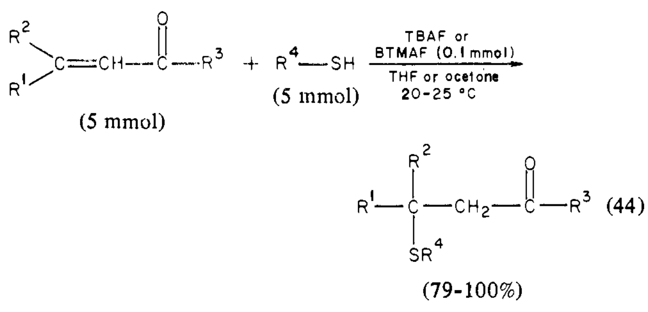


33

34 (52%)



The addition of thiols to α,β-unsaturated ketones may not normally be considered as examples of Michael reactions, but their essential similarity permits their inclusion here. Kuwajima and co-workers have shown that in the presence of a catalytic amount of quaternary ammonium fluoride, various thiols undergo smooth conjugate addition to α,β-unsaturated carbonyl compounds[6] (eq 44). Reactions were usually complete in less than 1 h.



$R^1 = R^2 = H$, $R^3 = CO_2Me$, $R^4 = Ph$; $R^1 = R^2 = R^3 = Me$, $R^4 = Bzl$

Miller and co-workers selected the addition of benzenethiol to buten-3-one for comparative studies on the efficiency of the fluoride forms of various resins as basic catalysts.[12] Optimum reaction efficiency (80% product recovered after 24 h at room temperature) was achieved using Dowex MSA-1 macroporous resin.

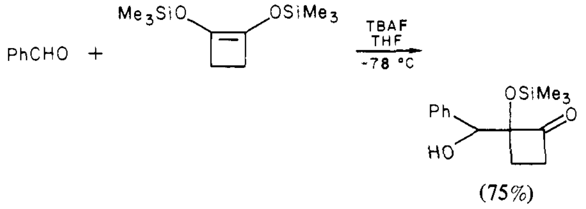
B. Aldol

Addition of an enolate anion to the carbonyl group of an aldehyde or ketone followed by protonation constitutes a reaction known as aldol condensation. These reactions are normally carried out in the presence of bases such as hydroxide, alkoxide, or fluoride, but examples of acid-catalyzed aldol condensations are also known.

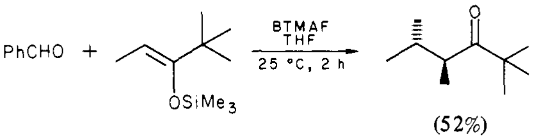
The aldol condensation of aldehydes and nitroalkanes (aldehyde reductive nitroalkylation) constitutes an important route to nitro alcohols. These reactions may be readily accomplished by using KF as the basic catalyst (eq 45).[100-102] Kambe and Yasuda synthesized 19 nitro alcohols by this method.[100] 2-Propanol has been suggested as a suitable solvent for such reactions,[102] and the reactions are accelerated by adding a catalytic quantity of 18-crown-6 (e.g., 0.05 mol equiv of 18-crown-6 and 0.05 mol equiv of KF).[102]

$$\mathrm{RCHO} + \mathrm{R^1CH_2NO_2} \xrightarrow[\sim 6\ \mathrm{h}]{\mathrm{KF}} \mathrm{RCH(OH)CH(R^1)NO_2} \quad (45)$$

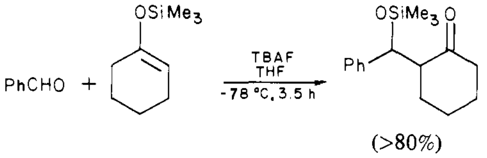
Rapid tetraalkylammonium fluoride catalyzed aldol condensations of aldehydes with enol silyl ethers have been reported by several research groups.[10,103,104] Examples of these reactions are given in eq 46–48.



(46)[103]

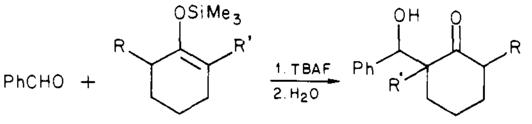


(47)[104]



(48)[10]

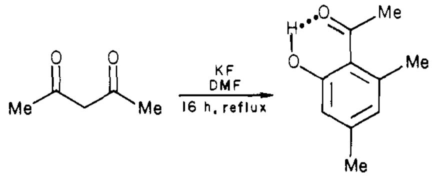
Treatment of silyl ethers with a fluoride in a protic medium has been shown to be an effective method for converting the silyl ether to the corresponding alcohol, and the products shown above may be readily converted to the respective alcohols by treatment with KF–MeOH,[10] for example. Thus Kuwajima and his co-workers have shown that the cross aldol reaction (eq 48) is of considerable generality in the preparation of keto alcohols.[10] Furthermore, fluoride-catalyzed reactions of this type proceed regiospecifically. Thus the enol silyl ethers **35** react with benzaldehyde to afford, without any crossover, the expected regioisomer of the aldol product (**36**) (eq 49).[10]



(49)

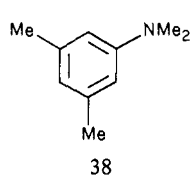
35 36

Another recent and somewhat controversial example of a fluoride-promoted aldol condensation with subsequent elimination of water is the KF-catalyzed self-condensation of enolizable β-diketones. 2,4-Pentanedione, for example, appears by ^{1}H NMR to be converted from 80% enol (in the pure liquid) to 100% enol on shaking with KF (excess)-DMF at room temperature,[14] although the spectroscopic observation may be best interpreted in terms of a highly mobile equilibrium between the keto and enol forms of the β-diketone.[105] When the KF–DMF–2,4-pentanedione mixture is refluxed, the β-diketone undergoes intermolecular self-condensation to produce 2′-hydroxy-4′,6′-dimethylacetophenone (**37**) (eq 50).[14] The absence of the 4′-hydroxy isomer was explained by a number of factors including the stabilization of the observed product by intramolecular H bonding.[14] More recently, it has been shown that this reaction may also produce three minor products, *N*,*N*,3,5-tetramethylaniline (**38**) (via deacetylation and transfer of the dimethylamino group from the solvent at some stage before cyclization), the biphenyl derivative **39** (from an acyclic intermediate by reaction with a third C_5 unit), and the 4-chromanone **40**.[106] It is interesting to note that the incorporation of the NMe$_2$ group into an aromatic system in reactions employing alkali metal fluoride–DMF is not without precedent (see section XI).

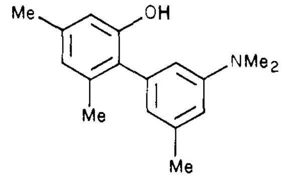


(50)

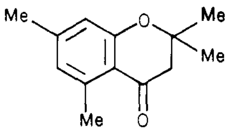
37 (64%)



38

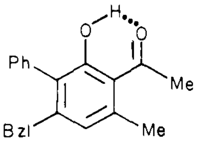


39

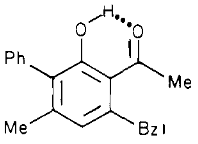


40

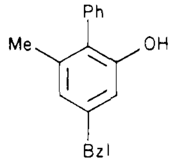
Reaction of 1-phenyl-2,4-pentanedione with KF–DMF under similar conditions yields 4′-benzyl-2′-hydroxy-6′-methyl-3′-phenylacetophenone (**41**) as the major product (48–52%),[14,106] with possible minor products[106] including the isomer **42** and the deacetylated product **43**. The preferential formation of the isomers **41** and **42** with respect to the six other isomers that might be formed may be readily explained by cyclization of the intermediate aliphatic condensation product preferentially occurring at the more acidic benzylic site and by the additional stabilization in the 2-hydroxy isomers brought about by intramolecular H bonding.[14]



41

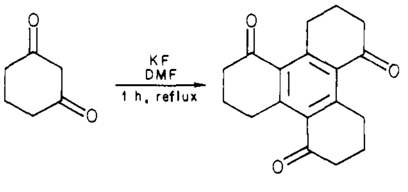


42



43

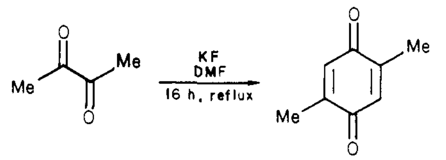
1,3-Cyclohexanedione undergoes self-condensation in the presence of KF–DMF to produce a mixture of isomeric hexahydrotriphenylenetriones (eq 51a).[14]



(51a)

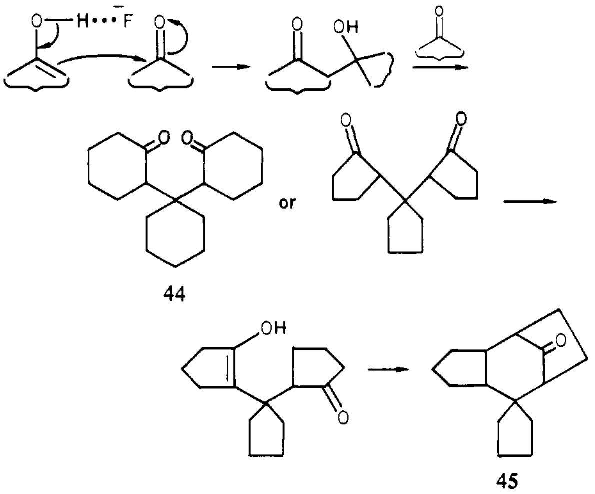
(plus isomers)

Refluxing 2,3-butanedione with KF-DMF produces 2,5-dimethyl-1,4-benzoquinone (eq 51b).[14]



(51b)

Monoketones react much less readily with KF-DMF, but TBAF effectively catalyzes the intermolecular self-condensation of cyclopentanone and cyclohexanone.[14] The product (**44**) from the reaction of the latter ketone arises from the condensation of three ketone molecules with loss of only one molecule of water, whereas the other product (**45**) requires that three ketone molecules condense with loss of two molecules of water. Both reactions probably involve initial H-bond-assisted enolization followed by addition to form the aldol adduct and subsequent condensation (eq 52).[14]



(52)

C. Knoevenagel

The condensation of an active methylene compound and an aldehyde or ketone with elimination of water from the intermediate aldol product is known as the Knoevenagel reaction. The ability of ionic fluorides such as KF and TBAF to effectively catalyze aldol condensations along with their high affinity for water suggests that these reagents should be useful Knoevenagel reaction catalysts.

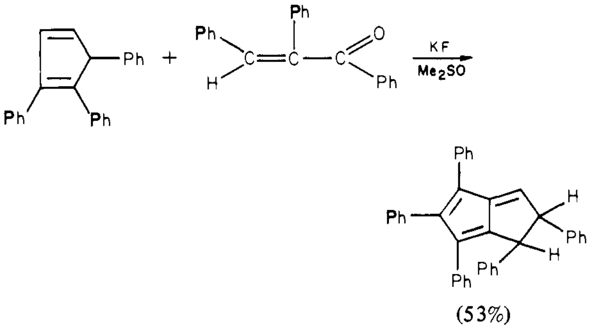
In a series of articles, Aoyoma, Sakurai, and co-workers demonstrated the use of KF as the catalyst in the Knoevenagel condensations of aldehydes and ketones with keto esters and cyano esters.[107-111] Examples of these reactions are given in eq 53–55. Reactions were usually carried out in ethanol or

$$MeCOCH_2Me + NCCH_2CO_2Et \xrightarrow{KF} MeC(Et) = C(CN)CO_2Et \tag{53}$$

$$MeCOMe + NCCH_2CO_2Et \xrightarrow{KF} Me_2C{=}C(CN)CO_2Et \tag{54}$$

$$HCHO + EtOCOCH_2CO_2Et \xrightarrow{KF} \underset{(61\%)}{CH_2{=}C(CO_2Et)_2} + \underset{(20\%)}{CH_2(CH(CO_2Et)_2)_2} \tag{55}$$

diethyl ether as solvent and generally required heating for several hours. The minor product in the last example (eq 55) presumably results from KF-catalyzed Michael addition of the Knoevenagel product with the reactant diester. Michael addition followed by Knoevenagel dehydration has also been observed in a KF-promoted reaction (eq 56).[112]



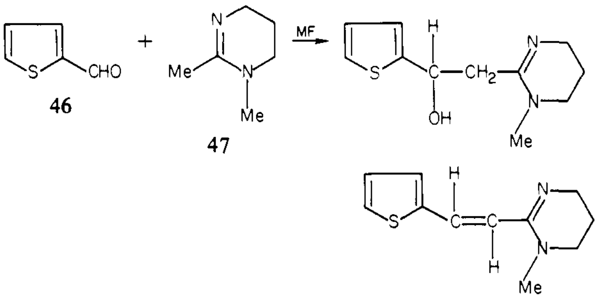
(56)

Rand and co-workers have carried out a detailed study of the ability of alkali metal fluorides to catalyze the Knoevenagel condensations of benzaldehyde and cyclohexanone with malononitrile, ethyl cyanoacetate, and ethyl malonate.[113] It was observed that KF is an effective catalyst in less than molar equivalent amounts and that RbF and CsF were somewhat more effective than KF while LiF and NaF were ineffective. This dependence on the cation was attributed to increasing solubility from LiF through to CsF.[113] Polar solvents usually gave better product yields than nonpolar solvents, although reactions involving malonitrile tended to be so rapid that the choice of solvent was either of little importance or was based on a desire to moderate the reaction so that the reaction of malonitrile with cyclohexanone was carried out in benzene rather than in more polar solvents which resulted in the formation of a tar.

Rand and co-workers have also reported their results from a kinetic study on the reaction of cyclohexanone with ethyl cyanoacetate in ethanol in the presence of KF, RbF or CsF in an attempt to elucidate the nature of the catalysis.[45] On the basis of the experimental rate data, Rand assumed that the fluoride ion serves to promote the dissociation of the methylene compound (eq 57), although he was unable to accurately determine the equilibrium constant for this dissociation in the presence of fluoride. The rate of reaction was found to follow the order CsF > RbF > KF. Hydrogen-bonded intermediates were postulated on the basis of the experimental data.[45]

$$CH_2(CN)CO_2Et \overset{F^-}{\rightleftharpoons} [CH(CN)CO_2Et]^- + H^+ \tag{57}$$

Leiean and Morris carried out rate measurement experiments on the fluoride-promoted Knoevenagel reaction of thiophene-2-carboxaldehyde (**46**) and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (**47**) (eq 58).[114] Tin(II) fluoride was found to be the most effective catalyst in this reaction, and the rate-determining step was thought to be the dehydration stage.



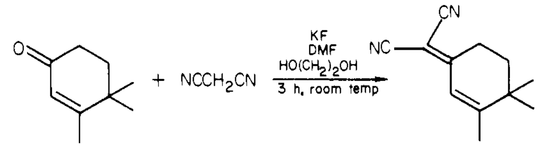
(58)

MF = LiF, NaF, KF, CsF, FeF_3, NiF_2, MgF_2, CaF_2, ZnF_2, BaF_2, AlF_3, CeF_4, PbF_2 or SnF_2

Knoevenagel-type condensations may sometimes occur in competition with Michael additions, and the course of the reaction may depend on steric factors. α,β-Unsaturated ketones containing an unencumbered carbonyl group will tend to undergo initial Knoevenagel condensation with an active methylene compound while those possessing unhindered carbonyl groups prefer Michael-type condensations.

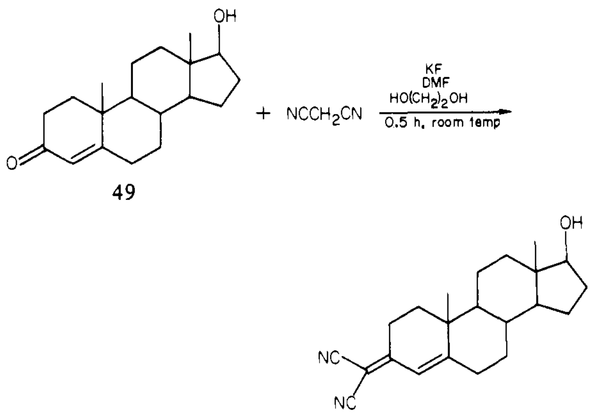
ApSimon and co-workers have demonstrated this reaction selection for KF-catalyzed condensations involving malonitrile.[115]

Thus, 3,4,4-trimethyl-2-cyclohexenone (**48**) and testosterone (**49**) react with malonitrile in the presence of KF (eq 59 and 60).



(59)

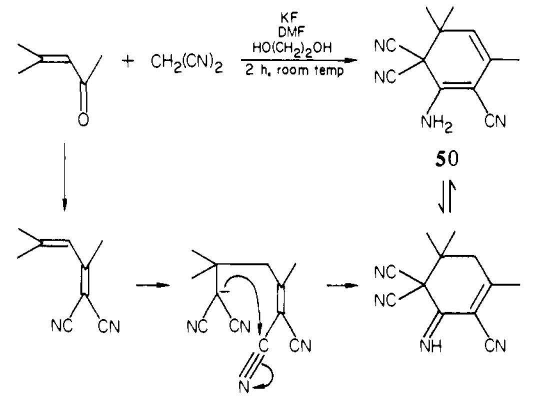
48



49

(60)

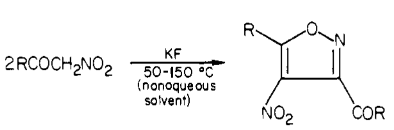
In many cases, Knoevenagel condensation is followed by conjugate addition and intramolecular condensation to yield compounds of unusual structure. Mesityl oxide, for example, reacts with KF–malonitrile to give the trinitrile **50** by the proposed mechanism shown in eq 61.[115]



50

(61)

An interesting example of a KF-promoted intermolecular self-condensation–dehydration involving the conversion of nitro ketones to nitroisoxazoles was reported in a recent patent[116] (eq 62). This represents a novel and potentially useful route to these interesting compounds.

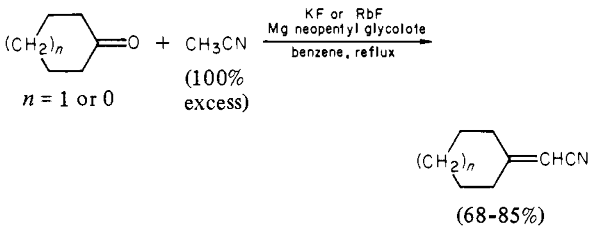


(62)

Possibly the least acidic compound that has been shown to undergo Knoevenagel condensation in the presence of an alkali metal fluoride is acetonitrile, which has been shown to react with cyclic alkanones in the presence of sodium octyl oxide or magnesium neophentyl glycolate and KF or RbF to produce nitriles which are useful as pharmaceutical intermediates[117] (eq 63).

D. Other Condensations

Several fluoride ion promoted intermolecular condensations which do not belong to the previous categories have been described in the literature. Some of the more interesting examples of these reactions are described below.



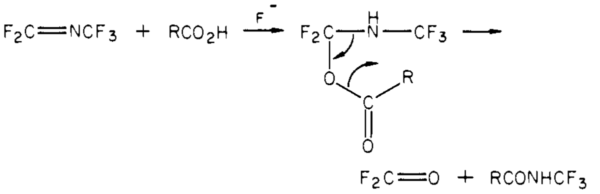
(63)

The facile dehydration of aldol intermediates in the presence of fluoride may be partly attributed to the strong H bond formed between the fluoride ion and water. It seems reasonable, therefore, to expect that fluoride may be capable of eliminating other good H-bond electron acceptors in condensation reactions, and this is exemplified in the KF-promoted condensation shown in eq 64.[118] The unsaturated product **51** is the result of condensation of the aldehyde with the ester with elimination of carbon dioxide and ethanol whereas the other product (**52**) is presumably the result of intermolecular self-condensation of the ester with elimination of $EtCO_2H$.

$$C_6F_5CH(CO_2Et)_2 + HCHO \xrightarrow[24\text{ h, }60\ ^\circ\text{C}]{KF,\ (CH_2OMe)_2} \underset{\mathbf{51}}{H_2C{=}C(CO_2Et)C_6F_5} + \underset{\mathbf{52}}{EtCO_2CH(C_6F_5)C(C_6F_5)(CO_2Et)_2} \qquad (64)$$

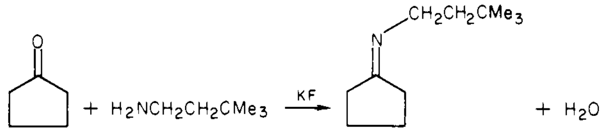
A fluoride-promoted condensation less readily explained is the reaction of a carboxylic acid with a perfluorinated *N*-alkylimine (**53**) in the presence of KF (eq 65).[119] One possible mechanism for this reaction would involve addition of the acid across the double bond followed by intramolecular rearrangement to produce the product and carbonyl fluoride (eq 66).

$$RCO_2H + \underset{\mathbf{53}}{F_2C{=}NCF_3} \xrightarrow[MeCN]{KF} RCONHCF_3 \qquad (65)$$



(66)

Cycloalkanones condense with amines in the presence of KF to produce imines.[120] These reactions, an example of which is shown in eq 67,[120] may be considered as being analogous to the Knoevenagel reaction.

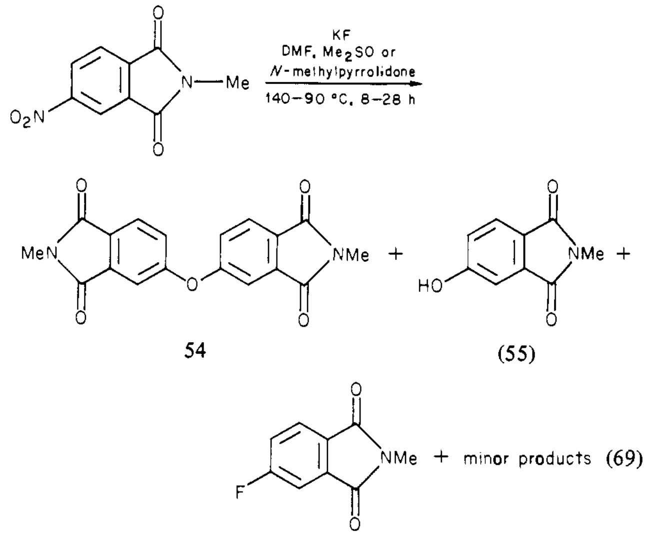


(67)

Protection of the indole ring of tryptophan by the 2,4-dichlorobenzyloxycarbonyl group, for example, requires a strong base in order to produce the indolide ion. Klausner and Chorev found that sodium hydride failed to catalyze such a reaction whereas use of KF–18-crown-6 resulted in reasonably good yields of the N-acylated product (eq 68).[121] The best solvent was found to be acetonitrile which gave yields of 60–65% compared to yields of 45% when THF is used as the solvent. No racemization occurred during these experiments.

$$\underset{(1\text{ mol equiv})}{\text{Boc-Trp-Ala-OMe}} + \underset{(1.2\text{ mol equiv})}{2,4\text{-}Cl_2C_6H_3CH_2OCOOC_6H_4NO_2} + \underset{(2\text{ mol equiv})}{KF} + \underset{(1\text{ mol equiv})}{\text{18-crown-6}} \xrightarrow[i\text{-}Pr_2NEt]{MeCN} \underset{\text{DCZ}}{\overset{}{\text{Boc-Trp-Ala-OMe}}} \qquad (68)$$

Markezich and co-workers have reported some interesting examples of fluoride-promoted reactions of 4-nitrophthalic acid derivatives.[112,113] 4-Nitrophthalic anhydride reacts with KF at 230–240 °C to produce the 4-fluoro derivative and the dipotassium salt of 4-nitrophthalic acid. The latter product is thought to be due to attack of KNO_2 (generated in the initial fluorination) on the anhydride, and fluoride was not considered to be involved beyond the fluorination step. Reaction of 4-nitro-*N*-methylphthalimide with KF in a high boiling point polar aprotic solvent gave a more complex product mixture. The components of this mixture, as identified by GC, GC/MS, and ^{13}C NMR analyses, included the diaryl ether, 4,4′-oxybis(*N*-methylphthalimide) (**54**), as the major product (up to 78%), 4-hydroxy-*N*-methylphthalimide (**55**), 4-fluoro-*N*-methylphthalimide (**56**), and a number of other products, the identity of which depended on the choice of solvent (eq 69). The intermediate in the mechanism proposed by Markezich for the formation of the ether **54** is the hydroxy derivative **55** which is thought to occur by attack of KNO_2 on the starting material.

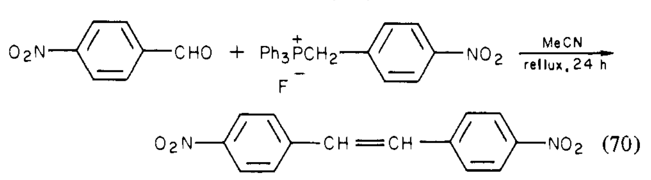


54 (55)

56

(69)

An unusual example of the Wittig reaction occurring in the presence of fluoride ion has been reported by Schiemanz and co-workers.[124] 4-Nitrobenzaldehyde slowly reacts with triphenyl(4-nitrobenzyl)phosphonium fluoride to give the stilbene **57** (eq 70). The fluoride was prepared from the chloride by ion exchange using the fluoride form of Amberlite IRA 400 resin in MeOH. The reaction may be explained as being due to attack of the fluoride ion on its own cation, that is, the fluoride ion functions as the Wittig base.



(70)

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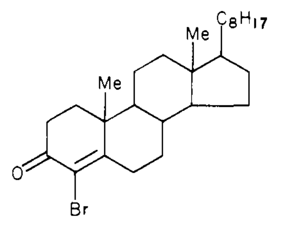
VI. Eliminations

A. Dehydrohalogenations

In his studies on eliminations from 2-halobutanes promoted by halide ions, Bartsch demonstrated that TBAF in DMF is an effective reagent for the dehydrohalogenation of 2-bromobutane and 2-iodobutane under mild conditions.[15] TMAF and LiF were found to be less reactive than TBAF presumably because of their lower solubilities in aprotic solvents. With all of the fluorides 2-butenes were the major products from the reaction of the 2-halobutanes and the amount of of 1-butene produced increased as the leaving group became poorer (i.e., I < Br < Cl), in accord with variable E2 transition-state theory,[15] and was also dependent on the identity of the cation (LiF < TBAF ~ TMAF). The latter effect may be a false one since the tetraalkylammonium fluorides undoubtedly contained traces of water which would lower the basicity of the fluoride ion by specific H bonding to the water.

There had been several reports of fluorides assisting alkene-forming eliminations prior to the work of Bartsch. As early as 1955, Kitano and Fukui had detected small amounts (2–7%) of alkenes during their attempted fluorination of C_4–C_8 haloalkanes with KF.[125] In a later article, the same authors reported the presence of fairly small amounts of 1-hexene (<20%) after reacting *n*-bromohexane with KF in 1,2-propanediol at 185 °C.[57]

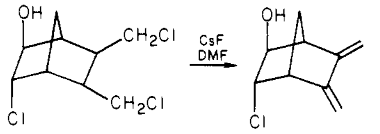
An early example of a deliberate attempt to induce dehydrohalogenation using a fluoride was provided by Kirk and co-workers in 1956.[126] 4-Bromocholest-4-en-3-one (**58**) is converted to its 4,6-diene on treatment with LiF–DMF.[126]



58

The majority of relevant articles published since Bartsch's work have dealt with the use of tetraalkylammonium fluorides as the elimination-promoting bases. Much of the early detailed work on TEAF-promoted dehydrohalogenations can be attributed to Ono and co-workers.[7,13,127–129] Possibly their most important contribution in this field was their studies on the effect of bases in promoting the E2 reaction of 2-chloroethylbenzene where they concluded that TEAF is about 800 times as effective as sodium ethoxide.[7] It is also interesting to note that while treatment of 2-haloethylbenzenes with TEAF resulted in virtually exclusive formation of phenylethene, use of tetraethylammonium chloride or bromide instead of the fluoride gave almost exclusive formation of the halogen-exchange product.[127]

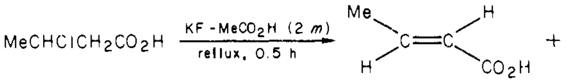
Despite the growing interest in the use of tetraalkylammonium fluorides as elimination-promoting reagents, there remains a steady flow of articles describing similar applications of alkali metal fluorides. KF has been used to convert α-bromocarboxylic acid anilides to the α,β-unsaturated anilides[130] and to improve the yield of 1-chloropropene at the expense of 3-chloropropene from the dehydrochlorination of 1,2-dichloropropane (KF being the most selective of several catalysts investigated)[131] while CsF has been used in the selective elimination of 2 equiv of HCl from the norbornane (**59**) (eq 71).[56] KF–18-crown-6 has also been reported as an effective reagent in the last reaction (eq 71)[56] and in the conversion of bromocyclohexane to cyclohexene and of 2-bromooctane to 1- and 2-octenes (68% total alkene yield and 32% 2-fluorooctene produced).[33]



(71)

59

Homogeneous solutions of KF in $MeCO_2H$ have been used in dehydrohalogenation reactions. For example, 3-chlorobutanoic acid gives *trans*-but-2-enoic acid (90%) as well as a little 3-acetoxybutanoic acid (eq 72).[28]

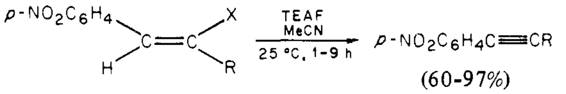


(90%)

$MeCH(O_2CMe)CH_2CO_2H$ (72)

(10%)

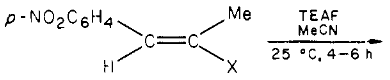
Fluorides may also be used to promote alkyne-forming eliminations, although there are few available reports on this subject. Naso and Ronzini examined the ability of several fluoride ion sources in alkyne- and allene-forming eliminations.[34] *cis*-β-Bromo- and *cis*-β-chloro-*p*-nitrostyrenes readily gave the anti-elimination products on treatment with TEAF in MeCN at 25 °C (eq 73). Reaction of the *trans*-styrene analogues under the same conditions gave allenes in modest yields and very low yields of alkynes (eq 74). KF in a variety of solvents including Me$_2$SO, MeCN, HMPA, or DMF also proved to be a good dehydrohalogenating agent in the above reactions (eq 73 and 74), although the reactions required higher temperatures (~100 °C) to produce good yields (50–93%).[34] The effect of crown ether catalysis on the KF-promoted reactions was found to depend on the nature of the solvent. For instance, it is quite dramatic in MeCN but much less important when DMF is the reaction medium. Thus the conversion of *cis*-β-bromo-*p*-nitrostyrene to the alkyne (eq 73) in MeCN gave ~0% after 1 h at 80 °C when KF alone is used and ~53% after using KF–18-crown-6 under the same conditions.[34]



(73)

(60-97%)

X = Br or Cl; R = H or Me)



p-$NO_2C_6H_4CH{=}C{=}CH_2$ + p-$NO_2C_6H_4C\equiv CMe$ (74)

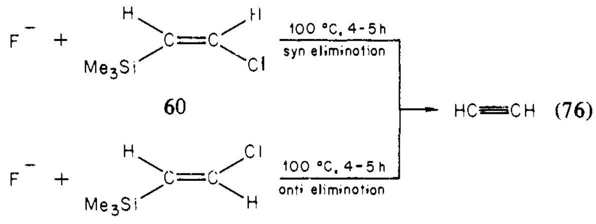
(45-48%) (5%)

X = Cl or Br

Morse and co-workers employed KF–18-crown-6 in the alkyne-forming elimination of 1,1,1-trifluoro-3-iodobut-2-ene (eq 75).[132] The 2-alkyne was obtained in 45% yield, and the total product yield (>55%) was in excess of that obtained from the three-stage method that had previously been employed in the synthesis of the alkynes.[132]

$$CF_3CH{=}CICH_3 \xrightarrow[3\text{-}4\ h]{\substack{16\text{-crown-6}\\ KF\\ dioxane}} CF_3C{\equiv}CCH_3 + CF_3CH_2C{\equiv}CH \quad (75)$$

An interesting example of a fluoride-promoted alkyne-forming elimination where the role of the fluoride is less than clear is the reaction of KF–Me$_2$SO with *cis*- and *trans*-β-chlorovinyltrimethylsilanes (**60**) which results in facile conversion to acetylene (eq 76).[29] When the same reaction is carried out by using aqueous or alcoholic alkali in place of KF–Me$_2$SO, the result is displacement of the halovinyl moiety from the silicon. Four possible mechanisms were put forward to explain the fluoride-promoted reaction,[29] two of which involved initial dehydrohalogenation (i.e., nucleophilic attack of the fluoride ion at hydrogen) (eq 77) and the other two required attack of the fluoride ion at silicon. The latter two mechanisms were favored by the authors partly on the basis of the observation that vinyl chloride is inert to treatment with KF–Me$_2$SO under the conditions required for reaction 76, although it has been reported that vinyl chloride does afford acetylene upon treatment with KF–*N*-methyl-2-pyrrolidone at 200 °C.[133]

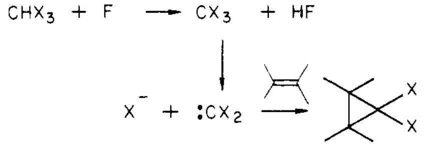


$$60 + F^- \longrightarrow Me_3SiC{\equiv}CH + HF + Cl^-$$

$$\big\downarrow{\scriptstyle HF}$$

$$HC{\equiv}CH + Me_3SiF \quad (77)$$

Fluorides are capable of affecting the elimination of hydrogen halide from haloforms in the presence of alkenes,[13,127,134,135] to produce the methylene addition product. In analogy with the well-established reaction of a conventional base such as an alkoxide, the reaction of the fluoride may be formulated as involving a carbene intermediate (eq 78). Thus, TEAF in MeCN reacts with cyclohexene and chloroform to produce dichloronorcarane (eq 79).[13]



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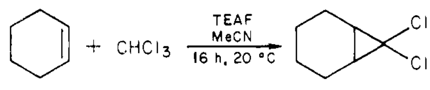
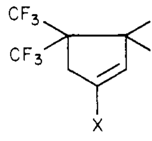


(79)

(20%)

CsF reacts with perfluoro-2-methylpropene (**61**) and haloform in diglyme to produce the product from addition of HF to the alkene (**62**) and a partially fluorinated cyclopentene (**63**), the latter presumably being built up from two molecules of the perfluoroalkene and one molecule of haloform (eq 80).[135]

$$\underset{61}{(CF_3)_2C{=}CF_2} + X_3CH \xrightarrow[\text{diglyme}]{CsF} \underset{62}{(CF_3)_3CH} +$$



(80)

63

X = Cl, Br, or I

While it would be possible to evoke a mechanism involving carbene generation by way of CsF-promoted dehydrohalogenation of the haloform, an alternative approach is to consider reaction of CsF directly with the alkene to give the carbanion (CF$_3$)$_3$C$^-$, which could then attack the haloform.[135] The latter mechanism would seem to be the most probable in view of the difficulty encountered in promoting carbene additions with even the most active fluorides (e.g., TEAF), although contributions from the former mechanism cannot be entirely ruled out.

In conclusion, fluorides are capable of assisting the dehydrohalogenation of a variety of haloalkanes and haloalkenes to produce alkenes and alkynes or allenes. On the basis of the evidence available, it would seem that the order of reactivity is R$_4$NF > KF–18-crown-6 > CsF ~ KF, the most active fluorides being at least as reactive as conventional strong bases such as metal alkoxides. Suitable reaction solvents include MeCN (for R_4NF and KF-18-crown-6) and DMF (for CsF and KF). Dehydrohalogenation of haloforms to produce methylene addition products is less readily accomplished by fluoride ion promotion, quaternary ammonium fluorides being the most effective. Water is likely to reduce the efficiency of all of these reactions.

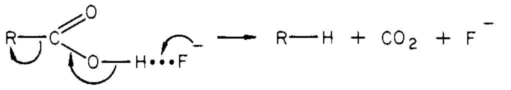
B. Dehydrations

In view of the many successful examples of fluoride-promoted Knoevenagel reactions that have been reported, it is perhaps a little surprising to discover that only a few examples of alkene-forming fluoride-promoted dehydrations are available in the literature.[136-136]

Alcohols of the camphane series react with KF to give camphenes.[137] Hydrogen fluoride itself may also be used in these reactions although this reagent has a tendency to cause subsequent hydrofluorination. Simple aliphatic alcohols such as ethanol[136] may also be dehydrated by treatment with KF or mixed fluoride catalysts such as CaF_2–NaF.

C. Other Eliminations

The importance of H bonding in determining the ease of decarboxylation of carboxylic acids is well established.[139] For example, hydroxy aromatic acids with the carbonyl group H bonded intramolecularly to an ortho hydroxy group decarboxylate more readily than their isomers. Strong H bonding of a carboxylic acid to fluoride ion should also assist decarboxylation (eq 81). Nesmeyanov was probably the first to recognize the basic properties of the fluoride ion when he discovered that KF reacted with some carboxylic acids to give products resulting from decarboxylation.[9] For example, trichloroacetic acid and 4-nitrophenylacetic acid react with KF at ~120 °C to give chloroform and 4-nitrotoluene, respectively.[9] Other examples of NaF- or KF-catalyzed carboxylic acid decarboxylations including those of L-glutamic acid[139] and perfluorocarboxylic acids[76] have been reported.



(81)

Fluorides have also been used to effect the elimination of carboxylic acids from esters in the camphane series to produce the corresponding camphenes.[137]

The ability of fluorides to behave as bases in elimination reactions, as well as many other reactions, has often been discovered accidentally and in particular where fluorination has been the initial goal. Thus, Lee and El Sawis' attempted preparation of fluorocarbohydrates using KF was hindered by fluoride-promoted elimination of the protecting groups with the formation of appreciable amounts of internal ethers.[140] Nowadays, fluorides and in particular TBAF are routinely used to deprotect various molecules although this commonly involves the removal of a silyl group which probably relies on nucleophilic attack of fluoride ion on the silicon center rather than on any basic properties of the fluoride ion.[1]

There are many examples in the literature of fluoride-promoted eliminations where the role of the fluoride is not clearly that of a base. In particular, a number of dehydrogenations have been carried out by using fluorides such as KF, NaF, FeF_3, CrF_3, and BaF_2, often in the presence of other catalysts such as silica or copper oxide.[141-144] These reactions, which are usually accomplished at high temperatures, include the conversion of 2-butene to butadiene,[141] the pyrolysis of CHF_3 to C_2F_6,[143] and the conversion of alcohols to aldehydes or ketones.[144] Fluorides have also been used in some dehalogenation experiments. For example, CsF with platinum(II) chloride and Et_4NSnCl_3 has been used as the catalyst in the dehalogenation-dimerization of haloalkenes to dienes.[145]

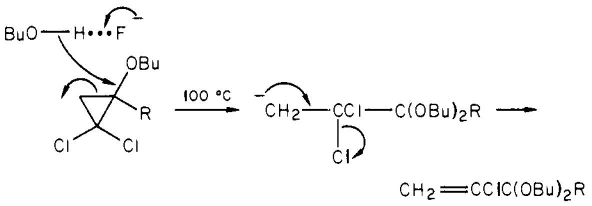
D. Eliminations with Accompanying Rearrangement

The reaction of KF with N-chlorobenzamide in benzene or cyclohexane is an unusual example of the Hofmann reaction occurring in a nonaqueous medium (eq 82).[146] The most probable mechanism for this reaction involves initial formation of phenyl isocyanate by dehydrochlorination of the starting material followed by reaction of the isocyanate with another molecule of N-chlorobenzamide (eq 83).[146,147]

$$\mathrm{PhCONHCl} \xrightarrow[\text{reflux, 2 h}]{\text{KF} \atop \text{benzene}} \mathrm{PhNHCONHCOPh} \quad (82)$$

$$\mathrm{PhCONHCl} \xrightarrow{\text{KF}} [\mathrm{PhCON}] \rightarrow [\mathrm{PhNCO}] \xrightarrow{\mathrm{PhCONHCl}}$$
$$\mathrm{PhNHCON(Cl)COPh} \xrightarrow{H_2O} \mathrm{HOCl} + \mathrm{PhNHCONHCOPh} \quad (83)$$

Aksenov and Min have reported that on alcoholysis of *gem*-dichloropropyl ethers with 1-butanol in the presence of KF, ring cleavage occurs at the bond opposite the chlorines with subsequent dehydrochlorination.[146] One possible mechanism for this reaction would involve attack by the alcohol–fluoride H-bonded complex on the ether followed by ring opening and dehydrochlorination (eq 84). When KF was replaced by sodium *n*-butoxide in the above reaction, both the above product (**64**) and *trans*-ClCH=CHCR(OBu)$_2$ (resulting from ring opening at the bond adjacent to the chlorine-carrying carbon) were detected.[148]

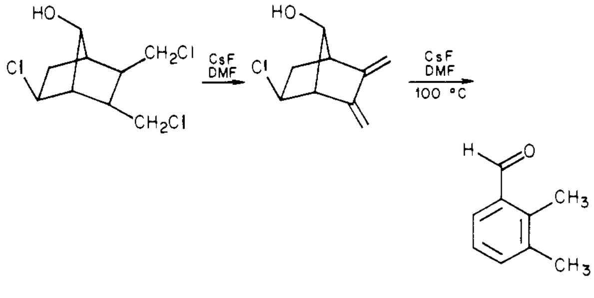


(84)

64 (40-55%)

R = H or Me

Dimethylenenorbornane, which can be prepared by dehydrochlorination of bis(chloromethyl)norbornane with CsF–DMF, is converted to 2,3-dimethylbenzaldehyde on prolonged treatment with CsF–DMF at 100 °C (eq 85).[58]

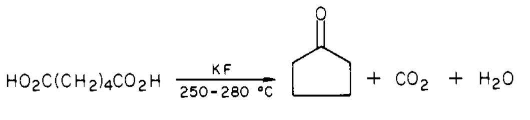


(85)

VII. Intramolecular Cyclizations

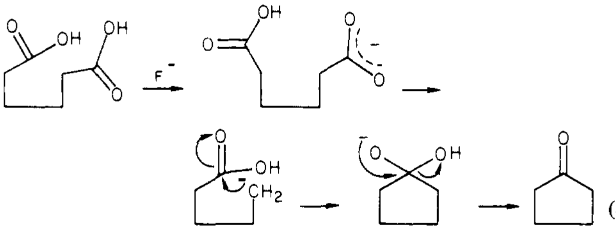
A. Carbocycle-Forming Cyclizations

One of the earliest examples of a fluoride-promoted intramolecular cyclization was the conversion of adipic acid to cyclopentanone (eq 86) first reported by Rand and co-workers.[149]



(86)

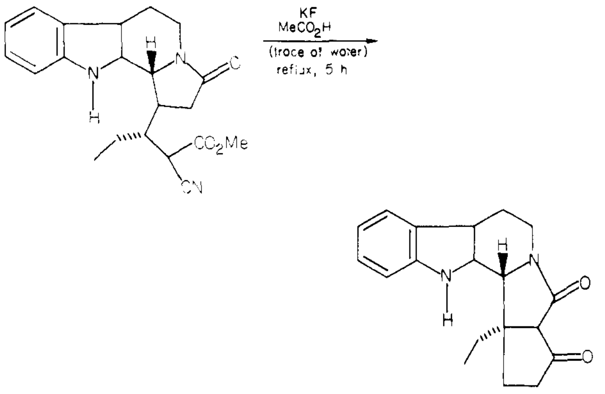
The optimum yield of the ketone (81%) was achieved using 0.05 mol equiv of KF; increasing the amount of fluoride enhanced the rate of reaction but resulted in significantly lower product yields. When the same reaction was attempted in the absence of KF, no ketone was obtained after prolonged heating at the above temperature. One possible mechanism for this reaction would involve abstraction of an α-hydrogen followed by Dieckmann condensation,[150] but this was ruled out by Rand when he observed that KF also promotes the intramolecular cyclization of 2,2,5,5-tetramethyladipic acid.[149] The mechanism in eq 87 has been proposed[149] and would explain the observed



(87)

inverse dependence of product yield on fluoride concentration since excess KF would hinder the desired reaction by formation of the dicarboxylate anion.

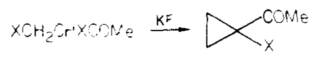
Cyclization to produce a cyclopentanone unit has also been observed by Winterfeldt and co-workers during their studies on indole derivatives (eq 88).[151]



(88)

(70%)

Ionic fluorides may also be used to promote the preparation of cyclopropanes by cyclization of activated haloaliphatics. Thus 3-chloronitropropane gives nitrocyclopropane on reaction with an ionic fluoride in an aprotic solvent such as Me_2SO or DMF[152] and 3,5-dihalopentan-2-one undergoes partial elimination of hydrogen halide in the presence of KF to produce the cyclopropane derivative (eq 89).[153]



(89)

X = Cl, Br, or F

B. Lactone-Forming Cyclizations

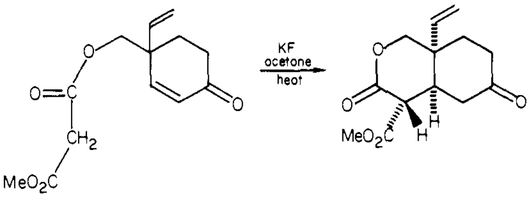
KF–$MeCO_2H$ has proven to be a useful and possibly general reagent for lactone formation from halocarboxylic acids.[28] 5-Chloropentanoic and 4-chlorobutanoic acids readily react with homogeneous solutions of KF in $MeCO_2H$ to give the corresponding lactones as the sole products (eq 90).[28] Similarly,

$$\underset{n\,=\,3\text{ or }4)}{Cl(CH_2)_nCO_2H} + \underset{(2\ m)}{KF\text{-}MeCO_2H} \xrightarrow[\text{reflux}]{\text{4–5 h}} \underset{(95\%)}{\overline{O\text{—}(CH_2)_nC}\!=\!O} \quad (90)$$

6-chloro-3-thiahexanoic acid gives the seven-membered ring 1,4-oxathiepan-2-one on treatment with KF–$MeCO_2H$ (eq 91).

$$Cl(CH_2)_3SCH_2CO_2H + KF\text{-}MeCO_2H \xrightarrow[\text{reflux}]{} \overline{SCH_2CH_2CH_2OC(:O)CH_2} \quad (91)$$

Ionic fluoride–aprotic solvent systems have rarely been used in the synthesis of lactones. One interesting example of this type was provided by Torri and co-workers who observed that the 2-oxa-3,6-dioxo-9-vinyl-*cis*-decalin skeleton found in vernolepin and vernomenin could be synthesized via a fluoride-catalyzed intramolecular Michael addition in acetone (eq 92).[154]

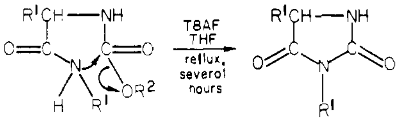


(92)

C. Other Heterocycle-Forming Cyclizations

Possibly the first reported example of a fluoride-promoted heterocycle synthesis is due to Kitano and co-workers who observed that reaction of KF with 2-chloroethanol at 120 °C gave ethylene oxide as well as 2-fluoroethanol.[155] 1,2-Ethanediol, which is capable of H-bonding to fluoride,[25] hence reducing its basicity, suppresses formation of the oxide.

The fluoride-promoted intramolecular cyclization of carbamates is one of the most attractive routes to hydantoins and is a striking example of the potential basic power of the fluoride ion (eq 93).[11] The reaction may be extended to include peptides; for example, carbobenzoxy dipeptides such as Z-Leu-Gly-OEt undergo cyclization on exposure to TBAF–THF.[11] These reactions can readily be explained by considering the H bonding between the fluoride and the N–H assisting nucleophilic attack on the carbonyl group opposite, thus releasing the alcohol, R^2OH, itself capable of strongly H bonding to the fluoride.[14] Previous methods for carrying out cyclizations of this type invariably relied on strongly alkaline media with resulting side reactions and often very low yields (typically 20–40%). It is interesting to note that protic solvents and low polarity solvents diminished the product yields and that salts of anions other than fluoride such as tetrabutylammonium chloride or bromide failed to catalyze the cyclization.[11]



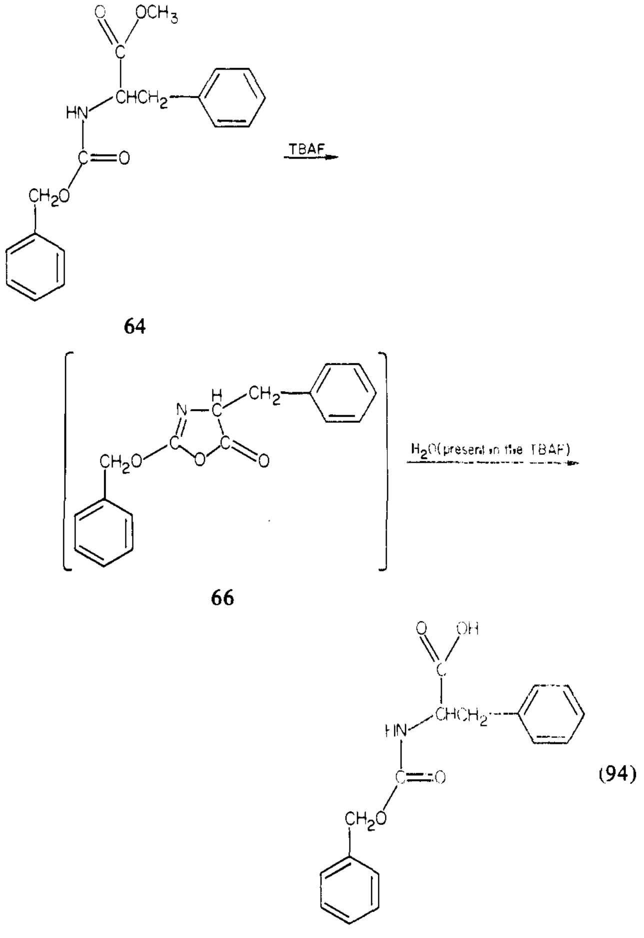
(93)

(>90%)

R^1 = H, Me or Bzl; R^2 = Me or Bzl

Indirect evidence of another type of TBAF-promoted cyclization was provided alongside the above results on hydantoin syntheses.[11] When carbobenzoxy-L-phenylalanine methyl ester (**64**) was treated with TBAF, the only product isolated, in nearly quantitative yields, was the carbobenzoxy-DL-phenylalanine (**65**). The formation of the azlactone **66** as an intermediate was proposed in an attempt to explain this saponification coupled with racemization (eq 94).[11]

Cyclization at a nitrogen center also occurs on reacting 2-(pentafluorophenyl)propylamine with KF–DMF to produce the indole **67** (eq 95).[156]

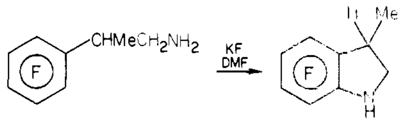


64

66

65

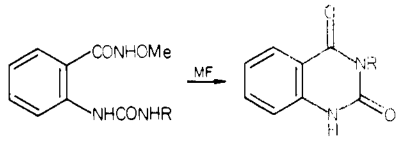
(94)



67

(95)

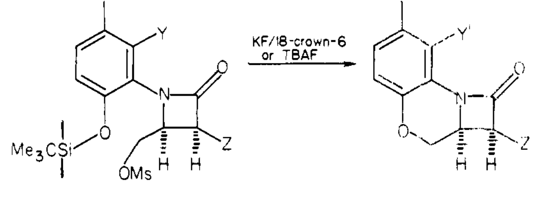
Phenylureas may be cyclized to quinazolinediones in the presence of fluorides (eq 96).[157]



(96)

Mizuno and Inoue have found that linear substrates of the type $CH_3C(=NOH)CH_2XCOR$ (e.g., X = NR′ and R = $CHCl_2$) can be successfully cyclized with the aid of a tetraalkylammonium fluoride to the corresponding heteroaromatic *N*-oxides.[158] Tetraalkylammonium chlorides or bromides were not effective in these transformations.

Just and co-workers have reported the fluoride-promoted cyclizations of silyl ethers to *O*-2-isocephems (eq 97).[32,159] The reaction with KF (1.1 → 2 mol equiv)–18-crown-6 (0.2–0.3 mol equiv) required several hours whereas TBAF induced virtually instantaneous reaction.

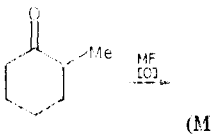


(97)

e.g., X = X′ = Y = Y′ = H; Z = N_3; OMs = Cl

VIII. Oxidations

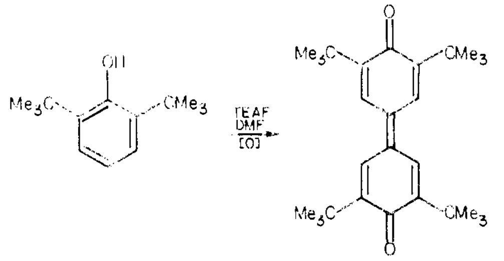
Several patents have described the use of alkali metal fluorides as catalysts for the autoxidation of ketones, alkanes, and alkenes.[160–163] Two examples of these reactions are given in eq 98 and 99. 2,6-Disubstituted phenols and *p*-fluorophenol ethers may undergo fluoride-catalyzed autoxidations. For example, 2,6-di-*tert*-butylphenol readily undergoes autoxidation in the presence of TEAF (eq 100),[82] and 4-fluorophenyl ethyl ether and 4-fluorophenyl methyl ether are oxidized to 4,4-difluorocyclohexa-2,5-dienone on electrolysis in MeCN in the presence of the hydrogen fluoride solvate of TEAF (eq 101).[164]



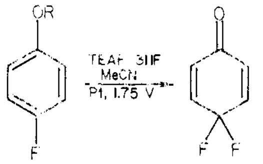
$MeCO(CH_2)_4CO_2H$ (98)[160]

(M = K, 63% product; M = Li, <14%;
M = Na, <5%; no fluoride, <1%)

$$PhCHMe_2 \xrightarrow[\text{heat under pressure}]{\text{NaF or KF, [O]}} PhC(Me)_2OOH \qquad (99)^{161,162}$$



(100)



(101)

R = Me or Et

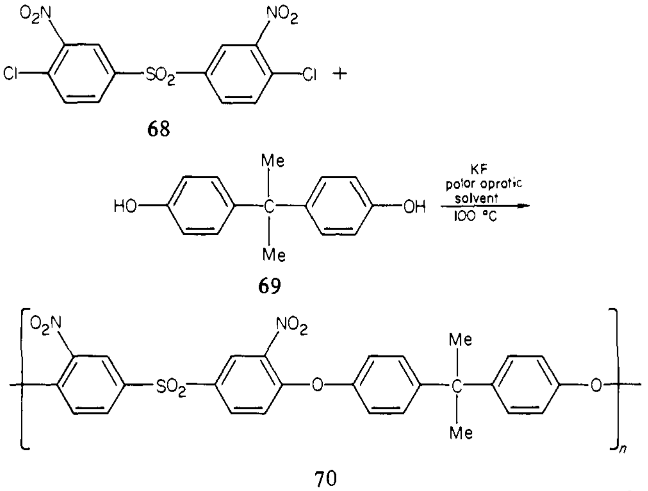
Aryl thiols are very susceptible to fluoride-catalyzed autoxidation to the corresponding disulfides. Various sources of fluoride, including TEAF,[165] TBAF–silica,[19] and the fluoride form of some ion-exchange resins,[12] have been successfully employed in these reactions.

IX. Polymerizations

There are numerous reports in the literature describing the use of ionic fluorides as catalysts in polymerizations although few of these are of general interest to the synthetic chemist. The most common types of fluoride-catalyzed polymerizations are those of alkenes (using an alkali metal fluoride with an aluminum halide and a titanium compound or a metal alkoxide),[166–168] ethers (using KF and diethyl zinc or KF and an acid anhydride),[169–171] and aldehydes (using aqueous LiF or KF).[172]

Some of the earliest examples of fluoride-catalyzed polymerizations occurred during attempted halocarbon fluorinations. For example, in attempting to prepare fluoro ethers by reacting chloro ethers with KF, Mason observed the formation of appreciable quantities of polymeric materials.[173] Similarly, heating KF and chloroacetic acid does not give the expected fluoroacetic acid product but instead results in controlled polymerization of the acid to give $ClCH_2CO_2(CH_2CO_2)_nH$ (*n* = 1–4)[28] (see section IVA).

Recently, Imai and co-workers reported the fluoride ion assisted polycondensation of bis(4-chloro-3-nitrophenyl) sulfone (**68**) with 2,2-bis(4-hydroxylphenyl)propane (**69**) to produce aromatic polyethers (**70**) (eq 102).[174] The solution polymerization was carried out in polar aprotic solvents such as DMF, dimethylacetamide, Me_2SO, tetramethylene sulfone or hexamethylphosphorus triamide, with DMF and tetramethylene sulfone being the most effective solvents for the production of polyethers of higher molecular weights. The optimum reaction temperature was found to be about 100 °C although reaction was noted at temperatures as low as 20 °C. No reaction occurred in the absence of KF. The reaction was explained as being due to the enhanced nucleophilicity of the bisphenol brought about by its strong H bond to fluoride.[174]



68

69

70

(102)

X. Other Reactions

The conversion of α-nitro ketones to esters and nitroalkanes has been accomplished using KF-alcohol (eq 103).[175] These

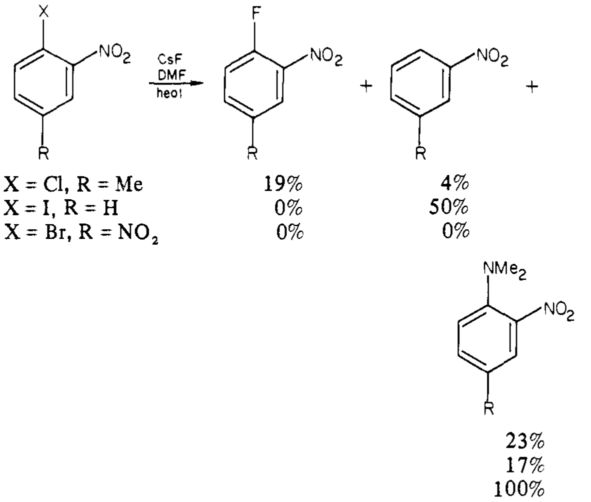
$$Me(CH_2)_nCOCHRNO_2 + R^1OH \xrightarrow{KF} Me(CH_2)_nCO_2R^1 + RCH_2NO_2 \quad (103)$$

reactions presumably involve nucleophilic attack of the fluoride-activated alcohol on the ketone carbonyl. 2-Nitrocycloalkanes undergo ring opening under the same reaction conditions to produce ω-nitro esters.[176]

Among the most unusual fluoride-assisted reactions are those of silanes with alcohols originally reported by Deneux and coworkers[177] and later developed by Andrianov and co-workers.[178] Alkylsilanes undergo partial stepwise replacement of their alkyl groups by alkoxy groups on reaction with alcohols in the presence of TMAF,[178] TEAF,[177] or even CsF.[177] The ease of replacement of alkyl groups was found to be $PhCH_2 > H > CH_2{=}CHCH_2$. Phenyl groups could not be replaced. Thus dibenzylmethylsilane reacts with methanolic TMAF to give dimethoxymethylsilane followed by trimethoxymethylsilane (eq 104).[178]

$$(PhCH_2)_2SiHMe \xrightarrow[MeOH]{TMAF} (MeO)_2SiHMe \xrightarrow[MeOH]{TMAF} (MeO)_3SiMe \quad (104)$$

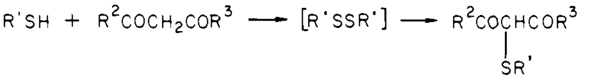
Although the use of polar aprotic solvents in fluoride-assisted reactions is usually recommended, one cannot disregard the possibility of solvent participation in the reactions.[5,8,106] Perhaps the clearest demonstration of this has been provided by Morgan and co-workers who, in attempting to introduce fluorine into nitrobenzene by halogen exchange in CsF-DMF systems, observed the formation of non-halogen-containing products.[179] The products identified in the reaction of 4-chloro-3-nitrotoluene with CsF-DMF were 4-methyl-2-nitro-*N*,*N*-dimethylaniline, 4-fluoro-3-nitrotoluene, and 3-nitrotoluene in 23%, 19%, and 4% yields, respectively. 2-Nitroiodobenzene and 2,4-dinitrobromobenzene gave no fluorinated products on reaction with CsF-DMF, the former aromatic giving a high yield of nitrobenzene and the latter being totally converted to 2,4-dinitro-*N*,*N*-dimethylaniline. These results are summarized in eq 105. A mechanism involving a radical-anion intermediate has been proposed to explain these results.[179]



X = Cl, R = Me	19%	4%	23%
X = I, R = H	0%	50%	17%
X = Br, R = NO_2	0%	0%	100%

(105)

α-Thio-β-dicarbonyls are valuable synthetic intermediates and a simple, one-pot method for their synthesis from aryl thiols and enolizable β-dicarbonyls using TEAF-DMF has been proposed (eq 106).[165] The reaction is thought to involve initial fluoride-catalyzed thiol autoxidation followed by attack of the resulting disulfide on the fluoride-activated dicarbonyl. Reactions were carried out over molecular sieves so as to alleviate the problem of fluoride deactivation due to the water produced in the reaction. More recently, TBAF-silica[19] and the fluoride form of some ion-exchange resins[12] have been shown to be capable of acting as catalysts in similar reactions, although their activities seem to be significantly lower than that of TEAF.



$$R'SH + R^2COCH_2COR^3 \longrightarrow [R'SSR'] \longrightarrow R^2CO\underset{\displaystyle SR'}{\underset{|}{C}}HCOR^3 \quad (106)$$

(41-86%)

R^1 = Ph, p-MeC_6H_4, p-$NO_2C_6H_4$ or py;
$R^2 = R^3$ = Me; $R^2 = R^3$ = EtO;
$R^2 = R^3$ = Ph; R^2 = MeO, R^3 = Et;
R^2 = Me, R^3 = Ph

XI. Summary and Conclusions

Ionic fluorides, with their variable basicity and relatively low nucleophilicity toward carbon, have proved to be versatile proton abstractors in a variety of typically base-assisted reactions where the strength of the base required has varied from weak to very strong and the role of the base has been catalytic and noncatalytic. Reactions that would seem to be particularly well suited to the fluoride ion method include Michael additions, alkylations, esterifications, eliminations, and Knoevenagel condensations. The fluoride ion method has many attractive features, including ease of use of, stability of, and recoverability of the fluoride, clean and efficient reactions, and easy workup of the product mixture. Reactions proceed under essentially neutral conditions, thus reducing the possibility of many unwanted side reactions.

The choice of fluoride and of the reaction solvent may be of paramount importance in determining the nature, rate, and efficiency of the reaction. Tetraalkylammonium fluorides and in particular TEAF, TBAF, and BTMAF, which are generally speaking the most active fluorides, are usually preferred for reactions carried out at or near room temperature, but their relatively low thermal stability precludes their use at temperatures above 80 °C. Alkali metal fluorides should be used when higher reaction temperatures or rigorously anhydrous conditions are required. Crown ethers such as 18-crown-6 may be used to improve the rate and efficiency of KF-promoted reactions. Other sources of the fluoride ion such as alkali metal and tetraalkylammonium fluorides impregnated on inert support materials and the fluoride forms of some ion-exchange resins have received relatively little attention, so far, but they promise to be of considerable importance in future applications. Polar aprotic solvents such as MeCN, THF, DMF, and Me_2SO are usually the best solvents for fluoride-assisted reactions, although the solubility of alkali metal fluorides in such solvents is very low and the solvents may react with the fluoride on prolonged heating. Fluorides are more soluble in protic solvents, but their activity is impaired in such media and the course of the reaction may be different from that observed in aprotic media. Solvent participation may be deliberately exploited so that $KF-RCO_2H$ solutions, for example, are extremely efficient sources of the carboxylate group. KF–crown reagents are best used in MeCN or benzene. The presence of water is likely to impair the activity of any fluoride, and this presents particular difficulties with the very hygroscopic tetraalkylammonium fluorides where efforts to remove as much water as possible (without decomposing the fluoride) are usually rewarded by improved reaction efficiency.

Fluoride ion assisted reactions are thought to occur via strong H bonding of the fluoride ion (the electron donor) to the reactant protic molecule (the electron acceptor), with resulting enhancement of the nucleophilicity of the protic compound. Ionic fluorides have been considered as weak bases, medium strength bases, or strong bases. The solubility of the fluoride and the presence of protic materials capable of masking the fluoride ion are basicity controlling factors. An alkali metal fluoride in a protic medium such as an alcohol or a diol will usually behave as a weak base, whereas a rigorously dried polar aprotic solution of TEAF, for example, is a powerful enough base to abstract the proton from such weak acids as Me_2SO or fluorene. Since it is doubtful that a truly anhydrous aprotic solution of TEAF, TBAF, or BTMAF has ever been prepared, the optimum basicity of tetraalkylammonium fluorides remains a matter for speculation.

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XII. References

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