2504 © *1982 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, **55**, *2504—2507 (1982)* [Vol. 55, No. 8

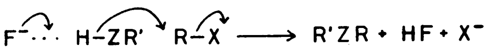
Fluoride Salts on Alumina as Reagents for Alkylation of Phenols and Alcohols

Takashi ANDO,* Junko YAMAWAKI, Takehiko KAWATE, Shinjiro SUMI,
and Terukiyo HANAFUSA
The Institute of Scientific and Industrial Research, Osaka University, Mihogaoka, Ibaraki, Osaka 567

(Received February 27, 1982)

The effectiveness of alkali metal fluorides impregnated on alumina as a reagent for promoting alkylation was optimized with respect to the metal cation, the amount of impregnation, and the reaction solvent. Potassium or caesium fluoride on alumina in acetonitrile or 1,2-dimethoxyethane was concluded to be the best reaction system for general use. *O*-Alkylation of substituted phenols, primary and secondary alcohols, and a glycol was carried out mostly in good yields under mild conditions with simple experimental procedures.

Increasing interest has been shown in the use of fluoride salts as potential bases to fascilitate a variety of synthetic reactions.[1,2)] In recent studies by Clark, Miller, and their coworkers,[3,4)] the effectiveness of alkali metal fluorides has been recognized in various types of alkylations with alkyl halides. According to them, nucleophilicity of protic organic compounds, *e.g.*, carboxylic acids or phenols, is greatly enhanced by the formation of strong hydrogen bonds with the fluoride anion; nucleophilic substitution proceeds with hydrogen bond assistance (Eq. 1). However, the low solubility of alkali fluorides in ordinary solvents disturbs their wide application in organic synthesis. In order to overcome this difficulty, the reactions have been carried out at high temperatures with preformed hydrogen-bonded complexes or in a high-boiling solvent such as *N,N*-dimethylformamide,[4)] but these methods are rather inconvenient.



$$F^-\cdots H{-}ZR' \quad R{-}X \longrightarrow R'ZR + HF + X^- \qquad (1)$$

On the other hand, there has been rapidly increasing use of organic and inorganic solids as supports of reagents or as reaction media in recent years.[5—8)] In general, several advantages can be expected for their use: (1) work-up and purification of products are quite simple, (2) reactivity of functional groups can be modified, *i.e.*, enhanced or reduced, and (3) selectivity in the courses of reactions may be different from that in solution. These advantages may arise from the large effective surface area, the presence of pores, and the adsorption of reactants on the surface. In 1979, we communicated the preliminary results that potassium fluoride supported on diatomaceous earth (KF–Celite) is more efficient for promoting alkylations of various types of protic compounds than unsupported KF.[9)] In this paper, we describe our detailed study on the scope and limitations of supported fluoride reagents for promoting *O*-alkylation of phenols and alcohols.

Results and Discussion

In order to optimize the efficiency of supported fluoride reagents, it is important to investigate the effects of the support, metal cation, amount of impregnation, and reaction solvent. We have previously discussed the efficiency of various inorganic solids as a support to enhance the reactivity of potassium fluoride,[10)] and will not repeat that discussion here. In *O*-methylation of phenol with methyl iodide, the order of the effectiveness of supports has been found to be alumina>molecular sieves (MS) 13X and SK-40>montmorillonite>MS 4A and 5A>Celite.[10)] Therefore, we used alumina as a support throughout this study.

The effect of varying the metal cation and the ratio of fluorides *vs.* alumina on the reactivity of alkali fluoride–alumina reagents was first studied. Various amounts of alkali metal fluorides (MF) and tetrabutylammonium fluoride (Bu_4NF) were impregnated on alumina; Classes I, II, III, and IV reagents were prepared with 0.1, 0.2, 0.5, and 1.0 mol of MF, respectively, impregnated on 100 g of alumina. Methylation of phenol with methyl iodide in acetonitrile was chosen as a reference

TABLE 1. METHYLATION OF PHENOL WITH MF–ALUMINA[a)]

Reagent	Class[b)]	Yield/%[c)]		
		1 h	24 h	48 h
LiF–Alumina	I	0	1.3	2.5
	II	0.1	0.7	1.5
	IV	0	0.2	0.3
NaF–Alumina	I	1.5	6.1	9.6
	II	1.8	12.5	15.2
	IV	3.6	11.0	12.4
KF–Alumina	I	17.4	41.8	41.9
	II	57.7	97.0	
	IV	98.8		
CsF–Alumina	I	69.3	90.4[d)]	
	II	99.6		
	III	100		
	IV	100[e)]		
Bu_4NF–Alumina	I	100		
LiF[f)]				0
NaF[f)]				0
KF[f)]				7.6
CsF[f)]		19.5[e)]		100
Bu_4NF[g)]		98.3[e)]		

a) Reaction of phenol (0.5 mmol) with methyl iodide (1 mmol) and MF–alumina (*ca.* 2.5 mmol MF) in 5 cm^3 of acetonitrile was carried out at room temperature. b) For Classes of reagents, see text. c) Yields were determined by GLPC using dodecane as an internal standard after a reaction time shown in Table. d) After 6 h. e) After 0.5 h. f) Without alumina. g) Trihydrate (Fluka) without alumina.

reaction, and the effectiveness of supported reagents was evaluated in terms of the yields of anisole after a definite time of reaction. The results are summarized in Table 1.

It is apparent from Table 1 that all the MF–alumina reagents are more effective than MF without a support and that the cation is a governing factor of the reactivity of the supported reagents. The order of effectiveness of MF–alumina is CsF>KF≫NaF>LiF. This is just the same as the reactivity order of MF without a support for the alkylation of phthalimide in *N*,*N*-dimethylformamide reported by Clark and Miller.[4] Although in general tetraalkylammonium fluorides are known as the most effective sources of the fluoride anion, they are expensive, hygroscopic, and thermally unstable. Clark reported that Bu_4NF supported on silica gel can be used as a non-hygroscopic source of the fluoride ion promoting various base-catalyzed reactions.[11] Bu_4NF–alumina prepared by us was somewhat easier to handle but not more effective than Bu_4NF alone. Although this Bu_4NF–alumina was most reactive among the supported reagents studied, CsF–alumina and KF–alumina can be regarded as more practical reagents than the Bu_4NF reagent when ease of handling and, especially for KF–alumina, economy of the reagents are taken into consideration. For these two reagents, the reactivity increased as the ratio of the fluoride *vs*. alumina was increased. However, as too much loading of the fluoride salts makes the reagents hygroscopic and thus cancels out their merit of easy handling, Class IV of KF–alumina and Class III of CsF–alumina are concluded to be the most practical reagents for general use.

The effect of varying the reaction solvent on the reaction rate was studied for these two reagents and for KF and CsF without a support (Table 2). Among the aprotic solvents used, the reaction became faster as the polarity of the solvent was increased. However, it was rather unexpected that the reaction was almost completed even in a nonpolar solvent such as hexane, although it took a longer reaction time. The adsorption of the reactants on the solid surface is obviously an important factor for the reaction. This is, to our knowledge, the first systematic study of the solvent effect on the reaction of supported reagents. KF and CsF both without alumina were effective only in very polar solvents; the effectivenesss might be due to the fact that they are slightly soluble in these solvents.[12] In conclusion, acetonitrile and 1,2-dimethoxyethane are adequate solvents for practical use with respect to their moderate boiling points and sufficient polarities.

Here we have reported that the effectiveness of the MF-support reagents is strongly affected by the metal cation, the amount of impregnation, and the reaction solvent. We have already reported that the kind and the form of solid supports and the drying conditions of the reagents are also important as factors which govern the efficiency of the supported fluoride reagents.[10] In this respect, the specific reactivities observed for "freeze-dried" and "spray-dried" potassium fluorides reported by Ishikawa and his coworkers is noteworthy;[13] the former is effective for alkylation and the latter is for fluorination. Although the role of the crystal structures of the supported fluorides and the role of a trace of the water remained in the reagents are not clear, the idea of the simple "hydrogen-bond-assistance" by the fluoride anion proposed by Clark and Miller[4] might be inapplicable in our case. Detailed study on the mechanism of the reaction promoted with MF–supports is now under way.

Applications of the most practical reagent, KF–alumina, were studied in some cases. As shown in

TABLE 2. METHYLATION OF PHENOL IN VARIOUS SOLVENTS[a)]

Solvent	Time/h	Yield/%[b)]			
		KF	CsF	KF–Alumina[c)]	CsF–Alumina[d)]
DMF	1	10	100	100	100
Diglyme	1	1	97	100	100
CH_3CN	1	1	31	95	92
DME	1	0	22	98	92
THF	1	0	3	53	49
Ether	1	0	0	0.3	5
	24	0	0	17	79
CH_2Cl_2	1	0.3	0.1	0.7	5
	48	0	0.7	41	93
Benzene	1	0	0.2	0.5	4
	24	0	0.3	13	64
Hexane	1	0	0	0.7	7
	24	0	0	30	80

a) Reaction of phenol (2.5 mmol) with methyl iodide (5 mmol) and MF or MF–alumina (12.5 mmol MF) in a solvent (5 cm³) was carried out at room temperature. b) Yields were determined by GLPC using dodecane as an internal standard. c) Class IV reagent. d) Class III reagent.

TABLE 3. *O*-ALKYLATION OF PHENOLS WITH KF–ALUMINA[a)]

Phenol	Halide	Yield/% (Time/h)		
		GLPC[b)]		Isolated
C_6H_5OH	MeI	84(0.25)	100(0.5)	
$2\text{-}CH_3C_6H_4OH$	MeI	100(0.25)		
$4\text{-}CH_3C_6H_4OH$	MeI	100(0.25)		
$2,6\text{-}(CH_3)_2C_6H_3OH$	MeI	100(0.25)		
$2,6\text{-}(t\text{-}Bu)_2C_6H_3OH$	MeI			78(2.0)
$4\text{-}ClC_6H_4OH$	MeI	100(0.5)		
$2\text{-}NO_2C_6H_4OH$	MeI	2(1.0)	8(20)	
$3\text{-}NO_2C_6H_4OH$	MeI	46(1.0)	88(20)	
$4\text{-}NO_2C_6H_4OH$	MeI	2(1.0)	10(20)	
C_6H_5OH	*n*-BuI	68(1.0)		
C_6H_5OH	*n*-BuBr	95(24)		80(24)
C_6H_5OH	*n*-BuCl			62(162)[c)]
C_6H_5OH	*s*-BuBr	26(24)	63(142)	30(144)
C_6H_5OH	*t*-BuBr	1(24)		

a) Unless otherwise mentioned, reaction of a phenol (1 equiv.) with an alkyl halide (1.2—1.5 equiv.) and KF–alumina (*ca*. 5 equiv. KF) was carried out in acetonitrile at room temperature. b) Yields determined with internal standards. c) Reaction was carried out in 1,2-dimethoxyethane at 60 °C.

TABLE 4. *O*-ALKYLATION OF ALCOHOLS WITH KF–ALUMINA[a)]

Alcohol	Halide	Product	Yield/% (Time/h)	
			GLPC[b)]	Isolated
$CH_3(CH_2)_7OH$	MeI	$CH_3(CH_2)_7OMe$	90(40)	
$CH_3(CH_2)_3OH$	$PhCH_2Br$	$CH_3(CH_2)_3OCH_2Ph$	86(20)	66(30)
$CH_3CH_2CH(OH)CH_3$	$PhCH_2Br$	$CH_3CH_2CH(OCH_2Ph)CH_3$	33(20)	
$PhCH_2CH_2OH$	MeI	$PhCH_2CH_2OMe$	82(20)	66(43)
$PhCH_2CH_2OH$	BuI	$PhCH_2CH_2OBu$		62(124)
$PhCH_2CH(OH)CH_3$	MeI	$PhCH_2CH(OMe)CH_3$	52(20)	72(42)
$HO(CH_2)_2O(CH_2)_2OH$[c)]	MeI	$MeO(CH_2)_2O(CH_2)_2OMe$	96(16)	

a) Reaction of an alcohol (1 equiv.) with an alkyl halide (1.2—1.5 equiv.) and KF–alumina (*ca.* 5 equiv. KF) was carried out in acetonitrile at room temperature. b) Yields determined with internal standards. c) Reagents were doubled for ethylene glycol.

Table 3, KF–alumina was effective for methylation of alkyl-substituted phenols with methyl iodide. Even methylation of sterically hindered 2,6-di-*t*-butylphenol proceeded quantitatively at room temperature in 2 h. When the substituent was electron attracting, the rate of methylation decreased. Methylation of *p*-Cl and *m*-NO_2 derivatives proceeded at room temperature, but *o*- and *p*-NO_2 derivatives were only slightly methylated under the same conditions. Alkylation of phenol with a variety of butyl halides was also examined (Table 3). The reaction with butyl bromide proceeded smoothly, although not as fast as with butyl iodide. The alkylation with *s*-butyl bromide proceeded with partial elimination to give a moderate yield of butyl phenyl ether. However, the reaction with *t*-butyl bromide gave only a trace of the product because of the elimination.

Alkylation of a less acidic hydroxyl group of an alcohol than that of a phenol by use of the fluoride anion has scarcely been reported.[1,14)] Nevertheless, KF–alumina was found to give satisfactory yields of alkyl ethers from alcohols (Table 4). It is noteworthy that methylation and benzylation of even secondary alcohols and a glycol proceeded smoothly at room temperature. Thus KF–alumina manifested the characteristic reactivity promoting alkylation of neutral alcohols under mild conditions.

In all cases studied, isolation procedures of reaction products were quite simple and nonaqueous: filtration, washing the solid with ether, evaporation of the solvent, and distillation or column chromatography when necessary. In conclusion, as reaction conditions are mild, yields are good in most cases, and work-up is simple, KF on alumina is a useful and practical supported reagent for promoting *O*-alkylation of phenols and alcohols.

Experimental

General. Unless otherwise mentioned, reagents were obtained commercially and used without further purification. Solvents were dried with molecular sieves 3A and 4A. Neutral alumina was purchased from Merck Japan Ltd. (Type 90 for column chromatography, activity I, 70—230 mesh) and used as obtained. Alkali metal fluorides were dried *in vacuo* at 120 °C for several hours. KF, CsF, and $Bu_4NF \cdot 3H_2O$ (Fluka, mp 60—61 °C) without a support were handled under nitrogen. GLPC analysis of product mixtures was carried out with a Varian Aerograph Model 2850-30 gas chromatograph with a flame ionization detector and a Hewlett-Packard 3370B digital integrator. A column packed with 20% Silicone DC 550 on Celite 545 was used. Yields were determined using internal standards.

Preparation of MF–Alumina Reagents. Alumina was mixed with metal fluoride in water, and the water was removed at 50—60 °C in a rotary evaporator. This impregnated alumina was further dried in a vacuum drying oven for several hours at 75 °C. Classes I, II, III, and IV of MF–alumina reagents were prepared from 100 g of alumina with 0.1, 0.2, 0.5, and 1.0 mol of MF, respectively. The typical KF–alumina reagent used for the alkylation of phenols and alcohols was prepared at the weight ratio of 2 : 3 which corresponds to 1.15 mol of KF on 100 g of alumina.

All these MF–alumina reagents except CsF–alumina (Class IV) and Bu_4NF–alumina can be handled in the atmosphere without special care. The effectiveness of the typical reagents remained unaltered after several months' storage in bottles kept in a desiccator.

Effectivity Determination of Supported Reagents. Methylation of phenol was carried out with methyl iodide and MF–alumina in a solvent, whose quantities are as shown below. Methylation of phenol with MF–alumina: phenol (47 mg, 0.5 mmol), methyl iodide (140 mg, 1.0 mmol), and MF–alumina (*ca.* 2.5 mmol MF) in 5 cm^3 of acetonitrile. Methylation of phenol in various solvent: phenol (0.24 g, 2.5 mmol), methyl iodide (0.71 g, 5.0 mmol), and MF–alumina (*ca.* 12.5 mmol MF) in 5 cm^3 of a solvent. The reaction mixture placed in a test tube with a Teflon-coated screw-cap was vigorously agitated at room temperature by a Vapor Mix S-10 vibrating apparatus (Tokyo Rikakikai Co., Ltd.). Yields of anisole formed after a definite reaction time were determined by GLPC with dodecane as an internal standard.

Alkylation with Supported Reagents. Experimental procedures for alkylation of phenols and alcohols in a preparative scale are given in the following typical examples. All the products are known compounds and gave ^1H NMR and IR spectra consistent with their structures and, when reported data are available, with those shown in the literature.

*Methyl 2,6-Di-*t*-butylphenyl Ether*: A mixture of 2,6-di-*t*-butylphenol (0.83 g, 4 mmol), methyl iodide (0.79 g, 5.6 mmol), and KF–alumina (3.00 g, *ca.* 20 mmol KF) in 6 cm^3 of acetonitrile was magnetically stirred at room temperature for 2 h. The solid material was filtered and washed with ether, and the solvent was evaporated. Purification by column chromatography (silica gel, hexane) gave 0.68 g of the product (78%): purity by GLPC 95%.

Butyl Phenyl Ether: Reaction of phenol (0.41 g, 4.4 mmol) with butyl bromide (0.75 g, 5.5 mmol) and KF–alumina (3.3 g, *ca.* 22 mmol KF) in 6.5 cm^3 of acetonitrile was carried out at room temperature for 24 h. Work-up as above and purification by column chromatography (silica gel, chloroform) gave 0.52 g of the product (80%): purity by GLPC 99.7%.

Benzyl Butyl Ether: Reaction of 1-butanol (1.55 g, 20.9 mmol) with benzyl bromide (4.28 g, 25.0 mmol) and KF–alumina (15.8 g, *ca.* 104 mmol KF) in 30 cm^3 of acetonitrile was carried out at room temperature for 30 h. Work-up as above and purification by distillation gave 2.25 g of the product (66%): bp 92—94 °C/1.20—1.33 kPa (lit,$^{15)}$ bp 88 °C/0.80—0.93 kPa); purity by GLPC 98.6%.

2-Methoxy-3-phenylpropane: A mixture of 3-phenyl-2-propanol (0.54 g, 4.0 mmol), methyl iodide (0.96 g, 6.8 mmol), and KF–alumina (3.0 g, *ca.* 20 mmol KF) in 6 cm^3 of acetonitrile was vigorously agitated at room temperature for 42 h. Work-up as above and purification by column chromatography (silica gel, chloroform) gave 0.43 g of the product (72%): purity by GLPC 97.9%.

The present work was supported in part by a Grant-in-Aid for Scientific Research No. 56740211 from the Ministry of Education, Science and Culture.

References

1) J. H. Clark, *Chem. Rev.*, **80**, 429 (1980).

2) T. Ando and J. Yamawaki, *J. Synth. Org. Chem. Jpn.*, **39**, 14 (1981).

3) J. H. Clark and J. M. Miller, *J. Am. Chem. Soc.*, **99**, 498 (1977).

4) J. H. Clark and J. Emsley, *J. Chem. Soc., Dalton Trans.*, **1973**, 2154, 1125; **1975**, 2129.

5) J. M. J. Fréchet, *Tetrahedron*, **37**, 663 (1981).

6) A. Akelah, *Synthesis*, **1981**, 413.

7) A. McKillop and D. W. Young, *Synthesis*, **1979**, 401, 481.

8) G. H. Posner, *Angew. Chem., Int. Ed. Engl.*, **17**, 487 (1978).

9) T. Ando and J. Yamawaki, *Chem. Lett.*, **1979**, 45.

10) J. Yamawaki and T. Ando, *Chem. Lett.*, **1979**, 755.

11) J. H. Clark, *J. Chem. Soc., Chem. Commun.*, **1978**, 789.

12) The solubility of KF in *N,N*-dimethylformamide was reported as less than 0.025 wt% under reflux; M. Mingin and R. Huisgen, *Tetrahedron Lett.*, **1979**, 719.

13) a) N. Ishikawa, T. Kitazume, and M. Nakabayashi, *Chem. Lett.*, **1980**, 1089; b) N. Ishikawa, T. Kitazume, T. Yamazaki, Y. Mochida, and T. Tatsuno, *ibid.*, **1981**, 761.

14) A. Chollet, J.-P. Hagenbuch, and P. Vogel, *Helv. Chim. Acta*, **62**, 511 (1979).

15) M. J. Murray and F. F. Cleveland, *J. Chem. Phys.*, **9**, 129 (1941).