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POTASSIUM FLUORIDE ON INORGANIC SOLID SUPPORTS. A SEARCH FOR FURTHER EFFICIENT REAGENTS PROMOTING HYDROGEN-BOND-ASSISTED ALKYLATIONS

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Effectiveness of various inorganic solids as a support of potassium fluoride for promoting "hydrogen-bond-assisted" alkylations was studied. Alumina was found most effective; even *O*-alkylation of an alcohol can be easily undertaken by use of KF-Al_2O_3. A variety of molecular sieves showed a selectivity in the case of *C*-alkylation.

The utility of the fluoride anion in hydrogen-bond-assisted reactions has been recognized in recent investigations by Clark, Miller, and their coworkers.$^{1-4)}$ In our previous paper, we reported that diatomaceous earth coated with potassium fluoride (KF-Celite) is an effective and economical reagent for various types of reactions.$^{5)}$ Thus, *C*-, *N*-, *O*-, and *S*-alkylations are conveniently performed in high yields under mild conditions by use of KF-Celite.

On the other hand, there has been the growing concept of utilizing solid surface as reaction media in recent years.$^{6)}$ The advantage of reactions on solid supports is the possibility of an enhanced reactivity and/or a great selectivity of the reagents as well as manipulative convenience in comparison to those in solution. Several groups reported that marked variations in reactivity $^{3,7,8)}$ and selectivity$^{9)}$ were observed when solid supports were varied. In order to find out a more reactive and/or selective reagent than KF-Celite for hydrogen-bond-assisted reactions by taking advantage of the solid surface, extensive studies have been carried out on the effectiveness of various inorganic solids as a support of potassium fluoride (KF), and also on the method for preparing effective reagents.

A KF-support was prepared by the following procedure: a solid support (15 g) was mixed with KF (10 g) in 200 ml of water, and the water was removed at 50-60 °C in a rotary evaporator (Type A). Then, this Type A reagent was further dried in a vacuum drying oven at 75 °C (Type B) or at 150 °C (Type C) for several hours. *O*-Methylation of phenol was chosen as a reference reaction for comparing the effectiveness of KF-supports. The reaction was carried out with phenol (1 equiv) and methyl iodide (1.5 equiv) in the presence of a KF-support (*ca.* 5 equiv) in acetonitrile. After the mixture was shaken for 4 h at room temperature, the yield of anisole was determined by GLPC using internal standards. The results obtained are summarized in Table 1.

Table 1. Comparative Effectiveness of Various Supports for the KF-Mediated Alkylations

Support	Form	Type[a]	*O*-Alkylation[b] Yield/%[d]	*C*-Alkylation, Yield/%[c,d]	
				Mono[e]	Di[f]
None[g]	—	—	1		
Celite 545[h]	powder	A	28	96	trace
		B	3		
Molecular Sieve 4A[i]	powder[j]	A	34	83	—
		B	8		
Molecular Sieve 5A[i]	powder[j]	A	34	47	36
		B	6		
Molecular Sieve 13X[i]	powder[j]	A	72	—	81
		B	69		
		C	11		
Molecular Sieve SK-40[i]	powder[j]	B	61		
K-10 Montmorillonite[k]	powder	A	52		
		B	13		
Alumina 90[m]	100-325 mesh	A	96		
		B	97		
		C	34-88	—	84
Alumina NB-MSC[n]	60-140 mesh	A	94		
		B	25		
Alumina NB-C[n]	6-10 mesh	B	1		
Silica Gel 60[p]	70-230 mesh	A	10		
		B	10		
Silica Gel[q]	8-12 mesh	A	7		

[a] Type A: KF-supports after removal of water in a rotary evaporator at 50-60 °C. Type B, C: Type A reagents were further dried in a vacuum oven at 75 °C (Type B) or at 150 °C (Type C) for several hours. [b] Reaction of phenol (2 mmol), methyl iodide (3 mmol), and KF-support (*ca.* 10 mmol KF) in 3 ml of acetonitrile at room temp for 4 h. [c] Reaction of 2,4-pentanedione (1 mmol), methyl iodide (3 mmol), and KF-support (*ca.* 10 mmol KF) in 3 ml of acetonitrile at room temp for 16 h. [d] Yields were determined by GLPC using internal standards. [e] $CH_3COCHCH_3COCH_3$. [f] $CH_3COC(CH_3)_2COCH_3$. [g] Powdered KF without a support. [h] Johns-Manville. [i] Union Carbide. [j] 0.5-5 μm. [k] Girdler Chemicals. [m] Merck, for column chromatography, active neutral, activity I. [n] Mizusawa Industrial Chemicals. [p] Merck, for column chromatography. [q] Alfa, for catalyst supports.

A low yield observed in the case when KF powder was used without a support clearly indicates the positive role of a support in enhancing the activity of KF. It is also apparent that Type A reagents are more effective than the corresponding Type B and C reagents in most cases.

As far as anisole formation with Type A reagents is concerned, various types of molecular sieves (MS), montmorillonite clay, and alumina were found more efficient than Celite as a support of KF. Among MS employed, 13X and SK-40 are much superior than 4A and 5A. Neutral alumina for column chromatography is the best of all the supports studied; almost quantitative methylation was observed after 4 h. Alumina without KF was found ineffective for the reaction under the conditions applied. In order to evaluate the effectiveness of KF-Al_2O_3, reaction of 1-octanol (1 equiv) with methyl iodide (1.5 equiv) was carried out in the presence of KF-Al_2O_3 (Type A, *ca.* 5 equiv) in acetonitrile at room temperature. Formation of the ether from the aliphatic alcohol did proceed 78% after 24 h and 90% after 40 h. KF-Celite (Type A) was completely inactive for the reaction. Thus, KF-Al_2O_3 proved to be an efficient reagent promoting *O*-alkylation of an aliphatic alcohol under mild conditions.

Clark reported that tetraalkylammonium fluorides supported on silica gel can be used as non-hygroscopic sources of the fluoride ion promoting efficiently various base-catalyzed reactions.3) In our study, however, silica gel was found even less effective than Celite as a support of KF.

With respect to the form of the supports, the particle size is apparently an important factor determining the effectiveness of the reagents. The fact that alumina NB-MSC is more effective than alumina NB-C clearly demonstrates that smaller particles are better than larger ones, as they are different only in particle sizes. It was also found that MS of pellet forms (1/16 in.) were unable to hold that much of KF on their surface, and were less effective than the corresponding powder forms. The importance of the effective surface area holding KF has thus been concluded.

Study on effectiveness in *C*-alkylation of 2,4-pentanedione with methyl iodide by use of some representative KF-supports revealed an interesting selectivity of mono- and di-alkylations (Table 1). Whereas the Celite and MS 4A reagents gave the mono-alkylated product almost exclusively, the MS 13X and Al_2O_3 reagents gave the di-alkyl derivative as a sole product. KF-MS 5A gave a mixture of the mono- and di-alkyl derivatives, exhibiting an intermediate selectivity. As the particle sizes of all the MS can be considered similar (0.5-5 μm), the selectivity must be derived from the difference in the structure of the solid surface.

It is important that drying KF-supports with heating reduces their effectiveness. Although the role of the water remained on the solid surface in the reaction is not clear, the idea of the simple "hydrogen-bond-assistance" by the fluoride anion proposed by Clark and Miller1,10) might be inapplicable in our case. In this respect, it is interesting to point out that an aqueous solution of KF varies from neutral to basic when a support is added to the solution. On the other hand, it was confirmed in the case of KF-MS 5A that even the Type B reagent with a reduced activity is still fairly wet.[11)] Further study on the mechanism of the reaction on the solid surface is desirable.

In conclusion, KF-Al_2O_3 is the most effective reagent to facilitate various types of alkylations including preparation of ethers from aliphatic alcohols. KF-MS are the next effective ones with a possible selectivity depending on their types.

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References and Notes

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11) After shaking 10 mmol equiv of KF-MS 5A in 3 ml of dry acetonitrile for 4 h, 2290 ppm of water was detected in the acetonitrile suspending the Type B reagent, in contrast to 7090 ppm in the case of the Type A suspension.

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