
Surface Modification of Inorganic Supports for Nucleophilic Substitutions

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Nucleophilic substitutions, *e.g.* organo-fluorination and -iodination and esterification of organic halides were greatly promoted by the dispersion of their corresponding potassium salts onto surface-modified inorganic supports.

The development of inorganic reagents dispersed on high-surface-area supports resulting in improved reagent activity or selectivity has recently received much attention.¹ These novel reagents have considerable advantages over conventional techniques in ease of work-up and mild experimental conditions combined with high activity or selectivity. In the course of searching for supported reagents for nucleophilic fluorinations, it was found that alkali metal fluorides adsorbed on carriers such as alumina, silica, Celite, or molecular sieves (MS) failed to facilitate heterogeneous nucleophilic substitution owing to strong surface OH-F⁻ hydrogen bonding.^{2,3} However, Clark *et al.*² and Ichihara and co-workers³ reported the successful application of non-surface hydroxylated high-surface-area calcium fluoride in organofluorination and further we have recently developed a highly reactive KF-Poly reagent (KF on inert polymer supports).⁴ High-surface-area calcium fluoride, however, is an unconventional support with much less surface area (*ca.* 10 m² g⁻¹) than more conventional ones (commonly *ca.* 100–500 m² g⁻¹). In the case of a polymer support, alkali salts barely wet the organic surface, a situation which gives rise to poorer dispersion of the salts and lower efficiency. In the light of these problems, we decided to examine the possibility of using surface-dehydroxylated pretreatment of inorganic supports in order to enhance the reactivity of potassium fluoride in organofluorination as well as of potassium salts in other nucleophilic substitutions. Potassium salts are the most practical reagents for general use in terms of economy and efficiency. Here we report preliminary results for a study of

the use of potassium salts on surface-dehydroxylated inorganic supports as nucleophiles.

Different surface dehydroxylation methods were tested with a variety of conventional supports. Surface dehydroxylated modification of inorganic supports by organosilylation⁵ was brought about by a vapour-phase procedure at 100 °C, hexamethyldisilazane (SiN) and cyclo-octamethyltetrasilicone (SiO) being used as modifiers. In the treatment of alumina, surface coverage by organo group was estimated to be *ca.* 28% based on the results of elementary analysis; reduction of surface area after modification was <7%, *i.e.* from an original 82.3 m² g⁻¹ to 76.6 m² g⁻¹. Surface-hydroxy group replacement of alumina by fluoride with ammonium fluoride (F) was carried out according to a reported technique;⁶ the fluorine content of fluorinated alumina is 5%, the reduction of surface area after treatment being *ca.* 10%. A supported reagent was prepared by mixing potassium salts with a modified support at a wt. ratio of 1:4; the mixture was then put into an electric mill and ground at 20 000 rpm for 1 min, dried at 40 °C under reduced pressure for 1 h and then heated at 180 °C for a further 4 h.

The heterogeneous potassium fluoride reagents were successfully used in organofluorination. Typical examples, along with literature data, are listed in Table 1. Fluorination of benzoyl chloride and benzyl bromide proceeded smoothly with KF on inorganic supports treated with SiN (entries 4–9, 15, 16, 18–20), surface treatment of the supports with SiO, F, or F–SiN was less effective than that with SiN (entries 4, 10–20). Although KF on

Table 1. Fluorination using KF on surface-modified inorganic supports.

Entry	Substrate	Reagent ^a	Solvent	Temp. (°C)	Time (h)	Product	Yield (%) ^b
1	PhCOCl	KF-CaF ₂ ^c	None ^c	Room temp.	3.0	PhCOF	81 ^c
2	PhCOCl	KF-CaF ₂ ^d	Sulpholane	19	0.2	PhCOF	71
3	PhCOCl	KF-Poly4 ^e	Dioxane	Room temp.	0.2	PhCOF	95
4	PhCOCl	KF-Al ₂ O ₃ (SiN)	MeCN	Room temp.	0.2	PhCOF	99
5	PhCOCl	KF-SiO ₂ (SiN)	MeCN	Room temp.	0.2	PhCOF	99
6	PhCOCl	KF-MS 3A(SiN)	MeCN	Room temp.	0.2	PhCOF	99
7	PhCOCl	KF-MS 5A(SiN)	MeCN	Room temp.	0.2	PhCOF	96
8	PhCOCl	KF-MS Y(SiN)	MeCN	Room temp.	0.2	PhCOF	79
9	PhCOCl	KF-Celite(SiN)	MeCN	Room temp.	0.2	PhCOF	99
10	PhCOCl	KF-Al ₂ O ₃ (SiO)	MeCN	Room temp.	0.2	PhCOF	88
11	PhCOCl	KF-Al ₂ O ₃ (F)	MeCN	Room temp.	0.2	PhCOF	95
12	PhCOCl	KF-Al ₂ O ₃ (F-SiN)	MeCN	Room temp.	0.2	PhCOF	84
13	PhCH ₂ Br	KF-CaF ₂ ^d	MeCN	Reflux	16	PhCH ₂ F	68
14	PhCH ₂ Br	KF-Poly1 ^e	MeCN	Reflux	16	PhCH ₂ F	32
15	PhCH ₂ Br	KF-Al ₂ O ₃ (SiN)	MeCN	Reflux	14.6	PhCH ₂ F	61
16	PhCH ₂ Br	KF-SiO ₂ (SiN)	MeCN	Reflux	16	PhCH ₂ F	42
17	PhCH ₂ Br	KF-CaF ₂ ^d	Sulpholane	120	2.0	PhCH ₂ F	92
18	PhCH ₂ Br	KF-Al ₂ O ₃ (SiN)	Sulpholane	120	2.0	PhCH ₂ F	96
19	PhCH ₂ Br	KF-SiO ₂ (SiN)	Sulpholane	120	2.2	PhCH ₂ F	35
20	PhCH ₂ Br	KF-Celite(SiN)	Sulpholane	120	2.0	PhCH ₂ F	16

Experimental conditions: solvent, 10 ml, substrate (5 mmol) with fluoride ion (8 mmol). ^a Symbols in parentheses indicate the modification of supports: SiN designates the treatment with 1,1,1,3,3,3-hexamethyldisilazane; SiO with cyclo-octamethyltetrasilicone; F with ammonium fluoride; F-SiN with ammonium fluoride followed with 1,1,1,3,3,3-hexamethyldisilazane. ^b GLC conversion. ^c Data from ref. 3, without solvent, isolated yield. ^d Data from ref. 2. ^e Data from ref. 4.

Table 2. Heterogeneous substitution reactions using potassium salts on surface-modified inorganic supports^a

Entry	Substrate	Reagent	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
21	C ₈ H ₁₇ Br	KI-Al ₂ O ₃ ^b	Toluene	90	44	C ₈ H ₁₇ I	95
22	C ₈ H ₁₇ Br	KI-Al ₂ O ₃	MeCN	60	2.0	C ₈ H ₁₇ I	55
23	C ₈ H ₁₇ Br	KI-Al ₂ O ₃ (SiN)	MeCN	60	4.0	C ₈ H ₁₇ I	61
					1.0	C ₈ H ₁₇ I	68
24	C ₈ H ₁₇ Br	KI-Al ₂ O ₃ (SiN)	Sulpholane	120	4.5	C ₈ H ₁₇ I	83
					0.5	C ₈ H ₁₇ I	66
25	C ₈ H ₁₇ Br	KOAc-Al ₂ O ₃ ^b	Toluene	90	100	C ₈ H ₁₇ OAc	89
26	C ₈ H ₁₇ Br	KOAc-Al ₂ O ₃ (SiN)	Sulpholane	90	1.0	C ₈ H ₁₇ OAc	95
27	C ₈ H ₁₇ Br	PhCO ₂ K-Al ₂ O ₃ ^c	None ^c	85	40	PhCO ₂ -C ₈ H ₁₇	58 ^c
28	C ₈ H ₁₇ Br	PhCO ₂ K-Al ₂ O ₃ (SiN)	Sulpholane	90	0.5	PhCO ₂ -C ₈ H ₁₇	91

^a As in Table 1. ^b Data from ref. 7. ^c Data from ref. 8, without solvent, isolated yield.

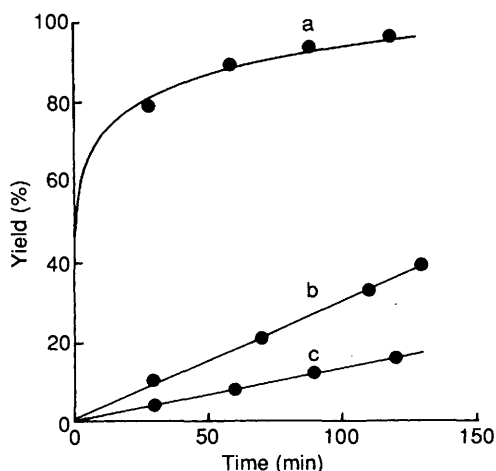


Figure. Fluorination of benzyl bromide using KF dispersed on modified supports in sulpholane at 120°C: a, KF on Al₂O₃(SiN); b, KF on SiO₂(SiN); c, KF on Celite(SiN).

all inorganic supports other than MS Y treated with SiN has nearly the same reactivity for fluorination of benzoyl chloride and the reactions are almost complete within 0.2 h (entries 4–9), KF-Al₂O₃ (SiN) shows much higher activity than those of KF-SiO₂ (SiN) and KF-Celite (SiN) for the fluorination of benzyl bromide (*cf.* entries 18–20, and the Figure). The data in Table 1 show that KF on inorganic supports modified by SiN and SiO is an excellent nucleophilic fluorinating reagent. The effectiveness of KF-Al₂O₃ (SiN) for promoting fluorination was superior to those of the supported KF reagents reported in the literature.

We have also found that the modification of inorganic supports can appreciably accelerate a series of related nucleophilic substitutions. Experimental results are summarized in Table 2. Although our results could not be compared directly with literature data since the reactions were conducted under different conditions (see Table), it is clear that organosilylation makes the supported reagent more reactive than the untreated ones for iodine substitution (*cf.* entries 22 and 23). Further, iodide and acetate as well as benzoate can be easily and efficiently prepared by using the corresponding potassium salts adsorbed on Al₂O₃ (SiN) as the nucleophiles. It should be noted that the results described were not optimized.

In all the cases studied, the isolation procedures for the reaction products were quite simple: filtration, washing the solid with ether, evaporation of solvents, and distillation. In conclusion, potassium salts on dehydroxylated inorganic supports constitute a versatile, heterogeneous nucleophilic reagent the reaction conditions for which are mild, the yields are good in most cases, and the work-up is simple.

Experimental

Surface Silylation of Alumina.—Alumina (20 g) was dried at 400 °C for 4 h and *in vacuo* for a further 4 h; the alumina was then cooled to 100 °C when hexamethyldisilazane (5 ml) was added with a syringe. The mixture was kept under reduced pressure at 100 °C for 10 h with frequent shaking. After dehydroxylation, the vapour product and the excess of silazane were removed by evacuation.

Preparation of Supported Potassium Fluoride.—KF·2H₂O (0.75 g) and dehydroxylated alumina were mixed in an electric mill and ground at 20 000 rpm for 1 min, dried at 40 °C under reduced pressure for 1 h and then at 180 °C for a further 4 h.

Fluorination of Benzyl Bromide.—Well-dried KF on alumina (2.5 g) and benzyl bromide (0.6 ml) in dried acetonitrile (10 ml) were stirred under reflux for a specific time after which the product was identified and analysed by MS-GLC.

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References

- 1 A. McKillop and D. W. Young, *Synthesis*, 1970, 401, 481; M. Hojo, *J. Synth. Org. Chem. Jpn.*, 1984, **42**, 635; P. Elecko and S. Toma, *Chem. Listy*, 1987, **81**, 1058, and references cited therein.
- 2 J. H. Clark, A. J. Hyde, and D. K. Smith, *J. Chem. Soc., Chem. Commun.*, 1986, 791.
- 3 J. Ichihara, T. Matsuo, T. Hanafusa, and T. Ando, *J. Chem. Soc., Chem. Commun.*, 1986, 793.
- 4 H. Liu, P. Wang, and P. Sun, *J. Fluorine Chem.*, 1989, **43**, 429.
- 5 P. K. Iler, 'The Chemistry of Silica,' John Wiley and Sons, New York, 1979, pp. 574, 695.
- 6 P. O. Scokart, S. A. Selim, J. P. Damon, and P. G. Rouxhet, *J. Colloid Interface Sci.*, 1979, **70**, 209.
- 7 S. Quici and S. L. Regen, *J. Org. Chem.*, 1979, **44**, 3436.
- 8 G. Bram, T. Fillebeen-Khan, and N. Geraghty, *Synth. Commun.*, 1989, **10**, 279.

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