The Combination of Potassium Fluoride and Calcium Fluoride: A Useful Heterogeneous Fluorinating Reagent

Junko Ichihara,*a Toshiya Matsuo,a Terukiyo Hanafusa,a and Takashi Andob

^a The Institute of Scientific and Industrial Research, Osaka University, Mihogaoka, Ibaraki, Osaka 567, Japan

^b Department of Chemistry, Shiga University of Medicinal Science, Otsu, Shiga 520–21, Japan

The combination of potassium fluoride and calcium fluoride was found to be an effective and practical solid reagent for the fluorination of various organic chlorides and bromides under mild conditions.

Among the methods available for the introduction of fluorine into organic compounds, the substitution of organic halides and sulphonates by the fluoride anion has widely been used. However use of alkali metal fluorides generally requires high temperatures and/or long reaction times because of both the low solubility and the low nucleophilicity of fluoride salts in polar aprotic solvents. There have been a number of reports of methods of improving the reaction.1-6 Heterogeneous nucleophilic substitution of alkyl halide with alkali metal acetate or cyanide in organic solvents is promoted by use of alumina, silica gel, or molecular sieve.⁷ We have previously reported that alkali metal fluorides supported on alumina are versatile solid reagents for alkylation, elimination, addition, and condensation reactions.8 In these cases, however, impregnated fluoride reagents did not promote heterogeneous nucleophilic substitution, but enhanced the potential basicity of the potassium fluoride. Taking into account this behaviour of the fluoride anion, we have investigated effective solid reagents for fluorination. In this communication we report that a calcined mixture of potassium fluoride and calcium fluoride is a useful solid fluorinating reagent.

The heterogeneous fluorination of benzyl bromide was carried out as follows. Commercially available potassium fluoride was mixed with calcium fluoride (Wako's guaranteed reagent)† at a 1:2 or 1:4 weight ratio. After grinding, the mixture was dried at 150 °C under vacuum for several hours.

Table 1. The substitution of benzyl bromide with fluoride ion.^a

| | G.l.c. yield of $PhCH_2F/\%$ | | | |
|-----------------------------|------------------------------|--------------|--|--|
| Fluoride reagent | 70 °C, 24 h | reflux, 10 h | | |
| KF | 1.5 | 0.6 | | |
| CaF ₂ | 0.1 | 0.3 | | |
| KF-CaF ₂ | 38 | 89 | | |
| Spray-dried KF ^b | | 68 | | |
| KF-18-crown-6° | | 50 | | |

^a The reaction of benzyl bromide (5 mmol) with fluoride ion (10 mmol) was carried out in acetonitrile. ^b Data from ref. 4. ^c Data from ref. 1.

[†] Finely powdered fluorite was not effective. Surface areas were measured by the Brunauer-Emmett-Teller method using argon gas on a Micromeritics High Speed Surface Area Analyzer 2205. Interestingly, the effective calcium fluoride showed much greater specific surface area (*ca.* 14 m²/g) than that of natural fluorite (unmeasurable value) or potassium fluoride (0.1 m²/g).⁴

Table 2. Heterogeneous fluorination using the KF-CaF₂ reagent.^a

| | | | | | Yield/% | |
|--|------------|------------|--------|---|---------|----------|
| Substrate | Solvent | Temp/°C | Time/h | Product | G.l.c. | Isolated |
| PhCOCl | b | Room temp. | 3 | PhCOF | | 81 |
| MeSO ₂ Cl | ь | Room temp. | 3 | MeSO ₂ F | | 78 |
| PhSO ₂ Cl | b | Room temp. | 5 | PhSO ₂ F | 100 | 87 |
| p-MeC ₆ H ₄ SO ₂ Cl | MeCN | Room temp. | 4 | p-MeC ₆ H ₄ SO ₂ F | 100 | 82 |
| p-BrC ₆ H ₄ SO ₂ Cl | MeCN | Room temp. | 3 | p-BrC ₆ H ₄ SO ₂ F | | 68 |
| EtOCOCI | MeCN | Room temp. | 24 | EtOCOF | 95 | |
| Me ₂ NCOCl | MeCN | 50 | 24 | Me ₂ NCOF | 100 | |
| CH ₂ OCH ₂ CH ₂ Cl | b | 110 | 60 | CH ₂ OCH ₂ CH ₂ F | 46 | |
| ClCH ₂ CO ₂ Et | b | 110 | 48 | FCH ₂ CO ₂ Et | 75 | |
| PhCH ₂ Cl | MeCN | Reflux | 48 | PhCH ₂ F | 77 | |
| PhCH ₂ Br | MeCN | Reflux | 15 | PhCH ₂ F | 95 | 81 |
| p-ClC ₆ H ₄ CH ₂ Br | MeCN | Reflux | 45 | p-ClC ₆ H ₄ CH ₂ F | 99 | 73 |
| $1 - C_8 H_{17} Br$ | Tetraglyme | 100 | 48 | $1 - C_8 H_{17} F$ | 40° | |

^a The molar ratio of substrate to KF in the KF-CaF₂ reagent was 1:2. ^b Without solvent. ^c 2% Oct-1-ene was formed.

This heterogeneous mixture of KF–CaF₂ (2.5 g, containing 8 mmol of KF) and benzyl bromide (0.69 g, 4 mmol) was heated to reflux with stirring in acetonitrile (3.5 cm^3). The reaction proceeded smoothly to afford the corresponding fluoride in 69, 89, and 95% yield after 6, 10, and 15 h, respectively, as determined by g.l.c. analysis. After 15 h, the solid materials were filtered off and washed with diethyl ether, and solvent was then evaporated. Benzyl fluoride was isolated in 81% yield by molecular distillation.

Under the same conditions nucleophilic substitution hardly occurred when either KF powder or CaF_2 powder were used separately. Thus, it is the combination of KF and CaF_2 that accelerates the heterogeneous fluorination. As shown in Table 1, the reactivity of this KF–CaF₂ reagent is higher than that of agents such as 'spray-dried' KF and the KF–18-crown-6 complex.

The KF-CaF₂ reagent was used successfully in the preparation of various organo fluorine compounds. Typical examples are summarised in Table 2. Moderately reactive and moisture sensitive chlorides or bromides were fluorinated by use of the KF-CaF₂ reagent in good yields. The fluorination of carboxylic and sulphonic acid chlorides proceeded very slowly with KF powder alone in acetonitrile at room temperature, but the reaction was completed within a few hours when the KF-CaF₂ reagent was used. In these experiments the reaction could be carried out with or without solvent.

Other combinations of alkali metal fluorides and alkaline earth metal fluorides were found to produce higher nucleophilicity than either of the individual fluorides. For example, a CsF-BaF₂ reagent was more efficient than CsF, and a NaF-CaF₂ reagent was able to promote fluorination of aroyl and sulphonyl chlorides on gentle heating.

From powder X-ray diffraction analysis of the KF–CaF₂ reagent no chemical interaction was observed between the two fluorides. Analysis of the inorganic materials recovered after use in the fluorination of benzyl bromide showed the presence of KBr together with KF and CaF₂, but no CaBr₂. Thus,

calcium fluoride may act as a simple support to disperse potassium fluoride on its surface and enhance the nucleophilicity of the KF, possibly by physical interaction.

The results from the fluorination of chloroarenes bearing electron attracting groups such as NO_2 or CN will be published elsewhere.

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