

Drifluor Reagents: Non-Hygroscopic Sources of the Fluoride Ion

By JAMES H. CLARK

(Department of Chemistry, University of Exeter, Exeter EX4 4QD)

Summary Fluorides may be bound to silica gel and other porous solid supports providing non-hygroscopic sources of the fluoride ion which may be used to promote various typically base-assisted reactions.

TETRA-ALKYLAMMONIUM FLUORIDES have been increasingly used for different purposes in synthetic chemistry in the last few years, *e.g.*, in a number of elimination reactions,¹ Michael additions,² condensations,³ and fluorinations.⁴ Unfortunately, their utility has been severely limited

owing to their extreme hygroscopic nature and since the function of these salts has been shown usually to depend on the initial formation of a hydrogen bond to a reactant molecule^{3,5} any water that is present must reduce their effectiveness. The best method in the literature for rendering these salts anhydrous relies on providing an alternative H-bond electron acceptor during the evaporation of the aqueous fluoride.³ This method is only effective, however, for a few highly acidic organic compounds^{3,6} and for the majority of reactions the chemist must resort to tedious and prolonged methods of drying of doubtful efficiency.

hydrochloric acid (to remove iron), thoroughly washed with water, and dried at 150 °C for a long period, was shaken, when it became warm. Water was then removed under reduced pressure in a rotary evaporator. After most of the water had been removed, 100 cm³ of methanol was added and the evaporation was continued. On removal of the solvents, the resulting solid was washed with ether and dried in air at 100 °C. The yield of the product (14.0 g) suggested that all the water had been removed.[†] The final material is stable, non-hygroscopic, and remains an effective catalyst (see later) after being left in air for several days. Silica-supported tetraethylammonium, benzyltri-

TABLE

| Reactions ^a | Products | Time/h | Temp./°C | Solvent | Yield/% |
|---|---|--------|----------|---------|------------------|
| (1) MeNO ₂ + PhCH=CHCOPh ^b | PhCH(CH ₂ NO ₂)CH ₂ COPh | 1 | 60 | THF | 86 |
| " " " ^b | " | 6 | 20 | THF | 75 |
| " " " ^{b,c} | " | 6 | 20 | THF | 70 |
| " " " ^{b,d} | " | 12 | 20 | THF | 0 |
| (2) Me ₂ CHNO ₂ + PhCH=CHCOPh | PhCH[C(Me ₂)NO ₂]CH ₂ COPh | 3 | 20 | DMF | 65 |
| (3) PhSH + MeCOCH=CH ₂ | MeCOCH ₂ CH ₂ SPh | 1 | 20 | THF | 75 |
| Thiol addition | | | | | |
| (4) PhCOCH ₂ Br + AcOH ^e | PhCOCH ₂ OAc | 4 | 20 | DMF | 75 [†] |
| Phenacyl ester synthesis | | | | | |
| (5) PhCOCH ₂ COPh + EtI ^e | PhCOCH(Et)COPh | 6 | 20 | DMF | 55 [†] |
| C-Alkylation | | | | | |
| (6) Pentane-2,4-dione (80% enol) | MeCOCH=C(OH)Me | — | 20 | DMF | 100 ^b |
| Enolisation ^g | | | | | |
| (7) Fluorene | Fluorenone | 24 | 20 | THF | 30 |
| (8) PhSH | PhSSPh | 6 | 20 | DMF | 100 ^b |
| Sulphenylation | | | | | |
| (9) MeCOCH ₂ COMe + PhSH | MeCOCH(SPh)COMe | 48 | 20 | DMF | 60 |

^a Unless noted otherwise, reactions were carried out using 0.01 mol. equiv. of the indicated reagents and 1 g of TBAF-silica (0.001 mol. equiv. of fluoride). In reactions (1)–(3), (7), and (8), the TBAF-silica was recovered by filtration in >95% yield. In reactions (6) and (9), it was necessary to add a large volume of ether to the reaction mixture before filtration so as to free most of the TBAF-silica which was then recovered in ca. 95% yield. Reactions (4) and (5) are non-catalytic and the bulk of fluoride was consumed during the reaction. ^b 0.005 mol of chalcone and 0.1 mol of MeNO₂. ^c Using recovered TBAF-silica. ^d Using pure silica gel alone. ^e 0.002 mol of the indicated reagents and 4 g of TBAF-silica. A quantitative amount of Buⁿ₄NBr (or Buⁿ₄NI) was recovered by washing the residue with chloroform and extracting the combined filtrates. [†] The final recovered yield of gel (after CHCl₃ washing) corresponded approximately to the amount of silica gel originally present (ca. 3.2 g). ^g Measured in solution by ¹H n.m.r. spectroscopy using ca. 0.1 g of TBAF-silica (0.1 mmol fluoride), 0.2 g (2 mmol) of the diketone, and 2 g of dimethylformamide (DMF). ^h Measured in solution by ¹H n.m.r. spectroscopy.

Silica gel presents a surface having many hydroxy groups; indeed it has been shown to be capable of extensive strong H-bonding to H-bond electron acceptors and donors.⁷ There have been several recent reports on the advantages of using functionalised insoluble polymers in organic synthesis;⁸ the reactivity of permanganate is enhanced when it is impregnated on inorganic support materials.⁹ We have now discovered that tetrabutylammonium fluoride (TBAF), a powerful H-bond electron donor, may be rendered apparently anhydrous by the very simple process of binding it to silica gel and we now report a number of preliminary results on the scope of this method and the utility of this and similar materials in fluoride-assisted reactions.

The following serves as an example of the preparation and application of the TBAF-silica reagent. A slurry of 20 g of 20% aqueous TBAF and 10 g of 60–120 mesh silica gel which had been previously purified by treatment with

methylammonium, potassium, and caesium fluorides have also been prepared by similar methods, as anhydrous, air stable materials. In a typical reaction, 1 g of TBAF-silica (ca. 1 mmol. equiv. fluoride) was suspended in 20 cm³ of tetrahydrofuran (THF) containing 6.1 g (0.1 mol) of nitromethane and 1.04 g (5 mmol) of chalcone and the resulting mixture was stirred at 20 °C for 6 h. Separation and recrystallisation of the product from ethanol gave 1.08 g (75%) of 4-nitro-1,3-diphenylbutanone, m.p. 99–100 °C (lit.¹⁰ 101 °C). The TBAF-silica was recovered in 99% yield. Similar results were obtained using silica-supported tetraethylammonium and benzyltrimethylammonium fluorides. Further examples of fluoride-assisted reactions using TBAF-silica, both catalytic and non-catalytic, are given in the Table. Alumina, diatomaceous earths, zeolites,[‡] and porous glasses also bind fluoride to give materials which catalyse Michael reactions,

[†] The yield of product corresponds to 1 mmol TBAF (0.26 g)/g TBAF-silica. A typical surface area of the silica used is 850 m²/g which for a normal silica with 4–5 surface hydroxy groups/nm² corresponds to ca. 3.5 × 10²¹ hydroxy groups/g. The TBAF-silica material described here has therefore an F[−]: surface OH ratio of ca. 1:5. Preliminary experiments on varying the concentration of F[−] suggest that air-stable materials containing >1 mmol/g reagent may be prepared although other properties such as solvent stability may be affected.

[‡] 5 Å molecular sieves do not give a non-hygroscopic material with TBAF which suggests that pore size may be a critical factor. The silica used here has a mean pore diameter of 21 Å which is larger than any of the tetra-alkylammonium cations used so far.

but they tend to lose fluoride under the reaction conditions. § All the supported tetra-alkylammonium fluorides discussed slowly lose fluoride when heated in air at 130 °C.

The author is indebted to Professor Jack Miller for his continued support and advice, to B.D.H. Chemicals Ltd.

for providing the surface area and pore diameter of the silica gel, and to A. J. Pidduck for helpful discussions.

(Received, 8th June 1978; Com. 600.)

§ The silica based materials lose fluoride on treatment with protic solvents such as water, methanol, and carboxylic acids.

¹ T. H. Chan and W. Mychajlowskij, *Tetrahedron Letters*, 1974, 171; J. Hayami, N. Ono, and A. Kaji, *ibid.*, 1968, 1385; 1970, 2727; R. F. Cunico and E. M. Dexheimer, *J. Amer. Chem. Soc.*, 1972, **94**, 2868.

² J. H. Clark and J. M. Miller, *J.C.S. Perkin I*, 1977, 2063; S. Hoz, M. Albeck, and Z. Rappoport, *Synthesis*, 1975, 162.

³ J. H. Clark and J. M. Miller, *J.C.S. Perkin I*, 1977, 1743; *Canad. J. Chem.*, 1978, **56**, 141.

⁴ C. M. Skarts and W. A. Sheppard, *Org. Reactions*, 1974, **21**, 174.

⁵ J. H. Clark and J. M. Miller, *J. Amer. Chem. Soc.*, 1977, **99**, 498.

⁶ J. H. Clark and J. Emsley, *J.C.S. Dalton*, 1973, 2154.

⁷ A. Terenin and V. Filimonov, in 'Hydrogen Bonding,' ed. D. Hadzi, Pergamon, London, 1959, p. 545 and references therein.

⁸ C. C. Leznoff, *Chem. Soc. Rev.*, 1974, **3**, 65; C. G. Overberger and K. N. Sannes, *Angew. Chem. Internat. Edn.*, 1974, **13**, 99; D. C. Neckers, *J. Chem. Educ.*, 1975, **52**, 695; R. J. Mulder, *Chem. Weebklad*, 1966, **62**, 421; J. H. Clark, J. M. Miller, and K. H. So, *J.C.S. Chem. Comm.*, 1978, 466; P. Tundo, *ibid.*, 1977, 641.

⁹ S. L. Regen and C. Koteel, *J. Amer. Chem. Soc.*, 1977, **99**, 3837.

¹⁰ I. Belsky, *J.C.S. Chem. Comm.*, 1977, 237.

¹¹ C. G. Armistead, A. J. Tyler, F. H. Hambleton, S. A. Mitchell, and J. A. Hockey, *J. Phys. Chem.*, 1969, **73**, 3947.