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Mendeleev Commun., 2013, **23**, 257–259

Mendeleev Communications

Potassium fluoride on calcium fluoride – a practical reagent for removal of organotin residues from reaction mixtures

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DOI: 10.1016/j.mencom.2013.09.006

Potassium fluoride deposited on calcium fluoride serves as an easily available and convenient reagent for the removal of all major types of organotin residues from reaction mixtures by a simple filtration.

Various organotin reagents, especially Bu_3SnH, Bu_3SnX (X = F, Cl, Br), $(Bu_3Sn)_2O$ and $(Bu_3Sn)_2$, have found wide application in modern organic synthesis as indispensable reagents for a variety of radical and ionic reactions.[1(a),(b)] The common drawback of these reactions is the necessity to remove the reaction mixtures from all organotin residues (OTR) originating in the excesses and chemical transformations of the organotin reagents. This type of purification is important not only to gain a high purity of the synthetic product but also in connection with the high toxicity of organotin compounds.[1(c)] The problem of OTR removal arises from the similarity of OTR and the reaction products in some physical properties, very often resulting in an inadequate effectiveness of common extractive treatment followed by chromatography (for excellent illustration, see ref. 2).

In the period of more than the last 30 years this problem and its solutions were the main object of several articles[2–8] and sections in reviews[9,10] as well as valuable episodes in many papers.[11–17] The majority of the purification methods were based on a chemical transformation of OTR to facilitate its removal. The reagents being proposed for this transformation include Me_3Al,[5] DBU,[14] $NaBH_3CN$,[4] NaOH,[5] KOH[17] and CsOH,[6] which are not chemoselective and not acceptable for the variety of target products. The most widely-used method is the treatment with fluoride ion which converts some types of OTR into the corresponding insoluble stannyl fluorides.[3] The source of fluoride ion is usually KF in aqueous[3,7] or alcoholic[11] solution, or as a mixture with silica gel,[2] but sometimes CsF,[6,12] Bu_4NF[17] and Py·HF[13] were used as well.

The methods with fluoride ion are experimentally simple and chemoselective, however, sometimes they do not provide a sufficiently complete (<1%) removal of OTR.[2,12,17,18] Moreover, with the single exception of chromatography on a mixture of silica gel with KF,[2] the methods with fluoride ion imply an extractive treatment of reaction mixtures.

The treatment of reaction mixtures with a suspension of a solid source of fluoride ion in an inert solvent followed by filtration appears to be a much more convenient method to OTR removal. This method has been realized yet only with a help of hygroscopic and alkaline solid solution CsF·CsOH as a reagent.[6] Herein, we found that potassium fluoride deposited on calcium fluoride (KF/CaF_2, 20–22% KF) could serve as a very effective source of fluoride ion in this method. The system KF/CaF_2 is a cheap and easily available reagent,[†] and can be readily prepared in the laboratory by evaporation of a CaF_2 suspension in aqueous KF solution.[‡]

The relative effectiveness of various solid ‘forms’ of KF as a heterogeneous source of fluoride ion has already been investigated in the reactions of nucleophilic substitution. Exactly KF/CaF_2 was found to be the most active ‘form’,[19] followed by the mechanical mixture KF + CaF_2[19,20] and fine-powdered ‘spray-dried’ KF.[20,21] Other studied supports for KF, namely silica gel,[22] celite,[22,23] Al_2O_3[22,24] and analogues,[22] diminish fluoride ion nucleophilicity[25] and are not chemically inert to a contact with KF.[§] As an example, highly alkaline ‘KF/Al_2O_3’ is in fact $(K_3AlF_6 + KAlO_2 + KOH)/Al_2O_3$.[26] In KF/CaF_2 any chemical interaction of the components is absent.[19,27]

Additional favorable properties of KF/CaF_2 are its essential neutrality and non-hygroscopicity. A sample of the completely dried reagent contained only 0.4% of water after 5 years of the occasional using. The same quantity of water was absorbed by anhydrous KF/CaF_2 exposed to air within 24 h with a relative humidity 22% at 25 °C. Similar unexpected negligible hygroscopicity of fine-powdered KF has already been known but remained unexplained.[21,24,28] Mechanical mixtures of KF with CaF_2[20] or silica gel[2] are hygroscopic.[8]

Some time ago KF/CaF_2 was used as a reagent for the hydrolysis of dibutylchlorostannyl ethers.[16] In the course of that study we discovered a significant increase of the KF/CaF_2 activity on the addition of 1 equiv. of water. A similar effect of small water quantities was reported for KF on other supports.[19,22,23] Therefore, it is expedient and convenient to moisten the reagent in advance up to a ratio $KF : H_2O = 1 : 1$.[‡] The following discussion in this paper assumes KF/CaF_2 containing KF and H_2O 3.5 mmol g^{-1} each.

A practical, without chromatography, general method of OTR removal from reaction mixtures with the aid of KF/CaF_2 is very simple. It consists in stirring (6–12 h) of a mixture containing OTR (for example, ~1 mmol of [Sn]) with suspended KF/CaF_2 (600–900 mg, ~2–3 mmol of KF), dilution (2–5 times) with

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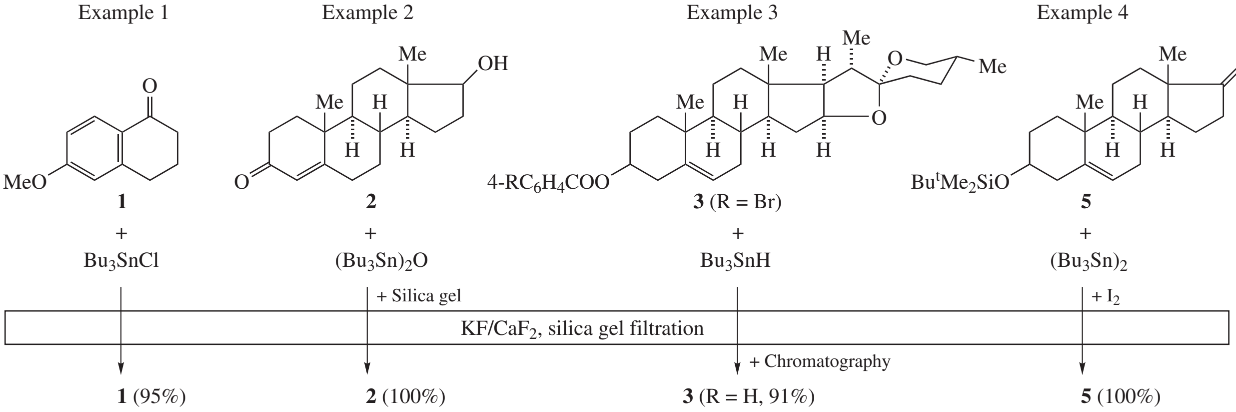
[†] Potassium fluoride on calcium fluoride (20% KF) (Cat. No. 316636) could be found in the electronic catalogue on Sigma-Aldrich site, but at present this reagent ‘has been discontinued’.

[‡] *Preparation of KF/CaF_2.* The powdered (20–100 μm) CaF_2 (66.69 g) was added portionwise to a solution of $KF{\cdot}2H_2O$ (30.0 g) in water (30 ml) with mixing by spatula. The formed thick wet mass was dried in air first at room temperature and then at 130–140 °C for 2 h. The brittle dry mass was then finely powdered by a short grinding in a mortar (yield 84.89 g of white anhydrous KF/CaF_2). This reagent (30.0 g) was stored in desiccator containing a cup with 3–4 ml of water until it reached the weight 32.0–32.1 g which corresponds to the contents of KF and H_2O 3.5 mmol g^{-1} each.

[§] The appearance of an unpleasant, potentially toxic odour was sensed during preparation of KF/SiO_2 by grinding of silica gel in a mortar together with a concentrated aqueous solution of KF.



Scheme 1 Examples of various organotin residue removals.

Bu^{t}OMe, Et_2O, MeCN or EtOAc (depending on the product polarity), and filtering through a short plug of silica gel[¶] (1–2 g). If some traces of OTR remained in a product the same filtering should be repeated in the pure chosen solvent. Specific details of this general method as well as a pre-treatment of reaction mixtures needed for some types of OTR are commented below.

In all fluoride-based methods of OTR removal the final operation is filtering off of insoluble Bu_3SnF formed. However, the complete removal of Bu_3SnF by filtering may be problematic because the filtrate is usually saturated with Bu_3SnF which remains in the product. The quantity of remained Bu_3SnF depends critically on the solubility of this substance in the solvent(s) used. Et_2O,[3,18] EtOAc,[12] MeCN and Me_2CO[10] are recommended in the literature as the solvents for Bu_3SnF removal by filtering. Nevertheless, we were unable to find in the literature any quantitative data on the Bu_3SnF solubility in the mentioned solvents,[††] and therefore we determined the solubility in these as well as in some other solvents (Table 1). The data show that the solubility in Me_2CO is too high and Bu^{t}OMe appears to be an optimal solvent for the purpose.

Filtering through a short plug of silica gel is an important additional factor which makes it possible to diminish Bu_3SnF concentration in filtrates down to $\ll 0.1$ mg cm^{-3}. Silica gel was reported to irreversibly absorb $(Bu_3Sn)_2O$ thus removing its last traces.[8,10,14] We found that Bu_3SnF possesses the same ability – 1 g of silica gel can irreversibly absorb up to 11 mg of Bu_3SnF from solutions during filtrations.

Table 1 Solubility of Bu_3SnF in organic solvents at 24 °C.[a]

Solvent	Solubility[b]/mg cm^{-3}	Solvent	Solubility[b]/mg cm^{-3}
C_6H_6	0.4[c]	Et_2O	0.2
Toluene	0.8	Bu^{t}OMe	0.1
CH_2Cl_2	2.8	THF	6.9
$CHCl_3$	>20[d]	MeCN	0.24
EtOAc	0.26	Me_2CO	0.50

[a] A suspension of Bu_3SnF (50–300 mg) in a solvent (15 ml) was stirred for 1 h at 40 °C (30 °C for Et_2O) and then stored at least 24 h at 24 °C. Supernatant aliquots (5.00 ml) were evaporated in vacuum to dryness and the crystalline residues were weighted. [b] 1 mg cm^{-3} = 3.24×10^{-3} mol dm^{-3}. [c] Lit.,[29(b)]: ~0 (25 °C). [d] Lit.,[29(a)] ~20 mg cm^{-3} (37 °C).

Removal of Bu_3SnCl and $(Bu_3Sn)_2O$ (and their homologues) from reaction mixtures with KF/CaF_2 needs no pre-treatment of the mixtures. To compare the activities of KF/CaF_2 and CsF·CsOH we reproduced the model experiment[6] with a replacement of CsF·CsOH by an equivalent quantity of KF/CaF_2 (Example 1 in Scheme 1).[‡‡] The result, *i.e.* the complete purification of 6-methoxy-1-tetralone **1** from an equimolar admixture of Bu_3SnCl, remained unchanged. An increased quantity of silica gel (3.5 g mmol^{-1} [Sn]) made it possible to fulfill the Bu_3SnF filtering off in CH_2Cl_2 despite significant solubility of Bu_3SnF in this solvent (see Table 1).

Oxide $(Bu_3Sn)_2O$ is probably the most common component of OTR despite its only limited application as a reagent for organic synthesis.[12,15,30] Nevertheless, various quantities of $(Bu_3Sn)_2O$ could be formed in the reactions with all other types of tributylstannanes due to main or side oxidative or hydrolytic reactions. The transformation of $(Bu_3Sn)_2O$ on contact with KF/CaF_2 proceeds according to the equation $(Bu_3Sn)_2O + KF + H_2O \rightarrow Bu_3SnF + KOH$ generating a strong base. Indeed, we observed the appearance of a medium alkaline condition in the process. Therefore with alkali-sensitive substrates it is advisable to add some silica gel to a reaction mixture of $(Bu_3Sn)_2O$ for removal by the general method. This small modification was demonstrated in the model experiment of the quantitative testosterone **2** isolation from its mixture with an equimolar quantity of $(Bu_3Sn)_2O$ (Example 2[§§]).

Two other popular organotin reagents, Bu_3SnH and $(Bu_3Sn)_2$, do not react under mild conditions with KF/CaF_2 or other sources of fluoride ion. An attempt to get around this obstacle was made in Example 3,[¶¶] during the treatment of a reaction mixture after

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[¶] Deactivated silica gel 20–100 μm (Chemapol) with water content 9–10% was used.

[††] The only published solubilities of Bu_3SnF are >10 mg cm^{-3} at 37 °C in MeOH, *n*-hexane, $CHCl_3$, CCl_4 and $Cl_2C{=}CCl_2$.[29]

[‡‡] *Example 1*. The suspension of KF/CaF_2 (330 mg, 1.14 mmol KF) and silica gel (120 mg) in a solution of 6 methoxy-1-tetralone **1** (100 mg, 0.57 mmol) and Bu_3SnCl (153 μl, 0.57 mmol) in CH_2Cl_2 (2 ml) was stirred overnight. Filtering through a short plug of silica gel (2 g) with CH_2Cl_2 elution afforded crystalline ketone **1** (95 mg, 95%), pure by NMR.

[§§] *Example 2*. The suspension of KF/CaF_2 (862 mg, 3 mmol KF) and silica gel (431 mg) in a solution of testosterone **2** (145 mg, 0.50 mmol) and $(Bu_3Sn)_2O$ (300 mg, 0.5 mmol) in CH_2Cl_2 (8.6 ml) was stirred for 6 h, then diluted with EtOAc (20 ml) and filtered through silica gel (1 g). Filtrate evaporation remained 184 mg of crystalline mass incompletely soluble in 0.5 ml of EtOAc. This mass in EtOAc (3 ml) was filtered again through silica gel (500 mg) affording crystalline hydroxyketone **2** (145 mg, 100%), pure according to TLC and NMR, Sn content <0.1% (semi-quantitative atom-emission analysis).

[¶¶] *Example 3*. The solution of bromobenzoate **3** (200 mg, 0.33 mmol), Bu_3SnH (290 mg, 1.0 mmol) and AIBN (8 mg, 0.05 mmol) in toluene (6.3 ml) was heated for 4 h at 80 °C in Ar atmosphere. Extractive work-up and evaporation at 100 °C (0.4 Torr) produced 302 mg (174%) of semi-solid mass. This mass was vigorously stirred for 6 h in air with KF/CaF_2 (740 mg, 2.6 mmol KF) in toluene (7 ml). Filtration through silica gel (500 mg, CH_2Cl_2 elution) gave 253 mg (146%) of crystalline mass heavily contaminated by OTR (NMR spectrum). Repeated treatment with KF/CaF_2 (in THF) did not change anything. Only by chromatography on silica gel (6 g) in toluene, Bu_3SnH (64 mg, R_f 0.95, toluene) and pure benzoate **4** (158 mg, 91%, R_f 0.10) were isolated.

reductive debromination of diosgenin *p*-bromobenzoate **3** with 3 equiv. of Bu_3SnH. Neither stripping off at 100 °C (0.4 Torr) of the excessive volatile Bu_3SnH [bp 80 °C (0.4 Torr)], nor the double treatment with KF/CaF_2 according to the general method *in the air* [for oxidation of Bu_3SnH into $(Bu_3Sn)_2O$] did result in complete purification of the formed benzoate **4**. The remained Bu_3SnH, very unpolar compound, can be removed by chromatography, with a significant decrease in a preparative value of the synthesis.[4]

The similar situation is observed with high-boiling $(Bu_3Sn)_2$,[18] which could be present in OTR not only as an excess of the reagent but very often as a product of Bu_3SnH transformation under diverse reaction conditions.[31] For both of these OTR components the best modification of the general method is pre-treatment of reaction mixtures with iodine solution.[6,7,14] This pre-treatment smoothly converts both Bu_3SnH and $(Bu_3Sn)_2$ into Bu_3SnI which is easily removed on subsequent KF/CaF_2 treatment by the general method. In a model experiment an equimolar quantity of $(Bu_3Sn)_2$ was successfully removed from the mixture with silyl ether **5** using this modification of the method (Example 4[†††]). Moreover, the choice of an optimal (by solubility of Bu_3SnF) solvent (Bu^tOMe) in this experiment made it possible to use a single silica gel filtration only. Simultaneously the stability of Bu^tMe_2SiO group towards KF/CaF_2 was found.

In summary, KF/CaF_2 is an easily available and convenient reagent in this simple method of organotin residue removal from reaction mixtures without chromatography.

This work was supported by the Presidium of the Russian Academy of Sciences (program 2011–2012). Authors are grateful to Dr. O. D. Vernidub (Metaltest, Moscow) for atom-emission analyses.

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Received: 8th July 2013; Com. 13/4152

[†††] *Example 4*. The solution of iodine in Bu^tOMe (0.25 mol dm^{-3}, ~2 ml) was added dropwise to the solution of silyl ether **5** (201 mg, 0.50 mmol) and $(Bu_3Sn)_2$ (290 mg, 0.50 mmol) in Bu^tOMe (5 ml) until appearance of light-yellow coloration. Thereafter KF/CaF_2 (714 mg, 2.5 mmol KF) was added and thickening white suspension was stirred for 6 h. The filtration through silica gel (1 g) with Bu^tOMe elution afforded crystalline silyl ether **5** (201 mg, 100%), according to TLC and NMR not contaminated neither by OTR nor by desilylation product, with Sn content < 0.05% (semi-quantitative atom-emission analysis).