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### IMPROVED ONE-POT PREPARATION OF TETRAMETHYLFLUOROFORMAMIDINIUM HEXAFLUOROPHOSPHATE

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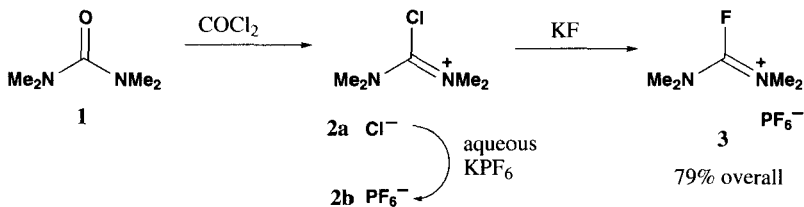
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**IMPROVED ONE-POT PREPARATION OF  
TETRAMETHYLFLUOROFORMAMIDIUM HEXAFLUOROPHOSPHATE**

Submitted by Tomas Vojkovsky\* and Brian Drake  
(11/21/96)

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Acyl fluorides are stable and powerful acylating agents that have been successfully applied in peptide synthesis. While racemization-safe, N-protected amino acid fluorides undergo a clean and rapid condensation with amines, including cases where other methods have proven to be unsatisfactory.<sup>1-5</sup> Tetramethylfluoroformamidinium hexafluorophosphate (TFFH, **3**), is an excellent reagent for *in situ* formation of acyl fluorides from carboxylic acids.<sup>6</sup> The reagent is usually prepared from tetramethylurea-derived chloroformamidinium salt **2**.<sup>6,7</sup>



In our hands, the original procedure<sup>6</sup> was impractical for preparations on a hundred-gram scale. Hydrolysis during the first step (**1** to **2b**) and slow conversion of **2b** to **3** in the next step lowered the yield (50-65%) and purity of the product (mp. lowered by 5-20°) when batches over 50 mmol were attempted. We now describe a simplified, expeditious one-pot procedure that provides high yield of TFFH in excellent purity. With common glassware, 2 mols of TFFH were prepared in one and half day.

### EXPERIMENTAL SECTION

Reagents were purchased from Aldrich. Solvents were Burdick & Jackson HPLC brand (water content < 0.005%). <sup>1</sup>H NMR spectra were recorded on Bruker Avance DPX 300 instrument at 300 MHz.

**Tetramethylfluoroformamidinium Hexafluorophosphate (TFFH).**- In a 2 L three-necked flask equipped with a mechanical stirrer, addition funnel and reflux condenser, oxalyl chloride (70 mL, 0.80 mol) was added in one portion to a solution of tetramethylurea (69.7g, 72.6mL, 0.60 mol) in toluene (1 L) with vigorous stirring. The reaction temperature (oil bath) was increased to 60° over 20 min. The mixture was stirred at 60° for 2 h and then cooled to R.T. The addition funnel was replaced with a fritted adapter and the supernatant was expelled using positive pressure of nitrogen. The precipitate was washed with toluene (2 x 300 mL). A pre-dried mixture (Kugelrohr apparatus, 160°/0.3 Torr/1hr)

of KF (Aldrich 'spray-dried', 40.1 g, 0.69 mol) and  $KPF_6$  (116.0 g, 0.63 mol) was added together with anhydrous acetonitrile (1 L) to the reaction flask. The reaction mixture was stirred at 55° for 3 h, then cooled to R.T. and filtered through a large coarse filtration funnel (the salts were washed with 3 x 150 mL of acetonitrile). The combined filtrates were evaporated and the resulting oily residue was taken up in hot dichloroethane (700 mL). The cloudy solution was filtered while hot using a medium-porosity filtration funnel and then concentrated to approximately 450 mL of volume. THF (600 mL) was added under stirring and the mixture was then shaken for 2 min to promote crystallization. The flask was cooled to R.T. The precipitate was collected under positive pressure of nitrogen and washed with THF (2 x 250 mL). A stream of nitrogen was passed through the product for 20 min, the drying process was completed in vacuum (0.3 mm Hg, 2 h), to yield 143.0 g (90 %) of white crystalline product, mp. 112-113°, lit.<sup>6</sup> 111-112°.

<sup>1</sup>H NMR spectra (DMSO,  $\delta$  3.150, d) were in accordance with published values.<sup>6</sup>

The above procedure was performed four times, with yields ranging from 86 to 90%.

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