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# Tetramethyl Fluoro Formamidinium Hexafluorophoshate - An Improved Synthesis and Some New Uses.

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SYNTHETIC COMMUNICATIONS, 28(7), 1223-1231 (1998)

# TETRAMETHYL FLUORO FORMAMIDINIUM HEXAFLUOROPHOSHATE - AN IMPROVED SYNTHESIS AND SOME NEW USES.

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## ABSTRACT

A non-phosgene, cheap synthesis of Tetramethyl Fluoro Formamidinium Hexafluorophosphate (TFFH) has been developed, and TFFH has been shown to be an useful reagent for preparation of isothiocyanates and hydrazides.

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Tetramethyl fluoro formamidinium hexafluorophosphate (**1**) was introduced recently by Carpino and his coworkers[1,2] and shown to be almost the perfect peptide coupling reagent. It has a long shelflife, is non-hygroscopic and reacts very fast with a carboxylic acid to give the corresponding acidfluoride or mixed anhydride depending the on conditions. Furthermore **1** was shown to be highly useful for coupling of very hindered aminoacids. With applications in mind as a general activating reagent for solid phase chemistry, we were interested in the utility of **1** for formation of other carboxylic acid/amine derivatives than amides and needed access to large amounts of the reagent.

The published synthesis[2,3] involves the reaction between N,N,N',N'-tetramethylurea and phosgene in toluene to form tetramethyl chloro formamidiunium chloride followed by exchange of the chloride-ion by treatment with ammonium hexafluorophosphate[3]. The C-chlorine is substituted with fluorine by treatment with potassium fluoride in acetonitrile[2]. We have developed the sequence shown in Scheme 1, where N,N,N',N'-tetramethylurea is treated with $POCl_3$ to give tetramethyl chloro formamidinium dichlorophosphate, which is converted to the hexafluorophosphate by treatment with aqueous hexafluorophosphoric acid. The halogen exchange is also performed by treatment with KF in $CH_3CN$. Thus in the present procedure the handling of phosgene is completely avoided, and the rather expensive ammonium hexafluorophosphate is replaced by the corresponding acid.

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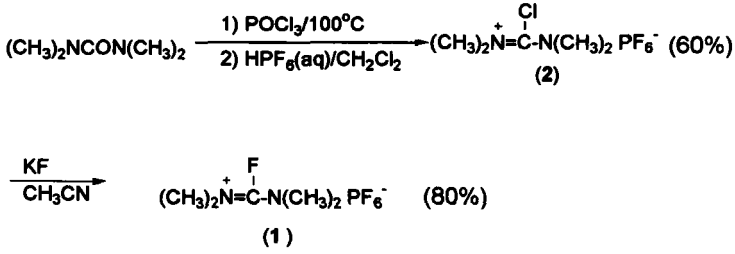
**Scheme 1.**

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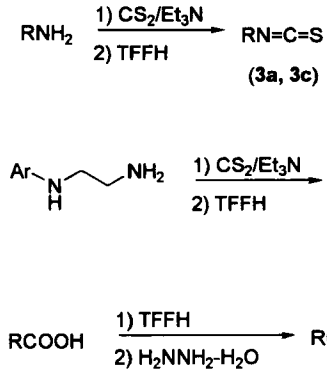
A mild and quick method for the synthesis of isothiocyanates from the corresponding amines was another area of interest. The reaction between a primary amine, carbondisulfide and TFFH (**1**) proceeds fast and gives the corresponding isothiocyanates in good yields (Scheme 2).

Using the reaction on a substituted 1,2-ethanediamine gives the corresponding substituted imidazolidine-2-thione presumably with the isothiocyanate as intermediate.

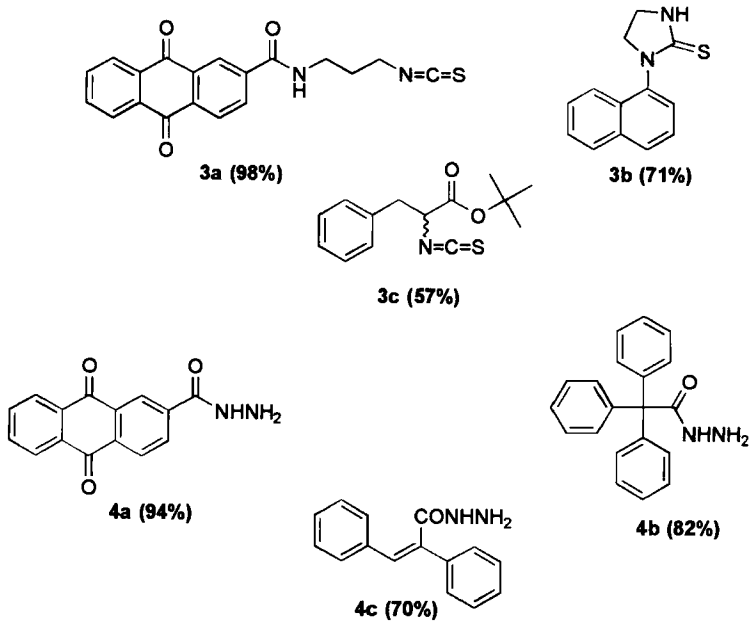
Acylhydrazides are classically synthesized by the reaction between an ester and a very large excess of hydrazine. The reaction between acid anhydrides or acidchlorides and hydrazine usually gives considerable amounts of bisacylhydrazides [4,5].

Using TFFH (**1**) for activation of the carboxylic acid allows the use of an equimolar amount of hydrazine without formation of bisacylhydrazides (Scheme 2). This is advantageous in cases such as compound **4a**, where reported synthesis by hydrazinolysis of the ethylester gives the hydroquinone as the primary product due to the reducing properties of hydrazine[6].

**Scheme 2.**




**Scheme 3.**

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The compounds prepared by the TFFH (**1**) coupling protocol are shown in Scheme 3.

## Experimental:

General remarks:

Proton NMR was performed on a Bruker 250 MHz spectrometer. Melting points were measured at a Büchi melting point apparatus and are uncorrected. Mass analysis were performed by EI and $FAB^+$. FAB analysis was run in m-nitrobenzyl alcohol as matrix.

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**Tetramethyl fluoro formamidinium hexafluorophosphate (1).**

A mixture of compound **2** (143.6 g; 0.52 mol) and KF (dried at 125°C) (30.2 g; 0.52 mol) in $CH_3CN$ (250 mL) was stirred at room temperature overnight. The mixture was filtered and concentrated *in vacuo*. The crude product was redissolved in $CH_3CN$, precipitated with diethyl ether, filtered and dried to give 108.8 g (80%) of white crystals. Mp. 108-110°C (111-112°C[1]). $^1$H-NMR: δ 3.35 (d). $^{13}$C-NMR: δ 118.44; 40.40. MS (FAB+): 119.1 ($MH^+$). Elemental analysis: Found (calcd.) 22.38 % C (22.74); 4.29 % H (4.58); 10.61 % N (10.61).

**Tetramethyl chloro formamidinium hexafluorophosphate (2).**

A stirred mixture of N,N,N',N'-tetramethylurea (100 g; 0.86 mol) and $POCl_3$ (90 mL; 0.95 mol) is heated to 100°C for 1 hr. After cooling to room

temperature, $CH_2Cl_2$ (2.2 L) is added, and aqueous 75% $HPF_6$ (100 mL) is added dropwise with good stirring. **CAUTION! This reaction is highly exothermic!** The mixture is washed with $H_2O$ (400 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give compound **2** as a white material. Yield: 143.5 g (60%). Mp. 92-94°C. $^1$H-NMR: ($CD_3CN$): δ 3.25 (s). $^{13}$C-NMR ($CD_3CN$): δ 118.36; 44.77. MS (FAB+): 135.56 ($MH^+$). Elemental analysis: Found (calcd.): 21.82 % C (21.40); 4.16 % H (4.31); 10.08 % N (9.98).

**Isothiocyanates, general procedure:**

The primary amine (10 mmol), carbon disulfide (20 mmol) and triethyl amine (20 mmol) are dissolved in DMF, the mixture is cooled on an ice bath, and TFFH (10 mmol) is added in the cold. The ice bath is removed and the mixture is stirred for 15 minutes at room temperature. Excess carbondisulfide is removed by evaporation. The isothiocyanate is precipitated by adding an equal volume of ice-cold water to the mixture. The isothiocyanate is collected by filtration and dried in vacuo.

**N-(3-Isothiocyano-1-propyl)-9,10-anthraquinone-2-carboxamide (3a).**

Yield: 98 %; $R_f$ (ethyl acetate): 0.73. Mp. 173-176°C (169-172°C[7]). MS ($FAB^+$): 351.11 ($MH^+$). $^1$H-NMR (DMSO-$D_6$): δ 9.0 (t, 1H); 8.6 (s, 1H); 8.3 (dd, 1H, $J_1$= 8 Hz, $J_2$= 2 Hz ); 8.2 (m, 3H); 7.9 (m, 2H); 3.7 (t, 2H), 3.5 (t, 2 H); 1.9 (qn, 2H).

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**1-(1-Naphthyl)-imidazolidine-2-thione (3b).**

Yield: 71%; $R_f$ (ethyl acetate): 0.43. Mp. 178-181°C (208°C[8]). MS (EI): 228 ($M^+$). $^1$H-NMR (DMSO-$D_6$): δ 8.7 (t, 1H); 8.0 (m, 3H): 7.5 (m, 4H); 4.1 (q, 2H); 3.7 (t, 2H). $^{13}$C-NMR (DMSO-$D_6$): δ 137.43; 134.10; 130.24; 128.33; 127.94; 126.51; 126.47; 126.27; 125.89; 123.22; 53.12; 42.18.

***rac*-2-Isothiocyano-3-phenylpropionic acid t-butyl ester (3c).**

The product comes out as an oil, which gradually solidifies, when stirred vigorously with ice / water. Yield: 57 %; $R_f$ (ethyl acetate): 0.73. Mp. 49-50°C. MS (FAB$^+$): 264.14 ($MH^+$). $^1$H-NMR (DMSO-$D_6$): δ 7.25 (m, 5H); 4.95 (t, 1H); 3.2 (m, 2H); 1.4 (s, 9H). Elemental analysis: Found (calcd.): 63.64 %C (63.85); 6.34 % H (6.51); 5.35 % N (5.32); 12.41 % S (12.17).

**Hydrazides, general procedure:**

The carboxylic acid (10mmol), TFFH (10 mmol) is suspended in DMF, The mixture is cooled on ice bath and triethyl amine (20 mmol) folloved by hydrazine hydrat (20 mmol) is added in the cold, the ice bath is removed and the mixture is stirred for 15 minutes at r.t.. The hydrazide is precipitated by adding an equal amount of ice/water. The hydrazide is collected by filtration and dried in vacuo.

**9,10-Anthraquinone-2-carboxylic acid hydrazide (4a).**

Yield: 94%. $R_f$ (ethyl acetate/methanol 6:4): 0.64 (Kaiser test gives yellow

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spot). Mp. 250°C (dec) (240-242°C[6]). MS (FAB$^+$): 267.00 (MH$^+$). $^1$H-NMR (DMSO-$D_6$): δ 10.3 (br. s, 1H); 8.6 (m, 1H); 8.3-8.1 (m, 4H); 3.7 (br. s, 2H).

**Triphenylacetic acid hydrazide (4b).**

Yield: 82 %; $R_f$ (ethyl acetate/methanol 6:4): 0.71 (Kaiser test gives yellow spot). Mp. 167-170°C (196°C[5]). MS (FAB$^+$):303.23 (MH$^+$).$^1$H-NMR (DMSO-$D_6$): δ 8.3 (br. s, 1H); 7.2 (m, 15H); 5.0 (br. s, 2H).

**Z-1,3-Diphenylpropenoic acid hydrazide (4c).**

Yield: 70 %; $R_f$ (ethyl acetate/methanol 6:4): 0.65 (Kaiser test gives yellow spot). Mp. 128-130°C (134°C[9]). MS (FAB$^+$): 239.14 (MH$^+$).$^1$H-NMR (DMSO-$D_6$): δ 9.0 (br. s, 1H); 7.35 (m, 3H); 7.25 (s, 1H); 7.10 (m, 5H); 6.9 (dd, 2H, $J_1$= 5 Hz, $J_2$=2 Hz); 4.5 (br. s, 2H).

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