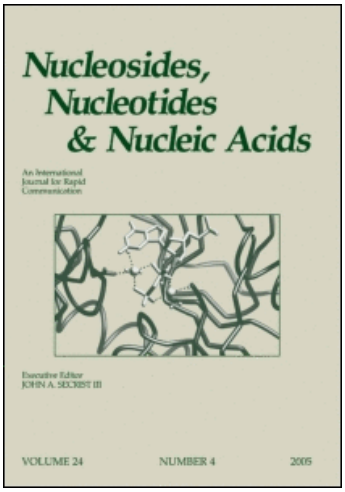

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Vadim Gurvich[a]; Hye-Young Kim[a]; Richard P. Hodge[a]; Constance M. Harris[a]; Thomas M. Harris[a]
[a] Department of Chemistry and Center in Molecular Toxicology, Vanderbilt University, Nashville, Tennessee

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UTILIZATION OF TETRABUTYLAMMONIUM TRIPHENYLDIFLUOROSILICATE (TBAT) IN THE SYNTHESIS OF 6-FLUOROPURINE NUCLEOSIDES

Vadim Gurvich, Hye-Young Kim, Richard P. Hodge, Constance M. Harris, and Thomas M. Harris*

Department of Chemistry and Center in Molecular Toxicology, Vanderbilt University, Nashville, Tennessee 37235

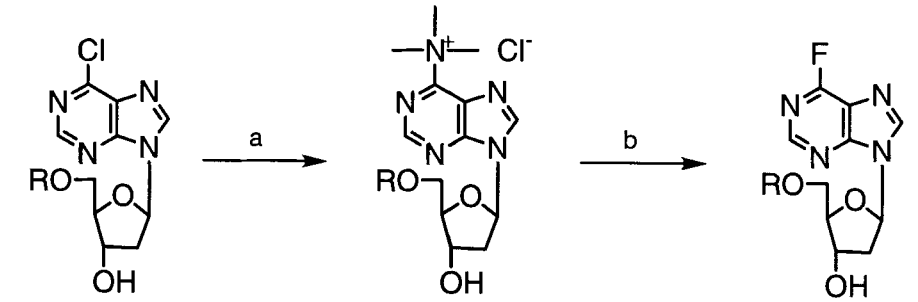
ABSTRACT: Tetrabutylammonium triphenydifluorosilicate (TBAT) has been found to be a useful reagent for the conversion of 6-chloropurine nucleosides to 6-fluoropurine derivatives. The 6-chloropurine nucleosides were reacted with trimethylamine to form quaternary trimethylammonium salts which were treated in situ with TBAT in DMF to effect conversion to the 6-fluoro derivatives in yields of 59-72%.

The synthesis of halopurine nucleosides has been under investigation for many years because of interest in these compounds as possible chemotherapeutic agents.[1] Recent examples include several papers on the synthesis of 2-amino-6-fluoropurine analogs of acyclovir and related antiviral compounds.[2-4] In addition, the halopurines are convenient reagents for the introduction of a wide variety of substituents via reactions with nucleophiles such as amines and thiols. For synthesis of adducts at the 6 position of purine nucleosides, the 6-chloro derivative is usually sufficiently reactive; however, for severely hindered nucleophiles, such as the aminotriol derived from opening of benzo[*a*]pyrene diol epoxide by ammonia, the 6-fluoro derivative is required.[5,6] More recently, phosphoramidites prepared from 6-chloro- or 6-fluoropurine-2'-deoxyriboside have been used to prepare oligonucleotides in which the halogen could be displaced with nucleophiles following DNA synthesis.[7-10]

The most widely used synthesis of 6-fluoropurine nucleosides, developed originally by Kiburis and Lister,[11-13] for purines and ribosides and extended to 2'-deoxyribosides by Robins and Basom[1] starts with a 6-chloro derivative which is reacted with trimethylamine to give a trimethylammonium salt. Treatment of the salt with anhydrous KF in DMF yields the 6-fluoro

nucleoside. We have found the yield in this synthesis to be highly variable, depending on the quality of the KF, whose hygroscopic character and relatively high basicity can lead to hydrolysis and Hoffman degradation of the trimethylammonium salt. Thus, the reaction mixture can contain 6-oxo (i.e., hypoxanthine or guanine) and 6-dimethylamino purine compounds which can be quite difficult to remove from the desired product. The formation of the dimethylamino sideproduct is reported to be more serious in reactions conducted at higher temperatures[11] and in the attempted synthesis of 2-fluoropurine derivatives by this route;[14] however we have detected it in preparations of the 6-fluoropurine 2'-deoxyriboside carried out at 40 °C.

We report herein that tetrabutylammonium triphenyldifluorosilicate (TBAT; Bu_4N^+ $Ph_3SiF_2^-$) can be used as an effective fluoride source in this reaction. This reagent, developed by DeShong and coworkers[15] for use in nucleophilic fluorination reactions, is a commercially available, anhydrous, crystalline, non-hygroscopic solid which is soluble in most organic solvents.



1a R = H
b R = DMT

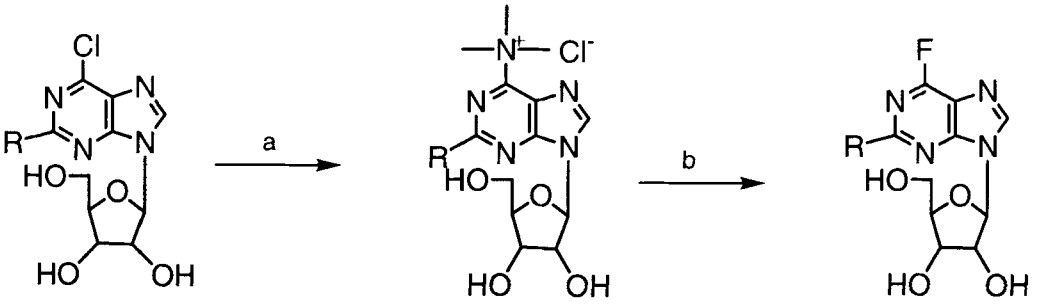
2a R = H
b R = DMT

3a R = H
b R = DMT

(a) trimethylamine; dimethoxyethane (b) TBAT/DMF

The initial reaction studied was the conversion of 6-chloropurine 2'-deoxyriboside **1a**[1,16] to fluoro derivative **3a**. Compound **1a** was treated with excess anhydrous trimethylamine in dimethoxyethane to form trimethylammonium salt **2a**. This is a crystalline compound which can be isolated;[1] however, it is satisfactory to evaporate the solvent and excess trimethylamine under reduced pressure and continue the synthesis without isolation of **2a**. Conversion of **2a** to **3a** was accomplished in DMF with 2 equivalents of TBAT at room temperature. Removal of solvents and chromatography on silica gel yielded **3a** in 68% yield, comparable to the 66%[1] and 77%[5] reported previously. Although the yield was not improved in this case, the TBAT reaction was more reproducible than the KF reaction. The 5'-*O*-dimethoxytrityl derivative (**1b**) of **1a** was

similarly converted to 6-fluoro derivative **3b** in 72% yield, versus 51% with KF.[9] In the case of the riboside derivatives, the yields were also significantly improved. 6-Chloropurine riboside (**4a**) was converted to 6-fluoro derivative **6a** in 59% yield versus 31% with KF.[11] The method worked equally well for the conversion of 2-amino-6-chloropurine riboside (**4b**) to fluoro analog **6b** (72% versus 47%[13]), although in this case the reaction with TBAT required heating at 70 °C for 2 hours.



4 a R = H
b R = NH_2

5 a R = H
b R = NH_2

6 a R = H
b R = NH_2

(a) trimethylamine; dimethoxyethane; DMF (b) TBAT/DMF

We have also investigated direct conversion of **1a** to **3a**; **1a** was treated with increasing amounts of TBAT in DMSO at 65 °C for 9 days. The reaction was monitored by ^{1}H NMR (**1a**, H8 and H2 are at 8.86 and 8.75 ppm; and **3a**, H8 and H2 are at 8.84 and 8.66 ppm) and ^{19}F NMR because the starting material and product have very similar R_f's. Little conversion to **3a** occurred with 2 equiv of TBAT; increasing the excess of TBAT to 7 equiv increased the extent of conversion to ~ 80% but also increased degradation.

We believe that TBAT is a better reagent than KF for these syntheses because it is a stable, crystalline compound which is non-hygroscopic thus leading to decreased hydrolysis of the intermediate trimethylammonium salts and products. Formation of the N^6-dimethylamino byproduct is also decreased because TBAT is less basic than KF or tetrabutylammonium fluoride. In addition, reactions with TBAT can be carried out at lower temperatures than with KF.

Experimental Section

All reactions were carried out under argon atmosphere. All solvents were anhydrous grade. DMF was distilled from calcium hydride immediately prior to reaction. TBAT was

purchased from Aldrich. 6-Chloropurine riboside and 2-amino-6-chloropurine riboside were purchased from Sigma. Anhydrous trimethylamine was purchased from Matheson. ^{1}H NMR spectra were recorded at 300.13 MHz on a Bruker AC 300 NMR. ^{19}F NMR spectra were recorded at 282.40 MHz on a Bruker 300 NMR spectrometer with $CFCl_3$ as the internal standard. Thin layer chromatography was performed on silica gel-coated glass plates. Detection was by UV (254 nm) or staining with an anisaldehyde/sulfuric acid solution, followed by heating. Column chromatography was performed using silica gel 60, 63-200 mesh.

General procedure. Step 1. To the chloronucleoside contained in a 14/20 2- or 3-necked flask equipped with a magnetic stirring bar and a Dewar condenser connected to the center joint of the flask via a small addition funnel was added 1,2-dimethoxyethane (monoglyme). For riboside derivatives insoluble in monoglyme, anhydrous DMF was added. Trimethylamine gas was introduced into the Dewar condenser and allowed to condense in the addition funnel. The gas cylinder was disconnected and the condensed amine was introduced into the reaction flask. The solution was stirred at room temperature while the progress of the reaction was monitored by TLC. When the reaction was complete, the solvent and residual trimethylamine were removed under reduced pressure (vacuum pump) at room temperature. **Step 2.** TBAT dissolved in anhydrous DMF was added by syringe to the residue. The reaction was allowed to stir at room temperature (at 70°C for less reactive 2-amino derivatives) and monitored by TLC. When the reaction appeared to be complete (the baseline trimethylammonium salt had disappeared), the solvent was removed *in vacuo* and the product was purified by column chromatography on silica gel.

6-Fluoropurine 2'-deoxyriboside (3a). 6-Chloro-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (6-chloropurine 2'-deoxyriboside)[16] (**1a**, 50 mg, 0.185 mmol) was converted to 6-fluoro compound **3a** by the general procedure described above. **Step 1:** The reaction was carried out in a 25 ml flask with dimethoxyethane (1 ml), and trimethylamine (1 ml). The solution was stirred at room temperature for 30 min. Progress of the reaction was monitored by TLC; salt **2a** remained at the baseline. **Step 2:** TBAT (200 mg, 0.37 mmol, 2 equiv) dissolved in DMF (1.5 ml) was added. The reaction was stirred at room temperature with monitoring by TLC. After the reaction was complete (*ca.* 1 h), the solvent was removed in vacuo. Several additions and evaporations of toluene were made to remove traces of DMF. The residue was purified by chromatography on silica gel with elution by ethyl acetate to give 32 mg (68%) of **3a**.[1] TLC **2a** R_f 0; **3a** R_f 0.47 (CH_2Cl_2-MeOH, 9:1); ^{1}H NMR (300 MHz, D_2O) δ 8.52 (1 H, s, H-8), 8.48 (1 H, s, H-2), 6.47 (1 H, t, J = 6.7 Hz, H-1'), 4.51 (1 H, m, H-3'), 4.01 (1 H, ~q, J = ~3.6 Hz H-4'), 3.59-3.71 (2 H, m, H-5',5"), 2.74 (1 H, m, H-2'), 2.46 (1 H, m, H-2"). ^{19}F NMR (300 MHz, D_2O) δ -72.00.

5'-*O*-(Dimethoxytrityl)-6-fluoropurine 2'-deoxyriboside (3b). The fluorination of 5'-*O*-(dimethoxytrityl)-6-chloropurine 2'-deoxyriboside[9] (**1b**, 200 mg, 0.35 mmol) was carried out as above. **Step 1:** The reaction was carried out in a 25 ml flask with dimethoxyethane (10 ml), and trimethylamine (2 ml). The solution was stirred at room temperature for 30 min and the solvent and trimethylamine were removed *in vacuo* at room temperature. **Step 2:** TBAT (565 mg, 1.05 mmol, 3 equiv) dissolved in DMF (10 ml) was added by syringe to the residue (salt **2b**). The reaction was stirred at room temperature with monitoring by TLC. After the reaction was complete (*ca.* 2 h), the solvent was removed *in vacuo*. The product was isolated by chromatography on silica gel with isocratic elution by EtOAc/CH_2Cl_2 (7:3) to give 140 mg (72%) of **3b** as a white foam, identical spectroscopically to previously reported material.[9] TLC **2b** R_f 0; **3b** R_f 0.5 (EtOAc).

6-Fluoropurine riboside (6a). The fluorination of 6-chloropurine riboside (50 mg, 0.174 mmol) was carried out by the general procedure with the exception that DMF was used in the first step in addition to dimethoxyethane. **Step 1:** The reaction was performed in a 10 ml flask with dimethoxyethane (2 ml), anhydrous DMF (1 ml), and trimethylamine (1 ml). The solution was stirred at room temperature for 15 min. Progress of the reaction was monitored by TLC; salt **5a** remained at the baseline. When the reaction appeared complete, the solvents were removed *in vacuo* at room temperature. **Step 2:** TBAT (188 mg, 0.35 mmol, 2 equiv) dissolved in DMF (1.0 ml) was added. The reaction was stirred at room temperature with monitoring by TLC. After the reaction was complete (*ca.* 2 hrs), the solvent was removed *in vacuo*. Several additions and evaporations of toluene were made to remove traces of DMF. The residue was purified by flash chromatography on silica gel with elution by ethyl acetate-ethanol, 9:1, to give 28 mg (59 %) of **6a**.[11] TLC **5a** R_f 0; **6a** R_f 0.62 (ethyl acetate-ethanol, 9:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.93 (1 H, s, H-8), 8.73 (1 H, s, H-2), 6.06 (1 H, d, J = 5.2 Hz, H-1'), 5.60 (1 H, d, J = 5.9 Hz, OH-2'), 5.29 (1 H, d, J = 5.1 Hz, OH-3'), 5.11 (1 H, t, J = 5.4 Hz, OH-5'), 4.60 (1 H, ~q, J = ~5.3 Hz, H-2'), 4.19 (1 H, ~q, J = ~4.6 Hz, H-3'), 4.0 (1 H, ~q, J = ~3.8 Hz, H-4'), 3.69 (1H, m, H-5'), 3.58 (1H, m, H-5''). ^{19}F NMR (300 MHz, DMSO-d_6) δ -71.90.

2-Amino-6-fluoropurine riboside (6b). The conversion of 2-amino-6-chloropurine riboside (**4b**, 19 mg, 0.063 mmol) to compound **6b** was performed basically as above with a few changes as noted below. **Step 1:** The reaction was performed in a 25 ml flask with dimethoxyethane (2 ml), anhydrous DMF (1 ml), and trimethylamine (1.5 ml). The solution was stirred at room temperature for 30 min. Progress of the reaction was monitored by TLC; salt **5b** remained at the baseline. When the reaction appeared complete the solvents were removed *in vacuo* at room temperature. **Step 2:** TBAT (70 mg, 0.13 mmol, 2 equiv) dissolved in DMF (1.0 ml) was added. The reaction was vigorously stirred at 70 °C with monitoring by TLC After the

reaction was complete (*ca.* 2 h), the solvent was removed *in vacuo*. Several additions and reevaporations with toluene were made to remove traces of DMF. The residue was purified by chromatography on silica gel with elution by ethyl acetate-ethanol (5:1). Yield of **6b**:[13] 13 mg (72 %). TLC **5b** R_f 0; **6b** R_f 0.5 (EtOAc:EtOH, 9:1).^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (1 H, s, H-8), 6.99 (2 H, s, NH_2), 5.82 (1 H, d, J = 5.6 Hz, H-1'), 5.48 (1 H, d, J = 5.8 Hz, OH-2'), 5.18 (1 H, d, J = 4.5 Hz, OH-3'), 5.05 (1 H, t, J = 5.0 Hz, OH-5'), 4.48 (1 H, ~q, J = ~4.4 Hz, H-2'), 4.12 (1 H, m, H-3'), 3.91 (1 H, m, H-4'), 3.62 (1 H, m, H-5'), 3.56 (1 H, m, H-5"). ^{19}F NMR (300 MHz, DMSO-d_6) δ -71.95.

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References

1. Robins, M. J.; Basom, G. L. *Can. J. Chem.*, **1973** *51,* 3161-3169.

2. Kim, D. K.; Lee, N.; Kim, H. T.; Im, G. J.; Kim, K. H. *Bioorg. Med. Chem.*, **1999** *7,* 565-570.

3. Kim, D. K.; Chang, K.Y.; Im, G. J.; Kim, H. T.; Lee, N. K.; Kim, K. H. *J. Med. Chem.*, **1999** *42,* 324-328.

4. Kim, D. K.; Lee, N.; Im, G. J.; Kim, H. T.; Kim, K. H. *Bioorg. Med. Chem.*, **1998** *6,* 2525-2530.

5. Lakshman, M. K.; Sayer, J. M.; Jerina, D. M. *J.Am.Chem.Soc.*, **1991** *113,* 6589-6594.

6. Kim, S. J.; Harris, C. M.; Jung, K.-Y.; Koreeda, M.; Harris, T. M. *Tetrahedron Lett.*, **1991** *32,* 6073-6076.

7. Kim, S. J.; Stone, M. P.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.*, **1992** *114,* 5480-5481.

8. Harris, T. M.; Harris, C. M.; Kim, S. J.; Han, S.; Kim, H.-Y.; Zhou, L. *Polycyclic Aromat. Compds.*, **1994** *6,* 9-16.

9. Kim, S. J.; Jajoo, H. K.; Kim, H.-Y.; Zhou, L.; Horton, P.; Harris, C. M.; Harris, T. M. *Bioorg. Med. Chem.*, **1995** *3,* 811-822.

10. Kim, H.-Y.; Nechev, L.; Zhou, L.; Tamura, P.; Harris, C. M.; Harris, T. M. *Tetrahedron Lett.*, **1998** *39,* 6803-6806.

11. Kiburis, J.; Lister, J. H. *Chemical Communications,* **1969** 381.

12. Kiburis, J.; Lister, J. H. *J.Chem.Soc.(C),* **1971** 3942-3947.

13. Lister, J. H.; Kiburis, J. *Nucleic Acid Chemistry,* **1978** 639-643.

14. Robins, M. J.; Uznanski, B. *Can.J.Chem.,* **1981** *59,* 2601-2607.

15. Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.,* **1995** *117,* 5166-5167.

16. Robins, M. J.; Basom, G. L. *Nucleic Acid Chemistry,* **1978** 601-606.

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