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FACILE DIRECT CONVERSION OF AMINO-HETEROCYCLES TO FLUORO-HETEROCYCLES USING t-BUTYLTHIONITRITE OR t-BUTYLTHIONITRATE WITH SODIUM TETRAFLUOROBORATE

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Summary : Amino-nucleic acids and amino-heterocycles reacted readily with t-butylthionitrite or t-butylthionitrate in the presence of anhydrous sodium tetrafluoroborate in neutral and aprotic media to afford the corresponding fluoro-nucleic acids and fluoro-heterocycles respectively in good yields.

The modified nucleosides, nucleic acid bases, and heterocyclic compounds containing fluorine have been extensively investigated due to their potential activity as antibiotics, enzyme inhibitors, antitumor agents, and antivirus compounds. Synthesis of organic fluoro compounds has been stimulated interest in development of convenient fluorination reagent.[1,2] Although the modified Schiemann reactions[3] using diazonium salts in aqueous acidic media or anhydrous hydrogen fluoride under pressure due to the low boiling point of hydrogen fluoride have been widely used for the conversion of amino arenes into the corresponding fluoro arenes, the reaction conditions are generally vigorous and hazardous resulting in low yields.

Recently pyridinium poly(hydrogen fluoride) reagent[4] or anhydrous hydrogen fluoride-pyridine mixture[5] has been successfully used for the fluorination of amino arenes to the fluoro arenes or deaminations of amino-nucleosides and -nucleic acid bases to the fluoro-nucleosides and -nucleic acid bases. However, such reagents require polyethylene bottles or stainless steel vessels for the reactions due to the strong hazardous acidity of HF and the yields of fluorinated products are still moderate.

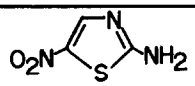
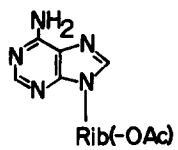
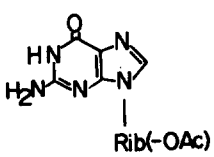
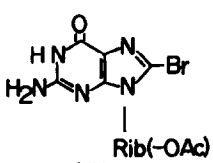
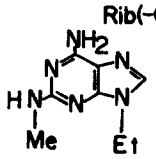
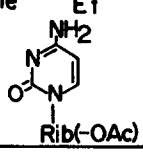
$$\text{R-NH}_2 + \underset{n=1,\,2}{\text{t-BuSNO}_n} \xrightarrow[\text{MeCN, 25 °C}]{\text{NaBF}_4} \text{R-F} + \text{N}_2 + (\text{t-Bu-})_2\text{S}_2 + \text{t-BuSO}_2\text{S-Bu-t}$$

R = Heterocycles, nucleosides, nucleic acid bases

During the course of investigations of deamination using t-butylthionitrite or t-butylthionitrate, we have found that various amino heterocycles reacted readily with either t-butylthionitrite[6] (t-BuS-N=O, 1) or t-butylthionitrate[7] (t-BuSNO$_2$, 2) in the presence of anhydrous sodium tetrafluoroborate ($NaBF_4$) under mild conditions in glass flasks to afford the corresponding fluorinated heterocycles in good yields.

Table I. Fluorination of amines with t-BuS-N=O (1) or t-BuSNO$_2$ (2) in the presence of $NaBF_4$ in acetonitrile.

$$R\text{-}NH_2 + NaBF_4 + 1 \text{ (or } 2) \xrightarrow{MeCN} R\text{-}F$$

Run	Amine	Reagent[a](1, 2)	Temp(°C)	Time(h)	Yield[b](%)	Ref.
1		1	25	5	100	8(a)
2		1	25	20	62	8(b)
3	//	2	25	20	26	
4		1	25	48	30	8(c)
5	//	2	25	15	48	
6		2	25	10	56	8(d)
7		2	25	2	50	8(e)
8		2	25	3	72	8(f)

a) Reagents (1, 2) were prepared before the use.

b) Isolated yields of the products purified by chromatography.

In general procedures, to a suspension of (2',3',5'-tri-O-acetyl)adenosine (197 mg; 0.5 mmol) and sodium tetrafluoroborate (110 mg; 1 mmol) in dry acetonitrile (4 ml) was slowly added t-butylthionitrite (1, 119 mg; 1 mmol) with stirring under argon in the dark at ca. 25 °C. After stirring for 20 h, the reaction mixture was concentrated and purified by the preparative TLC on silica gel (Merck; GF_{254}, 20 x 20 cm, eluent; CH_2Cl_2:MeOH = 15:1) to give the product of (2', 3', 5'-tri-O-acetyl)-6-fluoronebularine as an oil (123 mg; 62 %, see the ref. 8(b) and 9). The results obtained are shown in Table I. The products were identified by comparing their spectral and physical data with those from the known references.

Both the thionitrite (1) and thionitrate (2) were examined as diazotizating reagents in the fluorination reactions. The better yields obtained out of the use of 1 and 2 are listed in Table I (Runs 6, 7 and 8). When t-butylthionitrite (1) was used, the formation of t-butyldisulfide was identified as a main side product, in the case of t-butylthionitrate (2), t-butylthiosulfonate was isolated as a main side product.

Both the thionitrite (1) and thionitrate (2) are considered to be good diazotizating reagents due to their facile cleavage of S-N bonds for the deamination of aryl amines in the presence of copper (II) halides. The present fluorination reaction of amino heterocycles with 1 or 2 and sodium tetrafluoroborate appears to be initiated *via* the formation of diazonium salt following substantial fluorination. When copper (II) fluoride or sodium fluoride was used for this deamination instead of $NaBF_4$, no fluorinated product was obtained.[10]

Though the reaction mechanism is not yet clear, our new procedure for the synthesis of fluoro-heterocycles, fluoro-nucleosides, or fluoro-nucleic acid bases seems to be promising from the view of mild and neutral reaction conditions, aprotic anhydrous media and better yields than those from the known methods. The scope and reaction mechanism are under investigation.

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References and Notes

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8) (a) IR (neat) ν 1010, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.4 (s, 1H, H4); (b) oil; IR (neat) ν 2950, 1750, 1620, 1230, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (t, 9H, Ac s), 4.4 (m, 3H, H4', 5'), 5.6 (t, 1H, H3'), 5.9 (t, 1H, H2'), 6.3 (d, J=4 Hz, 1H, H1'), 8.2 (s, 1H, H8), 8.7 (s, 1H, H2); (c) oil; IR (neat) ν 1760, 1570, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (t, 9H, Ac s), 4.4 (m, 3H, H4', 5'), 5.6 (t, 1H, H3'), 6.0 (t, 1H, H2'), 6.2 (d, 1H, H1'), 8.0 (s, 1H, H8); (d) oil; ^1H NMR ($CDCl_3$) δ 2.1 (t, 9H, Ac s), 4.5-6.1 (m, 5H, ribose H s), 9.3 (br s, 1H, NH); (e) mp 175 °C (decomp.); ^1H NMR (DMSO-d_6) 1.5 (t, 3H, CCH_3), 3.5 (d, J=10 Hz, 3H, N-CH_3), 4.3 (q, 2H, NCH_2C), 7.6 (br s, 1H, NH), 8.2 (s, 1H, H8); UV (EtOH) λ_{max} 265, 295 nm; (f) oil; ^1H NMR ($CDCl_3$) δ 2.2 (t, 9H, Ac s), 4.4 (m, 3H, H4', 5'), 5.3-5.6 (m, 2H, H2',3'), 6.2 (d, J=3 Hz, 1H, H1'), 7.4 (pseudo t, J=10 Hz, 1H, H5), 7.9 (d, J=8 Hz, 1H, H6).

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10) When amino arenes and amino-nucleosides were treated with 1 or 2 in the presence of CuF_2 or NaF, the deaminated arenes and nucleosides were obtained as main products in low yields instead of fluorinated compounds.

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