167. Catalytic Effect of Tetrabutylammonium Fluoride in the Preparation of Secoribo-nucleosides

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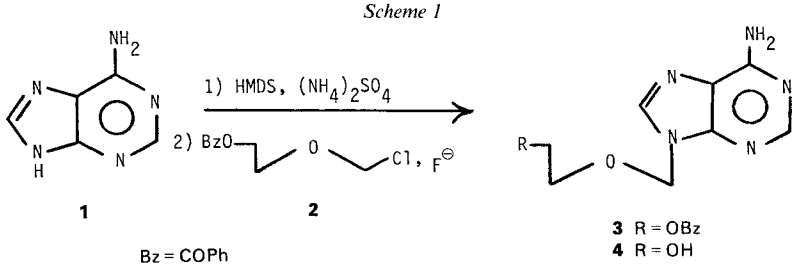
A general and rapid procedure is developed for the preparation of secoribo-nucleoside analogues. Bu_4NF has a marked effect on the condensation of guanine (**5**) with 2-(chloromethoxy)ethyl benzoate (**2**) or 1-halo-2-(chloromethoxy)ethanes **12** and **16**. Condensation and deprotection of the acyl protecting group and nucleophilic displacement of the halogen atoms to yield 9-[(2-hydroxyethoxy)methyl] guanine (**9**) occurred in one step.

Recently, we have reported the exclusive preparation of N(9)-alkylated secoribo-nucleosides which are potential antiviral drugs by condensation of silylated derivatives of nucleobases with chloromethyl ethers using an equimolar amount of Bu_4NF [1] [2]. This condensation and the deprotection of an acyl-protecting group in the ether moiety yielding the secoribo-nucleoside analogues occurred in one step. In this paper, we wish to describe a general procedure for the same reaction but involving the use of a catalytic amount of Bu_4NF.

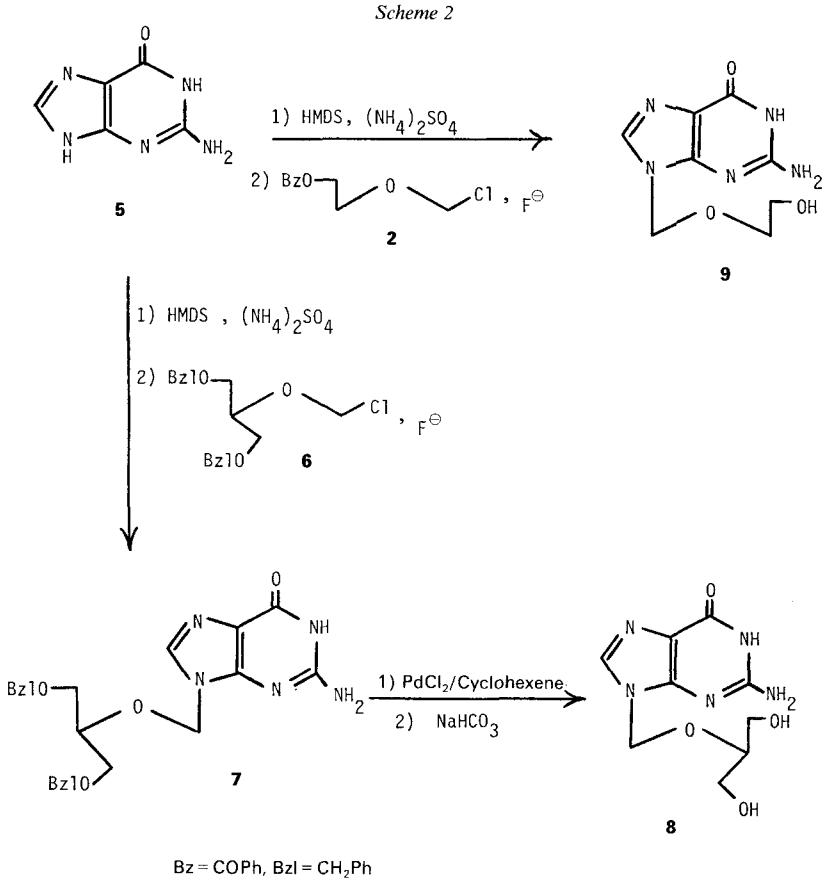
Our first approach involved the condensation of adenine (**1**) with 2-(chloro-methoxy)ethyl benzoate (**2**; *Scheme 1*). Thus, when bis(trimethylsilyl)adenine was prepared from **1** and hexamethyldisilazan (HMDS) and condensed with **2** in THF using a small amount of Bu_4NF, a fairly rapid reaction occurred. The desired product **3** was isolated in 85% yield. Treatment of **3** with $MeOH/NH_3$ at 25° gave the adenine derivative **4** (95%), identical with an authentic sample [1].

Scheme 1



Similarly, condensation of guanine (**5**) (as its tris(trimethylsilyl) derivative) with chloromethyl ether **6** in the presence of Bu_4NF as catalyst gave **7** (98%), and deprotection by catalytic transfer reduction [3] [4] afforded **8** (= BIOLF-62 [5]; 90%) *(Scheme 2)*. Using ether **2**, compound **9** (= Zovirax [6]; 92%) was prepared directly from **5**, after silylation and condensation (3 h) using Bu_4NF as catalyst *(Scheme 2)*. In the case of

Scheme 2

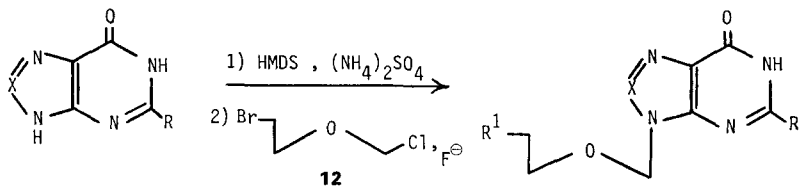


adenine (**1**), hydrolysis of the ester function occurred, after 30 h, only when 1 equiv. of Bu_4NF was used for the condensation [1].

Considering that even dried Bu_4NF contains 1–2 mol-equiv. of H_2O, the one-step condensation and deprotection of the acyl group is plausible in the presence of an equimolar amount of Bu_4NF (**1** → **4**) but rather surprising in the case of a catalytic amount of Bu_4NF (**5** → **9**). A reasonable explication would be the involvement of the NH_2 function of the guanine moiety in the ester hydrolysis.

In an attempt to clarify the scope of the Bu_4NF-catalyzed condensation, the following experiments were carried out. Guanine (**5**), hypoxanthine (**10**), and 8-azaguanine (**11**) were silylated with HMDS and coupled with 1-bromo-2-(chloromethoxy)ethane (**12**) in refluxing THF to give the secoribo-nucleosides **9** (95%), **13** *ca.* 80%, and **14** (*ca.* 80%), after 3 h, by means of catalytic Bu_4NF *(Scheme 3)*. Compound **9** was found to be identical with an authentic sample [6] [7] and was further characterized by preparing its (*tert*-butyl)dimethylsilyl derivative **15**. Moreover, the ^{1}H-NMR spectrum of **9** clearly indicates an A_2B_2 pattern for the OCH_2CH_2O moiety while the corresponding signals of **13–15** ($R^1CH_2CH_2O$) exhibit an A_2X_2 pattern.

Scheme 3



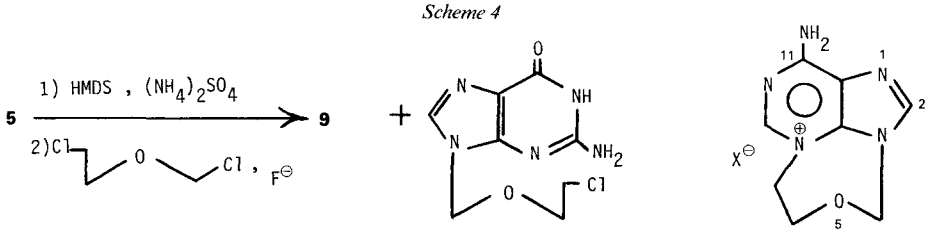
5 R = NH_2, X = CH
10 R = H, X = CH
11 R = NH_2, X = N

12

9 R^1 = OH, R = N_2, X = CH
13 R^1 = Br, R = H, X = CH
14 R^1 = Br, R = NH_2, X = N
15 R^1 = (*t*-Bu)Me_2Si, R = NH_2, X = CH

In another experiment, guanine (**5**) was silylated and condensed to 1-chloro-2-(chloromethoxy)ethane (**16**) using Bu_4NF as catalyst (*Scheme 4*). The condensation proceeded smoothly giving a 1:1 mixture **9**/**17** in high yield after 4 h. However, by prolonging the reaction time to 30 h, **9** was found to be the exclusive product. When special care was taken to run the reaction in H_2O-free solvent under a stream of N_2, **9** and **17** were obtained in a 1:3 ratio in high yield after 4 h. This ratio did not change much, even after 30 h.

Scheme 4



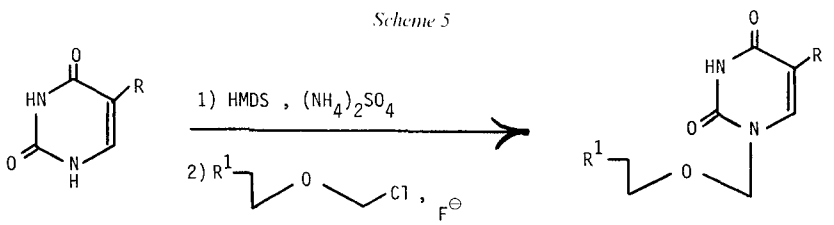
16

17

18 X = Br
19 X = Cl

The reaction of adenine (**1**) with chloromethyl ethers **12** and **16** in the presence of Bu_4NF as catalyst gave the expected products **18** and **19** (*ca.* 95%), respectively, the latter being identical with an authentic sample [8]. Finally, treatment of the silylated derivatives of uracil (**20**) and thymine (**21**) with chloromethyl ethers **12** or **16** in the presence of a small amount of Bu_4NF gave the corresponding pyrimidine secoribo-nucleosides **22–25** (*ca.* 80–90%; *Scheme 5*).

Scheme 5



20 R = H
21 R = Me

12 R^1 = Br
16 R^1 = Cl

22 R = H, R^1 = Br
23 R = Me, R^1 = Br
24 R = H, R^1 = Cl
25 R = Me, R^1 = Cl

When the reactions of *Schemes 1–5* were conducted in the absence of the F^- ion or in the presence of Bu_4NCl, they failed to produce the desired compounds. Therefore, Bu_4NF has to be considered as a novel catalyst for the high-yield preparation of secoribonucleoside analogues.

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Experimental Part

General. See [8].

General Procedure for Condensation of Nucleobases **1**, **5**, **10**, **11**, **20**, *and* **21** *with Chlormethyl Ethers* **2**, **6**, **12**, *and* **16** *Yielding* **3**, **7**, **9**, **13**, **14**, **17–19**, *and* **22–25** (Data: *Table*). *Representative Procedure* (yields 80–98%): Adenine (**1** 13.5 g, 0.1 mol) and $(NH_4)_2SO_4$ (500 mg) were suspended in hexamethyldisilazane (HMDS, 500 ml) and refluxed for 24 h. The solvent was evaporated and the residue dissolved in THF (650 ml). Bu_4NF (1 g) was dried by azeotrope distillation in benzene (80 ml) and added dropwise within 10 min at boiling temp. after the volume of the benzene soln. had been reduced to 10 ml. Then, **2** (21.5 g, 0.1 mol) was added dropwise within 15 min at the same temp. After 3 h, the soln. was diluted with AcOEt (600 ml) and H_2O (400 ml). The org. layer was separated, washed with H_2O (2 × 300 ml), dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on silica gel, and the impurities were eluted with CH_2Cl_2. Elution with AcOEt/acetone 2:1 afforded *2-[(adenin-9-yl)-methoxy]ethyl benzoate* (**3**; 85%). Data: *Table*. IR (KBr): 3400 (br.), 1725*s*, 1630*s*, 1585*m*, 1100*s*. ^{1}H-NMR ((D$_6$)DMSO): 3.85 (br. *t*, CH_2O); 4.35 (br. *t*, CH_2OCO); 5.56 (*s*, OCH_2N); 7.25–7.85 (*m*, Ph, NH_2); 8.05 (*s*, H–C(2)); 8.25 (*s*, H–C(8)). Anal. calc. for $C_{15}H_{15}N_5O_3$ (313.21): C 57.51, H 4.79, N 22.36; found: C 57.50, H 4.80, N 22.38.

Table. *Properties of Nucleoside Analogues*

Compound	M.p. [°]	λ_{max} [nm] (EtOH)	R_f (TLC)
3	120	260	0.85[a])
4	150	259	0.69[a])
7	182	252, 270 (sh)	0.42[b])
8	> 285 (dec.)	253, 272 (sh)	0.44[c])
9	> 280 (dec.)	253, 273 (sh)	0.39[b])
13	160	250	0.90[a])
14	> 275 (dec.)	254, 274 (sh)	0.50[b])
15	220	252, 271 (sh)	0.88[b])
17	260	252, 271 (sh)	0.63[b])
18	215	257.5	0.06[d])
19	225	257	0.04[d])
22	100	257	0.33[e])
23	110	264	0.30[e])
24	foam	257	0.61[e])
25	87	264	0.53[e])

[a]) CH_2Cl_2/MeOH 8:2.
[b]) AcOEt/MeOH 3:1.
[c]) i-PrOH/NH_4OH/H_2O 7:1:2.
[d]) AcOEt.
[e]) AcOEt/Et_2O 1:1.

9-[(2-Hydroxyethoxy)methyl]guanine (**9**): From **5** and **2** (92%), from **5** and **12** (95%), and from **5** and **16** (40%, along with **17** (40%) after 4 h, and 90% after 30 h). IR (nujol): 3100–3520 (br.), 1700–1720*s* (br.), 1610*s*,

1630*s*, 1110*s* (br.). ^{1}H-NMR ((D$_6$)DMSO): 3.62–3.92 (br. *s*, OCH_2CH_2O); 5.35 (*s*, OCH_2N); 6.52 (br. *s*, OH, NH_2, exchange with D_2O); 7.60 (br., NH, exchange with D_2O); 7.81 (*s*, H–C(8)). Anal. calc. for $C_8H_{11}N_5O_3$ (225.21): C 42.66, H 4.88, N 31.11; found: C 42.56, H 5.01, N 31.22.

9-[(2-Chloroethoxy)methyl]guanine (**17**): ^{1}H-NMR ((D$_6$)DMSO): 3.43–4.02 (*m*, $ClCH_2CH_2O$); 5.45 (*s*, OCH_2N); 6.61 (br., NH_2, exchange with D_2O); 7.71 (br., NH, exchange with D_2O); 7.90 (*s*, H–C(8)). Anal. calc. for $C_8H_{10}ClN_5O_2$ (243.71): C 39.42, H 4.11, Cl 14.58, N 28.75; found: C 39.38, H 4.05, Cl 14.60, N 28.81.

9-{{2-(Benzyloxy)-1-[(benzyloxy)methyl]ethoxy}methyl}guanine (**7**): ^{1}H-NMR ((D$_6$)DMSO): 3.32–3.61 (br., 2 CH_2O); 3.90–4.19 (*m*, CHO); 4.31 (*s*, 2 $PhCH_2O$); 5.55 (*s*, OCH_2N); 6.45 (br., NH_2, exchange with D_2O); 7.25 (br. *s*, 2 Ph); 7.88 (br., NH, exchange with D_2O); 7.93 (*s*, H–C(8)). Anal. calc. for $C_{23}H_{25}N_5O_4$ (435.32): C 63.45, H 5.75, N 16.09; found: C 63.43, H 5.85, N 16.18.

9-[(2-Bromoethoxy)methyl]hypoxanthine (**13**): ^{1}H-NMR ((D$_6$)DMSO): 3.20–3.50 (*m*, CH_2Br); 3.65–3.96 (*m*, CH_2O); 5.81 (*s*, OCH_2N); 7.80 (br., NH, exchanged with D_2O); 8.62 (*s*, H–C(2)); 8.78 (*s*, H–C(8)). Anal. calc. for $C_8H_9BrN_4O_2$ (273.32): C 35.16, H 3.30, Br 29.30, N 20.51; found: C 35.20, H 3.41, Br 29.18, N 20.61.

9-[(2-Bromoethoxy)methyl]-8-azaguanine (**14**): ^{1}H-NMR ((D$_6$)DMSO): 3.31–3.65 (*m*, CH_2Br); 3.70–4.08 (*m*, CH_2O); 5.83 (*s*, OCH_2N); 7.95 (br., NH, NH_2 exchange with D_2O). Anal. calc. for $C_7H_9BrN_6O_2$ (289.33): C 29.06, H 3.11, Br 27.68, N 29.06; found: C 29.26, H 3.18, Br 27.64, N 29.21.

1-[(2-Bromoethoxy)methyl]uracil (**22**): ^{1}H-NMR ($CDCl_3$): 3.22–3.60 (*m*, CH_2Br); 3.70–4.05 (*m*, CH_2O); 5.20 (*s*, OCH_2N); 5.75 (*d*, $J = 8$, H–C(5)); 7.31 (*d*, $J = 8$, H–C(6)); 10.33 (br. *s*, NH, exchange with D_2O). Anal. calc. for $C_7H_9BrN_2O_3$ (249.31): C 33.73, H 3.61, Br 32.13, N 11.24; found: C 33.85, H 3.60, Br 32.01, N 11.20.

1-[(2-Bromoethoxy)methyl]thymine (**23**): ^{1}H-NMR ($CDCl_3$): 1.91 (*s*, CH_3); 3.23–3.58 (*m*, CH_2Br); 3.69–4.01 (*m*, CH_2O); 5.21 (*s*, OCH_2N); 7.20 (*s*, H–C(6)); 10.43 (br. *s*, NH, exchange with D_2O). Anal. calc. for $C_8H_{11}BrN_2O_3$ (263.32): C 36.50, H 4.18, Br 30.42, N 10.65; found: C 36.61, H 4.19, Br 30.53, N 10.68.

1-[(2-Chloroethoxy)methyl]uracil (**24**): ^{1}H-NMR ($CDCl_3$): 3.41–4.01 (*m*, $ClCH_2CH_2O$); 5.21 (*s*, OCH_2N); 5.74 (*d*, $J = 8$, H–C(5)); 5.32 (*d*, $J = 8$, H–C(6)); 10.34 (br. *s*, NH, exchange with D_2O). Anal. calc. for $C_7H_9ClN_2O_3$ (204.63): C 41.07, H 4.40, Cl 17.36, N 13.69; found: C 41.12, H 4.51, Cl 17.40, N 13.71.

1-[(2-Chloroethoxy)methyl]thymine (**25**): ^{1}H-NMR ($CDCl_3$): 1.90 (*s*, CH_3): 3.50–4.11 (*m*, $ClCH_2CH_2O$); 5.22 (*s*, OCH_2N); 7.21 (*s*, H–C(6)); 9.99 (br. *s*, NH, exchange with D_2O). Anal. calc. for $C_8H_{11}ClN_2O_3$ (218.64): C 43.93, H 5.03, Cl 16.25, N 12.81; found: C 43.91, H 5.13, Cl 16.30, N 12.95.

11-Amino-6,7-dihydro-4H-[1,3,5]oxadiazepino[3,4,5-cd]purin-8-ium Bromide (**18**): ^{1}H-NMR ((D$_6$)DMSO): 3.79 (*s*, NCH_2CH_2O); 5.67 (*s*, OCH_2N); 7.68 (br. *s*, NH_2, exchange with D_2O); 8.30 (*s*, H–C(2)); 8.40 (*s*, H–C(8)). Anal. calc. for $C_8H_{10}BrN_5O$ (272.32): C 35.29, H 3.67, Br 29.41, N 25.73; found: C 35.32, H 3.70, Br 29.31, N 25.90.

19: Identical with the authentic sample [8].

9-[(2-Hydroxyethoxy)methyl]adenine (**4**): To a soln. of **3** (3.13 g, 0.01 mol) in MeOH (50 ml), 150 ml of sat. NH_3/MeOH were added. The flask was sealed and maintained at 25° for 24 h. The mixture was concentrated to 5 ml, and Et_2O (50 ml) was added to afford **4** as a white precipitate. Filtration gave **4** (95%), identical with an authentic sample [1]. Data: *Table*.

9-{[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl}guanine (**8**). To a soln. of **7** (5.20 g, 0.012 mol) in refluxing EtOH (280 ml), cyclohexene (200 ml) and $PdCl_2$ (3.5 g) were added, and refluxing was continued for 5 h. The soln. was collected by filtration and the catalyst washed with hot DMF (5 ml) and 3% aq. $NaHCO_3$ soln. (10 ml). The filtrate and washings were evaporated, and the residue was dissolved in hot EtOH/H_2O (100 ml) and filtered. The solvent was evaporated and the residue crystallized from EtOH/H_2O 4:1 to afford **8** (90%), identical with an authentic sample [9]. Data: *Table*.

9-{{2-[(tert-Butyl)dimethylsilyloxy]ethoxy}methyl}guanine (**15**). To a soln. of **9** (2.25 g, 0.01 mol) in DMF (50 ml), imidazol (2.04 g, 0.03 mol) and (*t*-Bu)Me_2SiCl (3.20 g, 0.02 mol) were added, the mixture was stirred for 48 h at 25° and then poured into H_2O (100 ml). The aq. soln. was extracted with AcOEt, and the extract was dried (Na_2SO_4), filtered, and evaporated. The residue was applied to a column of silica gel and **15** (97%) was eluted with AcOEt/MeOH 9:1 as a white precipitate. Data: *Table*. ^{1}H-NMR ((D$_6$)DMSO): 0.12 (*s*, $(CH_3)_2Si$); 0.91 (*s*, $(CH_3)_3C$); 3.30–3.78 (*m*, CH_2O); 3.80–4.28 (*m*, CH_2OSi); 5.45 (*s*, OCH_2N); 6.70–7.0 (br., NH_2, NH, exchange with D_2O); 7.90 (*s*, H–C(8)).

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