Selective Alkylation and Aralkylation of Cytosine at the 1-Position

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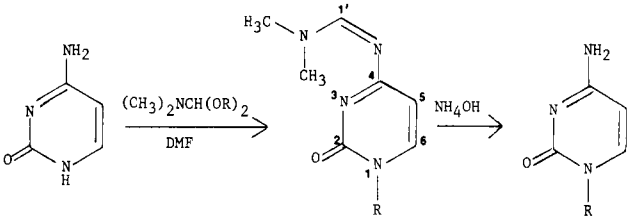
Our interest in 1-substituted cytosines stems from a spectrum of intriguing properties of these compounds such as their ability to serve as inhibitors of deoxycytidine kinase,[1,2] complementary base pairing with a 9-substituted guanine,[3,4] interpyrimidine base stacking and asymmetric interbase hydrogen bonding,[5] peptidyl transferase activity,[6] and spectroscopic detection of restricted rotation of the extranuclear amino function,[7] and, more importantly, to serve as precursors to many highly soluble, short-acting, potent antibacterials such as sulfacytine (i.e., 1-ethyl-N^4-sulfanilylcytosine).[8] Our experience with 1-alkylation of cytosine[9-11] coupled with the lack of availability of 1-alkylcytosines except by custom order led us to seek a better and more convenient approach to alkylation and aralkylation at the 1-position of cytosine.

The published procedures for the synthesis of 1-substituted cytosines suffer from a variety of problems—poor yields, multiple products, multi-step sequences, and/or isomer separation: (a) direct alkylation of cytosine employing dialkyl sulfates,[12,13] trialkyl phosphates,[14-16] or alkyl halides,[1,17] (b) cyclization of 1-alkyl-1-(2-cyanoethyl)ureas[18] or of ethoxyacrylamides with alkylamines,[19] and (c) rearrangement of 4-amino-2-alkoxypyrimidine by pyrolysis.[20]

We have now extended the 1-alkylation method that we recently communicated for the synthesis of 1-methylcytosine.[21] The method, which involves the reaction of cytosine with *N,N*-dimethylformamide dimethyl acetal (1,1-dimethoxy-*N,N*-dimethylmethanamine) followed by hydrolysis, required modification to be applied with the same efficiency to the synthesis of other alkylcytosines. In the first step, cytosine (1) is caused to react with an



1 2 3

excess of the appropriate *N,N*-dimethylformamide dialkyl acetal (1,1-dialkoxy-*N,N*-dimethylmethanamine) (5 molar equiv) in anhydrous *N,N*-dimethylformamide (4–5 equiv). With the use of DMF as cosolvent, acid catalysis[21] is not required, and product isolation is simplified. Best results are obtained when dry cytosine and dry reaction vessels are used. The corresponding 1-substituted N^4-[(dimethylamino)methylene]cytosines (**2**) are obtained in nearly quantitative yields (Table I) after a heating period of 24 h under nitrogen. Reaction pathways for alkylations involving dimethylformamide acetals are well documented.[22-26] Compounds of type **2** are hydrolyzed directly and almost quantitatively with concentrated ammonium hydroxide[21] to the corresponding 1-substituted cytosines (**3**) listed in Table I. The intermediates (**2**) could also be obtained analytically pure (in slightly lower yield) by recrystallization from the solvents indicated. The physicochemical data for the final products (**3**) are in close agreement with reported values. This facile and general method is applicable to large-scale preparation of 1-substituted cytosines. The intermediates **2** need not be purified but can be used directly in the hydrolysis step.

Experimental Section

Melting points were determined on a Büchi or a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H nuclear magnetic resonance spectra were recorded on a Varian EM-390 spectrometer operating at 90 MHz and using tetramethylsilane as an internal standard. Mass spectra were run on a Varian MAT CH-5 low-resolution spectrometer coupled with a 620i computer and a STATOS recorder. Microanalyses were performed by Mr. Josef Nemeth and his staff. Cytosine was purchased from Sigma Chemical Co., *N,N*-dimethylformamide dimethyl, diethyl, and dipropyl acetals were obtained from Aldrich Chemical Co., and *N,N*-dimethylformamide diallyl, dibutyl, and dibenzyl acetals were obtained from Tridom Chemical Co.

General Procedure for the Preparation of 1-Substituted N^4-[(Dimethylamino)methylene]cytosines (2). A mixture of dry cytosine (1 g, 9 mmol), *N,N*-dimethylformamide dialkyl (diaralkyl) acetal (45–80 mmol), and dry *N,N*-dimethylformamide (3–20 mL) was heated at 90 °C to reflux under nitrogen for 24 h. The reaction mixture was cooled and evaporated to dryness on a rotary evaporator at 60 °C in vacuo, and the solid obtained

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Table I. 1-Substituted N^4-[(Dimethylamino)methylene]cytosines (2) and 1-Substituted Cytosines (3)

	compd 2				compd 3			
R	yield,[a] %	solvent of recryst	molec formula[b]	mp, °C	yield, %	solvent of recryst	molec formula	mp, °C
a methyl	99	benzene-chloroform	$C_8H_{12}N_4O$	203-204[21]	98	MeOH-petroleum ether	$C_5H_7N_3O$	301-302 dec (lit.[26] 300-302)
b ethyl	99	benzene-petroleum ether	$C_9H_{14}N_4O$	147-148	99	H_2O	$C_6H_9N_3O$	244-246 (lit.[8] 245-247)
c propyl	99	toluene-petroleum ether	$C_{10}H_{16}N_4O$	142-143	96	*f*	$C_7H_{11}N_3O$	256-257.5 (lit.[8] 256-258)
d butyl	98	AcOEt-petroleum ether	$C_{11}H_{18}N_4O$	122-123	96	MeOH	$C_8H_{13}N_3O$	231-233 (lit.[8] 229-231)
e allyl	96	toluene	$C_{10}H_{14}N_4O$	133-134	99	*f*	$C_7H_9N_3O$	250.5-252 (lit.[8] 232-236)[g]
f benzyl[c]			$C_{14}H_{16}N_4O$[d]	192-193	96[e]	*f*	$C_{11}H_{11}N_3O$	300-301 dec (lit.[1] 301-303)

[a] Yield of isolated product before purification. [b] Satisfactory analytical data (±0.4% for C, H, and N) were obtained for all new compounds listed in the table. [c] The first two attempts gave 1-benzylcytosine directly in overall yields of 74% and 88%. A third attempt gave compound **2f** in 36% yield. [d] The crude product gave acceptable microanalyses, thus obviating recrystallization. [e] Hydrolysis of **2f** with concentrated ammonium hydroxide required initial gentle warming to achieve solution. [f] Physicochemical properties of the crude products were in close agreement with the literature values, thus eliminating the need for recrystallization. [g] The literature value is based upon a sample with an estimated 4.5% inert impurity.

was recrystallized from the appropriate solvent listed in Table I.

General Procedure for the Hydrolysis of Compounds of Type 2 to 1-Substituted Cytosines (3). A mixture of **2** (0.5 mmol) and concentrated ammonium hydroxide solution (10 mL) was stirred at room temperature for 17 h and then heated on a steam bath for 30 min to drive off excess ammonia. The solution was evaporated to dryness on a rotary evaporator, and the solid residue obtained was recrystallized from the appropriate solvent listed in Table I.

Spectroscopic Data. **N^4-[(Dimethylamino)methylene]-1-methylcytosine (2a)** has been described.[21] The conditions used in the present paper work equally well.

N^4-[(Dimethylamino)methylene]-1-ethylcytosine (2b): ^{1}H NMR ($(CD_3)_2SO$) δ 1.12 (t, *J* = 7.5 Hz, 3, CH_2CH_3), 3.04 (s, 3, $N(CH_3)_2$), 3.16 (s, 3, $N(CH_3)_2$), 5.88 (d, *J* = 7.5 Hz, 1, 5-H), 7.58 (d, *J* = 7.5 Hz, 1, 6-H), 8.58 (s, 1, 1′-H); mass spectrum (70 eV), *m/e* (relative intensity) 194 (M^+, 36), 151 ($M^+ + 1 - N(CH_3)_2$, 26), 150 ($M^+ - N(CH_3)_2$, 100), 122 ($M^+ - N(CH_3)_2 - CH_2CH_3$, 31), 111 (35), 44 ($N(CH_3)_2^+$, 84), 42 (61), 28 (57).

N^4-[(Dimethylamino)methylene]-1-propylcytosine (2c): ^{1}H NMR ($(CD_3)_2SO$) δ 0.82 (t, *J* = 7.5 Hz, 3, CH_2CH_3), 1.61 (m, *J* = 6.0, 7.5 Hz, 2, $CH_2CH_2CH_3$), 3.10 (s, 3, $N(CH_3)_2$), 3.20 (s, 3, $N(CH_3)_2$), 3.67 (t, *J* = 7.5 Hz, 2, $CH_2CH_2CH_3$), 5.87 (d, *J* = 7.5 Hz, 1, 5-H), 7.73 (d, *J* = 7.5 Hz, 1, 6-H), 8.59 (s, 1, 1′-H); mass spectrum (70 eV), *m/e* (relative intensity) 208 (M^+, 58), 166 ($M^+ + 1 - C_3H_7$, 42), 165 ($M^+ - C_3H_7$, 27), 164 ($M^+ - N(CH_3)_2$, 100), 151 (37), 123 (21), 122 ($M^+ + 1 - N(CH_3)_2 - C_3H_7$, 53), 44 ($N(CH_3)_2^+$, 63), 43 (35), 42 (37).

1-Butyl-N^4-[(dimethylamino)methylene]cytosine (2d): ^{1}H NMR ($(CD_3)_2SO$) δ 0.89 (t, *J* = 7.5 Hz, 3, $(CH_2)_3CH_3$), 1.37 (m, 4, $CH_2CH_2CH_2CH_3$), 3.0 (s, 3, $N(CH_3)_2$), 3.13 (s, 3, $N(CH_3)_2$), 3.69 (t, *J* = 7.5 Hz, 2, $CH_2(CH_2)_2CH_3$), 5.85 (d, *J* = 7.5 Hz, 1, 5-H), 7.74 (d, *J* = 7.5 Hz, 1, 6-H), 8.58 (s, 1,1′-H); mass spectrum (70 eV), *m/e* (relative intensity) 222 (M^+, 79), 178 ($M^+ - N(CH_3)_2$, 100), 166 ($M^+ + 1 - C_4H_9$, 43), 151 (65), 122 ($M^+ + 1 - N(CH_3)_2 - C_4H_9$, 79), 112 (56), 57 ($C_4H_9^+$, 49), 45 (40), 44 ($N(CH_3)_2^+$, 98), 42 (48), 41 (57).

1-Allyl-N^4-[(dimethylamino)methylene]cytosine (2e): ^{1}H NMR ($(CD_3)_2SO$) δ 3.05 (s, 3, $N(CH_3)_2$), 3.19 (s, 3, $N(CH_3)_2$), 4.36 (d, *J* = 4.5 Hz, 2, $CH_2CH{=}CH_2$), 5.10 (dd, *J* = 10.5, 1.8 Hz, 2, $CH_2CH{=}CH_2$), 5.92 (m, 1, $CH_2CH{=}CH_2$), 5.92 (d, *J* = 7.5 Hz, 1, 5-H), 7.70 (d, *J* = 7.5 Hz, 1, 6-H), 8.60 (s, 1,1′-H); mass spectrum (70 eV), *m/e* (relative intensity) 206 (M^+, 53), 162 ($M^+ - N(CH_3)_2$, 100), 44 ($N(CH_3)_2^+$, 54), 42 (52), 41 ($C_3H_5^+$, 81).

1-Benzyl-N^4-[(dimethylamino)methylene]cytosine (2f): ^{1}H NMR ($(CD_3)_2SO$) δ 3.0 (s, 3, $N(CH_3)_2$), 3.14 (s, 3, $N(CH_3)_2$), 4.90 (s, 2, $CH_2C_6H_5$), 5.90 (d, *J* = 7.5 Hz, 1, 5-H), 7.29 (s, 5, $CH_2C_6H_5$), 7.83 (d, *J* = 7.5 Hz, 1, 6-H), 8.59 (s, 1, 1′-H); mass spectrum (70 eV), *m/e* (relative intensity) 256 (M^+, 42), 212 ($M^+ - N(CH_3)_2$, 23), 91 ($C_7H_7^+$, 30), 44 ($N(CH_3)_2^+$, 18).

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Registry No. 1, 71-30-7; **2a**, 77738-01-3; **2b**, 79044-10-3; **2c**, 79044-11-4; **2d**, 79044-12-5; **2e**, 79044-13-6; **2f**, 79044-14-7; **3a**, 1122-47-0; **3b**, 25855-37-2; **3c**, 22919-46-6; **3d**, 25855-40-7; **3e**, 25855-43-0; **3f**, 60722-54-5; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; *N,N*-dimethylformamide diethyl acetal, 1188-33-6; *N,N*-dimethylformamide dipropyl acetal, 6006-65-1; *N,N*-dimethylformamide diallyl acetal, 61296-25-1; *N,N*-dimethylformamide dibutyl acetal, 18503-90-7; *N,N*-dimethylformamide dibenzyl acetal, 2016-04-8.

Selective Halogen-Lithium Exchange in Some Secondary and Tertiary (Bromophenyl)alkyl Halides[1]

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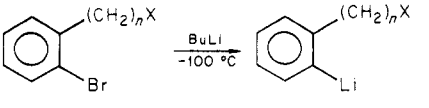
Parham et al.[3] discovered that when each of certain primary (*o*-bromophenyl)alkyl halides (1) is treated with



1	2
a, *n* = 1; X = Cl	a, *n* = 1; X = Cl
b, *n* = 2; X = Br	b, *n* = 2; X = Br
c, *n* = 3; X = Br	c, *n* = 3; X = Br
d, *n* = 3; X = Cl	d, *n* = 3; X = Cl

butyllithium at −100 °C there ensues a preferential halogen–lithium exchange of the *aryl* halogen. The resulting

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