A Convenient One-Pot Synthesis of Acyclonucleosides

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Bis(trimethylsilyl)pyrimidine bases were treated directly with 1,3-dioxolane (or 2-methyl-1,3-dioxolane), chlorotrimethylsilane and a metal iodide, such as KI or NaI, in acetonitrile at room temperature to afford acyclopyrimidine derivatives, including 2-thiopyrimidine derivatives, in good yields. Introduction of an acyclic chain into 2-thiopyrimidine bases, however, necessitated the use of 2 eq of the reagents.

Keywords acyclonucleoside; 1,3-dioxolane; chlorotrimethylsilane; metal iodide; 2-thiopyrimidine

Acyclonucleosides are of interest because of their significant antiviral activities.[1,2] Recently we found that 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) analogues were potent inhibitors of human immunodeficiency virus-1 (HIV-1) replication.[3] A number of synthetic approaches to introduce an acyclic chain into heterocyclic bases have been reported.[4] Keyser *et al.* reported that iodomethyl [(trimethylsilyl)oxy]ethyl ether (**2**), which was prepared just before use from 1,3-dioxolane (**1**) and iodotrimethylsilane at $-78\,^{\circ}C$ under N_2, efficiently reacted with the sodium salt of 6-chloropurine (**3**) or 4-methylthio-2-pyrimidone (**4**) at $-63\,^{\circ}C$ (Chart 1).[5] However the reagent is extremely sensitive to moisture and temperature.[6]

We have developed a simpler and more convenient method for the synthesis of acyclopyrimidines, using silylated pyrimidine bases instead of the sodium salt (**4**). The method rarely requires careful control of moisture and temperature.

Results and Discussion

Initially, we tried to synthesize 1-[(2-hydroxyethoxy)-methyl]thymine[7] (**10b**), using bis(trimethylsilyl)thymine (**8b**) with 1,3-dioxolane (**1**) and iodotrimethylsilane in acetonitrile at room temperature (Chart 2). A satisfactory yield was obtained after 16 h (98% peak area on HPLC).

Iodotrimethylsilane, however, is extremely sensitive to moisture and is expensive for industrial use. We therefore tried to use chlorotrimethylsilane with metal iodides, such as KI or NaI, instead of iodotrimethylsilane. The reaction proceeded at room temperature for 16 h, and resulted in almost the same yield on HPLC analysis.

This method was also applied to 2-thiopyrimidine bases. Introduction of an acyclic chain into such bases is often accompanied with many difficulties, as Kim and Kim noted.[8] Bis(trimethylsilyl)-2-thiothymine (**8f**) was allowed to react with equimolar 1,3-dioxolane, chlorotrimethylsilane and KI at room temperature. Even after 16 h of stirring, a fairly large amount of the starting material (**7f**) remained. On HPLC analysis of the reaction mixture, an unknown peak was observed, other than the starting material and the product (**10f**). When the reaction was quenched with methanol before HPLC analysis (the methanol solution was very acidic), the unknown peak disappeared and the peak of the starting material became higher. To push the reaction further, an additional amount of the reagents was supplied and the mixture was stirred for another 16 h. The above-mentioned unknown peak was lower this time, but an another new unknown peak appeared. The new unknown material was converted into the desired product by quenching with methanol. The highest yield was achieved when 2 eq of 1,3-dioxolane, chlorotrimethylsilane and metal iodide was used.

It is plausible to imagine that the alkylating reagent might attack first the sulphur atom and then the N-1 position of 2-thiothymine. The alkyl group on the 2-S atom should be easily hydrolyzed under acidic conditions. Alkylation of silylated 2-thiopyrimidine bases with

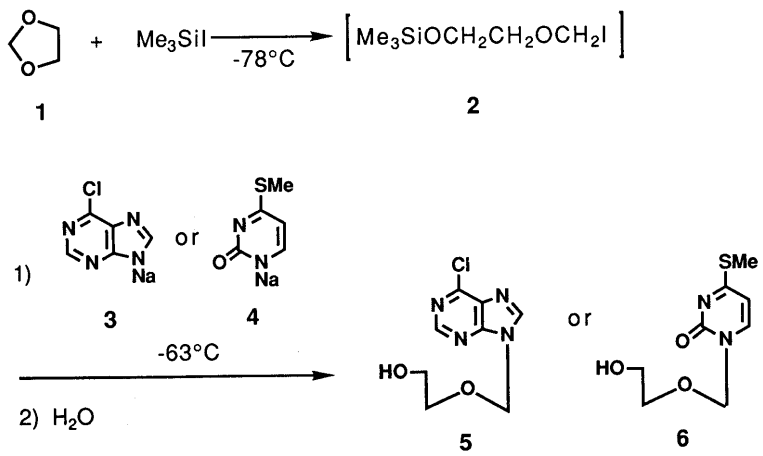

Chart 1

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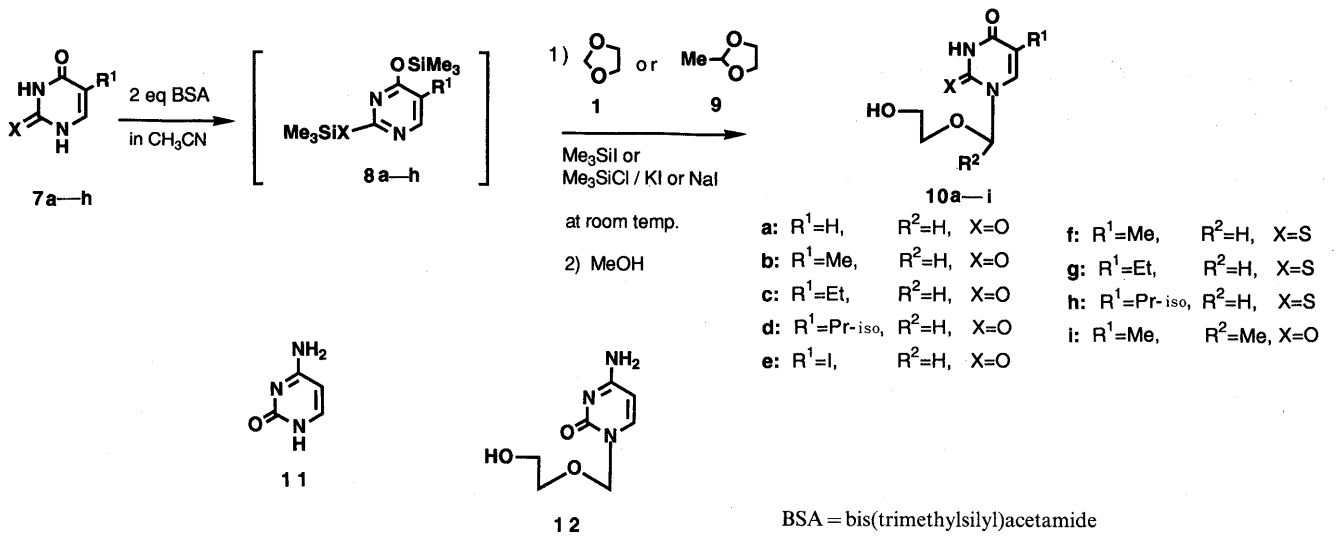

Chart 2

TABLE I. Introduction of an Acyclic Chain to Pyrimidine Bases

Starting material	Reagents		Product	Isolated yield (%)	Reference
7b	1,3-Dioxolane/Me_3SiCl/KI	(1 eq)	**10b**	73.8	7
7b	1,3-Dioxolane/Me_3SiCl/NaI	(1 eq)	**10b**	72.1	7
7a	1,3-Dioxolane/Me_3SiCl/KI	(1 eq)	**10a**	59.0	7
7c	1,3-Dioxolane/Me_3SiCl/KI	(1 eq)	**10c**	86.0	10
7d	1,3-Dioxolane/Me_3SiCl/KI	(1 eq)	**10d**	88.0	11
7e	1,3-Dioxolane/Me_3SiCl/KI	(1 eq)	**10e**	63.0	7
7b	2-Me-1,3-Dioxolane/Me_3SiCl/KI	(1 eq)	**10i**	64.0	12
7f	1,3-Dioxolane/Me_3SiCl/KI	(2 eq)	**10f**	64.5	3
7g	1,3-Dioxolane/Me_3SiCl/KI	(2 eq)	**10g**	80.0	
7h	1,3-Dioxolane/Me_3SiCl/KI	(2 eq)	**10h**	79.0	
11	1,3-Dioxolane/Me_3SiCl/KI	(1 eq)	**12**	63.1	7

ethoxymethyl chloride/KI or acetoxyethoxymethyl bromide[6] also required 2 eq of the reagent.[9]

Several acyclopyrimidine nucleosides synthesized in this way are listed in Table I.

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus, and were not corrected. ^{1}H-NMR spectra were recorded at 250 MHz on a AC-250 Bruker NMR spectrometer using tetramethylsilane as the internal standard; chemical shifts are recorded in parts per million (ppm). UV spectra were recorded on a Shimadzu UV-260 spectrophotometer. Mass spectra were taken on a Hitachi M-80A spectrometer. Silica gel column chromatography was carried out on Wakogel C-300. HPLC analyses were performed on a Shimadzu LC-10A equipped with a stainless-steel column (Inertsil ODS-2, 5 μm, 4.6 × 150 mm, GL Sciences inc.) and an UV detector set at 270 nm.

General Method for Preparation of Acyclonucleoside Derivatives A pyrimidine base (10 mmol) was suspended in 15 ml of acetonitrile and stirred with 5.4 ml (22 mmol) of bis(trimethylsilyl)acetamide to obtain a clear solution. To this solution, 0.7 ml (10 mmol) of 1,3-dioxolane (or 2-methyl-1,3-dioxolane (**9**)), 1.7 g (10 mmol) of potassium iodide (or sodium iodide) and 1.38 ml (10 mmol) of chlorotrimethylsilane were added. For 2-thiopyrimidine derivatives, 2 eq of the reagents was used. The mixture was stirred for 16 h at room temperature and checked by HPLC with acetonitrile–water (7:93, v/v) as the eluent. The reaction was quenched by the addition of 20 ml of methanol followed by neutralization with 4 g of sodium bicarbonate. The solid materials were removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The residual solid was applied on a silica gel column and the products were eluted with chloroform–methanol (95:5, v/v). The desired fractions were concentrated and the product was crystallized from an appropriate solvent.

5-Ethyl-1-[(2-hydroxyethoxy)methyl]-2-thiouracil (10g) mp 114—116 °C (crystallized from 2-butanone). UV $\lambda_{max}^{methanol}$ nm: 280 (ε=18000). MS *m/z*: 230 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7.5 Hz, 5-$CH_2\underline{CH_3}$), 2.42 (2H, dq, J=1.0 Hz, 7.5 Hz, 5-$C\underline{H_2}CH_3$), 3.80 (4H, aps, OCH_2CH_2O), 5.68 (2H, s, NCH_2O), 7.30 (1H, t, J=1.0 Hz, 6-H), 9.91 (1H, br, NH). *Anal.* Calcd for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.16. Found: C, 46.74; H, 6.27; N, 12.06

1-[(2-Hydroxyethoxy)methyl]-5-isopropyl-2-thiouracil (10h) mp 126.5—127.5 °C (crystallized from ethanol–water). UV $\lambda_{max}^{methanol}$ nm: 280 (ε=17000). MS *m/z*: 244 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.19 [6H, d, J=6.9 Hz, 5-CH($C\underline{H_3}$)$_2$], 2.93 [1H, dqq, J=0.8, 6.9 Hz, 5-$C\underline{H}$(CH_3)$_2$], 3.80 (4H, aps, OCH_2CH_2O), 5.67 (2H, s, NCH_2O), 7.23 (1H, d, J=0.8 Hz, 6-H), 9.40 (1H, br, NH). *Anal.* Calcd for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.47. Found: C, 49.06; H, 6.59; N, 11.24

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