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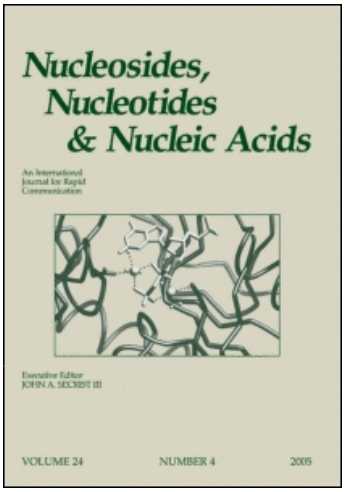

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Some Aspects on Acyclonucleoside Synthesis

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SOME ASPECTS ON ACYCLONUCLEOSIDE SYNTHESIS

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ABSTRACT: An acyclonucleoside synthesis was investigated on the regioselective introduction of an acyclochain. We found that iodotrimethylsilane catalyzed the reaction of acyclochain introduction as well as its migration from S^2 to N^1 of 2-thiothymine and from N^7 to N^9 position of guanine. By taking the findings into account, several acyclonucleosides were synthesized in a simple one-pot procedure.

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INTRODUCTION: Acyclonucleosides are highly attractive compounds 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 HIV-1 replication.[3)] In the course of our developing the related compounds, 2-thiouracil derivatives aroused our interest in the regioselective introduction of an acyclochain.

Previously we have reported a convenient one-pot synthesis of acyclopyrimidines, where a silylated base was treated at room temperature with dioxolane, chlorotrimethylsilane (TMSCl) and KI (or NaI) all together in a reaction medium.[4)] This method, when it is applied to 2-thiouracil derivatives, requires 2 eq of the alkylating agent and gives a transient intermediate with two acyclochains. The one is on the S^2 atom and the other on the N^1 position of 2-thiouracil. The S^2-alkyl group is easily hydrolyzed under acidic condition, which results in a desired product with N^1-acyclochain.

Kim et al.[5)] reported a method that was efficient for a regioselective alkylation at the N^1 position of 2-thiopyrimidines, and that required no more than equimolar amount

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of the alkylating agent. Nevertheless, the reproducibility of their method was invariably poor. However, that led us to find some interesting phenomena, as will be described here.

RESULTS & DISCUSSION: The Kim's procedure worked for thymine **(1)** when hexamethyldisilazane (HMDS) and ammonium sulphate was used for silylation followed by alkylation with 2-acetoxyethyl acetoxymethyl ether and CsI, to afford 1-[(2-acetoxyethoxy)methyl]thymine **(2)**. Whereas, what was recovered from the reaction with bis-(trimethylsilyl)acetamide (BSA) as a silylating agent and with the same alkylating agents was the starting material **(1)** alone. However, a catalytic amount of ammonium sulphate added into the BSA-treated medium did yield the desired product **(2)**[6]. In these reactions, both KI and NaI were practical alternatives to CsI. In the absence of such metal iodides the reaction does not occur at all. (**Scheme 1**) These observations suggested to us that, contrary to Kim's speculation, CsI might not catalyze the alkylation directly but changes *per se* into a certain active catalytic species by contact with ammonium sulphate. It is plausible to imagine that in the presence of ammonium sulphate combination of a silylating agent (HMDS or BSA) and CsI (KI or NaI) could generate iodotrimethylsilane (TMSI), which then may act as a real catalyst. D. C. Humber et al. reported that TMSI worked as a Lewis catalyst to activate acetoxyoxathiolane for synthesis of 3TC.[7]

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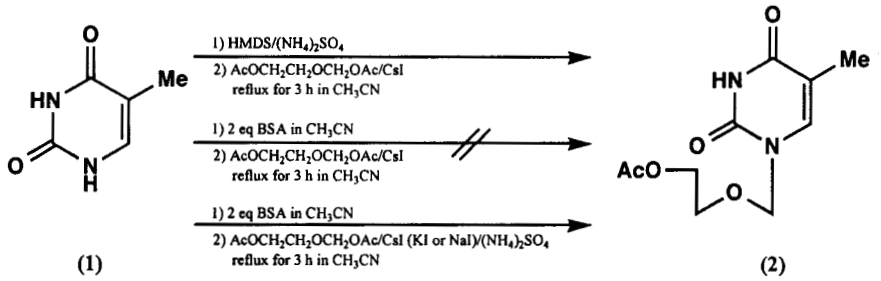
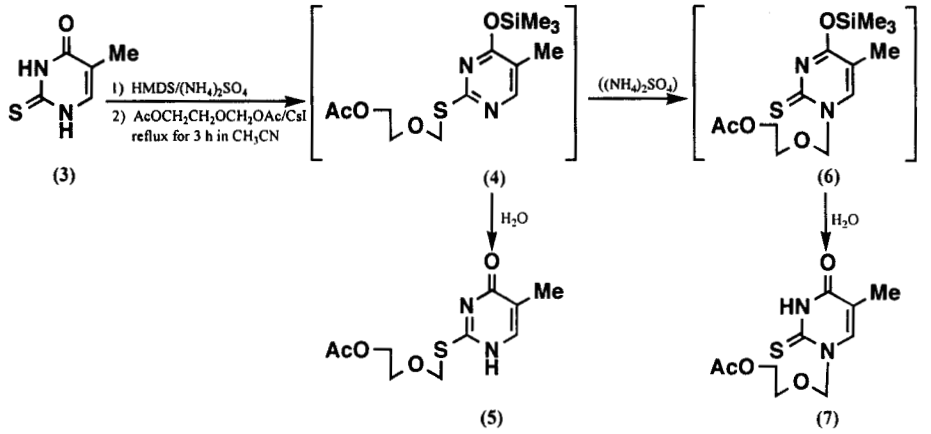
In fact, the mass spectrometry analysis confirmed the existence of TMSI in the reaction mixture of HMDS (or BSA), CsI (or KI) and ammonium sulphate. Another evidence is that silylated thymine was satisfactorily alkylated with TMSI used instead of CsI and ammonium sulphate.

When we pursued the Kim's method to synthesize 1-[(2-acetoxyethoxy)methyl]-2-thiothymine **(7)**, the HPLC analysis of the products showed a main peak (73% of total peak area) and a minor peak (2% of total peak area). Contrary to their findings, it turned out that the main product was not the desired one but 2-[[(2-acetoxyethoxy)methyl]thio]-5-methyl-4(1H)-pyrimidinone **(5)** (isolation yield was 40.3%), and the minor product was 1-[(2-acetoxyethoxy)methyl]-2-thiothymine **(7)**[8] (isolation yield was 4.6%). (**Scheme 2**) The structure of the compound **(5)** was determined by the NMR data including HMBC



Scheme 1



Scheme 2

and NOESY, as illustrated in **FIG. 1**. The compound **(5)** was very labile under acidic condition, and easily turned to the starting material, 2-thiothymine. The compound **(7)** was ascertained by the reaction with hydrogen peroxide in alkali solution[9] to afford 1-[(2-hydroxyethoxy)methyl]thymine[10].

The reaction medium in which the S^2-substituted intermediate **(4)** had been formed was kept heating, and the acyclochain gradually migrated to the N^1 position (30% after 40 h and no more progress). Instead of long-time reflux, a catalytic amount of ammonium sulphate considerably accelerated the migration (ca. 86% yield in 8 h).

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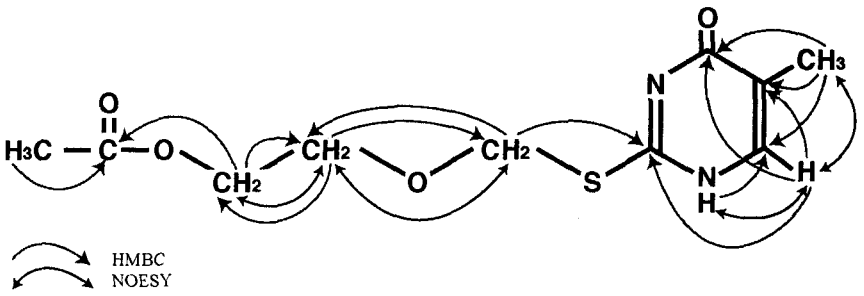

FIG. 1 Correlation observed in HMBC and NOESY of the compound (5).

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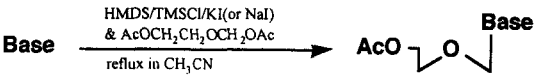
As described above, when BSA was used as a silylating agent for thymine, the acyclochain was not introduced at all, if ammonium sulphate was not added. 2-Thiothymine, however, was certainly alkylated without ammonium sulphate but on the S^2-position. The S^2-alkylation proceeded rather slowly (48 h). The reasonable yield of the compound (7) was not obtained until N-silylacetamide derived from BSA was not evaporated before addition of ammonium sulphate. The excess TMSI that may have formed from N-silylacetamide would disturb the migration.

The mechanism of the migration seems that the S^2-acyclochain is cleaved with TMSI to release (2-acetoxyethoxy)methyl iodide, which then reacts with the silylated base to yield thermodynamically stable N^1-substituted 2-thiothymine.

An advantage of the Kim's method is that, when the procedure is applied on purine bases, the main product is a N^9-isomer in compare with the other methods which usually give half mixture of N^7- and N^9-isomers. The mechanism of its regioselectivity must be in accord with our findings that the acyclochain migrates from S^2 to N^1 of 2-thiothymine in the presence of TMSI. Then we tried to synthesize the acycloguanine using TMSI instead of CsI and ammonium sulphate, and observed that guanine was alkylated at the N^7 position first at room temperature and then the acyclochain migrated to the N^9 position under heating condition.

By taking account of the above results, we offer a one-pot procedure: the two reactions, the silylation and the acyclochain introduction, proceed sequentially in a single



Scheme 3

TABLE The results of acyclonucleoside synthesis using the convenient method.

	HMDS (eq.)	TMSCl (eq.)	KI (eq.)	Ether (eq.)	Reaction Time (h)	Isolated Yields(%)	N^9:N^7	ref.
Thymine	0.7	1.0	1.0	1.2	1	84.2		6
Cytosine	0.7	1.0	1.0	1.2	2	78.0		6
2-Thiothymine	1.0	1.0	1.0	1.2	3	81.0		8
Adenine	1.1	1.5	1.5	1.7	19	51.4	$N^9 \fallingdotseq$ 100%	6
Guanine	1.4	2.0	2.0	1.2	4	70.5	20:1	11

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system. That is just heating all reagents, namely a base, HMDS, TMSCl, KI or NaI, and 2-acetoxyethyl acetoxymethyl ether, together in acetonitrile. (**Scheme 3**) Several acyclonucleosides synthesized by this way are listed in **TABLE**. Purine bases, such as adenine and guanine, yielded the N^9-isomer predominantly, and 2-thiothymine afforded the N^1-isomer alone.

EXPERIMENTAL: Melting points were measured with a Yanagimoto micro melting point apparatus, and were not corrected. ^{1}H-NMR spectra were recorded at 500 MHz on an AMX-500 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-2500 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 x 150 mm, GL Sciences inc.) and an ultraviolet detector set at 254 nm.

Preparation of 1-[(2-acetoxyethoxy)methyl]thymine (2) using BSA as a silylating reagent instead of HMDS in the absence or presence of a catalytic amount of ammonium sulphate (and using NaI or KI instead of CsI). Thymine (630 mg, 5 mmol) was suspended in acetonitrile (50 ml) and the solution was stirred with BSA (2.7 ml, 11 mmol) for 0.5 h at room temperature to afford a clear solution. It was treated with 2-acetoxyethyl acetoxymethyl ether (1.13 ml, 6 mmol), 1.3 g of CsI (5 mmol) (830 mg of KI, or 750 mg of NaI) and 50 mg of ammonium sulphate. The resulting medium was heated under reflux for 2 h. The mixture was poured into saturated aq. sodium bicarbonate, then the products were extracted with chloroform (50 ml x 3). The combined organic layer was dried on magnesium sulphate and concentrated under reduced pressure. The desired product was obtained as crystals from chloroform and ethyl

ether in 83% yield (m.p. 123-124 °C, lit. 123-125 °C [10]). In the absence of ammonium sulphate in the above reactions, only thymine was recovered.

Generation of TMSI by treating HMDS (or BSA) with CsI (or KI) and ammonium sulphate. A mixture of HMDS (0.2 ml) or BSA (0.28 ml), 260 mg of CsI (or 160 mg of KI) and 40 mg of ammonium sulphate was heated in acetonitrile (5 ml) under reflux for 2 days. Mass spectrometry analysis showed the generation of TMSI (*m/z*: 200 (M^+)) in the reaction mixture. In the absence of ammonium sulphate the reaction did not generate TMSI.

Preparation of 1-[(2-acetoxyethoxy)methyl]thymine (2) using TMSI as a catalyst. Thymine (630 mg, 5 mmol) and BSA (2.7 ml) were stirred in acetonitrile (50 ml) for 0.5 h to afford a clear solution, to which 2-acetoxyethyl acetoxymethyl ether (1.13 ml) and TMSI (0.07 ml, 0.5 mmol) was added. The reaction mixture was heated under reflux for 1 h. After purification by the same process as mentioned above, some crystals were obtained in 85% yield.

Isolation and identification of 2-[[(2-acetoxyethoxy)methyl]thio]-5-methyl-4(1H)-pyrimidinone (5), according to the Kim's method for preparation of 1-[(2-acetoxyethoxy)methyl]2-thiothymine (7). 2-Thiothymine (142 mg, 1 mmol) was heated under reflux in HMDS (10 ml) in the presence of ammonium sulphate (10 mg) for 6 h. The excess of HMDS was removed by evaporation under reduced pressure. Then the remaining glass material was dissolved in acetonitrile (10 ml) followed by addition of 2-acetoxyethyl acetoxymethyl ether (0.225 ml) and CsI (260 mg, 1 mmol). The mixture was heated under reflux for 3 h. HPLC analysis showed that the mixture contained a main product (73 %), a minor product (2 %) and 2-thiothymine (9 %). The solvent was evaporated, then to the residue water (20 ml) was added. The products were extracted with chloroform (20 ml x 4). The pooled organic layer was dried on magnesium sulphate, concentrated, and applied on a silicagel column. The products were eluted with chloroform followed by chloroform containing 5 % of methanol. The main product was crystallized from ethyl ether. The yield was 104 mg (40.3 %). mp: 149-151 °C; UV $\lambda_{max}^{methanol}$: 286 nm (ε = 9600); MS *m/z*: 258 (M^+); ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, 5-CH_3), 2.08 (3H, s, $COCH_3$), 3.85 (2H, t, J = 4.5 Hz, OCH_2CH_2OAc), 4.26 (2H, t, J = 4.5 Hz, OCH_2CH_2OAc), 5.42 (2H, s, NCH_2O), 7.75 (1H, s, 6-H), 11.84 (1H, br, NH); ^{13}C-NMR (77 MHz, $CDCl_3$) δ: 12.7 (5-CH_3), 20.8 (CH_3CO), 62.8 (OCH_2CH_2OAc), 67.3 (OCH_2CH_2OAc), 72.5 (SCH_2O), 121.3 (C-5), 151.5 (C-6), 156.9 (C-2), 164.4 (C-4), 170.9 (CH_3CO); *Anal.* Calcd. for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.29; H, 5.52; N, 10.83.

The minor product was also crystallized from ethyl ether that was characterized as 1-[(2-acetoxyethoxy)methyl]2-thiothymine (2). The yield was 12 mg (4.6%). mp: 115.5-117 °C; UV $\lambda_{max}^{methanol}$: 281 nm; MS *m/z*: 258 (M^+); ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, 5-CH_3), 2.09 (3H, s, $COCH_3$), 3.89 (2H, t, J = 4.5Hz, OCH_2CH_2OAc), 4.24 (2H, t, J = 4.5Hz, OCH_2CH_2OAc), 5.67 (2H, s, NCH) 7.32 (1H, s, 6-H), 9.90 (1H, Br, NCH); ^{13}C-NMR (77 MHz, $CDCl_3$) δ: 12.6 (5-CH_3), 20.8 (CH_3CO), 62.9 (OCH_2CH_2OAc), 68.0 (OCH_2CH_2OAc), 81.2 (NCH), 116.9 (C-5), 139.1 (C-6), 160.7 (C-2), 170.8 (C-4), 176.1 (CH_3CO).

Migration of (2-acetoxyethoxy)methyl group from S^2-position to N^1-position of 2-[[(2-acetoxyethoxy)methyl]thio]-5-methyl-4(1H)-pyrimidinone (5) to afford 1-[(2-acetoxyethoxy)methyl]2-thiothymine (7). Starting from 2-thiothymine (710 mg, 5 mmol), the compound **(5)** was obtained by the method as described above. The reaction mixture was checked by HPLC to be sure the main product was the compound **(5)** (75% of total peak area). Without isolation, 50 mg of ammonium sulphate was added to the reaction mixture, which was kept heating under reflux for 8 h. HPLC analysis showed that the compound **(5)** was changed to the compound **(7)** whose peak area was 86% of total peak area. Saturated aq. sodium bicarbonate was added to the mixture, and the products were extracted with chloroform (50 ml x 3). The combined organic layer dried on magnesium sulphate was concentrated under reduced pressure. The desired product was obtained as crystals from chloroform and ethyl ether in 80% yield.

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Migration of (2-acetoxyethoxy)methyl group from N^7-position to N^9-position of 7-[(2-acetoxyethoxy)methyl]guanine to afford 9-[(2-acetoxyethoxy)methyl]guanine with TMSI. Guanine (151 mg, 1 mmol) was suspended in acetonitrile (10 ml). After addition of BSA (1.08 ml, 4 mmol), the reaction mixture was stirred for 16 h at room temperature to afford a clear solution. Then 2-acetoxyethyl acetoxymethyl ether (0.225 ml) and TMSI (0.014 ml) were added to the reaction medium, and the resulting solution was kept stirring for 3 days at room temperature. The HPLC analysis revealed the peak area ratio of the starting material, 7-[(2-acetoxyethoxy)methyl]guanine and 9-[(2-acetoxyethoxy)methyl]guanine was 49.2:29.6:8.0, respectively. Then the reaction mixture was heated under reflux for 8 h, and the ratio resulted in 2.5:4.2:77.0, respectively. Sodium bicarbonate (2 g) was added to the reaction mixture and the mixture was stirred for 0.5 h. After removing the solid materials, the solution concentrated was applied on silica gel column chromatography. The desired product was eluted with chloroform containing 8% methanol. Some crystals were obtained from methanol-ethyl ether. The yield was 70%.

General method for preparation of acyclonucleoside derivatives. The mixture of a pyrimidine- or purine base (5 mmol), 2-acetoxyethyl acetoxymethyl ether, HMDS, TMSCl, KI and acetonitrile (50 ml) is heated for 1-19 h under reflux and the reaction is checked by HPLC with acetonitrile-water (15:85, v/v) as the eluent. The solvent is removed under reduced pressure. The residual solid is suspended with 50 ml of saturated aq. sodium bicarbonate and the products are extracted with chloroform (50 ml x 5). The organic layer dried on magnesium sulphate is concentrated. The desired product is crystallized from an appropriate solvent.

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