Table 3. Moles of Cu(II) and M(II) Transported Simultaneously in Bulk Liquid Membrane System

Source Phase[a]	moles transported × 10^8				
Cu(II)/M(II)	DB18C6	DB N_3O_2	DB N_2O_2	$Me_6N_4$14C4	DA18C6
Cu/Mn		38.9[b]/0	4.46/0	10.0/0	0.12/0
Cu/Co		38.7 /0	4.56/0	10.4/0	0.13/0
Cu/Ni		37.8 /0	4.56/0	9.8/0	0.21/0
Cu/Zn		36.9 /0.1	3.73/0.2	13.4/0.03	0.21/0
Cu/Cd		38.3/0.2	3.76/0.1	8.5/0	0.13/0.06
Cu/Pb		37.4/0.4	5.05/0.6	10.9/0	0.17/6.7

[a]Source phase is 0.1 M $Cu(NO_3)_2$ $3H_2O$ plus 0.1 M $M(NO_3)_2$ nH_2O in water. [b]Unit: moles transported/sec·m^2·(J_M).

DBN_3O_2 is an excellent carrier for the selective transport of Cu^{2+} in the presence of one other cation. The large transport selectivity for Cu^{2+}, which allowed only minimal flux of any other cation, unexpected in light of previous transport experimental results involving single cation source phases, wherein Co^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} were transported at significant rates by DBN_3O_2. For example, in single cation source phase experiments Cu^{2+} was transported at 33.7×10^{-8}mol/sec·m^2 and Cd^{2+} at 64.7×10^{-8} mol/sec·m^2 by DBN_3O_2. However, when the two metal ions are present in the source phase, the mole ratio of Cu^{2+}/Cd^{2+} transported is 38.3/0.2 (Table 3). This result is likely due to the relative stability of the complex of Cu^{2+} (log K, 14.0) and Cd^{2+} (log K, 8.7) with DBN_3O_2. Because stability constant of the DBN_3O_2 with Cu^{2+} in binary cation system is sufficiently large, release of other cation into receiving phase is inhibited. The high degree of transport selectivity for Cu^{2+} by the DBN_3O_2 carriers studied has significant implications. Incorporation of DBN_3O_2 which are selective for Cu^{2+} into liquid membranes may be used to remove Cu^{2+} from environmental system. In a broader sense, these experiments demonstrate the potential application to selective removal, concentration, purification of Cu^{2+} or other metallic elements from mixture.

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Synthesis of Acyclic Nucleosides of 2-Thio-Pyrimidines and -Purines Using a New Coupling Agent of Lithium Bromide

Joong Young Kim and Yong Hae Kim*

Department of Chemistry, Korea Advanced Institute of Scienc and Technology Seoul 130-650,
Received April 8, 1988

Acyclic nucleosides, 1-[[1,3-bis(benzyloxy)-2-propoxy]methyl]-2-thiopyrimidine, 9-[[1,3-bis(benzyloxy)-2-propoxy]methyl]-6-amino-2-thiopurine, 1-(2-acetoxyethoxymethyl)-2-thiopyrimidine, and 9-[[1,3-bis(benzyloxy)-2-propoxy]methyl]-6-amino-2-thiopurine have been synthesized by coupling pyrimidine and purine bases with acyclic acetates using a new coupling reagent of lithium bromide in the presence of trifluoro acetic acid in acetonitrile.

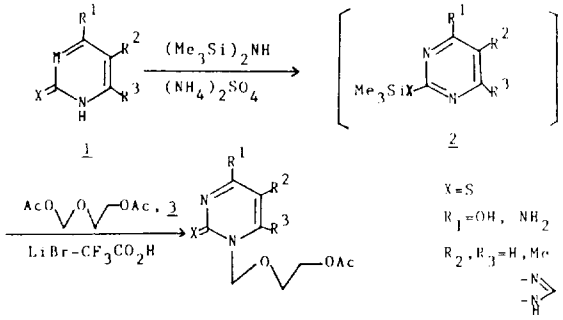
Introduction

Intensive study has been recently directed toward the synthesis of acyclic nucleosides including analogues of acyclovir since acyclic nucleosides such as 9-(1,3-dihydroxy-2-propoxy)methyl guanine,[1,2] and 9-(2-hydroxyethoxy methyl) guanine[3] of acyclic analogues of guanosine have been found to be a potent and selective antiherpetic agent together with less toxicity in side effects in comparison with those from guanosine derivatives and 2'-deoxy guanosine. Among the

various synthetic methods, the N-alkylation of silylated bases with peracyclated sugars in the presence of Friedel-Crafts catalyst[4-6] has become a standard procedure. For instance tin tetrachloride which is well used as a Friedel-Crafts catalyst has been reported to have an advantage of neighboring group effects in an oxonium ion formation for the coupling of bases and cyclic sugar acetates.[7]. But, 2'-deoxy system of the acyclic nucleosides and 2'-deoxynucleosides are not able to form an oxonium ion intermediate due to the lack of 2'-hydroxy group. Thus, the yields of acyclic nucleosides seem to be generally low in spite of long reaction time due perhaps to the lack of neighboring group effects. Friedel-Crafts catalysts such as tin tetrachloride lead to the mixture of colloids which causes difficulties in separation of product and in work up process. Therefore, it has been desired to develope a new efficient catalyst for the synthesis of acyclic nucleosides. A new N'-methyl-isoguanosine named doridosine, isolated from the shell less marine animal was reported to show a hypotensive effect in the rat[8] and a sulfur analogue, 2-thio-N^1-methylisoguanosine shows much less toxicity for liver damage[9] together with the same biological activity. Thus, we have examined to synthesize various 2-thiopyrimidine and purine acyclic nucleosides using 2-thiopyrimidine and purine derivatives as the bases

Results and Discussion

During the course of study on the coupling reagents for acyclic nucleosides we have found that lithium bromide is a good reagent for the alkylation at N^1-position of 2-thiopyrimidine and N^9-position of 2-thiopurine bases.

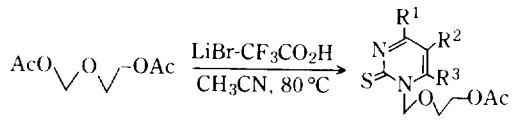


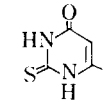
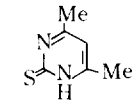
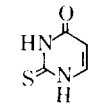
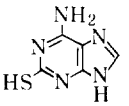
The reaction of trimethyl silylated pyrimidines[10] **2** which were obtained by trimethylsilylation of 2-thiopyrimidines **1** with hexamethyldisilazane and 2-acetoxyethylacetoxymethyl ether **3** with lithium bromide in the presence of trifluoroacetic acid in dry acetonitrile at 80 °C afforded 1-(2-acetoxyethoxymethyl)-2-mercapto pyrimidines and -2-mercapto purines in the moderate yields. The same coupling reactions in the absence of trifluoroacetic acid gave the lower yields (Table I, Run 1: 32%, Run 2: 28%, and Run 4: 30%). The trimethylsilylates (2-thiopyrimidine bases **2** were reacted with **3** in *situ* without isolation. The results obtained are summarized in Table 1.

Acylic nucleosides containing branched chain such as 1-[1,3-bis(hydroxy-2-propoxy)methyl]guanine were reported to be less toxic in comparison with guanosine.[7] Thus, synthesis of acyclic 2-thiopyrimidine and purine nucleosides **6** was examined.

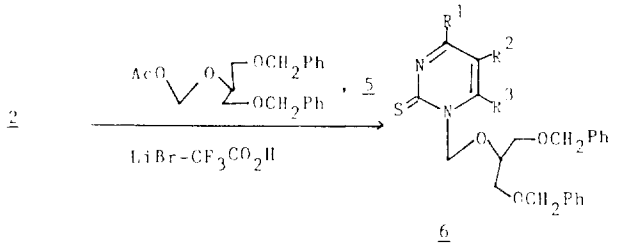
The reaction of silylated pyrimidine (**2**, 1 mmole) and O-acetyl methyl-1.,3-di-O-benzyl glycerol (1.2 mmole) with

Table 1.



Run	Substrate (Base)	Reactn. Time(h)	Yield (%)[a]	Product
1		6	40(32)[b]	**4a**
2		12	33(28)[b]	**4b**
3		10	43	**4c**
4		12	42(30)[b]	**4d**

[a]Isolated yield. [b]Isolated yields in the absence of CF_3CO_2H. N^9-Substituted isomer.



lithium bromide (0.3 mmole) and trifluoroacetic acid (1 mmole) in acetonitrile at 80 °C gave 1-[[1,3-bis(benzyloxy)-2-propoxy]methyl]-2-mercapto pyrimidine **6** (34-45%). The results obtained are summarized in Table 2.

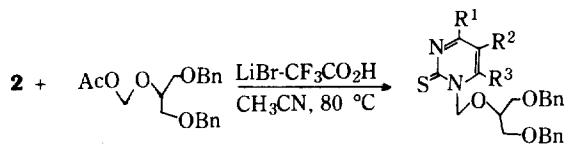
Acyclic nucleosides of 2-mercaptopyrimidine and -purine derivatives were successfully synthesized using a new coupling reagent of lithium bromide in the presence of trifluoroacetic acid in better yields in comparison with those obtained using tin tetrachloride or $Hg(CN)_2$[11] which are well used as Lewis acid. The coupling of 6-methyl-2-thiouracil and 2-acetoxyethyl acetoxymethyl ether using tin tetrachloride actually gave a lower yield (21%) of **4a**. Earlier, the 1-[[1,3-bis (benzyloxy)-2-propoxy]-2-mercaptopyrimidin-4-one was reported to be synthesized using $Hg(CN)_2$ catalyst in 23% yield.[11] But the same reaction using lithium bromide in the presence of trifluoroacetic acid gave ca. 43% yield (Run 2 in Table 2).

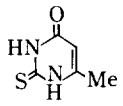
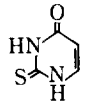
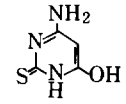
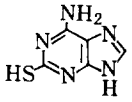
It is noteworthy that lithium bromide-trifluoroacetic acid system works fairly well for the 2-thiopyrimidine and purine nucleoside synthesis, but it is not effective for the 2-oxopyrimidines.

For instance, the reaction of trimethylsilylated uracil with **2** did not give 1-(2-acetoxyethoxymethyl)-2,6-dioxopyrimidine: the starting material was recovered quantitatively.

Though the role of lithium bromide in the formation of N-C bond of acyclic nucleosides is not clear, it was found that lithium bromide is a good coupling reagent for the selective alkylation at N^1-position of 2-thiopyrimidines and N^9-position

Table 2.



Run	Base	Time (h)	Yield (%)[a]	Product
1		10	34(20)[b]	**6a**
2		12	43	6b[9]
3		12	37	**6c**
4		10	45	6d[b]

[a]Isolated yields. [b]Isolated yields in the absense of CF_3CO_2H. [9]N-substituted isomer.

of 2-thiopurine bases.

Experimental Section

General. Melting points were determined on a Electrothermal melting point apparatus and were corrected. ^1H nmr were recorded on a Varian T-60A or on a Varian FT-80A spectrometer. I.R. spectra were obtained on a Perkin-Elmer Model 267 spectrophotometer. L.C was carried in Waters Associats Liquid Chromatography (Model No 244).

1. 1-[(2-Acetoxyethoxy)methyl]-6-methyl-2-thiouracil (4a). The 6-methyl-2-thiouracil (142 mg, 1 mmol) was refluxed in HMDS (10 m*l*), and then ammonium sulfate (10 mg) was added. Reflux was continued for 6h until the mixture became to clean solution. At this point, the excess of HMDS was removed by concentration under reduced pressure. The reaction mixture of trimethylsilylated base and 2-acetoxyethyl acetoxymethyl ether (225 u*l*, 1.2 mmol) was refluxed in the presence of lithium bromide (0.3 mmol, 27 mg) and trifluoroacetic acid (77 u*l*, 1 mmol) in acetonitrile for overnight. The mixture was poured into a mixture of aqueous solution of $NaHCO_3$ (10 m*l*) and $CHCl_3$(50 m*l*). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and chromatographed by preparative tlc (silica gel, 20 × 20 cm, 1mm, $CHCl_3$:MeOH = 20:1) to give 95 mg (40%).: ^1H nmr ($CDCl_3$), δ2.2(s, 3H, $COCH_3$), 2.4(s, 3H, CH_3), 4.0, 4.4(t, 4H, OCH_2CH_2O), 5.6(s, 2H, OCH_2N), 6.3(s, 1H, C_6H); mp: 129-130 °C; ir (KBr): 1750, 1700 cm^{-1}; ms (m/z) 258.

2. 1-[(2-Acetoxyethoxy)methyl]-4,6-dimethyl-2-thio pyrimidine (4b). Crystal(85 mg, 33%); mp 130-133 °C; ^1H nmr ($CDCl_3$), δ2.1(s, 3H, $COCH_3$), 2.4(s, 6H, CH_3), 3.8, 4.3(t, 4H, OCH_2CH_2O), 5.5(s, 2H, OCH_2N), 6.8(s, 1H, C_5H); ir (KBr): 1750, 1630, 1580 cm^{-1}.

3. 1-[(2-Acetoxyethoxy)methyl]-2-thiouracil (4c). Crystal(56 mg, 23%); mp 106-108 °C; ^1H nmr($CDCl_3$),δ2.2(s, 3H, $COCH_3$), 4.0, 4.3(t, 4H, OCH_2CH_2O), 5.8(s, 2H, OCH_2N), 6.1, 7.6(d, 2H, C_5H, C_6H), 8.1(b, 1H, NH); anal. cal. C, 44.1, H, 4.95, N, 11.5, found C, 44.1, H, 4.89, N, 11.6; ms(m/z) 244.

4. 9-[(2-Acetoxyethoxy)methyl]-6-amino-2-thio purine (4d). Crystal(127 mg, 45%); mp 152-154 °C; ^1H nmr (DMSO-d_6), δ2.05(s, 3H, $COCH_3$) 3.8, 4.2(t, 4H, OCH_2CH_2 O), 5.5(s, 2H, OCH_2N), 7.4(b, 2H, NH_2), 8.2(s, 1H, C_8H), 11.5(s, 1H, SH); anal. cal. C, 42.4; H, 4.62; N, 24.7, found C, 42.7; N, 23.8; ms(m/z) 283.

5. 1-[[1,3-Bis(benzyloxy)-2-propoxy]methyl]-6-methyl-2-thiouracil (6a). The 6-methyl-2-thiouracil (142 mg, 1 mmol) was refluxed in HMDS (10 m*l*) and then ammonium sulfate (10 mg) was added. Reflux was continued for 6h until the reaction mixture became to clean solution. At this point, the excess of HMDS was removed by concentration under reduced pressure. The reaction mixture of the trimethylsilylated base and 0-acetylmethyl-1,3-di-0-benzyl glycerol (415 mg, 1.2 mmol) was refluxed for 6h in the presence of lithium bromide (0.3 mmol, 27 mg) and trifluoroacetic acid (77 μl, 1 mmol) in acetonitrile for overnight. The reaction mixture was poured into a mixture of aqueous solution of $NaHCO_3$ (10 m*l*) and $CHCl_3$ (50 m*l*). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure and chromatographed by preparative tlc (silica gel, 20 × 20 cm, 1 mm, $CHCl_3$:MeOH = 20:1) to give the product (143 mg, 34%): ^1H nmr ($CDCl_3$), δ2.3 (s, 3H, CH_3), 4.0(m, 1H, CHO), 3.6, 3.7(d, 4H, CH_2O), 4.6(s, 4H, OCH_2Ph), 5.6(s, 2H, OCH_2N), 6.1(s, 1H, C_5H), 7.4(s, 10H, PhH); ir(KBr) 1700 cm^{-1}.

6. 1-[[1,3-bis(benzyloxy)-2-propoxy]methyl]-2-thiouracil (6b). (177 mg, 43%) ^1H nmr ($CDCl_3$), δ3.5, 3.55(d, 4H, CH_2O), 4.1(m, 1H, CHO), 4.4(s, 4H, OCH_2Ph), 5.7(s, 2H, OCH_2N), 5.88, 7.83(d, 2H, C_5H, C_6H), 7.3(s, 10H, PhH) (ref. 9).

7. 1-[[1,3-bis(benzyloxy)-2-propoxy]methyl]-4-amino-6-ol pyrimdine (6c). Liquid (154 mg, 37%): ^1H nmr ($CDCl_3$), δ3.6, 3.7(d, 4H, CH_2O), 4.6(s, 4H, OCH_2Ph), 5.4(s, 2H, OCH_2N), 5.6(s, 2H, C_5H), 7.2(s, 10H, PhH); ir(KBr) 3300, 1700 cm^{-1}.

8. 9-[[1,3-bis(benzyloxy)-2-propoxy]methyl]-6-amino-2-thiopurine (6d). Liquid(202 mg, 45%): ^1H nmr (DMSO-d_6), δ3.4, 3.5(d, 4H, CH_2O), 4.0(m, 1H, CHO), 4.4(s, 4H, OCH_2Ph), 4.4(s, 2H, OCH_2N), 7.0(s, 10H, PhH), 7.8(b, 2H, NH_2), 8.2(s, 1H, C_8H), 11.5(s, 1H, SH); ir(KBr) 3400, 1650, 1600 cm^{-1}; ms(m/z) 196, 168 (B + 1).

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Interaction of Metal Ions with NADH Model Compounds. Cupric Ion Oxidation of Dihydronicotinamides

Joon Woo Park*, Sung Hoe Yun, and Kwanghee Koh Park†

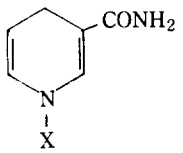
Department of Chemistry, Ewha Womans University, Seoul 120-750
†Department of Chemistry, Chungnam National University, Daejeon 302-764. *Received April 8, 1988*

Kinetic studies on cupric ion (Cu^{2+}) oxidation of 1-benzyl- and 1-aryl-1,4-dihydronicotinamides (XNAH) in aqueous solution were performed. In the presence of dioxygen (O_2), the reaction followed first order kinetics with respect to both XNAH and Cu^{2+}. The oxidation reaction was found to be independent and parallel to the acid-catalyzed hydration reaction of XNAH. The catalytic role of Cu^{2+} for the oxidation of XNAH in the presence of O_2 was attributed to Cu^{2+}/Cu^{+} redox cycle by the reactions with XNAH and O_2. The second order rate constants of the Cu^{2+} oxidation reaction k_{Cu} and acid-catalyzed hydration reaction k_H were strongly dependent on the nature of the substituents in 1-aryl moiety. The slopes of log k_{Cu} vs log K_H and log k_{Cu} vs σ_p of the substituents plots were 1.64 and −2.2, respectively. This revealed the greater sensitivity of the oxidation reaction rate to the electron density on the ring nitrogen than the hydration reaction rate. A concerted two-electron transfer route involving XNAH-Cu^{2+} complex was proposed for mechanism of the oxidation reaction.

Introduction

The redox couple NADH/NAD^+ is one of the most important coenzymes in biological systems. In consequence the chemical reactions of NADH model compounds in enzyme-free systems have been a major interest to chemists.[1] The detailed mechanism of NADH model compounds reduction of organic substances is still in controversy whether the net transfer of hydride from the 4-position of the dihydropyridine ring to the oxidizing agent is a single step process or via multi-step e^-, H^+, e^- mechanism.[2] Meanwhile, it was shown that oxidation of NADH and its analogues by inorganic one-electron oxidants such as ferrocenium cation[3,4] and ferricyanide anion[5-7] proceeds by rate-determining initial one-electron transfer from dihydronicotinamide moiety to the oxidizing agent. The logarithm of the reaction rate constant appeared to vary linearly with E^O for ferrocenium/ferrocene couples.[4] Divalent metal ions exert large effects on reduction of organic compounds by dihydronicotinamides.[1b,1c] They catalyze the reaction and, sometimes, increase stereoselectivity in the reduction.

In this paper we report oxidation of 1-benzyl- and 1-aryl-substituted-1,4-dihydronicotinamides **1-6** by Cu^{2+} in aqueous media. The effect of the nature of the 1-substituents on the oxidation rate was evaluated and correlated with that on the hydration reaction of the dihydronicotinamides.[8] We also show a large effect of oxygen on the kinetics of the oxidation reaction.



1, X = $C_6H_5CH_2$ **2,** X = p-$CH_3OC_6H_4$
3, X = p-$CH_3C_6H_4$ **4,** X = C_6H_5
5, X = p-ClC_6H_4 **6,** X = p-CNC_6H_4

Experimental

Materials. The NADH model compounds 1-benzyl-1,4-dihydronicotinamide(**1**), 1-(p-methoxyphenyl)-1,4-dihydronicotinamide(**2**), 1-(p-methylphenyl)-1,4-dihydronicotinamide(**3**), 1-phenyl-1,4-dihydronicotinamide(**4**), 1-(p-chlorophenyl)-1,4-dihydronicotinamide(**5**) and 1-(p-cyanophenyl)-1,4-dihydronicotinamide(**6**) were available from an earlier study.[8] Vacuum dried $CuCl_2$(Junsei) was used as a source of Cu^{2+}. Deionized glass-distilled water was used. All other chemicals were readily available from commercial sources.

Kinetic Studies. Rate constants for the disappearance of dihydronicotinamides (XNAH) **1-6** were determined at 25 °C with a Spectronic 21 or Beckman DU 8B UV-VIS spectrophotometer with a thermostatted cell holder. The ionic strength of solutions was held constant at 0.1 M by the addition of NaCl. The buffer system was 0.01 M cacodylate. The reaction was made by mixing a solution of XNAH in ethanol with an aqueous Cu^{2+} solution at a desired pH (or H^+ concentration) in a quartz mixing cell. The final solvent composition was 5% EtOH-95% H_2O and the concentration of XNAH was 1.0×10^{-4} M.