FACILE SYNTHESIS OF ACYCLIC NUCLEOSIDES USING A NEW COUPLING AGENT OF ZINC IODIDE

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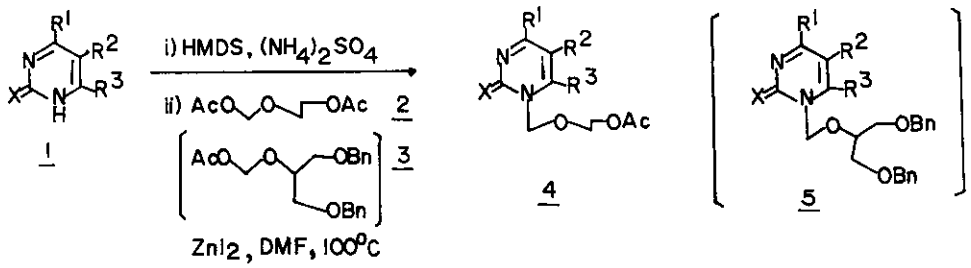
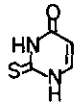
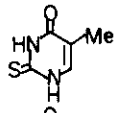
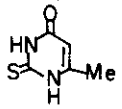
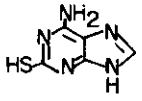
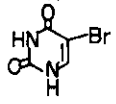
Abstract - ((1,3-Bis(benzyloxy)-2-propoxy)methyl)-2-thiopyrimidine-, uracil-, 2-thiouracil-, and 2-thioadenine- acyclic nucleosides and (2-acetoxyethoxy methyl)-2-thioadenine-, 2-thiopyrimidine-, uracil-, and 2-thiouracil- acyclic nucleosides have been successfully synthesized in good yields by N-alkylation using a new Lewis acid, zinc iodide in dimethylformamide.

Since acyclic analogues of 2'-deoxyguanosine such as 9-((1,3-dihydroxy-2-propoxy)methyl)-guanine,[1,2] and 9-(2-hydroxyethoxymethyl)guanine (acyclovir)[3] have been found to be a potent and selective antiherpes virus agent together with less toxicity in side effects. Thus, intensive study have been directed toward the synthesis of analogues of acyclovir and other acyclic nucleosides. Lewis acids,[4] Et_3N,[5] p-toluenesulfonic acid,[1] trifluoromethanesulfonic acid,[6] and mercuric cyanide[7] have been well used as the coupling agent for the preparation of acyclic nucleosides. However, the yields are generally poor in spite of long reaction time due perhaps to the lack of neighboring group effect in 2'-deoxy form of acyclic nucleosides. Therefore, it has been desirable and important to develop a new efficient coupling agent for the synthesis of acyclic nucleosides. Recently a new N^1-methylisoguanosine named doridosine, isolated from the shell less marine dorid nudibranch anisodoris nobilis 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] Thus, we have examined to synthesize various 2-thiopyrimidine and purine acyclic nucleosides and now found that zinc iodide is a good Lewis acid catalyst for the alkylation at 1-position of 2-thiopyrimidine and at 9-position of purine skeleton in dimethylformamide.



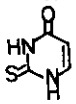
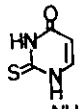
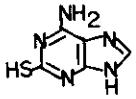
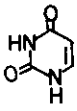
When the pyrimidine or purine derivatives trimethylsilylated were treated with 2-acetoxyethylacetoxymethyl ether[4] in the presence of zinc iodide, comparatively excellent yields of acyclic nucleosides were obtained. Treatment of zinc iodide and work up after the complete reaction are simple and easy. In a typical run, trimethylsilylated 2-thiopyrimidine base was prepared from 2-thiopyrimidine (112 mg, 1 mmol), hexamethyldisilazane (10 ml), and ammonium sulfate (10 mg).[10] The reaction mixture of the trimethylsilylated base and 2-acetoxyethylacetoxymethyl ether (225 μl, 1.2 mmol) was refluxed for 2 h in the presence of zinc iodide (1 mmol) in dimethylforamide. The organic solvent was concentrated under vacuum and then extracted with methylene chloride (50 mlx3) and H_2O (50 ml). The organic layer was concentrated and chromatographed by the preprative tlc (silica gel = 20 x 20 cm, 1 mm), or the column chromatography to give the product as a solid (175 mg, 76%), ^1H nmr ($CDCl_3$, δ, ppm) 8.7(d, 1H, C_4H or C_6H), 8.3(d, 1H, C_4H or C_6H), 6.9(t, 1H, C_5H), 5.8(s, 2H, NCH_2O), 4.3, and 4.0(each t, 4H, OCH_2CH_2O), 2.1(s, 3H, $COCH_3$), mass(m/z; 227). 1-((1,3-Bis(benzyloxy)-2-propoxy)methyl)-2-thiouracil was synthesized by the similar method as described above (85%). The results obtained are shown in Table I and II.

Table I. Silylated Base + AcO⌇O⌇OAc $\xrightarrow[\text{DMF, 100°C}]{ZnI_2}$ B⌇O⌇OAc

Run	Base (B)	Time (h)	Yield(%)[a]	Spectral data
1		2	76	see the text
2		4	73	12a
3		5	51	12b
4		7	35	12c
5		7	55[b]	12d
6		3	67	12e
7		7	60	4

a) Isolated yields. b) Mixture of two isomer (N-9 isomer : N-7 isomer = 3 : 1).

Table II. Silylated Base + AcO-(1,3-di-O-benzyl-2-propoxy) $\xrightarrow[\text{DMF, 100°C}]{ZnI_2}$ B-(1,3-di-O-benzyl-2-propoxy)

Run	Base (B)	Solvent	Time(h)	Yield(%)[a]	Spectral data
1		DMF	5	71	12f
2		DMF	5	85(92)[b]	7
3		CH_3CN[c]	5	82[d]	11
4		DMF	7	73[e]	12g
5		DMF	5	67	13

a) Isolated yields. b) Yields determinied by HPLC.
c) The reaction was done under reflux in CH_3CN
d) Two isomer (6:6' = 1:1) were formed[11]
e) N-9 : N-7 = 4:1

It is note worthy that there are different solvent effects between acetonitrile and dimethylformamide: the coupling reaction of 2-thiouracil with 1,3-di-o-benzyl-2-propoxy-1-acetoxy glycerol in acetonitrile formed two isomers, N^1-substituted 2-thiouracil(6) and N^3-substituted 2-thiouracil (6') (6:6' = 1:1).[11] While in the case of dimethylformamide regioselective alkylation at N^1-position occurred to give 6 without formation of 6'. Here a question is raised as to a possibility of S-alkylation instead of N^3-alkylation. If the product, 6', is a S-substituted compound, it will be readily oxidized to the corresponding sulfoxide. Therefore, 6 and 6' were actually separated by HPLC (RP-18, MeOH:H_2O=2:1, Ret. time; 6:25 min, 6':30 min). The oxidation of 6' did not form the sulfoxide. The structure of 6' was postulated by comparing ^1H nmr spectrum from that of 6 which is known compounds. Acyclic nucleosides of 2-thiopyrimidine and purine derivatives were successfully synthesized using a new catalyst of zinc iodide as a Lewis acid in much better yields in comparison with those obtained using tin tetrachloride[14] which is well used as Lewis acid. Earlier, the 1-((1,3-bis(benzyloxy)-2-propoxy)methyl)-2-thiouracil was reported to be synthesized using $Hg(CN)_2$ catalyst in 23% yield.[7] But the same reaction using new catalyst of zinc iodide gave ca. 85% yield (Run 2 in Table 2) comparatively for the short reaction time. Though the reaction role of zinc iodide in the formation of N-C bond of acyclic nucleosides is not yet clear, our new method may be widely available for the synthesis of acyclic nucleosides of purine and pyrimidine derivatives. The biological activity tests of these acyclic nucleosides prepared is being undertaken.

ACKNOWLEDGEMENTS

The generous support for this investigation by a research grant from Korea Science and Engineering Foundation is gratefully acknowledged.

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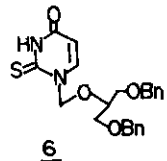
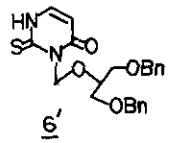
11. 6: Known compound.[7]



6



6'

6': ^{1}H nmr($CDCl_3$, δ, ppm), 3.5(d, 4H, OCH_2Ph), 4.3(m, 1H, OCH), 4.5(s, 4H, CH_2), 5.4(s, 2H, OCH_2N), 6.2, 7.7(d, 2H, C_5H, C_6H), 7.3(s, 10H, Ph).

12. a) ^{1}H nmr($CDCl_3$, δ, ppm) 2.2(s, 3H, OAc), 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), b) ^{1}H nmr($CDCl_3$, δ, ppm) 2.2(s, 3H, OAC), 2.3(S, 3H, CH_3), 4.0, 4.3(t, 4H, OCH_2CH_2O), 5.8(s, 2H, OCH_2N), 7.3(s, 1H, C_6H), mass(m/z):258, c) ^{1}H nmr($CDCl_3$, δ, ppm) 2.2(s, 3H, OAc), 2.4(s, 3H, CH_3), 4.0, 4.3(t, 4H, OCH_2CH_2O), 5.8(s, 2H, OCH_2N), 6.3(s, 1H, C_5H), mass(m/z): 258, d) N-9 isomer: ^{1}H nmr(DMSO, δ, ppm) 2.05(s, 3H, OAc), 3.8, 4.2(t, 4H, OCH_2CH_2O), 5.5(s, 2H, OCH_2N), 7.4(b, 2H, NH_2), 8.2(s, 1H, C_8H), 11.5(s, 1H, SH), mass(m/z): 283, N-7-isomer: ^{1}H nmr(DMSO, δ, ppm) 2.2(s, 3H, OAc), 4.0, 4.4(t, 4H, OCH_2CH_2O), 5.7(s, 2H, OCH_2N), 7.5(b, 2H, NH_2), 8.4(s, 1H, C_8H), 11.5(s, 1H, SH), e) ^{1}H nmr($CDCl_3$, δ, ppm) 2.2(s, 3H, OAc), 4.0, 4.2(t, 4H, OCH_2CH_2O), 5.6(s, 2H, OCH_2N), 7.2, 7.6, 8.5(m, 4H, C_2H, C_3H, C_4H, C_5H). f) ^{1}H nmr($CDCl_3$, δ, ppm), 3.5(d, 4H, CH_2O), 4.0(m, 1H, CHO), 4.4(s, 4H, OCH_2Ph), 5.5(s, 2H, NCH_2O), 6.9(t, 1H, C_5H), 8.3(d, 1H, C_5H, C_6H), 8.7(d, 1H, C_4H, C_6H). g) N-9-isomer: ^{1}H nmr(DMSO, δ, ppm) 3.4(d, 4H, CH_2O), 4.0(m, 1H, CHO), 4.4(s, 4H, OCH_2Ph), 5.5(s, 2H, NCH_2O), 7.0(s, 10H, PhH), 7.8(b, 2H, NH_2), 8.2(s, 1H, C_8H), 11.5(s, 1H, SH), N-7-isomer: ^{1}H nmr(DMSO, δ, ppm) 3.6(d, 4H, CH_2O), 4.2(m, 1H, CHO), 4.5(s, 4H, OCH_2PH), 5.6(s, 2H, NCH_2O), 7.1(s, 10H, PhH), 7.9(b, 2H, NH_2), 8.4(s, 1H, C_8H), 11.5(s, 1H, SH).
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14. cf, In case of $SnCl_4$ use: Table I (Run 4:20%, Run 5:40%).

Received, 21st September, 1987