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Efficient Synthesis of Acyclic Nucleosides by N-Alkylation of Pyrimidine and Purine-bases Using a New Coupling Agent of Cesium Iodide

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Acyclic nucleosides, ((1,3-bis(benzyloxy)-2-propoxy) methyl)-2-thio-pyrimidine, -uracil, -2-thiouracil, and -2-thioadenine, and (2-acetoxyethoxy methyl)-2-thioadenine, -2-thiopyrimidine, -uracil, and -2-thiouracil have been successfully synthesized in good yields by N-alkylations of the bases with the corresponding alkyl-acetate (2) and -chloride (3) using cesium iodide under neutral condition in acetonitrile.

Recently, significant progress has been made in the development of antiviral chemotherapy due to the discovery of nucleoside analogues with potent antiviral activities such as acyclovir, 9-(2-hydroxyethoxymethyl) guanine[1] and 9-(1,3-dihydroxy-2-propoxy)methyl)guanine[2] which show less toxic side effects. Thus, intensive studies have been directed toward the synthesis of analogues of acyclovir and other acycic nucleosides.[3] Friedel-Crafts catalysts,[4] Et$_3$N,[5] p-toluenesulfonic acid,[2] trifluoromethanesulfonic acid,[6] and mercuric cyanide[7] have been well used as the Lewis acid catalysts for the synthesis of acyclic nucleosides. For the preparation of general acyclic nucleosides a great number of catalysts have been developed. For instance, tin tetrachloride well used among the Friedel-Crafts catalysts has the advantage of neighboring group effect of an important oxonium formation for the formation of N-C bond of the general cyclic nucleosides. But, 2-deoxy system of the acyclic nucleosides is unable to form an oxonium intermediate due to the lack of neighboring group effect of 2-hydroxy group. The yields of acyclic nucleosides are generally low in the case of using Friedel-Crafts catalysts such as tin tetrachloride[4] and mercuric cyanide.[7] Thus, it is desirable to develop the new efficient Lewis catalysts for the preparation of acyclic nucleosides. During the course of the study on Lewis acid catalysts, we have found that cesium iodide was an excellent reagent for the

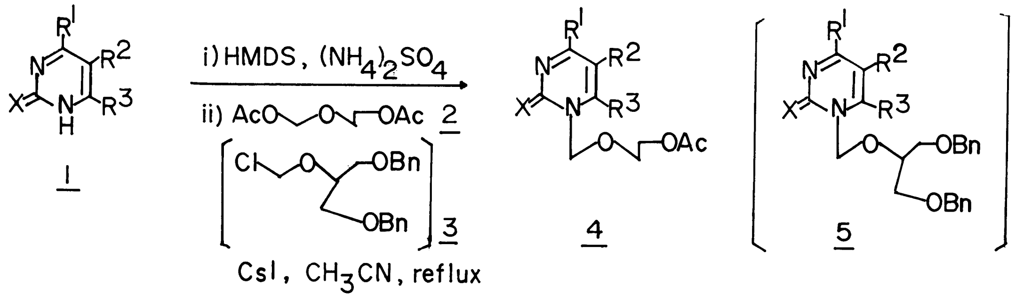
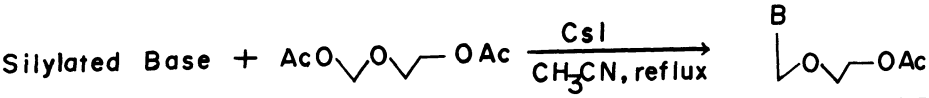
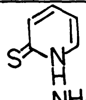
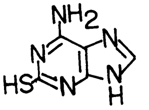
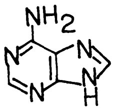
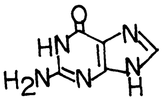
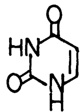
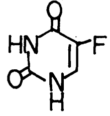
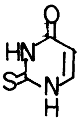
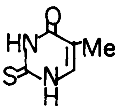
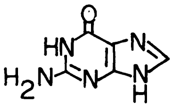
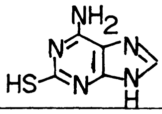


Table 1.



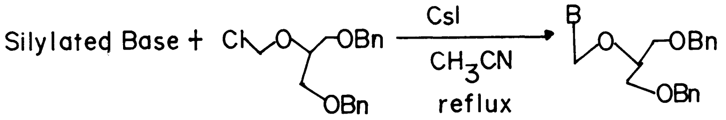
Run	Base (B)	Reactn. time / h	Yield/ % a)	N^9-/N^7-isomer	Ref. (Spectral data)
1		2	76		12a
2		2	92		12b
3		2	70		12c
4		3	72		9
5		3	75		4
6		4	51		12d
7		1	96		12e
8		12	80	2:1 b)	12f
9		12	47	10:1 c)	10
10		12	42	7:1 c)	1

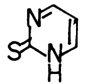
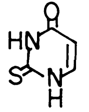
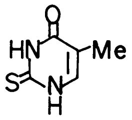
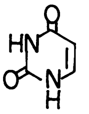
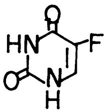
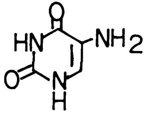
a) Isolated yields. b) The ratio of N^9- and N^7-substituted isomers which were separated each other. c) The ratio was determined by HPLC.

predominent alkylation at N^1-position of pyrimidine bases and for the highly regioselective alkylation at N^9-position of purine bases in acetonitrile. Trimethylsilylated bases of pyrimidine-, or purine- derivatives were treated with 2-acetoxyethyl acetoxymethyl ether in the presence of cesium iodide to give the corresponding acyclic nucleosides in excellent yields. Since cesium iodide is not hygroscopic, it is easier and simple to treat and work up.

In general procedure, trimethylsilyalted 2-thiopyrimidine base was prepared from 2-thiopyrimidine (112 mg, 1 mmol), hexamethyldisilazane (10 ml), and ammonium sulfate (10 mg).[8] The reaction mixture of trimethylsilylated 2-thiopyrimidine (1 mmol) and 2-acetoxyethyl acetoxymethyl ether (225 µl, 1.2 mmol)[4)] in the presence of cesium iodide (260 mg, 1 mmol, CH_3CN: 10 ml) was refluxed for 2 h. The reaction mixture was concentrated under vacuum and then extracted with methylene chloride (20 mlx3) after addition of water (20 ml). The organic layer was concentrated and chromatographed (silica gel column: 30x2 cm, $CHCl_3$: MeOH = 20:1) to give 1-(2-acetoxyethoxymethyl)-2-thiopyrimidine as a solid (175 mg, 76%, see Ref. 12a). The results obtained and references are summarized in Table 1.

Table 2.



Run	Base	Time/ h	Yield/ % a)	Ref. (Spectral data)
1		0.5	80	7
2		0.5	95	7
3		1	80	2
4		1	82	12g
5		2	80b)	10
6		2	83c)	12h

a) Isolated yields. b) The ratio of N^9-substituted- and N^7-substituted isomers = 3:2. c) The ratio of N^9-substituted- and N^7-substituted isomer = 3:1.

In order to compare the role of cesium halides, CsI, CsBr, CsCl, and CsF were examined to synthesize 9-(2-acetoxyethoxymethyl)-guanine. After the each reaction mixture was refluxed for 12 h in acetonitrile, the yield of the product was analysed by high pressure liquid chromatography (column: RP-18, MeOH : H_2O = 2 : 1, yields: CsI (42%) > CsBr (26%) > CsCl (11%) > CsF (6%)). Thus, acyclic nucleosides of pyrimidine and purine derivatives were successfully synthesized using cesium iodide as a Lewis acid catalyst. Acyclic pyrimidine nucleosides gave one N^1-substituted product. While purine nucleosides yielded two isomers of N^7- and N^9-substituted products, where fairly good regioselective alkylation at N^9-position was observed in acyclic adenine and guanine necleosides (Run 9 and Run 10). It is the first time to get 9-(2-acetoxyethoxymethyl)adenine and guanine by the direct N^9-alkylation with 2-acetoxyethoxy methyl ether though their yields are moderate. N^7- and N^9-isomers can be readily distinguishable by comparing their chemical shifts of C_8H in ^1H NMR spectrum ($CDCl_3$, ppm: N^7-isomer: 8.4, N^9-isomer: 8.2, cf, Ref. 12f). Branched chain acyclic nucleosides of 1-((1,3-bis(benzyloxy) propoxy)methyl)-pyrimidine and -purine derivatives were synthesized in excellent yields by the same method as described in Table 1. The results obtained are summarized in Table 2. The yields of acyclic nucleosides including branched chains are much higher than those from the known methods.[13] Though the role of cesium iodide is not clear, it may be assumed that oxygen of ether of 2 and 3 is activated first by interaction between cesium cation and ether oxygen to promote the carbonium electrophilicity at the carbon adjacent to the ether oxygen, which makes it easier to alkylate at N^1-position of pyrimidines and at N^9-position of purines. The present method may be widely available for the preparation of 2-thiopyrimidine-, uracil-, purine- and 2-thiopurine- acyclic nucleosides. The generous support for this investigation by a research grant from Korea Science and Engineering Foundation is gratefully acknowledged.

References

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11) J.C. Martin, G.A. Jeffery, D.P.C. MaGee, M.A. Tripllie, D.F. Smee, T.R. Matthews, and J.P.H. Verheyden, J. Med. Chem., 28, 358 (1985).
12) a) ^1H NMR($CDCl_3$, δ, ppm) 2.1(s, 3H, $COCH_3$), 4.0, 4.3(t, 4H, OCH_2CH_2), 5.8(s, 2H, NCH_2O), 6.9(t, 1H, C_4H), 8.3((d, 1H, C_4H or C_6H), 8.7(d, 1H, C_4H or C_6H), mass(m/z): 227; b) ^1H NMR($CDCl_3$, δ, ppm) 2.2(s, 3H, $COCH_3$), 8.1(b, 1H, NH); c) ^1H NMR($CDCl_3$, δ , ppm) 2.2(s, 3H, $COCH_3$), 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; d) ^1H NMR($CDCl_3$, , ppm) 2.2(s, 3H, $COCH_3$), 4.0, 4.3(t, 4H, OCH_2CH_2O), 4.3(b, 2H, NH_2), 5.8(s, 2H, OCH_2N), 7.3(s, 1H, C_6H); e) ^1H NMR($CDCl_3$, δ, ppm) 2.1(s, 3H, $COCH_3$), 4.0, 4.3(t, 4H, OCH_2CH_2O), 5.6(s, 2H, OCH_2N), 7.2(t, 1H, C_4H or C_5H), 7.4(t, 1H, C_4H or C_5H), 7.6(d, 1H, C_3H), 8.8(d, 1H, C_6H); f) ^1H NMR(DMSO, δ , ppm) N^9-isomer: 2.05(s, 3H, $COCH_3$), 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: ^1H NMR(DMSO, δ , ppm) 2.2(s, 3H, $COCH_3$), 4.0, 4.4(6, 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); g) ^1H NMR($CDCl_3$, δ , ppm) 2.2(s, 3H, CH_3), 3.5(d, 4H, OCH_2Ph), 4.0(m, 1H, CHO), 4.5(s, 4H, CH_2O), 5.6(s, 2H, OCH_2O), 7.3(s, 10H, Ph), 5.8, 7.5(d, 1H, C_5H, C_6H); h) ^1H NMR($CDCl_3$, δ, ppm) N^9-isomer: 3.5(d, 4H, CH_2O), 4.0(m, 1H, CHO), 4.4(s, 4H, OCH_2Ph), 4.4(s, 2H, CH_2OH), 7.0(s, 10H, Ph), 7.8(b, 2H, NH_2), 8.2(s, 1H, C_8H), 11.5(s, 1H, SH), N^7-isomer: 3.6(d, 4H, CH_2O), 4.2(m, 1H, CHO), 4.5(s, 4H, OCH_2Ph), 5.6(s, 2H, OCH_2N), 7.1(s, 10H, Ph), 7.9(b, 2H, NH_2), 8.3(s, 1H, C_8H), 11.5(s, 1H, SH).
13) For instance, 1-((1,3-bis(benzyloxy)-2-propoxy)methyl-2-mercapto-4-one pyrimidine was obtained in 23% yield using $Hg(CN)_2$[2] catalyst (cf. 80%, Run 3 in Table 2). n-Bu_4NI catalyst gave lower yields of acyclic pyrimidine- and purine-nucleoside(56-65%)[7,10] (cf. 80-95% Runs 1,2, and 5 in Table 2).

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