FACILE SYNTHESIS OF TETRAHYDRO-2-FURYLATED PYRIMIDINES AND PURINES USING A NEW CATALYST OF CESIUM CHLORIDE

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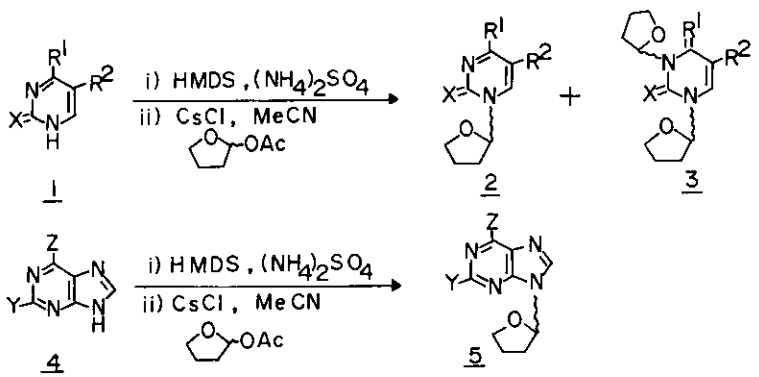
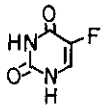
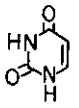
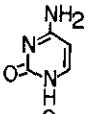
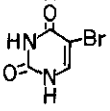
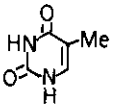
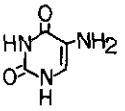
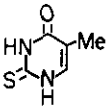
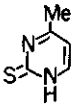
Abstract —— 1-(Tetrahydro-2-furyl)pyrimidine and 9-(tetrahydro-2-furyl)purine derivatives were successfully synthesized in good yields by the reactions of trimethylsilylated pyrimidine and purine bases with 2-acetoxytetrahydrofuran using a new catalyst of cesium chloride in acetonitrile under mild conditions.

A number of pyrimidine and purine derivatives containing modified sugar moieties instead of the naturally occurring ribose or deoxy ribose have been intensively studied.[1,2] Among these, 1-(tetrahydro-2-furyl)-5-fluorouracil was first synthesized by Hiller et al.[1] and shown to be an effective cancer therapeutic agent which can be given orally and shows relatively low toxicity.[2] Thus, intensive studies have been directed toward the synthesis of 1-(tetrahydro-2-furyl)pyrimidine derivatives where a large number of reports[1-6] dealing with the preparation have apeared. While, 9-(tetrahydro-2-furyl)purines exhibit significant antitumor activity against a varity of experimental tumors.[7] The previously reported synthesis involved the condensations of the bases or trimethylsilyl derivatives with 2,3-dihydrofuran or 2-substituted tetrahydrofuran (2-chloro, 2-acetoxy and 2-alkoxy) in the presence of catalysts,[1,2,4,7] or the fluorination of 1-(tetrahydro-2-furyl)uracil.[5] Friedel-Crafts catalysts[3] and p-toluenesulfonic acid[7] have been well used as the Lewis acid catalysts. During a course of the studies on a new Lewis acid catalysts, we have found that cesium chloride (CsCl) is an excellent agent for the condensation reaction, to yield a predominent alkylation at N^1-position of pyrimidines and a highly regioselective alkylation at N^9-position of purines, in anhydrous acetonitrile under mild conditions. Trimethylsilylated bases of pyrimidines or purines were treated with 2-acetoxytetrahydrofuran (Thf-OAc)[6] in the presence of catalytic amount of cesium chloride (CsCl; 0.1 equivalent amount) to give the corresponding tetrahydro-2-furylated derivatives in good yields.



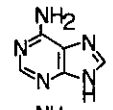
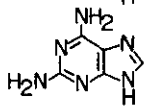
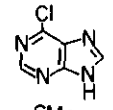
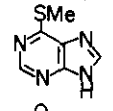
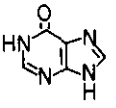
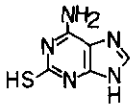
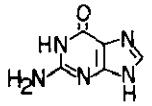
In general procedures, trimethylsilylated bases were prepared by the previously reported methods.[8] 2-Acetoxytetrahydrofuran (2.4-3.0 mmol) and cesium chloride (0.2 mmol) were added to a solution of trimethylsilylated base (2mmol; MeCN: 5ml) with vigorous stirring at 25 °C.
After the complete reaction, the reaction mixture was concentrated and chromatographed on a short column of silica gel (Merck Co., 70-230 mesh, column; 2.5 cm x 5 cm) to afford the corresponding product. The results obtained are shown in Table I and Table II.

Table I

Run	Base	Thf-OAc[a]	Time (h)	Temp (°C)	Yield[b] (%) (2/3)[c]	Ref
1		1.2	3	25	87 (100/-0)	1a
2		2.0	2	25	93 (50/43)	
3		1.5	3	25	93 (78/20)	5a
4		1.5	5	25	83 (100/-0)	9b
5		1.2	3	25	88 (100/-0)	9b
6		1.2	3	50-55	95 (73/22)	9b
7		1.5	0.5	reflux	98 (53/45)	
8		1.5	4	25	50 (100/-0)	10
9		1.5	1.5	50-55	50 (100/-0)	
10		1.5	3	50-55	96 (100/-0)	11a
11		1.5	1.5	25	91 (100/-0)	11b

a) molar ratio b) isolated yields
c) the ratio of two isomers (N^1-substituted isomer/N^1,N^3-disubstituted isomer)

Table II.

Run	Base (B)	Thf-OAc[a]	Time (h)	Temp (°C)	Yield (%)[b] (5)	Ref
1		1.5	5	25	92	7b
2		1.5	4	25	98	11c
3		1.5	3	25	96	7b
4		1.5	1.5	25	98	7b
5		1.5	4	25	97	7a
6		1.5	4	25	70	11d
7		1.5-2.0	4	25	50	7a
8		1.5	3	50-55	50	

a) molar ratio

b) isolated yields (N^9-isomer). In these reactions, only N^9-substituted isomer (5) was isolated.

It is note worthy that the condensation using cesium chloride showed the regioselectivity for the alkylation at N^1-position of pyrimidines and at N^9-position of purines.[12] Cesium chloride seems to be more promising catalyst in comparison with such Lewis acids as $SnCl_4$, $AlCl_3$, and $TiCl_4$, because it gives higher yields under mild conditions and is easier to handle, and simpler to work up. The best yields were obtained using small excess amount of Thf-OAc over the trimethylsilylated bases (1.2~1.5 equivalent amount). When the relative amount of Thf-OAc and the reaction temperature were increased, the reaction time was reduced. However, in the cases of pyrimidines, 3-isomer, overalkylated at N^3-position was also obtained together with 2 (Table I, Runs 2,3,6 and 7). Cesium chloride was proved to be a good catalyst for the condensation reaction. It may be assumed that Thf-OAc is activated first by cesium chloride through the interaction between cesium cation and the tetrahydrofuran ether oxygen to promote the carbonium electrophilicity at the C^2-posion.[13]

Though the role of cesium chloride is not yet clear, it may be promising catalyst and widely applicable for the preparation of pyrimidine and purine derivatives containing tetrahydrofuran analogue moiety.

ACKNOWLEDGEMENTS

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10. Japan Kokai Pat., 53-95980 (1978).
11. (a) ^{1}H Nmr (Me_2SO-d_6, δ, ppm) 2.0 (s, 3H, CH_3), 2.2 (m, 4H, CH_2), 4.2 (m, 2H, OCH_2C), 6.6 (t, J=2Hz, 1H, OCHC), 7.5 (s, 1H, C_6H), 12.5 (br s, 1H, 2-SH), mass (m/z): 212 (M^+). (b) ^{1}H Nmr ($CDCl_3$, δ, ppm) 2.0 (m, 4H, CH_2), 2.5 (s, 3H, CH_3), 4.0 (m, 2H, OCH_2C), 6.5 (t, J = 2 Hz, 1H, OCHC), 6.9-8.5 (dd, J = 5 Hz and 5 Hz, C_5H, C_6H), mass (m/z): 196 (M^+). (c) ^{1}H Nmr (Me_2SO-d_6, δ, ppm) 2.3 (m, 4H, CH_2), 4.0 (m, 2H, OCH_2C), 6.0 (br s, 2H, 6-NH_2), 7.9 (s, 1H, C_8H), mass (m/z): 220 (M^+). (d) ^{1}H Nmr (Me_2SO-d_6, δ, ppm) 2.2 (m, 4H, CH_2), 4.0 (m, 2H, OCH_2C), 6.2 (t, J = 2 Hz, 1H, OCHC), 6.8 (br s, 2H, 6-NH_2), 8.2 (d, 2H, C_2H, C_8H).
12. The products were analyzed by hplc (RP-18, MeOH : H_2O = 2 : 1).
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