Aldol Reaction of Enol Acetates and Lactols with *N*-Chlorosuccinimide and Tin(") Chloride. Diastereoselective Synthesis of Disubstituted Cyclic Ethers

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Lactols reacted with enol acetates by a Lewis acid reagent, derived from *N*-chlorosuccinimide and tin(II) chloride, to produce 2-acetonyl cyclic ethers diastereoselectively.

N-Chlorosuccinimide (NCS)/tin(11) chloride/alcohol reagents can be used in the aldol reaction of isopropenyl acetate with aldehydes to produce 4-alkoxybutan-2-ones.¹ The key steps of this reaction are the formation of alkoxytrichlorotins having Lewis acidity, followed by formation of hemiacetals from the alkoxytrichlorotins and aldehydes. We tried to apply NCS/ SnCl₂ reagent to the aldol reaction of enol esters with cyclic hemiacetals (lactols), cyclic tautomers of ω -hydroxy aldehydes. Lactols react in two ways with carbon nucleophiles in the presence of a Lewis acid; one is as with ω -hydroxy aldehyde,² the other is *via* cyclic oxycarbenium ion.^{3,4} We report here the selective aldol reaction of enol acetates and lactols proceeding by the cyclic oxycarbenium ion mode: the formation of cyclic oxycarbenium ions from lactols and NCS/SnCl₂.

An aldol reaction of 2-hydroxy-5-pentyltetrahydrofuran (1;



Scheme 1 Reagents and conditions: lactol 1 (1 mmol), enol acetate 2 (2 mmol), $SnCl_2$ (2 mmol), NCS (2 mmol), CH_2Cl_2 (3 ml), -30-5 °C



Scheme 2 Reagents and conditions: ω -hydroxy aldehyde 4 (1 mmol), isopropenyl acetate (2 mmol), SnCl₂ (2 mmol), NCS (2 mmol), CH₂Cl₂ (3 ml), 5 °C, 20 min

Table 1 Aldol reaction of lactols and enol acetates with NCS/SnCl2^a

n = 1, $R^1 = H$, $R^2 = C_5 H_{11}$) and isopropenyl acetate (2, $R^3 =$ Me, $R^4 = H$) was investigated with SnX_2 (X = F, Cl, Br) and NCS (or NBS) under various conditions. Using SnCl₂ and NCS in dichloromethane at -30-5 °C led to the formation of 2-acetonyl-5-pentyltetrahydrofuran in good yields (80-88%, diastereoisomer ratio; 60:40). The aldol reaction of other lactols 1 (n = 1 and 2) with enol acetates 2 proceeded under the same conditions as those of 1 (n = 1, $R^1 = H$, $R^2 = C_5 H_{11}$) to produce cyclic ethers 3 (Scheme 1). Several representative results are summarized in Table 1. In the reaction of fivemembered lactols, the substituent on position 3 influenced the addition (diastereoselectivity) more strongly than that on position 5 (entries 1-12). The reaction of a 5-substituted sixmembered lactol exhibited high diastereoselectivity, in contrast with that of five-membered lactols (entries 13 and 14). ω -Hydroxy aldehydes 4 also reacted with $2(R^3 = Me, R^4 = H)$ in the presence of NCS/SnCl₂ via internal hemiacetalization¹ to produce 2-acetonyl cyclic ethers 5 diastereoselectively. These results suggest that this reaction proceeded via the formation of tin alkoxide of lactol, followed by that of cyclic oxycarbenium ion.

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Entry	R۱	Lactol 1 R ²	n	Enol ace R ³	etate 2 R ⁴	<i>Т/</i> °С	Yield of 3 (%)	Diastereoisomer ratio ^b
1	н	C ₅ H ₁₁	1	Ме	Н	5	82	42:58
2	Н	C ₅ H ₁₁	1	Me	н	-10	88	40:60
3	н	C ₅ H ₁₁	1	Me	н	-30	80	41:59
4	н	C ₄ H ₁₁	1	Ph	н	5	26	43 : 57
5	н	C _s H ₁₁	1	(CH ₂) ₄		5	51	<i>c</i>
6	Н	Me	1	Me	Й Н	5	43	47 : 53
7	н	Ph	1	Me	н	5	44	50:50
8	C_6H_{13}	н	1	Me	н	5	98	19:81
9	C ₆ H ₁₃	н	1	Me	н	-20	86	20:80
10	C ₆ H ₁₃	Н	1	Ph	н	5	94	10:90
11	C ₆ H ₁₃	н	1	$(CH_2)_4$		5	45	
12	Me	н	1	Mc	Н	5	40	27:73
13	н	C ₅ H ₁₁	2	Me	н	5	64	11:89 ^d
14	н	C _s H ₁₁	2	Me	н	-20	72	$2:98^{d}$
15	C_5H_{11}	H	2	Me	Н	5	60	30:70

^{*a*} The reaction was almost complete after adding NCS for 20 min. ^{*b*} The stereochemistry (*syn* and *anti*) of the diastereoisomers was not confirmed. The ratio was determined by 270 MHz ¹H NMR (JEOL GX-270) and GC (PEG 20M capillary column, 0.25 mm \times 30 m). ^{*c*} The diastereoisomer ratio was not confirmed. ^{*d*} Anti isomer was found to be major by ¹³C NMR. See ref. 5.