

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

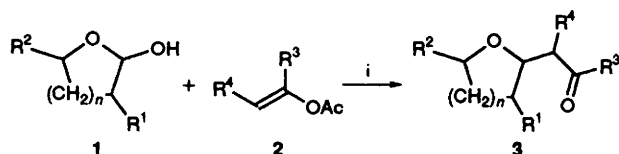
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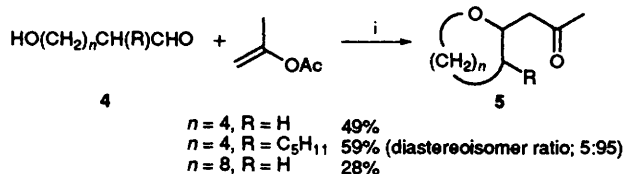
Lactols reacted with enol acetates by a Lewis acid reagent, derived from *N*-chlorosuccinimide and tin(II) chloride, to produce 2-acetyl cyclic ethers diastereoselectively.

*N*-Chlorosuccinimide (NCS)/tin(II) chloride/alcohol reagents can be used in the aldol reaction of isopropenyl acetate with aldehydes to produce 4-alkoxybutan-2-ones.<sup>1</sup> 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/SnCl<sub>2</sub> 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,<sup>2</sup> the other is *via* cyclic oxycarbenium ion.<sup>3,4</sup> 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/SnCl<sub>2</sub>.

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



**Scheme 1** Reagents and conditions: lactol **1** (1 mmol), enol acetate **2** (2 mmol), SnCl<sub>2</sub> (2 mmol), NCS (2 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3 ml), -30–5 °C



**Scheme 2** Reagents and conditions: ω-hydroxy aldehyde **4** (1 mmol), isopropenyl acetate (2 mmol), SnCl<sub>2</sub> (2 mmol), NCS (2 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3 ml), 5 °C, 20 min

$n = 1, R^1 = H, R^2 = C_5H_{11}$ ) and isopropenyl acetate (**2**, R<sup>3</sup> = Me, R<sup>4</sup> = H) was investigated with SnX<sub>2</sub> (X = F, Cl, Br) and NCS (or NBS) under various conditions. Using SnCl<sub>2</sub> and NCS in dichloromethane at -30–5 °C led to the formation of 2-acetyl-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** ( $n = 1, R^1 = H, R^2 = C_5H_{11}$ ) to produce cyclic ethers **3** (Scheme 1). Several representative results are summarized in Table 1. In the reaction of five-membered 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 six-membered 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<sup>3</sup> = Me, R<sup>4</sup> = H) in the presence of NCS/SnCl<sub>2</sub> *via* internal hemiacetalization<sup>1</sup> to produce 2-acetyl 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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### References

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**Table 1** Aldol reaction of lactols and enol acetates with NCS/SnCl<sub>2</sub><sup>a</sup>

| Entry | R <sup>1</sup>                 | Lactol 1<br>R <sup>2</sup>     | <i>n</i> | Enol acetate 2<br>R <sup>3</sup> | R <sup>4</sup> | T/°C | Yield of 3<br>(%) | Diastereoisomer<br>ratio <sup>b</sup> |
|-------|--------------------------------|--------------------------------|----------|----------------------------------|----------------|------|-------------------|---------------------------------------|
| 1     | H                              | C <sub>5</sub> H <sub>11</sub> | 1        | Me                               | H              | 5    | 82                | 42:58                                 |
| 2     | H                              | C <sub>5</sub> H <sub>11</sub> | 1        | Me                               | H              | -10  | 88                | 40:60                                 |
| 3     | H                              | C <sub>5</sub> H <sub>11</sub> | 1        | Me                               | H              | -30  | 80                | 41:59                                 |
| 4     | H                              | C <sub>5</sub> H <sub>11</sub> | 1        | Ph                               | H              | 5    | 26                | 43:57                                 |
| 5     | H                              | C <sub>5</sub> H <sub>11</sub> | 1        | (CH <sub>2</sub> ) <sub>4</sub>  | H              | 5    | 51                | — <sup>c</sup>                        |
| 6     | H                              | Me                             | 1        | Me                               | H              | 5    | 43                | 47:53                                 |
| 7     | H                              | Ph                             | 1        | Me                               | H              | 5    | 44                | 50:50                                 |
| 8     | C <sub>6</sub> H <sub>13</sub> | H                              | 1        | Me                               | H              | 5    | 98                | 19:81                                 |
| 9     | C <sub>6</sub> H <sub>13</sub> | H                              | 1        | Me                               | H              | -20  | 86                | 20:80                                 |
| 10    | C <sub>6</sub> H <sub>13</sub> | H                              | 1        | Ph                               | H              | 5    | 94                | 10:90                                 |
| 11    | C <sub>6</sub> H <sub>13</sub> | H                              | 1        | (CH <sub>2</sub> ) <sub>4</sub>  | H              | 5    | 45                | — <sup>c</sup>                        |
| 12    | Me                             | H                              | 1        | Me                               | H              | 5    | 40                | 27:73                                 |
| 13    | H                              | C <sub>5</sub> H <sub>11</sub> | 2        | Me                               | H              | 5    | 64                | 11:89 <sup>d</sup>                    |
| 14    | H                              | C <sub>5</sub> H <sub>11</sub> | 2        | Me                               | H              | -20  | 72                | 2:98 <sup>d</sup>                     |
| 15    | C <sub>5</sub> H <sub>11</sub> | H                              | 2        | Me                               | H              | 5    | 60                | 30:70                                 |

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