REACTIVITY OF THE PYRIDYLTHIOSILYL ENOL ETHER -ROUTE TO β-LACTONE AND β-LACTAM -

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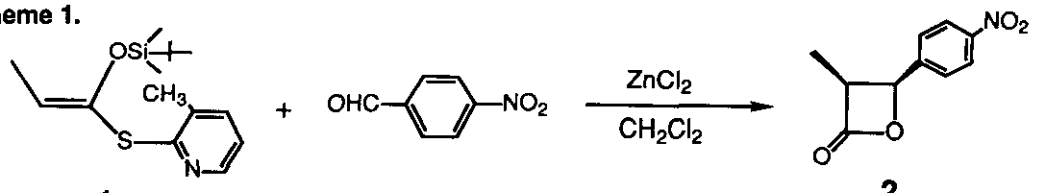
Abstract- A simple and facile method for β-lactone and β-lactam syntheses based on a Lewis acid promoted pyridylthiosilyl enol ether (1) addition to an aldehyde or Schiff base is described.

In the foregoing paper we have reported a high yielding and convenient method for the preparation of Z(O)-pyridylthiosilyl enol ether(1) and it's successful application to the synthesis of a key intermediate for the 1β-methylcarbapenem antibiotics. The latent reactivity of this active silyl enol reagent which can be activated simply by releasing the pyridylthio leaving group is a feature which we sought to investigate further. Here we describe our preliminary results of the work directed toward that purpose.

As a first trial of the reaction of reagent (1) to an aldehyde, a reaction of the silyl enol ether with *p*-nitrobenzaldehyde was performed in methylene chloride in the presence of 1 *eq.* of $ZnCl_2$ at room temperature(r.t.) for 5 h. After work up as per usual, the tlc separation from the uv detectable region gave the 3,4-*cis*-β-lactone in 23 % isolated yield. Ir($CHCl_3$) cm^{-1}: 1830, 1535, 1345. Ms *m/z* : 207(M^+), 163. Nmr($CDCl_3$) δ: 0.97(3H, d, J=7.9 Hz), 4.29(1H, dq, J=7.9 and 6.6 Hz), 5.76(1H, d, J= 6.6 Hz), 7.63~7.68(2H), 8.20~8.28(2H).

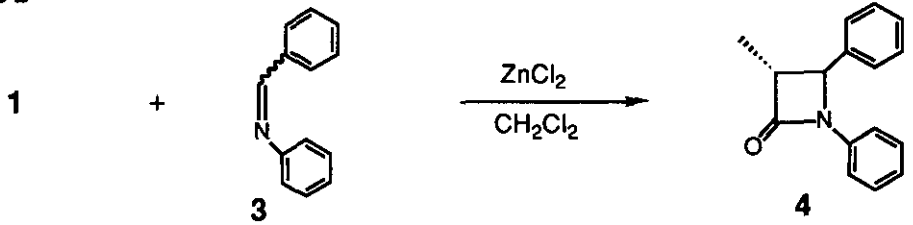
Scheme 1.



1 **2**

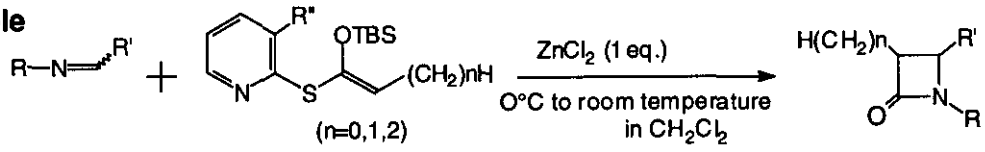
The next application was directed towards the synthesis of a new β-lactam system. The typical Schiff base, benzylideneaniline (1 *eq.*) was mixed with the the pyridylthiosilyl enol ether (1)(1 *eq.*) in methylene chloride, and then to this mixture was added $ZnCl_2$(1 *eq.*) under ice-cooling.

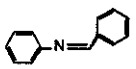
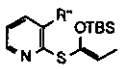
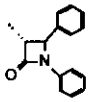
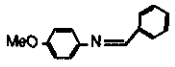
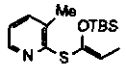
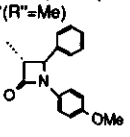
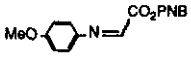
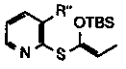
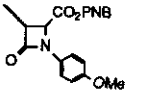
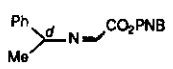
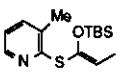
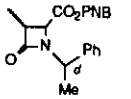
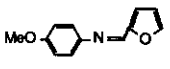
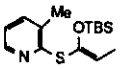
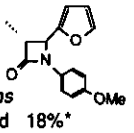
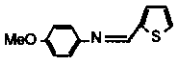
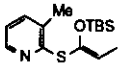
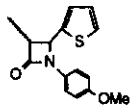
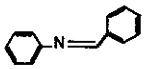
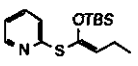
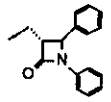
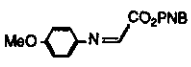
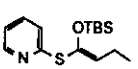
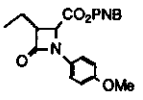
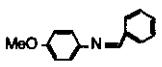
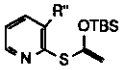
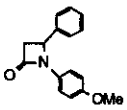
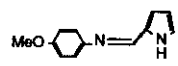
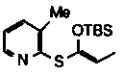
Scheme 2



3 **4**

Table



Run	Imine	Enol ether (n= 0, 1, 2)	Products (*dl*)
1.		 n=1	 *trans* m p 110°C yield 80%(R"=Me), 50%(R"=H) 94%*(R"=Me)
2.		 n=1	 *trans* m p 94°C yield 68%
3.		 n=1	 *trans:cis* =1:1 m p 146°C (*trans*) yield 87%(R"=Me), 73%(R"=H)
4.		 n=1	 *diastereomers* 1:1:1:1 yield 61%
5.		 n=1	 *trans* yield 18%*
6.		 n=1	 *trans:cis* =1:1 yield 34%*
7.		 n=2	 *trans* m p 120°C yield 41%
8.		 n=2	 *trans:cis* =2:1 yield 48%
9.		 *n=0*	 m p 86°C yield 29%(R"=H) 31%(R"=Me)
10.		 n=1	no reaction* ($ZnCl_2$ 2 eq.)

* silyl enol ether 2 eq.

After stirring for 3h at room temperature (by tlc monitoring) methylene chloride was added and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave the crystalline *trans*-β-lactam in 80 % yield, *mp* 110~110.5 °C. Nmr($CDCl_3$) δ: 7.46 ~ 6.97(10H, arom), 4.57(1H, d, J=2.7 Hz), 3.10(1H, dq, J= 7.3 and 2.7 Hz), 1.46(3H, d, J=7.3 Hz). The representative examples are listed in the **Table.** The order of the reactivity of the Lewis acids is as follows: $ZnCl_2$=$AlCl_3$=$ZnCl_2$ >BF_3·OEt_2 =$BiCl_3$ =$SnCl_4$. The use of a catalytic amount of $ZnCl_2$ in the reaction of the run 2. in the Table gave the yield of 23 % after 2 days, therefore the use of 1 *eq.* of Lewis acid is necessary for adequate levels of conversion.

In view of the stereoselectivity attained we are assuming the mechanism of this β-lactam formation reaction to be step-wise, and the present method is a novel one for the β-lactam ring formation reaction.[1]

REFERENCES

1) K.Hirai, J. Syn. Org. Chem. Jpn., **1992**, *50*, 112. and the references cited therein.

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