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

Koichi Hirai*, Hiroshi Homma , and Isamu Mikoshiba

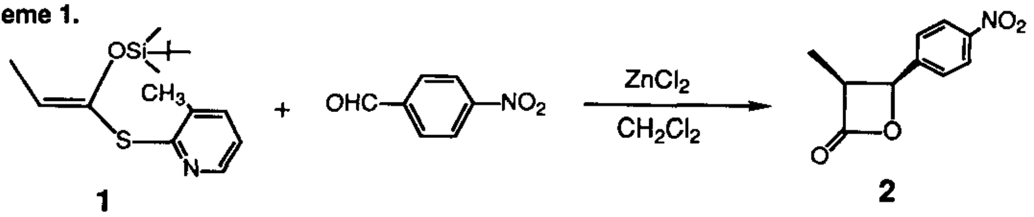
New Lead Research Lab., Sankyo Co.,Ltd.,
1-2-58 Hiromachi, Shinagawa-ku,Tokyo140, Japan

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.

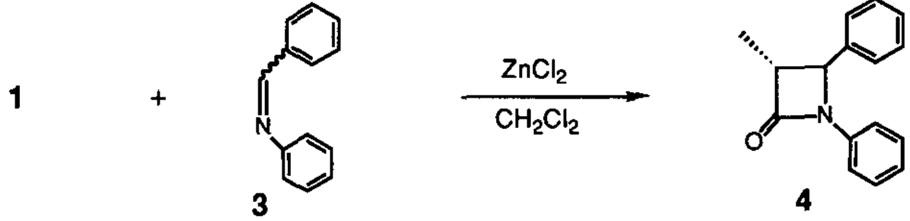
As a first trial of the reaction of reagent (1) to an aldehyde, a reaction of the silyl enol ether with *p*-nitrobenzaldehyde was performed in methylene chloride in the presence of 1 *eq.* of $ZnCl_2$ at room temperature(r.t.) for 5 h. After work up as per usual, the tlc separation from the uv detectable 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.

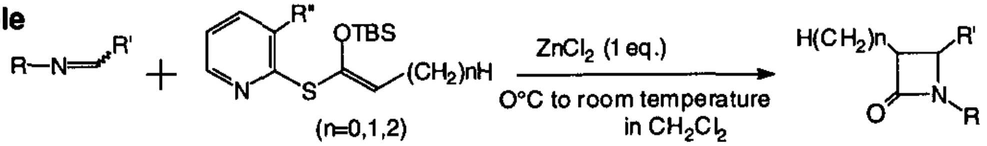


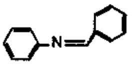
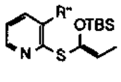
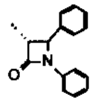
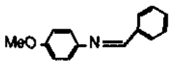
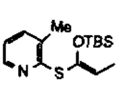
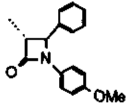
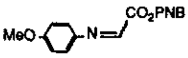
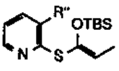
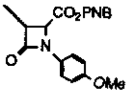
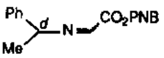
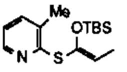
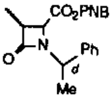
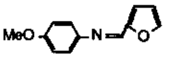
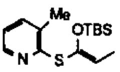
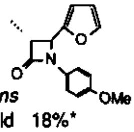
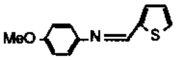
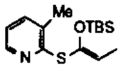
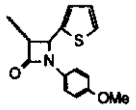
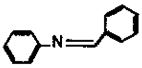
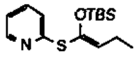
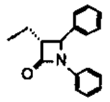
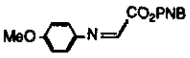
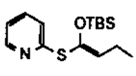
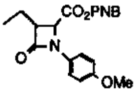
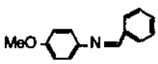
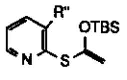
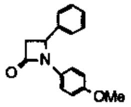
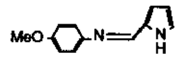
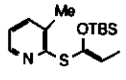
The next application was directed towards the synthesis of a new β-lactam system. The typical Schiff base, benzylideneaniline (1 *eq.*) was mixed with the the pyridylthiosilyl enol ether (1)(1 *eq.*) in methylene chloride, and then to this mixture was added $ZnCl_2$(1 *eq.*) under ice-cooling.

Scheme 2



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* (ZnCl2 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 MgSO4. Evaporation of the solvent gave the crystalline *trans*-β-lactam in 80 % yield, *mp* 110~110.5 °C. Nmr(CDCl3) 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: $ZnCl_2$=$AlCl_3$=$ZnCl_2$ >$BF_3 \cdot OEt_2$ =$BiCl_3$ =$SnCl_4$. 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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