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Synthesis of β-Lactams from Novel Stannous Enolates and Imines

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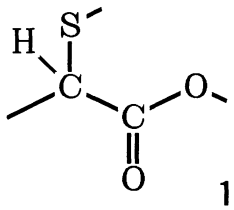
From the oxygen esters containing sulfur α-substituent, corresponding stannous enolates were prepared by the use of stannous trifluoromethanesulfonate. The enolates reacted with various imines to provide β-lactams.

We previously reported[1] that the electron withdrawing effect of sulfur atom[2] made possible to prepare boron enolates of α-substituted ester (1) by the use of dialkylboryl trifluoromethanesulfonate(triflate) and that they reacted with aldehydes to provide aldol products stereoselectively. Subsequently we found that stannous enolates could also be generated from oxygen esters 1 in the same manner using stannous triflate. In this communication, we would like to report the preparation of these novel stannous enolates of oxygen ester 1, and their reaction with imines.



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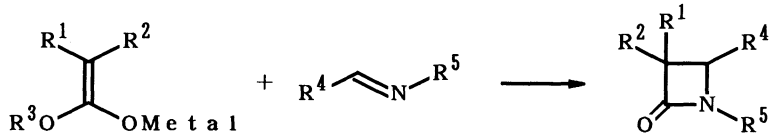
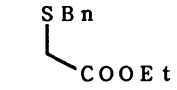
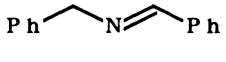
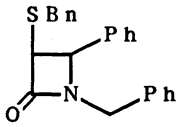
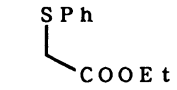
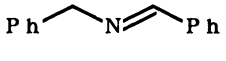
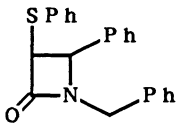
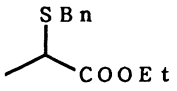
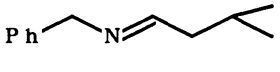
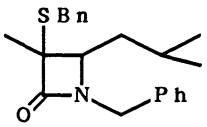
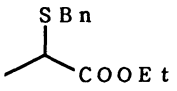
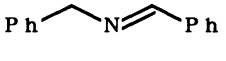
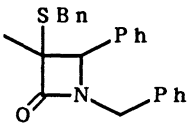
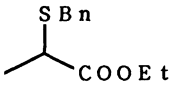
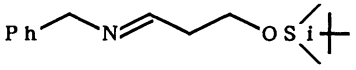
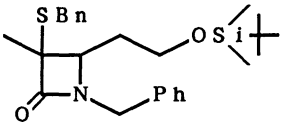
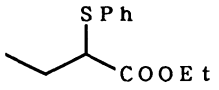
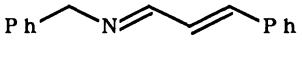
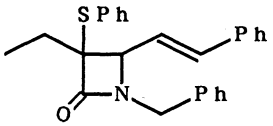
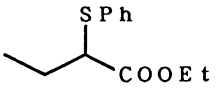
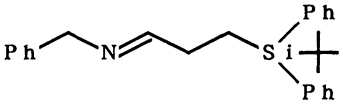
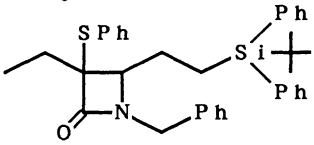
In recent few years, among the several methods developed for the construction of β-lactam ring, ester-imine condensation cyclization route has been recognized to be one of the most useful method.[3] They directly and simply provide the desired substituted β-lactam ring system based on the easy availability of the corresponding imines.



2 + 3 → 4

Nevertheless, the main drawback of this approach relies on the difficulty to use enolizable imines prepared from the α-hydrogen atom containing aldehydes.[4] There are only a few reports in particular on reactions using enolizable imines as acceptors of enolate,[5] because usually used strongly basic lithium enolates give rise to various type of competitive side reactions, elimination and oligomerization, caused by α-proton abstraction of imines during the condensation reaction.[6]

Table 1. Preparation of β-Lactams from α-Substituted Esters and Imines

Entry	Ester (1)	Imine (3)	Lactams (4) [a]	Yield/%[b]	Isomer[c]
a				80	trans
b				82	trans
c				85	2 : 1[d]
d				91	2 : 1[d]
e				86	5 : 2[d]
f				86	3 : 2[d]
g				79	5 : 2[d]

a) All the products gave satisfactory IR, ^{1}H NMR, and MS spectra.

b) Reaction conditions were not optimized and the yields were calculated from used starting ester 1.

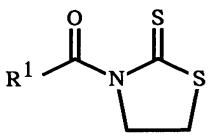
c) The ratio was estimated by ^{1}H NMR (270 MHz) spectra.

d) Relative stereochemistries were not assigned.

In order to overcome this problem, we examined to use stannous enolates of oxygen esters. A series of β-lactams was synthesized by the use of these novel stannous enolates. A typical experimental procedure was as follows. An ester possessing sulfur α-substituent (1.0 mmol) was added to a suspension of stannous triflate (1.5 mmol) and diisopropylethylamine (2.0 mmol) in 10 ml of dichloromethane at -40 °C. After enolization was completed to be clarified reaction mixture, this enolate was allowed to react with an imine (1.0 mmol) at -20 °C. At lower temperature, this reaction proceeded very slow and significant quantities of starting material were recovered. Subsequent usual work-up and following purification by silica-gel chromatography furnished β-lactam compounds in high yield.

Thus, a series of β-lactams were synthesized from a variety of α-substituted oxygen ester and imines by the novel addition cyclization reaction. All results are collected in Table 1. and in every cases β-lactams were obtained in good yields. When phenylthioacetate or benzylthioacetate were used as starting material, exclusive formation of the 3,4-*trans* β-lactam was observed (entries a and b). The enolizable imines containing appropriate functional group also reacted satisfactorily (entries c, e, and g), even though the imines susceptible to β-elimination (entry e). The arbitrariness of imine was advantageous for the further elaboration, and generality of this reaction was recognized. Improvement of *cis* and *trans* stereoselectivity are now under way.

Other related stannous enolates were also investigated for the construction of β-lactam ring. Generally used stannous enolates of 3-acylthiazolidine-2-thione (5)[7] were inert to imines and did not provide β-lactams at all, because imines usually have only poor electrophilicity toward the enolates compared with the corresponding carbonyl compounds.[8] Stannous enolate of 5 does not have sufficient ability to activate imino group by the assuming internal chelation of stannous cation. The stannous atom in our novel oxygen ester enolate has considerable affinity to the nitrogen atom[9] to activate efficiently the imino



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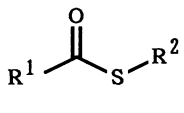

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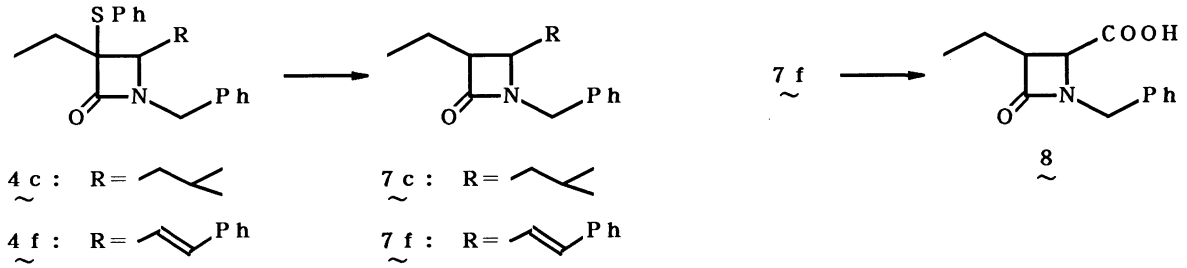
group and promote effectively the condensation. All attempts to prepare stannous enolate using stannous triflate from thiol esters (6) were also failed. Thus, stannous enolate of oxygen ester prepared by the now developed method was inevitably used, and much milder reaction conditions were adequate to the condensation with enolizable imines.

These β-lactams synthesized by the new method were containing sulfur atom at 3-position, which allowed further elaboration towards various useful precursors. The reductive removal of the phenylthio group was accomplished by the treatment with AIBN and tributyltin hydride without any side reactions. For example, compound (4c) (2:1 mixture of isomer) was reduced to (7c) in 95% yield in favor of *trans* isomer (*trans*:*cis*=7:1),[10] and compound (4f) (3:2) was reduced to (7f) in the same way in 93% yield (*trans*:*cis*=5:1). Oxidative cleavage of the double bond in 7f with osmium tetroxide and sodium periodate and following oxidation by potassium permanganate afforded an azetidinone-4-carboxylic acid derivative (8).[3]



Consequently, this newly developed method for the β-lactam synthesis is quite favorable compares with the existing methods in terms of simplicity, flexibility and availability of the versatile starting materials.

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