CHEMISTRY LETTERS, pp. 2035-2038, 1992.

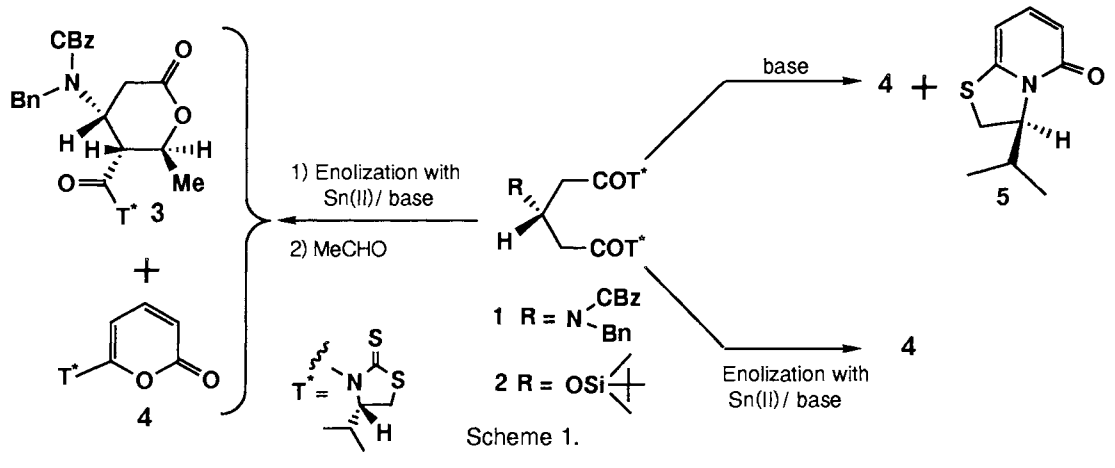
A New Convenient Synthesis of α-Pyrone and α-Pyridone Derivatives

Yoshimitsu NAGAO,* Toshiaki TOHJO,† Motoo SHIRO,††
Yusuke YUKIMOTO,† and Sadakatsu SHIMADA†
Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770
†Production Technology Research Laboratories, Daiichi Pharmaceutical Co., Ltd.,
16-13, Kitakasai 1-Chome, Edogawa, Tokyo 134
††Rigaku Corporation, 3-9-12, Matsubara-cho, Akishima, Tokyo 196

(4*S*)-Isopropyl-1,3-thiazolidine-2-thione diamide of 3-(*t*-butyldimethylsilyloxy)glutaric acid was treated with bases to give α-pyrone and α-pyridone derivatives possessing a chiral thiazolidine moiety. On the other hand, treatment of the diamide with $Sn(CF_3SO_3)_2$ and *N*-ethylpiperidine afforded the α-pyrone derivative exclusively.

Naturally occurring α-pyrone derivatives seem to be attractive from the viewpoints of their various physiological activities; cardiac, local anesthetic, antiinflammatory, amebicidal, and anticonvulsive activities.[1] Therefore, a number of α-pyrone derivatives have been synthesized.[2] We now describe a convenient synthesis of new α-pyrone and α-pyridone derivatives possessing a chiral thiazolidine moiety.

Recently, we reported that aldol reaction of (4*S*)-isopropyl-1,3-thiazolidine-2-thione[(4*S*)-IPTT] diamide **1** of 3-(*N*-benzyl-*N*-benzyloxycarbonyl)aminoglutaric acid with acetaldehyde gave the δ-lactone **3** bearing three consecutive asymmetric centers and a product **4** as a yellow oil (Scheme 1).[3] Crystallization of the oily substance from AcOEt-hexane afforded yellow plates [mp 95.5-96 °C, $[\alpha]_D^{23}$ -305.2°(c 1.2, $CHCl_3$)]. The structure of **4** was determined by its X-ray analysis as an α-pyrone derivative as shown in Fig. 1.[4] Then,



Scheme 1.

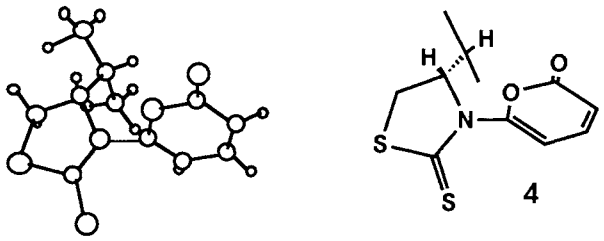


Fig. 1. Crystallographic structure of **4**.

the preparation of **4** has been investigated employing (4*S*)-IPTT diamide **2** of 3-(*t*-butyldimethylsilyloxy)glutaric acid[5] which seemed to be more suitable for the formation of the α-pyrone moiety than compound **1**. Cyclization reaction of **2** (1 mmol) was attempted in the presence of several bases (1.1 mmol) such as K_2CO_3, NaH, KH, and $NaCH_2SOCH_3$ in DMF (1 ml), THF (1 ml), or DMSO (1 ml) at room temperature for 1-3 h. Under the basic conditions described above, the α-pyrone derivative **4** (17-37% yields)[6] and a bicyclic α-pyridone derivative **5** [colorless oil, $[\alpha]_D^{23}$ +210.5° (c 0.5, $CHCl_3$), 44-63% yields][7] were obtained respectively (Scheme 1 and Runs 1-4 in Table 1). However, treatment of **2** (1 mmol) with a mixture of $Sn(CF_3SO_3)_2$ (1 mmol)[8] and *N*-ethylpiperidine (1.1 mmol)[8] in CH_2Cl_2 (7.5 ml) at -40 °C for 2 h afforded the α-pyrone derivative **4** as a sole product in 63% yield (Run 5 in Table 1). Chemical structure of the α-pyridone derivative **5** was assigned on the basis of the similarity of its ^1H and ^{13}C NMR spectra[6,7] and EI-mass fragmentation mode[9] to those of the α-pyrone derivative **4** (Figs. 2 and 3).

Table 1. Synthesis of α-Pyrone and α-Pyridone Derivatives, **4** and **5**, from **2**

Run	Reagent	Solvent	Temp / °C	Time / h	Yield[a]/% **4**	Yield[a]/% **5**
1	K_2CO_3	DMF	rt[b]	3	37	44
2	NaH	THF	〃	1	19	47
3	KH	〃	〃	1	17	51
4	$NaCH_2SOCH_3$	DMSO	〃	1	19	63
5	$Sn(CF_3SO_3)_2$ *N*-ethylpiperidine	CH_2Cl_2	-40	2	63	none

a) Isolated yield based on (4*S*)-IPTT diamide **2**. b) rt = Room temperature.

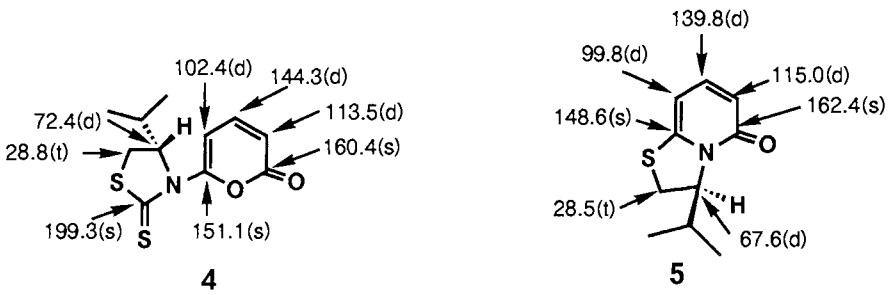


Fig. 2. ^{13}C NMR (125.7 MHz, δ ppm in $CDCl_3$-TMS) spectral data of **4** and **5**.

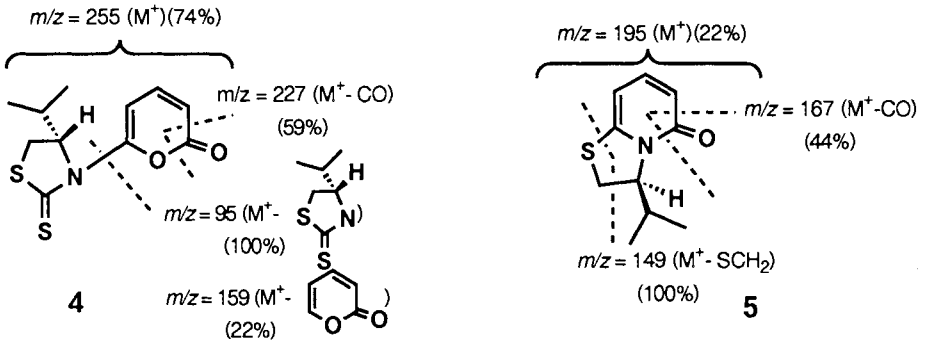
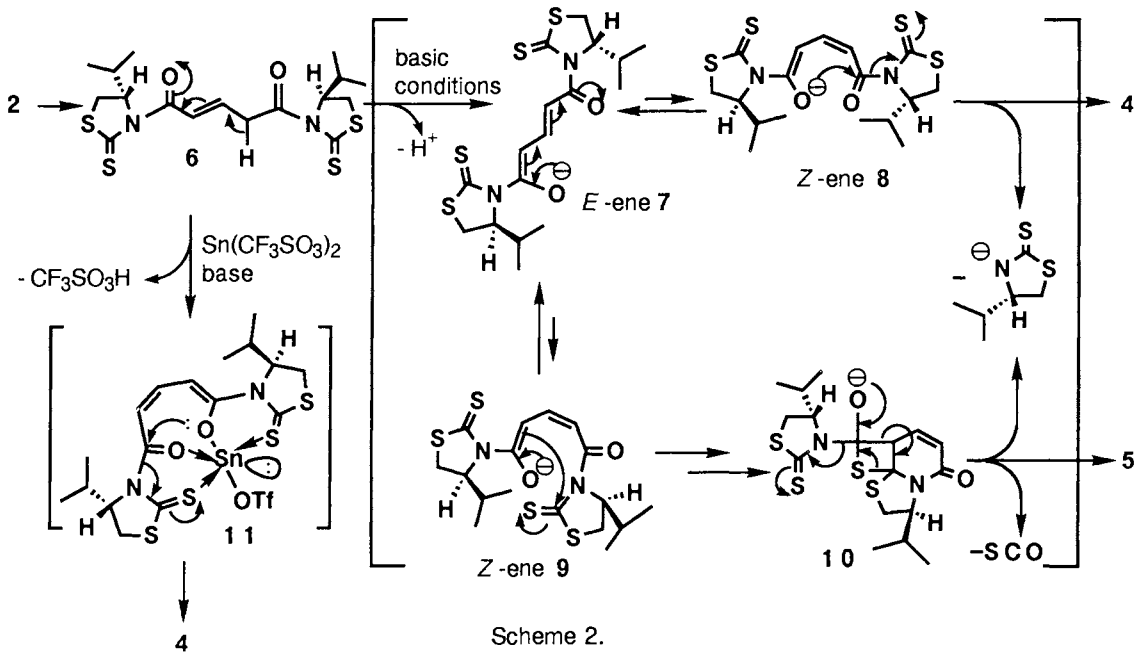


Fig. 3. Fragmentation mode of **4** and **5** on their EI-Mass spectra.

Different reaction aspect of **2** under basic conditions or Sn(II)-promoted conditions may be explained as follows. Elimination of the silyloxy group of **2** affords an *E*-α,β-unsaturated amide **6** which may be converted to two kinds of *Z*-ene enolates **8** and **9** via *E*-ene enolate **7** in the presence of base as shown in Scheme 2. Thus, the compounds **4** and **5** would be derived from each corresponding *Z*-ene enolate **8** or **9** followed by **10** in a characteristic cyclization manner based on the principle of hard base - hard acid specific affinity[10] for the former or soft base - soft acid specific affinity[10] for the latter (Scheme 2). On the other hand, the Sn(II)-promoted cyclization of **2** may proceed via a chelation-controlled transition state **11**, where the enolate oxygen readily attack the neighboring amide carbonyl carbon to give the α-pyrone **4** exclusively (Scheme 2).



Scheme 2.

Thus, we found a new expedient preparation method for α-pyrone and α-pyridone derivatives (**4** and **5**) which would be promising not only as a candidate of physiologically active agents but also as a chiral synthon for Diels-Alder[11] and Michael type reactions.

References

1) H. J. Mayer, "Ethnopharmacol. Search Psychoact. Drugs [Proc. Symp.]," (1967), pp. 133-140, *Chem. Abstr.*, **92**, 121862r (1980); U. K. Sonfi, S. Dutta, and C. P. Dutt, *Natl. Acad. Sci. Lett.*, **6**, 271 (1983); R. Kretzschmar and H. J. Meyer, *Arch. Int. Pharmacodyn. Ther.*, **175**, 1 (1968); R. Kretzschmar and H. J. Meyer, *ibid.*, **177**, 261 (1969).

2) G. P. Ellis, "Comprehensive Heterocyclic Chemistry," ed by A. J. Boulton and A. Mckilop, Pergamon Press, Oxford (1984), Vol. 3, pp. 647-736 and references cited therein.

3) Y. Nagao, T. Tohjo, M. Ochiai, and M. Shiro, *Chem. Lett.*, **1992**, 335.

4) Crystallographic data of **4**: $C_{11}H_{13}NO_2S_2$, M=255.35, orthorhombic, space group $P2_12_12_1$, a=9.971(2)Å, b=16.249(3)Å, c=7.738(3)Å, V=1254(1)Å^3, Z=4, D_{calc}=1.353 g/cm^3, R=0.055.

5) Y. Nagao, Y. Hagiwara, Y. Hasegawa, M. Ochiai, T. Inoue, M. Shiro, and E. Fujita, *Chem. Lett.*,**1988**, 381.

6) Physical data of **4**: ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.00 (3H, d, J=7.2 Hz), 1.01 (3H, d, J=5.6 Hz), 2.18-2.24 (1H, m), 3.20 (1H, dd, 4.8, 11.1 Hz), 3.52 (1H, dd, J=8.7, 11.1 Hz), 5.02-5.06 (1H, m), 6.24 (1H, d, J=9.5 Hz), 6.93 (1H, d, 7.1 Hz), 7.47 (1H, dd, J=7.1, 9.5 Hz); ^{13}C-NMR (125.7MHz, $CDCl_3$) δ 16.6 (q), 19.5 (q), 28.8 (t), 30.8 (d), 72.4 (d), 102.4 (d), 113.5 (d), 144.3 (d), 151.1 (s), 160.4 (s), 199.3 (s); IR 1730, 1630 cm^{-1}; λmax (EtOH) 292, 235, 335 nm; EI-MS *m/z* 255 (M^+); HRMS Found: *m/z* 255.0401. Calcd for $C_{11}H_{13}NO_2S_2$: M, 255.0388.

7) Physical data of **5**: ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.93 (3H, d, J=6.8 Hz), 1.03 (3H, d, J=7.3 Hz), 2.6-2.7 (1H, m), 3.19 (1H, d, 11.2 Hz), 3.52 (1H, dd, J=8.3, 11.2 Hz), 5.06 (1H, dd, J=4.9, 8.3 Hz), 6.05 (1H, d, J=6.8 Hz), 6.23 (1H, d, 8.8 Hz), 7.22 (1H, dd, J=6.8, 8.8 Hz); ^{13}C-NMR (125.7MHz, $CDCl_3$) δ 15.9 (q), 18.6 (q), 28.5 (t), 29.2 (d), 67.6 (d), 99.8 (d), 115.0 (d), 139.8 (d), 148.6 (s), 162.4 (s); IR 1640, 1560 cm^{-1}; λmax (EtOH) 245, 330, 340 nm; EI-MS *m/z* 195 (M^+); HRMS Found: *m/z* 195.0694. Calcd for $C_{10}H_{13}NOS$: M, 195.0718.

8) N. Iwasawa and T. Mukaiyama, *Chem. Lett.*, **1983**, 297.

9) W. H. Pirkle, *J. Am. Chem. Soc.*, **87**, 3022(1965).

10) T.-L. Ho, "Hard and Soft Acids and Bases Principle in Organic Chemistry," Academic Press, New York (1977).

11) G. H. Posner, T. D. Nelson, C. M. Kinter, and N. Johnson, *J. Org. Chem.*, **57**, 4083(1992); G. H. Posner, H. Vinader, and K. Afarinkia, *ibid.*, **57**, 4088(1992).

(Received July 27, 1992)