# Formation of Three-membered Rings from γ-Iodoketones and γ-Iodoesters *via* 1,3-Elimination

**Miwako Mori,*[a] Nana Kanda,[a] Yoshio Ban,[b] and Keiichi Aoe[c]**

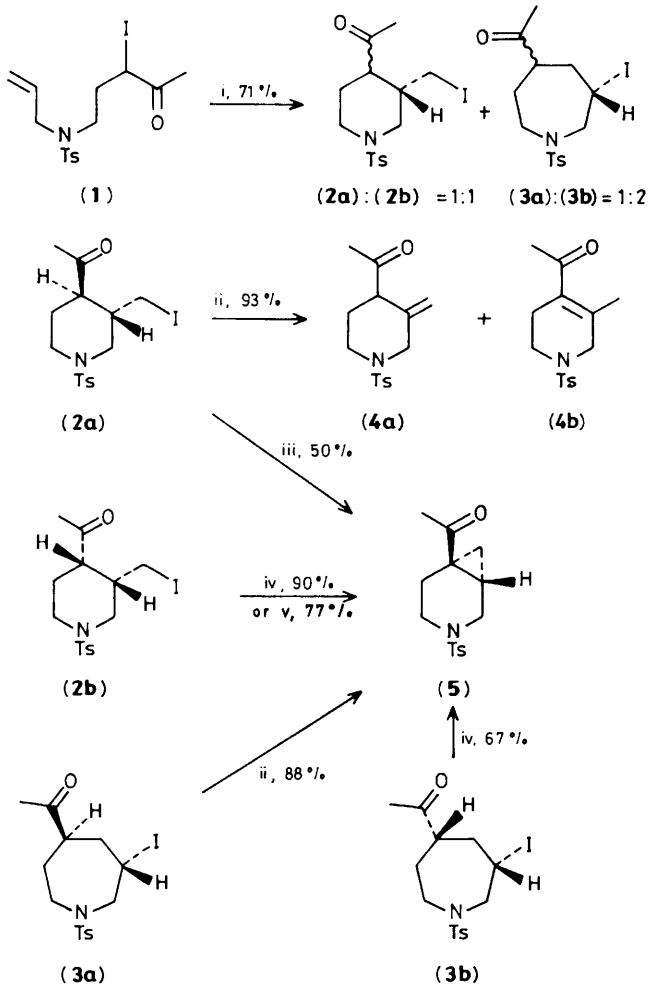
[a] *Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan*
[b] *School of Pharmaceutical Science, Toho University, Miyama 2-2-1, Funabashi 274, Japan*
[c] *Analytical Center, Tanabe Seiyaku Co., Ltd., Toda, Saitama 335, Japan*

γ-Iodoketones, prepared by ene–halogenocyclization of α-haloketones with $Pd(PPh_3)_4$, on treatment with diazabicyclo[5.4.0]undec-7-ene afford three-membered ring compounds in good yield *via syn*-1,3-elimination, presumably *via* W-shaped transition states.

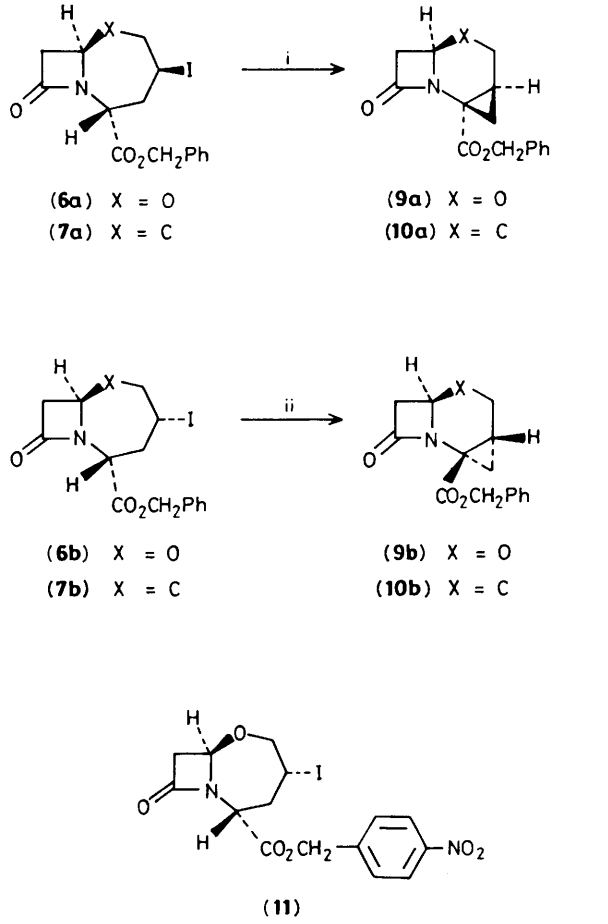
The formation of three-membered rings *via* 1,3-elimination[1] is an important process in organic synthesis. From the results reported to date it appears that base-initiated 1,3-elimination proceeds by a two-step rather than a one-step mechanism and that there is no dominant stereochemical pattern.[2] During the course of our study of ene–halogenocyclization,[3] we have found that the formation of three-membered rings proceeds *via syn*-1,3-elimination, presumably *via* a W-shaped transition state.[1]

When γ-iodoketones (**2a**), (**2b**), (**3a**), and (**3b**), obtained by ene–halogenocyclization[3] of α-iodoketone (**1**) using $Pd(PPh_3)_4$,† were treated with base,[3b] the results were of interest in connection with 1,3-elimination (Scheme 1). Compound (**2a**) was allowed to react with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (benzene, room temp., 5 min) to produce alkenes (**4a**) and (**4b**) in 93% yield [(**4a**) : (**4b**) = 1 : 1], but compound (**2b**) afforded a product (**5**) containing a fused three-membered ring when treated in a similar manner for 1 h (90%). However, when compound (**2a**) was treated with $Bu^tOK$ in $Bu^tOH$ for 1 h it also produced (**5**) in 50% yield along with recovered starting material (33%). In a similar treatment of compound (**2b**) with $Bu^tOK$–$Bu^tOH$, the same product (**5**) was obtained in 77% yield after only 5 min. The same product (**5**) was obtained from compounds (**3a**) and (**3b**) on treatment with DBU but (**3a**) reacted within 5 min while (**3b**) required 1 h. The formation of a three-membered ring from compound (**2a**) on treatment with $Bu^tOK$–$Bu^tOH$ indicates that 1,3-elimination has occurred after epimerization of the carbanion generated on the α-carbon of (**2a**). However, on treatment with DBU if 1,2-elimination in compound (**2a**) or 1,3-elimination in compound (**2b**) proceeds *via* the freely convertible carbanion or the enolate anion, the formation of different products cannot be explained. Furthermore, the

† A solution of α-iodoketone (**1**) and $Pd(PPh_3)_4$ (10 mol%) in the presence of isobutylene oxide[4] in dioxane was stirred at room temperature for 10 min to afford six-membered products (**2a**) (17% yield) and (**2b**) (17%), and seven-membered products (**3a**) (14%) and (**3b**) (23%), but the stereochemistry of these compounds could not be determined from their $^1H$ n.m.r. spectra.




**Scheme 1.** *Reagents:* i, $Pd(PPh_3)_4$; ii, DBU, benzene, room temp., 5 min; iii, Bu$^t$OK, Bu$^t$OH, 1 h; iv, DBU, benzene, 1 h; v, Bu$^t$OK, Bu$^t$OH, 5 min.




**Scheme 2.** *Reagents*: i, DBU, benzene, room temp., 5 min; ii, DBU, benzene, 48 h (X = O) or 24 h (X = C).

difference in the rate of 1,3-elimination for compounds (**3a**) and (**3b**) on treatment with DBU also cannot be explained because the rates of enolate formation for (**3a**) and (**3b**) are considered to be almost the same. *X*-ray analysis‡ shows that the iodomethyl and acetyl substituents of (**2a**) and the iodo and acetyl substituents of (**3a**) are *trans* to each other. Since the proton and the iodomethyl group of the *cis*-compound (**2b**) can easily adopt the W-shaped transition state for 1,3-elimination,[1] the carbanion generated from compound (**2b**) with DBU will attack the iodo group to form the three-membered ring prior to epimerization. However, since the proton and the leaving group in compound (**2a**) cannot adopt the W-shaped geometry without epimerization, 1,2-elimination to give (**4a**) will be favourable.§ On the other hand, since the proton and the iodo group of compound (**3a**) can adopt the W-shaped geometry, three-membered ring formation proceeds rapidly, but the formation of a three-membered ring from (**3b**) can proceed only after epimerization with DBU or conversion into the unstable W-shaped conformation.

We have already demonstrated a synthetic route to oxa- and carba-homocephams using ene–halogenocyclization of α-halgenoesters in the presence of $Pd(PPh_3)_4$.[5] When oxa- and carba-homocephams (**6a,b**) and (**7a,b**) were converted into oxa- and carba-cephams (**9a,b**) and (**10a,b**) respectively, by treatment with DBU (Scheme 2), similar results were

‡ *Crystal Data* for (**2a**): $C_{15}H_{20}NO_3SI$, $M$ = 421.30, monoclinic, space group $P2_1/c$, $a$ = 14.146(3), $b$ = 5.441(1), $c$ = 23.908(4) Å, β = 109.601(8)°, $U$ = 1899.4(5) Å$^3$, $Z$ = 4.

For (**3b**): $C_{15}H_{20}NO_3SI$, $M$ = 421.30, triclinic, space group $P\bar{1}$, $a$ = 11.775(1), $b$ = 13.559(1), $c$ = 5.268(3) Å, α = 97.167(5), β = 92.519(5), γ = 94.844(6)°, $U$ = 830.4(1) Å$^3$, $Z$ = 2.

For (**11**): $C_{15}H_{15}N_2O_6I$, $M$ = 446.20, triclinic, space group $P\bar{1}$, $a$ = 7.944(2), $b$ = 15.908(6), $c$ = 6.860(1) Å, α = 90.34(2), β = 88.50(2), γ = 102.63(3)°, $U$ = 845.7(4) Å$^3$, $Z$ = 2.

Suitable crystals were obtained from n-hexane–ethyl acetate for (**2a**) and (**3b**) and from n-hexane–methyl ethyl ketone for (**11**). Intensity data for both crystals were measured on an automated Rigaku AFC-5 diffractometer using graphite-monochromated Cu-$K_\alpha$ radiation (λ = 1.5418 Å). 2961 Reflections for (**2a**), 2816 for (**3b**), and 2880 for (**11**) were measured, of which 2502, 2645, and 2484, respectively, were judged significant ($|F_o| = 2.67\ \sigma\ |F_o|$). The structures were solved by Patterson and difference Fourier methods and refined by block-diagonal least-squares with anisotropic temperature factors for all non-hydrogen atoms and isotropic ones for all hydrogen atoms. Final $R$ values were 0.048, 0.068, and 0.068 for (**2a**), (**3b**), and (**11**), respectively.

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ An intimate ion pair was generated from compounds (**2a**) and (**2b**) on treatment with DBU in benzene, which prevented epimerization, but the separated anions generated from (**2a**) or (**2b**) by treatment with Bu$^t$OK in Bu$^t$OH had more opportunity to epimerize.[2a]

obtained with respect to 1,3-elimination.[8]‖ Since the proton and the iodo group of the *trans*-substituted (**6a**) and (**7a**)¶ can easily form the W-shaped transition state, the treatment of (**6a**) and (**7a**) gave the three-membered ring at once (5 min). However, formation of (**9b**) and (**10b**) required a long reaction time (24 and 48 h, respectively), because the necessary W-shaped geometry for 1,3-elimination can be adopted only after epimerization or change in conformation.**

We thank Dr. H. Tanida, Shionogi Research Laboratories, Shionogi and Co., Ltd and Professor W. Tagaki, Faculty of Engineering, Osaka City University, who suggested the 1,3-elimination mechanism.

*Received, 23rd December 1986; Com. 1823*

‖ Oxahomocepham (**6b**) was treated with DBU for 48 h to afford oxacepham (**9b**) (80%). However, the other oxacepham (**9a**) was obtained from (**6a**) after only 5 min (85%). Carbahomocephams (**7a**) and (**7b**), obtained as an inseparable mixture, were treated with DBU (5 min) to give carbacepham (**10a**) (55%) and recovered (unreacted) (**7b**) (45%), which was treated again with DBU for 24 h to afford the other carbacepham (**10b**) (79%).

¶ *X*-ray analysis‡ of oxahomocepham (**11**) showed that the iodo and acetyl substituents were *cis*. Comparison of their $^1$H-n.m.r. spectra showed the stereochemistry of (**6b**) to be the same as that of compound (**11**).

** Conversion of oxa- and carba-homocephams (**6b**) and (**7b**) to oxa- and carba-cephams (**9b**) and (**10b**) required a longer reaction time than the conversion of (**3b**) into (**5**) because the seven-membered ring is fused to an azetidinone ring, which inhibits isomerization and adoption of the highly strained W-shaped configuration.

## References

1 For 1,3-elimination, Nickson–Werstiuk notation provides a useful shorthand description of the apparent overall molecular geometry (U, W, *exo*-Sickle, and *endo*-Sickle): A. Nickon and N. H. Werstiuk, *J. Am. Chem. Soc.*, 1967, **89**, 3914.

2 (a) Bordwell and Jarvis have suggested that overall *W*- and *exo*-Sickle geometry is the rule for base-initiated 1,3-elimination: B. B. Jarvis, S. D. Dutkey, and H. L. Ammon, *J. Am. Chem. Soc.*, 1972, **94**, 2136; F. G. Bordwell and B. B. Jarvis, *ibid.*, 1973, **95**, 3585; F. G. Bordwell and E. Doomes, *J. Org. Chem.*, 1974, **39**, 2531; (b) B. M. Trost, W. L. Schinski, F. Chen, and I. R. Mants, *ibid.*, 1971, **93**, 676; (c) E. J. Corey and E. Block, *J. Org. Chem.*, 1969, **34**, 1233.

3 (a) M. Mori, I. Oda, and Y. Ban, *Tetrahedron Lett.*, 1982, **23**, 5315; M. Mori, N. Kanda, I. Oda, and Y. Ban, *Tetrahedron*, 1985, **41**, 5465; (b) M. Mori, Y. Kubo, and Y. Ban, *Tetrahedron Lett.*, 1985, **26**, 1519.

4 K. Uchimoto, N. Yanagihara, H. Shiragami, Y. Fukuda, and H. Nozaki, 31st Symposium on Organometallic Chemistry, 1984, p. 10.

5 M. Mori, N. Kanda, and Y. Ban, *J. Chem. Soc., Chem. Commun.*, 1986, 1375.