# Synthesis of β-Lactams by the Photolysis of Cyclohexyl Benzoylformate in the Presence of Imines



Hiromu Aoyama*, Masami Sakamoto, Katsuhiko Yoshida and Yoshimori Omote

Department of Chemistry, The University of Tsukuba, Sakuramura, Ibaraki, 305 Japan

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Reaction of imines with hydroxyphenylketene which was produced by photolysis of cyclohexyl benzoylformate gave β-lactams in good yields.

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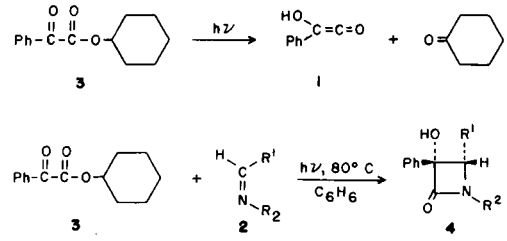
It is well-known that addition of imines with ketenes gives azetidin-2-ones (β-lactams) [1]. Although various ketenes have been used for this reaction, most of them are alkyl or aryl ketenes. Thus, the 1:1 addition of imines with ketene having hydroxy groups are hitherto unknown. The reaction of hydroxy ketenes with imines is expected to afford azetidin-2-ones bearing a hydroxy group at the 3-position. These lactams are of interest synthetically in relation to antibiotics [2]. Hydroxyketenes do not exist as stable compounds since they readily ketonize to yield α-oxoaldehydes. However, it is known that hydroxyphenylketene (**1**) is produced by photolysis of benzoylformic acid esters and they can be trapped by alcohols to give mandelic acid esters [3]. The synthetic application of this reaction has not been reported. In our recent study on the mechanism of photochemical reactions of α-oxoamides, we reported the formation of a β-lactam **4a** in the photolysis of cyclohexyl benzoylformate (**3**) in the presence of *N*-benzylidenebenzylamine (**2a**) [4]. We now wish to report the application of this reaction to the synthesis of 3-hydroxyazetidin-2-ones.

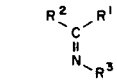
Photolysis of the ester **3** in the presence of imines **2** was carried out using benzene as a solvent at 80° since the photolysis of **3** is reported to be efficient at high temperatures [3]. The solution was dried completely before irradiation in order to preclude hydrolysis of the imines. The results are summerized in Table. In the case of *N*-benzylidenebenzylamine derivatives **2b-g** and *N*-benzylidenealkylamines **2h-j**, the corresponding β-lactams were obtained in good or moderate yields, whereas β-lactams were not produced in the case of *N*-isopropylideneisopropylamine (**2k**). These substituent effects in the photoreactions are not unreasonable since the formation of β-lactams from ketenes and imines has been limited to imines which have aromatic groups at the imino carbons with few exceptions [5]. The photolysis of **3** in the presence of *N*-benzylideneaniline (**2l**) was quite sluggish and the corresponding β-lactam was not obtained in spite of the fact that this imine is quite reactive toward usual ketenes [5]. The imines might act as a quencher or an internal filter in the photolysis of **3**.



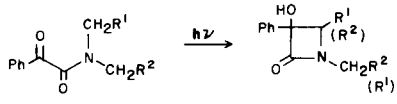

| R¹ | R² | Yields (%) (a) |
|---|---|---|
| **a** $C_6H_5$ | $C_6H_5CH_2$ | 73 |
| **b** *p*-$MeC_6H_4$ | $C_6H_5CH_2$ | 76 |
| **c** *p*-$MeOC_6H_4$ | $C_6H_5CH_2$ | 50 |
| **d** *p*-$CNC_6H_4$ | $C_6H_5CH_2$ | 77 |
| **e** *p*-$ClC_6H_4$ | $C_6H_5CH_2$ | 60 |
| **f** $C_6H_5$ | *p*-$MeC_6H_4CH_2$ | 46 |
| **g** $C_6H_5$ | *p*-$ClC_6H_5CH_2$ | 60 |
| **h** $C_6H_5$ | Et | 56 |
| **i** $C_6H_5$ | *i*-Pr | 27 |
| **j** $C_6H_5$ | *t*-Bu | 45 |

(a) The products contained small amounts of stereoisomers of **4**. The yields are combined yields.

These reactions, except for that of **2d**, are stereoselective and the β-lactams contained only small amounts of stereoisomers. The major isomers were isolated by a single recrystallization of the mixture of two isomers, while the minor isomers were not completely purified. The C(3)-phenyl group of the major isomers is presumed to be trans to the C(4)-aryl group on the basis of nmr spectra [6] and by analogy to the stereochemistry of the β-lactams formed in the reactions of usual ketenes with imines [7]. The reaction of **1d** with hydroxyphenylketene gave a 6:4 mixture of two stereoisomers of the corresponding β-lactam, and they could not be separated.



**2k**, $R^1 = R^2 = Me$, $R^3 = i\text{-}Pr$
**2l**, $R^1 = R^3 = Ph$, $R^2 = H$



Azetidin-2-ones having a hydroxy group at the 3-position can be synthesized also by photocyclization of *N,N*-disubstituted benzoylformamides as we previously reported [8]. However, the present synthetic method is superior to the previous one because of the following reasons: (a) the substituents on the β-lactam ring can be regiospecifically introduced in the case of the former method, while two positional isomers are produced in the case of the latter method when the benzoylformamides possess two different substituents on the nitrogen; (b) the imine **2** can be readily prepared from aldehydes and amines whereas the synthesis of benzoylformamides is not always simple.

## EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded on Jasco IRA-1 spectrophotometer. The nmr spectra were measured on Hitachi R-24 spectrometer using TMS as an internal standard.

General Method of Photolysis of Cyclohexyl Benzoylformate in the Presence of Imines.

The ester **3** (200 mg) and an equimolar amount of the imine **2** were dissolved in dry benzene (10-15 ml). The solution was placed in a Pyrex tube and molecular sieves (Wako 4A, 1.5-2 g) was added. The tube was sealed and set aside overnight in order to dry the solution completely, and then irradiated with a 1000 W high pressure mercury lamp at 80° for 3 hours. After removal of the solvent, the β-lactam (**4**) was isolated by flash chromatography on silica gel. The β-lactam contained a small amount a stereoisomer (~ 10%). The major stereoisomer was isolated by recrystallization from chloroform-hexane, whereas the minor isomer could not be purified. The spectral data of 3,4-diphenyl-1-benzyl-3-hydroxylazetidin-2-one (**4a**) are described in the previous paper [8].

1-Benzyl-3-hydroxy-4-(*p*-methylphenyl)-3-phenylazetidin-2-one (**4b**).

This compound had mp 121.5-122°: ir (chloroform): 3300 and 1740 $cm^{-1}$; nmr (deuteriochloroform): δ 2.37 (s, 3H, Me), 3.54 (s, 1H, OH), 4.64 (s, 1H, 4 − H), 3.89 and 4.98 (ABq, J = 15 Hz, 2H, $CH_2$), and 6.9-7.5 (m, 14 H, aromatic protons).

*Anal.* Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.07. Found: C, 80.14; H, 6.14; N, 4.05.

1-Benzyl-3-hydroxy-4-(*p*-methoxyphenyl)-3-phenylazetidin-2-one (**4c**).

This compound had mp 135-136.5°: ir (chloroform): 3340 and 1740 $cm^{-1}$; nmr (deuteriochloroform): δ 3.77 (s, 3H, OMe), 4.50 (s, 1H, 4 − H), 3.88 and 4.92 (ABq, J = 15 Hz, $CH_2$), 6.8-7.5 (m, 14H, aromatic protons).

*Anal.* Calcd. for $C_{23}H_{21}NO_3$: C, 76.85; H, 5.88; N, 3.90. Found: C, 76.82; H, 5.89; N, 3.88.

1-Benzyl-4-(*p*-cyanophenyl)-3-hydroxy-3-phenylazetidin-2-one (**4d**).

This product was a 6:4 mixture of two stereoisomers and they could not be completely purified: ir (chloroform); 3310, 2240. 1740 $cm^{-1}$; nmr (deuteriochloroform): of the major stereoisomer δ 3.97 and 4.85 (ABq, J = 15 Hz, 2H, $CH_2$), 4.53 (s, 1H, 4 − H), 6.8-7.7 (m, 14H, aromatic protons); that of the minor stereoisomer δ 3.88 and 4.85 (ABq, J = 15 Hz, 2H, $CH_2$), 4.57 (s, 1H, 4 − H), 6.8-7.7 (m, 14H, aromatic protons).

1-Benzyl-4-(*p*-chlorophenyl)-3-hydroxy-3-phenylazetidin-2-one (**4e**).

This compound had mp 102-104°: ir (chloroform): 3300 and 1740 $cm^{-1}$; nmr (deuteriochloroform): δ 3.90 and 4.91 (ABq, J = 16 Hz, 2H, $CH_2$), 4.57 (s, 1H, 4 − H), 6.7-7.7 (m, 14H, aromatic protons).

*Anal.* Calcd. for $C_{22}H_{18}ClNO_2$: C, 72.62; H, 4.98; N, 3.84. Found: C, 72.39; H, 4.93; N, 3.98.

3,4-Diphenyl-3-hydroxy-1-(*p*-methylbenzyl)azetidin-2-one (**4f**).

This compound had mp 150-153°: ir (chloroform): 3300 and 1740 $cm^{-1}$; nmr (deuteriochloroform): δ 2.30 (s, 1H, Me), 3.87 and 4.97 (ABq, J = 15 Hz, 2H, $CH_2$), 4.58 (s, 1H, 4 − H), 6.9-7.6 (m, 14H, aromatic protons).

*Anal.* Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.07. Found: C, 80.33; H, 6.15; N, 4.17.

3,4-Diphenyl-1-(*p*-chlorobenzyl)-3-hydroxyazetidin-2-one (**4g**).

This compound had mp 138-140°: ir (chloroform): 3300 and 1740 $cm^{-1}$; nmr (deuteriochloroform): δ 3.82 and 4.80 (ABq, J = 15 Hz, 2H, $CH_2$), 4.50 (s, 1H, 4 − H), 6.8-7.6 (m, 14H, aromatic protons).

*Anal.* Calcd. For $C_{22}H_{18}ClNO_2$: C, 72.62; H, 4.98; N, 3.84. Found: C, 72.23; H, 4.93; N, 3.79.

3,4-Diphenyl-1-ethyl-3-hydroxyazetidin-2-one (**4h**).

This compound had mp 115-116°: ir (chloroform): 3320 and 1740 $cm^{-1}$; nmr (deuteriochloroform): δ 1.10 (t, J = 7 Hz, 3H, Me), 2.2-4.0 (m, 2H, $CH_2$), 4.3 (m, 1H, OH), 4.71 (s, 1H, 4 − H), 7.0-7.7 (m, 14H, aromatic protons).

*Anal.* Calcd. for $C_{17}H_{17}NO_2$: 76.38; H, 6.41; N, 5.23. Found: C, 76.09; H, 6.38; N, 5.23.

3,4-Diphenyl-3-hydroxy-1-isopropylazetidin-2-one (**4i**).

This compound had mp 137-139°: ir (chloroform): 3320 and 1735 $cm^{-1}$; nmr (deuteriochloroform): δ 1.11 (d, J = 6.5 Hz, 3H, Me), 1.33 (d, J = 6.5 Hz, 3H, Me), 3.77 (m, 1H, C*H*$Me_2$), 4.63 (s, 1H, 4 − H), 7.1-7.5 (m, 10H, aromatic protons).

*Anal.* Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.49; H, 6.82; N, 4.94.

3,4-Diphenyl-1-(t-butyl)-3-hydroxyazetidin-2-one (**4j**).

This compound had mp 196-198°: ir (chloroform): 3340 and 1740 $cm^{-1}$; nmr (deuteriochloroform): δ 1.28 (s, 9H, *t*-butyl), 4.77 (s, 1H, 4 − H), 6.8-7.4 (m, 10H, aromatic protons).

*Anal.* Calcd. for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.16; N. 4.74. Found: C, 76.99; H, 7.19; N, 4.76.

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sponding minor isomers. The fact suggests that the methine hydrogens of the major isomers are cis to the adjacent C(3)-phenyl groups since in β-lactams the signal of the substituent which is cis to an adjacent phenyl group appears at a higher field than that of the corresponding trans substituent; T. J. Batterham, in "NMR Spectra of Simple Heterocycles". John Wiley & Sons, New York, N.Y., 1973, p 143.

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