CROATICA CHEMICA ACTA CCACAA 59 (1) 121—128 (1986)

CCA-1631

YU ISSN 0011-1643
UDC 547.447.6
Original Scientific Paper

# Synthesis of 1,3-Substituted 4-(2-Furyl)-2-azetidinones[1]

*Ryuji Niwa,[a] Nobuya Katagiri,[b] and Tetsuzo Kato[b]*

*Central Research Institute, MECT Corporation,[a] 1780 Kitano, Tokorozawa 359, Japan and Pharmaceutical Institute, Tohoku University,[b] Aobayama, Sendai 980, Japan*

Received June 4, 1985

The reaction of azidoketene (*1*) and haloketenes (*2*—*4*) with Schiff bases such as *N*-furfurylideneamines (*5*—*9*) gave the [2 + 2] cycloadducts, 1,3-substituted 4-(2-furyl)-2-azetidinones (*10*—*18*).

It is a well documented fact that ketenes undergo the [2+2]cycloaddition with unsaturated double bonds to form the four membered cyclic ring system. However, previous investigations of this reaction have dealt exclusively with C=C double bonds, and only a few references are available concerning such reaction with C=N double bonds such as Schiff bases[2-8]. Previously, we have reported the reaction of ketene with Schiff bases such as *N*-furfurylideneaniline (*5*) to give a [2+2]cycloadduct, 4-(2-furyl)-1-phenyl-2-azetidinone[9]. On the other hand, reactions of haloketenes[10-12] and azidoketene[13,14] with Schiff bases such as *N*-benzylideneaniline have been also reported to give 2-azetidinones. The present paper reports a continuation of our study on the synthesis of β-lactam by the reaction of substituted ketenes such as azidoketene (*1*)[13,14], chloroketene (*2*)[10-12], dichloroketene (*3*)[15-17], and chlorophenylketene (*4*)[18,19] with *N*-furfurylideneamines (*5*—*9*). These ketenes (*1*—*4*) were prepared according to the literature from the corresponding α-substituted acetyl chloride and triethylamine in situ.

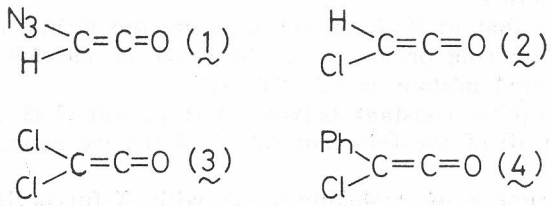


Chart 1

Schiff bases used in this reaction were prepared from furfural and the corresponding primary amines. The results are summarized in Table I. Reactions with aromatic amine were carried out in the presence of anhydrous magnesium sulfate in benzene, and the reaction with ethyl glycinate was done in the presence of triethylamine in water.

First, reaction of azidoketene (*1*) was carried out. Azidoketene (*1*) was prepared from azidoacetyl chloride[20,21] in the presence of triethylamine in

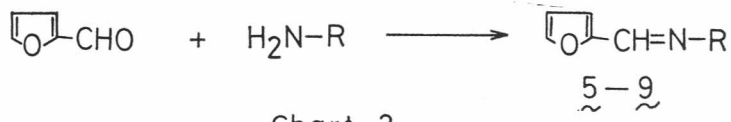
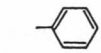
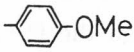
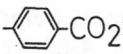


Chart 2

Table I. N-Furfurylideneamines (5—9)

| Compd. No. | R | mp°C ( bp°C/mmHg ) | Yield (%) |
|---|---|---|---|
| 5 |  | 58 [lit.[23] 56-57] | 93 |
| 6 |  | 67—68 | 82 |
| 7 |  | ( 85—90/5 ) | 69 |
| 8 |  | ( 80—90/4 ) | 81 |
| 9 | $-CH_2CO_2Et$ | ( 75—85/0.002 ) [lit.[9] 69—75/0.001] | 51 |

benzene or dichloromethane. Thus, when *N*-furfurylideneaniline (*5*) was allowed to react with azidoketene (*1*) in benzene, 3-azido-4-(2-furyl)-1-phenyl-2-azetidinone (*10*) was obtained in 68% yield. As detailed in the experimental section, elemental analyses and spectroscopic data are well consistent with the β-lactam structure.

It is reported that in $^1$H-NMR spectroscopy the vicinal coupling constant of the *cis*-β- lactam ring protons is in the range of 4.9—5.9 Hz whereas that of the *trans*-oriented protons is 2.2—2.8 Hz[22].

Since the coupling constant between 3-H proton (4.93 ppm, d) and 4-H proton (5.33 ppm, d) of the β-lactam ring is 5 Hz, we assigned the structure being the *cis*.

Similarly, reaction of azidoketene (*1*) with *N*-furfurylidene-*p*-methoxyaniline (*6*) gave rise to the *cis* isomer of 3-azido-4-(2-furyl)-1-(*p*-methoxy-

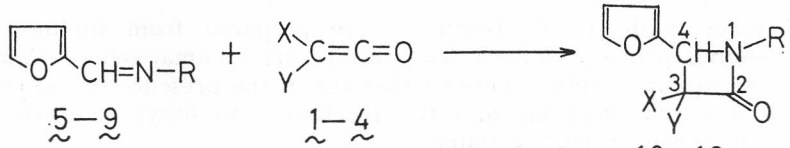
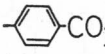
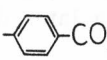


Chart 3

Table II. 4-(2-Furyl)-2-azetidinones (10–18)

| Compd. No. | R | X | Y | mp (°C) | Yield (%) |
|---|---|---|---|---|---|
| 10 |  | $N_3$ | H | 106–107 | 68 |
| 11 |  | $N_3$ | H | 81–82 | 91 |
| 12 |  | $N_3$ | H | oil | 8 |
| 13 |  | $N_3$ | H | oil | 61 |
| 14 | $-CH_2CO_2Et$ | $N_3$ | H | oil | 63 |
| 15 |  | Cl | H | 120–121 | 8 |
| 16 |  | Cl | Cl | 107–108 | 64 |
| 17 |  | Cl | Cl | 72–73 | 38 |
| 18 |  | Cl | Ph | 115–116 | 9 |

phenyl)-2-azetidinone (*11*) in a good yield (91%). Reaction of azidoketene (*1*) with *N*-furfurylidene-*o*-ethoxycarbonylaniline (*7*) afforded 3-azido-4-(2-furyl)--1-(*o*-ethoxycarbonylphenyl)-2-azetidinone (*12*) in a low yield (8%).

The coupling constant of this β-lactam ring protons (3-H, 4.88 ppm, d and 4-H, 5.20 ppm, d) is 2 Hz. Therefore, we assigned this as being *trans*.[22] In this reaction the product corresponding to the *cis* isomer could not be detected.

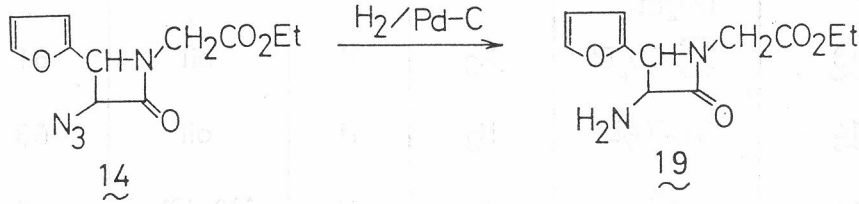
Reaction of azidoketene (*1*) with *N*-furfurylidene-*p*-ethoxycarbonylaniline (*8*) and ethyl *N*-furfurylideneglycinate (*9*) gave rise to the corresponding *cis*-3-azido-4-(2-furyl)-2-azetidinones *13* and *14* in 61 and 63% yields, respectively.

Next, reactions of chloroketene derivatives (*2*, *3*, and *4*) were investigated. When *N*-furfurylideneaniline (*5*) was allowed to react with monochloroketene (*2*) generated *in situ* from chloroacetyl chloride in the presence of triethylamine in ether, 3-chloro-4-(2-furyl)-1-phenyl-2-azetidinone (*15*) was obtained in a low yield (8%). Coupling constant of the β-lactam ring protons (5.20 ppm, d, $J = 5$ Hz and 5.43 ppm, d, $J = 5$ Hz) suggested the structure to be *cis*.

Reaction of chloroketene (*2*) with the Schiff base *6* under the same conditions given for the lactam *15* resulted in the formation of a resinous product, and reaction with other Schiff bases *7*—*9* gave oily substances whose IR spectra showed the carbonyl absorption at around 1770—1790 $cm^{-1}$, suggesting the formation of the 2-azetidinone structure. However, purification of the product failed.

Similar reaction of dichloroketene (*3*) with *N*-furfurylideneaniline (*5*) and *N*-furfurylidene-*o*-methoxyaniline (*6*) afforded the corresponding 3,3-dichloro-4-(2-furyl)-2-azetidinones *16* and *17* in 64 and 38% yields, respectively.

In the case of chlorophenylketene (*4*), only *N*-furfurylidene-*p*-ethoxyaniline (*8*) afforded the product, 3-chloro-1-(*p*-ethoxycarbonylphenyl)-4-(2-furyl)-3-phenyl-2-azetidinone (*18*) in 9% yield. Configuration of *18* could not be identified.




14 19

Chart 4

Lastly, reduction of 3-azido-1-ethoxycarbonylmethyl-4-(2-furyl)-2-azetidinone (*14*) was carried out. Thus, upon catalytic reduction with palladium — charcoal in methanol, compound *14* absorbed hydrogen to convert into the 3-amino-2-azetidinone derivative (*19*).

Further work is in progress on the chemistry of adjacent furyl group in other heterocyclic system and will be reported at a later date.

## EXPERIMENTAL

Melting points and boiling points are uncorrected. IR spectra were taken on a JASCO IR—S spectrophotometer. $^1$H-NMR spectra were recorded on a JEOL JNM-PMX60 spectrometer with tetramethylsilane as internal standard. MS spectra were obtained on a Hitachi M-52G and JEOL JMS-01SG-2 machine. Wakogel (C-200) was employed for column chromatography.

### N-*Furfurylideneaniline* (5)

To a mixture of aniline (2.79 g, 0.03 mol) and anhydrous magnesium sulfate (7.2 g, 0.06 mol) in dry benzene (50 ml) furfural (2.88 g, 0.03 mol) was added dropwise with stirring and ice-cooling. The addition required about 20 min to complete. The mixture was stirred at room temperature for 30 min, and magnesium sulfate was filtered off by suction. The filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from hexane to give the product *5* as pale yellowish leaves, m. p. 58 °C (lit.[23] m. p. 56—57 °C). Yield, 4.77 g (93%). IR ($CHCl_3$): 1630 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 6.50 (1H, dd, $J$ = 2 Hz, 4 Hz, furyl 4-H), 6.90 (1H, d, $J$ = 4 Hz, furyl 5-H), 7.27 (5H, s, Ph), 7.57 (1H, d, $J$ = 2 Hz, furyl 3-H), 8.23 (1H, s, CH=N).

### N-*Furfurylidene*-p-*methoxyaniline* (6)

Employing the same procedure described above, reaction of furfural (2.88 g) with *p*-methoxyaniline (3.69 g) in the presence of anhydrous magnesium sulfate (7.2 g) afforded the product *6*, m.p. 67—68 °C, pale yellowish leaves (hexane). Yield, 4.95 g (82%).

*Anal.* $C_{12}H_{11}NO_2$ (201.22) calc'd.: C 71,62; H 5.51; N 6.96%
found: C 71.72; H 5.41; N 7.04%

IR ($CHCl_3$): 1630 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.77 (1H, s, $OCH_3$), 6.50 (1H, dd, $J = 2$ Hz, 4 Hz, furyl 4-H), 6.90 (1H, d, $J = 4$ Hz, furyl 5-H), 6.90 (2H, d, $J = 9$ Hz, phenyl H), 7.23 (2H, d, $J = 9$ Hz, phenyl H), 7.57 (1H, d, $J = 2$ Hz, furyl 3-H), 8.27 (1H, s, CH=N).

N-*Furfurylidene*-o-*ethoxycarbonylaniline* (7)

Employing the same procedure described above, reaction of furfural (2.88 g) with ethyl 2-aminobenzoate (4.96 g) gave the product *7* as an oil, b. p. 85——90 °C (5 mmHg). Yield, 5.06 g (69%).

*Anal.* $C_{14}H_{13}NO_3$ (243.25) calc'd.: C 69.12; H 5.39; N 5.76%
found: C 69.01; H 5.30; N 5.49%

IR ($CHCl_3$): 1690, 1615 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.33 (3H, t, $J = 7$ Hz, $CH_2CH_3$), 4.30 (2H, q, $J = 7$ Hz, $CH_2CH_3$), 6.50—8.00 (7H, m, furyl H and phenyl H), 8.20 (1H, s, CH=N).

N-*Furfurylidene*-p-*ethoxycarbonylaniline* (8)

According to the procedure described above, furfural (2.88 g) was allowed to react with ethyl 4-aminobenzoate (4.96 g) to give the product *8*, b. p. 80—90 °C (4 mmHg). Yield, 5.91 g (81%).

*Anal.* $C_{14}H_{13}NO_3$ (243.25) calc'd.: C 69.12; H 5.39; N 5.76%
found: C 69.21; H 5.44; N 5.82%

IR ($CHCl_3$): 1700, 1620 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.33 (1H, t, $J = 7$ Hz, $CH_2CH_3$), 4.25 (2H, q, $J = 7$ Hz, $CH_2CH_3$), 6.50 (1H, dd, $J = 2$ Hz, 4 Hz, furyl 4-H), 6.93 (1H, d, $J = 4$ Hz, furyl 5-H), 7.16 (2H, d, $J = 9$ Hz, phenyl H), 7.57 (1H, d, $J = 2$ Hz, furyl 3-H), 8.00 (2H, d, $J = 9$ Hz, phenyl H), 8.16 (1H, s, CH=N).

*Ethyl* N-*Furfurylideneglycinate* (9)

To a suspension mixture of furfural (2.88 g, 0.03 mol) and ethyl glycinate hydrochloride (6.28 g, 0.045 mol) in water (20 ml), triethylamine (3.04 g, 0.03 mol) was added dropwise under ice-cooling. The mixture was stirred for 30 min, during which time the temperature was kept at room temperature. The reaction mixture was extracted with ether.

The ether solution was washed with water, dried over anhydrous sodium sulfate, and distilled after removal of the solvent to yield the product *9*, b. p. 75—85 °C (0.002 mmHg) [lit. 7) b. p. 69—75 °C (0.001 mmHg)]. Yield, 3.26 g (60%). IR ($CHCl_3$): 1650 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.25 (3H, t, $J = 7$ Hz, $CH_2CH_3$), 4.20 (2 H, q, J = 7 Hz, $CH_2CH_3$), 4.30 (1H, dd, $J = 2$ Hz, 4 Hz, furyl 4-H), 6.80 (1H, d, $J = 4$ Hz, furyl 5-H), 7.50 (1H, d, $J = 2$ Hz, furyl 3-H), 8.10 (1H, s, CH=N).

*3-Azido-4-(2-furyl)-1-phenyl-2-azetidinone* (10)

To a solution of *N*-furfurylideneaniline (5) (3.42 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in dry benzene (100 ml), a benzene (10 ml) solution of azidoacetyl chloride (2.39 g, 0.02 mol) was added with stirring while the temperature was maintained at about 15—20 °C. Stirring was continued for an additional 30 min at the same temperature to give a crystalline precipitate ($Et_3N \cdot HCl$), which was filtered off by suction. The filtrate was evaporated under reduced pressure. The residue (7.16 g) was purified by silica gel (200 g) column chromatography using a mixture of hexane-ethyl acetate (10 : 1) as eluent to afford the product *10* as needles (from benzene), m. p. 106—107 °C. Yield, 3.44 g (68%).

*Anal.* $C_{13}H_{10}N_4O_2$ (254.24) calc'd.: C 61.41; H 3.96; N 22.04%
found: C 61.65; H 3.95; N 22.22%

IR ($CHCl_3$); 2100, 1770 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 4.93 (1H, d, $J = 5$ Hz, 2-azetidinone 3-H), 5.33 (1H, d, $J = 5$ Hz, 2-azetidinone 4-H), 6.47 (2 H, s, furyl 4, 5-H), 7.27 5H, s, phenyl H), 7.47 (1H, s, furyl 3-H).

*3-Azido-4-(2-furyl)-1-(p-methoxyphenyl)-2-azetidinone* (11)

According to the procedure described above, *N*-furfurylidene-*p*-methoxyaniline (*6*) (2.01 g, 0.01 mol) was treated with azidoacetyl chloride (1.20 g, 0.01 mol) in the presence of triethylamine (1.01 g, 0.01 mol) in dry benzene (60 ml).

The reaction mixture was treated in the similar fashion as described above to give a residual solid (3.09 g). Purification by silica gel (100 g) column chromatography using a mixture of hexane-ethyl acetate (3 : 1) as eluent gave the product *11*, m. p. 81—82 °C, colorless needles (benzene-ether). Yield, 2.59 g (91%).

*Anal.* $C_{14}H_{12}N_4O_3$ (284.67) calc'd: C 59.15; H 4.26; N 19.71%
found: C 59.42; H 4.15; N 19.87%

IR ($CHCl_3$): 2100, 1760 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.77 (1 H, s, $OCH_3$), 4.95 (1 H, d, $J = 5$ Hz, 2-azetidinone 3-H), 5.30 (1H, d, $J = 5$ Hz, 2-azetidinone 4-H), 6.47 (2 H, s, furyl 4, 5-H), 6.83 (2 H, d, $J = 9$ Hz, phenyl H), 7.27 (2 H, d, $J = 9$ Hz, phenyl H), 7.50 (1 H, s, furyl 3-H).

*3-Azido-4-(2-furyl)-1-(o-ethoxycarbonylphenyl)-2-azetidinone* (12)

According to the procedure described above, *N*-furfurylidene-o-ethoxycarbonylaniline (*7*) (2.43 g, 0.01 mol) was allowed to react with azidoacetyl chloride (1.20 g, 0.01 mol) in the presence of triethylamine (1.01 g, 0.01 mol) in dry benzene (50 ml). The reaction mixture was filtered, and the filtrate was condensed. The resulting residue (2.83 g) was submitted to silica gel (100 g) column chromatography using hexane-ethyl acetate (3 : 1) as eluent to give the product *12* as a yellowish oil. Yield, 0.25 g (58%).

*Anal.* $C_{16}H_{14}N_4O_4$ (362.30) calc'd: C 58.89; H 4.32; N 17.17%
found: C 58.59; H 4.44; N 16.98%

IR ($CHCl_3$): 2100, 1775, 1720 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.40 (3 H, t, $J = 7$ Hz, $CH_2CH_3$), 4.40 (2 H, q, $J = 7$ Hz, $CH_2CH_3$), 4.88 (1 H, d, $J = 2$ Hz, 2-azetidinone 3-H), 5.20 (1 H, d, $J = 2$ Hz, 2-azetidinone 4-H), 6.20—8.00 (7 H, m, furyl H and phenyl H).

*3-Azido-4-(2-furyl)-1-(p-ethoxycarbonylphenyl)-2-azetidinone* (13)

Following the same procedure described above, *N*-furfurylidene-*p*-ethoxycarbonylaniline (*8*) (2.43 g) was allowed to react with azidoacetyl chloride (1.20 g) in the presence of triethylamine (1.01 g) in dry benzene (100 ml) to give an oily residue (3.1 g).

Purification by silica gel (100 g) column chromatography using hexane-ethyl acetate (5 : 1) as eluent gave the product *13* as a yellowish oil. Yield, 2.00 g (61%).

*Anal.* $C_{16}H_{14}N_4O_4 \cdot 1/4H_2O$ (330.81) calc'd: C 58.09; H 4.42; N 16.94%
found: C 58.32; H 4.35; N 16.77%

IR ($CHCl_3$): 2100, 1770, 1710 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.33 (3 H, t, $J = 7$ Hz, $CH_2CH_3$), 4.33 (2 H, q, $J = 7$ Hz, $CH_2CH_3$). 5.03 (1 H, d, $J = 5$ Hz, 2-azetidinone 3-H), 5.40 (1 H, d, $J = 5$ Hz, 2-azetidinone 4-H), 6.33—6.67 (2 H, m, furyl 4, 5-H), 7.33 (2 H, d, $J = 9$ Hz, phenyl H), 7.43 (1 H, s, furyl 3-H), 8.00 (2 H, d, $J = 9$ Hz, phenyl H).

*3-Azido-1-ethoxycarbonylmethyl-4-(2-furyl)-2-azetidinone* (14)

To a solution of ethyl *N*-furfurylideneglycinate (*9*) (3.62 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in dry dichloromethane (100 ml), a solution of azidoacetyl chloride (2.39 g, 0.02 mol) in dichloromethane (10 ml) was added dropwise with stirring under ice-salt cooling (—15 ~ —10 °C). After stirring at room temperature for 1 hr, the reaction mixture was washed with water (100 ml x 3), dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was purified by silica gel (100 g) column chromatography using hexane-ethyl acetate (4 : 1) as eluent to give the oily product *14*. Yield, 3.32 g (63%).

*Anal* $C_{11}H_{12}N_4O_4$ (264.24) calc'd: C 50.00; H 4.58%
found: C 49.78; H 4.37%

IR ($CHCl_3$): 2100, 1775, 1735 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) $\delta$: 1.27 (3 H, t, $J = 7$ Hz, $CH_2CH_3$), 3.55 (1 H, d, $J = 18$ Hz, NCHH), 4.20 (2 H, q, $J = 7$ Hz, $CH_2CH_3$), 4.42 (1 H, d, $J = 18$ Hz, NCHH), 4.90 (1 H, d, $J = 5$ Hz, 2-azetidinone 3-H), 5.15 (1 H, d, $J = 5$ Hz, 2-azetidinone 4-H), 6.43 (2 H, s, furyl 4, 5-H), 7.50 (1 H, s, furyl 3-H). High resolution MS *m/e* ($M^+ - N_2$) calc'd.: 236.0798. found: 236.0798.

*3-Chloro-4-(2-furyl)-1-phenyl-2-azetidinone* (15)

To a solution of *N*-furfurylideneaniline (5) (7.10 g, 0.0415 mol) and triethylamine (8.39 g, 0.083 mol) in anhydrous ether (100 ml), a solution of chloroacetyl chloride (9.37 g, 0.083 mol) in ether (10 ml) was added dropwise with stirring while the temperature was maintained at about 15 ~ 20 °C. The addition required about 30 min to complete.

After stirring for additional 30 min, the mixture was filtered by suction. The filtrate was evaporated to dryness in vacuo. The residue (7.44 g) was submitted to silica gel (150 g) column chromatography using hexane-ethyl acetate (30 : 1) as eluent to give the product *15*, m. p. 120—121 °C, colorless leaves (hexane-ether). Yield, 0.8 g (8%).

*Anal.* $C_{13}H_{10}ClNO_2$ (247.67) calc'd: C 63.04; H 4.07; N 5.66%
found: C 62.93; H 3.58; N 5.31%

IR ($CHCl_3$): 1775 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) $\delta$: 5.20 (1 H, d, $J = 5$ Hz, 2-azetidinone 3-H), 5.43 (1 H, d, $J = 5$ Hz, 2-azetidinone 4-H), 6.43 (2 H, s, furyl 4, 5-H), 7.10—7.50 (6 H, m, furyl 3-H and phenyl H). MS *m/e*: 247 ($M^+$), 249 ($M^+ + 2$).

*3,3-Dichloro-4-(2-furyl)-1-phenyl-2-azetidinone* (16)

Employing the similar fashion given for compound *15*, a solution of dichloroacetyl chloride (2.95 g, 0.02 mol) in benzene (10 ml) was added dropwise to a solution of *N*-furfurylideneaniline (5) (1.71 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in dry benzene (50 ml). The resulting residue, after removal of the solvent, was purified by silica gel (100 g) column chromatography using hexane-ethyl acetate (100 : 1) as eluent to give the product *16*, m. p. 107—108 °C, colorless needles (hexane). Yield, 1.80 g (64%).

*Anal.* $C_{13}H_9Cl_2NO_2$ (282.12) calc'd: C 55.34; H 3.22; N 4.97%
found: C 55.36; H 3.19; N 4.78%

IR ($CHCl_3$): 1785 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) $\delta$: 5.50 (1 H, s, 2-azetidinone 4-H), 6.40 (1 H, dd, $J = 2$ Hz, 4 Hz furyl 4-H), 6.50 (1 H, d, $J = 4$ Hz, furyl 5-H), 7.27 (5 H, s, phenyl H), 7.47 (1 H, d, $J = 2$ Hz, furyl 3-H).

*3,3-Dichloro-4-(2-furyl)-1-(*p*-methoxyphenyl)-2-azetidinone* (17)

Following the procedure described above, *N*-furfurylidene-*p*-methoxyaniline (6) (6.03 g, 0.03 mol) was treated with dichloroacetyl chloride (9.00 g, 0.06 mol) in the presence of triethylamine (6.06 g, 0.06 mol) in dry benzene (100 ml). The product was purified by silica gel (200 g) column chromatography. The hexane-ethyl acetate (20 : 1) elution afforded a crystalline substance, which was recrystallized from hexane to give colorless needles of m. p. 72—73 °C. Yield, 3.58 g (38%).

*Anal.* $C_{14}H_{11}Cl_2NO_3$ (312.14) calc'd.: C 53.87; H 3.55; N 4.49%
found: C 53.85; H 3.65; N 4.41%

IR ($CHCl_3$): 1780 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) $\delta$: 3.77 (1 H, s, $OCH_3$), 5.50 (1 H, s, 2-azetidinone 4-H), 6.33—6.60 (2 H, m, furyl 4, 5-H), 6.80 (2 H, d, $J = 9$ Hz, phenyl H), 7.23 (2 H, d, $J = 9$ Hz, phenyl H), 7.50 (1 H, d, $J = 2$ Hz, furyl 3-H).

*3-Chloro-1-(*p*-ethoxycarbonylphenyl)-4-(2-furyl)-3-phenyl-2-azetidinone* (18)

To a solution of *N*-furfurylidene-*p*-ethoxycarbonylaniline (4) (4.38 g, 0.018 mol) and triethylamine (2.73 g, 0.027 mol) in dry benzene (100 ml), a solution of chloroacetyl chloride (4.08 g, 0.022 mol) in benzene (10 ml) was added dropwise with stirring under ice-cooling (5 ~ 10 °C). After stirring for 2 hr at room temperature, the mixture was filtered. The filtrate was condensed *in vacuo*, and the residue (8.0 g) was submitted to silica gel (150 g) column chromatography. The hexane-ethyl acetate (5 : 1) elution gave a crystalline substance. Purification by recrystallization

from hexane-ether gave the product *18*, m. p. 115—116 °C, yellowish needles, Yield, 0.70 g (9%).

*Anal.* $C_{22}H_{18}ClNO_4$ (395.83) calc'd: C 66.75; H 4.58; N 3.54%
found: C 66.74; H 4.72; N 3.28%

IR ($CHCl_3$): 1775, 1710 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) $\delta$: 1.33 (3 H, t, $J = 7$ Hz, $CH_2CH_3$), 4.30 (2 H, q, $J = 7$ Hz, $CH_2CH_3$), 5.60 (1 H, s, 2-azetidinone 4-H), 6.00—6.20 (2 H, m, furyl 4, 5-H), 7.00—7.50 (8 H, m, furyl 3-H and phenyl H), 7.93 (2 H, d, $J = 9$ Hz, phenyl H).

*Acknowledgement.* — Thanks are due to the staff of the Central Analyses Room of Pharmaceutical Institute, Tohoku University for spectral measurements and elemental analyses.

REFERENCES

1. This forms Part CXXIII *Studies on Ketene and Its Derivatives.* Part CXXII: R. Niwa, N. Katagiri, and T. Kato, *Chem. Pharm. Bull.* **32** (1984) 4149.
2. H. Staudinger, *Justus Liebigs Ann. Chem.* **356** (1970) 51.
3. H. Staudinger, *Ber.* **40** (1907) 1145.
4. H. Staudinger, *ibid.* **50** (1917) 1035.
5. A. K. Mukerjee and A. K. Singh, *Synthesis* (1975) 547.
6. P. G. Sammes, *Chem. Rev.* **76** (1976) 1.
7. M. Sakamoto, K. Miyazawa, and Y. Tomimatsu, *Chem. Pharm. Bull.* **24** (1976) 2532.
8. A. K. Mukerjee and A. K. Singh, *Tetrahedron* **34** (1978) 1931.
9. N. Katagiri, Y. Miura, R. Niwa, and T. Kato,, *Chem. Pharm. Bull.* **31** (1983) 538.
10. F. Duran and L. Ghosez, *Tetrahedron Lett.* (1970) 245.
11. D. A. Nelson, *ibid.* (1971) 2543.
12. A. O. Fitton, J. R. Frost, P. G. Houghton, and H. Suschitzky, *J. Chem. Soc. Perkin Trans.* **1** (1977) 1450.
13. A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron* **23** (1967) 4769.
14. A. K. Bose, M. S. Manhas, J. S. Chib, H. P. S. Chawla, and B. Dayal, *J. Org. Chem.* **39** (1974) 2877.
15. H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Am. Chem. Soc.* **87** (1965) 5257.
16. W. T. Brady, H. G. Liddell, and W. L. Vaughn, *J. Org. Chem.* **31** (1966) 626.
17. L. Ghosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.* (1966) 135.
18. W. T. Brady, E. D. Dorsey, and F. H. Parry, *J. Org. Chem.* **34** (1969) 2846.
19. W. T. Brady, F. H. Parry, R. Roe, and E. F. Hoff, *Tetrahedron Lett.* (1970) 819.
20. A. Bertho and J. Maier, *Justus Liebigs Ann. Chem.* **498** (1932) 52.
21. J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.* **77** (1955) 951.
22. L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,* Pergamon Press, New York, 1969, P. 287.
23. V. Hahn, R. Hansal, I. Morkavic, and D. Vargazon, *Arkiv. Khim.* **26** (1954) 21.
24. A. Schönberg, *Preparative Organic Photochemistry,* Chapter 42, Springer--Verlag, New York, 1968, p. 426.

## POVZETEK

### Sinteze 4-(2-furil)-2-azetidinonov

*R. Niwa, N. Katagiri in T. Kato*

Pri reakciji med azidoketenom oziroma haloketeni in Schiffovimi bazami kot je na primer *N*-furfurilidenamin, nastanejo ustrezni [2+2] cikloadukti, 1,3-disubstituirani 4-(2-furil)-2-azetidinoni.