A Convenient Conversion of 2-Acyloxy-3-chlorocarboxamides to 3-Acyloxy-2-azetidinones in Heterogeneous Media

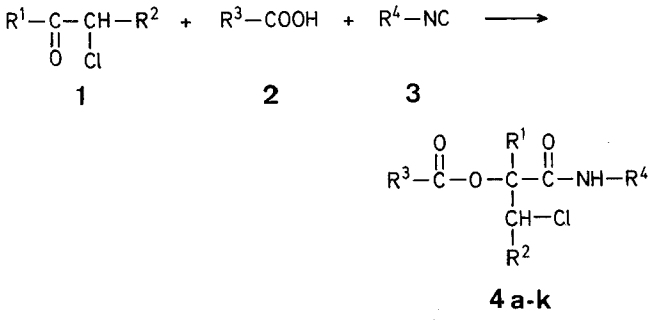
Saïd SEBTI, André FOUCAUD*

Groupe de Physicochimie Structurale associé au C.N.R.S., Université de Rennes, Campus de Beaulieu, F-35042 Rennes, France

The synthesis of monocyclic β-lactams from β-halocarboxamides required intramolecular *N*-alkylation[1]. These methods involved the use of sodium amide in liquid ammonia[2] or in organic solvents[3], dimsylsodium in dimethyl sulfoxide[4], or sodium hydride in dimethylformamide and dichloromethane[5,6], thus highly anhydrous solvents were necessary. Recently, methods of synthesis of β-lactams by means of solid-liquid phase transfer reactions, using resins[7,8] or powdered potassium hydroxide as bases and high dilution[9,10], were proposed.

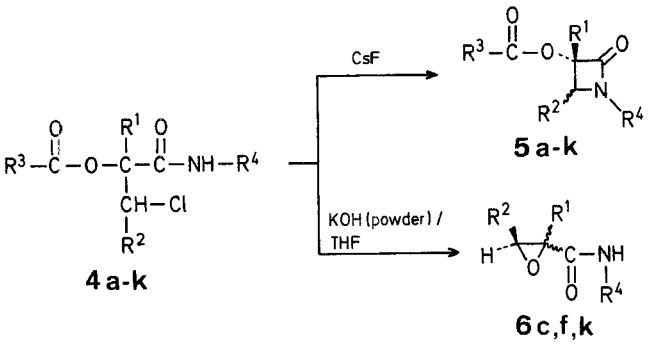
Despite of the possibility of selective phase transfer-catalysed *N*-alkylation of carboxamides, the 2-acyloxy-3-chloropropanamides **4** ($R^2 = H$) are converted into the corresponding oxiranes **6** or into a mixture of oxiranes **6** and azetidinones **5** by the use of potassium hydroxide powder and tetrahydrofuran. We report here a convenient synthesis of 3-acyloxy-2-azetidinones **5** from the easily available 2-acyloxy-3-chlorocarboxamides **4** by anionic activation with caesium fluoride[11].

The 2-acyloxy-3-chlorocarboxamides **4** are prepared by the reaction of the chloro ketone **1** with the isocyanide **3** and the acid **2** (Passerini reaction[12]) (Table 1).



1 2 3

4 a-k



4 a-k 5 a-k 6 c,f,k

When the 2-acyloxy-3-chlorocarboxamides **4c, f, g, h, k** are treated with potassium hydroxide powder at room temperature, the corresponding oxiranes **6c, f, k** are obtained almost quantitatively. They are accompanied by traces of corresponding azetidinone **5** (Table 2). In some cases (carboxamides **4a, b, e**), a mixture of oxirane **6** and azetidinone **5** is obtained: carboxamide **4a** gives a mixture of **5a**:**6c** in a 4:1 ratio; carboxamide **4b** gives a mixture of **5b**:**6k** in a 1:9 ratio and **4e** gives a mixture of **5e**:**6c** in a 4:1 ratio (as determined by ^{1}H-N.M.R. spectrometry).

We have found that the azetidinones **5** are obtained in high yields when the carboxamides **4** are treated with caesium fluoride in tetrahydrofuran, with benzyltriethylammonium chloride as catalyst (Method A). Other reaction conditions have been examined with two examples (Method B) and may be a useful alternative. The carboxamide **4** is heated at 85–90 °C with caesium fluoride, without solvent and phase transfer catalyst. These conditions give good yields of 2-azetidinones **5b** and **5c**.

4	R^1	R^2	R^3	R^4
a	CH_3	H	C_6H_5	t-C_4H_9
b	CH_3	H	C_6H_5	i-C_3H_7
c	CH_3	H	CH_3	t-C_4H_9
d	CH_3	H	n-C_3H_7	t-C_4H_9
e	CH_3	H	C_6H_5–CH=CH–	t-C_4H_9
f	CH_3	CH_3	C_6H_5	t-C_4H_9
g	CH_3	CH_3	CH_3	t-C_4H_9
h	CH_3	CH_3	n-C_3H_7	t-C_4H_9
i	CH_2Cl	H	C_6H_5	t-C_4H_9
j	CH_2Cl	H	CH_3	t-C_4H_9
k	CH_3	H	CH_3	i-C_3H_7

These observations suggest that the reaction can take place on the surface of the alkali metal fluoride.

2-Acyloxy-3-chlorocarboxamides 4; General Procedure:
α-Chloro ketone **1** (10 mmol) is added dropwise over 15 min to an ice-cooled mixture of carboxylic acid **2** (10 mmol) and isocyanide **3** (10 mmol). The mixture is stirred for 15 h at room temperature. The resulting product is purified by distillation or by crystallisation from petroleum ether to afford the carboxamide **4** (Table 1).

Table 1. 2-Acyloxy-3-chloropropanamides (**4**) prepared

Product	Yield[a] [%]	b.p./torr [°C] or m.p. [°C]	Molecular Formula[b]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. [$CDCl_3$/TMS_{int}] δ [ppm]
4a	98	76°	$C_{15}H_{20}ClNO_3$ (297.6)	1674; 1715; 3400	1.42 (s, 9H); 1.82 (s, 3H); 4.34, 4.20 (ν_A, ν_B, 2H, J_{AB}=12 Hz); 6.25 (br. s, 1H, NH); 7.5 (m, 3H_{arom}); 7.9 (m, 2H_{arom})
4b	82	64°	$C_{14}H_{18}ClNO_3$ (283.8)	1692; 1730; 3285	1.20 (d, 6H, J_{HH}=7.2 Hz); 1.82 (s, 9H); 4.10 (m, 1H); 4.20, 4.32 (ν_A, ν_B, 2H, J_{AB}=12 Hz); 6.17 (br. s, 1H, NH); 7.5 (m, 3H_{arom}); 8.0 (m, 2H_{arom})
4c	78	46°	$C_{10}H_{18}ClNO_3$ (235.7)	1680; 1746; 3425	1.40 (s, 9H); 1.67 (s, 3H); 2.15 (s, 3H); 4.26, 4.05 (ν_A, ν_B, 2H, J_{AB}=11.2 Hz)
4d	73	150–155°/20	$C_{12}H_{22}ClNO_3$ (263.8)	1685; 1744; 3435	1.00 (t, 3H, J_{HH}=7.2 Hz); 1.37 (s, 9H); 1.7 (m, 3H, 2H); 2.4 (m, 2H); 4.05, 4.26 (ν_A, ν_B, 2H, J_{AB}=12 Hz)
4e	73	139°	$C_{17}H_{22}ClNO_3$ (323.8)	1620; 1654; 1706; 3370	1.41 (s, 9H); 1.75 (s, 3H); 4.14, 4.31 (ν_A, ν_B, 2H, J_{AB}=12 Hz); 6.22 (br. s, 1H, NH); 6.43 (d, 1H, J_{trans}=16 Hz); 7.4 (m, 5H_{arom}); 7.70 (d, 1H, J_{trans}=16 Hz)
4f	90	85°	$C_{16}H_{22}ClNO_3$ (311.8)	1692; 1700; 3400	1.34, 1.39 (2s, 9H); 1.57, 1.69 (2d, 3H, J_{HH}=6.4 Hz); 1.79, 1.86 (2s, 3H); 4.70, 4.50 (2q, 2H, J_{HH}=6.4 Hz); 5.78, 6.05 (2 br. s, 1H, NH); 7.3 (m, 3H_{arom}); 8.0 (m, 2H_{arom})
4g	84	74°	$C_{11}H_{20}ClNO_3$ (249.7)	1670; 1745; 3340	1.34, 1.36 (2s, 9H); 1.49, 1.55 (2d, 3H, J_{HH}=7.2 Hz); 1.65, 1.71 (2s, 3H); 2.11 (s, 3H); 4.39, 4.59 (2q, 1H, J_{HH}=7.2 Hz); 5.90, 6.00 (2 br. s, 1H, NH)
4h	69	42°	$C_{13}H_{24}ClNO_3$ (277.8)	1685; 1745; 3345	0.98 (t, 3H, J_{HH}=7.2 Hz); 1.33, 1.35 (2s, 9H); 1.51, 1.57 (2d, 3H, J_{HH}=7.2 Hz); 1.6 (m, 2H); 1.65, 1.72 (2s, 3H); 2.35 (m, 2H); 4.41, 4.62 (2q, 1H, J_{HH}=7.2 Hz); 5.80, 6.00 (2 br. s, 1H, NH)
4i	68	94°	$C_{15}H_{19}Cl_2NO_3$ (332.2)	1685; 1705; 3395	1.43 (s, 9H); 4.11, 4.37 (ν_A, ν_B, 4H, J_{AB}=12 Hz); 6.40 (br. s, 1H, NH); 7.50 (m, 3H_{arom}); 8.00 (m, 2H_{arom})
4j	53	90°	$C_{10}H_{17}Cl_2NO_3$ (270.2)	1660; 1750; 3362	1.39 (s, 9H); 2.22 (s, 3H); 3.99, 4.24 (ν_A, ν_B, 4H, J_{AB}=11.2 Hz); 6.32 (br. s, 1H, NH)
4k	70	74°	$C_9H_{16}ClNO_3$ (221.7)	1652; 1745; 3376	1.15 (d, 6H, J_{HH}=8 Hz); 1.66 (s, 3H); 2.12 (s, 3H); 4.1 (m, 1H); 4.05, 4.25 (ν_A, ν_B, 2H, J_{AB}=12 Hz); 6.25 (br. s, 1H, NH)

[a] Yield of isolated product.
[b] The microanalyses were in good agreement with the calculated values: C, ±0.23; H, ±0.19; N, ±0.47; Cl, ±0.40.

Table 2. Reaction of Amides **4** with Powdered Potassium Hydroxide; Oxiranes **6** prepared

Educt	Product	Yield[a] [%]	b.p./torr [°C] or m.p. [°C]	Molecular Formula	M.S. *m/e* (M^+)	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
4c	**6c**	91	100–105°/15[c]	$C_8H_{15}NO_2$ (157.2)	calc. 157.1102 found 157.1097	1675 3395	1.32 (s, 9H); 1.54 (s, 3H); 2.27 (s, 2H)[d]; 6.20 (br. s, 1H, NH)
4k	**6k**	98	54°	$C_7H_{13}NO_2$ (143.2)	calc. 143.0946 found 143.0949	1652 3320	1.10, 1.15 (2d, 6H); 1.56 (s, 3H); 2.77 (s, 2H)[d]; 4.0 (m, 1H); 6.17 (br. s, 1H, NH)
4f (or **4g**, **4h**)	**6f**	95[b]	85–90°/20[c]	$C_9H_{17}NO_2$ (171.2)	calc. 171.1259 found 171.1259	1675 3385	1.32; 1.4 [m, 12H, CH_3, $(CH_3)_3$]; 1.47, 1.51 (2s, 3H); 2.96 (q, 1H); 6.20 (br. s, 1H, NH)

[a] Yields of isolated products; chemical purities (by ^{1}H-N.M.R.) ≥95%.
[b] The product is a mixture of *cis* and *trans* isomers.
[c] Bulb to bulb distillation.
[d] The protons of ring CH_2 group of **6c** and **6k** appear as d, d in C_6D_6: **6c**, δ=2.17; 2.25; J_{HH}=5 Hz; **6k**, δ=2.15; 2.23; J_{HH}=4.5 Hz.

Table 3. 3-Acyloxy-2-azetidinones **5** prepared by Method A

Product	Yield[a] [%]	b.p./torr [°C][b] or m.p. [°C]	Molecular Formula[c]	I.R. ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
5a	95	140–145°/0.05	$C_{15}H_{19}NO_3$ (261.3)	1720 (COO); 1750 (CO)	1.36 (s, 9H); 1.71 (s, 3H); 3.39, 3.68 (ν_A, ν_B, 2H, J_{AB}=5.6 Hz); 7.5 (m, 3H_{arom}); 8.0 (m, 2H_{arom})	166.2 (C=O); 165.5 (COO); 133.5; 130.0; 129.8; 128.5 (C_6H_5); 82.9 (C_3); 53.1 [$C(CH_3)_3$]; 50.9 (C_4); 18.9 (CH_3); 27.5 [$C(CH_3)_3$]
5b	81	145–150°/5	$C_{14}H_{17}NO_3$ (247.3)	1720 (COO); 1755 (CO)	1.20, 1.24 (2d, 6H, J=7 Hz); 1.75 (s, 3H); 3.41, 3.75 (ν_A, ν_B, 2H, J_{AB}=6.4 Hz)	166.6 (C=O); 165.4 (COO); 133.5; 130.0; 129.7; 128.5 (C_6H_5); 83.6 (C_3); 50.4 (C_4); 43.4 [$CH(CH_3)_2$]; 20.1; 20.2 [$CH(CH_3)_2$]; 18.9 (CH_3)
5c	91	110–115°/8	$C_{10}H_{17}NO_3$ (199.3)	1740 (COO); 1755 (CO)	1.32 (s, 9H); 1.60 (s, 3H); 2.07 (s, 3H); 3.28, 3.55 (ν_A, ν_B, 2H, J_{AB}=6.4 Hz)	170.0 (COO); 166.3 (CO); 82.5 (C_3); 53.1 [$C(CH_3)_3$]; 50.7 (C_4); 27.5 [$C(CH_3)_3$]; 21.1 (CH_3—CO); 18.9 (CH_3)
5d	85	100–105°/0.08	$C_{12}H_{21}NO_3$ (227.2)	1730 (COO); 1755 (CO)	0.95 (t, 3H J=7 Hz); 1.34 (s, 9H); 1.60 (s, 3H); 1.7 (m, 2H); 2.34 (t, 2H, J=7 Hz); 3.30, 3.55 (ν_A, ν_B, 2H, J_{AB}=6.4 Hz)	172.7 (COO); 166.4 (CO); 82.4 (C_3); 53.1 [$C(CH_3)_3$]; 50.9 (C_4); 36.2 (CH_2—CO); 27.5 [$C(CH_3)_3$]; 18.9 (CH_3); 18.4 (CH_3CH_2); 13.5 (CH_3—CH_2)
5e	93	82°	$C_{17}H_{22}NO_3$ (287.4)	1637 (C=C); 1712 (COO); 1745 (CO)	1.36 (s, 9H); 1.69 (s, 3H); 3.37, 3.64 (ν_A, ν_B, 2H, J_{AB}=6.4 Hz); 6.42 (d, 1H, J=6 Hz); 7.4 (m, 5H_{arom}); 7.70 (d, 1H, J=6 Hz)	166.3 (CO); 165.8 (COO); 146.0 (CH=CH—CO); 134.3; 130.7; 129.1; 128.3 (C_6H_5); 117.6 (CH=CH—CO); 82.7 (C_3); 53.1 [$C(CH_3)_3$]; 50.9 (C_4); 27.5 [$C(CH_3)_3$]; 18.9 (CH_3)
5f	91[d]	90°	$C_{16}H_{21}NO_3$ (275.4)	1716 (COO); 1754 (CO)	1.4–1.6 [m, 12H, CH_3—CH, $C(CH_3)_3$]; 1.80 (s, 3H, CH_3—C—CO); 3.88, 4.00 (2q, 1H, J_{HH}=6.4 Hz); 7.5 (m, 3H_{arom}); 8.1 (m, 2H_{arom})	*trans*-methyl isomer[e]: 166.4 (CO); 165.3 (COO); 133.5; 130.1; 128.5 (C_6H_5); 85.2 (C_3); 60.5 (C_4); 53.9 [$C(CH_3)_3$]; 28.4 [$C(CH_3)_3$]; 18.8 (3-CH_3); 16.5 (4-CH_3) *cis*-methyl isomer[e]: 166.6 (CO); 165.7 (COO); 133.5, 130.1, 128.5 (C_6H_5); 86.5 (C_3); 59.0 (C_4); 54.2 [$C(CH_3)_3$]; 28.4 [$C(CH_3)_3$]; 16.8 (3-CH_3); 14.4 (CH_3—CH)
5g	97[d]	155–160°/20	$C_{11}H_{19}NO_3$ (213.3)	1744; 1755	1.3–1.7 [m, 15H, $C(CH_3)_3$, CH_3, CH_3]; 2.09, 2.10 (2s, 3H, CH_3—CO); 3.79, 3.86 (2q, 1H, J_{HH}=6.4 Hz)	170.2; 169.8 (COO); 166.8; 166.4 (CO); 85.9; 84.7 (C_3); 60.3; 58.8 (C_4); 54.2; 53.8 [$C(CH_3)_3$]; 28.4 [$C(CH_3)_3$]; 21.2 (CH_3—CO); 18.6; 16.7 (CH_3); 16.3; 14.3 (CH_3—CH)
5h	97[d]	170–175°/20	$C_{13}H_{23}NO_3$ (241.3)	1735 (COO); 1758 (CO)	0.95 (t, 3H, J_{HH}=6.8 Hz, CH_3—CH_2); 1.37–1.72 [m, 17H, $C(CH_3)_3$, CH_3, CH_3, CH_2]; 2.30 (m, 2H); 3.77; 3.85 (2q, 1H, J_{HH}=6.4 Hz)	*trans*-methyl isomer[e]: 172.6 (COO); 166.6 (CO); 85.9 (C_3); 60.3 (C_4); 53.8 [$C(CH_3)_3$]; 36.2 (CH_2CO); 28.5 [$C(CH_3)_3$]; 18.7 (3-CH_3); 18.4 (CH_3CH_2); 16.4 (4-CH_3); 13.6 (CH_3—CH_2) *cis*-methyl isomer[e]: 173.0 (COO); 166.8 (CO); 84.6 (C_3); 59.0 (C_4); 54.2 [$C(CH_3)_3$]; 36.4 (CH_2CO); 28.4 [$C(CH_3)_3$]; 16.8 (3-CH_3); 18.4 (CH_3CH_2); 14.3 (4-CH_3); 13.6 (CH_3CH_2)

Table 3. (Continued)

Product	Yield[a] [%]	b.p./torr [°C][b] or m.p. [°C]	Molecular Formula[c]	I.R. ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
5i	94	73°	$C_{15}H_{18}ClNO_3$ (295.8)	1720 (COO); 1750 (CO)	1.40 (s, 9H); 3.63, 3.72 (ν_A, ν_B, 2H, J_{AB}=5.6 Hz, CH_2); 3.87, 4.09 (ν_A, ν_B, 2H, J_{AB}=12 Hz, CH_2Cl); 7.5 (m, 3H_{arom}); 8.0 (m, 2H_{arom})	165.1 (COO); 163.0 (CO); 133.9; 130.2; 129.1; 128.7 (C_6H_5); 84.6 (C_3); 53.7 [$C(CH_3)_3$]; 47.3 (C_4); 43.4 (CH_2Cl); 27.5 [$C(CH_3)_3$]
5j	94	95–100°/0.04	$C_{10}H_{16}ClNO_3$ (233.7)	1750; 1756	1.39 (s, 9H); 2.13 (s, 3H); 3.54, 3.59 (ν_A, ν_B, 2H, J_{AB}=6.4 Hz, CH_2); 3.75, 3.95 (ν_A, ν_B, 2H, J_{AB}=11.2 Hz, CH_2Cl)	169.6 (COO); 162.9 (CO); 84.4 (C_3); 53.6 [$C(CH_3)_3$]; 47.1 (C_4); 43.1 (CH_2Cl); 27.4 [$C(CH_3)_3$]; 20.9 (CH_3—CO)
5k	78	100–105°/10	$C_9H_{15}NO_3$ (185.2)	1735 (COO); 1755 (CO)	1.14, 1.17 (2d, 6H, J_{HH}=6.4 Hz); 1.59 (s, 3H, CH_3—C—CO); 2.05 (s, 3H, CH_3—COO); 3.27, 3.55 (ν_A, ν_B, 2H, J_{AB}=6.4 Hz); 3.92 (m, 1H)	170.0 (COO); 166.8 (CO); 83.2 (C_3); 50.3 (C_4); 43.5 [$CH(CH_3)_2$]; 21.1 (CH_3—CO); 20.1; 19.9 [$CH(CH_3)_2$]; 18.9 (CH_3)

[a] Yield of isolated product, based on **4**.

[b] Bath temperature of bulb to bulb distillation.

[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.34; H, ±0.20; N, ±0.46; Cl, ±0.23; exception: **5b**; C, −0.46.

[d] The product is a mixture of *cis* and *trans* isomers which is not separated preparatively.

[e] Assignment of the isomers is based on the different proportion of *cis* and *trans* for **5f** and **5h** and on the premise that the 3-CH_3 is shielded by the *cis* 4-CH_3 (γ-effect[13]). The ratio *cis*/*trans* for **5g** is 50/50.

Oxiranes 6c, f, k; General Procedure:

Powdered potassium hydroxide (2.5 g, 45 mmol) is added to a solution of the carboxamide **4** (5 mmol) in tetrahydrofuran (5 ml) and the mixture is stirred for 40 min (1.5 h for the carboxamide **4e**) at room temperature. The potassium hydroxide is separated by filtration and washed with tetrahydrofuran. The solvent is evaporated, giving a residual oil which is distilled to afford the oxirane or a mixture of oxirane **6**/2-azetidinone **5**. This mixture is analysed by N.M.R. spectroscopy.

3-Acyloxy-2-azetidinones 5; General Procedure:

Method A: Caesium fluoride (3 g, 20 mmol) and benzyltriethylammonium chloride (0.2 g, 0.9 mmol) are added to a solution of the carboxamide **4** (5 mmol) in tetrahydrofuran (10 ml). The mixture is stirred and heated under reflux for 1 h (R^2=H) or 12 h (R^2=CH_3). The caesium fluoride is filtered off and the tetrahydrofuran is evaporated. The residue is extracted with chloroform (20 ml). The extract is washed with water (10 ml), dried with anhydrous sodium sulfate, and concentrated in vacuo. The resultant residue is purified by distillation or by crystallisation from petroleum ether to afford the 3-acyloxy-2-azetidinones **5**.

Method B: The mixture of carboxamide **4** (2 mmol) and powdered caesium fluoride (1.2 g, 8 mmol) is heated at 85–90 °C (bath) for 6 h. The mixture is cooled and then extracted with dichloromethane (20 ml). The dichloromethane is removed to afford the 3-acyloxy-2-azetidinone **5b**; yield: 0.48 g (96%) or **5c**; yield: 0.38 g (95%).

Received: December 13, 1982
(Revised form: January 26, 1983)

[1] A. K. Mukerjee, R. C. Srivastava, *Synthesis* **1973**, 327.
[2] I. L. Knunyants, N. P. Gambaryan, *Izv. Akad. Nauk SSSR Otdel. Khim. Nauk.* **1955**, 1037; *C. A.* **50**, 1127 (1956).
[3] I. L. Knunyants, E. E. Rytslin, N. P. Gambaryan, *Izv. Akad. Nauk. SSSR Otdel. Khim. Nauk.* **1960**, 527; *C. A.* **54**, 22467 (1960).
[4] M. S. Manhas, S. J. Jeng, *J. Org. Chem.* **32**, 1246 (1967).
[5] H. H. Wasserman, D. J. Hlaste, A. W. Tremper, J. S. Wu, *Tetrahedron Lett.* **1979**, 549.
[6] H. H. Wasserman, D. J. Hlasta, *J. Am. Chem. Soc.* **100**, 6780 (1978).
[7] T. Okawara, Y. Noguchi, T. Matsuda, M. Furukawa, *Chem. Lett.* **1981**, 185.
[8] R. F. Abdulla, J. C. Williams, Jr., *Tetrahedron Lett.* **21**, 997 (1980).
[9] H. Takahata, Y. Ohnishi, T. Yamazaki, *Heterocycles* **14**, 467 (1980).
[10] H. Takahata, Y. Ohnishi, H. Takehara, K. Tsuritani, T. Yamazaki, *Chem. Pharm. Bull.* **29**, 1063 (1981).
[11] J. H. Clark, *Chem. Rev.* **80**, 429 (1980).
[12] M. Passerini, *Gazz. Chim. Ital.* **51**, II, 126, 181 (1921).
[13] D. K. Dolling, D. M. Grant, *J. Am. Chem. Soc.* **89**, 6612 (1967).