Synthetic Approaches to 2-Substituted 1-Oxo- and 3-Oxotetrahydroisoquinolines

Chen-Yu Cheng*, Hui-Bing Tsai and Mei-Shan Lin

School of Pharmacy, College of Medicine, National Taiwan University,
1, Section 1, Jen-Ai Rd., Taipei, Taiwan 10018, Republic of China

Received October 25, 1993
Revised September 9, 1994

2-Substituted homophthalimides **2a-c** were reduced regioselectively with sodium borohydride to carbinol-lactam intermediates **3a-c**, which were dehydrated, followed by hydrogenation, to give 1-oxotetrahydroisoquinolines or 3,4-dihydroisoquinolin-1(2*H*)ones **5a-c**. The isomeric 3-oxo-tetrahydroisoquinolines or 1,4-dihydroisoquinolin-3(2*H*)-ones **8a-i** were obtained in satisfactory yields *via* heating 3-isochromanone (**6**) with the corresponding amines **7a-i** in the presence of aluminum chloride.

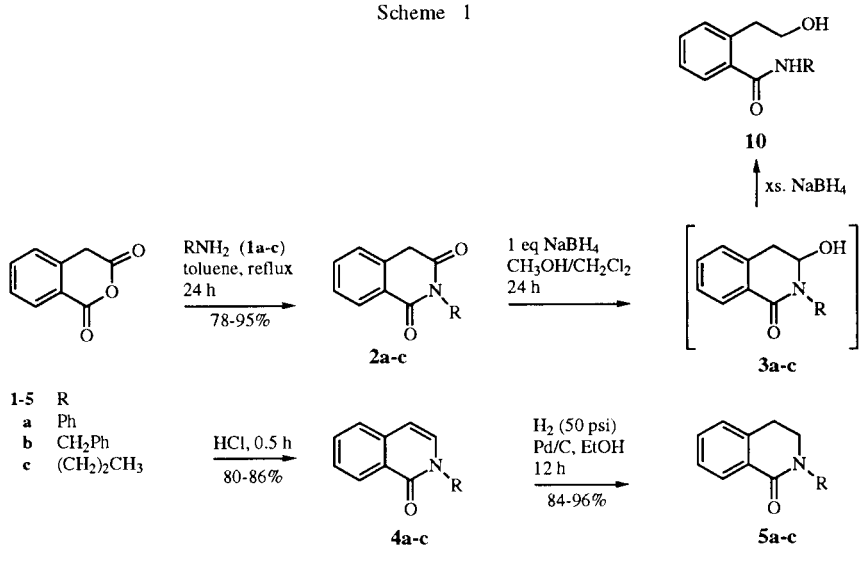
J. Heterocyclic Chem., **32**, 73 (1995).

Isoquinolones are important structural components in plant alkaloids and useful synthetic intermediates for biologically active compounds [1]. Isoquinolin-1(2*H*)-ones and isoquinolin-3(2*H*)-ones have been prepared *via* condensation of appropriate amino esters [2,3,4]. Other literature methods for the preparation of isoquinolin-1(2*H*)ones include Pd-assisted cyclization of 2-allylbenzamides [5], thermal cyclization of styryl isocyanates [6], and palladium-catalyzed CO insertion reaction of *o*-bromophenylethylamines [7]; while 1,4-dihydro-1-phenylisoquinolin-3(2*H*)-ones have been prepared by polyphosphoric acid-catalysed condensation of phenylacetonitriles with benzaldehydes [8]. Complimentary to the above described methods, we have developed practical and efficient routes to 2-substituted 3,4-dihydroisoquinolin-1(2*H*)-ones **5** (Scheme 1) and the isomeric 1,4-dihydroisoquinolin-3(2*H*)-ones **8** (Scheme 2) during our search for biologically active isoquinolones.

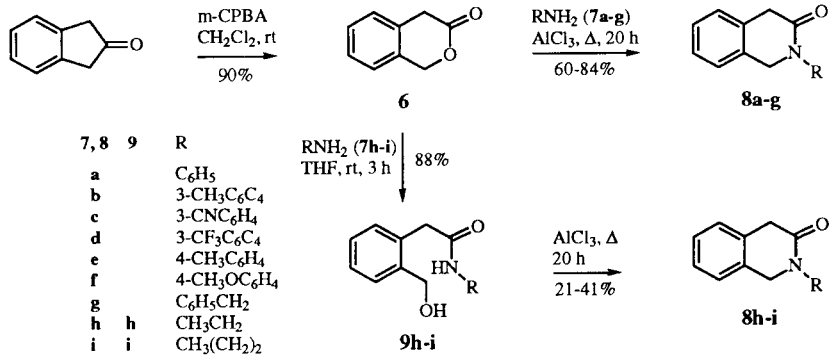
As outlined in Scheme 1, homophthalic anhydride condensed with amine **1** to give homophthalimide **2**. When **2** was treated with sodium borohydride [9], the carbonyl group at C-3 was selectively reduced to give the carbinol-lactam intermediate **3**, which, without isolation, was dehydrated upon treatment with hydrochloric acid to afford isoquinolin-1(2*H*)-ones **4**. When a large excess (≥ 5 equivalents) of sodium borohydride was used, the carbinol-lactam intermediate **3** was further reduced to the amide-alcohol **10**. The desired 3,4-dihydroisoquinolin-1(2*H*)-one **5** was obtained from **4** *via* palladium-catalysed hydrogenation.

The synthesis of 2-substituted 1,4-dihydroisoquinolin-3(2*H*)-ones **8** starts from indanone, which was first oxidized to 3-isochromanone (**6**) with *m*-chloroperbenzoic acid. 3-Isochromanone (**6**) was found to condense with high-boiling amines, such as anilines **7a-f** or benzylamine (**7g**), in the presence of aluminum chloride at 160° to afford directly the desired lactams **8a-g** in satisfactory yields; while the condensation of **6** with low-boiling amines to give lactams **8h-i** was accomplished in two steps. Thus, 3-isochromanone (**6**) was treated with ethyl-

Scheme 1



Scheme 2



amine (**7h**) or propylamine (**7i**) to form the intermediate amide-alcohols **9h-i**, which were then heated in the presence of aluminum chloride to afford lactams **8h-i** in lower yields (Scheme 2). Aluminum chloride has been reported to facilitate the aminolysis of esters with dialkylamines [10], but its effect on facilitating the conversion of lactones to lactams as described here has not been reported.

Table 1

Analytical Data of Compounds Synthesized

No.	Yield (%)	mp (°C) ethyl acetate/ *n*-hexane	Molecular formula	Analysis (%) Calcd./Found C	H	N	HRMS M+, m/z Calcd./Found
2a	95	189-191.5 (ethyl acetate)	$C_{15}H_{11}O_2N$	75.94 75.62	4.67 4.54	5.90 5.51	237.0790 237.0803
2b	80	128.5-129.5	$C_{16}H_{13}O_2N$	76.48 76.61	5.21 5.27	5.57 5.51	251.0946 251.0950
2c	78	61.5-62.5	$C_{12}H_{13}O_2N$	70.92 70.72	6.45 6.32	6.89 6.81	203.0946 203.0944
4a	86	103.5-105	$C_{15}H_{11}ON$	81.43 81.28	5.01 4.87	6.33 6.21	221.0840 221.0826
4b	80	66.5-68.5	$C_{16}H_{13}ON$	81.68 81.80	5.57 5.72	5.95 5.76	235.0997 235.0982
4c	81	liquid	$C_{12}H_{13}ON$				187.0997 187.0992
5a	86	98-100 [a] (acetone)	$C_{15}H_{13}ON$				223.0997 223.0996
5b	96	liquid [b]	$C_{16}H_{15}ON$				237.1153 237.1156
5c	84	liquid	$C_{12}H_{15}ON$				189.1153 189.1148
8a	72	97.5-98.5 (cyclohexane)	$C_{15}H_{13}ON$	80.69 80.56	5.87 5.67	6.27 6.13	223.0997 223.0986
8b	73	139-140	$C_{16}H_{15}ON$	80.67 80.87	6.72 6.61	5.88 5.63	237.1154 237.1166
8c	69	114-118	$C_{16}H_{12}ON_2$	77.11 77.05	5.22 4.89	11.24 11.07	248.0950 248.0949
8d	64	96-97	$C_{16}H_{12}ONF_3$	65.75 65.85	4.45 4.14	4.79 4.79	291.0871 291.0875
8e	84	124.5-126	$C_{16}H_{15}ON$	80.67 80.63	6.72 6.39	5.88 5.74	237.1154 237.1165
8f	60	122-123	$C_{16}H_{15}O_2N$	75.59 75.52	6.30 6.06	5.51 5.49	253.1103 253.1100
8g	73	91-92	$C_{16}H_{15}ON$	80.98 80.75	6.37 6.39	5.90 5.95	237.1154 237.1163
8h	21	32-34 [c]	$C_{11}H_{13}ON$				175.0997 175.0987
8i	41	liquid	$C_{12}H_{15}ON$				189.1154 189.1155

[a] Lit [11] mp 101-103°. [b] *cf* ref [7]. [c] Lit [12] mp 32°.

Table 2

Spectroscopic Data of Compounds Synthesized

No.	IR cm^{-1}	^1H NMR (CDCI3) δ, J (Hz)	^{13}C NMR ($CDCl_3$), δ	MS (70 eV) m/z (%)
2a	1715 1682	8.23 (d, 1 H, J = 8 Hz),7.60-7.65 (m, 1H), 7.40-7.53 (m, 4H), 7.32 (d, 1H, J = 8 Hz), 7.14-7.21 (m, 2H), 4.20 (s, 2 H)	169.8, 165.0, 135.0, 134.2, 133.9, 129.4, 129.3, 128.6, 128.4, 127.8, 127.3, 125.4, 36.9	237 (100), 209 (33), 181 (18), 118 (67), 90 (55)
2b	1707 1667	8.19 (dd, 1H, J = 8 & 1 Hz), 7.55 (dt, 1H, J = 7.5 & 1 Hz), 7.36-7.46 (m, 3H), 7.22-7.30 (m, 4H), 5.17 (s, 2H), 4.04 (s, 2H)	169.7, 164.7, 136.9, 134.0, 133.5, 129.2, 128.8, 128.3, 127.6, 127.4, 127.0, 125.3, 43.2, 36.4	251 (100), 223 (47), 146 (12), 132 (22), 118 (47), 91 (35)
2c	1713 1681	8.18 (dd, 1H, J = 8 & 1 Hz), 7.55 (dt, 1H, J = 7.5 & 1 Hz), 7.4 (t, 1H, J = 7.6 Hz), 7.23 (t, 1H, J = 7.6 Hz), 4.00 (s, 2H), 3.92 (m, 2H), 1.63 (m, 2H), 0.92 (t, 3H)	169.9, 164.9, 134.1, 133.5, 129.2, 127.7, 127.1, 125.5, 41.7, 36.4, 21.3, 11.4	203 (100), 162 (43), 145 (61), 134 (26), 118 (51), 104 (38), 89 (49)
4a	3046 1661 1626	8.47 (d, 1H, J = 8 Hz), 7.62-7.68 (m, 1H), 7.36-7.54 (m, 7H), 7.16 (d, 1H, J = 7.4 Hz), 6.54 (d, 1H, J = 7.4 Hz)	162.0, 141.4, 137.1, 132.5, 132.1, 129.2, 128.3, 128.0, 127.1, 126.8, 126.6, 125.9, 106.1	221 (69), 220 (100), 165 (8), 89 (9), 77 (10)
4b	3063 1651 1623	8.45 (d, 1H, J = 8 Hz), 7.59-7.61 (m, 5H), 7.45-7.50 (m, 1H), 7.24-7.32 (m, 2H), 7.06 (d, 1H, J = 7.4 Hz), 6.46 (d, 1H, J = 7.4 Hz), 5.21 (s, 1H)	162.3, 137.0, 136.9, 132.2, 131.3, 128.8, 128.1, 127.9, 127.8, 126.9, 126.3, 125.9, 106.4, 51.7	235 (94), 218 (10), 129 (27), 116 (6), 91 (100), 65 (16)
4c	3063 1657 1627	8.40 (d, 1H, J = 7.3 Hz), 7.56-7.64 (m, 1H), 7.41-7.48 (m, 2H), 7.02 (d, 1H, J = 7.3 Hz), 6.45 (d, 1H, J = 7.3 Hz), 3.93 (t, 2H), 1.78 (m, 2H), 0.95 (t, 3H)	162.1, 137.0, 131.9, 131.7, 127.8, 126.6, 126.3, 125.7, 105.8, 50.9, 22.5, 11.1	187 (98), 172 (14), 158 (12), 145 (100), 128 (45), 118 (15), 89 (12)
5a	1651	8.15 (dd, 1H, J = 8 & 1 Hz), 7.33-7.48 (m, 6H), 7.21-7.30 (m, 2H), 3.95 (t, 2H), 3.12 (t, 2H)	164.2, 143.1, 138.3, 132.0, 129.7, 128.9, 128.7, 127.2, 126.9, 126.2, 125.4, 49.4, 28.6	223 (92), 149 (10), 118 (100), 104 (15), 90 (51), 77 (35)
5b [b]	1651	8.14 (dd, 1H, J = 8 & 1 Hz), 7.24-7.40 (m, 7 Hz), 7.12 (d, 1H, J = 1 Hz), 4.78 (s, 2H), 3.47 (t, 2H), 2.92 (t, 2H)	164.5, 138.0, 137.4, 131.7, 129.4, 128.6, 128.4, 128.0, 127.4, 127.0, 126.8, 50.4, 45.3, 28.1	237 (100), 160 (8), 146 (37), 133 (28), 118 (27), 91 (24)
5c	1651	8.04 (dd, 1H, J = 8 & 1 Hz), 7.24-7.39 (m, 2H), 7.13 (d, 1H, J = 7 Hz), 3.52 (m, 4H), 2.95 (t, 2H), 1.63 (m, 2H), 0.95 (t, 3H)	164.3, 137.9, 131.4, 129.7, 128.2, 127.0, 126.7, 49.1, 46.1, 28.2, 20.9, 11.3	189 (71), 174 (11), 160 (100), 145 (16), 130 (12), 118 (15), 90 (10)
8a	1667	7.38-7.43 (m, 2H), 7.24-7.33 (m, 6H), 7.18 (d, 1H, J = 7.3 Hz), 4.84 (s, 2H), 3.78 (s, 2H)	169.1, 142.4, 132.6, 132.1, 129.1, 127.8, 127.2, 126.7, 125.6, 125.1, 54.1, 38.8	223 (61), 194 (25), 131 (12), 118 (10), 104 (100), 91 (9), 77 (41)
8b	1651	7.21-7.41 (m, 5H), 7.08-7.15 (m, 3H), 4.79 (s, 2H), 3.75 (s, 2H), 2.37 (s, 3H)	169.0, 142.5, 139.0, 132.7, 132.3, 128.9, 127.8, 127.6, 126.7, 126.5, 125.2, 122.7, 54.2, 38.8, 21.3	237 (19), 208 (8), 131 (9), 118 (9), 104 (100), 91 (12), 77 (10)
8c	2237 1662	7.36-7.63 (m, 4H), 7.13-7.29 (m, 4H), 4.79 (s, 2H), 3.70 (s, 2H)	169.3, 143.0, 132.1, 131.7, 129.9, 129.7, 128.9, 128.1, 127.3, 127.0, 125.3, 118.2, 112.9, 53.4, 38.8	248 (80), 219 (35), 203 (15), 131 (38), 118 (11), 104 (100)
8d	1668	7.64 (s, 1H), 7.49 (m, 3H), 7.23 (m, 4H), 4.81 (s, 2H), 3.73 (s, 2H)	169.2, 143.0, 132.3, 132.1, 131.9, 130.6, 129.5, 129.0, 128.0, 127.2, 126.9, 125.2, 123.1, 122.3, 117.2, 53.6, 38.8	291 (52), 262 (21), 131 (19), 104 (100), 77 (12)
8e	1651	7.17-7.28 (m, 8H), 4.77 (s, 2H), 3.73 (s, 2H), 2.35 (s, 3H)	169.0, 140.0, 136.4, 132.7, 132.3, 129.7, 127.8, 127.2, 126.7, 125.5, 125.2, 54.1, 38.7, 21.0	237 (51), 208 (11), 192 (8), 131 (13), 118 (8), 104 (100), 91 (13)

Table 2 (continued)

No.	IR cm^{-1}	^1H NMR (CDCl3) δ, J (Hz)	^{13}C NMR ($CDCl_3$), δ	MS (70 eV) m/z (%)
8f	1651	7.12-7.27 (m, 6H), 6.84-6.99 (m, 2H), 4.76 (s, 2H), 3.76 (s, 3H), 3.73 (s, 2H)	169.1, 158.2, 135.4, 132.6, 132.2, 127.8, 127.2, 126.9, 126.7, 125.1, 114.5, 55.4, 54.4, 38.6	253 (71), 224 (12), 208 (10), 131 (18), 118 (7), 104 (100), 77(20)
8g	1646	7.00-7.26 (m, 9H), 4.73 (s, 2H), 4.34 (s, 2H), 3.66 (s, 2H)	168.9, 136.8, 132.2, 131.3, 128.7, 128.0, 127.5, 127.2, 126.6, 50.2, 49.9, 37.4	237 (42), 146 (38), 132 (58), 118 (21), 104 (88), 91 (100)
8h	1651	6.84-7.05 (m, 4H), 4.19 (s, 2H), 3.28 (s, 2H), 2.32 (q, 2H), 0.94 (t, 3H)	168.0, 132.2, 131.4, 127.2, 126.9, 126.3, 124.9, 49.9, 41.3, 37.2, 12.1	189 (71), 175 (61), 146 (48), 118 (69), 104 (100)
8i	1651	6.84-7.09 (m, 4H), 4.21 (s, 2H), 3.33 (s, 2H), 3.27 (t, 2H), 1.42 (tq, 2H), 0.71 (t, 3H)	168.9, 132.4, 131.5, 127.4, 127.1, 126.4, 124.9, 50.8, 48.5, 37.4, 20.4, 11.1	189 (28), 160 (19), 146 (16), 132 (28), 118 (13), 104 (100)

[b] The spectral data is consistent with the literature [7].

EXPERIMENTAL

Melting points were taken in a capillary tube by using a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 1760-X spectrometer. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AM-300 or AM-80 spectrometer. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Electron impact mass spectra were obtained at 70 eV on a JEOL JMS-D300 mass spectrometer. High resolution mass spectra were obtained with a JEOL JMS-HX110 spectrometer. Elemental analyses were performed with a Perkin-Elmer 240C instrument. Analytical thin layer chromatography was performed on Merck (Art. 5717) silica gel plates and visualized with uv light (254 nm) or upon heating after treatment with 2% phosphomolybdic acid in ethanol. Medium pressure liquid chromatography was performed with Merck 40-63 μm silica gel. All reagents were of commercial quality from freshly opened containers. Reagent quality solvents were used without further purification.

2-Substituted 1,3-Dioxotetrahydroisoquinolines **2**.

General Procedure.

A solution of homophthalic anhydride (2.2 g, 12.3 mmoles) and an amine **1a-c** (13.6 mmoles) in toluene (8 ml) is refluxed under nitrogen for 24 hours. The mixture is cooled to room temperature, diluted with methylene chloride, and washed with 2 *N* hydrochloric acid to remove the excess amine. The organic layer is washed with water and brine, dried with magnesium sulfate, and evaporated to give a crude, which is purified with medium pressure liquid chromatography (silica gel, 0-5 % of methanol in methylene chloride) to give **2a-c** (Tables 1 and 2).

2-Substituted Isoquinolin-1(2*H*)-ones **4**.

General Procedure.

To a solution of homophthalimide **2a-c** (0.42 mmole) in methanol (3 ml) and methylene chloride (7 ml) at room temperature is added portionwise sodium borohydride (16 mg, 0.42 mmole). After 24 hours, 2 drops of concentrated hydrochloric acid is added, and the stirring is continued for 0.5 hour. The mixture is evaporated to dryness. The residue is treated with water and extracted with methylene chloride. The combined organic extracts are dried with magnesium sulfate, evaporated, and purified with medium pressure liquid chromatography (silica gel, methylene chloride/*n*-hexane = 1:1) to give **4a-c** (Tables 1 and 2).

2-Substituted 3,4-Dihydroisoquinolin-1(2*H*)-ones **5**.

General Procedure.

A mixture of isoquinolin-1(2*H*)-one **4a-c** (0.59 mmole), 5% palladium on charcoal (60 mg), and 95% ethanol (10 ml) is agitated at room temperature under hydrogen (50 psi) in a Parr shaker overnight. The resulting mixture is filtered through celite and evaporated to give **5a-c** (Tables 1 and 2).

1,4-Dihydrobenzo[*c*]pyran-3-one (**6**).

To a solution of indanone (5.0 g, 37.8 mmoles) in methylene chloride (50 ml) is added *m*-chloroperbenzoic acid (26.1 g, 75.7 mmoles). After stirring under nitrogen for 24 hours, the reaction mixture is poured into a solution of sodium bisulfite (16 g) in water (100 ml), and extracted with methylene chloride. The combined extracts are washed with saturated aqueous solution of sodium carbonate, water, and brine, dried and evaporated to give **6** (5.0 g, 90%), mp 81-81.5° (ethyl acetate/cyclohexane); ir (nujol): 1747 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 7.13-7.39 (m, 4 H), 5.29 (s, 2 H), 3.69 (s, 2 H); ^{13}C nmr (deuteriochloroform): δ 170.5, 131.6, 131.0, 128.7, 127.3, 127.0, 124.6, 70.0, 36.1; ms: m/z 148 (40), 104 (100), 91 (32), 78 (23); hrms: m/z (M^+) Calcd. 148.0524. Found: 148.0517.

Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.65; H, 5.52.

2-Substituted 1,4-Dihydroisoquinolin-3(2*H*)-ones **8**.

General Procedure.

Method A for **8a-g**.

A mixture of **6** (2.0 g, 13.5 mmoles), an arylamine **7a-g** (20.2 mmoles), and aluminum chloride (0.36 g, 2.7 mmoles) is heated in a sealed vessel at 160° for 20 hours. After cooling, the mixture is treated with water and methylene chloride. The organic

layer is separated, washed with 2 *N* hydrochloric acid, dried and evaporated. The residue is purified with medium pressure liquid chromatography (silica gel, methylene chloride/*n*-hexane = 1:1) to give **7a-g** (Tables 1 and 2).

Method B for **8h-i**.

To a solution of **6** (3.0 g, 20.3 mmoles) in tetrahydrofuran (20 ml) is introduced an alkylamine (**7h-i,** 30 mmoles). The mixture is stirred at room temperature for 3 hours and evaporated to give **9h-i**. A mixture of the crude amide-alcohol (**9h-i**) and aluminum chloride (0.47 g, 3.6 mmoles) is heated at 160° in a sealed vessel for 20 hours. The reaction mixture is worked up and purified as described in Method A to give **8h-i** (Tables 1 and 2).

Acknowledgment.

This work was supported by a grant (NSC80-0420-B002-230) from the National Science Council of the R.O.C.

REFERENCES AND NOTES

[1] F. S. Yates, Comprehensive Heterocyclic Chemistry, Vol **2**, A. J. Boulton and A. Mckillop, eds, Pergamon Press, Oxford, 1984, p 511.

[2] J. Finkelstein and A. Brossi, *J. Heterocyclic Chem.*, **4**, 315 (1967).

[3] Y. Tominaga, S. Hidaki, Y. Matsuda, G. Kobayashi and K. Sakemi, *Yakugaku Zasshi,* **100**, 456 (1980); *Chem. Abstr.*, **93**, 239176 (1980).

[4] N. G. Kundu, J. A. Wright, K. L. Perlman, W. Hallett and C. Heidelberger, *J. Med. Chem.*, **18**, 395 (1975).

[5] D. E. Korte, L. S. Hegedus and R. K. Wirth, *J. Org. Chem.*, **42**, 1329 (1977).

[6] A. R. Katritzky, Handbook of Heterocyclic Chemistry, 1st Ed, Pergamon Press, Oxford, 1985, p 464.

[7] M. Mori, K. Chiba and Y. Ban, *J. Org. Chem.*, **43**, 1684 (1978).

[8] V. St Georgiev, R. G. Van Inwegen and P. Carlson, *Eur. J. Med. Chem.*, **25**, 375 (1990).

[9] For a detailed study on sodium borohydride reduction of cyclic imides, see: J. C. Hubert, J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron,* **31**, 1437 (1975).

[10] R. D. Gless, Jr., *Synth. Commun.*, **16**, 633 (1986).

[11] E. Hoeft and H. Schultze, *J. Prakt. Chem.*, **32**, 12 (1966); *Chem. Abstr.*, **65**, 7140c (1966).

[12] R. Ushijima, K. Osumi and I. Matsumoto, Japanese Patent 54138577 (1979); *Chem. Abstr.*, **92**, 128757 (1979).