Facile Synthesis of Novel Spiro[azetidine-2,4'(1'*H*)-isoquinoline-1',3',4(2'*H*)-triones]

Michael S. Malamas

Department of Medicinal Chemistry, Wyeth-Ayerst Research, Inc.,
CN 8000 Princeton, New Jersey 08543-8000

Received November 10, 1993

A convenient general method for the synthesis of a new heterocycle, spiro[azetidine-2,4'(1'*H*)-isoquinoline-1',3',4(2'*H*)-trione] is described. The key intermediate **2** was prepared by direct halogenation of position-4 of acid **3** with thionyl chloride, and subsequent treatment of the generated 4-Cl, 4-acetyl chloride **11** with a THF/NH_3 solution at low temperature.

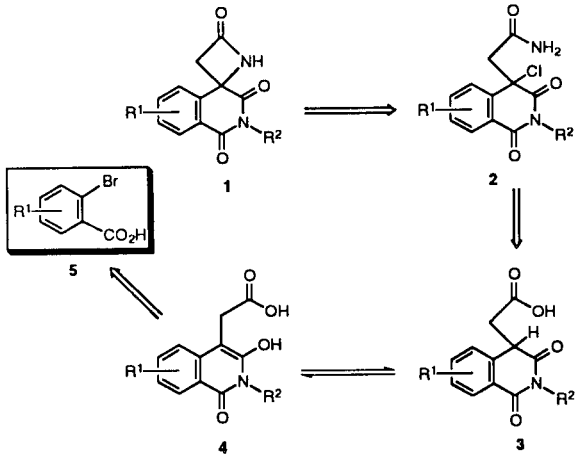
J. Heterocyclic Chem., **31**, 565 (1994).

The homophthalimide group has been extensively studied [1] and two distinct families of spiro heterocycles based on the homophthalimide framework, the spiro-[homophthalimide-4,3'-(3'*H*-pyrrolidines)] and the spiro-[homophthalimide-4,4'-(4'*H*-pyrans)], have been previously reported [2,3].

As part of our efforts to identify novel aldose reductase inhibitors (ARIs), we have studied the synthesis and biological activity of a novel tricyclic heterocycle, the spiro[azetidine-2,4'(4'*H*)-homophthalimide] (**1**). We report herein a facile synthesis of these spiroazetidines **1**. The biological evaluation of these compounds as ARIs will be reported in another journal.

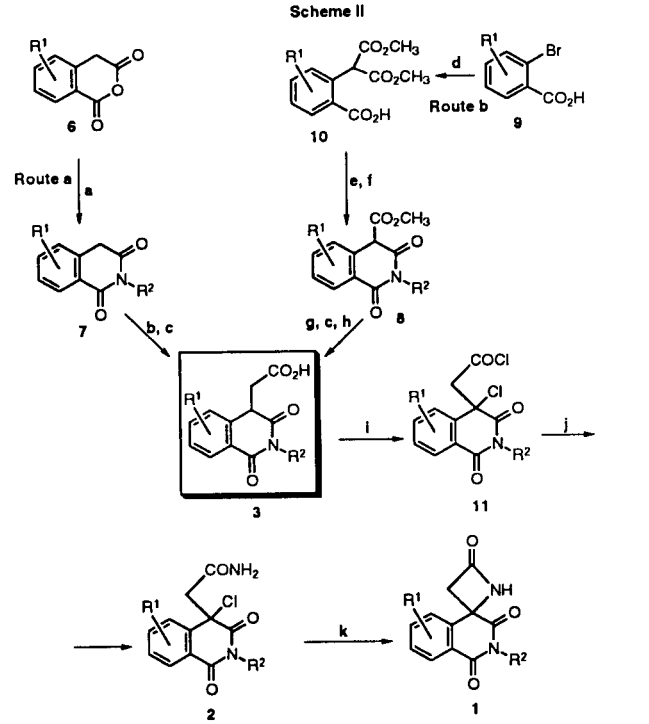
Retrosynthetic analysis of the spiroazetidines **1** suggests that the target compound **1** could be prepared *via* an intramolecular cyclization of the chloroamide **2**. The highly acidic nature of the methylene functionality of the homophthalimide moiety, that can favorably exist in its tautomeric form **4** (Scheme I), renders this position high reactivity towards halogenation. Thus, the key intermediate **2** could be obtained from acid **3** upon halogenation. Furthermore, compound **3** could efficiently be prepared from *o*-halobenzoic acid **5** (Scheme I).

Scheme I



Acid **3** was prepared by two synthetic routes, **a** and **b**. In route **a**, homophthalic anhydride **6** was reacted with the required amine to give homophthalimide **7**. Alkylation of **7** with *tert*-butyl bromoacetate followed by acidic hydrolysis, afforded acid **3**. This short process requires tedious purification, due the di-alkylated by-product. In route **b**, *o*-halogenated benzoic acid **9** was converted to diester **10** by the Hurtley reaction [4]. Treatment of **10** with thionyl chloride and subsequent reaction of the generated acid chloride with an appropriate amine gave ester **8**.

Scheme II



Reagents: (a) R^2-NH_2, DMF (R^2= alkyl or aralkyl); (b) $LiN(SiMe_3)_2$, $BrCH_2CO_2CMe_3$; (c) CF_3CO_2H, CH_2Cl_2; (d) $CH_2(CO_2Me)_2$, NaH, CuBr; (e) $SOCl_2$; (f) R^2-NH_2, THF (R^2= alkyl, aralkyl); (g) $BrCH_2CO_2CMe_3$, K_2CO_3; (h) 2N NaOH; (i) $SOCl_2$, toluene (j) NH_3/THF; (k) NaH, DMF

Conversion of ester **8** to acid **3** was accomplished by alkylation of **8** with *tert*-butyl bromoacetate, followed by

acidic hydrolysis and saponification. Alkylation of **8** with methyl bromoacetate and subsequent saponification of the generated methyl diester failed to afford acid **3**, primarily due to the extensive decomposition of the methyl diester during the basic hydrolysis process. The availability of *o*-halobenzoic acids, and the absence of chromatographic purification, makes route **b** the process of choice for the production of acid **3**. Treatment of **3** with thionyl chloride in toluene at 85° for 4 hours afforded the 4-chloro-4-acetyl chloride **11**. Compound **11** was carefully treated with a dilute THF/ammonia solution at low temperatures (0°) to yield chloroamide **2**. Intramolecular cyclization of **2** to the final spiroazetidine **1** was effected by treatment with sodium hydride in DMF. Representative compounds of this process are outlined in Table 1.

In conclusion, a facile synthesis of the novel spiro[azetidine-2,4'(4'*H*)-homophthalimide] was developed by direct halogenation of acid **3** at position-4 of the homophthalimide moiety, and subsequent treatment of the generated 4-Cl, 4-acetyl chloride **11** with a THF/NH_3 solution, to afford key intermediate **2**.

Table 1
Chemical Data of Spiro[azetidine-2,4'(1'*H*)-isoquinoline]-1',3',4(2'*H*)triones

Compound	R^1	R^2 [a]	mp °C	Formula	Elemental Analyses Calculated C	H	N	Found C	H	N
1a	6-Cl	CH_3	325-327	$C_{12}H_9ClN_2O_3$	54.44	3.43	10.58	54.06	3.46	10.23
1b	6-Br	CH_3	306-308	$C_{12}H_9BrN_2O_3$	46.63	2.93	9.06	46.73	2.89	8.84
1c	6-H	A	225-227	$C_{18}H_{12}BrFN_2O_3$	53.62	3.00	6.95	53.52	3.15	6.78
1d	6-F	A	244-246	$C_{18}H_{11}BrF_2N_2O_3$	51.33	2.63	6.65	51.07	2.74	6.41

[a] A = 4-Br, 2-$FC_6H_3CH_2$.

EXPERIMENTAL

Chemistry.

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus, and reported uncorrected. ^1H nmr spectra were determined in the cited solvent on a Bruker AM 400 (400 MHz) or a Varian XL-200 (200 MHz) instrument, with tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer as potassium bromide pellets or as solutions in chloroform. Mass spectra were recorded on either a Finnigan model 823 or a Hewlett-Packard model 5995A spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240 analyzer and all compounds are within ±0.4% of theory unless otherwise indicated. All products, unless otherwise noted, were purified by "flash chromatography" [5] with use of 220-400 mesh silica gel. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was accomplished with uv light and/or 10% phosphomolybdic acid in ethanol. Unless otherwise noted, all materials were obtained commercially and used without further purification. All reactions were carried out under an atmosphere of dry nitrogen.

General Procedure for the Synthesis of Spiro[azetidine-2,4'(1'*H*)-isoquinoline-1',3',4(2'*H*)-triones].

Compounds of the general structure **1** were synthesized from commercially available, appropriately substituted starting materials by the representative procedure illustrated for analog **1c** (Table 1).

Preparation of Acetic Acids (**3**).

Route **a**.

Step a). 2-[(4-Bromo-2-fluorophenyl)methyl]-1,3(2*H*,4*H*)-isoquinolinedione (**7**, R^1 = H, R^2 = 4-Br, 2-$FC_6H_3CH_2$).

4-Bromo-2-fluorobenzylamine hydrochloride (22.0 g, 91.5 mmoles) and triethylamine (12.75 ml, 91.5 mmoles) were added to a suspension of homophthalic anhydride (**6**, R^1 = H, 14.8 g, 91.36 mmoles) in anhydrous THF (200 ml). The mixture was stirred at room temperature for 1 hour and the volatiles were removed *in vacuo*. The residue was taken in DMF (150 ml) and refluxed for 15 hours. After cooling to room temperature, the brownish solution was poured into water and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. Evaporation and purification by flash chromatography (hexane/ethyl acetate 2:1) gave a white solid (16.1 g, 51%), mp 128-129°; ^1H nmr (DMSO-d_6, 200 MHz): δ 4.24 (s, 2H, -CH_2CON-), 5.04 (s, 2H, -NC*H*2-), 7.23 (t, J = 7.8 Hz, 1H, Ar-*H*), 7.3 (d, J = 7.65 Hz, 1H, Ar-*H*), 7.4-7.56 (m, 3H, Ar-*H*), 7.65 (t, J = 7.6 Hz, Ar-*H*), 8.06 (d, J = 7.8 Hz, 1H, Ar-*H*); ir (potassium bromide, cm^{-1}): 1675 (CO); ms: (m/z) 347 (M^+).

Anal. Calcd. for $C_{16}H_{11}BrFNO_2$: C, 55.19; H, 3.18; N, 4.02. Found: C, 54.83; H, 3.14; N, 4.07.

Step b). 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic Acid (**3**, R^1 = H, R^2 = 4-Br, 2-$FC_6H_3CH_2$).

Lithium bis(trimethylsilyl)amide (10.0 ml, 10.0 mmoles, 1.0 *M* in THF) was added dropwise over a 10 minute period to a cold (-78°) solution of 2-[(4-bromo-2-fluorophenyl)methyl]-

1,3(2*H*,4*H*)-isoquinolinedione (**7**, R^1 = H, R^2 = 4-Br, 2-$FC_6H_3CH_2$, 3.5 g, 10.0 mmoles) in anhydrous THF (80 ml). After stirring for 2 hours, *tert*-butyl bromoacetate (1.61 ml, 10.0 mmoles) was added, and the reaction mixture was allowed to warm up gradually to room temperature. The mixture, during that period, turned dark in color. It was stirred an additional 2 hours and quenched with aqueous ammonium chloride. The dark solution was poured into water, acidified with hydrochloric acid (2*N*), and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. Evaporation gave a yellowish oil (3.9 g), which was dissolved in dichloromethane (50 ml) and treated with trifluoroacetic acid (5 ml). The mixture was stirred at room temperature for 8 hours and the volatiles were removed *in vacuo*. The residue was purified by flash chromatography using acid washed (5% orthophosphoric acid/methanol) silica gel (hexane/ethyl acetate 2:1) to yield a white solid (1.6 g, 39%): mp 175-176°; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 3.34 (d, 2H, -C*H*$_2$CO$_2$H), 4.36 (t, J = 4.11 Hz, 1H, -ArC*H*CH$_2$CO$_2$H), 5.05 (dd, J = 15.5 Hz, 2H, -NC*H*$_2$-), 7.2 (t, J = 8.13 Hz, 1H, Ar-*H*), 7.23 (dd, J = 8.35 Hz, 1.76 Hz, 1H, Ar-*H*), 7.48 (t, J = 7.57 Hz, 1H, Ar-*H*), 7.52 (dd, J = 9.77, 1.78 Hz, 1H, Ar-*H*), 7.58 (d, J = 7.83 Hz, 1H, Ar-*H*), 7.70 (dt, J = 7.73 Hz, 1.2 Hz, 1H, Ar-*H*), 8.06 (dd, J = 7.86 Hz, 1.02 Hz, 1H, Ar-*H*), 12.43 (s, 1H, -CO$_2$*H*); ir (potassium bromide, cm^{-1}): 3350-2700 (CO$_2$H), 1730 (CO), 1710 (CO), 1670 (CO); ms: (m/z) 405 (M$^+$).

Anal. Calcd. for $C_{20}H_{15}BrFNO_6$: C, 53.22; H, 3.23; N, 3.45. Found: C, 52.88; H, 3.49; N, 3.57.

Route **b**.

Step a). 2-(Carboxyphenyl)propanedioic Acid Dimethyl Ester (**10**, R^1 = H).

Sodium hydride (80% in mineral oil, 10.75 g, 358.4 mmoles) was added over a 30 minute period to a rapidly stirred cold suspension (0°) of 2-bromobenzoic acid (**9**, R^1 = H, 30.0 g, 149.3 mmoles), cuprous bromide (2.14 g, 14.93 mmoles) and dimethyl malonate (300 ml), while a stream of dry nitrogen was passed over the mixture. After the addition of the sodium hydride had been completed, the mixture was stirred for 10 minutes at room temperature, and 30 minutes at 70° (external oil bath temperature). At this point, the suspension had turned to a solid mass, which was dissolved in water (1000 ml). The aqueous layer was extracted with diethyl ether (3 x 500 ml) and then was acidified with hydrochloric acid (2*N*). The acidic aqueous layer was extracted with ethyl acetate, and the organic extracts were dried over magnesium sulfate. Evaporation gave an off-white solid, which was recrystallized from diethyl ether/hexane (after cooling to -20°) to give a white solid (34.2 g, 91%): mp 119-120°; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 3.67 (s, 6H, -CH(CO$_2$C*H*$_3$)$_2$) 5.72 (s, 1H, -C*H*(CO$_2$CH$_3$)$_2$), 7.3 (d, J = 7.76 Hz, 1H, Ar-*H*), 7.45 (dt, J = 7.66 Hz, 1.12 Hz, 1H, Ar-*H*), 7.6 (dt, J = 7.66 Hz, 1.45 Hz, 1H, Ar-*H*), 7.94 (dd, J = 7.8 Hz, 1.33 Hz, 1H, Ar-*H*), 13.2 (s, 1H, -CO$_2$*H*); ir (potassium bromide, cm^{-1}): 3300-2700 (CO$_2$H), 1750 (CO), 1730 (CO), 1680 (CO); ms: (m/z) 252 (M$^+$), 220 (M$^+$ -CH$_3$OH).

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.05; H, 4.78.

Step b). 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester (**8**, R^1 = H, R^2 = 4-Br, 2-$FC_3H_6CH_2$).

A mixture of (2-carboxyphenyl)propanedioic acid dimethyl ester (**10**, R^1 = H, 5.0 g, 19.84 mmoles) and thionyl chloride (20 g) was refluxed for 1.5 hours. The volatiles were removed *in vacuo*, and the acid chloride was dissolved in THF (20 ml). 4-Bromo-2-fluorobenzylamine (4.67 g, 22.91 mmoles), triethylamine (15.96 ml, 114.55 mmoles) and THF (150 ml) were placed into a second flask. The contents of the first flask were added slowly into this second flask and the mixture was stirred for 30 minutes. The formed suspension was poured into water (1000 ml), stirred for 10 minutes and acidified with hydrochloric acid (2*N*). The mixture was extracted with ethyl acetate, and the organic extracts were dried over magnesium sulfate. Evaporation gave a yellowish solid which was recrystallized from acetone/ether/hexane (after cooling at -20°) to yield a white solid (6.91 g, 86%), mp 149-150°; ^{1}H nmr (DMSO-d_6, 400 MHz): δ [3.67, 4.00 (s, 3H, -CO$_2$C*H*$_3$ tautomeric)], [5.05 (q, J = 15.43 Hz, 5.4 (s), 2H, -NC*H*$_2$-), tautomeric], 5.03 (s, 1H, -C*H*CO$_2$CH$_3$, tautomeric), 7.06-8.4 (m, 7H, Ar-*H*, tautomeric); ir (potassium bromide, cm^{-1}): 1675 (CO), 1610 (CO); ms: (m/z) 405 (M$^+$), 373 (M$^+$ -MeOH).

Anal. Calcd. for $C_{18}H_{13}BrFNO_4$: C, 53.22; H, 3.23; N, 3.45. Found: C, 52.91; H, 3.20; N, 3.27.

Step c). 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecaetic Acid (**3**, R^1 = H, R^2 = 4-Br, 2-$FC_6H_3CH_2$).

To a suspension of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (**8**, R^1 = H, R^2 = 4-Br, 2-$FC_6H_3CH_2$, 4.7 g, 11.58 mmoles) and potassium carbonate (3.19 g, 23.16 mmoles) in DMF (100 ml), was added *tert*-butyl bromoacetate (2.81 ml, 17.37 mmoles). The mixture was stirred at 85° for 1 hour, poured into water (1000 ml), and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. Evaporation gave a yellowish oil (6.5 g), which was dissolved in dichloromethane (100 ml) and treated with trifluoroacetic acid (20 ml). The mixture was stirred at room temperature for 5 hours, and then the volatiles were removed *in vacuo*. The residue was treated with sodium hydroxide (2*N*, 15 ml) in THF (50 ml) and methanol (50 ml) for 30 minutes. The mixture was poured into water, acidified with hydrochloric acid (2*N*), and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. Evaporation and crystallization from ethyl ether/hexane afforded a white solid (3.1 g, 66% yield). All spectroscopic data were identical to the compound prapared in Route **a**, step b.

Preparation of Azetidines **1** from Acetic Acids **3**.

Step a). 2-[(4-Bromo-2-fluorophenyl)methyl]-4-chloro-1,2,3,4,-tetrahydro-1,3-dioxo-4-isoquinolineacetamide (**2**, R^1 = H, R^2 = 4-Br, 2-$FC_6H_3CH_2$).

A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic acid (**3**, R^1 = H, R^2 = 4-Br, 2-$FC_6H_3CH_2$, 1.5 g, 3.69 mmoles), toluene (25 ml), and thionyl chloride (5 ml), was stirred at 85° for 4 hours. The volatiles were removed *in vacuo* and the residue was dissolved in THF (10 ml). THF (40 ml) was placed into a second flask, and ammonia gas was bubbled through the solution for 1 minute. The THF/ammonia solution was then cooled to 0°, and the contents of the first flask were added slowly. After 20 minutes the mixture was poured into water (500 ml), acidified with hydrochloric acid (2*N*) and extracted with ethyl acetate. The

organic extracts were dried over magnesium sulfate. Evaporation and purification by flash chromatography on acid washed (5% orthophosphoric acid in methanol) silica gel (hexane/ethyl acetate 1:1), followed by crystallization from ether/hexane (after cooling to -20°) gave a white solid (0.83 g, 51%), mp 91-93°; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 3.8 (d, J = 16.4 Hz, 1H, -*H*CHCONH$_2$), 3.85 (d, J = 16.4 Hz, 1H, -HC*H*-CONH$_2$), 5.12 (s, 2H, -NCH_2-), 7.05 (s, 1H, -CON*H*-), 7.22-7.29 (m, 2H, Ar-*H*), 7.54-7.64 (m, 3H, Ar-*H*, -CON*H*-), 7.84-7.89 (m, 2H, Ar-*H*), 8.1 (d, J = 7.9 Hz, 1H, Ar-*H*); ir (potassium bromide, cm^{-1}): 3400 (NH), 1725 (CO), 1670 (CO); ms: (m/z) 439 (M+H)$^+$.

Anal. Calcd. for $C_{18}H_{13}BrClFN_2O3$): C, 49.17; H, 2.98; N, 6.37. Found: C, 49.56; H, 2.95; N, 6.40.

Step b). 2'-[(4-Bromo-2-fluorophenyl)methyl]spiro[azetidine-2,4'(1'*H*)isoquinoline-1',3',4(2'*H*)-trione] (**1**, R^1 = H, R^2 = 4-Br, 2-F$C_6H_3CH_2$, **1c**).

Sodium hydride (80% dispersion in oil, 51.0 mg, 1.69 mmoles) was added portionwise to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-4-chloro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetamide (**2**, R^1 = H, R^2 = 4-Br, 2-F$C_6H_3CH_2$, 340 mg, 0.77 mmoles) in DMF (15 ml). After stirring for 30 minutes, the mixture was poured into water, acidified with hydrochloric acid (2*N*) and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. Evaporation and purification by flash chromatography on acid washed (5% orthophosphoric acid in methanol) silica gel (hexane/ethyl acetate 1:1), followed by crystallization from hexane/ether (after cooling to -20°), gave a yellow solid (220 mg, 71%): mp 225-227°; ^{1}H nmr (DMSO-d_6, 400 MHz): δ 3.15 (d, J = 18.5 Hz, 1H, -*H*CHCONH-), 3.31 (d, J = 18.5 Hz, 1H, -HC*H*CONH-), 4.63 (d, J = 16.2 Hz, 1H, -NHC*H*-), 4.79 (d, J = 16.2 Hz, 1H, -NHC*H*-), 7.26 (t, J = 8.09 Hz, Ar-*H*), 7.34 (dd, J = 8.3 Hz, 1.87 Hz, 1H, Ar-*H*), 7.5 (dd, J = 9.75 Hz, 1.87 Hz, 1H, Ar-*H*), 7.59-7.62 (m, 2H, Ar-*H*), 7.67 (dt, J = 7.68 Hz, 1.04 Hz, 1H, Ar-*H*), 7.78 (d, J = 7.47 Hz, Ar-*H*), 11.94 (s, 1H, -CON*H*-); ir (potassium bromide, cm^{-1}): 3050 (NH), 1720 (CO), 1675 (CO); ms: (m/z) 402 (M$^+$).

Anal. Calcd. for $C_{18}H_{12}BrFN_2O_3$: C, 53.62; H, 3.00; N, 6.95. Found: C, 53.52; H, 3.15; C, 6.78.

REFERENCES AND NOTES

[1] [a] J. M. Muchowski, *Can. J. Chem.*, **47**, 857 (1969); [b] N. P. Buu-Hoi, G. Saint-Ruf and J. C. Bourgeade, *J. Heterocyclic Chem.*, **5**, 545 (1968).

[2] M. S. Malamas, U. S. Patent, 4,927,831 (1990).

[3] T. Fujimaki and H. Otomasu, *Chem. Pharm. Bull.*, **30**, 1215 (1982).

[4] A. McKillop and K. A. Bruggin, *Tetrahedron*, **31**, 2607 (1975).

[5] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).