Synthesis of 1-Substituted 3-Nitroquinolin-4(1*H*)-ones

Stanislav Radl*† and Ka-Kong Chan

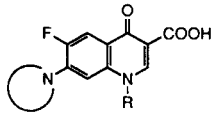
Roche Research Center, Hoffmann-La Roche, Inc.,
Nutley, NJ 07110, U.S.A.

Received May 10, 1993

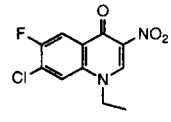
A versatile synthetic method for preparing 1-substituted 3-nitroquinolin-4(1*H*)-ones from corresponding 2-fluoro-α-nitroacetophenones is demonstrated by the synthesis of 6,7-difluoro derivatives **7a-c**. The method involves sequential treatment of the starting nitroacetophenone with triethyl orthoformate and the appropriate amine, followed by a nucleophilic cyclization reaction under mild conditions. The C-7 fluorine atom of **7** can be displaced by cyclic amines. Substituted 6-fluoro-7-(4-methyl-1-piperazinyl)-3-nitroquinolin-4(1*H*)-ones **8a-c** were prepared in this way.

J. Heterocyclic Chem., **31**, 437 (1994).

Antibacterial quinolones have attracted an increasing attention as a source of clinically useful drugs [1]. During our research into antibacterial quinolones we were also interested in compounds having at the position 3 various groups which could mimic the carboxylic group present in these drugs of a general formula **1**.



1



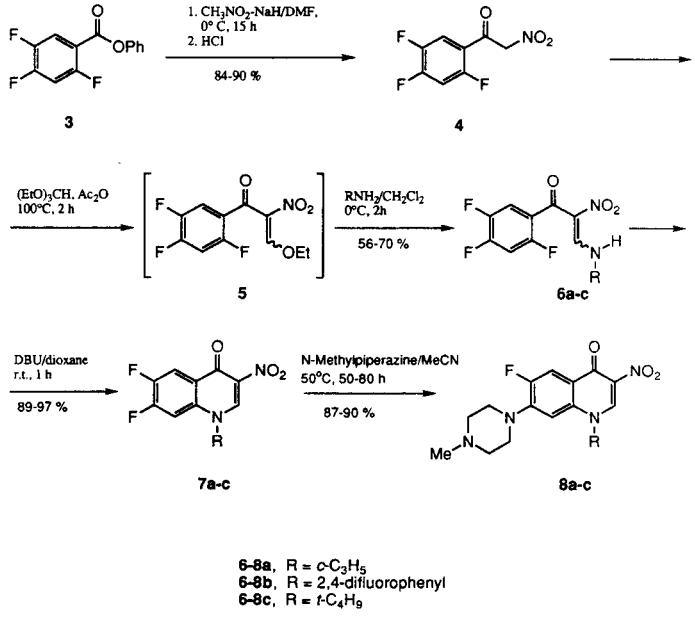
2

We found that surpisingly little had been reported on the respective 3-nitro derivatives. To the best of our knowledge, the only report [2] on 1-substituted 3-nitroquinolin-4(1*H*)-ones described the synthesis of **2** based on the classical synthesis of 4-hydroxy-3-nitroquinolines [3] followed by *N*-ethylation with iodoethane. In spite of the fact that a cyclic amine together with the C-6 fluorine atom is essential for high activity of the quinolones, no attempts to introduce a basic group to the position 7 were described, probably due to the low reactivity of the chlorine atom. Therefore, we decided to investigate the question of possible activity of these compounds, by preparing 3-nitro derivatives **8a-c** having N-1 substituents present in the most active quinolones and a 4-methyl-1-piperazinyl group at the position 7.

We needed a new method capable of providing 6,7-difluoro-3-nitroquinolin-4(1*H*)-ones **7a-c**, that cannot be prepared by *N*-alkylation of the corresponding 4-hydroxy-3-nitroquinolines. Our synthetic approach, which is depicted in Scheme 1, was inspired by a method of preparation of analogous quinolone-3-carboxylates discovered by Bayer chemists [4], which has become the method of choice for the synthesis of various types of quinolones [5].

Despite the nature of the methanenitronate anion, *O*-acylation is generally favored over *C*-acylation. However, several methods for *C*-acylation are described in the literature [6,7]. Field and Zally [7] prepared in high yields several nitroacetophenones, including 2-fluoro-α-nitroacetophenone, using a potassium *t*-butoxide in dimethyl sulfoxide to generate the methanenitronate anion, and phenyl benzoates as electrophiles. Under the same conditions we obtained only low yields of **4** (less than 20%) but when the conditions were modified (0°, sodium hydride in *N,N*-dimethylformamide), yields increased to the range of 84-90%. Compound **4** was treated with triethyl orthoformate and acetic anhydride and the residue after evaporation of volatile components was dissolved in methylene chloride. The solution of **5** was without further purification treated with the appropriate amine at 0° to provide compounds **6a-c**. The ^{1}H nmr spectra revealed that both *E* and *Z* isomers were present. The nucleophilic cyclization reaction of these compounds proceeds under very mild conditions (1,8-diazabicyclo[5.4.0]undec-7-ene, dioxane, room temperature, 1-2 hours) and affords compounds **7a-c** in high yields. Because only *E* isomers of the compounds

Scheme 1



6-8a, R = *c*-C_3H_5
6-8b, R = 2,4-difluorophenyl
6-8c, R = *t*-C_4H_9

6a-c are capable of the cyclization, an equilibrium of the *E* and *Z* isomers should be supposed. The C-7 fluorine atom of quinolone-3-carboxylic acids or their esters can be displaced by cyclic amines, including *N*-methylpiperazine, under mild conditions [5]. No reaction was observed with compounds **7a-c** at ambient temperature and mixtures were obtained at higher temperatures in various systems usually used for the reaction with quinolone-3-carboxylic acids. The desired products **8a-c** were obtained in high yields when the reaction was performed at 50° in acetonitrile using triethylamine as a base, although extended reaction times were required (50-80 hours).

Elemental analyses and spectral data (^{1}H nmr, ir, uv, ms) of all the prepared compounds are in accordance with the proposed structures. Compounds **8** were virtually inactive as antibacterials when tested *in vitro* against a variety of organisms.

In conclusion, we have developed a versatile method useful for preparation of 3-nitroquinolin-4(1*H*)-ones bearing various substituents at the position 1, including secondary and tertiary alkyl groups or aryl groups. This four step method (from commercially available 2,4,5-trifluorobenzoic acid) provided 6,7-difluoro-3-nitroquinolin-4(1*H*)-ones **7a-c** in overall yields in the range of 38-40%. The previously reported method of Krishnan, *et al.* [2] provided **2** in 6 steps from commercially available 3-chloro-4-fluooraniline in a 13% overall yield. Furthermore, their approach is limited to the synthesis of compounds having such N-1 substituents as could be introduced by N-1 alkylation. The approach described herein thus appears superior in respect to ease of operation, overall yield and scope.

EXPERIMENTAL

Melting points were measured on Thomas Hoover capillary apparatus and are uncorrected. The ir spectra were taken on a Digilab FTS 15E spectrophotometer and uv spectra on a Cary 17D spectrometer. The ^{1}H nmr spectra were recorded on a Varian XL-200 instrument (200 MHz). Mass spectra were obtained on a VG 7070 E-HF spectrometer.

2,4,5-Trifluorobenzoic acid was purchased from Mallincrodt, sodium hydride (80% dispersion in mineral oil) from Fluka, other chemicals were commercial quality. Chemically pure solvents (Fisher Scientific) were used as received. Flash and vacuum chromatography were done on silica gel 60 (230-400 mesh) from EM Science.

Phenyl 2,4,5-Trifluorobenzoate (**3**).

One drop of *N,N*-dimethylformamide was added to a mixture of 2,4,5-trifluorobenzoic acid (35.2 g, 0.2 mole) and thionyl chloride (100 ml) and the mixture was stirred at 60-65° and then refluxed for 2 hours. Thionyl chloride was removed *in vacuo*, the residue was mixed with phenol (18.8 g, 0.2 mole) and the mixture was stirred at 100° for 2 hours. The cold mixture was dissolved in dichloromethane (200 ml) and washed with 5% sodium hydrogen carbonate solution (100 ml) and brine (100 ml) and the organic layer was dried over magnesium sulfate. After vacuum distillation, the fraction boiling at about 130°/4 mbar was crystallized from hexane providing 40 g (79%) of white crystals, mp 38-39°; ^{1}H nmr (deuteriochloroform): δ 7.05 (m, 1H, H-3), 7.2-7.5 (m, 5H, phenyl H), 7.95 (m, 1H, H-6); ir (chloroform): ν = 1732, 1749 cm^{-1} (COO); uv (ethanol): λ max (log ε) 226 (4.18), 275 (3.58); ms: m/z (%) 252 (M$^+$, 10), 159 (100), 131 (30), 81 (20).

Anal. Calcd. for $C_{13}H_7F_3O_2$: C, 61.92; H, 2.80; F, 22.60. Found: C, 61.64; H, 2.66; F, 22.53.

2-Nitro-1-(2,4,5-trifluorophenyl)ethanone (**4**).

Sodium hydride (80% dispersion) (2.5 g, 83 mmoles) was added to a solution of nitromethane (12 ml) in dry *N,N*-dimethylformamide (100 ml) and the mixture was stirred at room temperature for 2 hours. The mixture was cooled to 0° and a solution of **3** (6.3 g, 25 mmoles) in *N,N*-dimethylformamide (50 ml) was added dropwise during 4 hours. After stirring at 0° overnight the mixture was poured into a mixture of ice water (100 ml), concentrated hydrochloric acid (12 ml) and urea (12 g) and extracted with ethyl acetate. The extract was washed with brine, dried with magnesium sulfate, and the residue after evaporation was dissolved in methylene chloride and purified by vacuum chromatography (methylene chloride). The product was crystallized from ethanol to provide 4.9 g of yellowish crystals (89%), mp 77-79°; ^{1}H nmr (deuteriochloroform): δ 5.75 (d, 2H, CH_2, J = 2 Hz), 7.10 (m, 1H, H-3), 7.90 (m, 1H, H-6); ir (chloroform): ν = 1707 (CO), 1569, 1344 cm^{-1} (NO_2); uv (ethanol): λ max (log ε) 241 (3.98), 285 (3.49), 350 (3.42); ms: m/z (%) 219 (M$^+$, 12), 159 (100), 145 (40), 131 (35), 81 (33).

Anal. Calcd. for $C_8H_4F_3NO_3$: C, 43.85; H, 1.84; F, 26.01; N, 6.39. Found: C, 43.79; H, 1.77; F, 25.88; N, 6.21.

General Procedure for the Preparation of 3-Amino-2-nitro-1-(2,4,5-trifluorophenyl)-2-propen-1-ones **6**.

A mixture of **4** (2.19 g, 10 mmoles), triethyl orthoformate (2.5 ml) and acetic anhydride (5 ml) was stirred at 100° for 2 hours, evaporated *in vacuo* and dissolved in methylene chloride (40 ml). The solution was cooled to 0° and a solution of the respective amine (12 mmoles) in methylene chloride (20 ml) was added dropwise. The mixture was stirred at 0° for 2 hours, evaporated *in vacuo* and the residue was purified by flash chromatography (methylene chloride).

3-(Cyclopropylmino)-2-nitro-1-(2,4,5-trifluorophenyl)-2-propen-1-one (**6a**).

This compound was obtained in 63% yield as colorless crystals (ethanol), mp 118-119°; ^{1}H nmr (deuteriochloroform): δ 0.95-1.05 (m, 4H, CH_2), 3.05 (m, 1H, CH), 6.95 (m, 1H, H-3), 7.40 (m, 1H, H-6), 8.05 (d, 0.35H, J = 14 Hz, CH), 8.70 (d, 0.65H, J = 14 Hz, CH), 9.70 (bs, 0.35H, NH), 10.45 (bs, 0.65H, NH); ir (chloroform): ν = 3291 (NH), 1660 (CO), 1641 (-C=C), 1508, 1331 cm^{-1} (NO_2); uv (ethanol): λ max (log ε) 245 (3.79), 310 (4.25); ms: m/z (%) 286 (M$^+$, 4), 159 (100), 131 (35), 95 (55), 53 (32), 41 (33), 28 (32).

Anal. Calcd. for $C_{12}H_9F_3N_2O_3$: C, 50.36; H, 3.17; F, 19.91; N, 9.79. Found: C, 50.39; H, 3.08; F, 19.73; N, 9.62.

3-[(2,4-Difluorophenyl)amino]-2-nitro-1-(2,4,5-trifluorophenyl)-2-propen-1-one (**6b**).

This compound was obtained in 70% yield as yellow crystals (ethanol), mp 138-139°; ^{1}H nmr (deuteriochloroform): δ 6.95-7.50 (m, 5H, arom), 8.30 (d, 0.2H, J = 14 Hz, CH), 8.95 (d, 0.8H, J = 14 Hz, CH), 11.10 (bs, 0.2H, NH), 12.00 (bs, 0.80, NH); ir (chloroform): ν = 1662 (CO), 1510, 1333 cm^{-1} (NO_2); uv (ethanol): λ max

(log ε) 218 (4.22), 352 (4.27) λ infl 290 (3.95); ms: m/z (%) 358 (M^+, 63), 339 (74), 312 (32), 159 (100), 140 (51).

Anal. Calcd. for $C_{15}H_7F_5N_2O_3$: C, 50.29; H, 1.97; F, 26.52; N, 7.82. Found: C, 50.14; H, 1.87; F, 26.23; N, 7.74.

3-(*tert*-Butylamino)-2-nitro-1-(2,4,5-trifluorophenyl)-2-propen-1-one (**6c**).

This compound was obtained in 56% yield as colorless crystals (ethanol), mp 164-166°; ^1H nmr (deuteriochloroform): δ 1.50 (s, 9H, CH_3), 6.95 (m, 1H, H-3), 7.45 (m, 1H, H-6), 8.10 (d, 0.35H, J = 14 Hz, CH), 8.70 (d, 0.65H, J = 14 Hz, CH), 9.90 (bs, 0.35H, NH), 10.80 (bs, 0.65, NH); ir (chloroform): ν = 3226 (NH), 1643 (CO), 1513, 1357 cm^{-1} (NO_2); uv (ethanol): λ max (log ε) 217 (3.07), 304 (3.27), λ infl 245 (2.83); ms: m/z (%) 302 (M^+, 28), 159 (50), 57 (100), 41 (40).

Anal. Calcd. for $C_{13}H_{13}F_3N_2O_3$: C, 51.66; H, 4.34; F, 18.86; N, 9.27. Found: C, 51.41; H, 4.27; F, 18.43; N, 9.47.

General Procedure for the Preparation of 6,7-difluoro-3-nitroquinolin-4(1*H*)-ones **7**.

A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (3.75 ml) in dry dioxane (15 ml) was added dropwise to a solution of **6** (12.5 mmoles) in dry dioxane (30 ml) and the mixture was stirred at room temperature for 2 hours. Then the mixture was poured into ice water, the insoluble portion was filtered off, washed with water, dried and crystallized from ethanol.

1-Cyclopropyl-6,7-difluoro-3-nitroquinolin-4(1*H*)-one (**7a**).

This compound was obtained in 93% yield as colorless crystals, mp 188-189°; ^1H nmr (DMSO-d_6): δ 1.15-1.35 (m, 4H, CH_2), 3.75 (m, 1H, N-CH), 8.15-8.35 (m, 2H, H-5, H-8), 9.05 (s, 1H, H-2); ir (potassium bromide): ν = 1653 (CO), 1521, 1349 cm^{-1} (NO_2); uv (ethanol): λ max (log ε) 218 (4.35), 255 (3.98), 265 (3.95), 320 (4.09), λ infl 238 (4.13), 345 (3.82); ms: m/z (%) 266 (M^+, 65), 231 (36), 218 (26), 190 (24), 41 (100), 39 (38), 32 (28), 28 (100).

Anal. Calcd. for $C_{12}H_8F_2N_2O_3$: C, 54.14; H, 3.03; F, 14.27; N, 10.52. Found: C, 54.16; H, 3.02; F, 14.01; N, 10.27.

1-(2,4-Difluorophenyl)-6,7-difluoro-3-nitroquinolin-4(1*H*)-one (**7b**).

This compound was obtained in 89% yield as colorless crystals, mp 250-252°; ^1H nmr (DMSO-d_6): δ = 7.30-7.70 (m, 2H, 2,4-dinitrophenyl H), 7.75 (m, 1H, H-8) 7.95 (m, 1H, H-5), 8.30 (m, 1H, 2,4-dinitrophenyl H) 9.40 (s, 1H, H-2); ir (potassium bromide): ν = 1653 (CO), 1521, 1349 cm^{-1} (NO_2); uv (ethanol): λ max (log ε) 214 (4.41), 261 (4.03), 317 (4.08), λ infl 253 (4.06); ms: m/z (%) 338 (M^+, 100), 280 (40), 237 (34).

Anal. Calcd. for $C_{15}H_6F_4N_2O_3$: C, 53.27; H, 1.79; F, 22.47; N, 8.28. Found: C, 53.26; H, 1.73; F, 22.40; N, 8.13.

1-*tert*-Butyl-6,7-difluoro-3-nitroquinolin-4(1*H*)-one (**7c**).

This compound was obtained in 89% yield as colorless crystals, mp 320-325° dec; ^1H nmr (DMSO-d_6): δ 1.90 (s, 9H, CH_3), 8.25-8.45 (m, 2H, H-5, H-8), 9.25 (s, 1H, H-2); ir (potassium bromide): ν = 1664 (CO), 1359 cm^{-1} (NO_2); uv (ethanol): λ max (log ε) 218 (4.39), 255 (4.03), 265 (3.99), 316 (4.11), λ infl 238 (4.15), 340 (3.42); ms: m/z (%) 282 (M^+, 15), 227 (27), 226 (22), 57 (100), 41 (33), 29 (25).

Anal. Calcd. for $C_{13}H_{12}F_2N_2O_3$: C, 55.32; H, 4.29; F, 13.46; N, 9.92. Found: C, 55.56; H, 4.04; F, 13.11; N, 10.07.

General Procedure for the Preparation of 1-Substituted 6-fluoro-7-(4-methyl-1-piperazinyl)-3-nitroquinolin-4(1*H*)-ones **8**.

A mixture of **7** (5 mmoles), acetonitrile (30 ml), triethylamine (4 ml) and *N*-methylpiperazine (0.7 ml, 6.3 mmoles) was stirred at 50° for 50-80 hours (monitored by tlc). Then the mixture was evaporated *in vacuo* and purified by flash chromatography (methylene chloride:methanol 95:5) and crystallized from ethanol.

1-Cyclopropyl-6-fluoro-7-(4-methyl-1-piperazinyl)-3-nitroquinolin-4(1*H*)-one (**8a**).

This compound was obtained in 87% yield (reaction time 50 hours) as yellowish crystals, mp 265-272° dec; ^1H nmr (deuteriochloroform): δ 1.20-1.45 (m, 4H, CH_2), 2.35 (s, 3H, CH_3), 2.65 (t, 4H, N-CH_2, J = 4 Hz), 3.35 (t, 4H, N-CH_2, J = 4 Hz), 3.55 (m, 1H, N-CH), 7.30 (d, 1H, $J_{H,F}$ = 7 Hz, H-8), 8.05 (d, 1H, $J_{H,F}$ = 12 Hz, H-5), 8.95 (s, 1H, H-2); ir (potassium bromide): ν = 1652 (CO), 1348 cm^{-1} (NO_2); uv (ethanol): λ max (log ε) 213 (4.32), 302 (4.44), λ infl 260 (4.43), 315 (4.41); ms: m/z (%) 346 (M^+, 42), 316 (47), 71 (58), 70 (53), 57 (39), 42 (42), 41 (42).

Anal. Calcd. for $C_{17}H_{19}FN_4O_3$: C, 58.95; H, 5.53; F, 5.49; N, 16.18. Found: C, 59.16; H, 5.42; F, 5.71; N, 16.27.

The compound was converted by a standard procedure to its water soluble monohydrochloride monohydrate that decomposes over 300° without melting.

Anal. Calcd. for $C_{17}H_{19}FN_4O_3 \cdot HCl \cdot H_2O$: C, 50.94; H, 5.53; Cl, 8.85; F, 4.74; N, 13.98. Found: C, 50.84; H, 5.34; Cl, 8.84; F, 5.01; N, 13.81.

1-(2,4-Difluorophenyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-3-nitroquinolin-4(1*H*)-one (**8b**).

This compound was obtained in 90% yield (reaction time 80 hours) as colorless crystals, mp 270-272° dec; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 255 (t, 4H, N-CH_2, J = 4 Hz), 3.15 (t, 4H, N-CH_2, J = 4 Hz), 6.15 (m, 1H, 2,4-dinitrophenyl H), 7.15-7.30 (m, 2H, H-8, 2,4-difluorophenyl H), 7.60 (m, 1H, 2,4-difluorophenyl H), 8.10 (d, 1H, $J_{H,F}$ = 12 Hz, H-5), 8.75 (s, 1H, H-2); ir (potassium bromide): ν = 1639 (CO), 1507, 1345 cm^{-1} (NO_2); uv (ethanol): λ max (log ε) 299 (4.45), 307 (4.44), λ infl 262 (3.98); ms: m/z (%) 419 (M + 1, 36), 279 (38), 217 (100), 181 (70), 149 (44), 126 (68), 109 (100), 105 (48).

Anal. Calcd. for $C_{20}H_{17}F_3N_4O_3$: C, 57.42; H, 4.10; F, 13.62; N, 13.39. Found: C, 57.22; H, 3.86; F, 13.42; N, 13.28.

The compound was converted by a standard procedure to its water soluble monohydrochloride that decomposes over 300° without melting.

Anal. Calcd. for $C_{20}H_{17}F_3N_4O_3 \cdot HCl$: C, 52.81; H, 3.99; Cl, 7.79; F, 12.53; N, 12.32. Found: C, 52.59; H, 3.98; Cl, 7.69; F, 12.08; N, 12.24.

1-*tert*-Butyl-6-fluoro-7-(4-methyl-1-piperazinyl)-3-nitroquinolin-4(1*H*)-one (**8c**).

This compound was obtained in 90% yield (reaction time 60 hours) as yellowish crystals, decomposition at about 250° without melting up to 300°; ^1H nmr (deuteriochloroform): δ 1.95 (s, 9H, CH_3), 2.40 (s, 3H, CH_3), 2.65 (t, 4H, N-CH_2, J = 4 Hz), 3.30 (t, 4H, N-CH_2, J = 4 Hz), 7.30 (d, 1H, $J_{H,F}$ = 7 Hz, H-8), 8.20 (d, 1H, $J_{H,F}$ = 12 Hz, H-5), 9.25 (s, 1H, H-2); ir (potassium bromide): ν = 1652 cm^{-1} (CO); uv (ethanol): λ max (log ε) 212 (4.31), 298 (4.44), λ infl 260 (3.86); ms: m/z (%) 362 (M^+, 28), 306 (20), 276 (20), 71 (48), 70 (80), 43 (100), 42 (38), 41 (48).

Anal. Calcd. for $C_{18}H_{23}FN_4O_3$: C, 59.66; H, 6.40; F, 5.24; N, 15.46. Found: C, 59.83; H, 6.45; F, 5.20; N, 15.42.

The compound was converted by a standard procedure to its water soluble monohydrochloride that decomposes over 300° without melting.

Anal. Calcd. for $C_{18}H_{23}FN_4O_3$·HCl: C, 54.20; H, 6.06; Cl, 8.89; F, 4.76; N, 14.05. Found: C, 54.17; H 6.18; Cl, 8.73; F, 4.66; N, 14.09.

REFERENCES AND NOTES

† Present address: Research Institute for Pharmacy and Biochemistry, Kourimska 17, 13060 Prague, Czech Republic.

[1] S. Radl, *Pharmacol. Ther.*, **48**, 1 (1990).

[2] K. Krishnan, S. S. Lang and M. M. Siegel, *J. Heterocyclic Chem.*, **23**, 1801 (1986).

[3] G. B. Bachman and D. E. Welton, *J. Am. Chem. Soc.*, **69**, 365 (1947).

[4] K. Grohe and H.-J. Zeiler, *Liebigs Ann. Chem.*, 29 (1987).

[5] D. Bouzard, In Recent Progress in the Chemical Synthesis of Antibiotics: Recent Advances in the Chemistry of Quinolones, G. Lukacz and M. Ohno, eds, Springer, Berlin 1990, pp 249-283; S. Radl and D. Bouzard, *Heterocycles*, **34**, 2143 (1992).

[6] B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4882 (1959); D. Seebach and F. Lehr, *Angew. Chem., Int. Ed. Engl.*, **15**, 505 (1976); D. C. Baker and S. R. Putt, *Synthesis*, 478 (1978); T. Shioiri and Y. Hamada, *J. Org. Chem.*, **43**, 3631 (1978); Y. Hamada, K. Ando and T. Shioiri, *Chem. Pharm. Bull.*, **29**, 259 (1981).

[7] G. F. Field and W. J. Zally, *Synthesis*, 295 (1979).