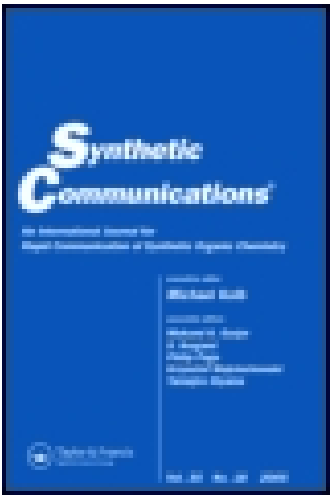

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One-Pot Synthesis of Rufloxacin

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ONE-POT SYNTHESIS OF RUFLOXACIN

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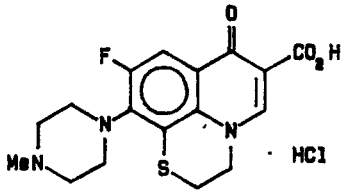
ABSTRACT: Rufloxacin (MF-934) was prepared in one-pot synthesis in 61% yield by treatment of the 2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)-benzoyl acetate, first with *N*,*N*-dimethylformamide dimethyl acetal, then with 2-aminoethanethiol, followed by cyclization and hydrolysis.

Rufloxacin (MF-934) 9-fluoro-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido [1,2,3-de] [1,4] benzothiazine-6-carboxylic acid (1)[1] is a new potent antibacterial quinolone which, after



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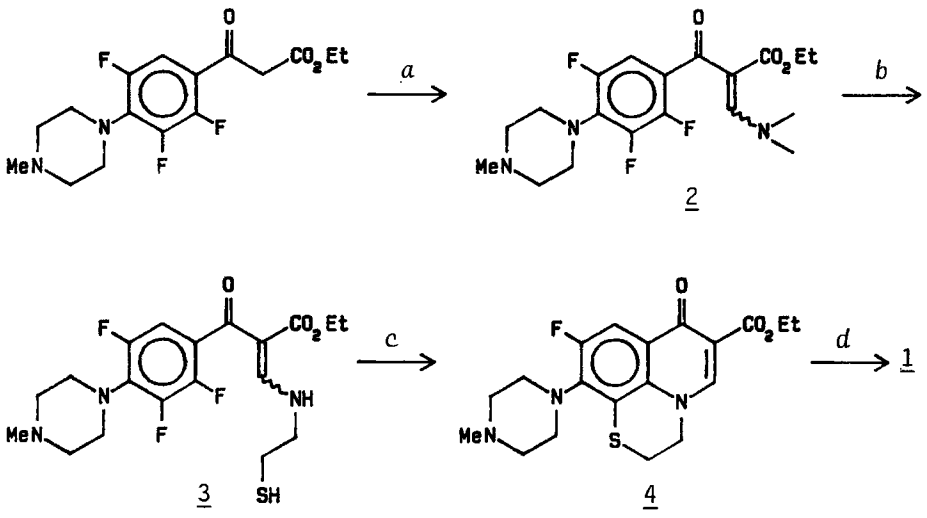
completing phase III, is ready to be marketed as a once-daily antibacterial quinolone[2].

The reported synthesis for rufloxacin requires several tedious and laborious steps[1,3] that finally involve the solfoxidation of thiazinic sulfur of ethyl 10-chloro-9-fluoro-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzothiazin-6-carboxylate in order to increase the reactivity of the aromatic nucleus to permit the regiospecific substitution of chlorine at C-10 with *N*-methylpiperazine. Therefore this involves successive deoxigenation with PCl_3 after nucleophilic substitution.

We, herein, report a simple and shorter synthesis in a one-pot serial operation as follows: first conversion of 2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)-benzoyl acetate to dimethylacrylate derivative 2, by treatment with *N*,*N*-dimethylformamide dimethyl acetal, then reaction with 2-aminoethanethiol followed by intramolecular cyclization with NaH of obtained intermediate 3 and, finally, hydrolisis by water dilution and heating to give, after salification, rufloxacin hydrochloride (1) in 61% total yield (Scheme I). The same reaction sequence was also carried out in single steps , isolating the various intermediates to caracterize them.



Scheme I: [a] $(MeO)_2CHNMe_2$, toluene, Δ ; [b] $SH(CH_2)_2NH_2$, EtOH; [c] NaH, THF, 0 °C; [d] OH, H_2O, Δ .

EXPERIMENTAL SECTION

Melting points were determined in capillary tubes (Büchi melting point apparatus) and are uncorrected. Elemental analyes were performed on a Carlo Erba elemental analyzer, Model 1106, and the data for C, H and N are within ±0.4% of the theoretical values. ^1H NMR spectra were recorded on a Bruker AC 200 spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard. Reagents and solvent were purchased from common commercial suppliers and were

used as received. Column chromatography separations were carried out on Merck silica gel 40 (mesh 70-230). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with Büchi rotary evaporator at low pressure.

9-Fluoro-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido-[1, 2,3-de][1,4]benzothiazine-6-carboxylic acid hydrochloride (1)

N,N-Dimethylformamide dimethyl acetal (1.2 mL, 9.1 mmol) was added to a solution of ethyl 2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)-benzoyl acetate[4] (2.0 g, 5.8 mmol) in toluene (10 mL). The mixture was heated at reflux for 1 h and concentrated to dryness to give a viscous oil which was dissolved in EtOH (20 mL).

To this ethanolic solution, cooled in an ice-bath, a solution of 2-aminoethanethiol (0.6 g, 7.8 mmol) and EtOH (10 mL) was then added. The resulting mixture was stirred at room temperature for 5 h and then concentrated to dryness to give a viscous oil which was dissolved in dry THF (30 mL).

Sodium hydride (60% NaH in oil suspension 0.5 g, 12.5 mmol) was then added to the above solution cooled in an ice-bath. The suspension was stirred under nitrogen atmosfere at 0 °C for 15 min and followed by the addition of water (30 mL).

The resulting suspension was refluxed for 15 min until dissolution occurred. The cooled solution was then neutralized with AcOH and concentrated to dryness. Ethanol (20 mL) was added to the residue and the insoluble material was filtered off and discarded. A saturated solution of HCL gas in diethyl ether was added to the above clear solution and the separated solid was collected by filtration and crystallized from 7:3 EtOH/H_2O to give 0.7 g (61% total yield) of 1, mp 322-324 °C (lit.1, mp 322-324 °C).

Ethyl 2-[2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)-benzoyl]-3-dimethylaminoacrylate (2)

A mixture of ethyl 2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)-benzoylacetate[4] (2.0 g, 5.8 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.2 mL, 9.1 mmol) in toluene (10 mL) was refluxed for 1 h and then concentrated to dryness. The residual viscous oil was purified by fast filtration on silica gel column, eluting with $CHCl_3$ to give 2.11 g (91%) of viscous oil 2 as a 7:3 or 3:7 mixture of (E)- and (Z)-isomers, as revealed by its ^1H NMR spectrum. ^1H NMR δ 1.05 and 1.10 (3H, each t, J=7 Hz, $CH_2\underline{CH}_3$), 2.40 (3H, s, NCH_3), 2.50-2.70 (4H, m, piperazinic CH_2), 3.10 [6H, bs, $N(CH_3)_2$], 3.25-3.50 (4H, m, piperazinic CH_2), 4.05 and 4.10

(2H, each q, J=7 Hz, $C\underline{H}_2CH_3$), 7.00-7.30 (1H, m, aromatic H), 7.75 and 7.90 (1H, each s, olefinic H).

Ethyl 2-[2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)-benzoyl]-3-(1-mercaptoeth-2-ylamino)-acrylate (3)

A solution of 2-aminoethanethiol (0.6 g, 7.8 mmol) in EtOH (5 mL) was added to a cooled solution of 2 (2.0 g, 5.0 mmol) in EtOH (20 mL). The reaction mixture was stirred at room temperature for 5 h and then concentrated to dryness. The residual viscous oil was purified by silica gel column chromatography, eluting with $CHCl_3$ to give 1.7 g (77%) of viscous oil 3 as a 7:3 or 3:7 mixture of (E)- and (Z)-isomers. ^{1}H NMR δ 0.90-1.35 (4H, m, $CH_2\underline{CH}_3$ and SH), 2.45 (3H, s, NCH_3), 2.50-2.65 (4H, m, piperazinic CH_2), 2.85-3.10 (2H, m, $NCH_2\underline{CH}_2S$), 3.25-3.45 (4H, m, piperazinic CH_2), 3.65-3.90 (2H, m, $NHC\underline{H}_2CH_2S$), 4.05 and 4.10 (2H, each q, J=7 Hz, $C\underline{H}_2CH_3$), 6.75-7.05 (1H, m, aromatic H), 7.95 and 8.05 (1H, each d, J=15 Hz, olefinic H), 9.30-9.70 and 10.80-11.00 (1H, each m, NH).

Ethyl 9-fluoro-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido [1,2,3-de][1,4]benzothiazine-6-carboxylate (4)

Sodium hydride (60% NaH in oil suspension 0.35 g, 8.75 mmol) was slowly added to a cooled solution of 3 (1.5 g, 3.5 mmol) in dry

THF (30 mL). The reaction mixture was stirred at 0 °C for 15 min under nitrogen athmosphere, then poured into ice-water (100 mL) and extracted with $CHCl_3$. The organic phases were combined, washed with water , dried and evaporated to dryness. The solid residue was crystallized from EtOH to give 1.2 g (88%) of 4, mp 160-163 °C. ^1H NMR δ 1.40 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 2.35 (3H, s, NCH_3), 2.50-2.70 (4H, m, piperazinic CH_2), 3.05-3.50 (6H, m, piperazinic CH_2 and $NCH_2\underline{CH}_2S$), 4.35 (2H, q, J=7 Hz, $\underline{CH}_2CH_3$), 4.50-4.75 (2H, m, $NC\underline{H}_2CH_2S$), 7.80 (1H, d, J=12 Hz, aromatic H), 8.30 (1H, s, olefinic H).

9-Fluoro-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido-[1, 2,3-de][1,4]benzothiazine-6-carboxylic acid hydrochloride (1) A stirred suspension of 4 (0.2 g) in 15% NaOH (10 mL) was refluxed for 15 min until dissolution occurred. The cooled mixture was neutralized with AcOH and then evaporated to dryness. To the solid residue, EtOH (10 mL) was added and the insoluble material filtered off and discarded. A saturated solution of HCl gas in diethyl ether was added to the above filtrate and the separated solid was collected by filtration and crystallized from 7:3 EtOH/H_2O to give 0.16 g (86%) of 1.

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