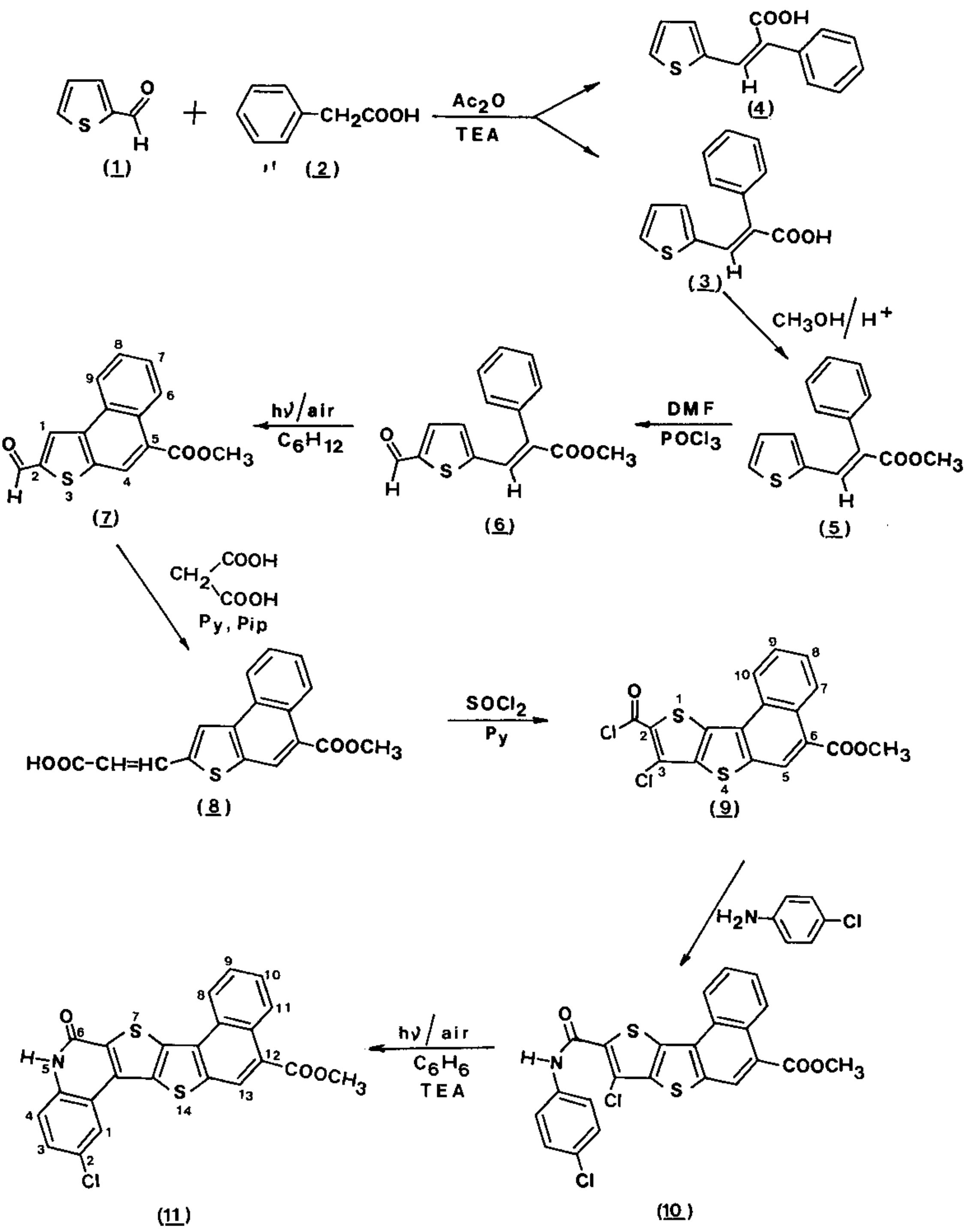
THE SYNTHESIS OF NEW HETEROPOLYCYCLIC QUINOLONE BY TWOFOLD PHOTOCYCLIZATION: METHOXYCARBONYLNAPHTHO[2'',1'':2',3'-b]-THIENO[4',5':2,3]THIENO[5,4-c]QUINOLIN-6(5H)-ONE

Grace Karminski-Zamola,* Davorka Pavličić, Miroslav Bajić,
and Nikola Blažević
Department of Organic Chemistry, Faculty of Technology,
University of Zagreb, 41000 Zagreb, Croatia, Yugoslavia

Abstract - New heterocyclic ring system namely 12-methoxycarbonylnaphtho[2'',1'':2',3-b]thieno[4',5':2,3]thieno[5,4-c]quinolin-6(5H)-one (11) is prepared by multistep synthesis introducing twofold photochemical cyclization.

In our previous papers we reported on the preparation of various quinolones condensed with heterocyclic nuclei by photochemical dehydrocyclization reaction: furoquinolones,[1] furobisquinolones,[2] benzofurophenanthridones and benzothienophenanthridones.[3] In order to continue our efforts to synthesize new polycyclic heterocycles of the quinolone type, we prepared 12-carbomethoxynaphtho[2'',1'':2',3'-b]thieno[4',5':2,3]thieno[5,4-c]quinolin-6(5H)-one (11) by multistep synthesis introducing twice photochemical cyclization reaction according to the Scheme 1.

2-Thiophenecarboxaldehyde was allowed to react with phenylacetic acid to give the mixture of E- and Z-3-(2-thienyl)-2-phenylacrylic acids in the yield from 50-70%. The E-isomer (3) was converted to the corresponding methyl ester (5) which was formylated by Vilsmeier method[4] (DMF+$POCl_3$) in the position 5 of the thiophene nucleus to methyl 3-(5-formyl-2-thienyl)-2-phenylacrylate (6). Formylated product (6) was photochemically dehydrocyclized into methyl-2-formylnaphtho[2,1-b]thiophene-5-carboxylate (7) in the yield of about 50%. Condensation of the product (7) with malonic acid afforded 3-{2-(5-carbomethoxynaphtho[2,1-b]thiophene)}acrylic acid (8) in good yield. Treatment of 8 with thionyl chloride and pyridime[5] provided 6-carbomethoxy-3-chloronaphtho[2',1':2,3-b]-thieno[4,5-d]thiophene-2-carboxyl chloride (9). The yield is about 17%. The reaction of p-chloroaniline with (9) in benzene gave 6-carbomethoxy-3-chloro-N-(p-chlorophenyl)naphtho[2',1':2,3-b]-thieno[4,5-d]thiophene-2-carboxamide (10) in 36.3% yield.


(1)
CH2COOH
(2)
Ac2O
TEA
COOH
(4)
COOH
(3)
CH3OH/H+
COOCH3
(5)
DMF
POCl3
COOCH3
(6)
hν/air
C6H12
COOCH3
(7)
CH2(COOH)2
Py, Pip
HOOC-CH=HC
COOCH3
(8)
SOCl2
Py
Cl
COOCH3
(9)
H2N-C6H4-Cl
H-N
COOCH3
(10)
hν/air
C6H6
TEA
H-N
COOCH3
(11)

Photodehydrochlorination of 10 in benzene and methanol solution containing triethylamine afforded 12-carbomethoxy-2-chloronaphtho[2'',1'':2',3'-b]thieno[4',5':2,3]thieno[5,4-c]quinolin-6(5H)-one (11).

EXPERIMENTAL

Melting points were taken on a Kofler microhot stage and are uncorrected. The ir spectra were recorded on a PERKIN-ELMER M-257 spectrophotometer in KBr discs. The ^{1}H nmr spectra were recorded on a 360 JOEL JNM - FX 100 FT spectrometer with tetramethylsilane as the internal reference. Irradiations were performed with a water cooled quartz immersion mercury arch lamp TQ 150 W Original Hanau.

3-(2-Thienyl)-2-phenylacrylic acid (3) was prepared from 2-thiophenecarboxaldehyde and phenylacetic acid by the known method[6] and E isomer was isolated and detected according to the literature data.[7] Methyl E-3-(2-thienyl)-2-phenylacrylate (5) was prepared from acid (3) and methanol in the presence of conc. H_2SO_4 by the known method.[8]

Methyl E-3-(5-Formyl-2-thienyl)-2-phenylacrylate (6)

Corresponding methyl ester (5) was formylated by Vilsmeier formilation.[4] Phosphorus oxychloride (45 ml, 0.49 mol) was added dropwise at 0°C to the stirred mixture of methyl ester (5) (24.5 g, 0.5 mol) and dimethylformamide (40 ml, 0.52 mol). When the addition was over, the mixture was stirred at room temperature for 1 h and then at 90-100°C for 3 h, cooled and poured onto crushed ice (200 g). The resulting mixture was made weakly alkaline with the saturated solution of sodium carbonate and left overnight. The solid was filtered off, washed with water and recrystallized from methanol giving 21.5 g (79%) of formylated product (6), mp 74-79°C; ir (KBr): 1700 cm^{-1} ($COOCH_3$), 1660 cm^{-1} (CHO), 1612 cm^{-1} (C=C); ^{1}H nmr ($CDCl_3$) (δ ppm): 9.79 (s, 1H, formylic), 8.09 (s, 1H, ethylenic), 7.88 (d, $J_{3',4'}$=4.1 Hz, 1H, H^4), 7.65-7.46 (m, 3H, arom.), 7.49 (d, $J_{3',4'}$=4.1 Hz, 1H, H^3), 7.29-7.19 (m, 2H, arom.), 3.72 (s, 3H, OCH_3).

Anal. Calcd for $C_{15}H_{12}O_3S$: C, 66.18; H, 4.41; Found: C, 66.48; H, 4.20.

Methyl 2-Formylnaphtho[2,1-b]thiophene-5-carboxylate (7)

A solution of 6 (2 g, 7 mmol) in cyclohexane (2 l) was added I_2 (0.02 g, 0.78 mmol) and irradiated for 48 h at room temperature. Photochemical change was monitored by uv spectroscopy. When the irradiation was over the solvent was evaporated in vacuo, the residue was collected and recrystallized from benzene: hexane (1:1) to give the cyclized product (7) (0.5 g, 25%), mp 183-185°C, ir (KBr): 1720 cm^{-1} ($COOCH_3$), 1680 cm^{-1}, 1665 cm^{-1} (CHO); ^{1}H nmr ($CDCl_3$) (δ ppm): 10.22 (s, 1H, formylic), 9.16 (s, 1H), 8.82-8.60 (m, 3H), 7.82-7.69 (m, 2H), 4.00 (s, 3H, OCH_3).

Anal. Calcd for $C_{15}H_{10}O_3S$: C, 66.67; H, 3.70; Found: C, 66.90; H, 7.43.

3-{2-(5-Carbomethoxynaphtho[2,1-*b*]thiophene)}acrylic Acid (8)

Aldehyde (7) (1.7 g, 6 mmol) was heated by the boiling point with malonic acid (0.64 g, 6 mmol) in 30 ml of pyridine in the presence of few drops of piperidine for 18 h. Reaction mixture was poured onto crushed ice, the yellow crystals were filtered off and recrystallized from acetic acid to afford the carboxylic acid (8) (1.85 g, 94.2%), mp 200°C, ir (KBr): 1710 cm^{-1} ($COOCH_3$), 1685 cm^{-1} (COOH), 1616 cm^{-1}; ^1H nmr ($CDCl_3$) (δ ppm): 8.99-8.76 (m, 1H), 8.65 (s, 2H), 8.60-8.48 (m, 1H), 7.93 (d, J = 15.8 Hz, 1H), 7.76-7.65 (m, 2H), 6.43 (d, J = 15.8 Hz, 1H), 3.98 (s, 3H, OCH_3).

Anal. Calcd for $C_{17}H_{12}O_4S$: C, 65.38; H, 3.85. Found: C, 65.09; H, 4.01.

6-Carbomethoxy-3-chloronaphtho[2',1':2,3-*b*]thieno[4,5-*d*]thiophene-2-carboxylic Chloride (9)

A stirred mixture of acrylic acid (8) (1.85 g, 6 mmol), thionyl chloride (3.4 ml, 0.048 mol), pyridine (0.2 ml, 0.0025 mol) and chlorbenzene (6 ml) was heated at reflux for 68-70 h. Excess thionyl chloride was removed under reduced pressure and the remaining material was suspended in hot hexane (250 ml), then filtered. The hot filtrate was treated with charcoal, allowed to cool, and the crystalline product was recrystallized from hexane or benzene. The yield is 0.4 g, 17.4%, mp 113-116°C, ir (KBr): 1740 cm^{-1} (COCl), 1690 cm^{-1} ($COOCH_3$); ^1H nmr ($CDCl_3$) (δ ppm): 9.05-8.93 (m, 1H), 8.72 (s, 1H), 8.34-8.22 (m, 1H),7.87-7.72 (m, 2H), 4.03 (s, 3H, OCH_3).

Anal. Calcd for $C_{17}H_8O_3S_2Cl_2$: C, 51.65; H, 2.03. Found: C, 51.37; H, 1.90.

6-Carbomethoxy-3-chloro-*N*-(p-chlorophenyl)naphtho[2',1':2,3-*b*]thieno[4,5-*d*]thiophene-2-carboxamide (10)

A solution of *p*-chloroaniline (0.1 g, 0.55 mmol) in benzene (50 ml) was added dropwise to a stirred solution of 9 (0.22 g, 0.55 mmol) in benzene (450 ml) at room temperature. After the addition was complete the mixture was allowed to reflux for 1 h. The solution was filtered and concentrated on the volume to 50 ml. After cooling the crystals were collected by filtration and recrystallized from ethanol to yield 0.1 g (36.3%) of 10 as light yellow crystals, mp 195-199°C; ir (KBr): 3450 cm^{-1}(NH), 1715 cm^{-1} ($COOCH_3$), 1660 cm^{-1} (C=O, amidic), ^1H nmr ($CDCl_3$) (δ ppm): 9.08-8.92 (m, 1H), 8.72 (s, 1H, amidic), 8.48 (d,J = 9.08 Hz, 2H), 8.34-8.12 (m, 1H), 7.76-7.29 (m, 1H), 7.60 (d,J = 9.08 Hz, 2H), 4.04 (s, 3H, OCH_3).

Anal. Calcd for $C_{23}H_{13}NO_3S_2Cl_2$: C, 56.79; H, 2.67. Found: C, 56.99; H, 2.39.

12-Carbomethoxy-2-chloronaphtho[2'',1'':2',3'-*b*]thieno[4',5':2,3]thieno[5,4-*c*]quinolin-6(5H)-one (11)

A solution of 10 (0.15 g, 0.3 mmol) and triethylamine (0.03 g, 0.29 mmol) in benzene-methanol (3:1) (200 ml) was irradiated at room temperature with 150 W high pressure mercury arch lamp for 10 h. During the reaction a weak stream of air was bubbled through the solution. After the reaction was over the solvent was evaporated under reduced pressure and the residue was recrystallized from methanol to yield 0.07 g (50%) of 11, mp 300°C, ir (KBr): 3250 cm^{-1}, (NH), 1715 cm^{-1} (COOCH$_3$), 1680 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): (δ ppm): 8.36-7.05 (m, 8H), 8.17 (m, 1H), 3.92 (s, 3H, OCH$_3$). Anal. Calcd for $C_{23}H_{12}NO_3ClS_2$: C, 61.40; H, 2.67. Found: C, 61.08; H, 2.39.

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