SYNTHESIS AND PHOTOSYNTHESIS OF SUBSTITUTED BENZO[b]THIENO[3,2-c]QUINOLONES

Jasna Dogan, Grace Karminski-Zamola* and David W. Boykin+
*Department of Organic Chemistry, Faculty of Chemical Engineering and Technology, University of Zagreb, 10000 Zagreb, Croatia
and
+Department of Chemistry, Georgia State University, Atlanta, Georgia 30303-3083 USA

Abstract: Two benzo[*b*]thieno[3,2-*c*]quinolones with 3- dimethylaminopropyl substituent in the quinolono or amido part of the molecule: 9-(3-dimethylaminopropyl)benzo[*b*]thienyl[3,2-*c*]quinolin-6(*5H*)-one **7** and 5-*N*-(3-dimethylaminopropyl)-9-carbomethoxybenzo[*b*]thienyl[3,2-*c*]quinolin-6-one **9** are prepared by multistep synthesis involving, as key step a photochemical dehydrohalogenation reaction.

Introduction

Recently, we reported the synthesis of new heteropolycyclic quinolones from corresponding anilides applying the photochemical dehydrohalogenation reaction (1). In our previous papers we reported on the usefulness of monofold photochemical dehydrocyclization reaction for preparing quinolones condensed with heterocyclic nuclei: furoquinolones (2), furo-bis-quinolones(3), benzofurophenenthridones and benzothienophenenthridones (4). Although the photochemical dehydrohalogenation reaction improved by Castle and coworkers (5) is widely used in the preparation of condensed heterocyclic quinolones (6-10) the reaction of twofold photochemical dehydrohalogenation reaction was first introduced in our laboratory in the synthesis of heteropolycyclic diquinolones (11).

Results and Discussion

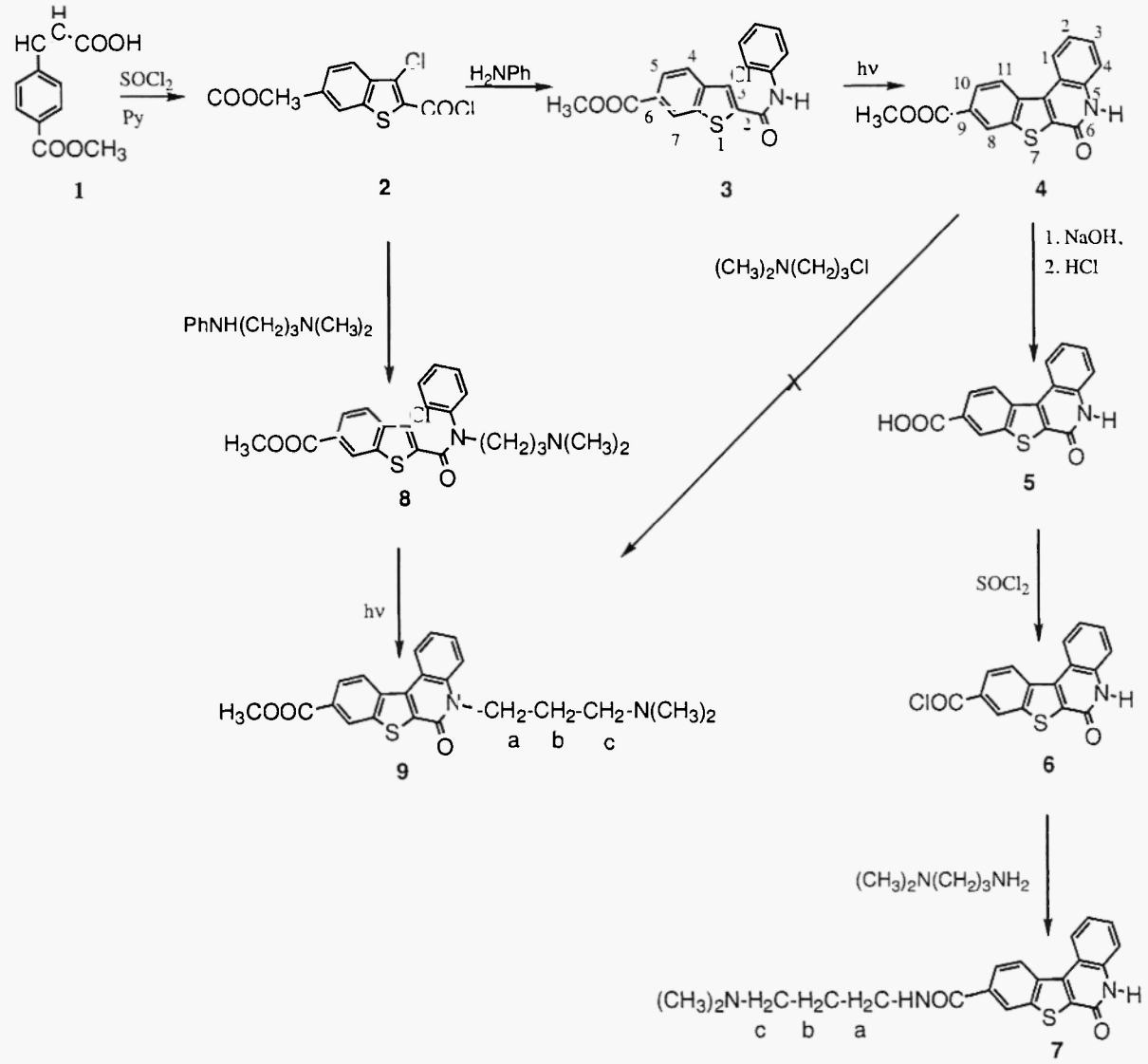
In this work we noticed that the the photochemical dehydrohalogenation reaction was more successful when carried out with unsubstituted anilides rather than with N-substituted anilides, where the yields were lower. On the other hand, it is very important that we succeeded to introduce 3-dimethylaminopropyl substituent on the quinolono part of the molecule because the presence of the mentioned substituent could change the biological properties of the quinolones and make them biologicaly active in contrast to the 3-dimethylaminopropyl substituted amides. That was the reason why we tried to prepare corresponding N-3-dimethylaminopropyl-substituted quinolone **9** in analogy to 3-dimethylaminopropylamide **7**.

p-Carbomethoxy cinnamic acid **1** was converted into 6-carbomethoxy-3-chlorobenzo[*b*]thiophene-2-carbonyl chloride **2** in a 82% yield by the method described recently (1). 6-Carbomethoxy-3-chlorobenzo[*b*]thiophene-2-carboxanilide **3** was prepared from **2** in the yield of over 82%. 9-Carbomethoxybenzo[*b*]thienyl[3,2-*c*]quinolin-6(*5H*)-one **4** was prepared by photochemical dehydrohalogenation reaction in a 79.5% yield. The reactions **4**--**5**--**6**--**7** are routine and were performed in very good yields. *N*-(3-Dimethylaminopropyl)-3-chloro-6-carbomethoxy-

benzo[b]thiophen-2anilide **8** was prepared by reaction of the carbonyl chloride **2** with 3-dimethylaminopropylaniline in a 44.4% yield by the method described earlier (1). The photochemical dehydrohalogenation of the compound **8** into quinolone **9** proceeded with a 39% yield.

The substitution reaction of unsubstituted quinolone **4** with 3-dimethylaminopropylchloride to introduce the side chain in the quinolone, was unsuccessful.

Scheme



Experimental

Mps were determined on a Kofler hot stage microscope and are uncorrected. Ir spectra were recorded on a PERKIN-ELMER Model 257 spectrophotometer in KBr discs or as a liquid film between sodium chloride plates. ^{1}H NMR spectra were recorded on a VARIAN M 360 (60 MHz) or on VARIAN GEMINI 300(300 MHz) with TMS as internal standard in $CDCl_3$ or DMSO-d_6. Irradiation was performed at room temperature with a water cooled immersion well fitted with an "Hanovia" 450 W medium pressure mercury arc lamp using quartz or pyrex filter.

6-Carbomethoxy-3-chlorobenzo[*b*]thiophene-2-carbonyl chloride 2

Compound **2** was prepared from p-carbomethoxy-cinnamic acid (10.00 g, 0.05 mol) in chlorobenzene (50 ml) to which was added catalytic amount of pyridine (0.55 ml)[1]. Thionyl chloride (28 ml, 0.38 mol) was added dropwise in the mixture cooled in ice bath, then the mixture was heated by stirring at 140 °C for 5 h. Excess thionyl chloride was removed under reduced pressure and the remaining material was suspended in hot cyclohexane. The filtrate was allowed to cool. Yellow crystals, 11.36 g (81.84%), mp 182-185°C, were obtained. Ir (cm^{-1}) (KBr): 1745 (COCl), 1720 ($COOCH_3$). ^1H NMR ($CDCl_3$) (∂ ppm): 8.59 (s, 1H, H_4), 8.18 (d, $J_{6,7}$=8.45 Hz, 1H, H_6), 8.08 (d, $J_{6,7}$=8.63 Hz, 1H, H_7), 4.01 (s, 3H, CH_3). Anal. Calcd for $C_{11}H_6O_3Cl_2S$: C, 45.70; H, 2.09. Found: C, 45.95; H, 2.38.

6-Carbomethoxy-3-chlorobenzo[*b*]thiophene-2-carboxanilide 3

A solution of compound **2** (5.00 g, 0.017 mol) and aniline (1.73 ml, 0.017 mol) in toluene (150 ml) was refluxed for 1 h. After cooling, precipitated crystals were filtered off and recrystallized from acetone. White crystals, 4.83 g (82.14%), mp 197-198°C were obtained. Ir (cm^{-1}) (KBr): 3380 (NH), 1705 ($COOCH_3$), 1650 (CONH). ^1H NMR (DMSO-d_6) (∂ ppm): 10.69 (s, 1H, NH), 8.86 (s, 1H, H_4), 8.14 (dd, $J_{6,7}$=8.46 Hz, $J_{4,6}$=1.31 Hz, 1H, H_6), 8.04 (d, $J_{6,7}$=8.40 Hz, 1H, H_7), 7.74-7.16 (m, 5H, H arom.), 3.93 (s, 3H, OCH_3). Anal. Calcd for $C_{17}H_{12}NO_3ClS$: C, 59.05; H, 3.50; N, 4.05. Found: C, 58.92; H, 3.25; N, 4.35.

9-Carbomethoxybenzo[*b*]thienyl[3,2-*c*]quinolin-6(*5H*)-one 4

A solution of **3** (2.40 g, 6.94 mmol) and triethylamine (1 ml, 7 mmol) in methanol : benzene (220 : 2200 ml) was irradiated with 450 W medium pressure mercury arc lamp in quartz vessel at room temperature for 2 h. The air was bubbled through the solution. After concentration under reduced pressure to 100 ml, the crystallized solid was collected by filtration, washed with water and recrystallized from DMF. White crystals, 1.71 g (79.53%) mp >300°C, were obtained. Ir (cm-1) (KBr): 1705 ($COOCH_3$), 1660 (CONH). ^1H NMR (DMSO-d_6) (∂ ppm): 12.13 (s, 1H, NH), 9.01 (d, $J_{10,11}$=8.7 Hz, 1H, H_{11}), 8.85 (s, 1H, H_8), 8.75-8.73 (m, 1H, H_1), 8.18 (dd, $J_{10,11}$=8.7 Hz, $J_{8,10}$= 1.6 Hz 1H, H_{10}), 7.60-7.59 (m, 2H, H arom), 7.45-7.41 (m, 1H, H arom.), 3.96 (s, 3H, CH_3). Anal. Calcd for $C_{17}H_{11}NO_3S$: C, 66.00; H, 3.58; N, 4.53. Found: C, 66.09; H, 3.29; N, 4.32.

9-Carboxybenzo[*b*]thienyl[3,2-*c*]quinolin-6(*5H*)-one 5

Acid **5** was prepared by hydrolysis of **4** (1.50 g, 5 mmol) in ethanol (250 g), which was added to a solution of NaOH (0.60 g, 0.015 mol) in water (300 ml) and refluxed for 1h. Ethanol was distilled off in vacuo, the residue was dissolved in water, acidified with HCl and the solid so obtained recrystallized from dimethylsulfoxyde. White cristals, (1.35 g, 95.13%) were obtained, mp > 300°C. Ir (cm^{-1}) (KBr): 1680 (COOH), 1645 (CONH). ^1H NMR (DMSO-d_6) (∂ ppm): 12.36 (s, 1H, NH), 9.03 (d, $J_{10,11}$= 8.71 Hz, 1H, H_{11}), 8.86 (s, 1H, H_8), 8.80-8.77 (m, 1H, H_1), 8.17 (dd, $J_{10,11}$=8.70 Hz, $J_{8,10}$=1.55 Hz, 1H, H_{10}), 7.65-7.41 (m, 3H, H arom). Anal. Calcd for $C_{16}H_9NO_3S$: C, 66.07; H, 3.07 ; N, 4.74. Found: C, 65.92; H, 2.89; N, 4.37.

9-Chlorocarbonylbenzo[*b*]thienyl[3,2-*c*]quinolin-6(*5H*)-one 6

A mixture of the compound **5** (1.00 g, 3.39 mmol) and thionyl chloride (3.30 ml, 0.045 mol) was heated with stirring for 4 h at 80 °C. Excess thionyl chloride was removed under reduced pressure. 0.86 g (80.36 %), mp

>300°C of crude product was obtained as yellow crystals. Ir (cm^{-1}) (KBr): 1730 (COCl), 1645 (CONH). ^1H NMR (DMSO-d_6) (∂ ppm): 12.39 (s, 1H, NH), 9.16 (d, $J_{10,11}$=8.70 Hz, 1H, H_{11}), 8.95 (s, 1H, H_8), 8.74-8.73 (m, 1H, H_1), 8.64 (d, $J_{10,11}$=8.70 Hz, 1H, H_{10}), 7.69-7.61 (m, 2H, H arom), 7.50-7.45 (m, 1H, H arom).
Anal. Calcd for $C_{16}H_8NO_2Cl_2S$: C, 61.25; H, 2.57; N, 4.46. Found C; 61.32; H, 2.88; N, 4.26.

9-(3-Dimethylaminopropyl)benzo[*b*]thienyl[3,2-*c*]quinolin-6(*5H*)-one 7

A solution of a compound **6** (0.82 g, 2.61 mmol) and 3-dimethylaminopropylamine (12 ml, 95.36 mmol) in toluene (35 ml) was refluxed for 1/2 h. After cooling, precipitated crystals were filtered off, washed with 20% HCl, then with water and recrystallized from dimethylsulfoxide. White crystals, (0.59 g, 59.60%), mp 275-280°C were obtained Ir (cm^{-1}) (KBr): 3350-2450 (CH_2 str.), 1640 (CONH). ^1H NMR (DMSO-d_6) (∂ ppm): 12.37 (s, 1H, NH-quinolonic), 9.05 (t, J=5.51 Hz, 1H, NH- amidic), 8.99 (d, $J_{10,11}$= 8.72 Hz, 1H, H_{11}), 8.79-8.76 (m, 2H, H_8 and H arom), 8.15 (d, $J_{10,11}$=8.72 Hz, 1H, H_{10}), 7.61-7.58 (m, 2H, H arom), 7.45-7.40 (m, 1H, H arom), 3.48-3.40 (m, 2H, a/CH_2), 3.18-3.11 (m, 2H, c/CH_2), 2.78 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 2.05-1.97 (m, 2H, b/CH_2). Anal. Calcd for $C_{21}H_{21}N_3O_2S$: C, 66.47; H, 5.58 ; N, 11.07. Found: 66.18; H, 5.70; N, 11.27.

***N*-(3-Dimethylaminopropyl)-1-chloro-5-carbomethoxybenzo[*b*]thiophene-2-anilide** 8

To a cold mixture of 3-dimethylaminopropylaniline (0.16 g, 0.90 mmol) and 5% NaOH (0.3 ml) at 2°C is added dropwise with stirring between 3 and 5°C, a solution of the compound **2** (0.20 g, 0.69 mmol) in chloroform (50 ml). After addition of the compound **2** , the reaction mixture was stirried 1/2 h more at the same temperature, then 1 h at room temperature. The organic layer was separated and washed first with 20% HCl, then with water and dried o ($MgSO_4$). After evaporation of the solvent, the crude product was recrystallized from cyclohexane: ethyl acetate (1:3). White crystals, (0.13 g ,44.44%), mp 191-195°C, were obtained. Ir (cm^{-1}) (KBr): 3400-2400 (CH_2 str.), 1705 (COOCH3), 1640(CONR). ^1H NMR($CDCl_3$) (∂ ppm): 8.38 (s, 1H, H_4), 8.04 (dd, $J_{6,7}$=8.50 Hz, $J_{4,6}$=1.35 Hz, 1H, H_6), 7.77 (d, $J_{6,7}$=8.57 Hz, 1H, H_7), 7.35-7.18 (m, 5H, H arom), 4.08 (t, $J_{a,b}$=6.70 Hz, 2H, a/CH_2), 3.93 (s, 3H, OCH_3), 3.21 (t, $J_{b,c}$=6.85 Hz, 2H, c/CH_2), 2.84 (s, 6H, CH3), 2.35 (t, $J_{a,b}$= 6.67 Hz, 1H, b/CH_2), 2.30 (t, $J_{b,c}$= 6.85 Hz, 1H, b/CH_2). Anal. Calcd for $C_{22}H_{23}ClN_2O_3S$: C, 61.31; H, 5.38; N, 6.50. Found: C, 61.03; H, 5.17, N; 6.38.

5-*N*-(3-Dimethylaminopropyl)-9-carbomethoxybenzo[*b*]thienyl[3,2-*c*]quinolin-6-one 9

A solution of **8** (0.76 g, 1.76 mmol) and triethylamine (0.25 ml, 1.76 mmol) in methanol : benzene (55 ml : 550 ml) was irradiated as described for 4 during 20 min. After removing of the solvent the oily residue was recrystallized from chloroform : benzene (1: 3), gave 0.27 g, (38.94%) of yellow crystals, mp 170°C. Ir (cm^{-1}) (KBr): 1705 ($COOCH_3$), 1625 (CONR). ^1H NMR (∂ ppm) ($CDCl_3$) (d ppm): 8.75-8.68 (m, 2H, H_1, H_4), 8.73 (s, 1H, H_8), 8.22 (dd, $J_{10,11}$=8.62 Hz, $J_{8,10}$=1.57 Hz, 1H, H_{10}), 7.70 (d, $J_{10,11}$=8.58 Hz, 1H, H_{11}), 7.64 (t, $J_{2,3}$=7.04 Hz, 1H, H_2), 7.46 (t, $J_{2,3}$=6.96 Hz, 1H, H_3), 4.54 (t, $J_{a,b}$=7.68 Hz, 2H, a/CH_2), 4.01 (s, 3H, OCH_3), 2.52 (t, $J_{b,c}$=7.02 Hz, 2H, c/CH_2), 2.31 (s, 6H, CH_3), 2.06 (t, $J_{a,b}$=7.60 Hz, 1H, b/CH_2), 2.01 (t, $J_{b,c}$=6.96 Hz, 1H, b/CH_2). Anal.Calcd for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10. Found: C, 66.82; H, 5.89; N, 7.23.
We tried to synthesize **9** from **4** (1.00 g, 3.23 mmol) with NaH (0.59 g, 22 mmol) in toluene (50 ml) and 3-dimethylaminopropylchloride (0.54 g, 22 mmol) in toluene (35 ml), by the method described earlier[12], but the reaction was unsuccessful.

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