A Thieno-2*H*-chromene α -Amino Acid Derivative: Synthesis and Photochromic Properties

Maria-João R. P. Queiroz,^{a*} Ana S. Abreu,^a Paula M. T. Ferreira,^a M. Manuel Oliveira,^b Roger Dubest,^c Jean Aubard^c and André Samat^d

^a*Departamento de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal*

^b*Centro de Química – Vila Real, Universidade de Trás-os-Montes e Alto Douro, 5001-911 Vila Real, Portugal*

^c*ITODYS UMR 7086 CNRS Université Denis Diderot Paris7, 75005 Paris, France*

^d*GCOM2, UMR 6114CNRS, Université de la Méditerranée, 13288 Marseille, France*

mjrpq@quimica.uminho.pt

Experimental Section

General Remarks: Melting points were determined on a Gallenkamp apparatus and are uncorrected. The ¹H-NMR spectra were measured on a Varian Unity Plus at 300 MHz. Spin-spin decoupling techniques were used to assign the signals. The ¹³C-NMR spectra were measured in the same instrument at 75.4 MHz (using DEPT θ 45°). Elemental analyses were determined on a LECO CHNS 932 elemental analyser. Mass spectra (EI and FAB) and HRMS were made by the mass spectrometry service of University of Vigo-Spain.

Column chromatography was performed on Macherey-Nagel silica gel 230-400 mesh. Petroleum ether refers to the boiling range 40-60 °C. Ether refers to diethyl ether. When solvent gradient was used the increase of polarity was done gradually from neat petroleum ether to mixtures of ether/petroleum ether increasing 10% of ether until the isolation of the product.

4-Bromo-5-methoxy-2,3-dimethylbenzo[*b*]thiophene
dimethylbenzo[*b*]thiophene:

and

6-bromo-5-methoxy-2,3-

To a 0 °C cooled solution of 5-methoxy-2,3-dimethylbenzo[*b*]thiophene¹ (0.385g, 2 mmol) in dry diethyl ether (20 mL) protected from light, bromine (1 equiv.) was added dropwise and a small amount of iron was also added. The reaction was left stirring for 30 min. Iced water (10mL) was then added and the mixture was left stirring for 30 min. The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 20 mL). The organic extracts were collected, washed with a 5% solution of sodium sulfite and a 10% solution of sodium carbonate and dried (MgSO₄). Removal of the solvent gave an oil that showed on ¹H-NMR two products, 4-bromo-5-methoxy-2,3-dimethylbenzo[*b*]thiophene and 6-bromo-5-methoxy-2,3-dimethylbenzo[*b*]thiophene as a 1.1:1 mixture (0.412g, 76%). It was not possible to separate the compounds by column chromatography.

4-Bromo-5-hydroxy-2,3-dimethylbenzo[*b*]thiophene
dimethylbenzo[*b*]thiophene:

and

6-bromo-5-hydroxy-2,3-

In a Schlenk flask a solution of the mixture of 4-bromo-5-methoxy-2,3-dimethylbenzo[*b*]thiophene and 6-bromo-5-methoxy-2,3-dimethylbenzo[*b*]thiophene (1.1:1) (0.412g, 1.52 mmol) in dry CH₂Cl₂ (20 mL) was stirred under Ar and a solution of BBr₃ 1M in CH₂Cl₂ (1.07 equiv.) was added dropwise at 0 °C. The mixture was heated at reflux for 2h. After cooling, water (20mL) and CH₂Cl₂ (10mL) were added, the phases were separated and the aqueous phase was extracted with more CH₂Cl₂ (2 x 25mL). The organic phase was dried (MgSO₄), filtered and removal of solvent gave a solid which was submitted to column chromatography using a solvent gradient from neat petroleum ether to 20% diethyl ether/petroleum ether. The less polar product isolated as a brown oil, showed to be 4-bromo-5-hydroxy-2,3-dimethylbenzo[*b*]thiophene (0.058 g, 15%). ¹H-NMR (300 MHz, CDCl₃): δ 2.45 (s, 3 H, ArCH₃), 2.58 (s, 3 H, ArCH₃), 5.83 (s, 1 H, OH), 7.00 (d, J = 8.7 Hz, 1 H, 6-H), 7.54 (d, J = 8.7 Hz, 1 H, 7-H)

ppm. ^{13}C -NMR (75.4 MHz, CDCl_3): δ 14.45 (CH_3), 15.24 (CH_3), 103.51 (C), 112.77 (CH), 122.37 (CH), 127.93 (C), 131.76 (C), 136.92 (C), 137.77 (C), 149.84 (C) ppm. m/z EI (%) 257.95 ($\text{M}^+ {}^{81}\text{Br}$, 100), 255.95 ($\text{M}^+ {}^{79}\text{Br}$, 95), 242.90 ($\text{M}^+ {}^{81}\text{Br}-15$, 63), 240.91 ($\text{M}^+ {}^{79}\text{Br}-15$, 64). HRMS: Calcd for $\text{C}_{10}\text{H}_9\text{BrOS}$ [$\text{M}^+ {}^{81}\text{Br}$] 257.9537, [$\text{M}^+ {}^{79}\text{Br}$] 255.9557. Found [$\text{M}^+ {}^{81}\text{Br}$] 257.9533, [$\text{M}^+ {}^{79}\text{Br}$] 255.9551.

6-bromo-5-hydroxy-2,3-dimethylbenzo[*b*]thiophene (0.195 g, 50%) was isolated as a white solid, m.p. 79.0-80.0 °C. ^1H -NMR (300 MHz, CDCl_3): δ 2.24 (s, 3 H, ArCH_3), 2.46 (s, 3 H, ArCH_3), 5.45 (s, 1 H, OH), 7.21 (s, 1 H, 4-H), 7.81 (s, 1 H, 7-H) ppm. ^{13}C -NMR (75.4 MHz, CDCl_3): δ 11.33 (CH_3), 13.90 (CH_3), 106.98 (CH), 107.45 (C), 124.44 (CH), 126.50 (C), 131.03 (C), 135.98 (C), 142.14 (C), 149.16 (C) ppm. Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{BrOS}$: C, 46.71; H, 3.53; S, 12.47. Found: C, 47.00; H, 3.71; S, 12.66.

As the most polar product 5-hydroxy-2,3-dimethylbenzo[*b*]thiophene¹ was also isolated (0.029 g) as by product.

5-Bromo-7,7-bis(4-methoxyphenyl)- 1,2-dimethyl-7*H*-thieno[3,2-*f*]chromene (1):

6-Bromo-5-hydroxy-2,3-dimethylbenzo[*b*]thiophene (0.103 g, 0.400 mmol) and 1,1-bis(4-methoxyphenyl)prop-2-yn-1-ol (0.119 g, 0.440 mmol) were dissolved in dry toluene (12 mL) under Ar at 60 °C for 5 min in a dry Schlenck tube. Then dry acidic alumina Brockmann I (1.00 g) was added and the mixture was heated at 80 °C for 15 min. After cooling the mixture was filtered and the solid washed with chloroform. The solvent removal gave an orange oil which was submitted to column chromatography using a solvent gradient from neat petroleum ether to 5% diethyl ether/petroleum ether, giving compound **1** (0.142 g, 70%), as a white solid, m.p. 209.0-210.5 °C. UV (closed form) λ_{max} CH_2Cl_2 ($\epsilon \text{ dm}^3 \text{ cm}^{-1} \text{ mol}^{-1}$) 355 (5074), 324 (12872), 277 (26902), 268 (24657) nm. ^1H -RMN (300 MHz, CDCl_3): δ 2.41 (s, 3 H, ArCH_3), 2.45 (s, 3 H, ArCH_3), 3.78 (s, 6 H, 2 x OCH_3), 6.22 (d, $J = 10.2$ Hz, 1 H, 8-H), 6.84 (d, $J = 8.7$ Hz, 4 H, 3', 5' and 3'', 5''-H), 7.39-7.46 (m, 5 H, 9-H, 2', 6' and 2'', 6''-H), 7.69 (s, 1 H, 4-H) ppm. ^{13}C -NMR (75.4 MHz, CDCl_3): δ 14.16 (CH_3), 15.45 (CH_3), 55.17 (OCH_3), 81.84 (7-C), 108.27 (C), 113.38 (2xCH), 117.64 (C), 121.00 (CH), 125.20 (CH), 127.37 (C), 127.98

(2xCH), 129.07 (CH), 132.20 (C), 135.82 (C), 136.16 (C), 136.80 (C), 146.84 (C), 158.78 (C) ppm.

Anal. Calcd. for $C_{27}H_{23}BrO_3S$: C, 63.91; H, 4.57; S, 6.32. Found: C, 63.80; H, 4.80; S, 6.35.

Methyl 3-{4-[7,7-bis(4-methoxyphenyl)-1,2-dimethyl-7H-thieno[3,2-f]chromen-5-ylamino]phenylthio}-2-[bis(*tert*-butoxycarbonyl)amino]propanoate (2):

A dried Schlenk tube was charged under Ar with dry toluene (2 mL), compound **1** (0.0510 g, 0.100 mmol), $Pd(OAc)_2$ (10 mol%), BINAP (15 mol%) and Cs_2CO_3 (1.4 equiv.) and the mixture was heated for 10 min at 80 °C. Boc-Ala[*N*-Boc- β -(4-aminophenylsulphonyl)]-OMe² (0.064 g, 0.150 mmol) was then added in dry toluene (2 mL) and the mixture was heated with stirring at 100 °C under Ar for 3h. The reaction was followed by TLC and stopped when no starting chromene was present. Water (20 mL) and ether (20 mL) were added, the phases separated and the aqueous phase washed with ether (3x10 mL). The organic phases were collected, dried ($MgSO_4$), filtered and removal of solvent gave a brown oil. This oil was submitted to column chromatography using solvent gradient from neat petroleum to 40% diethyl ether/petroleum ether giving compound **2** (0.060 g, 70%) as a yellow solid, m.p. 90.5-91.5 °C. UV (closed form) λ_{max} CH_2Cl_2 (ϵ $dm^3\ cm^{-1}\ mol^{-1}$) 378 (8155), 308 (31591), 273 (22300), 267 (22451) nm. λ_{max} toluene (ϵ) 375 (10100), 339 (18500), 327sh (30500), 309 (41300), 286 (26700), 280 (35490) nm. ¹H-NMR (300 MHz, $CDCl_3$): δ 1.50 (s, 18 H, CH_3 Boc), 2.40 (s, 3 H, $ArCH_3$), 2.44 (s, 3 H, $ArCH_3$), 3.41 (dd, J = 14.7 and 9.9 Hz, 1 H, βCH_2), 3.66 (dd, J = 14.7 and 4.5 Hz, 1 H, βCH_2), 3.72 (s, 3 H, OCH_3), 3.78 (s, 6 H, 2 x $ArOCH_3$), 5.09 (dd, J = 9.9 and 4.5 Hz, 1 H, αCH), 6.15 (d, J = 10.2 Hz, 1 H, 8-H), 6.22 (broad s, 1 H, NH), 6.82 (d, J = 8.7 Hz, 4 H, 3', 5'-and 3'', 5''-H), 7.06 (d, J = 8.4 Hz, 2 H, ArH), 7.33 (d, J = 8.7 Hz, 4 H, 2', 6' and 2'', 6''-H), 7.38 (d, J = 8.4 Hz, 2 H, ArH), 7.44 (d, J = 10.2 Hz, 1 H, 9-H), 7.45 (s, 1 H, 4-H) ppm. ¹³C-NMR (75.4 MHz, $CDCl_3$): δ 13.91 (CH_3), 15.41 (CH_3), 27.97 ($C(CH_3)_3$), 37.01 (βCH_2), 52.36 (OCH_3), 55.20 (OCH_3), 57.94 (αCH), 81.90 (7-C), 83.20 ($OC(CH_3)_3$), 108.19 (CH), 113.37 (CH), 116.31 (C), 118.96 (CH), 121.10 (CH), 125.98 (C), 127.27 (C), 128.28 (CH), 128.36 (CH), 129.28 (C), 129.94 (C), 131.64 (C), 132.23 (C), 133.39 (CH), 136.57 (C), 140.08 (C), 142.42 (C), 151.96 (C=O), 158.96 (C), 170.32 (C=O) ppm. m/z (%): FAB 854.37 ($M^+ + 2$),

27), 853.37 ($M^+ + 1$, 58), 852.39 (M^+ , 100). HMRS: Cald for $C_{47}H_{52}N_2O_9S_2$ M^+ 852.3114; found 852.3107.

Spectrokinetic measurements:

Spectrokinetic Studies under flash photolysis:

For spectrokinetic studies under flash photolysis 2.5×10^{-5} M toluene solutions were used. The flash photolysis experiments were monitored by a Warner and Swasey rapid spectrometer, allowing to record visible absorption spectra of coloured forms in the 400-700 nm range (acquisition time 1 ms, repetitivity 1.25 ms).^{3,4} Flashes (duration 50 μ s) were generated by two xenon tubes with a quartz envelope. The energy of the flashes was 60 J for whole polychromatic emission spectrum. For measurements, thermostated (25 °C) 100 mm cells were used. The light from the analysis lamp (50 W, quartz-iodide) was filtered using a Schott GC 400 high-pass filter.

Photodegradation measurements:

The measurements of degradation for A_{0d} and $t(A_{0d}/2)$ were performed with the “Degraphot” apparatus,⁵ using the following conditions: 0.5×10^{-5} M toluene solutions, optical way = 5 cm, temperature = 25 °C, degradation lamp XBO 250 W + Schott filters and R114.

Spectrokinetic Studies under continuous irradiation:

For the determination of absorption spectra of closed form and open form 1×10^{-5} M toluene solutions were used. For measurements of A_{eq} and k_A under continuous irradiation 1×10^{-4} M toluene solutions were used. Irradiation experiments were made using a CARY 50 Varian spectrometer coupled to a 150 W Ozone free Xenon lamp (6255 Oriel Instruments). The light from the UV lamp was filtered using a water filter (61945 Oriel Instruments) and then carried to the spectrophotometer holder at the right angle to the monitoring beam using a fiber-optic system (77654 Oriel Instruments). A light flux of 40 W m^{-2} , measured with a Goldilux Photometer with a UV-A probe was used. Visible irradiation experiments were performed using a long-pass filter, Schott GG 420 (Oriel 59480). A thermostated (20 °C) 10 mm quartz cell, containing the sample solution (3.5 mL), equipped with magnetic stirring was used. In a preliminary experiment, the visible absorption spectrum of the closed form and the λ_{max} of the open form were determined. In a second experiment the absorbance at photostationary equilibrium, A_{eq} , was measured at λ_{max} and then the decrease in the absorbance with the time was monitored. The rate constants were calculated using mono and multiexponential models.

References

- 1- Queiroz, M.-J. R.P.; Dubest, R.; Aubard J., Faure, R.; Guglielmetti, R. *Dyes and Pigments*, **2000**, 219-229.
- 2- Ferreira, P.M.T. ; Maia, H. ; Monteiro, L.S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 3167-3174.
- 3- Meyer, J.J.; Levoir, P.; Dubest, R. *Analyst*, **1995**, 120,447-452.
- 4- Pottier, E.; Dubest, R.; Guglielmetti, R.; Tardieu, P.; Kellmann, A.; Tfibel, F.; Levoir, P.; Aubard, J. *Helv. Chim. Acta*, **1990**, 73, 303-315.
- 5- Dubest, R.; Levoir, P.; Meyer, J. J. ; Aubard, J. ; Baillet, G. Giusti, G. ; Guglielmetti, R. *Rev. Sci. Instrum.* **1993**, 64, 1803-1808.