Tetrahedron 64 (2008) 5454–5458

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A prominent C-acylation–cyclisation synthetic sequence and X-ray structure elucidation of benzothiopyranone derivatives

Stefanos Kikionis [a], Vickie McKee [b], John Markopoulos [c], Olga Igglessi-Markopoulou [a,*]

[a] National Technical University of Athens, School of Chemical Engineering, Laboratory of Organic Chemistry, Zografou Campus, Athens 15773, Greece
[b] University of Loughborough, Chemistry Department, Leicestershire LE113TU, UK
[c] University of Athens, Department of Chemistry, Laboratory of Inorganic Chemistry, Panepistimiopolis, Zografou, Athens 15771, Greece

ARTICLE INFO

Article history:
Received 21 December 2007
Received in revised form 17 March 2008
Accepted 3 April 2008
Available online 8 April 2008

Keywords:
Benzothiopyranones
Thiocoumarins
Thiochromones
C-Acylation
N-Hydroxysuccinimide ester

ABSTRACT

A novel short-step methodology to benzothiopyranone derivatives has been developed starting from an activated precursor, *N*-hydroxysuccinimide ester of thiosalicylic acid. The procedure is based on a tandem C-acylation–cyclisation process under mild reaction conditions in good yields. The structure elucidation has been established using X-ray crystallography and NMR spectral data.

1. Introduction

The development of new methodologies for the synthesis of functionalized benzothiopyran-2-ones (thiocoumarins) and benzothiopyran-4-ones (thiochromones) (Fig. 1) is a topic of continuing interest, because of their biological and pharmacological interest.

The benzothiopyran skeleton is an important structural motif in the preparation of pharmaceuticals,[1] showing a higher biological activity compared to the corresponding benzopyran.[2] Benzothiopyranones serve as key intermediates for the synthesis of biologically active compounds.[3,4]

Benzothiopyran-2-one derivatives have been prepared and studied as matrix metalloproteinase inhibitors,[5] as 5-HT3 (serotonin 3) receptor antagonist[6] for the treatment of inflammation,[7] as bacteriocides and anticancer agents.[1c,4] A series of 4,6-dimethylthiocoumarins and related compounds, containing an aminoethyl group in the thiocoumarin ring, were tested and showed significant insecticidal activity.[8] Substituted benzothiopyranones are widely used against hypertension,[9] and have been tested for antimicrobial and antitumour activity.[8] Some thiocoumarins have exhibited anti-vitamin K activity, and plant and animal growth arrest activity.[10]

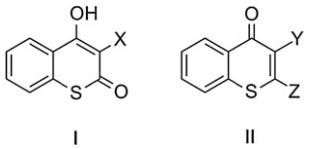


Figure 1. Thiocoumarin (**I**) and thiochromone (**II**) structure.

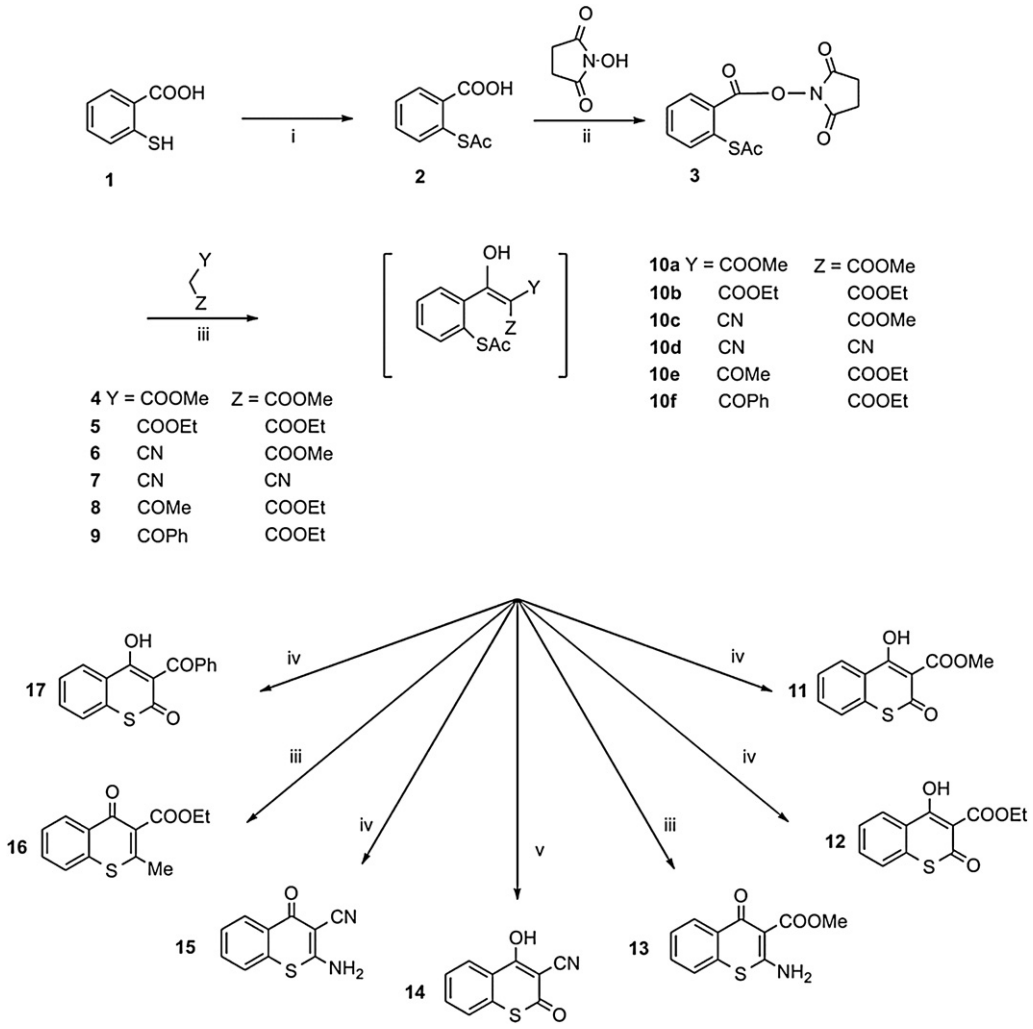
The synthesis of thiochromones and thiocoumarins has been achieved by various methods.[1b,8,11,12] Standard syntheses of the benzothiopyran skeleton typically involve multi-step procedures, unstable starting material and the harsh reaction conditions, are not suitable for highly functionalized benzothiopyranones.

During the course of our studies towards the development of a new methodology on the synthesis of heterocycles containing the β,β′-dicarbonyl system, we became interested in the possibility of developing a new approach to the synthesis and structural elucidation of fused sulfur heterocycles.

Recently, we reported[13] a new synthetic route to 3-substituted thiotetronic acids via a C-acylation reaction of active methylene compounds with activated derivatives of *S*-protected thioglycolic acids followed by an in situ cyclisation reaction. In this paper we wish to report an extension of this coupling–cyclisation strategy for the synthesis of biologically interesting fused sulfur heterocycles. This chemistry proceeds by a tandem intermolecular nucleophilic coupling of the activated ester **3** with the active methylene compound and a subsequent intramolecular cyclisation to a stable six-membered ring system (Scheme 1).

* Corresponding author. Tel.: +30 210 772 3 079; fax: +30 210 772 3 072.
E-mail address: ojmark@orfeas.chemeng.ntua.gr (O. Igglessi-Markopoulou).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.04.009



Scheme 1. Reagents and conditions: (i) $(CH_3CO)_2O$, CH_3CO_2H, reflux; (ii) THF, DCC; (iii) NaH, THF; (iv) NaOEt/EtOH; (v) HCl/MeOH.

This approach would provide an alternative and ultimately more general method to the preparation of thiocoumarins and thiochromones, and an extended system containing the benzothiopyranone ring.

Herein, we provide a full account of this efficient synthesis of thiocoumarin and thiochromone ring system.

2. Results and discussion

In continuation of our programme on the chemistry of fused heterocyclic systems, quinolinones, naphthyridines, coumarins, as potential pharmacological agents[14] we report herein an improved methodology to 3-substituted 4-hydroxythiocoumarin-2-ones and 2-methyl-2-amino-thiochrom-4-ones (Scheme 1). The key control element of these 'benzothiopyranone' heterocycles was the utilisation of the *N*-hydroxysuccinimide ester of *S*-acetylthiosalicylic acid as a promising precursor for the synthesis of polyfunctional 'thiocoumarin and thiochromone' derivatives. The requisite acylating agent **3**, *N*-hydroxysuccinimide ester of *S*-acetylthiosalicylic acid, was prepared by a standard protocol involving condensation of equimolar quantities of the *S*-acetyl protected thiosalicylic acid **2** and *N*-hydroxysuccinimide in the presence of 1.2 equiv of *N*,*N*′-dicyclohexylcarbodiimide. This excellent activating system **3** was isolated in very good yield as a white solid and used in the C-acylation reaction without further purification.

The C-acylation protocol involved the reaction of equimolar amounts of sodium hydride (2 equiv) in anhydrous tetrahydrofuran with the appropriate active methylene compound (2 equiv) (**4**–**9**), at 0 °C. After 1 h, 1 equiv of the *N*-hydroxysuccinimide ester **3** was added and the mixture was stirred at room temperature for 2 h. We noted that the C-acylation intermediates **10a**–**f** were obtained in admixture with the corresponding cyclised compounds, as determined on the basis of the NMR data. Ring closure of the intermediates was achieved by treating them in sodium ethoxide in ethanol for 24 h or with aqueous HCl (10%) in MeOH for 48 h. The cyclisation of **10a**,**b**,**c**,**f** by intramolecular nucleophilic attack of the sulfur lone pair on the ester carbonyl group would produce structures such as **11**, **12**, **14** and **17**. However, we noticed an alternative reaction path, under the C-acylation–cyclisation reaction conditions. The intermediate **10e** undergoes spontaneous cyclisation to the thiochromone **16**. This cyclisation clearly involves attack of the sulfur nucleophile on the ketonic group of this intermediate, producing the 2-methyl-4-keto-thiochromone **16**.

Then, our attention was concentrated on the use of the C-acylation intermediates **10c**,**d** possessing the CN group as synthons for the construction of novel 2-amino-3-methoxycarbonylthiochromone **13** and 2-amino-3-cyanothiochromone **15**. The electron-deficient carbon atom interacts with the nucleophilic sulfur in the cyclisation process.[15] These 2-amino-thiochromones are valuable synthetic building blocks and have attracted considerable interest because of their biological significance.[16]

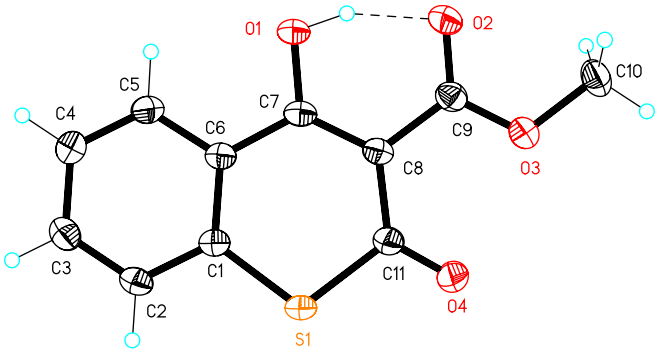


Figure 2. Molecular structure of **11**, the dashed line represents a hydrogen bond. Thermal ellipsoids drawn at the 50% probability level.

Additionally, we noticed that on treating with aqueous HCl (10%) in methanol, the C-acylation intermediate **10c** easily undergoes an intramolecular heterocyclisation reaction to give the 3-cyanothiocoumarin **14** (Scheme 1).

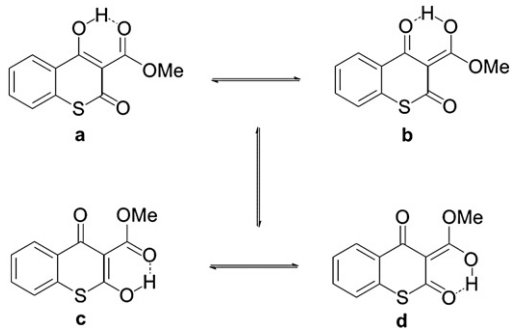
An X-ray structure determination of compound **11** was carried out to confirm the structure in the solid state. The molecular structure and numbering scheme are shown in Figure 2, and bond lengths and angles are given in Table 1. The structure resembles that of tautomer **a** (Scheme 2) with an endocyclic C=C double bond. There is some double bond character evident in the C(7)–C(8) bond (1.3930(19) Å) and the O(1)–C(7) bond is distinctly longer than the conventional carbonyl distance for O(4)–C(11) (1.3245(15) and 1.2132(17) Å, respectively). There is a quite short intramolecular hydrogen bond between the enol and ester oxygen atoms (O(1)–O(2) 2.4496(14) Å). Figure 3 shows the intermolecular interactions. The molecules show π–π stacking, unusually this principally involves the carbonyl and C=C portions of the molecule rather than the phenyl rings. The stacks are linked by two weak intermolecular C–H···O interactions (Table 2).[17–20]

3. Conclusions

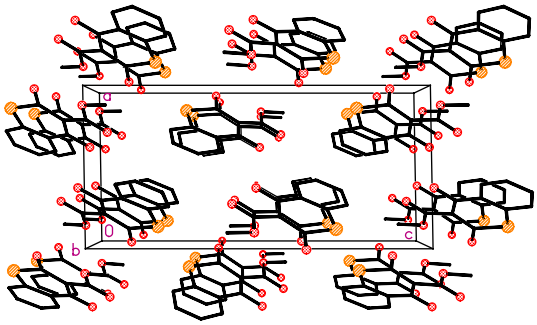
In summary, the *N*-hydroxysuccinimide ester of thioacetylsalicylic acid has been introduced as a new efficient precursor for the synthesis of the target compounds with interesting biological properties. The activation of thioacetylsalicylic acid as the *N*-hydroxysuccinimide ester is an attractive alternative to other thiosalicylic acid species[11] permitting mild reaction conditions and short reaction times. Availability, simplicity, ease of handling of reagents, satisfactory yields and mildness of the reaction conditions make the proposed methodology prominent for the preparation of functionalized thiocoumarins and thiochromones. Our further efforts are directed towards the synthesis of more complex substrates in the 'benzothiopyranone' series.

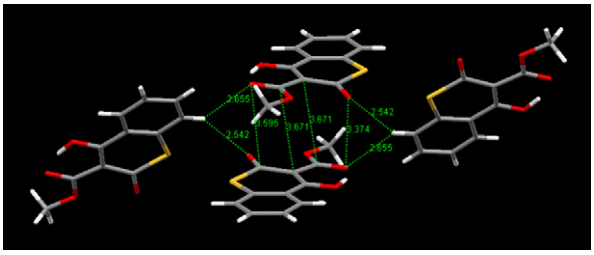
Table 1
Bond lengths [Å] and angles [°] for **11**

S(1)–C(1)	1.7394(13)	C(7)–O(1)	1.3245(15)
S(1)–C(11)	1.7807(14)	C(7)–C(8)	1.3930(19)
C(1)–C(2)	1.3988(18)	C(8)–C(11)	1.4637(17)
C(1)–C(6)	1.4031(17)	C(8)–C(9)	1.4763(18)
C(2)–C(3)	1.380(2)	C(9)–O(2)	1.2368(16)
C(3)–C(4)	1.396(2)	C(9)–O(3)	1.3122(17)
C(4)–C(5)	1.376(2)	O(3)–C(10)	1.4568(16)
C(5)–C(6)	1.4033(19)	C(11)–O(4)	1.2132(17)
C(6)–C(7)	1.4557(18)		
C(1)–S(1)–C(11)	106.00(6)	O(1)–C(7)–C(6)	113.39(11)
C(2)–C(1)–C(6)	120.23(12)	C(8)–C(7)–C(6)	125.95(11)
C(2)–C(1)–S(1)	116.84(10)	C(7)–C(8)–C(11)	122.80(12)
C(6)–C(1)–S(1)	122.92(10)	C(7)–C(8)–C(9)	117.21(11)
C(3)–C(2)–C(1)	120.23(12)	C(11)–C(8)–C(9)	119.98(12)
C(2)–C(3)–C(4)	120.00(13)	O(2)–C(9)–O(3)	121.20(12)
C(5)–C(4)–C(3)	120.01(13)	O(2)–C(9)–C(8)	122.18(12)
C(4)–C(5)–C(6)	121.16(13)	O(3)–C(9)–C(8)	116.62(11)
C(1)–C(6)–C(5)	118.36(12)	C(9)–O(3)–C(10)	116.03(11)
C(1)–C(6)–C(7)	122.03(12)	O(4)–C(11)–C(8)	126.22(13)
C(5)–C(6)–C(7)	119.61(11)	O(4)–C(11)–S(1)	114.07(10)
O(1)–C(7)–C(8)	120.65(12)	C(8)–C(11)–S(1)	119.70(10)



Scheme 2. Enol–enol equilibrium of the 4-hydroxy-3-methoxycarbonylthiocoumarin (**11**).





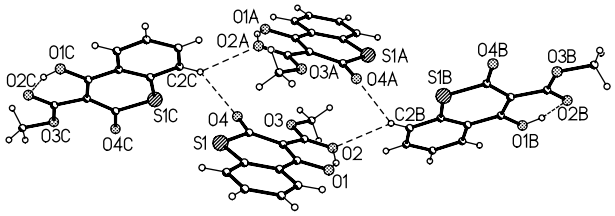


Figure 3. Intermolecular interactions in **11**, dashed lines represent hydrogen bonds. The central molecules are parallel, which means interplanar separation 3.488 Å (symmetry codes: A, −*x*, −*y*, −*z*; B, *x*, (1/2)−*y*, −(1/2)+*z*, C, −*x*, −(1/2)+*y*, (1/2)−*z*).

Table 2
Hydrogen bonds in **11** [Å and °]

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	<(DHA)
O(1)–H(1)···O(2)	0.91(2)	1.59(2)	2.4496(14)	156.6(18)
C(2)–H(2)···O(2)$1	0.95	2.66	3.2941(17)	125.0
C(2)–H(2)···O(4)$2	0.95	2.54	3.3732(17)	146.3

Symmetry codes: $1, *x*, (1/2)−*y*, (1/2)+*z*; $2, −*x*, (1/2)+*y*, (1/2)−*z*.

4. Experimental section

4.1. General

Melting points were determined on a Gallenkanp MFB-595 melting point apparatus and are uncorrected. The FTIR spectra were recorded on a FTIR Jasco 4200 instrument. Mass spectra were obtained on a TSQ 7000 Finnigan MAT (ESI) instrument. The NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Varian Gemini-2000 300 MHz spectrometer; chemical shifts are quoted in parts per million (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad); *J* values are given in hertz. Elemental analyses were obtained on a Euro EA3000 Series Euro Vector CHNS Elemental Analyzer. Petroleum ether refers to the fraction with bp 40–60 °C. Commercially available THF was dried prior to use by refluxing over Na. All other solvents (puriss quality) were used without further purification. Origin and purity of the other reagents are as follows: thiosalicylic acid, puriss; *N*-hydroxysuccinimide, purum; DCC, puriss.

4.2. Synthesis

*4.2.1. Synthesis of S-acetylthiosalicylic acid (**2**)*[21]

A mixture of thiosalicylic acid (50 mmol, 7.7 g), acetic anhydride (60 mmol, 6.1 g) and acetic acid (21.5 mL) was heated to reflux for approximately 6 h. The reaction progress was monitored by TLC. After cooling to room temperature the solution was poured into aqueous hydrochloric acid (10%). The product was filtered off, washed with water and petroleum ether, and dried in vacuo to afford the corresponding *S*-acetylthiosalicylic acid as a white solid.

*4.2.1.1. S-Acetylthiosalicylic acid (**2**).* Yield: 75%; mp 124–126 °C (lit.[21] 127–129 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.40 (s, 3H, $COCH_3$), 7.53–7.86 (m, 4H, aromatic H), 13.16 (br s, 1H, CO_2H). Anal. Calcd for $C_9H_8O_3S$: C, 55.09; H, 4.11; O, 24.46; S, 16.34. Found: C, 55.22; H, 4.03; O, 24.57; S, 16.23.

*4.2.2. General procedure for the synthesis of N-hydroxysuccinimide ester of S-acetylthiosalicylic acid (**3**)*

S-Acetylthiosalicylic acid (10 mmol, 1.96 g) was treated under argon with *N*-hydroxysuccinimide (10 mmol, 1.16 g) in THF (11.5 mL). A solution of DCC (12 mmol, 2.47 g) in THF (8.5 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to stir at 0 °C for 2 h. The resulting suspension was refrigerated overnight at 3–5 °C. The precipitated solid (DCCU) was filtered off and discarded, the THF filtrate was evaporated under reduced pressure and dried in vacuo to afford a solid product. The product was washed with diethyl ether and dried in vacuo to afford *N*-hydroxysuccinimide ester of the corresponding *S*-acetylthiosalicylic acid as a white solid.

*4.2.2.1. N-Hydroxysuccinimide ester of S-acetylthiosalicylic acid (**3**).* Yield: 92%; mp 112–114 °C. IR (ATR): 2117, 1776, 1740, 1700, 1650, 1627, 1575, 1637 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.44 (s, 3H, $COCH_3$), 2.88 (s, 4H, $CO_2N(CO)_2(CH_2)_2$), 7.69–8.09 (m, 4H, aromatic H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.6 ($COCH_3$), 30.2 ($CO_2N(CO)_2(CH_2)_2$), 128.8, 129.4, 130.4, 131.2, 134.3, 137.5 (C_6H_4), 161.3 ($COCH_3$), 170.1 ($CO_2N(CO)_2(CH_2)_2$), 192.0 ($CO_2N(CO)_2(CH_2)_2$). Anal. Calcd for $C_{13}H_{11}O_5NS$: C, 53.24; H, 3.78; N, 4.77; O, 27.27; S, 10.93. Found: C, 53.38; H, 3.63; N, 4.52; O, 27.39; S, 10.78.

4.2.3. General procedure for the synthesis of 3-substituted thiocoumarins and thiochromones

NaH (60% suspension in oil) (20 mmol, 0.8 g) was added in anhydrous THF (65 mL) at 0 °C and the resulting mixture was stirred under argon for 15 min at room temperature. The appropriate active methylene compound (dimethyl malonate, diethyl malonate, methyl cyanoacetate, malonitrile, ethyl acetoacetate and ethyl benzoylacetate) (20 mmol) was then added at 0 °C and after a period of 1 h stirring at room temperature, *N*-hydroxysuccinimide ester was added. The reaction mixture was allowed to stir at room temperature for 2 h and then concentrated under reduced pressure. The obtained gummy solid was diluted with H_2O (10 mL) and washed with Et_2O (5 mL). The aqueous extract was acidified with aqueous HCl (10%) in an ice-H_2O bath to afford an oily product, which was extracted with CH_2Cl_2 (3×15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and dried in vacuo to give an oily residue, which was treated either with method A, B or C.

(A) Treatment with dichloromethane, diethyl ether or petroleum ether to afford as solids the corresponding products.

(B) The C-acylation compounds (1 mmol) were treated with a solution of sodium (4.6 g, 20 mmol) in absolute EtOH (20 mL) and stirred at room temperature for 24 h. The mixture was evaporated under reduced pressure and the residue was diluted with H_2O and washed with Et_2O. The aqueous layer was acidified with aqueous HCl (10%) to afford the functionalized products as solids. All products were filtered off, washed with petroleum ether and dried in vacuo.

(C) The C-acylation compounds (1 mmol) were dissolved in MeOH (20 mL) and treated with aqueous HCl (10%, 20 mL) for 48 h at room temperature to afford a gummy solid, which was extracted with CH_2Cl_2 (3×15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and dried in vacuo to afford the corresponding products.

*4.2.3.1. 4-Hydroxy-3-methoxycarbonylthiocoumarin (**11**).* Using dimethyl malonate as the active methylene compound, according to method (B), compound **11** was obtained as white crystals. Yield: 67% (recrystallisation from methanol); mp 110–111 °C. MS (ESI) m/z=237.2 ($[M+H]^+$). IR (ATR): 1698, 1650, 1630, 1538 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.84 (s, 3H, CO_2CH_3), 7.49–8.27 (m, 4H, aromatic H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=52.8 (CO_2CH_3), 108.2 (C-3), 123.0, 125.6, 126.9, 127.6, 132.7, 136.2 (C_6H_4), 168.0 (CO_2CH_3), 169.1 (C-2), 179.1 (C-4). Anal. Calcd for $C_{11}H_8O_4S$: C, 55.92; H, 3.41; O, 27.09; S, 13.57. Found: C, 55.79; H, 3.29; O, 26.92; S, 13.65.

*4.2.3.2. 3-Ethoxycarbonyl-4-hydroxythiocoumarin (**12**).* Using diethyl malonate as the active methylene compound, according to method (B), compound **12** was obtained as a yellow solid. Yield: 62%; mp 103–104 °C (lit.[11] 115–116 °C). IR (ATR): 1734, 1680, 1650, 1633, 1590, 1540 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.28 (t, J=6.9 Hz, 3H, $CO_2CH_2CH_3$), 4.31 (q, J=6.9 Hz, 2H, $CO_2CH_2CH_3$), 7.53–8.28 (m, 4H, aromatic H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=13.8 ($CO_2CH_2CH_3$), 61.9 ($CO_2CH_2CH_3$), 108.0 (C-3), 122.9, 125.5, 126.8, 127.5, 132.7, 136.3 (C_6H_5), 167.8 ($CO_2CH_2CH_3$), 169.4 (C-2), 179.0 (C-4). Anal. Calcd for $C_{12}H_{10}O_4S$: C, 57.59; H, 4.03; O, 25.57; S, 12.81. Found: C, 57.74; H, 4.18; O, 25.49; S, 12.68.

*4.2.3.3. 2-Amino-3-methoxycarbonylthiochromone (**13**).* Using methyl cyanoacetate as the active methylene compound, according to method (A), compound **13** was obtained as a yellow solid. Yield: 57%; mp 205–207 °C. IR (ATR): 2215, 1745, 1679, 1633, 1590, 1530 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.74 (s, 3H, CO_2CH_3), 7.43–8.17 (m, 4H, aromatic H), 8.31 (br s, 2H, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ=51.5 (CO_2CH_3), 102.1 (C-3), 125.0, 126.0, 128.1, 131.6, 133.3, 138.9 (C_6H_5), 161.6 (C-2), 167.6 (CO_2CH_3), 175.9 (C-4). Anal. Calcd for $C_{11}H_9O_3NS$: C, 56.16; H, 3.86; N, 5.95; O, 20.40; S, 13.63. Found: C, 56.30; H, 3.71; N, 5.84; O, 20.55; S, 13.49.

*4.2.3.4. 3-Cyano-4-hydroxythiocoumarin (**14**).* Using methyl cyanoacetate as the active methylene compound, according to method (C), compound **14** was obtained as yellow solid. Yield: 60%; mp 229–232 °C. MS (ESI) m/z=204.1 ($[M+H]^+$). IR (ATR): 2233, 1747, 1680, 1630, 1583, 1530 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=7.30–8.16 (m, 4H, aromatic H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=88.5 (C-3), 119.0 (CN), 125.3, 125.6, 127.6, 129.1, 131.1, 135.1 (C_6H_4), 178.1 (C-2), 178.2 (C-4). Anal. Calcd for $C_{10}H_5O_2NS$: C, 59.10; H, 2.48; N, 6.89; O, 15.74; S, 15.78. Found: C, 59.22; H, 2.53; N, 6.95; O, 15.59; S, 15.61.

*4.2.3.5. 2-Amino-3-cyanothiochromone (**15**).* Using malonitrile as the active methylene compound, according to method (B), compound **15** was obtained as a brown solid. Yield: 62%; mp 295–297 °C (lit.[16] 291–293 °C). IR (ATR): 2213, 1683, 1642, 1633, 1580, 1538 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=7.47–8.20 (m, 4H, aromatic H), 8.74 (br s, 2H, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ=84.1 (C-3), 115.7 (CN), 126.1, 127.5, 127.6, 127.9, 130.7, 132.3 (C_6H_4), 166.1 (C-2), 176.5 (C-4). Anal. Calcd for $C_{10}H_6ON_2S$: C, 59.39; H, 2.99; N, 13.85; O, 7.91; S, 15.85. Found: C, 59.45; H, 3.13; N, 13.69; O, 7.83; S, 15.71.

*4.2.3.6. 3-Ethoxycarbonyl-2-methylthiochromone (**16**).* Using ethyl acetoacetate as the active methylene compound, according to method (A), compound **16** was obtained as a yellow solid. Yield: 56%; mp 125–127 °C (lit.[11] 145–146 °C). IR (ATR): 1705, 1678, 1602, 1538 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.24 (t, J=7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.43 (s, 3H, CH_3), 4.12 (q, J=7.3 Hz, 2H, $CO_2CH_2CH_3$), 7.40–8.08 (m, 4H, aromatic H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.4 ($CO_2CH_2CH_3$), 20.7 (CH_3), 60.1 ($CO_2CH_2CH_3$), 99.3 (C-3), 116.8, 128.6, 132.1, 133.2, 133.6, 135.3 (C_6H_5), 156.8 (C-2), 165.4 ($CO_2CH_2CH_3$), 170.4 (C-4). Anal. Calcd for $C_{13}H_{12}O_3S$: C, 62.88; H, 4.87; O, 19.33; S, 12.91. Found: C, 62.75; H, 4.96; O, 19.48; S, 12.81.

*4.2.3.7. 3-Benzoyl-4-hydroxythiocoumarin (**17**).* Using ethyl benzoylacetate as the active methylene compound, according to method (B), compound **17** was obtained as yellow crystals. Yield: 65% (recrystallisation from methanol); mp 150–153 °C. MS (ESI) m/z=283.2 ($[M+H]^+$). IR (ATR): 1698, 1630, 1595, 1530 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=7.49–8.29 (m, 9H, aromatic H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=116.4 (C-3), 123.7, 126.0, 126.8, 127.0, 128.8, 128.8, 131.8, 133.5, 136.0, 137.0 (C_6H_5), 164.8 (COC_6H_5), 181.1 (C-2), 193.8 (C-4). Anal. Calcd for $C_{16}H_{10}O_3S$: C, 68.07; H, 3.57; O, 17.00; S, 11.36. Found: C, 68.17; H, 3.43; O, 16.86; S, 11.29.

4.3. Crystal structure determination of 11

Compound **11**: $C_{11}H_8O_4S$, monoclinic, $P2_1/c$, α=8.2037(5), b=6.9587(4), c=17.4291(11) Å, β=90.949(1)°, V=994.84(10) $Å^3$, T=150(2) K, λ=0.71073 Å, Z=4,9239 reflections measured, 2272 unique (R_{int}=0.0233), $wR2$=0.0830 (all data), $R1$=0.0302 ($I>2\sigma(I)$). Data were collected on a Bruker APEX II diffractometer. The structure was solved by direct methods and refined on F^2 using all the reflections.[22] All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model, except for the hydrogen bonded to O1, which was located and refined with a fixed, isotropic displacement parameter. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 682433. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

S.K. would like to thank the National Technical University of Athens, Chemical Engineering Department for financial support. J.M. would like to thank the National and Kapodistrian University of Athens for financial support (special account for research grant No. 70/4/3337).

References and notes

1. (a) Nakazumi, H.; Kitao, T. *Chem. Lett.* **1978**, 929; (b) Nakazumi, H.; Asada, A.; Kitao, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2046; (c) Nakazumi, H.; Ueyama, T.; Sonoda, H.; Kitao, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2323; (d) Tamura, K.; Ishihara, T.; Yamanaka, H. *J. Fluorine Chem.* **1994**, *68*, 25.
2. Rios, R.; Sundèn, H.; Ibrahem, I.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 8679.
3. Panetta, J. A.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 2626.
4. Kumar, P.; Bodas, M. S. *Tetrahedron* **2001**, *57*, 9755.
5. Watanabe, K.; Saito, T.; Niimura, K. Eur. Pat. Appl. EP 758649, 1997; *Chem. Abstr.* **1997**, *126*, 199456.
6. Sano, T.; Saijo, K.; Tomizawa, K.; Kameo, K.; Yokomori, S.; Hatayama, K. Jpn. Kokai Tokkyo Koho JP 04082887, 1992; *Chem. Abstr.* **1992**, *117*, 150893.
7. Carter, J. S.; Obukowicz, M. G.; Devadas, B.; Talley, J. J.; Brown, D. L.; Graneto, M. J.; Bertenshaw, S. R.; Rogier, D. J., Jr.; Nagarajan, S. R.; Hanau, C. E.; Hartmann, S. J.; Ludwig, C. L.; Metz, S. PCT Int. Appl. WO 9847890, 1998; *Chem. Abstr.* **1998**, *129*, 330653.
8. Nakazumi, H.; Kobara, Y.; Kitao, T. *J. Heterocycl. Chem.* **1992**, *29*, 135.
9. Prasanna, B.; Chandramouli, G. V. P. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 2059.
10. Meth-Cohn, O.; Tarnowski, B. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, NY, 1980; Vol. 26, p 122.
11. Jung, J.-C.; Kim, J.-C.; Park, O.-S. *Synth. Commun.* **2000**, *30*, 1193.
12. Huang, B.-N.; Liu, J.-T.; Huang, W.-Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 101.
13. Kikionis, S.; Prousis, K. C.; Detsi, A.; Igglessi-Markopoulou, O. *ARKIVOC* **2006**, 28.
14. (a) Mitsos, C. A.; Zografos, A. L.; Igglessi-Markopoulou, O. *J. Org. Chem.* **2003**, *68*, 4567; (b) Zografos, A.; Mitsos, C.; Igglessi-Markopoulou, O. *Heterocycles* **1999**, *51*, 1609; (c) Athanaselis, G.; Melagraki, G.; Chatzidakis, H.; Afantitis, A.; Detsi, A.; Igglessi-Markopoulou, O.; Markopoulos, J. *Synthesis* **2004**, *11*, 1775.
15. Stacy, G. W.; Eck, D. L.; Wollner, T. E. *J. Org. Chem.* **1970**, *35*, 3495.
16. Rudorf, W. D.; Augustin, M. *J. Prakt. Chem.* **1981**, *323*, 55.
17. Munshi, P.; Row, T. N. G. *J. Phys. Chem. A* **2005**, *109*, 659.
18. Steiner, T. *Crystallogr. Rev.* **2003**, *9*, 177.
19. Taylor, R.; Kennard, O. *J. Chem. Am. Soc.* **1982**, *104*, 5063.
20. Sarma, J. A. R. P.; Desiraju, G. R. *Acc. Chem. Res.* **1986**, *19*, 222.
21. Taiyoung, S. J.; Russell, M. P.; Howard, J. Eur. Pat. Appl. EP 54936, 1982; *Chem. Abstr.* **1982**, *97*, 198562.
22. Sheldrick, G. M. *SHELXTL Version 6.12*; Bruker AXS: Madison WI, 2001.