Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 198 (2018) 290–296

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

One-pot synthesis, quantum chemical calculations and X-ray diffraction studies of thiazolyl-coumarin hybrid compounds

Aamer Saeed [a,*], Mubeen Arif [a], Mauricio F. Erben [b,*], Ulrich Flörke [c], Jim Simpson [d]

[a] Department of Chemistry, Quaid-I-Azam University, Islamabad 45320, Pakistan
[b] CEQUINOR (UNLP, CONICET-CCT La Plata), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Bv. 120 1465, 1900 La Plata, Argentina
[c] Department of Chemistry, University of Paderborn, 33098 Paderborn, Germany
[d] Department of Chemistry, University of Otago, P.O. Box 56, Dunedin 9054, New Zealand

ARTICLE INFO

Article history:
Received 20 December 2017
Received in revised form 9 February 2018
Accepted 12 March 2018
Available online 13 March 2018

Keywords:
Coumarin
Thiazolyl
Crystal structure
Hydrogen bonding
Natural Bond Orbital

ABSTRACT

Two closely related hybrid species containing both, thiazolyl and coumarin groups, were synthesized by using two different one-pot procedures from a common precursor. The reaction of α-bromoacetylcoumarin with thioacetamide in methanol furnished 3 (2 methylthiazol 4 yl) 2*H* chromen 2 one (**2**), whereas refluxing α bromoacetylcoumarin with potassium thiocyanate in ethanol afforded 3 (2 ethoxythiazol 4 yl) 2*H* chromen 2 one (**3**). Both derivatives were fully characterized by spectroscopic methods, elemental analysis and X-ray diffraction studies. Intramolecular C4—H···N and C5′—H···O═C hydrogen bonds between the heterocycles determine the conformational behavior. The co-planarity of the coumarin and thiazolyl rings favors the occurrence of two *remote* orbital interactions involving the oxygen and nitrogen lone pairs and the corresponding σ*C—H electron acceptor, as demonstrated by Natural Bond Orbital population analysis. The 2-substitution of the thiazol 4 yl group has little effect on the molecular structures but causes significant differences in the crystal packing of the two compounds.

1. Introduction

Coumarin (2*H* 1 benzopyran 2 one) is the simplest member of an extensive series of naturally occurring lactones found to exhibit diverse therapeutic applications. These include use as antifungal, antibacterial [1], anti-HIV, antitubercular [2], antiacetylcholinesterase, anticancer [3,4] anticoagulant, antimutagenic, anti-hepatites C antiinflammatory [5], and analgesic [6] agents. Moreover many coumarin derivatives are used as non-peptidic protease [7], 17 β hydroxysteroid dehydrogenase [8], heat shock protein [9,10], monoamine oxidase [11] and TNF-α inhibitors [12]. Coumarinyl sulfonamides are good to excellent antibacterial agents while 4 methylcoumarin derivatives exhibit promising radical scavenging and antioxidant properties. Warfarin, a 4 hydroxycoumarin derivative, is a clinical anticoagulant and a widely used rodenticide also acting as vitamin K antagonist [13] while sodium salt of warfarin is known to inhibit HIV infections [14].

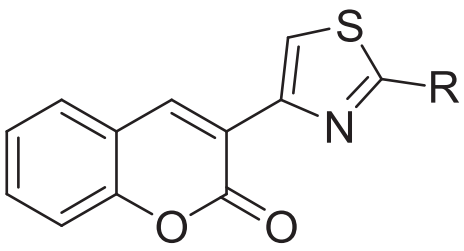
Compounds containing a thiazole ring are known to have versatile pharmacological roles. Some of the thiazole derivatives are used as fungicidal [15], antitumor, heart stimulant [16], antibacterial [17], antiviral and anti-inflammatory agents. Thiazole based drugs are also used for treating high blood pressure [18], HIV infections [19], and pain [20]. Thiazole analogues are used as antithrombotic agents [21], inhibitors of bacterial DNA gyrase B [22] and lypoxegenase [23], adenosine receptor antagonists and as anti-arrhythmic agents [24]. Much used drugs containing the thiazole ring include the anti-inflammatories fantizole, meloxicam and fentiazac, nizatidine (an antiulcer agent), the antibiotic penicillin, and ravucunazole (an antifungal agent), thus underlining the importance of the thiazole ring in pharmaceutical applications [25].

With the importance of both coumarin and thiazole based pharmaceuticals in mind we were interested in developing a synthetic route to molecules that contain both entities with the ultimate aim of exploring whether or not the effects of the two units would work in concert in a pharmaceutical sense in the combined molecules [26,27]. We describe here the synthesis and characterization of two closely related thiazol-coumarin species, 3 (2 methylthiazol 4 yl) 2*H* chromen 2 one (**2**) and 3 (2 ethoxythiazol 4 yl) 2*H* chromen 2 one (**3**). To the best of our knowledge, this is the first report on the synthesis of compound (**2**), whereas Rao and Reddy reported the preparation of compound (**3**) [28] (Scheme 1).

X-ray structure determinations of 3 (thiazol 4 yl) 2*H* chromen 2 one derivatives are rare, *vide infra*, and only two compounds are known with simple substituents, NH_2 and $NHCH_3$ at the 2-position of the thiazole ring [29,30]. So in addition to the synthesis, we report here a structural characterization of the molecules together with a quantum chemical

* Corresponding authors.
E-mail addresses: asaeed@qau.edu.pk (A. Saeed), erben@quimica.unlp.edu.ar (M.F. Erben).

https://doi.org/10.1016/j.saa.2018.03.036
1386-1425/



Scheme 1. 3 (2 substituted thiazol 4 yl) 2*H* chromen 2 one derivatives [R = CH_3 (**2**) and OC_2H_5 (**3**)].

analysis of their conformations at the B3LYP/6-311++G(d,p) level of approximation.

2. Experimental

Melting points were determined using a Stuart melting point apparatus (SMP3) and are uncorrected. Chromatographic R_f-values were determined by using aluminum pre-coated silica gel plates Kiesel 60 F_{254} from Merck (Germany). FTIR data was collected using an FTS 3000 MS, Bio-Rad Merlin (Excalibur Model) spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker spectrophotometer at 300 and 75 MHz in $CDCl_3$ solution. Chemical shifts are recorded on the δ-scale (ppm). LCMS data were taken on Agilent technologies 6890 N by using a 70 Ev EI source). Elemental analyses were carried out on a CHNS 932 LECO instrument.

*2.1. Synthesis of 3 (2 Methyl thiazol 4 yl) 2H chromen 2 one (**2**)*

3 (2 Bromoacetyl) 2*H* chromene 2 one (0.01 mol) (**1**) was dissolved in 30 mL of methanol followed by the addition of thioacetamide (0.01 mol) in methanol and stirred at room temperature for 30 min. The resulting mixture was refluxed for 4 h and, at completion monitored by TLC, the reaction mixture was poured into ice-cold water. The product (**2**) was recrystallized by slow evaporation from methanol. Yield: 79%; Yellowish brown crystals; m.p.: 259–261 °C; R_f: 0.36; FTIR (ATR, υ/cm^{-1}): 3077 (Csp^2-H), 1693 (C═O), 1605 (C═N), 1538 (C═C aromatic); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (s, 1H, H-4 lactone), 7.64 (d, *J* = 6.9 Hz, 1H, Ar—H), 7.54 (dd, *J* = 7.6, 1.2 Hz, 1H, Ar—H); 8.31 (s, 1H, thiazole) 7.28–7.21 (m, 2H, Ar—H); 2.91 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO d_6): δ 163.2 (C═N, thiazole), 160.8 (C═O, lactone), 152.7, 144.0, 140.3, 139.2, 132.2, 129.4, 129.4, 123.1, 120.6, 117.6,57.2; LC-MS (*m*/*z*): 243.0 (M)$^+$; Elemental analysis Found (%): C, 64.18; H, 3.73; N, 5.76; S, 13.18; Calc. for $C_{13}H_9NO_3$: S: C, 64.21; H, 3.71; N, 5.69; S, 13.20.

*2.2. Synthesis of 3 (2 Ethoxythiazol 4 yl) 2H chromen 2 one (**3**)*

A modification of the method reported by Rao and Reddy for the preparation of compound **(3)** [28] was used. Thus, 3 (2 bromoacetyl) 2*H* chromene 2 one (0.01 mol) (**1**) was dissolved in 30 mL of ethanol and potassium thiocyanate (0.01 mol) was added, the resulting mixture was stirred at room temperature for 30 min and refluxed for 4 h. On completion the reaction, the mixture was poured into ice-cold water and the precipitated product (**3**) was recrystallized from ethanol. Yield: 76%; Yellowish crystals; m.p.: 255–257 °C (Lit. 253–255 °C [28]); R_f: 0.32; FTIR (ATR, υ/cm^{-1}): 3075 (Csp^2-H), 1697 (C═O), 1601 (C═N), 1534 (C═C aromatic); ^{1}H NMR (300 MHz, DMSO d_6): δ 8.71 (s, 1H, H-4), 7.62 (d, *J* = 6.9 Hz, 1H, Ar—H), 7.59 (dd, *J* = 7.7, 1.2 Hz, 1H, Ar—H); 7.43 (s, 1H, thiazole) 7.31–7.26 (m, 2H, Ar—H); 3.95 (q, *J* = 7.2 2H, CH_2), 1.31 (t, *J* = 7.2, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO d_6): δ 160.4 (C═O, lactone), 159.1 (C═N, thiazole), 152.3, 143.6, 139.3, 139.0, 131.7, 128.5, 128.1, 123.7, 121.7, 117.8, 59.2, 15.2; LC-MS (*m*/*z*): (M)$^+$, 274; Elemental analysis Found (%): C, 61.57; H, 4.03; N, 5.14; S, 11.71; Calc. for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12; S, 11.73.

2.3. X-ray Crystal Structure Determination

The X-ray measurements on single crystals of **2** were carried out on an Agilent Duo diffractometer using CuK$_\alpha$ radiation (λ = 0.71073 Å) with data collection, reduction and absorption corrections controlled using CrysAlisPro [31] with data collected at 100(2) K. Data were reduced and multi-scan absorption corrections were applied using CrysAlisPro. Data for **3** were obtained on a Bruker SMART APEX diffractometer using MoK$_\alpha$ radiation (λ = 1.5418 Å) at 130(2) K. The data collection was controlled by SMART with cell refinement and data reduction performed using SAINT, and multi-scan absorption corrections were applied using SADABS [32]. The structures were solved by direct methods with SHELXS-97 [33] and refined using full-matrix least-squares procedures (SHELXL-2014/7 [33] and Titan2000 [34]). All non hydrogen atoms were refined anisotropically and all hydrogen atoms bound to carbon were placed in the calculated positions, and their thermal parameters were refined isotropically with U_{eq} = 1.2–1.5 U_{eq}(C). All molecular plots and packing diagrams were drawn using Mercury [35] and additional metrical data were calculated using PLATON [36]. Details of the X-ray measurements and crystal data for all of the complexes are given in Table 1. CCDC 1588720 and CCDC-1511416 contain the supplementary crystallographic data for 2 and 3. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data

Table 1
Crystal data and structure refinement for **2** and **3**.

	2	**3**
Empirical formula	$C_{13}H_9NO_2S$	$C_{14}H_{11}NO_3S$
Formula weight	243.27	273.30
Temperature K	100(2)	100(2)
Wavelength Å	1.54184	0.71073
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	P -1
Unit cell dimensions		
a Å	4.7558(1)	7.2629(7)
b Å	14.2599(2)	9.1428(9)
c Å	15.6511(2)	9.6560(10)
α °	90	93.829(2)
β °	95.253(1)	105.896(2)
γ °	90	95.165(2)
Volume Å^3	1056.96(3)	611.36(11)
Z	4	2
Density (calculated) Mg/m^3	1.529	1.485
Absorption coefficient mm^{-1}	2.621	0.267
F(000)	504	284
Crystal size mm^3	0.46 × 0.22 × 0.17	0.44 × 0.21 × 0.09
Theta range for data collection °	4.202 to 74.244	2.203 to 27.875
Index ranges	−5 ≤h ≤5, −17 ≤k ≤17, −19 ≤l ≤18	−9 ≤h ≤9, −12 ≤k ≤12, −11 ≤l ≤12
Reflections collected	9914	5804
Independent reflections	2110 [R(int) = 0.0226]	2896 [R(int) = 0.0210]
Completeness to theta = 67.684° (25.242°)	99.4%	100%
Absorption correction	Multi-scan	
Max. and min. transmission	1.00000 and 0.67706	0.9763 and 0.8915
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2110/18/154	2896/0/172
Goodness-of-fit on F^2	1.081	1.047
Final R indices [*I* > 2sigma(I)]	R1 = 0.0418, wR2 = 0.1180	R1 = 0.0453, w*R*2 = 0.1153
R indices (all data)	R1 = 0.0423, wR2 = 0.1184	R1 = 0.0554, wR2 = 0.1227
Largest diff. peak and hole	1.048 and − 0.501 e·Å^{-3}	0.445 and − 0.240 e·Å^{-}
CCDC reference	CCDC 1588720	CCDC 1511416