Synthesis and Structure of Novel 3,4-Annelated Coumarin Derivatives

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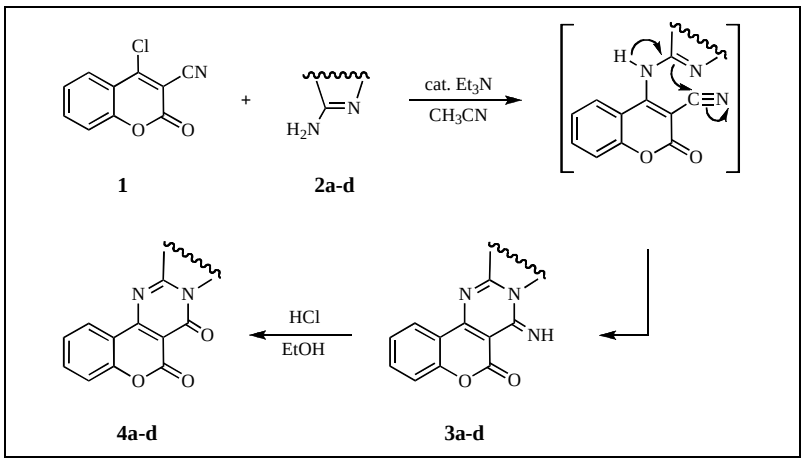
Received February 4, 2007



Condensation of 4-chloro-2-oxo-2*H*-chromene-3-carbonitrile (**1**) with heteroarylamines **2a**-**d** in acetonitrile containing a catalytic amount of triethylamine followed by spontaneous intramolecular cyclization gave the novel coumarin derivatives **3a-d**, respectively. These compounds underwent acid hydrolysis giving the corresponding oxoderivatives **4a-d**. The structural assignments of the synthesized compounds were based on elemental, IR, ^{1}H and ^{13}C NMR analyses.

J. Heterocyclic Chem., **45**, 295 (2008).

INTRODUCTION

The synthesis of coumarin (2-oxo-2*H*-chromene) derivatives has attracted considerable attention of organic and medicinal chemists as these are widely used as fragrances, pharmaceuticals and agrochemicals [1]. Coumarins have a variety of bioactivities including anticoagulant, estrogenic, dermal photosensitizing, antimicrobial, vasodilator, molluscacidal, antihelminitic, sedative and hypnotic, analgesic and hypothermic activity [1,2]. Furthermore, coumarin and its derivatives cause significant changes in the regulation of immune responses, cell growth and differentiation in sensitive tumor cells [1]. Bearing in mind the wide range of bioactivities, we thought it worthwhile to synthesize new coumarin derivatives. As a continuation of our previous work [3], we report on the synthesis and characterization of new derivatives containing the coumarin moiety.

RESULTS AND DISCUSSION

Several new coumarin derivatives (Figure 1) were prepared in the following one-pot reaction manner [4]: an acetonitrile solution of 4-chloro-2-oxo-2*H*-chromene-3-carbonitrile (**1**) and a heteroarylamine (4-methyl-benzothiazol-2-ylamine (**2a**), 4-methoxy-benzothiazol-2-ylamine (**2b**), 4,5-dimethyl-thiazol-2-ylamine (**2c**), 3-methyl-pyridin-2-ylamine (**2d**), respectively, 1:1 mole ratio of starting materials) was reacted at reflux temperature in the presence of triethylamine as a base catalyst, leading to the formation of an intermediate product. No efforts were made to isolate that intermediate, but instead, it was cyclized *in situ* into the desired heteroaromatic products **3a-d**, presumably by means of a mechanism involving a proton transfer from amino to cyano group with the synchronous building of a pyrimidine ring. The obtained polycyclic imines **3a-d** were subjected to acid hydrolysis to afford the corresponding oxoderivatives **4a-d**. The synthetic approach is illustrated in Scheme 1.

Product **3a** was synthesized starting from 4-methyl-benzothiazol-2-ylamine and obtained as a yellow crystalline substance. The IR spectra showed strong band at 1622 cm^{-1} corresponding to absorption of the C=N bond. The IR absorptions due to the imino and α-pyrone carbonyl functions appeared at 3280 cm^{-1} and 1705 cm^{-1}, respectively. In ^{1}H NMR spectrum aromatic protons appeared as a multiplet between 8.15 and 7.23 ppm.

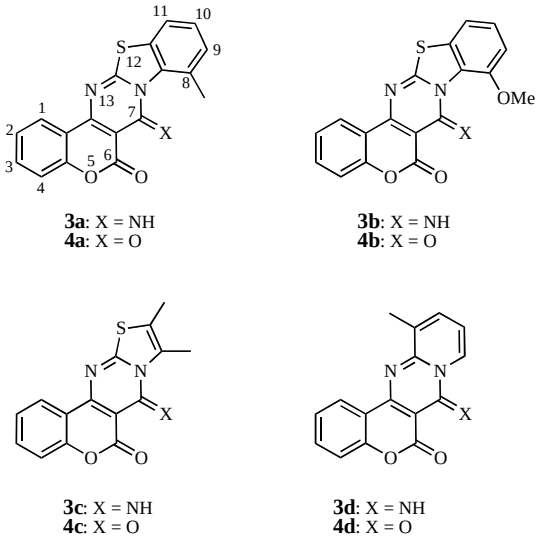
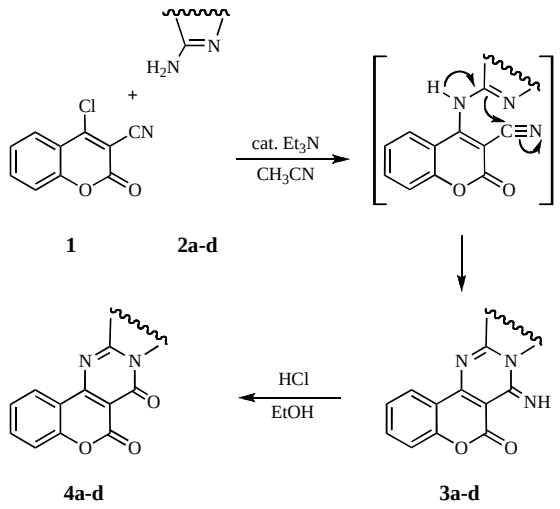


Figure 1. Structures of the new synthesized 3,4-annelated coumarin derivatives

Singlet at δ 9.72 ppm corresponding to the proton of the pyrimidine ring NH group. The ^{13}C NMR showed 18 resonances, one conjugated lactone carbonyl (δ 162.4 ppm), additional six signals (C-12a, C-4a, C-7, C-13a, C-7b, C-11a) corresponding to quaternary heteroatom bonded C-sp^2 with chemical shifts at δ 158.7-135.6 ppm, three signals corresponding to quaternary C-sp^2 (C-8, C-6a, C-13b), seven aromatic methyne shifts (C-1, C-2, C-3, C-4, C-9, C-10, C-11) and CH_3 carbon atom shift at δ 20.1 ppm. The compounds **3b-d** were prepared by analogous synthetic method and characterized by elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy.

An additional proof of **3a-d** was obtained by chemical transformation of the imino function of the pyrimidine ring into carbonyl group. As expected, this conversion was smoothly achieved with boiling 15%-ethanolic solution of hydrochloric acid leading to corresponding oxoderivatives **4a-d.** The hydrolysis was confirmed by elemental and spectral analyses. The IR spectra of compounds **4a-d** revealed a strong band in the 1767-1755 cm^{-1} region due to the absorption of carbonyl group of the pyrimidone ring, whereas the carbonyl group constituting a part of the α-pyrone ring revealed band at 1715-1702 cm^{-1}. The disappearance of ν N-H bands in the IR spectra is compatible with their assigned structures. As expected, the ^1H NMR spectra showed a loss of NH proton.



Scheme 1. General reaction sequence leading to the new heterocyclic 3,4-annelated coumarin derivatives

All structures were corroborated by comparison of their spectral data to those published in the literature for related systems [3, 5-8].

This paper describes the synthesis, characterization and chemical transformation of 3,4-annelated coumarin derivatives, which could possess interesting physiological properties. Moreover, this one-pot reaction can successfully be employed in the preparation of new polyheterocyclic coumarin derivatives having useful biological activity.

EXPERIMENTAL

General Methods. Melting points were determined on a Kofler hot-plate apparatus and are uncorrected. Microanalysis of carbon, hydrogen, nitrogen and sulfur were carried out with a Carlo Erba 1106 microanalyser. The IR measurements were carried out with a Perkin-Elmer 457 grating FT instrument in KBr tablets. The NMR spectra were recorded on a Varian Gemini 200 (^1H at 200 MHz, ^{13}C at 50 MHz) spectrometer, using DMSO-d_6 as the solvent. Chemical shifts are expressed in δ (ppm) using TMS (tetramethylsilane) as an internal standard. For TLC, silica gel plates (Kiesel 60 F_{254}, Merck) were used.

Starting Material. 4-Hydroxy-2-oxo-2*H*-chromene-3-carbonitrile was prepared following the method of Anschutz [9]. Starting compound **(1)** was prepared from 4-hydroxy-2-oxo-2*H*-chromene-3-carbonitrile according to the method of Chechi *et al.* [4], modified by Kaljaj *et al.* [6] that allowed obtaining the compound in higher yield (96%) and shorter time (less then 1 hour), instead of 35-40% within 7 h reported for the original method. The preparation was carried out in the following manner: 1.85 mL of *N*,*N*-dimethylformamide (DMF) was cooled to 10°C using an ice bath. Under stirring, 4 g of $POCl_3$ was added dropwise, and the prepared mixture was stirred for 15 min. Then, the ice bath was removed and the reaction proceeded at room temperature for additional 15 min. Finally, the solution of 4-hydroxy-2-oxo-2*H*-chromene-3-carbonitrile (4.67 g) in DMF (12.5 mL) was added dropwise. After 15 minutes of stirring, the reaction was stopped by adding cold water (15 mL). The precipitate solid was collected by filtration and washed with a saturated sodium-bicarbonate solution and with water. Recrystallization from glacial acetic acid yielded yellow crystals of **1** (4.8 g) in 96% yield, mp 199-200°C. Finally, all other chemicals were commercially available and used as received, except that the solvents were purified by distillation.

General Procedure for the Synthesis of 3a-d. A solution of **1** (2.0 g, 10 mmol) and the appropriate heteroarylamine (4-methyl-benzothiazol-2-ylamine (**2a**), 4-methoxy-benzothiazol-2-ylamine (**2b**), 4,5-dimethyl-thiazol-2-ylamine (**2c**), 3-methyl-pyridin-2-ylamine (**2d**), 10 mmol) in acetonitrile (30 mL) in the presence of catalytic amounts of triethylamine (2 mL) was refluxed for 1-2 hours. After cooling, the precipitate solid was collected by filtration and washed with acetonitrile. Recrystallization from the stated solvents yielded compound **3a-d**, respectively. The purity of the synthesized compounds was checked by TLC.

7-Imino-8-methyl-7*H*-5-oxa-12-thia-7a,13-diazaideno[1,2-*b*]-phenanthren-6-one (3a). Yellow crystals (from CH_3CN), yield 50% (1.83 g), mp 238-240°C; IR ν (KBr, cm^{-1}): 3280 (N-H), 3105 (Ar-H), 2944 (C-H), 1705 (C=O), 1622 (C=N), 1611 (C=C), 1596, 765; ^{1}H NMR (DMSO-d_6): δ = 9.72 (brs, 1H, N-H), 8.15-7.23 (m, 7H, arom.), 2.82 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 162.4 (C-6), 158.7 (C-12a), 153.3 (C-4a), 150.9 (C-7), 148.8 (C-13a), 142.1 (C-7b), 135.6 (C-11a), 133.9 (C-8), 130.2, 127.2, 126.7, 125.5, 122.4, 121.8, 119.4 (C-6a), 117.9, 96.0 (C-13b), 20.1 (CH_3) ppm. *Anal*. Calcd. for $C_{18}H_{11}N_3O_2S$ (333.37): C, 64.85; H, 3.33; N, 12.60; S, 9.62. Found: C, 64.90; H, 3.56; N, 12.44; S, 9.39.

7-Imino-8-methoxy-7*H*-5-oxa-12-thia-7a,13-diazaindeno-[1,2-*b*]phenanthren-6-one (3b). Yellow crystals (from DMF), yield 33% (1.25 g), mp 260-262°C; IR ν (KBr, cm^{-1}): 3284 (N-H), 3089 (Ar-H), 2955 (C-H), 1720 (C=O), 1621 (C=N), 1609 (C=C), 752; ^{1}H NMR (DMSO-d_6): δ = 9.95 (brs, 1H, N-H), 8.06-6.95 (m, 7H, arom.), 3.82 (s, 3H, CH_3O) ppm; ^{13}C NMR (DMSO-d_6): δ = 161.8 (C-6), 160.3 (C-12a), 155.6 (C-8), 152.8 (C-4a), 151.3 (C-7), 149.8 (C-13a), 140.8 (C-7b), 134.0 (C-11a), 129.6, 123.8, 121.8, 119.0, 118.3, 117.6 (C-6a), 117.0, 94.5 (C-13b), 55.2 (OCH_3) ppm. *Anal*. Calcd. for $C_{18}H_{11}N_3O_3S$ (349.37): C, 61.88; H, 3.17; N, 12.03; S, 9.18. Found: C, 61.96; H, 3.30; N, 12.05; S, 9.12.

7-Imino-8,9-dimethyl-7*H*-5-oxa-10-thia-7a,11-diazacyclo-penta[*b*]phenanthren-6-one (3c). Yellow crystals (from DMF), yield 55% (1.8 g), mp 240-242°C; IR ν (KBr, cm^{-1}): 3280 (N-H), 3095 (Ar-H), 2945 (C-H), 1712 (C=O), 1625 (C=N), 1605 (C=C), 759; ^{1}H NMR (DMSO-d_6): δ = 9.84 (brs, 1H, N-H), 8.28 (d, 1H, H-1), 7.72 (t, 1H, H-3), 7.45 (t, 1H, H-2), 7.32 (d, 1H, H-4), 2.61 (s, 6H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 162.1 (C-6), 159.2 (C-10a), 151.5 (C-4a), 149.8 (C-7), 148.5 (C-11a), 133.6, 128.8, 126.7, 126.1, 123.2, 120.7 (C-6a), 119.5, 96.3 (C-11b), 12.6 (CH_3), 12.4 (CH_3) ppm. *Anal*. Calcd. for $C_{15}H_{11}N_3O_2S$ (297.34): C, 60.59; H, 3.73; N, 14.13; S, 10.78. Found: C, 60.70; H, 3.72; N, 14.37; S, 10.52.

7-Imino-11-methyl-7*H*-5-oxa-7a,12-diazabenzo[*a*]anthra-cen-6-one (3d). Intensively yellow needles (from DMF), yield 55% (1.7 g), mp 270-271°C; IR ν (KBr, cm^{-1}): 3277 (N-H), 3098 (Ar-H), 2948 (C-H), 1705 (C=O), 1632 (C=N), 1602 (C=C), 756; ^{1}H NMR (DMSO-d_6): δ = 9.58 (brs, 1H, N-H), 8.12 (d, 1H, H-1), 7.95 (t, 1H, H-9), 7.72-7.65 (m, 2H, H-3, H-10), 7.57 (d, 1H, H-8), 7.44 (d, 1H, H-4), 7.36 (t, 1H, H-2), 2.72 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 161.5 (C-6), 155.4 (C-11a), 152.4 (C-4a), 151.2 (C-12a), 149.7 (C-7), 130.1, 129.3, 125.6, 125.1, 122.5, 118.2 (C-6a), 115.7, 97.3 (C-12b), 17.8 (CH_3) ppm. *Anal*. Calcd. for $C_{16}H_{11}N_3O_2$ (277.28): C, 69.31; H, 4.00; N, 15.15. Found: C, 69.35; H, 4.18; N, 14.97.

General Procedure for the Preparation of 4a-d. Each of compounds **3a-d** (1 g) was heated under reflux (1-2 hours) with 15% hydrochloric acid (20 mL) in ethanol (50 mL). After cooling, a precipitate was formed which was collected by filtration and washed with a saturated sodium bicarbonate solution, and then with water. Recrystallization from the stated solvents yielded compounds **4a-d**, respectively.

8-Methyl-5-oxa-12-thia-7a,13-diaza-indeno[1,2-*b*]phenan-threne-6,7-dione (4a). Yellow crystals (from EtOH), yield 75% (0.75 g), mp 225-228°C; IR ν (KBr, cm^{-1}): 3106 (Ar-H), 2950 (C-H), 1758 (C=O), 1711 (C=O), 1628 (C=N), 1607 (C=C), 761; ^{1}H NMR (DMSO-d_6): δ = 8.02-7.09 (m, 7H, arom.), 2.70 (s, 3H, CH_3) ppm. *Anal*. Calcd. for $C_{18}H_{10}N_2O_3S$ (334.36): C, 64.66; H, 3.01; N, 8.38; S, 9.59. Found: C, 64.52; H, 2.85; N, 8.54; S, 9.50.

8-Methoxy-5-oxa-12-thia-7a,13-diaza-indeno[1,2-*b*]phenan-threne-6,7-dione (4b). Yellow crystals (from CH_3CN), yield 45% (0.45 g), mp 278-280°C; IR ν (KBr, cm^{-1}): 3096 (Ar-H), 2940 (C-H), 1760 (C=O), 1715 (C=O), 1621 (C=N), 1611 (C=C), 755; ^{1}H NMR (DMSO-d_6): δ = 8.15-7.08 (m, 7H, arom.), 3.82 (s, 3H, CH_3O) ppm. *Anal*. Calcd. for $C_{18}H_{10}N_2O_4S$ (350.36): C, 61.71; H, 2.88; N, 8.00; S, 9.15. Found: C, 61.55; H, 3.07; N, 8.07; S, 8.93.

8,9-Dimethyl-5-oxa-10-thia-7a,11-diazacyclopenta[*b*]phen-anthrene-6,7-dione (4c). Yellow crystals (from DMF), yield 72% (0.72 g), mp 336-338°C; IR ν (KBr, cm^{-1}): 3087 (Ar-H), 2946 (C-H), 2930, 1755 (C=O), 1702 (C=O), 1606 (C=C), 761; ^{1}H NMR (DMSO-d_6): δ = 8.15 (d, 1H, H-1), 7.79 (t, 1H, H-3), 7.52 (t, 1H, H-2), 7.28 (d, 1H, H-4), 2.67 (s, 6H, CH_3) ppm. *Anal*. Calcd. for $C_{15}H_{10}N_2O_3S$ (298.32): C, 60.39; H, 3.38; N, 9.39; S, 10.75. Found: C, 60.26; H, 3.43; N, 9.32; S, 10.69.

11-Methyl-5-oxa-7a,12-diaza-benzo[*a*]anthracene-6,7-di-one (4d). Yellow crystals (from EtOH), yield 80% (0.80 g), mp 290-291°C; IR ν (KBr, cm^{-1}): 3102 (Ar-H), 2945 (C-H), 1767 (C=O), 1711 (C=O), 1630 (C=N), 1599 (C=C), 760; ^{1}H NMR (DMSO-d_6): δ = 8.34 (d, 1H, H-1), 8.07 (t, 1H, H-9), 7.80-7.48 (m, 3H, H-3, H-10, H-8), 7.33 (d, 1H, H-4), 7.18 (t, 1H, H-2), 2.95 (s, 3H, CH_3) ppm. *Anal*. Calcd. for $C_{16}H_{10}N_2O_3$ (278.27): C, 69.06; H, 3.62; N, 10.07. Found: C, 69.23; H, 3.49; N, 10.30.

Acknowledgement. The authors acknowledge the Ministry of Science and Environmental Protection of Serbia for financial support.

REFERENCES

[1] *Coumarins–Biology, Applications and Mode of Action*; O'Kennedy, R.; Thornes, R. D., Eds.; John Wiley & Sons: Chichester, UK, 1997.

[2] Soine, T. O. *J. Pharm. Sci*. **1964**, *53*, 231.

[3] Radulovic, N.; Stojanovic, G.; Vukicevic, R.; Dekic, V.; Dekic, B.; Palic, R. *Monatsh. Chem*. **2006**, *137*, 1477.

[4] Chechi, S.; Vettori, L. P.; Mambagiotti, M. *Gazz. Chim. Ital*. **1968**, *98*, 1448.

[5] Kaljaj, L.; Kaljaj, V.; Dekic, S.; Sokolic, L.; Palic, R. *J. Serb. Chem. Soc*. **1996**, *61*, 419.

[6] Kaljaj, V.; Trkovnik, M.; Stefanovic-Kaljaj, L. *J. Serb. Chem. Soc*. **1987**, *52*, 183.

[7] Stefanovic-Kaljaj, L.; Kaljaj, V.; Trkovnik, M.; Mladenovic, S. *J. Serb. Chem. Soc*. **1989**, *54*, 169.

[8] Govori, S.; Kaljaj, V.; Rapic, V.; Kaljaj, L.; Dakovic, S. *Heterocycl. Commun*. **2002**, *8*, 129.

[9] Anschutz, R. *Ber. Dtsch. Chem. Ges*. **1903**, *36*, 463.