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Cascade Sulfa-Michael/Aldol Reaction of (Het)Arylmethylidenefuran-2(3*H*)-Ones with 1,4-Dithiane-2,5-Diol †

Ekaterina M. Arzyamova *, Olga A. Mazhukina and Alevtina Yu. Yegorova

Institute of Chemistry, N.G. Chernyshevsky Saratov National Research State University, 83 Ulitsa Astrakhanskaya, 410012 Saratov, Russia; mazhukinaoa@gmail.com (O.A.M.); yegorovaay@mail.ru (A.Y.Y.)

* Correspondence: katerina285@yandex.ru

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Abstract

A series of hybrid heterocyclic spiro compounds containing a tetrahydrothiophene moiety were prepared by the cascade sulfa-Michael/aldol reaction of (*E*)-3-[(2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl]-4*H*-chromen-4-ones with 1,4-dithiane-2,5-diol under mild conditions. The composition and structure of 3-(3-aryl-9-hydroxy-1-oxo-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4*H*-chromen-4-ones were characterized by elemental analysis, IR, and complex NMR spectroscopy.

Keywords: hybrid structures; 1,4-dithiane-2,5-diol; (*E*)-3-[(2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl]-4*H*-chromen-4-ones; tetrahydrothiophene moiety; spectroscopy

1. Introduction

Currently, increasing attention is being paid to the construction of polyheterocyclic derivatives of spirotetrahydrothiophene. This is due to the fact that tetrahydrothiophenes are unique sulfur-containing heterocycles that attract particular attention due to their special place as building blocks in natural compounds, pharmaceutical agents, and materials [1,2]. The simplest, most effective and classical method for obtaining systems with this structural fragment is the cascade sulfur-Michael/aldol reaction between a sulfur-containing bisnucleophilic reagent, 1,4-dithiane-2,5-diol, and electron-deficient alkenes [3].

Thus, in this work, the possibility of modifying (*E*)-3-[(2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl]-4*H*-chromen-4-ones with 1,4-dithiane-2,5-diol at the exocyclic multiple C=C bond with the formation of new spiro compounds with one spiro unit, including a tetrahydrothiophene fragment, was studied.

2. Materials and Methods

2.1. Physical Measurements

Elemental analysis was done on an Elementar Vario MICRO cube CHNS analyzer. The FTIR spectrum was recorded using a FSM-1201 spectrometer with a KBr with a spectral resolution of 4 cm^{-1} pellet (wavenumber range of 4000–400 cm^{-1}).

^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), as well as ^{1}H-^{13}C heteronuclear correlation HSQC and HMBC spectra were recorded on a Varian (Agilent) 400 spectrometer at 20–

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25 °C, with tetramethylsilane (TMS) as the internal standard. TLC analysis was conducted on Alugram® Sil G UV-254 plates, eluent—acetone: ethyl acetate: hexane (1:1:3); developer—UV radiation. Melting points were measured on a Stuart™ SMP10 melting point apparatus in open capillaries.

2.2. Synthesis and Characterization of Compounds **3a–d**

A suspension containing 1.5 mmol of 1,4-dithiane-2.5-diol (**2**) and 2 mmol of the corresponding (*E*)-3-[(2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl]-4*H*-chromen-4-one (**1a–d**) in 20 mL of acetonitrile was stirred at room temperature for 9 to 12 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure on a rotary evaporator, and the resulting residue was washed with EtOAc/hexane (1:1) and dried.

*3-(9-Hydroxy-1-oxo-3-phenyl-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4H-chromen-4-one (***3a***)*

Light yellow crystals, yield 0.41 g (69%), mp 191–192 °C; FTIR (KBr) ν, cm^{-1}: 3493 (OH), 1781 (O–C=O), 1637 (C=O), 1608 (C=C); ^{1}H NMR (400 MHz, acetone-d_6): δ 3.16 (dd, *J* = 10.5 Hz, *J* = 5.9 Hz, 1H, CH_2), 3.29 (dd, *J* = 10.5 Hz, *J* = 5.9 Hz, 1H, CH_2), 4.76 (dt, *J* = 10.5 Hz, *J* = 5.5 Hz, 1H, CH–OH), 5.10 (s, 1H, CH–S), 5.19 (d, *J* = 7.9 Hz, 1H, OH), 6.12 (s, 1H, C–$H_{Furanone}$), 7.32–7.43 (m, 4H, Ar–H), 7.50–7.59 (m, 3H, Ar–H), 7.73 (t, J = 8.7 Hz, 1H, Ar–H), 8.01 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.55 (s, 1H, C–$H_{Chromone}$); ^{13}C NMR (100 MHz, acetone-d_6): δ 34.9 (CH_2), 43.6 (CH–S), 64.5, 81.7 (CH–OH), 100.3 (C–$H_{Furanone}$), 118.1, 121.6, 122.9, 124.8, 125.4, 125.5, 128.5, 128.6, 129.6, 134.0, 153.3, 155.7, 156.1, 156.8, 157.9 (C–$H_{Chromone}$), 175.9 (C=O), 176.8 (O–C=O). Anal. Calcd. for $C_{22}H_{16}O_5S$: C: 67.33%; H: 4.11%; S: 8.17%; Found: C: 67.47%; H: 4.24%; S: 8.03%.

*3-(9-Hydroxy-1-oxo-3-(p-tolyl)-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4H-chromen-4-one (***3b***)*

Light yellow crystals, yield 0.40 g (67%), mp 202–203 °C; FTIR (KBr) ν, cm^{-1}: 3481 (OH), 1769 (O–C=O), 1644 (C=O), 1612 (C=C); ^{1}H NMR (400 MHz, acetone-d_6): δ 2.37 (s, 3H, CH_3), 3.18 (dd, *J* = 10.5 Hz, *J* = 5.9 Hz, 1H, CH_2), 3.33 (dd, *J* = 10.5 Hz, *J* = 5.9 Hz, 1H, CH_2), 4.71 (dt, *J* = 10.8 Hz, *J* = 5.8 Hz, 1H, CH–OH), 5.11 (s, 1H, CH–S), 5.17 (d, *J* = 8.0 Hz, 1H, OH), 6.15 (s, 1H, C–$H_{Furanone}$), 7.31–7.45 (m, 3H, Ar–H), 7.54–7.58 (m, 3H, Ar–H), 7.74 (t, *J* = 8.6 Hz, 1H, Ar–H), 8.00 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.59 (s, 1H, C–$H_{Chromone}$); ^{13}C NMR (100 MHz, acetone-d_6): δ 21.5 (CH_3), 34.9 (CH_2), 43.5 (CH–S), 64.6, 81.5 (CH–OH), 100.3 (C–$H_{Furanone}$), 118.2, 121.4, 122.9, 124.9, 124.9, 125.9, 127.9, 128.4, 129.3, 134.1, 153.7, 155.6, 156.3, 156.8, 157.9 (C–$H_{Chromone}$), 175.8 (C=O), 176.8 (O–C=O). Anal. Calcd. for $C_{23}H_{18}O_5S$: C: 67.97%; H: 4.46%; S: 7.89%; Found: C: 67.82%; H: 4.59%; S: 7.70%.

*3-(3-(4-Chlorophenyl)-9-hydroxy-1-oxo-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4H-chromen-4-one (***3c***)*

Light yellow crystals, yield 0.44 g (68%), mp 225–226 °C; FTIR (KBr) ν, cm^{-1}: 3489 (OH), 1785 (O–C=O), 1647 (C=O), 1601 (C=C); ^{1}H NMR (400 MHz, acetone-d_6): δ 3.15 (dd, *J* = 10.5 Hz, *J* = 5.9 Hz, 1H, CH_2), 3.29 (dd, *J* = 10.5 Hz, *J* = 5.9 Hz, 1H, CH_2), 4.80 (dt, *J* = 10.7 Hz, *J* = 5.7 Hz, 1H, CH–OH), 5.12 (s, 1H, CH–S), 5.21 (d, *J* = 7.9 Hz, 1H, OH), 6.15 (s, 1H, C–$H_{Furanone}$), 7.34–7.46 (m, 3H, Ar–H), 7.52–7.63 (m, 3H, Ar–H), 7.75 (t, *J* = 8.6 Hz, 1H, Ar–H), 8.10 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.57 (s, 1H, C–$H_{Chromone}$); ^{13}C NMR (100 MHz, acetone-d_6): δ 34.9 (CH_2), 43.7 (CH–S), 64.6, 81.8 (CH–OH), 100.3 (C–$H_{Furanone}$), 118.4, 121.5, 123.1, 124.7, 125.4, 125.7, 128.4, 128.7, 129.3, 134.2, 153.2, 155.9, 156.2, 156.9, 158.0 (C–$H_{Chromone}$), 175.9 (C=O), 176.9 (O–C=O). Anal. Calcd. for $C_{22}H_{15}ClO_5S$: C: 61.90%; H: 3.54%; S: 7.51%; Cl: 8.31%; Found: C: 61.85%; H: 3.28%; S: 7.60%; Cl: 8.42%.

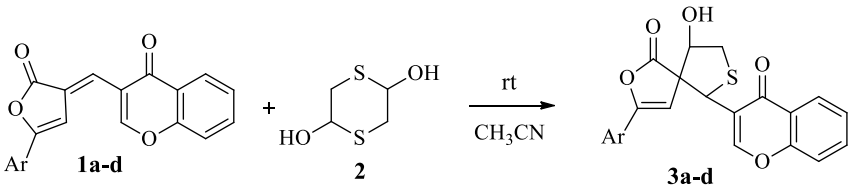
*3-(9-Hydroxy-3-(4-methoxyphenyl)-1-oxo-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4H-chromen-4-one (***3d***)*

Light yellow crystals, yield 0.40 g (64%), mp 184–185 °C; FTIR (KBr) ν, cm^{-1}: 3470 (OH), 1742 (O–C=O), 1631 (C=O), 1614 (C=C); ^{1}H NMR (400 MHz, acetone-d_6): δ 3.88 (s, 3H, OCH_3), 3.14 (dd, *J* = 10.5 Hz, *J* = 5.9 Hz, 1H, CH_2), 3.40 (dd, *J* = 10.5 Hz, *J* = 5.9 Hz, 1H,

CH_2), 4.84 (dt, *J* = 10.8 Hz, *J* = 5.8 Hz, 1H, CH–OH), 5.09 (s, 1H, CH–S), 5.23 (d, *J* = 8.0 Hz, 1H, OH), 6.19 (s, 1H, C–$H_{Furanone}$), 7.29–7.46 (m, 3H, Ar–H), 7.57–7.64 (m, 3H, Ar–H), 7.77 (t, *J* = 8.6 Hz, 1H, Ar–H), 8.02 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.57 (s, 1H, C–$H_{Chromone}$); ^{13}C NMR (100 MHz, acetone-d_6): δ 34.8 (CH_2), 43.7 (CH–S), 55.5 (OCH_3), 64.6, 81.4 (CH–OH), 100.4 (C–$H_{Furanone}$), 118.4, 121.2, 122.8, 124.9, 125.1, 125.8, 128.1, 128.5, 129.5, 134.2, 153.6, 155.8, 156.6, 156.9, 157.9 (C–$H_{Chromone}$), 175.9 (C=O), 176.7 (O–C=O). Anal. Calcd. for $C_{23}H_{18}O_6S$: C: 65.39%; H: 4.29%; S: 7.59%; Found: C: 65.48%; H: 4.15%; S: 7.70%.

3. Results and Discussion

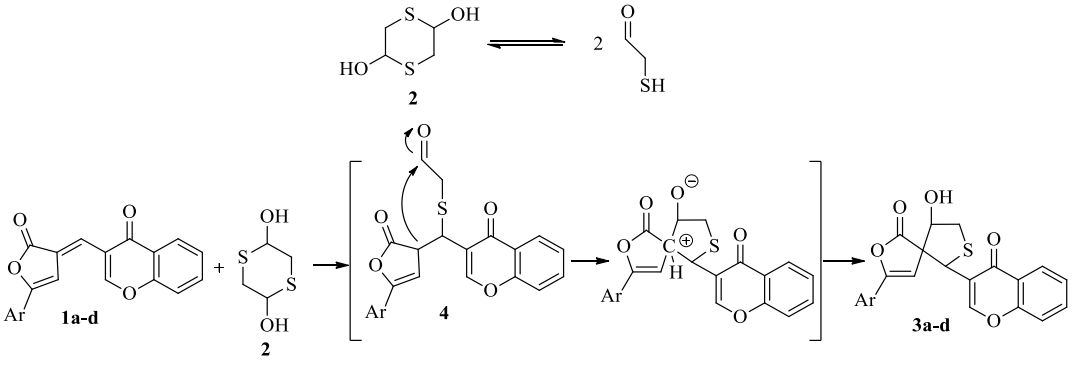
Continuing our work on the synthesis of hybrid heterocyclic systems [4,5], in this work we report the preparation of 3-(3-aryl-9-hydroxy-1-oxo-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4*H*-chromen-4-ones (**3a–d**) via a cascade sulfa-Michael/aldol reaction of (*E*)-3-[(2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl]-4*H*-chromen-4-ones (**1a–d**) with 1,4-dithiane-2,5-diol (**2**) (Scheme 1). It was found that the most optimal reaction conditions were the use of an aprotic polar solvent, acetonitrile, and the absence of any catalysts. Under these conditions, the reaction proceeded at room temperature and yielded spiro compounds in 64–69% yield.



Ar = C_6H_5 (**a**), 4-CH_3-C_6H_4 (**b**), 4-Cl-C_6H_4 (**c**), 4-OCH_3-C_6H_4 (**d**)

Scheme 1. Synthesis of hybrid spiro compounds—3-(3-aryl-9-hydroxy-1-oxo-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4*H*-chromen-4-ones.

The process under study is a cascade reaction that occurs in two stages. The first stage involves the thio-Michael addition of 2-mercaptoacetaldehyde (generated in situ from 1,4-dithiane-2,5-diol) to substrates **1a–d**, resulting in the formation of intermediates **4**. Subsequent intramolecular condensation of these intermediates leads to the construction of a five-membered tetrahydrothiophene framework and the formation of spiro compounds **3a–d** (Scheme 2).



Scheme 2. Probable scheme for the formation of hybrid spiro compounds **3a–d**.

The structure of new spiro compounds **3a–d** was established based on ^{1}H, ^{13}C, HSQC, and HMBC NMR spectroscopy. The ^{1}H NMR spectra of spiro compounds **3a–d**, recorded in acetone-d_6, contain key signals of the tetrahydrothiophene ring. The signal of the 5′-CH proton appears as a singlet at 5.09–5.12 ppm. Diastereotopic protons at 2′-CH2 resonate at

3.14–3.18 and 3.29–3.40 ppm, respectively. The doublet of triplets at 4.71–4.84 ppm corresponds to the 3′-CH proton. The hydrogen atom of the hydroxyl group in this case gives a doublet at 5.17–5.23 ppm.

The two-dimensional ^{1}H-^{13}C HMBC correlation spectra of products **3a–d** contain cross peaks indicating a correlation between the 5′-CH proton of the tetrahydrothiophene ring and the carbon atoms at the carbonyl groups of the furan-2-one and chromen-4-one fragments, respectively. In addition, the two-dimensional spectra contain cross peaks showing the correlation interaction of the 5′-CH proton with the C-2 carbon atom of the chromen-4-one fragment; this proton also correlates with the quaternary (nodal) carbon atom 4′-C. In the ^{1}H-^{13}C HMBC spectra of spiro compounds **3a–d**, correlation signals are observed that are responsible for the interaction of the 2′-CH2 protons, the hydroxyl group proton, and the 4′-C nodal carbon atom in the tetrahydrothiophene ring (Figure 1).

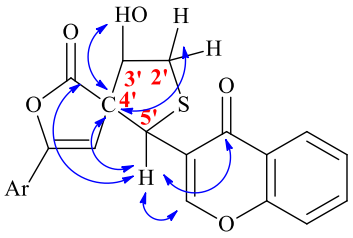


Figure 1. Key correlation interactions in ^{1}H-^{13}C HMBC spectra of 3-(3-aryl-9-hydroxy-1-oxo-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4*H*-chromen-4-ones.

4. Conclusions

A method for modification of (*E*)-3-[(2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl]-4*H*-chromen-4-ones using 1,4-dithiane-2,5-diol was found. This method opens up possibilities for targeted synthesis of hybrid spiro compounds containing a tetrahydrothiophene fragment—3-(3-aryl-9-hydroxy-1-oxo-2-oxa-7-thiaspiro[4.4]non-3-en-6-yl)-4*H*-chromen-4-ones. The structure of the obtained hybrid spiro compounds was established using IR and NMR spectroscopy (including two-dimensional correlation experiments HSQC, HMBC).

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