Tetrahedron Letters 52 (2011) 266–269

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A study of the reactions of 2-aryl-4-hydroxy-6*H*-1,3-thiazin-6-ones with chromone-3-carboxaldehydes

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ARTICLE INFO

Article history:
Received 16 August 2010
Revised 23 October 2010
Accepted 5 November 2010
Available online 11 November 2010

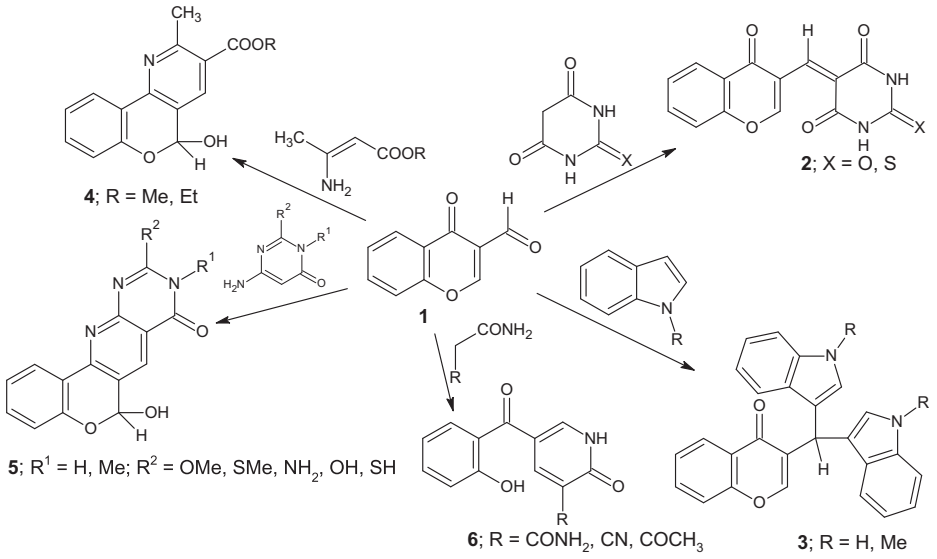
Keywords:
3-Formylchromone
1,3-Thiazine
Active methylene compounds
Pyridine

ABSTRACT

Reaction of 3-formylchromones with 2-aryl-4-hydroxy-6*H*-1,3-thiazin-6-ones in the presence of pyridine leads to formation of a mixture of novel *N*-thioaroyl-5-hydroxy-2*H*,5*H*-pyrano[3,2-*c*]chromen-2-one-3-carboxamides and 2-aryl-5-(4′-oxochromen-3′-yl)-6,7-dihydro-4*H*,5*H*-pyrano[2,3-*d*][1,3]thiazine-4,7-diones. The yields of these compounds clearly depend on the nature of the substituent on the 3-formylchromone and on the reaction conditions.

1. Introduction

According to the literature, chromone-3-carboxaldehydes react with active methylene compounds (Scheme 1), including barbituric acids.[1] The products formed are predominantly 4′-oxochromen-3′-ylmethylene compounds **2**,[2] 3-diheteroarylmethyl-4*H*-chromen-4-ones **3**,[3] substituted aryl heteroaryl ketones **6**,[4] and, less commonly, tricyclic pyridochromenes **4** or **5**.[5] No data were



Scheme 1.

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doi:10.1016/j.tetlet.2010.11.023

found describing the reaction of 3-formylchromones with pyrimidine thia-analogues, for example, 4-hydroxy-6*H*-1,3-thiazin-6-ones, as active methylene compounds.

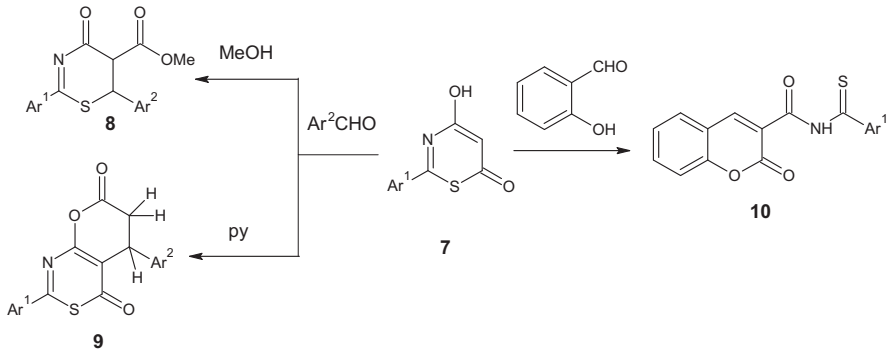
It has previously been shown that 2-aryl-4-hydroxy-6*H*-1,3-thiazin-6-ones **7** react with aromatic aldehydes in a way that differs from the respective pyrimidines. The products are methyl 2,6-diaryl-4-oxo-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylates **8**, in absolute MeOH (Scheme 2),[6] and pyranothiazines **9** in the presence of pyridine.[7] When compound **7** was reacted with salicylaldehydes, *N*-thioacylcoumarin-3-carboxamides **10** were formed.[8] The reaction of **1** and **7** has been reported previously,[9] but after a more detailed study, new results were obtained supporting an alternative reaction mechanism and a different structure for the final product.

Herein, we report the formation of a mixture of novel *N*-thioaroyl-5-hydroxy-2*H*,5*H*-pyrano[3,2-*c*]-chromen-2-one-3-carboxamides **11a–h** and 2-aryl-5-(4′-oxochromen-3′-yl)-6,7-dihydro-4*H*,5*H*-pyrano[2,3-*d*][1,3]thiazine-4,7-diones **12a–h** via reaction of 3-formylchromones **1a–h**[10] with 1,3-thiazines **7a**,**b**[11] in the presence of pyridine (Scheme 3). Common by-products are (2*E*)-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enoic acids **13a–g**. The combined yields of **11**, **12** and **13** are 55–75%. All three groups of compounds could be easily isolated from the product mixture.

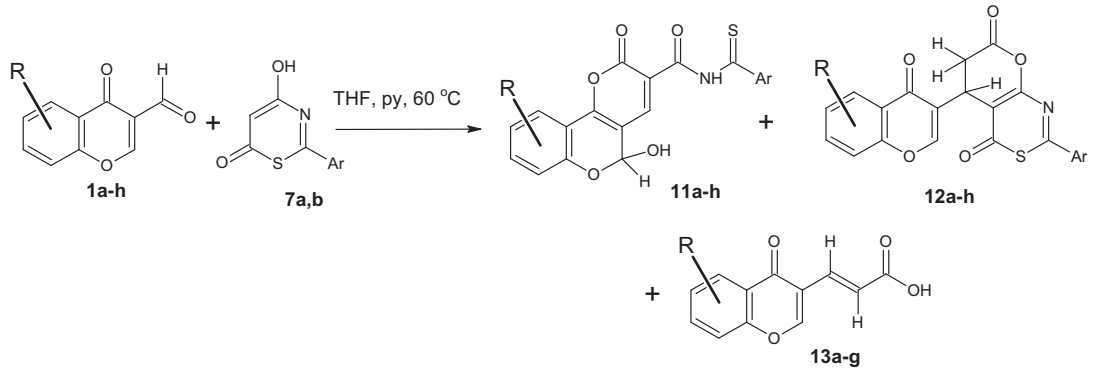
The yields of **11** and **12** depend on the nature of the substituent on the chromone **1** and on the reaction conditions. Chromones with electron-withdrawing substituents (Br, Cl, NO_2) form predominantly pyranochromenes **11**, while chromones with a strong electron-donating substituent (MeO) react with thiazines forming pyranothiazines **12**. Unsubstituted and alkylchromones produce a mixture of **11** and **12** in approximately equal yields.

The other important factor influencing the yield of pyranochromenes **11** was the solvent used. As mentioned above, compounds **11** are formed in the presence of pyridine. The use of THF or MeCN resulted in decreased yields of **11** and longer reaction times. Moreover, when thiazines **7** were reacted with 6-bromo- or 6-chlorochromones **1f,g** in glacial acetic acid, the corresponding pyranothiazines **12f,g** were obtained in ~60% yield. Alcohols could not be used as solvents due to the unstable nature of the thiazine under such conditions.

The formation of several types of products results from the presence of two electrophilic sites on the chromone: these are C-2 and CH=O. A possible mechanism for the reaction is shown in Scheme 4. Attack of the thiazine at C-2 of the chromone is followed by pyran ring-opening (1,4-addition, intermediate **A1**) with further ring closure by way of the free formyl group to produce **A2**. Addi-

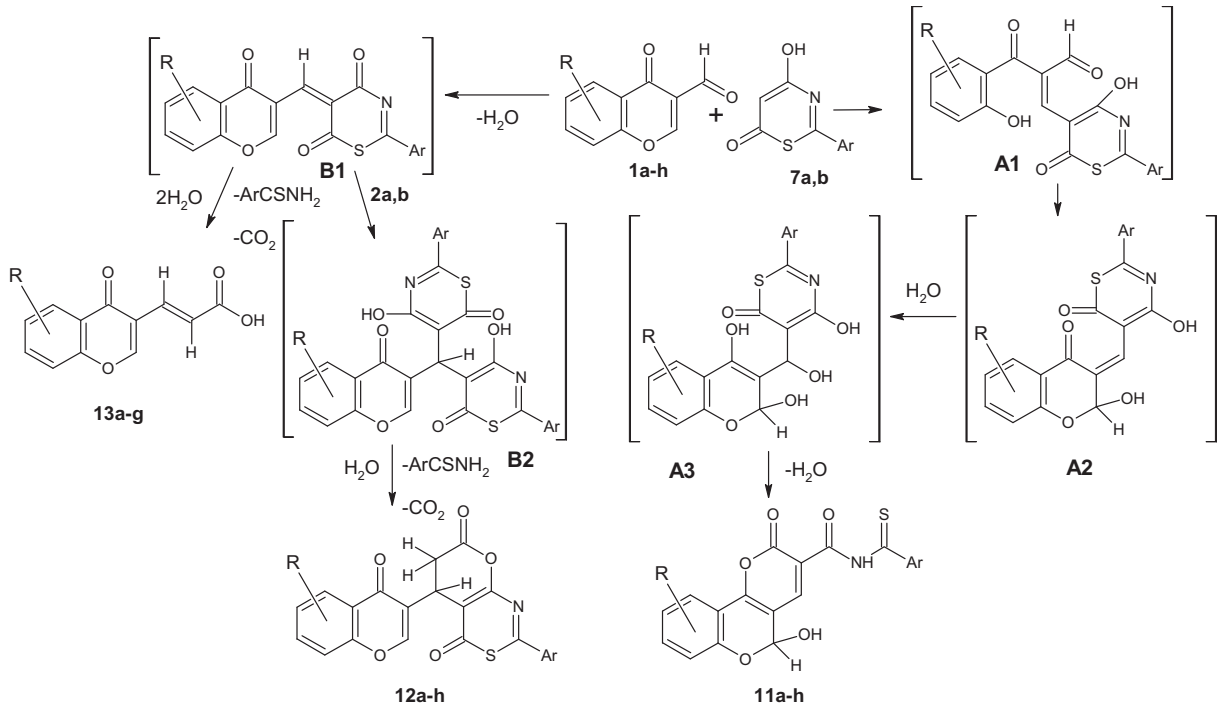


Scheme 2.



Thiazine	Ar	Chromone	R	Product (yield, %)		
7a	Ph	**1a**	7-Me	**11a** (33)	**12a** (32)	**13a** (16)
		1b	6-OMe	-	**12b** (52)	**13b** (18)
		1c	6-OH	-	**12c** (48)	**13c** (18)
		1d	6-Me	**11b** (35)	**12d** (31)	**13d** (17)
		1e	H	**11c** (40)	**12e** (29)	**13e** (14)
		1f	6-Cl	**11d** (60)	**12f** (5)	**13f** (17)
		1g	6-Br	**11e** (65)	**12g** (5)	**13g** (14)
		1h	6-NO_2	**11f** (52)	-	-
7b	4-$MeOC_6H_4$	**1d**	6-Me	**11g** (38)	**12h** (35)	**13d** (13)
		1g	6-Br	**11h** (66)	-	**13g** (14)

Scheme 3.



Scheme 4.

tion of a water molecule allows enolization of the C-4 keto group to give **A3** and subsequent cleavage of the thiazine ring form products **11**. Alternatively, attack at the aldehyde group follows a Knoevenagel type reaction leading to ylidenothiazines (intermediate **B1**), which combine with a second molecule of **7** to form bis(thiazine-5-yl)methanes **B2**. Subsequent intramolecular cyclization and hydrolysis leads to pyranothiazines **12**. The third reaction route is the direct hydrolysis of **B1** to form acids **13**.

The structures of the synthesized compounds were established by their elemental and spectral (^{1}H and ^{13}C NMR, APT, IR and mass spectral) analyses.

Pyranochromenes **11a–h** are characterized by ^{1}H NMR (DMSO-d_6) singlets for NH (12.5–12.9 ppm), CH-4 (8.6–8.9 ppm) and doublets for CH-5 (7.1–7.3 ppm, J = 6 Hz) and COH-5 (6.5–6.6 ppm, J = 6 Hz). The ^{13}C NMR spectra (DMSO-d_6) of **11a–h** revealed signals for the carbon atoms of the carbonyl and thiocarbonyl groups (159–161 and 198–202 ppm, respectively), and the pyran ring: C-2 (160–162 ppm), C-3 (110–115 ppm), C-4 (147–149 ppm) and C-5 (91–98 ppm).

Pyranothiazines **12a–h** are characterized by ^{1}H NMR (DMSO-d_6) signals due to the CH-5–CH_2-6 structural fragment of the dihydropyran ring that form the ABX spin system: doublet C-5–Hx (4.6–4.8 ppm, $J_{ax} \approx 8.4$–9.5 Hz), doublet of doublets C-6–Hb (3.2–3.5 ppm, $J_{ab} \approx 15$–17 Hz and $J_{bx} \approx 8.7$–9.5 Hz), doublet C-6–Ha (2.4–2.7 ppm, $J_{ab} \approx 15$–17 Hz). The ^{13}C NMR spectra (DMSO-d_6) of **12a-h** revealed signals for the two sp^3-hybridized carbon atoms of the pyran ring: C-6 (35–41 ppm) and C-5 (32–37 ppm), which were not present in the spectra of the original compounds.

Propenoic acids **13a–g** are characterized by ^{1}H NMR (DMSO-d_6) doublets for the olefinic protons CH-2–CH-3 with coupling constants of 15–16 Hz, which is indicative of the *trans*-configuration of this structural fragment. Additionally, a broad singlet for the carboxyl group was present at 12.3–12.5 ppm.

In conclusion, we have shown, that 2-aryl-4-hydroxy-6*H*-1,3-thiazin-6-ones react with 3-formylchromones to give mixtures of easily isolated products. The yields depended on the nature of the substituent on the chromone and the solvent used. Correct choice of these parameters meant that pyranochromenes and 5-(4-oxochromen-3-yl)pyranothiazines could be obtained in moderate yields. In addition, the reaction appears to be important for further understanding the reactivity of 3-formylchromones and 2-aryl-4-hydroxy-6*H*-1,3-thiazin-6-ones.

The starting compounds **1** and **7** were prepared according to described procedures.[10]

2. General procedure for pyranochromene-3-carboxamides 11a–h, pyranothiazine-4,7-diones 12a–h and (2*E*)-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enoic acids 13a–g

2-Aryl-4-hydroxy-6*H*-1,3-thiazin-6-one **7** (0.01 mol) was dissolved in 20 ml of THF, then 1 ml of pyridine was added. The solution was heated to 50 °C and the respective 3-formylchromone **1** was added (0.011 mol). Heating was continued at 50–60 °C for 2 h with intermittent stirring. The solvent was removed in vacuo (20 mmHg), EtOH (10 ml) was added to the residue, and the formed precipitate filtered, washed with EtOH (3 × 10 ml), and recrystallized from THF to give pyranochromenes **11** as brownish-orange powder. The ethanolic rinses were evaporated under a current of air to a volume of 5 ml. CH_2Cl_2 (20 ml) was added, the formed precipitate filtered, washed with CH_2Cl_2 (3 × 10 ml), and recrystallized from EtOH to give propenoic acids **13** as yellowish powders. The CH_2Cl_2 rinses were evaporated under a current of air to a volume of 5 ml and *n*-hexane (20 ml) was added. The formed precipitate was filtered, washed with *n*-hexane (3 × 10 ml), and recrystallized from CH_2Cl_2–C_6H_{14} (1:1) to give pyranothiazines **12** as yellow powders.

2.1. 5-Hydroxy-9-bromo-2-oxo-*N*-thiobenzoyl-2*H*,5*H*-pyrano[3,2-*c*]chromene-3-carboxamide (11e)

Yield 65%, Mp 235–237 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.59 (d, 1H, CH-5, J = 5.8 Hz), 7.14 (d, 1H, CH-7, J = 8.7 Hz), 7.45–7.81 (m,

5H, Ph), 7.71 (dd, 1H, CH-8, J = 7.6 Hz, 1.8 Hz), 7.83 (d, 1H, CH-10, J = 1.9 Hz), 8.06 (d, 1H, C-5OH, J = 6.0 Hz), 8.53 (s, 1H, CH-4), 12.75 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 91.4 (C-5), 110.8 (C-4A), 115.6 (C-9), 117.4 (C-3), 120.6 (C-7), 125.3 (C-10A), 127.4 (C–Ph), 128.6 (C–Ph), 132.4 (C–Ph), 135.4 (C-10), 136.9 (C-8), 142.3 (C–Ph), 148.5 (C-4), 153.3 (C-10B), 153.7 (C-6A), 160.3 (C-2), 160.8 (C=O), 202.3 (C=S); MS (70 eV): m/z 459 (M^+, ^{81}Br, 8%), 457 (M^+, ^{79}Br, 8%), 441 (12), 439 (12), 415 (13), 413 (13), 279 (80), 277 (78), 251 (100), 249 (100); IR (KBr) 1169, 1540, 1688, 1720, 3400 cm^{-1}; Anal. Calcd for $C_{20}H_{12}BrNO_5S$: C, 52.42; H, 2.64; N, 3.06. Found: C, 52.62; H, 2.47; N 3.16.

2.2. 5-(6′-Bromo-4′-oxo-4*H*-chromen-3′-yl)-2-phenyl-5,6-dihydro-4*H*,7*H*-pyrano[2,3-*d*][1,3]thiazine-4,7-dione (12g)

Yield 5%, Mp 246–249 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.82 (d, 1H, CH-6B, J = 16.0 Hz), 3.30 (dd, 1H, CH-6A, J = 16.1 Hz, 9.0 Hz), 4.28 (d, 1H, CH-5X, J = 9.0 Hz), 7.45–7.81 (m, 5H, Ph), 7.53 (d, 1H, CH-8′, J = 8.1 Hz), 7.78 (d, 1H, CH-7′, J = 8.2 Hz), 8.10 (d, 1H, CH-5′, J = 1.9 Hz), 8.45 (s, 1H, CH-2′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.1 (C-6), 32.9 (C-5), 103.0 (C-4A), 113.4 (C-3′), 118.8 (C-8′), 123.3 (C-6′), 126.2 (C-4A′), 127.3 (C-Ph), 129.8 (C-Ph), 130.3 (C-7′), 135.4 (C-5′), 134.3 (C-Ph), 142.4 (C-Ph), 146.1 (C-2′), 156.5 (C-8A′), 164.2 (C-4′), 165.6 (C-7), 173.3 (C-8A), 176.8 (C-4), 180.8 (C-2); MS (70 eV): m/z 483 (M^+, ^{81}Br, 100%), 481 (M^+, ^{79}Br, 90%), 455 (9), 453 (8), 427 (40), 425 (37), 324 (21), 322 (18), 172 (13), 158 (22), 121 (44); IR (KBr) 1190, 1680, 1745 cm^{-1}; Anal. Calcd for $C_{22}H_{12}BrNO_5S$: C, 54.79; H, 2.51; N, 2.90. Found: C, 55.21; H, 2.10; N 3.25.

2.3. (2*E*)-3-(6-Bromo-4-oxo-4*H*-chromen-3-yl)prop-2-enoic acid (13g)

Yield 14%, Mp 247–249 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.03 (d, 1H, CH-2, J = 16.2 Hz), 7.61 (d, 1H, CH-8′, J = 8.2 Hz), 7.73 (d, 1H, CH-7′, J = 8.1 Hz), 7.42 (d, 1H, CH-3, J = 16.0 Hz), 8.03 (d, 1H, CH-5′, J = 1.8 Hz), 8.92 (s, 1H, CH-2′), 12.5 (s, 1H, COOH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 118.2 (C-2), 121.0 (C-3′), 121.7 (C-4A′), 124.0 (C-6′), 125.0 (C-7′), 131.1 (C-8′), 135.1 (C-8A′), 148.1 (C-5′), 154.1 (C-2′), 159.8 (C-3), 163.5 (C-4′), 175.0 (C-1); IR (KBr) 1180, 1680, 2650 cm^{-1}; Anal. Calcd for $C_{12}H_7BrO_4$: C, 48.84; H, 2.39. Found: C, 49.11; H, 2.47.

2.4. General procedure for 6′-chloro- or 6′-bromopyranothiazine-4,7-diones 12f,g in glacial acetic acid

2-Phenyl-4-hydroxy-6*H*-1,3-thiazin-6-one (**7a**) (0.01 mol) was dissolved in 20 ml of glacial AcOH with heating at 50 °C, and the respective 6-chloro- or 6-bromo-3-formylchromone **1** was added (0.011 mol). Heating was continued at 50–60 °C for 2 h with intermittent stirring. The solvent was removed in vacuo (20 mmHg), EtOH (10 ml) was added to the residue, and the formed precipitate filtered, washed with EtOH (3 × 10 ml), and recrystallized from CH_2Cl_2–C_6H_{14} (1:1) to give pyranothiazines **12f,g** as yellow powders. Their physical and spectral properties were identical to those obtained by the previous method.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.023.

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