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SYNTHESIS OF SOME NEW TYPES OF 3-COUMARINYL-SUBSTITUTED PYRAZOLOPYRIMIDINES AND IMIDAZOTHIAZOLES

V. Rajeswar Rao and V. Ravinder Reddy

The treatment of 3-[3-(dimethylamino)-1-oxo-2-propenyl]chromen-2-ones with 3-amino-4-cyanopyrazole gives 7-(2-oxo-2H-chromen-3-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitriles. The reaction of 3-(2-bromoacetyl)coumarins with 2-amino-4-(methoxycarbonylmethyl)thiazole and 2-amino-4-methylthiazole gives methyl 2-(6-(2-oxo-2H-chromen-3-yl)imidazo[2,1-b]thiazol-3-yl)acetate and 3-(2-methylimidazo[2,1-b]thiazol-6-yl)-2H-chromen-2-ones, respectively.

Keywords: 3-acetylcoumarin, imidazothiazole, pyrazolopyrimidine.

Benzopyran-2-ones exhibit significant biological activities such as antifungal [1], anticoagulant [2], antibacterial [3], and insecticidal [4]. Coumarins bearing a heterocyclic moiety in position 3 are spasmolytic [5-7], uricosuric [8], and CNS active agents [9]. Pyrazolo[1,5-*a*]pyrimidines are very useful in the treatment of insomnia [10]. Promising anti-inflammatory, analgesic, anthelmintic, and antibacterial activities of a number of substituted imidazo[2,1-*b*]thiazoles [11] are described. In view of this, in continuation of our earlier work on the synthesis of heterocyclic systems from coumarin derivatives [12–14] we report here the synthesis of new 3-coumarinyl-substituted pyrazolopyrimidines and imidazothiazoles.

Condensation of 3-[3-(dimethylamino)-1-oxo-2-propenyl]chromen-2-ones **1a–d** with 3-amino-4-cyanopyrazole (**2**) in acetic acid resulted in the formation of 7-(2-oxo-2H-chromen-3-yl)pyrazolo-[1,5-*a*]pyrimidine-3-carbonitriles **3a–d**.

2-Aminothiazoles are known to react with 2-halo ketones to form imidazo[2,1-*b*]thiazoles through cyclization involving the 2-imino, carbonyl functions [15–17]; subsequently it was shown that the aryl group in these compounds was located in position 6 [18].

Accordingly, the treatment of 2-amino-4-(methoxycarbonylmethyl)thiazole (**5a**) and 2-amino-5-methylthiazole (**5b**) with various 3-(2-bromoacetyl)coumarins **4** under refluxing in anhydrous ethanol afforded the corresponding 2-(6-(2-oxo-2H-chromen-3-yl)imidazo[2,1-*b*]thiazol-3-yl)acetates **6a–e** and 3-(2-methylimidazo[2,1-*b*]thiazol-5-yl)-2H-chromen-2-ones **7**, respectively, in excellent yields (Scheme). 2-Amino-4-(methoxycarbonylmethyl)thiazole and 2-amino-5-methylthiazole are known to exist in equilibrium **8** ⇌ **8'**.

During their reaction with 3-(2-bromoacetyl)coumarins the more nucleophilic cyclic secondary nitrogen atom in position 3 displaces the bromine of the former to give the intermediate ketone. The latter subsequently cyclized to give compounds **6** and **7**, respectively.

Department of Chemistry, National Institute of Technology, Warangal–506 004, India; e-mail: vrajesw@yahoo.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 465-471, March, 2008. Original article submitted June 08, 2006.

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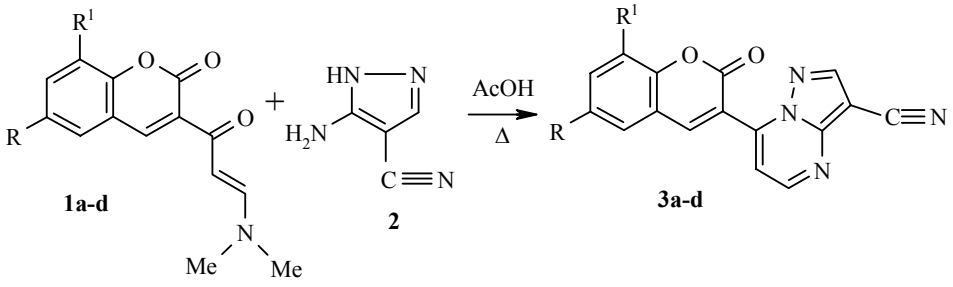
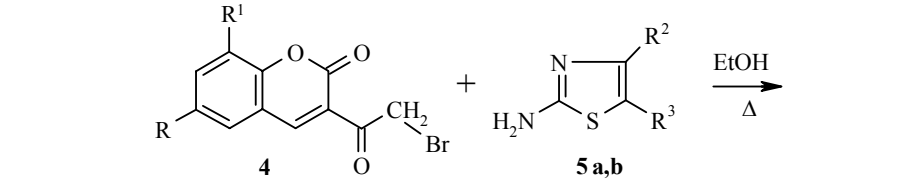
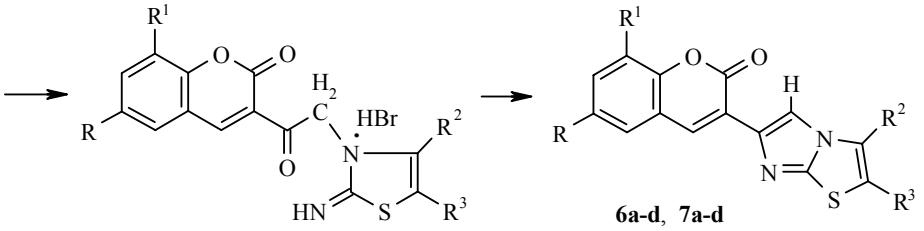
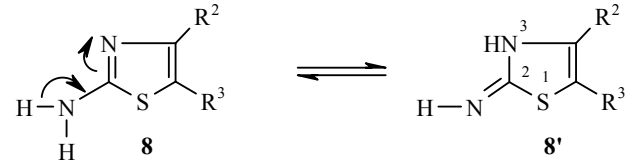


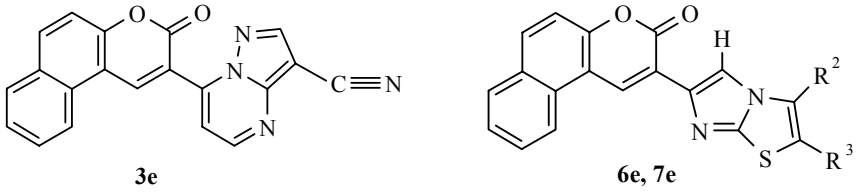
1e = 5,6-benzo derivative of **1a**





Intermediate ketone





1, 3 a R = R^1 = H, **b** R = Br, R^1 = H; **c** R = Cl, R^1 = H; **d** R = R^1 = Br;
5 a R^2 = CH_2COOMe, R^3 = H; **b** R^2 = H, R^3 = Me; **4**, **6 a** R = R^1 = H, R^2 = CH_2COOMe;
b R = Br, R^1 = H, R^2 = CH_2COOMe; **c** R = Cl, R^1 = H, R^2 = CH_2COOMe; **d** R = R^1 = Br,
R^2 = CH_2COOMe; **a–d** R^3 = H; **7 a** R = R^1 = R^2 = H, **b** R = Br, R^1 = R^2 = H, **c** R = Cl,
R^1 = R^2 = H; **d** R = R^1 = Br, R^2 = H; **a–d** R^3 = Me; **6e** R^2 = CH_2COOMe, R^3 = H;
7e R^2 = H, R^3 = Me

Attempts to isolate the intermediate ketone failed.

The reaction of compounds **1** with **2** in acetic acid gave carbonitrile **3** (Scheme). The IR spectrum of compound **3a** exhibited a strong absorption band at 2232 cm^{-1} for the nitrile group, a strong absorption band at 1713 cm^{-1} for the lactone carbonyl, and an absorption band at 1607 cm^{-1} for C=N. The ^1H NMR spectrum of compound **3a** exhibited a characteristic singlet at δ 8.82 for the pyrazole ring proton and a singlet for H-4 of coumarin at δ 8.87. The ^{13}C NMR of compound **3a** shows a characteristic signal for the nitrile carbon at δ 82.55 and a characteristic signal for the lactone carbonyl at δ 158.7.

TABLE 1. Analytical data of compounds **3a-e, 6a-e, 7a-e**

Compound*	Empirical formula	Found, % / Calculated, %		Mp, °C	Yield, %
		N	S		
3a	$C_{16}H_8N_4O_2$	19.32 / 19.44	—	279-281	92
3b	$C_{16}H_7BrN_4O_2$	15.21 / 15.26	—	248-250	86
3c	$C_{16}H_7ClN_4O_2$	17.42 / 17.36	—	>300	88
3d	$C_{16}H_6Br_2N_4O_2$	12.61 / 12.56	—	270-272	76
3e	$C_{20}H_{16}N_4O_2$	16.51 / 16.56	—	>300	72
6a	$C_{17}H_{12}N_2O_4S$	8.18 / 8.23	9.47 / 9.42	228-230	68
6b	$C_{17}H_{11}BrN_2O_4S$	6.60 / 6.68	7.56 / 7.65	220-222	62
6c	$C_{17}H_{11}ClN_2O_4S$	7.52 / 7.47	8.47 / 8.54	250-252	65
6d	$C_{17}H_{10}Br_2N_2O_4S$	5.7 / 5.62	6.36 / 6.44	196-198	60
6e	$C_{21}H_{17}N_2O_4S$	7.21 / 7.18	8.16 / 8.21	278-280	66
7a	$C_{15}H_{10}N_2O_2S$	9.85 / 9.92	11.22 / 11.36	235-237	78
7b	$C_{15}H_9BrN_2O_2S$	7.82 / 7.76	8.78 / 8.88	220-222	68
7c	$C_{15}H_9ClN_2O_2S$	8.79 / 8.84	10.02 / 10.10	218-220	75
7d	$C_{15}H_8Br_2N_2O_2S$	6.31 / 6.37	7.2 / 7.29	210-212	68
7e	$C_{19}H_{12}N_2O_2S$	8.38 / 8.43	9.7 / 9.63	280-282	70

* All compounds were recrystallized from methanol.

TABLE 2. Spectral Characteristics of compounds **3a-e**, **6a-e**, and **7a-e**

Compound	IR spectrum, ν_{max}, cm^{-1}				^{1}H NMR spectrum, δ, ppm (*J*, Hz)
	C=N	C=O (lactone)	C≡N (nitrile)	COO (ester)	
1	2	3	4	5	6
3a*	1607	1713	2232	—	7.51 (1H, t, *J* = 6, Ar-H); 7.57 (1H, d, *J* = 9, Ar-H); 7.70 (1H, d, *J* = 3, Ar-H); 7.78 (1H, t, *J* = 6, Ar-H); 7.90 (1H, d, *J* = 9, Ar-H); 8.82 (1H, s, pyrazole); 8.87 (1H, s, H-4 of coumarin); 8.99 (1H, d, *J* = 6, Ar-H)
3b	1608	1736	2235	—	7.56 (1H, d, *J* = 9, Ar-H); 7.67 (1H, d, *J* = 3, Ar-H); 7.90-7.94 (1H, m, Ar-H); 8.19 (1H, d, *J* = 3, Ar-H); 8.74 (1H, s, pyrazole); 8.88 (1H, s, H-4 of coumarin); 9.00 (1H, d, *J* = 3, Ar-H)
3c	1602	1727	2236	—	7.61-7.68 (2H, m, Ar-H); 7.84 (1H, d, *J* = 9, Ar-H); 8.07 (1H, s, Ar-H); 8.75 (1H, s, pyrazole); 8.88 (1H, s, H-4 of coumarin); 9.00 (1H, d, *J* = 3, Ar-H)
3d	1602	1738	2235	—	7.67 (1H, d, *J* = 6, Ar-H); 8.21 (1H, s, Ar-H); 8.34 (1H, s, Ar-H); 8.76 (1H, s, pyrazole); 8.89 (1H, s, H-4 of coumarin); 9.01 (1H, d, *J* = 3, Ar-H)

TABLE 2. (continued)

1	2	3	4	5	6
3e	1601	1728	2232	—	7.66-7.74 (3H, m, Ar-H); 8.09–8.36 (2H, m, Ar-H); 8.50-8.64 (2H, m, Ar-H); 8.92 (1H, s, pyrazole); 9.30 (1H, s, H-4 of coumarin); 9.46 (1H, d, *J* = 9, Ar-H)
6a**	1605	1708	—	1733	3.69 (3H, s, OCH_3); 4.17 (2H, s, CH_2); 7.17 (1H, s, thiazole); 7.36-7.47 (2H, m, Ar-H); 7.58-7.63 (1H, m, Ar-H); 7.87 (1H, d, *J* = 6, Ar-H); 8.33 (1H, s, imidazole); 8.69 (1H, s, H-4 of coumarin)
6b	1602	1723	—	1732	3.65 (3H, s, OCH_3); 4.18 (2H, s, CH_2); 7.18 (1H, s, thiazole); 7.48–7.51 (2H, m, Ar-H); 7.74-7.76 (1H, m, Ar-H); 8.15 (1H, s, imidazole); 8.35 (1H, s, H-4 of coumarin)
6c	1605	1728 (broad)	—	1728 (broad)	3.69 (3H, s, OCH_3); 4.18 (2H, s, CH_2); 7.18 (1H, s, thiazole); 7.49 (1H, d, *J* = 9, Ar-H); 7.62–7.65 (1H, m, Ar-H); 8.03 (1H, s, Ar-H); 8.36 (1H, s, imidazole); 8.67 (1H, s, H-4 of coumarin)
6d	1600	1692	—	1738	3.68 (3H, s, OCH_3); 4.19 (2H, s, CH_2); 7.19 (1H, s, thiazole); 8.09 (1H, d, *J* = 3, Ar-H); 8.30 (1H, s, Ar-H); 8.36 (1H, s, imidazole); 8.64 (1H, s, H-4 of coumarin)
6e	1588	1707	—	1729	3.70 (3H, s, OCH_3); 4.2 (2H, s, CH_2); 7.19 (1H, s, thiazole); 7.67 (2H, m, Ar-H); 7.76 (1H, t, *J* = 6, Ar-H); 8.10 (1H d, *J* = 9, Ar-H); 8.20 (1H, d, *J* = 9, Ar-H); 8.41 (1H, s, imidazole); 8.62 (1H, d, *J* = 9, Ar-H); 9.38 (1H, s, H-4 of coumarin)
7a	1605	1715	—	—	2.46 (3H, s, CH_3); 7.35–7.44 (2H, m, Ar-H); 7.61 (1H, t, *J* = 6, Ar-H); 7.74 (1H, d, *J* = 9, Ar-H); 7.93 (1H, s, thiazole); 8.58 (1H, s, imidazole); 8.61 (1H, s, H-4 of coumarin)
7b	1602	1725	—	—	2.41 (3H, s, CH_3); 7.48 (1H, d, *J* = 4.8, Ar-H); 7.70–7.73 (2H, m, Ar-H); 8.1 (1H, d, *J* = 3, Ar-H); 8.35 (1H, s, Ar-H); 8.58 (1H, s, H-4 of coumarin)
7c	1608	1733	—	—	2.42 (3H, s, CH_3); 7.49–7.61 (2H, m, Ar-H); 8.14 (1H, d, *J* = 2.7, Ar-H); 8.37 (1H, s, Ar-H, thiazole); 8.61 (1H, s, imidazole); 8.79 (1H, s, H-4 of coumarin)
7d	1610	1737	—	—	2.43 (3H, s, CH_3); 7.74 (1H, s, Ar-H, thiazole); 8.09 (1H, d, *J* = 3, Ar-H); 8.16 (1H, d, *J* = 2, ArH); 8.39 (1H, s, imidazole); 8.58 (1H, s, H-4 of coumarin)
7e	1603	1710	—	—	2.44 (3H, s, CH_3); 7.65 (2H, t, *J* = 6, Ar-H); 7.77 (2H, m, Ar-H); 8.09 (1H, d, *J* = 6); 8.19 (1H, d, *J* = 9, Ar-H); 8.45 (1H, s, imidazole); 8.60 (1H, d, *J* = 9, Ar-H); 9.33 (1H, s, H-4 of coumarin).

* ^{13}C NMR, δ, ppm: 113.3, 114, 117.0, 117.4, 118.4, 126, 130, 135, 143.3, 148, 148.1, 151.2, 154.6, 154.7, 158.7.

*2 ^{13}C NMR, δ, ppm: 33.3, 53.1, 112.2, 114, 116.7, 120.2, 125.6, 126.5, 129.5, 132, 137.2, 140.2, 150, 153, 159.5.

The mass spectrum of compound **3a** shows a molecular ion peak at 288 (30%). In the mass spectra all the compounds gave molecular ion peaks. All the compounds were characterized on the basis of spectral data and elemental analysis (Tables 1–3).

TABLE 3. Mass spectrum of compounds **3a**, **6a,e**, and **7a,b**

Compound	ESI, *m/z*
3a	289 [M^+ + H]
6a	363 [M^+ + Na], 341 [M^+ + H]
6e	413 [M^+ + Na], 391 [M^+ + H]
7a	305 [M^+ + Na], 283 [M^+ + H]
7b	363 [M^+ + H], 361 [M^+ + H]

The reaction of compound **4** with aminothiazole **5a** in ethanol under reflux at higher temperatures gave compounds **6** (Scheme). The IR spectrum of compound **6a** exhibited a strong absorption band at 1733 cm^{-1} for ester carbonyl, a strong absorption band at 1708 cm^{-1} for lactone carbonyl, and an absorption band at 1605 cm^{-1} for C=N. The ^{1}H NMR spectrum of compound **6a** shows a characteristic singlet for the imidazole ring proton at δ 8.33 and a characteristic singlet for H-4 of coumarin at δ 8.69. The ^{13}C NMR spectrum of compound **6a** shows a characteristic signal for the ester carbonyl at δ 169.8. The mass spectrum of compound **6a** showed a molecular ion peak at *m/z* 340.

The reaction of compound **4** with **5b** in ethanol at high temperatures gave compound **7**. The IR spectrum of compound **7a** exhibited strong absorption bands at 1715 for the lactone carbonyl and 1605 cm^{-1} for C=N. The ^{1}H NMR spectrum of compound **7a** exhibited a characteristic singlet at δ 8.61 for the H-4 of coumarin. The mass spectrum of compound **7a** shows the molecular ion peak at 282 (100%).

In summary, efficient syntheses of 3-coumarinyl-substituted imidazo[2,1-*b*]- thiazoles have been described.

EXPERIMENTAL

All melting points were determined by a POLMAN-MP apparatus (Model No. MP-96). IR spectra were recorded on a Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were recorded on a 300 MHz instrument in DMSO-d_6, using TMS as an internal standard. Mass spectra were scanned on a Perkin-Elmer SCIEX API-2000 instrument (ESI). The purity of all compounds was established by TLC analysis using Merck precoated silicagel $60F_{254}$ plates (0.2 mm thickness).

The enaminones 1 were smoothly obtained by heating 3-acetylcoumarins with dimethylformamide dimethylacetal [19] (DMF DMA).

Methyl α-bromoacetoacetate [20] on treatment with thiourea afforded 2-amino-4-(2-methoxycarbonyl-methyl)thiazole **5a** [21] in good yield.

7-(2-Oxo-2H-chromen-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles 3a–e (General Method). 3-[3-(Dimethylamino)-1-oxo-2-propenyl]chromen-2-one (1a) (0.01 mol) was added to a suspension of 3-amino-4-cyanopyrazole **2** (0.01 mol) in acetic acid (10 ml) at ambient temperature. The reaction mass was heated to 60°C for 1 h, and the reaction progress was monitored by TLC (mobile phase: ethyl acetate–hexane, 4:6). After completion of the reaction, the reaction mass was cooled to 20°C. The product 3a was filtered off and recrystallized from methanol.

Compounds 3b-e were prepared by a similar method; in the case of **3e** compound **1** was replaced by the analogous benzo[*f*]coumarin derivative.

Methyl 2-(6-(2-oxo-2H-chromen-3-yl)imidazo[2,1-*b*]thiazol-3-yl)acetates 6a–e (General Method). A mixture of 3-(2-bromoacetyl)coumarin (0.01 mol) and methyl 2-(2-aminothiazol-4-yl)acetate (5a) (0.01 mol) was refluxed in ethanol (25 ml) for 1 h. The reaction progress was monitored by TLC (mobile phase: ethyl acetate–hexane, 1:1). After completion of reaction, the reaction mixture was cooled to 20–25°C. Product 6a was filtered off, washed with 5% w/w aqueous $NaHCO_3$ solution, and recrystallized from methanol.

Compounds 6b-e were prepared by a similar method. For the preparation of **6e** 3-bromoacetylbenzo[*f*]coumarin was used.

3-(2-Methylimidazo[2,1-*b*]thiazol-6-yl)-2H-chromen-2-ones 7a-e (General Method). A mixture of 3-(2-bromoacetyl)coumarin (0.01 mol) and 2-amino-4-methylthiazole (0.01 mol) was refluxed in ethanol (25 ml) for 1 h. The reaction progress was monitored by TLC (mobile phase: ethyl acetate–hexane, 1:1). After completion of the reaction, the reaction mixture was cooled to 20–25°C. Product 7a was filtered off, washed with 5% w/w aqueous sodium bicarbonate solution, and recrystallized from methanol.

Compounds **7b–e** were prepared by a similar method. Compound **7e** was prepared from 3-bromoacetylbenzo[*f*]coumarin.

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