Chemistry of Heterocyclic Compounds, Vol. 40, No. 5, 2004

SYNTHESIS OF 3-(3-ALKYL-5-THIOXO-1H-4,5-DIHYDRO-1,2,4-TRIAZOL-4-YL)-AMINOCARBONYLCHROMONES

Linghua Cao[1,2], Lin Zhang[1], and Pengyuan Cui[1]

A series of 3-(3-alkyl-5-thioxo-1H-4,5-dihydro-1,2,4-triazol-4-yl)aminocarbonylchromones has been prepared by oxidation of 3-formylchromone with Jones' reagent followed by reaction with 3-alkyl-4-amino-4,5-dihydro-1,2,4-triazole-5(1H)-thione in the presence of $POCl_3$. The structures of the compounds were confirmed by IR, LC-MS, and ^1H NMR spectra and elemental analyses.

Keywords: 3-(3-alkyl-5-thioxo-1H-4,5-dihydro-1,2,4-triazol-4-yl)aminocarbonylchromones, 3-formylchromone, synthesis.

Compounds of chromone series have received considerable attention in the life sciences owing to their specific framework and their versatile and significant biological activities. In the study of modified chromones, compounds with antitumor, antibacterial, antiviral, hypolipidemic, and hypoglycemic activities have been discovered among 3-heterylsubstituted chromones [1]. 1,2,4-Triazoles are also reported to exhibit a broad spectrum of biological activity [2-4]. A series of investigations on combining these components together showed that the triazole-chromone systems formed display novel biological activities and could expand the scope of antibiotics. It stimulated us to introduce the 3-alkyl-4-amino-5-thioxo-1H-4,5-dihydro-1,2,4-triazole (**1**) fragment [5] into the parent chromone. The bioactivities of these compounds are under investigation.

Starting from *o*-hydroxyacetophenones **2** we obtained 3-formylchromones **3**; the latter, through oxidation with Jones' reagent [6], were transformed to 3-carboxychromones **4**, which then reacted with 3-alkyl-4-amino-5-thioxo-1H-4,5-dihydro-1,2,4-triazoles in the presence of $POCl_3$ to give the target compounds **5-28**. The structures of the compounds were characterized by elemental analyses, IR, LC-MS, and ^1H NMR spectra. The synthetic route is shown in Scheme 1.

In the synthesis of 3-formyl-substituted chromones reported by Nohara et al. [7], there were no variations in the molar ratio of substituted *o*-hydroxyacetophenone–$POCl_3$–DMF. We studied several ratios of the basic material to the reagents, such as 1:1:1, 1:3:3, 1:3:6, and 1:6:12. In the ratio 1:6:12, the yield of the product was 80-90%, which is higher than the reported yields.

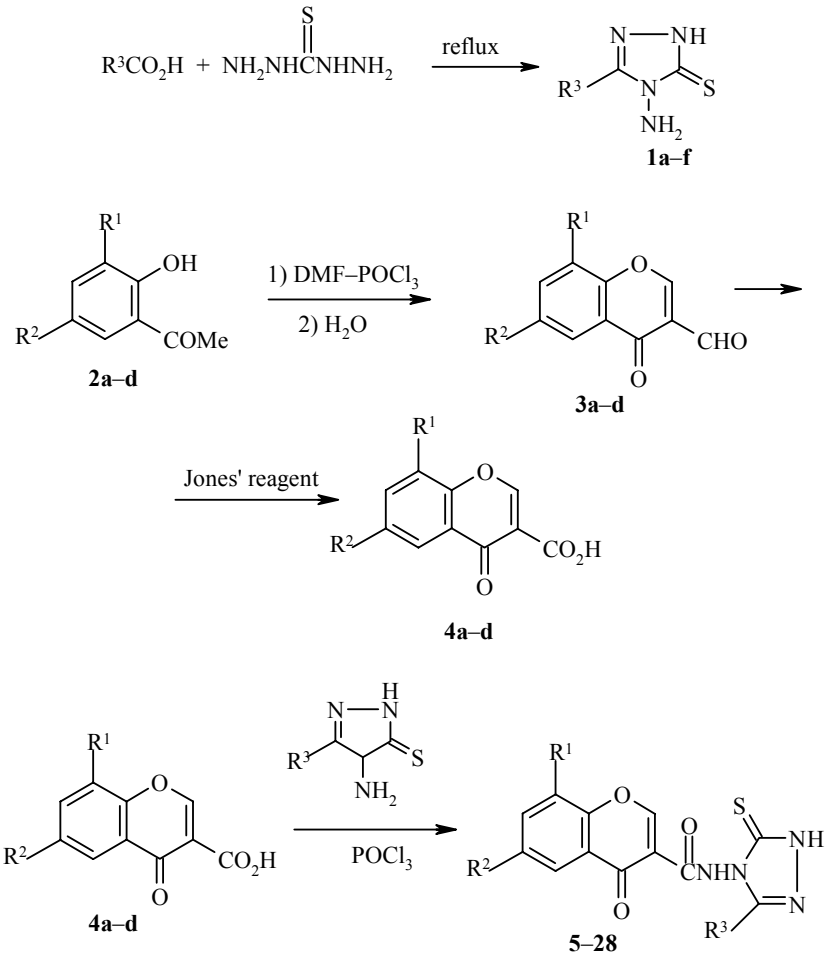
In the IR spectra, the absorption band of C=O of the carboxyl group of 3-carboxychromone appeared at 1750, which is higher than 1734 cm^{-1} of 2-carboxychromone. It was identical with that reported in [8].

In ^1H NMR spectra, the signal of 2-H in chromones appears at 6-8 ppm [9]. The electron-acceptor substituent at position 3 shifts this signal to a lower field. Therefore the H-2 signals in compounds **5-28** were consequently obtained at 9.1±0.1 ppm.

---

[1] College of Chemistry and Chemical Engineering, Xinjiang University, Urumqi 830046, P. R. China; e-mail: clhxj@xju.edu.cn. [2] State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 749-754, May, 2004. Original article submitted July 16, 2002.

Scheme 1



1 a R^3 = Me, **b** R^3 = Ph, **c** R^3 = *n*-C_3H_7, **d** R^3 = *n*-C_4H_9, **e** R^3 = *n*-C_5H_{11}, **f** R^3 = CF_3; **2-4 a** R^1 = R^2 = H, **b** R^1 = H, R^2 = Me, **c** R^1 = H, R^2 = Br, **d** R^1 = R^2 = Cl; **5-22** R^1 = H, **23-28** R^1 = Cl; **5-10** R^2 = H, **11-16** R^2 = Me, **17-22** R^2 = Br, **23-28** R^2 = Cl; **5**, **11**, **17**, **23** R^3 = Me, **6**, **12**, **18**, **24** R^3 = Et, **7**, **13**, **19**, **25** R^3 = *n*-Pr, **8**, **14**, **20**, **26** R^3 = *n*-Bu, **9**, **15**, **21**, **27** R^3 = *n*-C_5H_{11}, **10**, **16**, **22**, **28** R^3 = CF_3

The proton signals of the CONH group in compounds **5-28** appeared at 10.2-11.5 ppm as broad singlets. In the thiolactam group they were shifted to 13.6-14.5 ppm.

In the IR spectra of the products, the characteristic absorption band of C=O in pyrone appeared at 1620-1670 cm^{-1}, and the IR spectra of compounds **5-28** displayed a broad band at 3000 (CONH, CSNH), and a band at 1700 (C=O of CONH) or 1310 cm^{-1} (C=S).

All the compounds **5-28** had strong molecular-ion peaks in the LC-MS spectra (the relative abundance was >60% or even the base peak). The LC-MS spectra exhibited the peaks of retro-Diels–Alder cracking and the $[M+Na-H]^+$ peak.

EXPERIMENTAL

Melting points were recorded on a Yanaco MP-S3 microscopic melting point apparatus and are corrected. IR spectra were recorded on a Bruker FT-IR ERUINOX-55; FTS-40 (KBr pellets). ^1H NMR spectra were recorded on a Bruker AC-80 (80 MHz) spectrometer (TMS as internal standard, solvent $CDCl_3$ or DMSO).

TABLE 1. Physical Constants of Compounds **5-28**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
5	$C_{13}H_{10}N_4O_3S$	51.52 / 51.65	3.39 / 3.33	18.62 / 18.53	>300	51
6	$C_{14}H_{12}N_4O_3S$	53.10 / 53.16	3.89 / 3.82	17.80 / 17.71	>300	49
7	$C_{15}H_{14}N_4O_3S$	54.50 / 54.53	4.20 / 4.27	16.92 / 6.96	>300	41
8	$C_{16}H_{16}N_4O_3S$	55.89 / 55.80	4.60 / 4.68	16.31 / 16.27	289-291	40
9	$C_{17}H_{18}N_4O_3S$	43.86 / 43.83	1.86 / 1.98	15.79 / 15.73	247-248	38
10	$C_{13}H_7F_3N_4O_3S$	44.61 / 44.57	4.86 / 4.89	16.02 / 15.99	241-243	32
11	$C_{14}H_{12}N_4O_3S$	53.12 / 53.16	3.89 / 3.82	17.76 / 17.71	>300	53
12	$C_{15}H_{14}N_4O_3S$	54.56 / 54.53	4.31 / 4.27	16.89 / 16.96	>300	50
13	$C_{16}H_{16}N_4O_3S$	55.89 / 55.80	4.70 / 4.68	16.31 / 16.27	276-278	42
14	$C_{17}H_{18}N_4O_3S$	56.93 / 56.97	5.03 / 5.06	16.67 / 15.63	>300	39
15	$C_{18}H_{20}N_4O_3S$	57.96 / 58.05	5.44 / 5.41	15.09 / 15.04	278-280	33
16	$C_{14}H_{19}F_3N_4O_3S$	45.38 / 45.41	2.43 / 2.45	15.18 / 15.13	217-219	29
17	$C_{13}H_9BrN_4O_3S$	40.90 / 40.96	2.35 / 2.38	14.77 / 14.70	>300	51
18	$C_{14}H_{11}BrN_4O_3S$	42.51 / 42.55	2.79 / 2.81	14.07 / 14.18	>300	48
19	$C_{15}H_{13}BrN_4O_3S$	43.99 / 44.02	3.22 / 3.20	13.73 / 13.69	251-252	32
20	$C_{16}H_{15}BrN_4O_3S$	45.44 / 45.40	3.54 / 3.57	13.33 / 13.24	247-248	30
21	$C_{17}H_{17}BrN_4O_3S$	46.73 / 46.69	3.94 / 3.92	12.85 / 12.81	241-243	30
22	$C_{13}H_6BrF_3N_4O_3S$	35.83 / 35.88	1.41 / 1.39	12.94 / 12.87	233-234	35
23	$C_{13}H_8Cl_2N_4O_3S$	42.13 / 42.06	2.20 / 2.17	15.15 / 15.09	284-285	48
24	$C_{14}H_{10}Cl_2N_4O_3S$	43.72 / 43.65	2.69 / 2.62	14.62 / 14.54	248-249	47
25	$C_{15}H_{12}Cl_2N_4O_3S$	45.21 / 45.13	3.06 / 3.03	14.08 / 14.03	237-239	43
26	$C_{16}H_{14}Cl_2N_4O_3S$	46.60 / 46.50	3.37 / 3.41	13.64 / 13.56	230-231	40
27	$C_{17}H_{16}Cl_2N_4O_3S$	47.84 / 47.78	3.74 / 3.77	13.20 / 13.11	218-219	36
28	$C_{13}H_5Cl_2F_3N_4O_3S$	36.81 / 36.72	1.21 / 1.19	13.23 / 13.18	197-199	31

Elemental analysis were taken on a Perkin–Elmer 2400 CHN analyzer. TLC was carried out on precoated glass plates of silica gel GF 254. The spots were visualized by exposure under UV light or by the coloration of iodine vapor.

All reagents are analytically pure.

General Procedure for the Synthesis of 3-Alkyl-4-amino-4,5-dihydro-1,2,4-triazole-5(1H)-thione [5] 1a-f. Thiocarbohydrazide (3.18 g, 0.03 mol) and 0.04 mol of fatty acid were refluxed for 4 h. After that the reaction mixture was distilled in vacuum and the nonreacted fatty acid was taken off. The crude product obtained was recrystallized from EtOH or EtOH–H_2O; mean yield 76% with this reaction.

TABLE 2. Spectral data of compounds **5-28**

Com-pound	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm	Mass spectrum, *m/z* (*I*, %)
1	2	3	4
5	1700, 1616, 1312	2.20 (s, 3H, CH_3); 7.57-8.29 (m, 4H, H-5, H-6, H-7, H-8); 9.17 (s, 1H, H-2); 11.44 (s, 1H, CONH); 13.89 (br. s, 1H, CSNH)	325 $[M+Na]^+$ (55), 302 $[M]^+$ (98), 173 (100), 145 (35), 121 (52)
6	1701, 1621, 1310	1.07-2.37 (m, 5H, C_2H_5); 7.58-8.22 (m, 4H, H-5, H-6, H-7, H-8); 9.12 (s, H-2); 11.44 (s, 1H, CONH); 13.84 (br. s, 1H, CSNH)	355 $[M+K]^+$ (60), 316 $[M]^+$ (90), 173 (100), 145 (50), 121 (46)
7	1702, 1620, 1311	1.06-2.50 (m, 7H, C_3H_7); 7.54-8.17 (m, 4H, H-5, H-6, H-7, H-8); 9.15 (s, 1H, H-2); 11.42 (s, 1H, CONH); 13.86 (br. s, 1H, CSNH)	353 $[M+Na]^+$ (58), 330 $[M]^+$ (92), 173 (100), 145 (35), 121 (42)
8	1700, 1624, 1309	1.09-2.56 (m, 9H, C_4H_9); 7.58-8.25 (m, 4H, H-5, H-6, H-7, H-8); 9.11 (s, 1H, H-2); 11.38 (s, 1H, CONH); 13.79 (br. s, 1H, CSNH)	367 $[M+Na]^+$ (58), 344 $[M]^+$ (90), 173 (100), 145 (41), 121 (53)
9	1703, 1617, 1310	1.12-2.64 (m, 11H, C_5H_{11}); 7.54-8.17 (m, 4H, H-5, H-6, H-7, H-8); 9.15 (s,1H, H-2); 11.42 (s, 1H, CONH); 13.86 (br. s, 1H, CSNH)	397 $[M+K]^+$ (60), 358 $[M]^+$ (97), 173 (100), 145 (52), 121 (48)
10	1701, 1618, 1311	2.30 (s, 3H, CH_3); 7.43-8.04 (m, 4H, H-5, H-6, H-7, H-8); 9.06 (s, 1H, H-2); 10.63 (s, 1H, CONH); 14.02 (br. s, 1H, CSNH)	395 $[M+K]^+$ (60), 356 $[M]^+$ (100), 173 (90), 145 (57), 121 (32)
11	1701, 1621, 1319	2.19 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 7.73-8.02 (m, 3H, H-5, H-7, H-8); 9.09 (s, 1H, H-2); 11.45 (s, 1H, CONH); 13.61 (br. s, 1H, CSNH)	339 $[M+Na]^+$ (64), 316 $[M]^+$ (98), 187 (100), 159 (35), 135 (42)
12	1705, 1620, 1317	1.08-2.40 (m, 8H, CH_3, C_2H_5); 7.68-8.04 (m, 3H, H-5, H-7, H-8); 9.10 (s, 1H, H-2); 11.46 (s, 1H, CONH); 13.64 (br. s, 1H, CSNH)	369 $[M+K]^+$ (59), 330 $[M]^+$, (100), 187 (91), 159 (43), 135 (38)
13	1700, 1623, 1315	1.03-2.35 (m, 10H, CH_3, C_3H_7); 7.58-8.05 (m, 3H, H-5, H-7, H-8); 9.11 (s, 1H, H-2); 11.50 (s, 1H, CONH); 13.64 (br. s, 1H, CSNH)	383 $[M+K]^+$ (60), 344 $[M]^+$ (100), 187 (93), 159 (41), 135 (32)
14	1701, 1624, 1310	1.01-2.35 (m, 12H, CH_3, C_3H_7); 7.49-8.03 (m, 3H, H-5, H-7, H-8); 9.11 (s, 1H, H-2); 11.56 (s, 1H, CONH); 13.62 (br. s, 1H, CSNH)	381 $[M+Na]^+$ (57), 358 $[M]^+$ (94), 187 (100), 159 (36), 135 (40)
15	1702, 1621, 1310	1.03-2.30 (m, 10H, CH_3, C_3H_7); 7.51-8.09 (m, 3H, H-5, H-7, H-8); 9.13 (s, 1H, H-2); 11.49 (s, 1H, CONH); 13.65 (br. s, 1H, CSNH)	411 $[M+K]^+$ (60), 372 $[M]^+$ (100), 187 (90), 159 (42), 135 (50)
16	1701, 1617, 1313	2.33 (s, 3H, CH_3); 7.45-8.05 (m, 3H, H-5, H-7, H-8); 9.07 (s, 1H, H-2); 10.67 (s, 1H, CONH); 14.01 (br. s, 1H, CSNH)	409 $[M+K]^+$ (60), 370 $[M]^+$ (100), 187 (83), 159 (37), 135 (50)
17	1699, 1637, 1310	2.23 (s, 3H, CH_3); 7.70-8.35 (m, 3H, H-5, H-7, H-8); 9.13 (s, 1H, H-2); 11.33 (s, 1H, CONH); 13.63 (br. s, 1H, CSNH)	405 $[M+2+Na]^+$ (60), 403 $[M+ Na]^+$ (57), 382 $[M+2]^+$ (100), 380 $[M]^+$ (100)
18	1695, 1637, 1303	0.96-2.67 (m, 5H, C_2H_5); 7.75-8.30 (m, 3H, H-5, H-7, H-8); 9.17 (s, 1H, H-2); 11.34 (s, 1H, CONH); 13.62 (br. s, 1H, CSNH)	419 $[M+2+Na]^+$ (60), 417 $[M+ Na]^+$ (58), 396 $[M+2]^+$ (100), 394 $[M]^+$ (100)
19	1701, 1625, 1303	0.99-2.68 (m, 7H, C_3H_7); 7.73-8.31 (m, 3H, H-5, H-7, H-8); 9.15 (s, 1H, H-2); 11.30 (s, 1H, CONH); 13.66 (br. s, 1H, CSNH)	419 $[M+2+Na]^+$ (63), 417 $[M+ Na]^+$ (58), 397 $[M+2+H]^+$ (100), 395 $[M+H]^+$ (80)
20	1702, 1617, 1315	0.98-2.66 (m, 9H, C_4H_9); 7.75-8.30 (m, 3H, H-5, H-7, H-8); 9.19 (s, 1H, H-2); 11.31 (s, 1H, CONH); 13.64 (br. s, 1H, CSNH)	433 $[M+2+Na]^+$ (60), 431 $[M+ Na]^+$ (60), 411 $[M+2+H]^+$ (100), 409 $[M+H]^+$ (100)
21	1700, 1623, 1313	0.95-2.63 (m, 11H, C_5H_{11}); 7.75-8.30 (m, 3H, H-5, H-7, H-8); 9.17 (s, 1H, H-2); 11.34 (s, 1H, CONH); 13.62 (br. s, 1H, CSNH)	447 $[M+2+Na]^+$ (60), 445 $[M+ Na]^+$ (60), 425 $[M+2+H]^+$ (100), 423 $[M+H]^+$ (100)

TABLE 2 (continued)

1	2	3	4
22	1701, 1622, 1311	7.57-8.29 (m, 3H, H-5, H-7, H-8); 9.14 (s, 1H, H-2); 11.36 (s, 1H, CONH); 13.69 (br. s, 1H, CSNH)	459 $[M+2+Na]^+$ (60), 457 $[M+ Na]^+$ (62), 437 $[M+2+H]^+$ (100), 435 $[M+H]^+$ (100)
23	1723, 1641, 1357	2.31 (s, 3H, CH_3); 7.51-8.01 (m, 2H, H-5, H-7); 9.06 (s, 1H, H-2);11.12 (s, 1H, CONH); 13.93 (br. s, 1H, CSNH)	413 $[M+4+K]^+$ (100), 411 $[M+2+K]^+$ (70), 409 $[M+K]^+$ (12), 370 $[M]^+$ (75)
24	1722, 1641, 1356	1.01-2.59 (m, 5H, C_2H_5); 7.78-8.31 (m, 2H, H-5, H-7); 9.07 (s, 1H, H-2); 11.14 (s, 1H, CONH); 13.95 (br. s, 1H, CSNH)	427 $[M+4+K]^+$ (100), 425 $[M+2+K]^+$ (68), 423 $[M+K]^+$ (11), 384 $[M^+$ (67)
25	1721, 1643, 1357	0.99-2.55 (m, 7H, C_3H_7); 7.80-8.32 (m, 2H, H-5, H-7); 9.04 (s, 1H, H-2); 11.17 (s, 1H, CONH); 13.91 (br. s, 1H, CSNH)	441 $[M+4+K]^+$ (100), 439 $[M+2+K]^+$ (70), 437 $[M+K]^+$ (15), 398 $[M]^+$ (56)
26	1721, 1647, 1355	1.00-2.58 (m, 5H, C_2H_5); 7.81-8.33 (m, 2H, H-5, H-7); 9.09 (s, 1H, H-2); 11.19 (s, 1H, CONH); 13.90 (br. s, 1H, CSNH)	455 $[M+4+K]^+$ (100), 453 $[M+2+K]^+$ (66), 451 $[M+K]^+$ (13), 412 $[M]^+$ (54)
27	1723, 1646, 1356	0.97-2.49 (m, 11H, C_5H_{11}); 7.78-8.31 (m, 2H, H-5, H-7); 9.07 (s, 1H, H-2); 11.14 (s, 1H, CONH); 13.95 (br. s, 1H, CSNH)	469 $[M+4+K]^+$ (100), 467 $[M+2+K]^+$ (72), 465 $[M+K]^+$ (16), 426 $[M]^+$ (47)
28	1724, 1645, 1353	7.57-8.29 (m, 2H, H-5, H-7); 9.17 (s, 1H, H-2); 11.44 (s, 1H, CONH); 13.89 (br. s, 1H, CSNH)	467 $[M+4+K]^+$ (100), 465 $[M+2+K]^+$ (71), 463 $[M+K]^+$ (18), 424 $[M]^+$ (37)

Synthesis of 3-Formylchromones 3a-d. Phenol or substituted phenol (1 mol) was heated to melting, and an equimolar quantity of acetyl chloride was slowly added under vigorously stirring. Light heating was continued until HCl completely evolved. Then anhydrous $AlCl_3$ (2 mol) was added in separate batches in an ice-water bath. Then it was kept about 6-10 h in an oil bath (with phenol or 4-methylphenol the temperature was maintained at 120 ± 2°C; with 4-bromophenol and 2,4-dichlorophenol – at 125-130°C). Then the material was hydrolyzed by crushed ice. It was distilled with water vapor; the oil layer was extracted with CH_2Cl_2 and dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The substituted *o*-hydroxyacetophenone **2** was obtained. A solution of substituted *o*-hydroxyacetophenon **2** (0.1 mol) in anhydrous DMF (93 ml) was placed in a flask, and freshly distilled $POCl_3$ (0.6 mol) was added dropwise with mechanical stirring in an ice-water bath; the color of the solution changed from yellow to orange. After that, it was stirred for 12 h at room temperature. The reaction was monitored by TLC [ethyl acetate–petroleum ether (60-90°C)–acetic acid 50:50:3] to completion, and the mixture was decomposed by ice-water after the reaction was completed. The resulting residue was collected by filtration, washed with water, and recrystallized from ethanol–water. The 3-formyl-substituted chromones are listed below: 3-formylchromone (**3a**), yield 80%, R_f 0.83, mp 151-152°C; 3-formyl-6-methylchromone (**3b**), yield 85%, R_f 0.74, mp 173-174°C (lit. [7]: 174-175°C); 6-bromo-3-formylchromone (**3c**), yield 90%, R_f 0.73, mp 189-192°C; 6,8-dichloro-3-formylchromone (**3d**), yield 82%, R_f 0.80, mp 170-171°C.

General Procedure for the Synthesis of 3-Carboxychromones 4a-d. A solution of 3-formyl-substituted chromone (17.2 mmol) in acetone (240 ml) was added dropwise to 8.5 ml of Jones' reagent in 30 min. The temperature should be maintained at 10-15°C. The color of the solution turned into green, and the resinous precipitate was separated. The solution was poured into the other flask and concentrated by reduced pressure to 1/3 of initial volume. It was poured into water (500 ml) with stirring and allowed to stand for ~2 h.

The light yellow precipitate was filtered off, washed with water, then dried. The residue was recrystallized from acetone (3-carboxy-6-methylchromone was recrystallized from benzene).

General Procedure for the Synthesis of 3-(3-Alkyl-5-thioxo-1H-4,5-dihydro-1,2,4-triazole-4-yl)aminocarbonylchromones 5-28. Freshly distilled $POCl_3$ (20 ml) was added with stirring to a mixture of 3-carboxychromone **4a-d** (2 mmol) and compounds **1a-f** (2 mmol); the reaction was monitored by TLC [ethyl acetate–petroleum ether (60-90°C)–acetic acid 50:50:3] to completion. It was poured into crushed ice, filtered, washed with water, dried, and recrystallized from DMF–EtOH to yield compounds **5-28** (Tables 1 and 2).

This work was supported by the Natural Science Foundation (29962002) and the Nankai University State Key Laboratory of Elemento-Organic Chemistry.

REFERENCES

1. N. V. Gorbulenko, S. A. Kirpa, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 29 (1993).
2. Z. Y. Wang, H. X. Shi, and H. J. Shi, *J. Heterocycl. Chem.*, **38**, 355 (2001).
3. I. Chaaban and O. O. Oji, *J. Indian Chem. Soc*., **61**, 523 (1984).
4. A. Omar, M. E. Mohsen, and O. M. Aboulwafa (A.-Mohsen M. E. Omar, Omaiama M. Aboulwafa), *J. Heterocycl. Chem.*, **21**, 1415 (1984).
5. K. S. Dhaka, J. Mohani, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.*, **12**, 287 (1974).
6. A. Nohara, T. Umetani, K. Ukawa, and Y. Sanno, *Chem. Pharm. Bull.*, **22**, 2959 (1974).
7. A. Nohara, T. Umetani, and Y. Sanno, *Tetraherdron Lett.*, 1995 (1973).
8. A. Nohara, H. Kuriki, T. Saijo, H. Sugihara, M. Kanno, and Y. Sanno, *J. Med. Chem.*, **20**, 141 (1977).
9. P. Khilya, S. V. Kobalev, N. S. Miroshnichenko, and A. V. Turov, *Chem. Nat. Compd.*, **34**, 32 (1998).