Chemoselective Route for Synthesis of *N*-Aryl-3-oxochromeno[2,3-*c*]-pyrazole-2(3*H*)-carbothioamide Derivatives

by **Abdolali Alizadeh*** and **Rashid Ghanbaripour**

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran (phone: +98-21-88006631; fax: +98-21-88006544; e-mail: aalizadeh@modares.ac.ir, abdol_alizad@yahoo.com)

A chemoselective route for the synthesis of chromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide derivatives by a five-component reaction of salicylaldehyde, malononitrile, $NH_2NH_2 \cdot H_2O$, aryl isothiocyanate, and H_2O in EtOH/AcOH mixture is reported. This new protocol has the advantages of high yields, short reaction times, ease of operation, and simple purification. All structures were confirmed by IR, ^{1}H- and ^{13}C-NMR, and MS analyses. A plausible mechanism for this type of reaction is proposed (*Scheme 2*).

Introduction. – The development of new approaches for the efficient construction of specific heterocycles continues to be essential to access to natural products and their structural analogs. According to the report of *Volmajer* and co-workers [1], and in the course of our research program on design of new routes for synthesis of new heterocylic compounds [2–5], herein, we report the synthesis of chromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamides *via* five-component reactions.

Results and Discussion. – Our new synthetic route is outlined in *Scheme 1*. First, to achieve suitable conditions for the synthesis of 3-oxo-*N*-phenylchromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide (**3a**), the reaction of salicylaldehyde, malononitrile, $NH_2NH_2 \cdot H_2O$, and phenyl isothiocyanate has been selected as a model.

Different solvents and amounts of NH_4OAc for the model reaction were explored. As compiled in *Table 1*, the best results were obtained on reflux in EtOH/AcOH 1:1 in the presence of 1 equiv. NH_4OAc to yield product **3a** in good yield (*Table 1*, *Entry 8*).

Further experiments were carried out by using more than 1 mmol of NH_4OAc to compare the catalytic activities under similar conditions. The results were the same (*Table 1*, *Entries 9* and *10*). To explore the generality of the reaction, we extended our study to different salicylaldehydes and aryl isothiocyanates. The results are collected in *Table 2*.

Scheme 1. *Synthesis of Chromeno[2,3-c]pyrazole-2(3H)-carbothioamide Derivatives* **3**

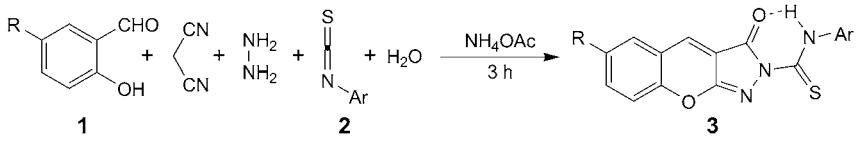


Table 1. *Optimization of the Reaction Conditions for the Formation of* **3a**

Entry	Solvent	Catalyst (mmol)	Yield [%]
1	MeCN	–	–
2	EtOH	–	–
3	EtOH/AcOH 1 : 1	–	–
4	EtOH	NH_4OAc (0.5)	–
5	EtOH/AcOH 1 : 1	NH_4OAc (0.5)	40
6	MeCN	NH_4OAc (0.5)	–
7	EtOH/AcOH 1 : 1	NH_4OAc (0.75)	55
8	EtOH/AcOH 1 : 1	NH_4OAc (1)	89
9	EtOH/AcOH 1 : 1	NH_4OAc (1.25)	89
10	EtOH/AcOH 1 : 1	NH_4OAc (1.5)	89

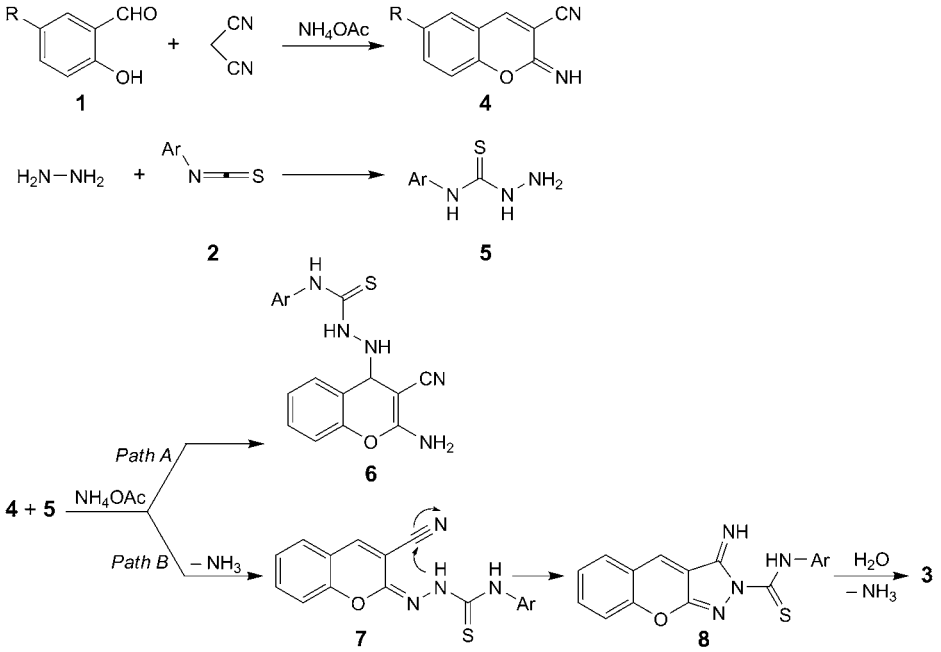
Table 2. *Prepared* N*-Aryl-3-oxochromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamides* **3**

Compound	R	Ar	Yield [%]
3a	H	Ph	89
3b	Br	Ph	83
3c	Br	4-F–C_6H_4	92
3d	NO_2	Ph	79
3e	H	4-Cl–C_6H_4	87
3f	Br	4-Cl–C_6H_4	75
3g	MeO	4-Cl–C_6H_4	80

The structures of compounds **3a** – **3g** were deduced from their elemental analysis, IR, and high-field ^{1}H- and ^{13}C-NMR spectra. The mass spectrum of **3a** displayed the molecular-ion peak at *m*/*z* 321, which is in agreement with the proposed structure. The IR spectrum of **3a** showed absorption bands due to the NH stretching frequency at 3339 cm^{-1}, and absorption bands at 1724, 1607, and 1566 cm^{-1} were assigned to the CO and C=C groups. The ^{1}H-NMR spectrum of **3a** showed four *triplet*s (δ(H) 7.02 (J = 8.6), 7.36 (J = 8.6), 7.43 (J = 8.6), and 7.69 (J = 8.6)), three *doublet*s (δ(H) 7.50 (J = 8.6), 7.64 (J = 8.6), and 7.97 (J = 8.6)) for aromatic H-atoms, and also two *singlet*s (8.96 and 10.52) for CH of the chromene ring and NH, respectively. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** exhibited 15 distinct resonances in agreement with the suggested structure. Although we have not established the mechanism of the reaction experimentally, a proposal is presented in *Scheme 2*.

It is conceivable that initially the salicylaldehyde **1** undergoes an NH_4OAc promoted *Knoevenagel* condensation and cyclization with malononitrile to give iminochromene-carbonitrile **4**, which has two electrophilic sites, namely a conjugated C=C bond (as a *Michael* acceptor) and an imino function. Next, arylthiosemicarbazide **5** is formed by addition of $NH_2NH_2 \cdot H_2O$ to phenyl isothiocyanate **2**. At this stage, considering the previous reports, we would normally expect **5** to undergo *Michael*-type addition *via* attack at the C=C bond to give the desired product **6** (Path *A*) or condensation with the imino group to give intermediate **7** (Path *B*). However, on the basis of IR, and ^{1}H- and ^{13}C-NMR spectra, product **6** was not formed, but another remarkable reaction took place. In fact, at this stage, the chemoselective condensation

Scheme 2. *Proposed Mechanism for the Formation of the Products* **3a**–**3g**



of the NH_2 group of **5** with the C=NH bond leads to intermediate **7**. Then, *N*-cyclization provides intermediate **8**. Finally, hydrolysis of **8** gives the title compounds **3** (Path *B*). To confirm this proposal, the intermediates **4** [1] and **5** were synthesized separately. The reaction of these intermediates in the presence of NH_4OAc led to compounds **3**. In another attempt, when we reacted compound **4** and **5** in the absence of NH_4OAc, no product **3** was observed. So, there is a clear evidence that NH_4OAc is also necessary at this stage of the reaction sequence.

In summary, we have disclosed a concise approach to the synthesis of new chromenopyrazole derivatives by one-pot reaction between salicylaldehyde, malononitrile, $NH_2NH_2 \cdot H_2O$, arylisothiocyanate, and H_2O. These types of heterocycles contain a number of functional groups that may lead to biological activity. Excellent yields of the products, fairly short reaction times, simple purifications, and the use of simple and inexpensive starting materials characterize this method. The simplicity of the present procedure renders it an interesting alternative to complex multistep approaches.

Experimental Part

General. All starting materials were obtained from *Merck* (Germany) and *Fluka* (Switzerland) and were used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: in KBr on a *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: at 400 and 100 MHz, resp., on a *Bruker DRX 400-AVANCE* FT-NMR instrument, in $CDCl_3$ if not otherwise stated. MS: *Finnigan-MAT* 8430 mass

spectrometer, at an ionization potential of 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN–O–Rapid* analyzer.

General Procedure (exemplified for **3a**). A soln. of phenyl isothiocyanate (0.135 g, 1 mmol) and $NH_2NH_2 \cdot H_2O$ (80%; 0.040 g, 1 mmol) in EtOH (3 ml) was magnetically stirred for 1 h at r.t. Then, malononitrile (0.066 g, 1 mmol), salicylaldehyde (0.122 g, 1 mmol), NH_4OAc (0.077 g, 1 mmol), and AcOH (3 ml) were added, and the mixture was stirred at reflux for 2 h. After completion, the hot mixture was filtered, and the precipitate was washed with EtOH to afford the pure product **3a**.

3-Oxo-N-*phenylchromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide* (**3a**). Yield: 268 mg (89%). Yellow powder. M.p. $>300°$ (dec.). IR: 3339 (NH), 1724 (C=O), 1607, 1566, 1498 (Ar), 1427 (C=S), 1211 (C–O). ^{1}H-NMR: 7.02 (*t*, *J* = 7.3, H_p of Ph); 7.36 (*t*, *J* = 7.4, 2 H_m of Ph); 7.43 (*t*, *J* = 7.4, H–C(6)); 7.50 (*d*, *J* = 8.2, H–C(8)); 7.63 (*d*, *J* = 6.1, 2 H_o of Ph); 7.69 (*t*, *J* = 7.5, H–C(7)); 7.97 (*d*, *J* = 7.4, H–C(5)); 8.96 (*s*, H–C(4)); 10.52 (*s*, NH). ^{13}C-NMR: 115.9; 117.6; 117.9; 118.8; 122.1; 125.2; 129.1; 129.6; 132.9; 138.8; 140.5; 149.3; 153.0; 159.4; 166.7. EI-MS (70 eV): 321 (90, M^+), 320 (23), 236 (16), 150 (83), 123 (26), 114 (32), 97 (49), 83 (56), 69 (75), 57 (100). Anal. calc. for $C_{17}H_{11}N_3O_2S$ (321.35): C 63.54, H 3.45, N 13.08; found: C 63.61, H 3.50, N 13.10.

6-Bromo-3-oxo-N-*phenylchromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide* (**3b**). Yield: 332 mg (83%). Orange powder. M.p. $>300°$ (dec.). IR: 3323 (NH), 1706 (C=O), 1602, 1547, 1488 (Ar), 1442 (C=S), 1210 (C–O). ^{1}H-NMR: 7.00 (*t*, *J* = 7.3, H_p of Ph); 7.34 (*t*, *J* = 7.4, 2 H_m of Ph); 7.44 (*d*, *J* = 6.6, H–C(8)); 7.60 (*d*, *J* = 6.1, 2 H_o of Ph); 7.79 (*d*, *J* = 8.4, H–C(7)); 8.21 (*s*, H–C(5)); 8.88 (*s*, H–C(4)); 10.55 (*s*, NH). ^{13}C-NMR: 117.2; 118.1; 119.0; 119.5; 121.3; 122.6; 129.7; 131.9; 135.5; 137.7; 140.9; 149.5; 152.5; 159.5; 167.3. EI-MS (70 eV): 401 (10, $[M+2]^+$), 399 (10, M^+), 368 (49), 268 (100), 251 (27), 236 (30), 150 (40), 135 (36), 93 (50). Anal. calc. for $C_{17}H_{10}BrN_3O_2S$ (400.25): C 51.02, H 2.52, N 10.50; found: C 51.10, H 2.59, N 10.40.

6-Bromo-N-*(4-fluorophenyl)-3-oxochromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide* (**3c**). Yield: 385 mg (92%). Orange powder. M.p. $>300°$ (dec.). IR: 3338 (NH), 1706 (C=O), 1555, 1508 (Ar), 1435 (C=S), 1223 (C–O). ^{1}H-NMR: 7.19–7.22 (*m*, 2 arom. H); 7.47 (*d*, *J* = 8.8, H–C(8)); 7.63–7.67 (*m*, 2 arom. H); 7.82 (*dd*, *J* = 8.8, 2.3, H–C(7)); 8.24 (*d*, *J* = 2.3, H–C(5)); 8.91 (*s*, H–C(4)); 10.53 (*s*, NH). ^{13}C-NMR: 115.7 (*d*, *J* = 22.3); 116.8; 118.5; 119.0; 119.4 (*d*, ^2J(C,F) = 109.8); 120.8; 131.5; 135.1; 136.9; 137.3; 149.1; 152.1; 157.4 (*d*, ^1J(C,F) = 239.2); 159.0; 167.0. EI-MS (70 eV): 368 (31), 304 (100), 251 (75), 223 (36), 194 (27), 152 (47), 111 (96), 83 (53), 57 (43). Anal. calc. for $C_{17}H_9BrFN_3O_2S$ (418.24): C 48.82, H 2.17, N, 10.05; found: C 48.65, H 2.29, N 10.14.

6-Nitro-3-oxo-N-*phenylchromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide* (**3d**). Yield: 289 mg (79%). Orange powder. M.p. $>300°$ (dec.). IR: 3210 (NH), 1718 (C=O), 1610, 1493 (Ar), 1537, 1344 (NO_2), 1449 (C=S), 1195 (C–O). ^{1}H-NMR: 7.04 (*t*, *J* = 7.2, H_p of Ph); 7.38 (*t*, *J* = 7.6, 2 H_m of Ph); 7.65 (*d*, *J* = 7.6, 2 H_o of Ph); 7.73 (*d*, *J* = 9.2, H–C(8)); 8.46 (*dd*, *J* = 9.2, 2.8, H–C(7)); 9.00 (*d*, *J* = 2.8, H–C(5)); 9.13 (*s*, H–C(4)); 10.63 (*s*, NH). ^{13}C-NMR: 117.6; 117.8; 119.4; 119.8; 122.2; 125.3; 127.0; 129.2; 137.3; 140.3; 144.0; 148.7; 156.4; 158.7; 166.9. EI-MS (70 eV): 268 (37), 209 (100), 167 (14), 150 (34), 135 (72), 118 (12), 104 (29), 93 (30), 77 (45). Anal. calc. for $C_{17}H_{10}N_4O_4S$ (366.35): C 55.74, H 2.75, N 15.29; found: C 55.86, H 2.69, N 15.40.

N-*(4-Chlorophenyl)-3-oxochromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide* (**3e**). Yield: 308 mg (87%). Yellow powder. M.p. $>300°$ (dec.). IR: 3313 (NH), 1683 (C=O), 1607, 1555 (Ar), 1492 (C=S), 1209 (C–O). ^{1}H-NMR: 7.38 (*t*, *J* = 7.5, H–C(6)); 7.42 (*d*, *J* = 8.6, 2 arom. H); 7.44 (*t*, *J* = 7.5, H–C(7)); 7.52 (*d*, *J* = 8.3, H–C(8)); 7.69 (*d*, *J* = 8.6, 2 arom. H); 7.96 (*d*, *J* = 7.4, H–C(5)); 8.98 (*s*, H–C(4)); 10.67 (*s*, NH). ^{13}C-NMR: 116.7; 118.2; 119.3; 119.5; 125.7; 125.9; 129.4; 130.2; 133.5; 139.4; 139.8; 150.3; 153.5; 159.9; 166.7. EI-MS (70 eV): 357 (36, $[M+2]^+$), 355 (89, M^+), 236 (30), 201 (22), 184 (38), 171 (56), 169 (100), 127 (61), 111 (28). Anal. calc. for $C_{17}H_{10}ClN_3O_2S$ (355.80): C 57.39, H 2.83, N 11.81; found: C 57.35, H 2.72, N 11.99.

6-Bromo-N-*(4-chlorophenyl)-3-oxochromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide* (**3f**). Yield: 326 mg (75%). Orange powder. M.p. $>300°$ (dec.). IR: 3329 (NH), 1704 (C=O), 1601, 1542 (Ar), 1490 (C=S), 1199 (C–O). ^{1}H-NMR: 7.39 (*d*, *J* = 8.7, 2 arom. H); 7.45 (*d*, *J* = 8.8, H–C(8)); 7.66 (*d*, *J* = 8.7, 2 arom. H); 7.80 (*dd*, *J* = 8.9, 2.0, H–C(7)); 8.22 (*d*, *J* = 2.0, H–C(5)); 8.89 (*s*, H–C(4)); 10.65 (*s*, NH). ^{13}C-NMR: 116.8; 118.5; 118.8; 119.1; 120.7; 125.5; 128.9; 131.5; 135.1; 137.4; 139.3; 149.5; 152.0; 159.0; 166.5. EI-MS (70 eV): 436 (1, $[M+4]^+$), 434 (8, $[M+2]^+$), 432 (6, M^+), 368 (21), 313 (8), 264 (8), 236

(18), 201 (20), 169 (100), 127 (43), 96 (11). Anal. calc. for $C_{17}H_9BrClN_3O_2S$ (434.69): C 46.97, H 2.09, N 9.67; found: C 46.92, H 2.18, N 9.78.

N-*(4-Chlorophenyl)-6-methoxy-3-oxochromeno[2,3-*c*]pyrazole-2(3*H*)-carbothioamide* (**3g**). Yield: 308 mg (80%). Yellow powder. M.p. $>300°$ (dec.). IR: 3432 (NH), 1724 (C=O), 1568, 1493 (Ar), 1446 (C=S), 1285, 1190 (C–O). ^{1}H-NMR: 3.80 (*s*, MeO); 7.37 – 7.40 (*m*, 3 arom. H); 7.51 – 7.52 (*m*, 1 arom. H); 7.65 – 7.68 (*m*, 3 arom. H); 8.88 (*s*, H–C(4)); 10.64 (*s*, NH). ^{13}C-NMR: 56.3; 111.8; 117.8; 118.3; 119.5; 119.7; 121.3; 125.9; 129.4; 139.1; 139.8; 148.0; 150.3; 156.5; 160.0; 166.7. EI-MS (70 eV): 201 (100), 186 (59), 173 (28), 158 (82), 143 (8), 130 (36), 114 (5), 102 (40), 76 (25). Anal. calc. for $C_{18}H_{12}ClN_3O_3S$ (385.82): C 56.04, H 3.13, N 10.89; found: C 56.22, H 3.21, N 10.84.

REFERENCES

[1] J. Volmajer, R. Toplak, I. Leban, A. M. Le Marechal, *Tetrahedron* **2005**, *61*, 7012.
[2] A. Alizadeh, M. Babaki, N. Zohreh, *Tetrahedron* **2009**, *65*, 1704.
[3] A. Alizadeh, R. Ghanbaripour, L.-G. Zhu, *Synth. Commun.* **2013**, *43*, 2575.
[4] A. Alizadeh, R. Ghanbaripour, *Helv. Chim. Acta* **2013**, *96*, 473.
[5] A. Alizadeh, R. Ghanbaripour, L.-G. Zhu, *Synlett* **2013**, *24*, 2124.

Received November 2, 2013