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Reactions of chromone-3-carboxamides with 2-cyanothioacetamides

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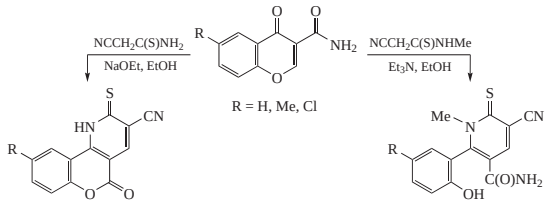
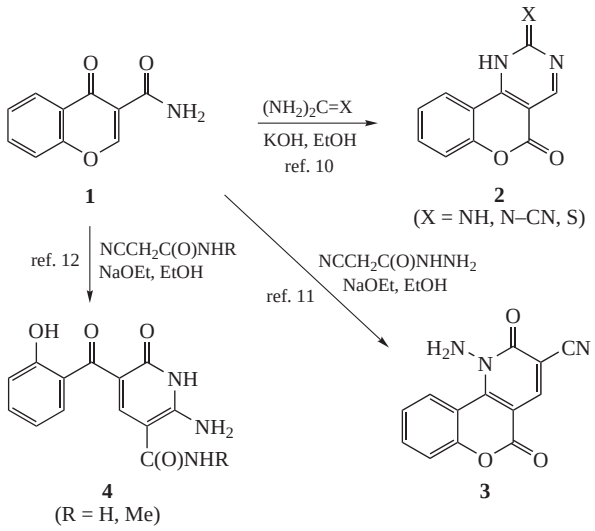
Chromone-3-carboxamides react with cyanothioacetamide in the presence of NaOEt in boiling ethanol to form 5-oxo-2-thioxo-1,5-dihydro-2*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles (67–87% yields), whereas their reaction with *N*-methylcyanothioacetamide and a catalytic amount of Et_3N in boiling ethanol affords 5-cyano-2-(2-hydroxyphenyl)-1-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamides in 57–73% yields.



Owing to its availability[1] and diverse reactivity, cyanothioacetamide is a convenient starting compound for synthesizing numerous nitrogen- and sulfur-containing heterocycles.[2] Cyanothioacetamides readily react with 1,3-diketones[3,4] and α,β-enones[5,6] in the presence of bases to give 3-cyano-2-thiopyridones that exhibit a broad spectrum of biological activity, including the vasodilatory effect[7] and antitumor activity toward human cancer cells.[8] 3-Substituted chromones such as chromone-3-carboxylic acid and its functional derivatives,[9] in distinction to simple diketones and enones have an additional electrophilic center. Therefore certain difficulties in determining their reaction sites sometimes arise. It is known[10–12] that chromone-3-carboxamide **1** reacts with such 1,3-N,N-dinucleophiles as guanidine, cyanoguanidine and thiourea at the C^2 and C^4 atoms with subsequent cyclization into 3,4-fused coumarins **2** involving the phenol hydroxyl and carbamoyl groups.[10] In a similar manner, chromone **1** reacts with cyanoacetohydrazide acting as a 1,3-C,N-dinucleophile, to form chromeno[4,3-*b*]pyridine-3-carbonitrile **3**.[11] However, its reactions with cyanoacetamide and *N*-methylcyanoacetamide occur differently: the attack at the C^2 atom and opening of the pyrone ring are followed by addition of the carbamoyl NH_2 group at the CN one to give 2-pyridones **4** containing a salicyloyl moiety.[12] In this reaction, cyanoacetamides act as 1,2-ambiphiles bearing both nucleophilic and electrophilic centers (see Scheme 1).

Since information on the reactions of 3-carbamoylchromones **1** with cyanothioacetamides is lacking, and it is impossible to predict which of the two pathways these reactions can follow, in this work we studied such reactions. Chromones **1a–c**, cyanothioacetamide and *N*-methylcyanothioacetamide were chosen as examples. In our hands, refluxing 3-carbamoylchromones **1a–c** with cyanothioacetamide (2 equiv.) in anhydrous ethanol in the presence of sodium ethoxide for 1.5 h afforded chromeno[4,3-*b*]-pyridines **5a–c** in 67–87% yields† whose structures were similar to those of compounds **2** and **3** (Scheme 2).

It is of interest that the appearance of a methyl group at the nitrogen atom of the thioamido group considerably affects the structure of the end product. In fact, the reaction of chromone **1a** with *N*-methylcyanothioacetamide[13] gave a mixture of products containing compound **6a** as the main component (^{1}H NMR data). The use of potassium *tert*-butoxide in *tert*-butanol did not result in the *N*-methyl analogue of pyridocoumarin **5a**, either. However, refluxing chromones **1a–c** with 2 equiv. of *N*-methylcyanothioacetamide in ethanol in the presence of triethylamine for 3–4 h

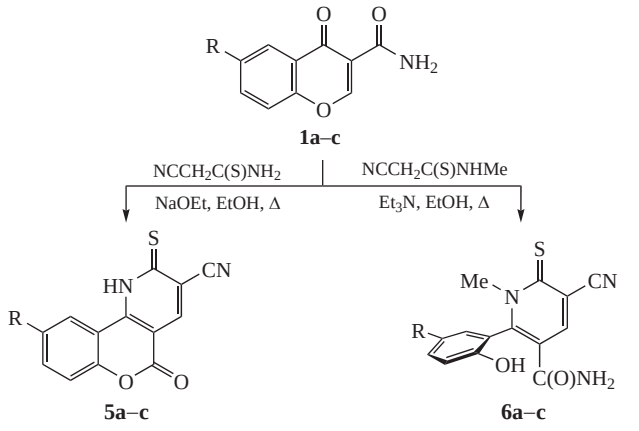


Scheme 1

† NMR spectra were recorded on Bruker DRX-400 and AVANCE-500 spectrometers with TMS as an internal standard. IR spectra were recorded on a Nicolet 6700 instrument (in KBr tablets). Melting points were obtained on a Stuart SMP30 apparatus in open capillaries.

Synthesis of **5a–c** *(general procedure)*. A mixture of chromone-3-carboxamide **1** (1.0 mmol), cyanothioacetamide (0.20 g, 2 mmol) and sodium ethoxide, which was prepared by dissolving sodium (0.046 g, 2.0 mmol) in anhydrous ethanol (5 ml), was refluxed for 1.5 h. After cooling, the reaction mixture was diluted with water (the resulting solid may dissolve) and neutralized with ~1 M HCl. The solid obtained was washed with ethanol and filtered to give product **5** as colored crystals.

*5-Oxo-2-thioxo-1,5-dihydro-2*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile* **5a**. Yield 87%, yellow powder, mp 263–264 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.48 (t, 1H, H-9, *J* 7.6 Hz), 7.51 (d, 1H, H-7, *J* 7.8 Hz), 7.81 (td, 1H, H-8, *J* 7.8, 1.2 Hz), 8.54 (s, 1H, H-4), 8.84 (d, 1H, H-10, *J* 8.0 Hz) (labile proton was not detected). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 107.3, 111.5, 115.8, 116.9, 117.7, 125.0, 125.3, 135.3, 141.9, 148.0, 153.3, 157.4 (C=O), 182.5 (C=S). IR (ν/cm^{-1}): 2231 (CN), 1728 (C=O), 1579 (Ar). Found (%): C, 59.63; H, 2.53; N, 10.98. Calc. for $C_{13}H_6N_2O_2S \cdot 0.5H_2O$ (%): C, 59.31; H, 2.68; N, 10.64.

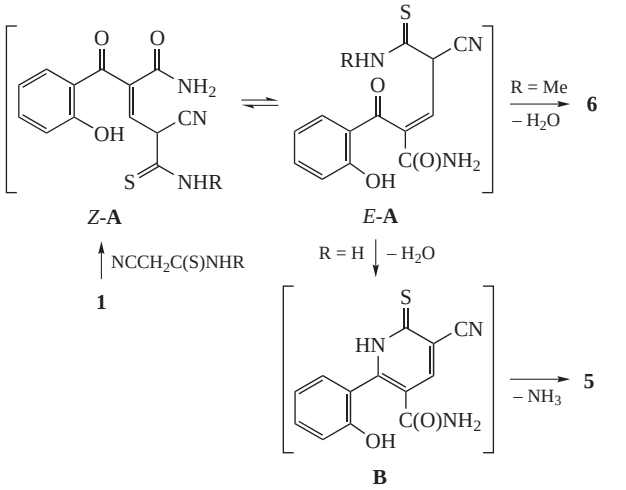


	R	Yield of **5** (%)	Yield of **6** (%)
a	H	87	57
b	Me	67	73
c	Cl	71	71

Scheme 2

led to 2-thiopyridones **6a–c** in 57–73% yields (see Scheme 2).‡ Note that, unlike the reaction of chromone-3-carboxamides **1** with cyanoacetamides,[12] no products of cyclization involving the CN group of cyanothioacetamides were found.

A possible reaction mechanism is presented in Scheme 3. Initial attack of the cyanothioacetamide as a C-nucleophile at the C^2 atom of chromone **1** results in the *Z*-**A** intermediate, which is in equilibrium with the *E*-**A** one owing to the push-pull effect. When R = Me, the latter undergoes cyclization to the end product **6**, while in the case of R = H, coumarin **5** is formed *via* the 2-thiopyridone intermediate **B**. Apparently, the reaction is terminated at the stage of compounds **6** due to the spatial hindrance created by the methyl group, which moves the phenol moiety away from the heterocycle plane and thus prevents cyclization *via* attack of the phenol hydroxyl on the carbonyl group (see Scheme 3).



Scheme 3

The structures of the products obtained were confirmed by elemental analyses, IR, ^{1}H and ^{13}C NMR spectroscopy. The chemical shifts of protons in compounds **5a** and **6a** are in good agreement with the suggested structures (see Figure S1, Online Supplementary Materials). The characteristic signals in the ^{13}C NMR spectra do not contradict the reported data.[14]

In conclusion, unlike cyanoacetamides[12] that act as 1,2-ambiphiles in reactions with chromone-3-carboxamides, cyanothioacetamides behave as 1,3-C,N-dinucleophiles. This difference in the behavior of closely related acetamides results from the replacement of an oxygen atom by a sulfur atom, which considerably increases the nucleophilicity of the amino group in the thioamide substituent and makes its attack on the carbonyl group more preferable. It has been found that, for sterical reasons, the reaction with *N*-methylcyanothioacetamide stops at the stage of 2-thiopyridones, while the reaction with cyanothioacetamide results in cyclization of 2-thiopyridones to chromeno[4,3-*b*]-pyridines.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.022.

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‡ *Synthesis of* **6a–c** *(general procedure).* A stirred mixture of chromone-3-carboxamide **1** (1.0 mmol), *N*-methylcyanothioacetamide (228 mg, 2 mmol) and triethylamine (3 drops) in ethanol (96%, 7 ml), was refluxed until all the solid dissolved and then for an additional 1 h (usually 3–4 h). After cooling, the reaction mixture was acidified with ~1 M HCl to pH 4–5 (if no precipitate appeared after that, the mixture was diluted with some amount of water). The solid obtained was filtered off and crystallized to give product **6** as colored crystals.

5-Cyano-2-(2-hydroxyphenyl)-1-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide **6a**. Yield 57%, orange powder, mp 247–248 °C (*n*-butanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.66 (s, 3H, Me), 6.92 (td, 1H, H-5′, *J* 7.4, 0.5 Hz), 6.96 (d, 1H, H-3′, *J* 8.1 Hz), 7.19 (dd, 1H, H-6′, *J* 7.6, 1.5 Hz), 7.35 (td, 1H, H-4′, *J* 7.8, 1.7 Hz), 7.39 (br.s, 1H, N*H*H), 7.55 (br.s, 1H, NH*H*), 8.23 (s, 1H, H-4), 10.25 (s, 1H, OH). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 42.1 (Me), 115.7, 116.2, 116.8, 119.2, 120.0, 124.2, 129.4, 131.8, 140.5, 153.5, 154.4, 165.3 (C=O), 178.9 (C=S). IR (ν/cm^{-1}): 3450–3200 (OH and NH_2), 2231 (CN), 1672 (C=O), 1585 (Ar). Found (%): C, 58.95; H, 3.89; N, 14.70. Calc. for $C_{14}H_{11}N_3O_2S$ (%): C, 58.93; H, 3.89; N, 14.73.