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Reactions of chromone-3-carboxylic acid and chromone-3-carboxamides with cyanoacetic acid hydrazide

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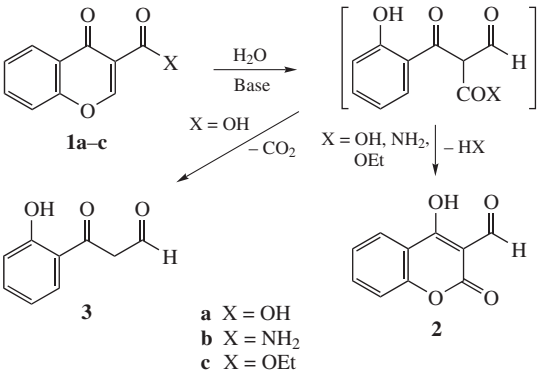
Chromone and chromone-3-carboxylic acid react with cyanoacetic acid hydrazide in the presence of NaOEt in boiling ethanol to form 6-(2-hydroxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3(2*H*)-one (58–62% yields), whereas reaction between chromone-3-carboxamides and cyanoacetic acid hydrazide under the same conditions affords 1-amino-2,5-dioxo-2,5-dihydro-1*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles (50–67% yields).

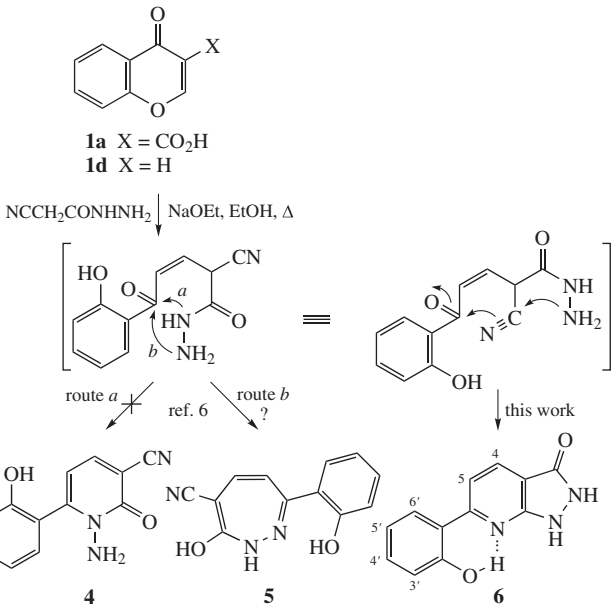
Recently, chromones bearing electron-withdrawing groups at the 3-position (CHO, COR or CN) received considerable attention since their γ-pyrone ring represents geminally activated alkene with three electrophilic centers (the C-2 and C-4 atoms and the 3-substituent) and a good leaving group at C-2 (the phenolate anion). Of the three possible sites of a nucleophilic attack, conjugated addition at C-2, which is usually accompanied by pyrone ring opening and recyclizations with the participation of the phenol oxygen atom or the second nucleophilic center of the reagent, most frequently occurs.[1] This provides great synthetic opportunities, however, it is difficult to define the site of an initial attack and the direction of the subsequent recyclization. Therefore, the regiochemistry of the end products formed from 3-substituted chromones is the problem of priority importance.[2]

In the series of 3-substituted chromones, the best studied compounds are 3-formyl-,[1] 3-aroyl-,[3] 3-polyhaloacyl-,[4] 3-methoxalyl-[3,5] and 3-cyanochromones.[2] At the same time, in spite of the high synthetic value of 3-R-chromones, chromone-3-carboxylic acid **1a** and its amide **1b** have been first systematically studied by Ibrahim.[6–8] In 1974, the rearrangement of ethyl chromone-3-carboxylate **1c** into 4-hydroxy-3-formylcoumarin **2** in a basic medium[9] was described for the first time. In this context, it would be reasonable to expect that compounds **1a** and **1b** could behave as the synthetic equivalents of coumarin **2** in reactions with nucleophiles. Indeed, chromones **1a** and **1b** give the appropriate derivatives of 4-hydroxy-3-formylcoumarin **2** with amines, hydrazines, hydroxylamine, guanidines and thiourea.[6–8] Furthermore, acid **1a** undergoes decarboxylation and acts as hidden ω-formyl-2-hydroxyacetophenone **3** in the reactions with amines and cyanoacetamide[6] (Scheme 1).



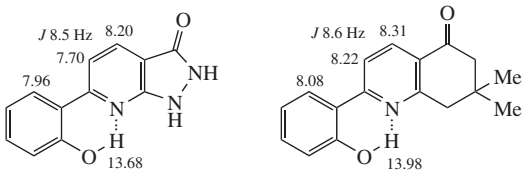
Scheme 1

On the basis of the ^{1}H NMR spectrum, Ibrahim[6] preferred the doubtful 1,2-diazepine structure of compound **5** with enolized amide carbonyl for the product of a reaction of acid **1a** with cyanoacetic acid hydrazide (CAH) among two proposed structures **4** and **5** (Scheme 2).



Scheme 2

On reproducing this synthesis (boiling in EtOH in the presence of NaOEt for 2 h), we isolated a product (62% yield), which coincided with that obtained by Ibrahim[6] in its spectral characteristics and elemental analysis data. We also obtained the same compound from unsubstituted chromone **1d**; this fact was indicative of the decarboxylation of acid **1a** in the course of reaction and its participation as a synthetic equivalent of ω-formyl-2-hydroxyacetophenone **3**. We assigned its structure to pyrazolo[3,4-*b*]-pyridine derivative **6** based on a comparison of its ^{1}H NMR spectra with that of close analogue 2-(2-hydroxyphenyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-one **7**[10] recorded in DMSO-d_6 (Figure 1). In the IR spectrum, an absorption band characteristic



6 **7**

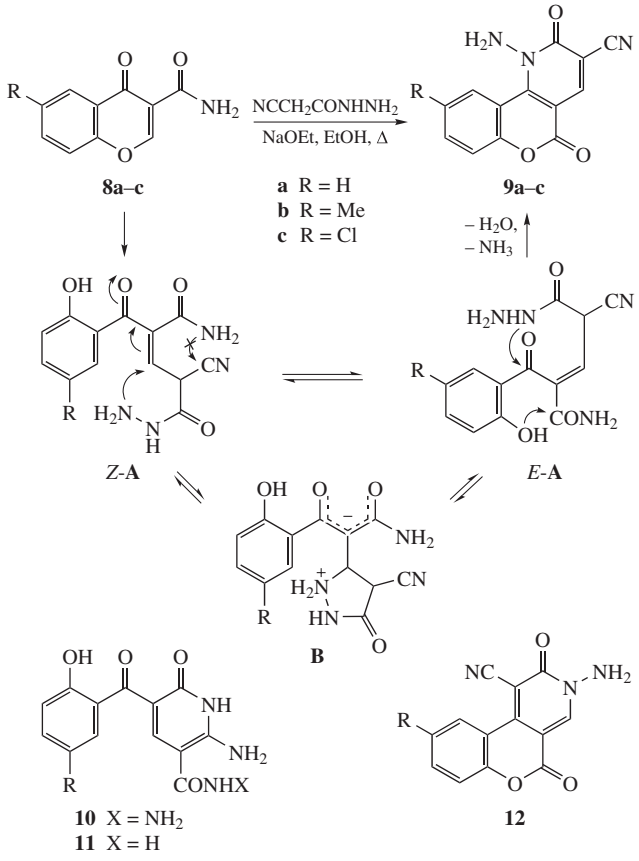
Figure 1 ^{1}H NMR (DMSO-d_6) data for compounds **6** and **7**.

of CN group in the region 2200–2250 cm^{-1} was absent.† Furthermore, it is well known that β-keto aldehydes,[11] β-diketones[12] and isoflavones[13] react with CAH or its cyclic form, 5-amino-1*H*-pyrazol-3(2*H*)-one, to afford pyrazolo[3,4-*b*]pyridines.

A probable reaction mechanism includes the nucleophilic addition of methylene active CAH at the C-2 atom of chromones **1a**,**d** with the subsequent pyrone ring opening, decarboxylation (in the case of **1a**) and tandem cyclization into pyrazolopyridine **6**, in which the carbonyl group of chromone is attacked by the nitrogen atom of the nitrile group rather than hydrazino group (see Scheme 2).

The reaction of 3-carbamoylchromones **8a–c** (**8a = 1b**) with CAH was not studied earlier. We established that, in contrast to acid **1a**, amides **8a–c** react with CAH under analogous conditions in a completely different manner to give previously unknown 1-amino-2,5-dioxo-2,5-dihydro-1*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles **9a–c** in 50–67% yields (Scheme 3).‡ Our attempts to isolate a corresponding product with 6-nitro-4-oxochromene-3-carboxamide **8d** failed (see Online Supplementary Materials). We assume that the initially formed intermediate **A** with the *Z*-configuration of the double bond is isomerized into *E*-**A** through bipolar intermediate **B**. Because of the contiguous arrangement of reaction centers, *E*-**A** is cyclized into coumarin derivative **9** with the release of water and ammonia molecules (Scheme 3). This isomerization occurs more rapidly than the interaction between the amino and cyano groups of intermediate *Z*-**A** since the formation of products **10** was not observed. In this context, note that the reaction of chromones **8** with cyanoacetamide gives 2-pyridones **11**.[7,14]

The regioisomeric structure **12** was excluded based on an analysis of the results of ^{1}H–^{13}C HSQC and HMBC 2D experiments performed for compound **9b**. The most informative cross peaks of the 2D HMBC spectrum are the peaks H^4/CN, H^4/C^{10b}, H^4/C^5, H^4/C^2, NH$_2$/C^{10b}, NH$_2$/C^2. In addition, the cross peaks of the H-4 atom with nitrogen atoms are absent from the 2D ^{1}H–^{15}N HMBC spectrum (see Online Supplementary Materials). Note that, in the ^{1}H NMR spectra of chromeno[4,3-*b*]pyridines **9a–c**, the signal of the H-10 proton occurs in an uncommonly low field at δ 9.62–9.90 ppm; this is due to the angular structure of the skeleton rather than the deshielding effect of the NH$_2$ group.[15] The synthesis of 1-amino-3-cyano-8-fluoro-2-oxo-1,2-dihydro[1,2]-benzoxathiino[4,3-*b*]pyridine 5,5-dioxide from phenyl 7-fluorochromone-3-sulfonate and CAH is the nearest analogue of the described reaction.[16]



Scheme 3

† The NMR spectra were recorded on Bruker DRX-400 and AVANCE-500 spectrometers with TMS as an internal standard. The IR spectra were recorded on a Nicolet 6700 instrument (FTIR mode, ZnSe crystal).

*6-(2-Hydroxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3(2*H*)-one* **6**. This compound was prepared according to a published procedure.[6] Yield, 140 mg (62%), yellow powder, mp > 300 °C (lit.,[6] mp > 300 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.89 (t, 1H, H-5′, *J* 7.7 Hz), 6.90 (d, 1H, H-3′, *J* 7.8 Hz), 7.27 (td, 1H, H-4′, *J* 7.7, 1.3 Hz), 7.70 (d, 1H, H-5, *J* 8.5 Hz), 7.96 (d, 1H, H-6′, *J* 7.8 Hz), 8.20 (d, 1H, H-4, *J* 8.5 Hz), 10.80 (br. s, 1H, NH), 12.12 (br. s, 1H, NH), 13.68 (s, 1H, OH). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 103.5, 111.7, 117.9, 119.1, 119.6, 128.1, 131.6, 131.7, 149.4, 154.2, 156.6, 158.8. IR (ν/cm^{-1}): 3279, 2936, 2567, 1663, 1603, 1578, 1556, 1505, 1490, 1430. Found (%): C, 63.30; H, 4.04; N, 18.10. Calc. for $C_{12}H_9N_3O_2$ (%): C, 63.43; H, 3.99; N, 18.49. Product **6** was also obtained from chromone **1d** under the same conditions in 58% yield.

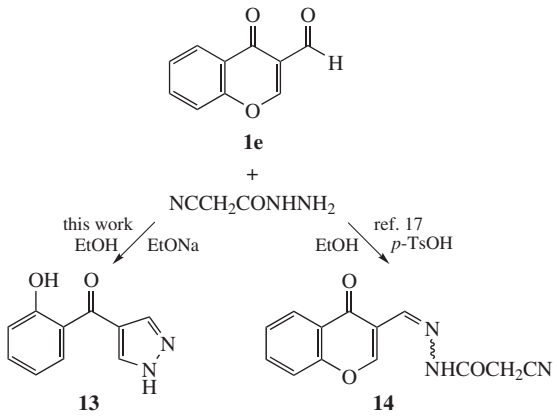
‡ A mixture of chromone-3-carboxamide **8** (1.0 mmol), CAH (0.10 g, 1 mmol) and sodium ethoxide, which was prepared by dissolving sodium (0.023 g, 1.0 mmol) in 4 ml of absolute ethanol, was refluxed for 2 h. After cooling, the reaction mixture was neutralized with dilute HCl. The solid obtained was filtered and crystallized from DMF–butanol (1:5) to give **9** as colored crystals.

*1-Amino-2,5-dioxo-2,5-dihydro-1*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile* **9a**. Yield, 126 mg (50%), red powder, mp 235 ° (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 6.51 (s, 2H, NH$_2$), 7.48 (td, 1H, H-9, *J* 7.8, 1.0 Hz), 7.51 (dd, 1H, H-7, *J* 8.3, 1.0 Hz), 7.81 (td, 1H, H-8, *J* 7.8, 1.2 Hz), 8.75 (s, 1H, H-4), 9.79 (dd, 1H, H-10, *J* 8.6, 1.2 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 100.7, 102.8, 113.1, 115.0, 117.9, 124.4, 130.6, 134.9, 144.9, 148.7, 153.6, 157.8, 159.8. IR (ν/cm^{-1}): 3297, 3204, 3133, 3063, 2235 (C≡N), 1730 (C=O), 1679 (C=O), 1609, 1526, 1488, 1455. Found (%): C, 61.40; H, 2.74; N, 16.54. Calc. for $C_{13}H_7N_3O_3$ (%): C, 61.66; H, 2.79; N, 16.59.

*1-Amino-9-methyl-2,5-dioxo-2,5-dihydro-1*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile* **9b**. Yield, 156 mg (58%), light brown powder, mp 244–247 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.42 (s, 3H, Me), 6.51 (s, 2H, NH$_2$), 7.41 (d, 1H, H-7, *J* 8.4 Hz), 7.63 (dd, 1H, H-8, *J* 8.4, 1.5 Hz), 8.73 (s, 1H, H-4), 9.62 (d, 1H, H-10, *J* 1.5 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 20.9, 100.6, 102.7, 112.7, 115.0, 117.6, 130.1, 133.5, 135.7, 144.9, 148.6, 151.7, 157.9, 159.7. IR (ν/cm^{-1}): 3300, 3228, 3211, 3133, 3062, 2235 (C≡N), 1730 (C=O), 1677 (C=O), 1614, 1594, 1527, 1487, 1455. Found (%): C, 62.61; H, 3.25; N, 15.65. Calc. for $C_{14}H_9N_3O_3$ (%): C, 62.92; H, 3.39; N, 15.72.

*1-Amino-9-chloro-2,5-dioxo-2,5-dihydro-1*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile* **9c**. Yield, 194 mg (67%), light brown powder, mp 237–239 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 6.49 (s, 2H, NH$_2$), 7.55 (d, 1H, H-7, *J* 8.5 Hz), 7.87 (d, 1H, H-8, *J* 8.5 Hz), 8.76 (s, 1H, H-4), 9.90 (s, 1H, H-10). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 101.6, 103.1, 114.3, 114.8, 119.8, 128.0, 129.5, 134.4, 144.9, 147.8, 152.3, 157.4, 159.7. IR (ν/cm^{-1}): 3304, 3199, 3133, 3056, 2232 (C≡N), 1729 (C=O), 1682 (C=O), 1632, 1605, 1593, 1569, 1514, 1474, 1410. Found (%): C, 54.04; H, 2.30; N, 14.56. Calc. for $C_{13}H_6ClN_3O_3$ (%): C, 54.28; H, 2.10; N, 14.61.

It is interesting that, under the conditions described above (NaOEt, EtOH, boiling for 2 h), CAH serves as hydrazine source in the reaction with 3-formylchromone **1e** and gives known 4-salicyloylpyrazole[17] **13** (see Online Supplementary Materials) in 37% yield. Note that, in the presence of a catalytic quantity of *p*-toluenesulfonic acid in ethanol at 60 °C, this reaction stops at the step of hydrazone **14**[18] (Scheme 4).



Scheme 4

Thus, the reactions of CAH with 3-R-chromones (R = CO_2H, $CONH_2$, and CHO) in the presence of NaOEt in boiling EtOH occur differently depending on the nature of the substituent R to give three types of products. In these cases, CAH acts either as a 1,3-C,N-dinucleophile with the participation of the nitrogen atom of hydrazino or cyano groups or as a source of hydrazine.

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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.2016.01.028.

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