

## Use of cyclic aliphatic ketones for spiro 2-amino-3-cyano pyrano[3,2-*c*]chromene formation

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### Abstract

The three component reaction between 4-hydroxycoumarin, malononitrile and carbonyl compounds in ethanol in the presence of morpholine as a catalyst was studied. Only cyclic aliphatic ketones afford spiro 2-amino-3-cyanopyrano[3,2-*c*]chromene derivatives.

**Keywords:** 4-Hydroxycoumarin, malononitrile, cyclic aliphatic ketone, spiro, pyrano[3,2-*c*]chromene

### Introduction

A key intermediate in the synthesis of warfarin (rodenticide, a blood anticoagulant) is 2-amino-3-cyano-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene **3** prepared by heating 4-hydroxycoumarin **1** with benzylidenemalononitrile **2** in pyridine<sup>1</sup> or water.<sup>2</sup> Acid hydrolysis of the pyrano[3,2-*c*]chromene **3** affords compound **4**, which is subsequently transformed into warfarin **5**.<sup>1-5</sup>

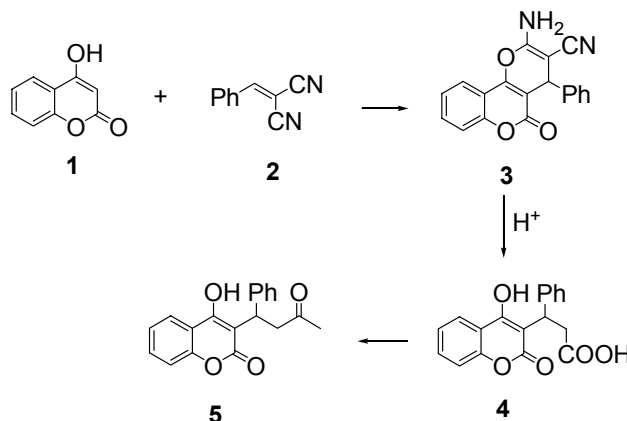


Figure 1

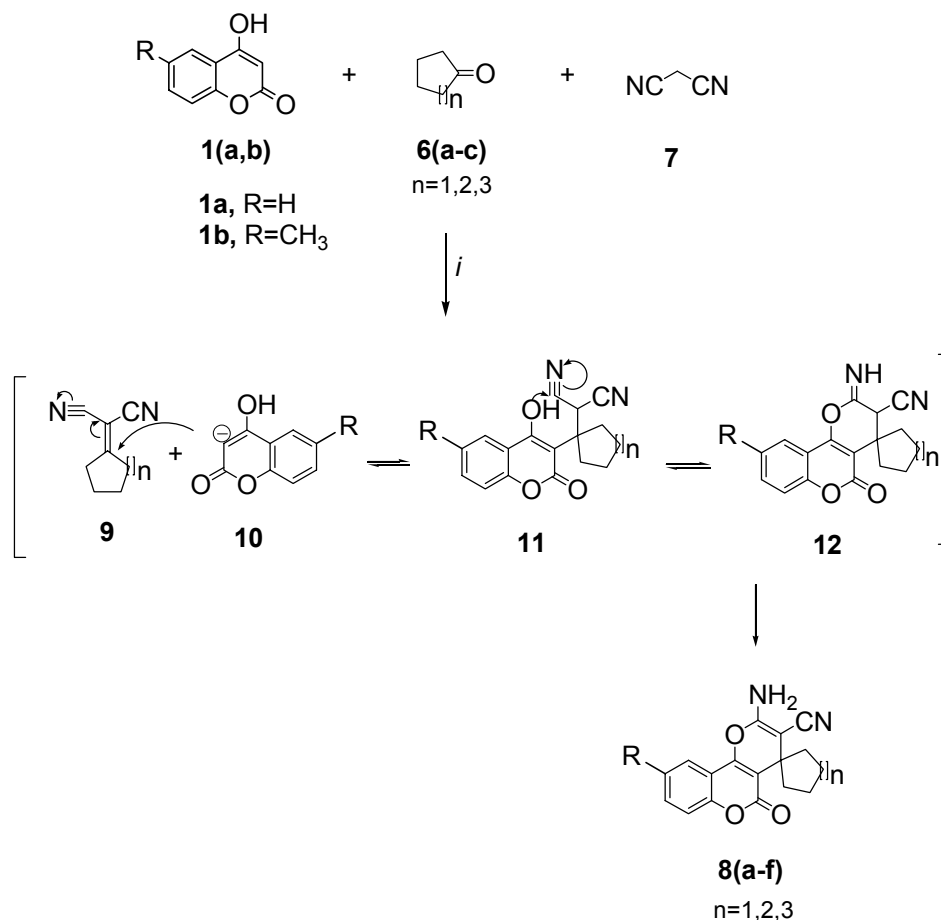
2-Amino-4-aryl-3-(thiocarbamoyl, alkoxy carbonyl, or cyano)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes were also obtained<sup>3,6</sup> by morpholine catalyzed reaction between 4-hydroxycoumarin with arylidenecyanothioacetamide, alkyl arylidenecyanoacetates, or arylidenemalononitrile in hot benzene or ethanol. Despite modest achievements in recent years for the synthesis of compounds of type **3** having substituents in position 4, the preparation and isolation of unsaturated nitriles **2**, which are analogs of toxic agents (2-chlorobenzylidene)malononitrile (CS),<sup>7-23</sup> may substantially complicate the aforementioned synthesis (Figure 1). In some cases, the condensation does not yield the target unsaturated nitrile at all. For instance reaction between pyridine-4-carbaldehyde and malononitrile yields 1-amino-2,4,4,6,6-pentacyano-3,5-di(4-pyridyl)cyclohex-1-ene.<sup>24</sup> This precludes the synthesis of pyrano[3,2-*c*]chromenes containing the 4-pyridyl substituent in position 4.

N-Substituted piperidine-4-one derivatives were failed to afford spiro[piperidine-4,4'-pyrano[3,2-*c*]chromenes],<sup>25</sup> while proficient to afford spiro[piperidine-4,4'-pyrano[3,2-*c*]quinoline]<sup>26</sup> derivatives by one-pot multicomponent reaction of 4-hydroxyquinolone, cyanoacetic acid derivatives and substituted piperidine-4-one derivatives. However, isatin derivatives are proficient as cyclic ketone to afford spiro[2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes]<sup>25</sup> by cross coupling reaction of 4-hydroxycoumarin, cyanoacetic acid derivatives and isatin derivatives.

In further investigations of cross coupling between cyanoacetic acid derivatives and carbonyl compounds with the aim of developing one step syntheses of functionalized heterocycles, we studied three component system reactions of 4-hydroxycoumarin, malononitrile, and carbonyl compounds (cyclic and non-cyclic aliphatic ketones).

## Results and Discussion

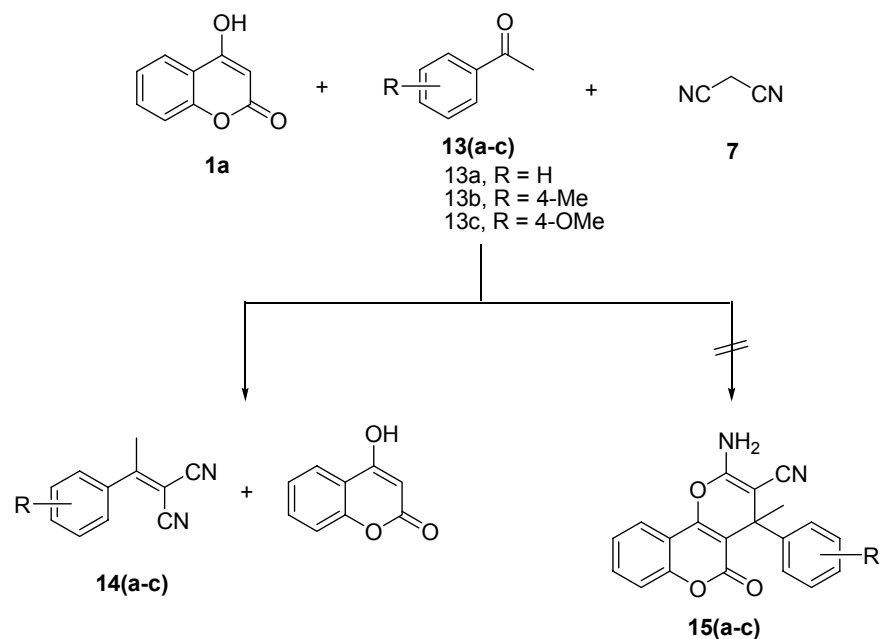
Brief heating of 4-hydroxycoumarin **1(a,b)** with cyclic aliphatic ketones (cyclopentanone, cyclohexanone, and cycloheptanone) **6(a-c)** and malononitrile **7** in boiling ethanol in the presence of morpholine as a catalyst gave 2-amino-3-cyanopyrano[3,2-*c*]chromene derivatives **8(a-f)** in high yields (65–85%). The observed high regioselectivity is most probably associated with the reaction sequence outlined in scheme **1**. Initial Knoevenagel reaction between cyclic ketones **6** and malononitrile **7** produces the unsaturated nitrile **9**, which, undergoes a Michael reaction with the base derived coumarin anion **10**. The resulting Michael adduct **11** then undergoes intramolecular cyclization producing the annelated iminopyran **12**. Subsequent tautomeric [1,3]sigmatropic shift gives compound **8** (Scheme 1).



**Scheme 1.** Mechanistic pathway towards **8(a-f)**.

Under these conditions, the reaction proceeds sufficiently rapidly and smoothly to afford the target chromenes **8(a-f)** in high yields without Michael adducts **11** being detected. However, the proposed mechanism is supported to some degree by isolation of analogous Michael adducts in the previously studied reaction of 4-hydroxycoumarin with arylidenecyanoacetamides.<sup>3</sup>

On the other hand the three component reaction system of 4-hydroxycoumarin **1a**, malononitrile **7** and substituted acetophenones **13(a-c)** as the carbonyl compound under analogous conditions failed to produce any chromenes **15(a-c)**. It was found that the acetophenones **13(a-c)** did react with malononitrile **7** to give unsaturated nitriles **14(a-c)** but these did not undergo Michael reaction with the coumarin anion. The plausible reason for the formation of spiro molecules with cyclic ketones is, in cyclic ketone the electrons are not localized in C–C bond but are actually spread out over the whole system, moreover the C in cyclic saturated ketones has  $sp^3$  hybridization. While in aromatic ketones C in benzene ring has  $sp^2$  hybridization due to this effect it may be cannot take part in cyclization.



**Scheme 2.** Synthetic approach towards spiro[3,2-c]chromene using acetophenones as carbonyl compounds.

The pyranochromenes **8(a-f)** obtained are air stable and colorless solid powders, which are well soluble in acetone, DMF and DMSO. The structures of these compounds were confirmed by IR, Mass spectrometry,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR spectroscopy and elemental analysis. The IR spectra of pyranochromene **8(a-f)** exhibit characteristic absorption bands of the amino, nitrile, and methylene fragments:  $\nu$  ( $\text{NH}_2$ )  $3300\text{-}3500\text{ cm}^{-1}$ ,  $\nu$  ( $\text{CN}$ )  $2200\text{-}2350\text{ cm}^{-1}$ , and  $\nu$  ( $\text{CH}_2$ )  $2800\text{-}2900\text{ cm}^{-1}$ . The IR spectra of pyranochromenes show a particular absorption band of the lactone group at  $1680\text{-}1720\text{ cm}^{-1}$ . All the mass spectra show a molecular ion peak in agreement with the molecular weight of the respective compound. The  $^1\text{H}$  NMR spectra show signals for the proton of amino group and methylene group at  $5.6$  to  $5.8\ \delta$  ppm and  $1.5$  to  $2.8\ \delta$  ppm, respectively. The signals for the benzenoid protons of coumarin are observed at in the interval  $7.3$  to  $7.8\ \delta$  ppm. The  $^{13}\text{C}$  NMR spectral data for compound **8a** are consistent with the assigned structure.

## Conclusions

In the three component system between 4-hydroxycoumarin, malonitrile and ketones for the formation of spiro 2-amino-3-cyanopyrano[3,2-c]chromene derivatives the ketones have to be cyclic in nature.

## Experimental Section

**General.** Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was performed on 0.2-mm precoated plates of silica gel G60 F<sub>254</sub> (Merck). Visualization was made with UV light (254 and 365nm) or with iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS (diffusion reflectant spectroscopy) probe. <sup>1</sup>H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in  $\delta$  ppm downfield from TMS as an internal standard. Mass spectra were determined using a direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). All reagents were purchased from Fluka, Sigma Aldrich, Merck and Rankem and used without further purification.

### Preparation of spiro pyrano[3,2-*c*]chromene derivatives: General procedure

A stirred mixture of 4-hydroxycoumarin **1(a,b)** (10 mmol), carbonyl compound **6(a-c)** (cyclopentanone, cyclohexanone, and cycloheptanone) (10 mmol), malononitrile **7** (10 mmol), and morpholine (0.5 mmol) in anhydrous EtOH (50 mL) was heated under reflux for 20 min and allowed to crystallize at 4 °C for 12 h. The precipitate that formed was filtered off, washed with ethanol and hexane, and recrystallized from 1,4-dioxane to give compounds **8(a-f)** as white powders.

**Spiro(2-amino-3-cyano pyrano[3,2-*c*]chromene-4,1'-cyclopentane) (8a).** White solid; mp 230-232°C; Yield – 83%. IR (KBr): 3450, 2928, 2904, 2865, 2845, 2360, 1724, 1602, 1558, 1313 cm<sup>-1</sup>. <sup>1</sup>H NMR:  $\delta$  = 7.82 (d, 1H, Ar), 7.60–7.55 (m, 1H, Ar), 7.34–7.30 (m, 2H, Ar), 5.78 (s, 2H, NH<sub>2</sub>), 2.39–2.33 (m, 2H, CH<sub>2</sub>), 2.06–1.90 (m, 4H, CH<sub>2</sub>), 1.89–1.64 (m, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR:  $\delta$  = 159.7, 154.6, 152.4, 152.2, 132.3, 124.3, 122.3, 119.2, 116.5, 113.0, 109.3, 70.9, 43.1, 41.0, 27.6. Mass:  $m/z$  = 295 [M<sup>+</sup>+1], 294 [M<sup>+</sup>]. Anal. Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.19; H, 4.51; N, 9.43.

**Spiro(2-amino-3-cyano pyrano[3,2-*c*]chromene-4,1'-cyclohexane) (8b).** White solid; mp 230-232 °C; Yield – 78 %. IR (KBr): 3595, 2928, 2368, 1718, 1678, 1649, 1539, 1321, 1084 cm<sup>-1</sup>. <sup>1</sup>H NMR:  $\delta$  = 7.78 (m, 1H, Ar), 7.60–7.54 (m, 1H, Ar), 7.29–7.28 (m, 2H, Ar), 5.78 (s, 2H, NH<sub>2</sub>), 2.41–2.35 (m, 4H, CH<sub>2</sub>), 2.12–2.01 (m, 4H, CH<sub>2</sub>), 1.89–1.61 (m, 2H, CH<sub>2</sub>). Mass:  $m/z$  = 308 [M<sup>+</sup>]. Anal. Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.06; H, 4.56; N, 8.82.

**Spiro(2-amino-3-cyano pyrano[3,2-*c*]chromene-4,1'-cycloheptane) (8c).** White solid; mp 225-226 °C; Yield – 66 %. IR (KBr): 3458, 2930, 2868, 2344, 1720, 1649, 1545, 1080 cm<sup>-1</sup>. <sup>1</sup>H NMR:  $\delta$  = 7.78 (m, 1H, Ar), 7.68–7.63 (m, 1H, Ar), 7.36–7.29 (m, 2H, Ar), 5.79 (s, 2H, NH<sub>2</sub>), 2.41–1.69 (m, 12H, CH<sub>2</sub>). Mass:  $m/z$  = 322 [M<sup>+</sup>]. Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.23; H, 5.34; N, 8.51.

**Spiro(2-amino-3-cyano-9-methyl pyrano[3,2-*c*]chromene-4,1'-cyclopentane) (8d).** White solid; mp 228-230 °C; Yield–85 %. IR (KBr): 3464, 2983, 2928, 2856, 2846, 2364, 1690, 1645,

1554, 1371, 1317, 1024  $\text{cm}^{-1}$ .  $^1\text{H NMR}$ :  $\delta = 7.83\text{--}7.65$  (m, 1H, Ar), 7.34–7.21 (m, 2H, Ar), 5.77 (s, 2H,  $\text{NH}_2$ ), 2.37–2.33 (m, 4H,  $\text{CH}_2$ ), 2.31 (s, 3H,  $\text{CH}_3$ ), 2.12–1.88 (m, 4H,  $\text{CH}_2$ ). Mass:  $m/z = 308$  [ $\text{M}^+$ ]. Anal. Calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ : C, 70.12; H, 5.23; N, 9.09. Found: C, 69.94; H, 5.08; N, 8.98.

**Spiro(2-amino-3-cyano-9-methyl pyrano[3,2-c]chromene-4,1'-cyclohexane) (8e)**. White solid; mp 231–232  $^\circ\text{C}$ ; Yield–72 %. IR (KBr): 3502, 2960, 2956, 2845, 2304, 1678, 1649, 1545, 1368, 1321, 1045  $\text{cm}^{-1}$ .  $^1\text{H NMR}$ :  $\delta = 7.68\text{--}7.54$  (m, 1H, Ar), 7.41–7.28 (m, 2H, Ar), 5.78 (s, 2H,  $\text{NH}_2$ ), 2.40–2.31 (m, 4H,  $\text{CH}_2$ ), 2.31 (s, 3H,  $\text{CH}_3$ ), 2.12–1.75 (m, 6H,  $\text{CH}_2$ ). Mass:  $m/z = 322$  [ $\text{M}^+$ ]. Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 70.79; H, 5.63; N, 8.69. Found: C, 70.55; H, 5.48; N, 8.51.

**Spiro(2-amino-3-cyano-9-methyl pyrano[3,2-c]chromene-4,1'-cycloheptane) (8f)**. White solid; mp 220–222  $^\circ\text{C}$ ; Yield–70 %. IR (KBr): 3478, 2928, 2910, 2300, 1692, 1664, 1539, 1380, 1308, 1023  $\text{cm}^{-1}$ .  $^1\text{H NMR}$ :  $\delta = 7.65\text{--}7.52$  (m, 1H, Ar), 7.40–7.29 (m, 2H, Ar), 5.78 (s, 2H,  $\text{NH}_2$ ), 2.32 (s, 3H,  $\text{CH}_3$ ), 2.34–1.60 (m, 12H,  $\text{CH}_2$ ). Mass:  $m/z = 336$  [ $\text{M}^+$ ]. Anal. Calcd for  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ : C, 71.41; H, 5.99; N, 8.33. Found: C, 71.30; H, 5.76; N, 8.24.

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