The Condensation of Active Methylene Reagents with Salicylaldehyde: Novel Synthesis of Chromene, Azaanthracene, Pyrano[3,4-*c*]chromene and Chromeno[3,4-*c*]pyridine Derivatives

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On heating of the cyanoacetic acid cyclopentylidene hydrazide **1** with salicylaldehyde in the presence of bases the azaanthracene derivative **6** was formed. Also, reaction of **3** with malononitrile and ketones **10a,b** afforded the pyrano[3,4-*c*]chromene **9** and chromeno[3,4-*c*]pyridine **11** respectively. A mechanism for these reactions is proposed.

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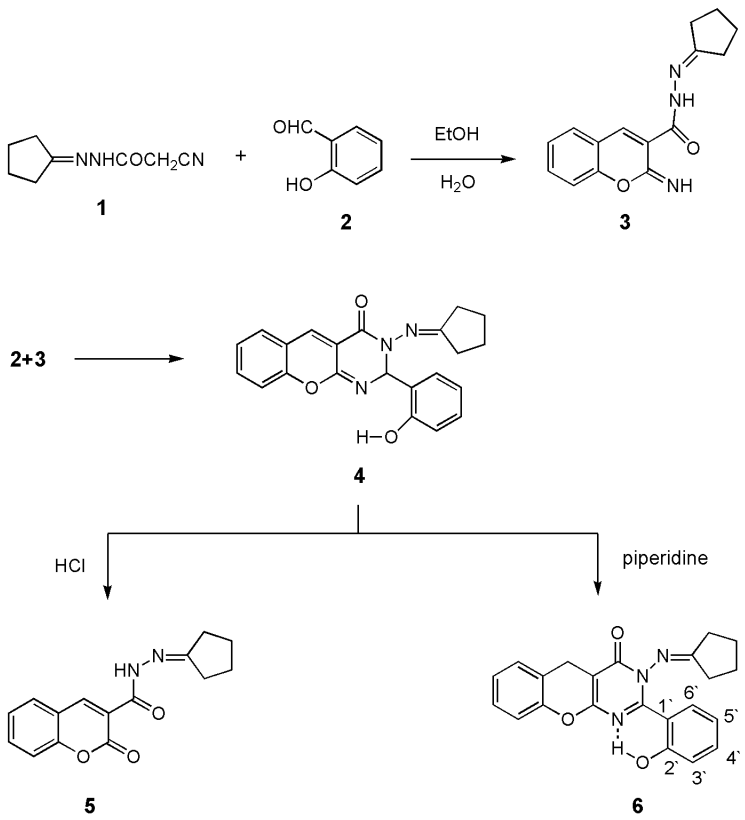
The condensation of acid derivatives containing an active methylene group with salicylaldehyde in the presence of a base is a well-known reaction that leads to the formation of coumarine imines [1,2] or coumarines [2,3]. Sheurmann *et al*. [4] noted that the reaction of 5-(phenylmethyl)-4*H*-1,2,4-triazol-3-acetonitrile with 5-(diethylamino)-2-hydroxybenzaldehyde in the presence of pyrrolidine gives coumarine imine which reacts with diphenylcarbonate affording 9-(diethylamino)-3-(phenylmethyl)-5*H*-[1]benzopyrano[3,2-*e*]1,2,4-triazolo[4,3-*c*]pyrimidine-5-one.

In the course of our investigation on the chemistry of heteroaromatic acetonitriles [5,6], and as a part of our program directed for development of new simple and efficient procedures for the synthesis of fused heterocyclic nitrogen compounds utilizing readily obtainable nitriles intermediates [7,8] we carried out the reaction of the nitrile **1** with salicylaldehyde **2** in the presence of bases such as piperidine in boiling ethanol. In contrast to Sheurmann's results [4] we have not obtained coumarine imine but the azaanthracene derivative **6** in quantitative yield. Apparently, the coumarine imine **3** initially formed, spontaneously under-

Scheme 1

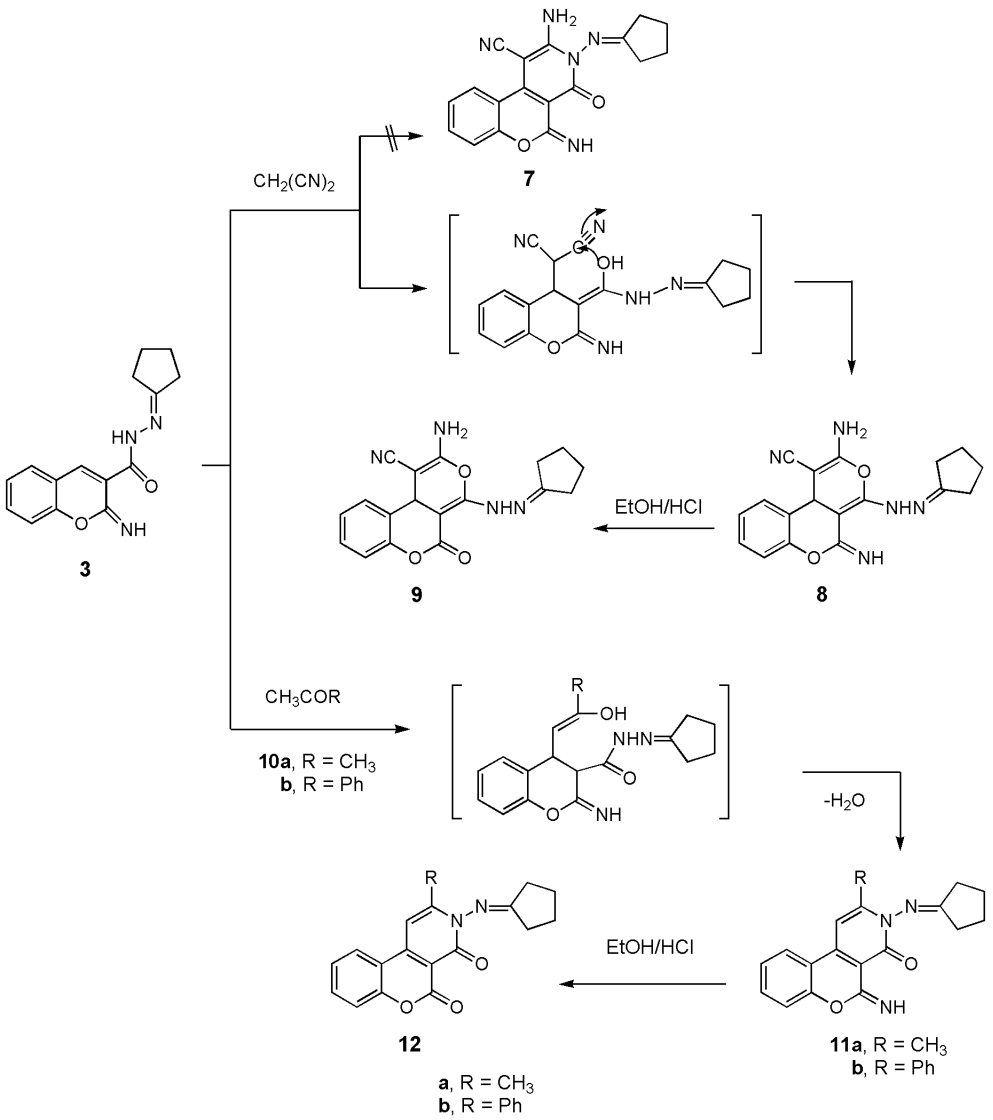


went cyclization with a second molecule of salicylaldehyde (**2**). The reaction could be stopped, however, at the stage of coumarine imine **3** by using 15% alcoholic sodium hydroxide as a catalyst. Compound of type **6** proved to be stable under acidic and basic conditions. The structure assignment of **6** is based mainly on spectroscopic evidences. The molecular mass of the product **6** is 373. The IR spectrum is consistent with the assigned structure, showing absorption at 3160 (OH) and 1620 cm^{-1} (C=N).

The first step of the reaction leading to **6** is the Knoevenagel condensation between salicylaldehyde (**2**) and the nitrile **1** with the formation of the coumarine imine **3**. Attack of a second molecule of **2** on the coumarine imine **3** leads to the formation of compound **4** with simultanous elimination of a water molecule. Base-catalysed rearrangment of **3** gives product **6**.

We isolated intermediates **3** and **4** and thus confirmed the proposed mechanism. Compound **3** was isolated when substrates **1** and **2** were heated without any catalyst, or the reaction was performed in the presence of ammonium acetate. As expected, the intermediate coumarine **3** upon treatment with **2** and piperidine in boiling ethanol gave the final product **6**. Hydrolysis of **4** gave the chromene **5**. The same product obtained from the hydrolysis of the coumarine imine **3**. Also, compound **3** was subjected to reaction with malononitrile in refluxing ethanol containing a catalytic amount of piperidine. Two structures **7** and **8** have been assigned as reaction products. The pyran structure **8** was preferred over the pyridine **7** based on ^{1}H NMR spectrum which revealed the presence of H-4 pyran signal at δ = 5.4 ppm. Compound **8** when heated with hydrochloric acid in ethanol, was converted to 5-oxo derivative **9**.

Scheme 2



Similarly, the coumarine imine **3** reacted with the ketones **10a,b** to afford the chromene[3,4-*c*]pyridine derivatives **11a,b** which then hydrolyzed to the corresponding ketones **12a,b** upon refluxing in EtOH/HCl.

In conclusion, this work demonstrates a very simple and efficient method for the synthesis of the targeted compounds in excellent yields.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR-740 spectrometer. Only the most significant IR absorption bands are listed. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz on a Brucker 300 spectometer. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on GC/MS INCOS XL Finnigan MAT. Elemental analysis were performed on a Earlo Ebra 1106 analyzer; for C, H, N, the results agreed within + or – 0.4 % of the theoretical values.

2-Imino-2-*H*-chromene-3-carboxylic Acid Cyclopentylidene Hydrazide (**3**).

To a solution of the nitrile **1** (0.01 mol) and salicylaldehyde (**2**) (0.01 mol) in anhydrous ethanol (5 ml) 1-2 drops of 15% ethanolic sodium hydroxide was added. The solution was heated under reflux for 2 h and then allowed to stand at room temp. for *ca*. 12 h. The product was collected by filtration and purified by crystallization from ethanol as orange crystals, yield 80%; m.p. 154 °C; ir: 3300 (NH), 1690 (CO-amide), 1620 (C=N) cm^{-1}; ^{1}H nmr: δ 1.40-1.80 (m, 8H, cyclopentane), 7.05 -7.60 (m, 4H, aromat.), 8.35 (s, 1H, coumarin imine 4-H).- ^{13}C nmr: δ 168 (CO amide), 164, 155.7 (imine carbons), 142, 120 (vinyl carbons), 155.1, 129.2, 127.5, 122.1, 121.0, 115.6 (aromatic carbons), 34.9, 28.9, 28.6, 28.6 (aliphatic carbons); ms: m/z 269 (M$^+$).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.92; H, 5.58; N, 15.63.

2-Cyclopentylideneamino-3-(2-hydroxyphenyl)-2,3-dihydro-10-oxa-2-azaanthracene-1-one (**4**).

To a solution of the nitrile **1** (0.01 mol) and salicylaldehyde (**2**) (0.02 mol) in anhydrous ethanol (5 ml) was added ammonium acetate (50 mg) and the mixture refluxed for 0.5 h. The precipitate formed was separated by filtration and crystallized from dioxane as yellow crystals, yield 70%, m.p. 220 °C; ir: 3360 (OH), 1700 (CO), 1650 (C=N) cm^{-1}; ^{1}H nmr: δ 1.40-1.80 (m, 8H, cyclopentane), 6.80-7.55 (m, 9H, aromat. and 5-H), 8.00 (s, 1H, 12-H), 9.4 (s, 1H, OH); ^{13}C nmr: δ167.0 (CO amide), 155.6 (imine carbon), 154.5, 134.6, 133.4, 98.9 (vinyl carbons), 155.9, 154.4, 129.6, 128.5, 128.4, 127.9, 126.9, 123.4, 122.6, 120.9, 115.6, 115.5 (aromatic carbons) 35.2, 29.2, 28.6, 28.6 (aliphatic carbons); ms: m/z 373 (M$^+$).

Anal. Calcd. for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.50; H, 5.02; N, 11.11.

2-Oxo-2*H*-chromene-3-carboxylic Acid Cyclopentylidene Hydrazide (**5**).

A solution of compound **4** (0.01 mol) in hydrochloric acid (10 ml) was refluxed for 5 min. The solution was made alkaline with aqueous 20% sodium hydroxide. The compound **5** which precipitated, was collected by filtration and crystallized from methanol as brown crystals, yield 75%, m.p. 210 °C; ir: 3280 (NH), 1710 (CO), 1690 (CO amide), 1620 (C=N) cm^{-1}; ^{1}H nmr: δ 1.40-1.80 (m, 8H, cyclopentane), 7.10 -7.70 (m, 4H, aromat.), 8.8 (s, 1H, coumarin 4-H); ^{13}C nmr: δ 168.0 (CO), 162.0 (CO amide), 155.6 (imine carbon), 151.4, 124.4 (vinyl carbons), 150.8, 128.1, 127.8, 125.6, 125.2, 121.3 (aromatic carbons), 34.9, 28.9, 28.5, 28.5 (aliphatic carbons); ms: m/z (M$^+$).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found C, 66.43; H, 5.00; N, 10.30.

Formation of Compound **6**.

To a solution of the nitrile **1** (0.01 mol) and compound **2** (0.02 mol) in anhydrous ethanol (0.01 mol) was added 2 drops of piperidine and the solution refluxed for 1 h. The solid formed was collected by filtration and crystallized from DMF as yellow crystals, yield 71%, m.p. 290 °C; ir: 3160 (OH), 1710 (CO), 1620 (C=N) cm^{-1}; ^{1}H nmr: δ 1.40-1.80 (m, 8H, cyclopentane), 4.2 (s, 2H, CH_2), 6.75-7.55 (m, 7H, aromat.), 9.10 (d, 1H, *J* = 8Hz, 6` H); ms: m/z 373 (M$^+$).

Anal. Calcd. for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found C, 70.70; H, 5.22; N, 11.23.

Reaction of **3** with Active Methylene Reagents: Formation of Compounds **8** and **11a,b**.

A mixture of compound **3** (0.01 mol) and the appropriate active methylene reagent (0.01 mol) in an anhydrous ethanol (20 ml) was refluxed for 3 h. The solid products that deposited upon cooling were collected by filtration and crystallized form the proper solvent to give compounds **8** and **11a,b** respectively.

2-Amino-4-(*N*-cyclopentylidenehydrazino)-5-imino-5*H*,10b*H*-pyrano[3,4-*c*]chromene-1-carbonitrile (**8**).

Compound **8** was obtained as yellow crystals from ethanol, yield 78 %; m.p. 245 °C; ir: 3320, 3315 (NH_2), 2210 (CN), 1620 (C=N) cm^{-1}; ^{1}H nmr: δ 1.40-1.85 (m, 8H, cyclopentane), 5.4 (s, 1H, pyran 4H), 6.88-7.90 (m, 4H, aromat.), 9.4, 9.54 (2s, 2H, 2NH); ^{13}C nmr: δ 164, 155.6 (imine carbons), 176, 162.0, 74.1, 57.3 (vinyl carbons), 158.0, 130.7, 126.8, 124.9, 115.6, 121.0 (aromatic carbons), 117.3 (CN), 35.3, 29.3, 28.6, 28.6, 14.5 (aliphatic carbons); ms: m/z (M$^+$).

Anal. Calcd. for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found C, 64.40; H, 5.21; N, 20.91.

3-Cyclopentylideneamino-5-imino-2-methyl-3,5-dihydrochromeno[3,4-*c*]pyridine-4-one (**11a**).

Compound **11a** was obtained as yellow crystals from ethanol, yield 71 %; m.p. 235 °C; ir: 3218 (NH), 1690 (CO), 1620 (C=N) cm^{-1}; ^{1}H nmr: δ 1.35 (s, 3H, CH_3), 1.4-1.8 (m, 8H, cyclopentane), 5.55 (s, 1H, CH), 7.15-8.0 (m, 4H, aromat.), 9.4 (s, 1H, NH); ^{13}C nmr: δ 164.0, 155.6 (imine carbons), 163.0 (CO), 155.1, 133.7, 113.2, 103.7 (vinyl carbons), 155.2, 129.1, 127.6, 122.1, 121.0, 115.6 (aromatic carbons), 35.3, 29.3, 28.6, 28.6, 20.3 (aliphatic carbons); ms: m/z 307 (M$^+$).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.30; H, 5.41; N, 13.91.

3-Cyclopentylideneamino-5-imino-2-phenyl-3,5-dihydrochromeno[3,4-*c*]pyridine-4-one (**11b**).

Compound **11b** was obtained as brown crystals from DMF, yield 70%; m.p. >300 °C; ir: 3218 (NH), 1690 (CO), 1620 (C=N) cm^{-1}; ^{1}H nmr: δ 1.35 (s, 3H, CH_3), 1.4-1.8 (m, 8H, cyclopentane), 6.13 (s, 1H, CH), 7.0-8.2 (m, 9H, aromat.), 9.35

(s, 1H, NH); ms: m/z 369 (M^+).

Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37. Found C, 74.50; H, 5.41; N, 11.61.

Reaction of Compounds **8** and **11a,b** with Hydrochloric Acid: Formatiom of Compounds **9** and **12a,b**.

A solution of **8** or **11a,b** (0.01 mol) in ethanol (30 ml) was treated with concentrated (37%) hydrochloric acid (10 ml). The reaction mixture was heated under reflux for 2 h. and then evaporated under reduced pressure. The remaining product was triturated with water and neutralized by addition of aqueous ammonia. The solid products that deposited were collected by filtration and crystallized from the proper solvent.

2-Amino-4-(*N*-cyclopentylidenehydrazino)-5-oxo-5*H*,10b*H*-pyrano[3,4-*c*]chromene-1-carbonitrile (**9**).

Compound **9** was obtained as colorless crystals from ethanol, yield 68 %; m.p. >300 °C; ir: 3320, 3315 (NH_2), 1705 (CO), 2210 (CN), 1625 (C=N) cm^{-1}; ^1H nmr: δ 1.40-1.85 (m, 8H, cyclopentane), 5.4 (s, 1H, pyran 4H), 6.88-7.90 (m, 4H, aromat.), 9.4 (s, 2H, NH); ms: m/z 336 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found C, 64.00; H, 4.53; N, 16.50.

3-Cyclopentylideneamino-2-methyl-3,5-dihydrochromeno[3,4-*c*]-pyridine-4,5-dione (**12a**).

Compound **12a** was obtained as colorless crystals from ethanol, yield 60 %; mp. 275 °C; ir: 1710,1690 (CO), 1620 (C=N) cm^{-1}; 1.40 (s, 3H, CH_3), 1.45-1.8 (m, 8H, cyclopentane), 5.55 (s, 1H, CH), 7.15-8.0 (m, 4H, aromat.); ms: m/z 308 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found C, 70.30; H, 5.31; N, 9.11.

3-Cyclopentylideneamino-2-phenyl-3,5-dihydrochromeno[3,4-*c*]-pyridine-4,5-dione (**12b**).

Compound **12b** was obtained as colorless crystals from ethanol, yield 63 %; mp. 281 °C; ir: 1710,1690 (CO), 1620 (C=N) cm^{-1}; ^1H nmr: δ 1.4 (s, 3H, CH_3), 1.45-1.8 (m, 8H, cyclopentane), 6.15 (s, 1H, CH), 7.0-8.2 (m, 9H, aromat.); ms: m/z 370 (M^+).

Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.30; H, 5.00; N, 7.63.

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