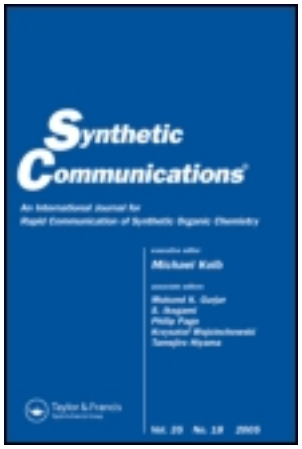

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STUDY ON THE CYCLIZATION METHODS OF 3-[1-(PHENYL-HYDRAZONO)ETHYL]-CHROMEN-2-ONES

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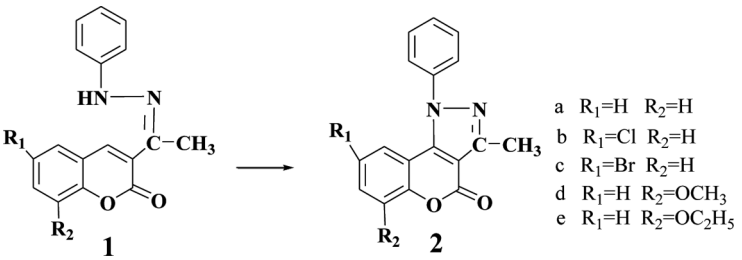
GRAPHICAL ABSTRACT



Abstract *Some new methods, such as air oxidation, catalytic oxidation, and solvent-free synthesis, are developed for the synthesis of 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-ones(**2**) from the cyclization of 3-[1-(phenyl-hydrazono)ethyl]-chromen-2-ones(**1**). Compared with air oxidation, catalytic oxidation can increase the rate of the cyclization of compound **1**, and the solvent-free synthesis showed advantages of no organic solvent pollution, elevated reaction rate, and higher selectivity.*

Keywords Benzopyrano-arylhydrazone; benzopyrano-pyrazol; coumarin derivatives; oxidative cyclization

INTRODUCTION

Recently, coumarin derivatives have received much attention in organic heterocyclic compounds, with powerful biological activities including antibacterial,[1,2] antiviral,[3] and anti-inflammatory [4] activities. Because of the structural features of larger conjugated system, coumarin derivatives are also used as fluorescent materials.[5,6] Pyrazole derivatives are known to exhibit impressive antibacterial, antidepressant, antiamoebic, anti-inflammatory, and antinociceptive[7–10] activities. The incorporation of a heterocyclic ring into the coumarin and pyrazole ring would make them more potent than coumarin and pyrazole alone.[11,12]

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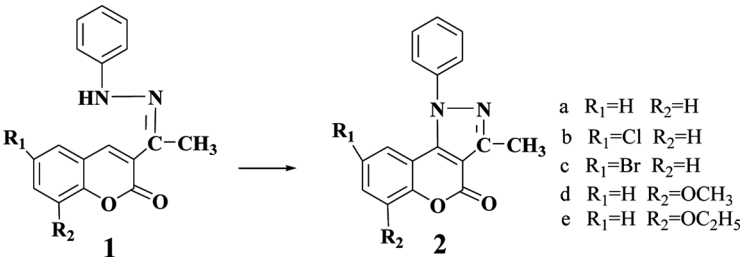
3-Methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-ones commonly are used for synthesis of inmunomodulatory drugs, which can interact with the benzodiazepine central receptor.[13] The synthesized methods of these compounds mostly use 3-acetyl-4-hydroxycoumarins [14] or 3-acetyl-4-chlorocoumarins [15] as row materials. In contrast, the use of 3-acyl-coumarins, which are easier to obtain, as reactants has been less studied because of their low reactivity. Recently, Padilla-Martinez et al.[16] reported 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1*H*)-ones were obtained by the oxidative cyclization of 3-[1-(phenyl-hydrazono)ethyl]-chromen-2-ones with copper acetate as catalyst, which prompted us to study the cyclization methods of 3-[1-(phenyl-hydrazono)ethyl]-chromen-2-ones.

In this contribution, some new methods, including air oxidation, catalytic oxidation, and solvent-free synthesis, are developed for the synthesis of 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1*H*)-ones(**2**) from the cyclization of coumarin hydrazones (Scheme 1).

In one recrystallization experiment, compound **1a** was unexpectedly converted to compound **2a**, whose crystal structure was determined by x-ray monocrystal diffraction (see Fig. 1) in the ethyl acetate. The crystal structure of compound **2a** is already deposited at the Cambridge Crystallographic Data Center (CCDC) and is available as a private communication.

Through many trials, it was found that the compound **1a** can spontaneously cyclize to form the compound **2a** in the ethyl acetate by slow oxidation in the air, and the conversion increased as the time lengthened. The yield of **2a** was up to 88% after 8 days (Table 1, entries 1–4). Padilla-Martinez et al.[16] also reported that compound **2a** was spontaneously formed in chloroform solution at room temperature, but the yield of **2a** was only 30%, and other 3-(phenyl-hydrazono)-chromen-2-ones **1b–1e** did not proceed under the same conditions as **1a**. In our experiments **1b–1e** could cyclize smoothly, and the results are shown in Table 1 (entries 5–8). The overall yield of product **2** was more than 75% under air oxidation and the activity order of the compounds (**2a–2e)** is **2a** > **2b** > **2c** > **2d** > **2e**. This suggests that the introduction of the bulky groups was not propitious for cyclization, especially for those electron-donating groups.

To accelerate the reaction rate, copper acetate was used as the catalyst in the cyclization reaction.[16] To expand the scope of catalyst, we tested many substances, and the results are shown in Table 2. Most of the substances could promote the cyclization of coumarin hydrazones **1** effectively. The conversion of compound **1c** was up



Scheme 1. Synthetic route to the compounds **2a–2e**.

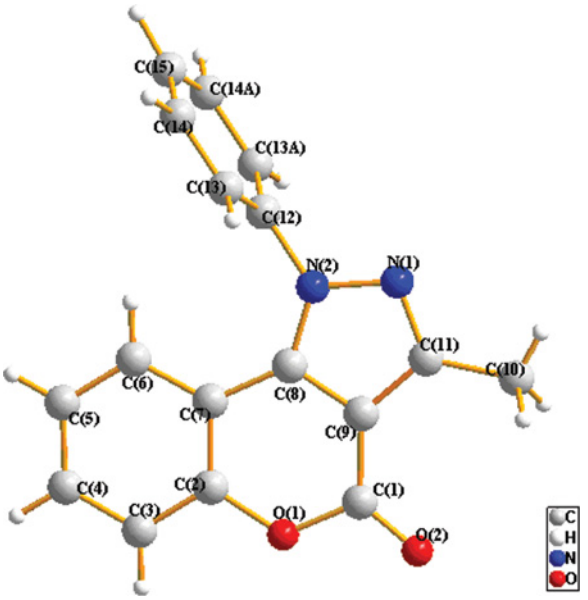


Figure 1. Molecular structure of compound **2a**. (Figure is provided in color online.)

Table 1. Synthesis of compounds **2a–2e** with air oxidation

Entry	Compound	Time (d)	Conversion (%)	Selectivity (%)	Yield (%)
1	**2a**	8	100	88	88
2	**2a**	6	65	95	62
3	**2a**	4	51	100	51
4	**2a**	2	33	100	33
5	**2b**	12	100	75	75
6	**2c**	12	100	94	94
7	**2d**	15	99	76	75
8	**2e**	25	99	93	92

Table 2. Synthesis of compound **2c** with catalytical oxidation

Entry	Catalyst	Time (h)	Conversion (%)	Selectivity (%)	Yield (%)	TOF
1	Cu	40	76	53	40	0.0034
2	CuCl	0.5	97	52	50	0.54
3	CuO	13	92	96	85	0.016
4	$Cu(CH_3COO)_2 \cdot H_2O$	1	100	88	88	0.56
5	$Cu\ (SO_3)_2\ CF_3$	0.5	90	89	80	1.5
6	$FeCl_3$	6	100	22	22	0.076
7	$AgNO_3$	6	100	47	47	0.080
8	$Mn(CH_3COO)_2 \cdot H_2O$	4	100	24	24	0.134
9	$Co(CH_3COO)_2 \cdot H_2O$	6	100	36	36	0.092

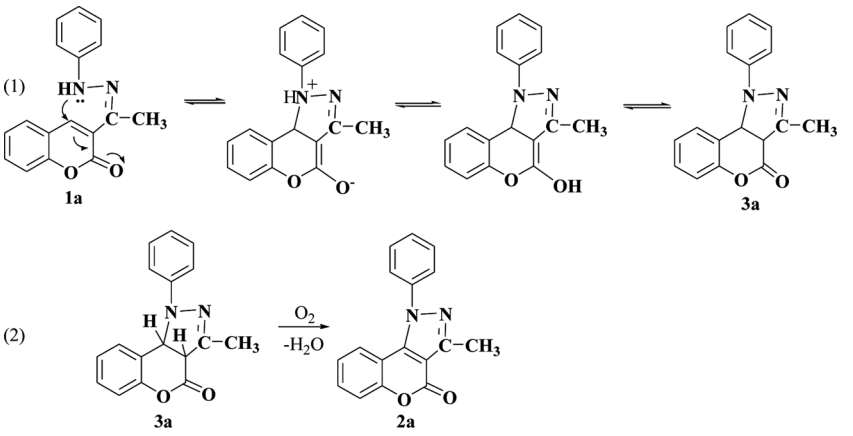
Table 3. Synthesis of compound **2a** with solvent-free synthesis

Temperature (°C)	Time (h)	Conversion (%)	Selectivity (%)	Yield (%)
110	34	69	96	66
120	33	99	96	95
130	4	91	96	87
140	2	100	100	100
150	0.5	97	95	92

to 90% in the presence of different catalysts within shorter time compared with air oxidation except for Cu. The catalyst Cu $(SO_3)_2CF_3$ has greater activity and the catalyst CuO showed greater selectivity than the other catalysts. As for the reason, further research is needed.

It is considered that organic solvents are harmful to the environment, so solvent-free synthesis was adopted to prepare the product **2a**, and the experimental data are listed in Table 3. From the results, we conclude that the reactive rate increased as the temperature increased. The conversion of **1a** was 100% and the selectivity of product **2a** was 100% at 140°C for 2 h. Compared with air oxidation, solvent-free synthesis showed advantages of no organic solvent pollution, elevated reaction rate, and higher selevtivity.

According to experimental results, we presume the mechanism for the cyclization of 3-(phenyl-hydrazono)-chromen-2-ones is shown in Scheme 2. Take the reactant **1a** as an illustration; First, reactant **1a** was changed into intermediate **3a** by intramolecular Michael addition. Then intermediate **3a** was oxidized to product **2a** by oxygen in the air. The first step is a reversible reaction and the second step is an irreversible reaction. When 95% ethyl alcohol was used as the solvent in the catalytical oxidation, the cyclization of the reactant **1a** cannot occur, which may prove that there is a dehydration reaction in the second step.



Scheme 2. Possible mechanism for the formation of compound **2a**.

CONCLUSION

In summary, we have developed some new methods, including air oxidation, catalytic oxidation, and solvent-free synthesis, for the synthesis of 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1*H*)-ones (**2**) from the cyclization of 3-[1-(phenyl-hydrazono)ethyl]-chromen-2-ones (**1**). Under air oxidation, the overall yield of the products **2** was up to 85–90%. Some catalysts, especially Cu $(SO_3)_2CF_3$, increased the rate of the cyclization of compound **1**. Compared with air oxidation, solvent-free synthesis showed advantages of no organic solvent pollution, elevated reaction rate, and higher selectivity.

EXPERIMENTAL

Melting points were determined on a X4 digital microscopic melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Nicolet IS10 Fourier transform IR spectrophotometer (4000–400 cm^{-1}) with a crystalline sample spread on KBr pellets. ^1H NMR spectra of compound **2a** was obtained by a Brucker 300-MHz spectrometer with tetramethylsilane (TMS) as an internal standard. ^1H NMR spectra of compounds **2b–2e** were obtained by a Bruker Advance DPX 400-MHz spectrometer with TMS as an internal standard. ESI^+ (electrospray ionization) mass spectra were obtained on a liquid chromatography (LC)–mass spectrometry (MS) system, Agilent MSD-Trap-SL. X-ray diffraction data were collected on a Rigaku RAXIAS-IV type diffractometer. All chemicals and reagents were of analytical reagent grade and were used as received without further purification. The compounds **1a–1e** were synthesized according to the standard procedures from phenyl hydrazine and 3-acyl-coumarins. The high-performance liquid chromatographic (HPLC) instrument from Agilent Company was used for the qualitative and quantitative analyses of the products.

Synthesis of Compounds 2a–2e by Air Oxidation

In a round-bottom flask, 3-[1-(phenyl-hydrazono)ethyl]-chromen-2-one (**1**) (0.1 g) was dissolved in ethyl acetate solution (20 mL) by refluxing for 10 min. Then the round-bottom flask was covered with a plastic membrane except for one small hole at the top and placed for some time in the air. The reaction was monitored by HPLC at intervals. After the completion of the reaction, the resulting mixture was removed from the bulk solvent by reduced pressure distillation, filtered, washed with cold ethyl alcohol (3 mL × 2), air dried, and recrystallized from ethyl acetate to obtain the compounds **2a–2e**.

Compound 2a. White powder, mp : 235–236 °C; IR (KBr pellets, ν/cm^{-1}): 3091, 2929, 1735, 1623, 1597, 1550, 1525, 1489, 1455, 1431, 1273, 1210, 1048, 1027, 970, 778, 756, 703. ^1H NMR data (300 MHz, $CDCl_3$, ppm): 7.64–7.54 (m, 5H, benzene-H), 7.48–7.39 (m, 2H, benzene-H), 7.13–7.01 (m, 2H, benzene-H), 2.68 (s, 3H, $-CH_3$).

Compound 2b. Pale yellow powder, mp : 280–281 °C; IR (KBr pellets, ν/cm^{-1}): 3473, 3092, 1751, 1544, 1522, 1444, 1207, 1129, 1002, 981, 832, 770, 720, 687. ^1H NMR

data (400 MHz, $CDCl_3$, ppm): 7.66–7.53 (m, 5H, benzene-H), 7.39–7.27 (m, 2H, benzene-H), 7.04–7.03 (d, 1H, benzene-H), 2.69 (s, 3H, -CH_3).

Compound 2c. White powder, mp : 287–288 °C; IR (KBr pellets, ν/cm^{-1}) 3434, 3088, 1758, 1542, 1521, 1267, 1206, 1085, 1001, 999, 829, 776, 703. ^1H NMR data (400 MHz, $CDCl_3$, ppm): 7.66–7.64 (m, 3H, benzene-H), 7.56–7.53 (m, 3H, benzene-H), 7.32–7.27 (m, 1H, benzene-H), 7.19–7.18 (d, 1H, benzene-H), 2.69 (s, 3H, -CH_3).

Compound 2d. White powder, mp: 235–236 °C; IR (KBr pellets, ν/cm^{-1}): 3443, 3056, 2977, 2929, 1532, 1454, 1241, 1208, 1104, 1018, 761, 726, 700. ^1H NMR data (400 MHz, $CDCl_3$, ppm): 7.62–7.53 (m, 5H, benzene-H), 7.02–6.95 (m, 2H, benzene-H), 6.67–6.65 (m, 1H, benzene-H), 3.97 (s, 3H, -CH_3), 2.70 (s, 3H, -CH_3).

Compound 2e. White powder, mp: 203–204 °C; IR (KBr pellets, ν/cm^{-1}): 3435, 1735, 1550, 1525, 1455, 1273, 1070, 1048, 1027, 778, 756, 703. ^1H NMR data (400 MHz, $CDCl_3$, ppm): 7.62–7.53 (m, 5H, benzene-H), 7.01–6.91 (m, 2H, benzene-H), 6.66–6.64 (m, 1H, benzene-H), 4.22–4.16 (m, 2H, -CH_2), 2.70 (s, 3H, -CH_3), 1.53–1.50 (m, 3H, -CH_3). LC/MS (ESI+) calcd. for $C_{19}H_{16}N_2O_3$, m/z: 321.1 $(M+H)^+$.

Procedure for the Synthesis of Compound 2c by the Catalytical Oxidation

The compound **1c** (0.1 g) was dissolved in ethyl alcohol (20 ml), and the metal catalyst (0.1 g) was added to the solution. The mixture was refluxed for some time and monitored at intervals. After the completion of reaction, as indicated by HPLC, the resulting mixture was removed from the bulk solvent by reduced pressure distillation, filtered, washed with cold ethyl alcohol (3 mL × 2), and distilled water (3 mL × 3), air dried, and recrystallized from ethyl acetate to obtain compound **2c**.

Procedure for the Synthesis of Compound 2a by the Solvent-Free Synthesis

The compound **1a** (0.1 g) was thoroughly mixed with silicon dioxide (2 g). The silicon dioxide–supported mixture was heated on an oil bath and monitored at intervals. After the completion of reaction, as indicated by HPLC, the resulting mixture was washed with ethyl acetate. The bulk solvent was removed by reduced pressure distillation, filtered, washed with cold ethyl alcohol (3 mL × 2), air dried, and recrystallized from ethyl acetate to obtain compound **2a**.

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