Copper-catalyzed Cyclization of 3-Acylcoumarin Hydrazone using Air as the Oxidant: Efficient Synthesis of Pyrazole-Fused Coumarin Derivatives

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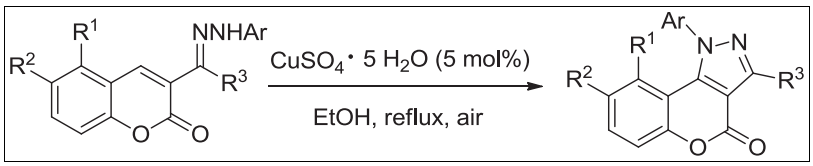

An efficient, convenient Cu-catalyzed formation of chromeno[4,3-*c*]pyrazol-4(1*H*)-ones is reported. In this atom economic process, readily available 3-acylcoumarin hydrazone is oxidative cyclized by direct C–N bond formation. Air has been successfully used as an oxidant, which has important economic and environmental advantages. A broad scope of 3-acylcoumarin hydrazones can be utilized in this process.

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INTRODUCTION

Compounds with two or more heterocycles fused play a vital role in bioactive compounds [1]. Pyrazoles are an intriguing class of important heterocycles. Their derivatives have a long history of application in the agricultral [2] and pharmaceutical industry [3] as part of biologically active compounds. The activities exhibited by them include, antitubercular [4], antitumor [5], anti-inflammatory [6], antihyperglycemic [7], antimalarial [8], and platelet anti-aggregating [9] activities.

Coumarin is one of the important parent compounds found in many plants and could be used as the important component of various functional materials. These versatile compounds have a wide range of uses in the fields of medicine [10], analysis [11], fluorescent materials [12], and optics [13]. The rapidly growing class of heteroaryl-condensed pyrazoles has begun to attract increasing interest because of their broad spectrum of useful biological activities. The 1-phenylchromeno [4,3-*c*]pyrazol-4-ones are important pyrazole derivatives that have been used for the synthesis of immunomodulatory drugs because of their interaction with the benzodiazepine central receptor [14]. Therefore, the synthesis of these compounds has become of interest to synthetic chemists and biologists. Two groups have reported the synthesis of chromeno[4,3-*c*]pyrazol-4-one derivatives starting from 3-acetyl-4-hydroxycoumarin and hydrazine catalyzed by Zn[L-proline]$_2$ or sulfuric acid [15].

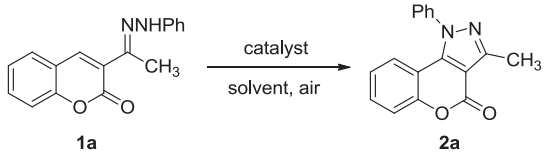
Meanwhile, the direct and selective functionalization of C–H bonds into C–N bonds has become an important topic, because this methodology can provide a series of intrinsic advantages, such as higher atom economy, shorter synthetic routes, and less energy and manpower usage [16]. Many efforts have been devoted to this methodology to improve its efficiency and selectivity, which made it more powerful and applicable [17]. Among them, the metal-catalyzed amination reactions have taken a dominant position, and a variety of transition metal species have been utilized in *N*-functionalization, such as Rh, Ru, Mn, Ag, Cu, Pd, Co, and Fe [18]. The design of efficient direct C–H amination of coumarin derivatives has remained as a challenge at the forefront of organic chemistry. As part of our interest in the green synthesis of fused heterocycles [19], we report herein the efficient synthesis of chromeno[4,3-*c*]pyrazol-4-one derivatives via the direct C–H amination of 3-acylcoumarin hydrazone catalyzed by copper salt by using air as an oxidant.

RESULTS AND DISCUSSION

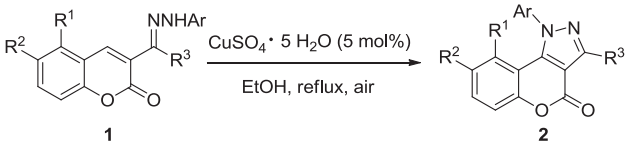
In a preliminary study, the reaction of 3-(1-(2-phenylhydrazono)ethyl)-2*H*-chromen-2-one **1a** was chosen as model reaction to optimize the reaction conditions (Scheme 1). The effects of catalyst and solvents were evaluated for this model reaction, and the results are summarized in Table 1.

It was found that when the reaction was carried out without any catalyst only trace product was detected even after 4 h (Table 1, entry 1). To improve the yields, we examined this reaction using different metal catalysts (Table 1, entries 2–7). Some metal catalysts, such as CuO, $CuCl_2 \cdot 2H_2O$, $Pd(OAc)_2$, and $FeCl_3$ cannot catalyze this reaction (Table 1, entries 2 and 3). Although some copper catalysts, such as $Cu(OAc)_2$ can catalyze this reaction with low yields (Table 1, entry 4). The use of $Cu(OAc)_2 \cdot H_2O$ and $CuSO_4$ lead to moderate product formation (Table 1, entries 5 and 6). Among them, $CuSO_4 \cdot 5H_2O$ was identified as the optimal catalyst with **2a** being isolated in 91% yield (Table 1, entry 7). Subsequently, we further evaluated the

Scheme 1. Model reaction.



Scheme 2. The synthesis of chromeno[4,3-*c*]pyrazol-4(1*H*)-one derivatives **2**.



effect of solvents. The results indicated that ethanol provided much better results than CH_3CN, DMF, toluene, 1,4-dioxane and THF (Table 1, entries 7–12).

To optimize the catalyst loading, 1, 5, 10, 15, and 20 mol % of $CuSO_4 \cdot 5H_2O$ was tested (Table 1, entries 7, 13 and 14, and 15 and 16). A 5 mol% loading of $CuSO_4 \cdot 5H_2O$ was sufficient to promote the reaction but 1 mol% of $CuSO_4 \cdot 5H_2O$ was not enough. Higher amounts of $CuSO_4 \cdot 5H_2O$ did not lead to significant change in the reaction yields.

Under these optimized reaction conditions, a series of chromeno[4,3-*c*]pyrazol-4(1*H*)-one derivatives were synthesized (Scheme 2). The results are summarized in Table 2.

As shown in Table 2, this catalytic cyclization procedure displayed good functional group tolerance and gave the chromeno[4,3-*c*]pyrazol-4(1*H*)-one derivatives in good to excellent yields. The electronic effect of substituent had no significant effect on the yield of the product. However, the reaction time was depended on the solubility of 3-acylcoumarin hydrazones **1** in ethanol solution. 3-Acylcoumarin hydrazones **1** with MeO, Me, and NO_2 required shorter reaction time, because they are easily dissolved in ethanol solution (Table 2, entries 1, 6, 7, 8, 11, 19–21). Although those 3-acylcoumarin hydrazones **1** that are difficult to dissolve in ethanol required longer reaction time (Table 2, entries 5, 13, 15 and 16). The yield of compound **2t** (92%) prepared by our method was higher than in a previously reported protocol (52%)[20].

All the structures of products **2** were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra. The structure of **2a** was further confirmed by X-ray diffraction analysis. The molecular structure of the product **2a** is shown in Figure 1 [21].

In summary, we developed a convenient method for preparation of chromeno[4,3-*c*]-pyrazol-4(1*H*)-one derivatives through the oxidation cyclization of 3-acylcoumarin hydrazones catalyzed by $CuSO_4 \cdot 5H_2O$ with air as oxidant in ethanol. A variety of substrates can participate in the process with moderate to good yields. This method has the advantage of accessible materials, mild reaction conditions, operational simplicity, cleaner reaction profiles, and higher yields.

EXPERIMENTAL

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded on Varian F-1000 spectrometer (Varian Inc., Palo Alto, CA) in KBr with absorptions in cm^{-1}. ^{1}H NMR and ^{13}C NMR were determined on Varian Invoa-400 MHz or Invoa-300 MHz spectrometer (Agilent Technologies, Santa Clara, CA) in $CDCl_3$ solution. *J* values are in hertz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. HRMS analyses were carried out using TOF-MS or GCT-TOF instruments Edinburgh Instruments (Edinburgh, Scotland, England). X-ray diffractions were recorded on a Bruker Smart Apex diffractometer.

Table 1

Optimizing reaction conditions in the synthesis of **2a**.

Entry	Catalyst (mol %)	Oxidant	Solvent	T (°C)	Time (h)	Yield[a] (%)
1	No	Air	EtOH	Reflux	4	trace
2	CuO(10)	Air	EtOH	Reflux	7	trace
3	$CuCl_2 \cdot 2H_2O$(10)	Air	EtOH	Reflux	7	trace
4	$Cu(OAc)_2$ (10)	Air	EtOH	Reflux	4	17
5	$Cu(OAc)_2 \cdot H_2O$ (10)	Air	EtOH	Reflux	5	82
6	$CuSO_4$(10)	Air	EtOH	Reflux	5	80
7	$CuSO_4 \cdot 5H_2O$(10)	Air	EtOH	Reflux	2	91
8	$CuSO_4 \cdot 5H_2O$(10)	Air	CH_3CN	Reflux	4	85
9	$CuSO_4 \cdot 5H_2O$(10)	Air	DMF	Reflux	1.5	84
10	$CuSO_4 \cdot 5H_2O$(10)	Air	toluene	Reflux	14	72
11	$CuSO_4 \cdot 5H_2O$(10)	Air	1,4-dioxane	Reflux	7	92
12	$CuSO_4 \cdot 5H_2O$(10)	Air	THF	Reflux	25	91
13	$CuSO_4 \cdot 5H_2O$ (1)	Air	EtOH	Reflux	12	trace
14	$CuSO_4 \cdot 5H_2O$ (5)	Air	EtOH	Reflux	2.5	91
15	$CuSO_4 \cdot 5H_2O$ (15)	Air	EtOH	Reflux	3	90
16	$CuSO_4 \cdot 5H_2O$ (20)	Air	EtOH	Reflux	4	87

[a]Isolated yields.

Table 2

Synthetic results of chromeno[4,3-*c*]pyrazol-4(1*H*)-one derivatives **2**.

Entry	R^1	R^2	R^3	Ar	Products	Time (h)	Yield[a] (%)
1	H	H	CH_3	C_6H_5	**2a**	2	91
2	H	H	CH_3	4-$CH_3C_6H_4$	**2b**	4	91
3	H	H	CH_3	4-$CH_3OC_6H_4$	**2c**	7	90
4	H	H	CH_3	4-FC_6H_4	**2d**	5	93
5	H	H	CH_3	3-ClC_6H_4	**2e**	18	92
6	H	H	CH_3	3-$CH_3C_6H_4$	**2f**	2	95
7	H	H	$CH_3(CH_2)_2$	C_6H_5	**2g**	2	87
8	H	H	$CH_3(CH_2)_2$	4-$CH_3C_6H_4$	**2h**	2	85
9	H	Cl	CH_3	C_6H_5	**2i**	5	93
10	H	Cl	CH_3	4-$CH_3C_6H_4$	**2j**	6	94
11	H	Cl	CH_3	4-$CH_3OC_6H_4$	**2k**	2	95
12	H	Cl	CH_3	4-ClC_6H_4	**2l**	9	95
13	H	Cl	CH_3	4-FC_6H_4	**2m**	11	91
14	H	Cl	CH_3	2-$CH_3C_6H_4$	**2n**	8	90
15	H	Br	CH_3	3-$CH_3C_6H_4$	**2o**	14	93
16	H	Br	CH_3	4-ClC_6H_4	**2p**	13	95
17	H	Br	CH_3	4-FC_6H_4	**2q**	6	93
18	H	Br	CH_3	2-$CH_3C_6H_4$	**2r**	9	90
19	H	OCH_3	CH_3	4-$CH_3C_6H_4$	**2s**	1	93
20	H	OCH_3	CH_3	C_6H_5	**2t**	2	92
21	H	NO_2	CH_3	4-$CH_3C_6H_4$	**2u**	3	95

[a]Isolated yields.

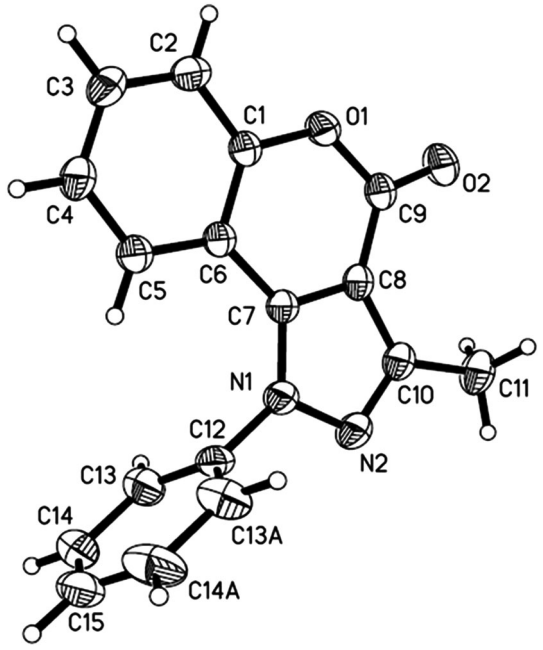


Figure 1. The crystal structure of compound **2a**.

General procedure for the synthesis of chromeno[4,3-*c*]pyrazol-4-one (2). A mixture of 3-acylcoumarin hydrazones **1** (1 mmol) and $CuSO_4 \cdot 5H_2O$ (0.05 mmol) in ethanol (20 mL) was stirred at 80 °C for 1–18 h. After completion of the reaction confirmed by TLC, the reaction mixture was concentrated *in vacuo* to remove the solvent. The residue was quenched with water and then filtered. The crude products were purified by recrystallization from ethanol to afford the pure products **2**.

3-Methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-one (2a). White solid; mp 224 ~ 226 °C (lit.[20] 227~230 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62–7.56 (m, 5H, ArH), 7.43 (t, J = 8.1 Hz, 2H, ArH), 7.10 (d, J = 8.1Hz, 1H, ArH), 7.03 (t, J = 7.8Hz, 1H, ArH), 2.69 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 153.3, 150.8, 141.7, 139.4, 131.1, 130.2, 129.9, 126.9, 123.9, 122.5, 118.0, 111.8, 106.4, 13.0; IR (KBr, cm^{-1}) : 3043, 2973, 1737, 1645, 1558, 1526, 1496, 1474, 1388, 969, 895, 829, 758 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{12}N_2O_2$ $[M]^+$ 276.0899; found 276.0894.

3-Methyl-1-(4-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2b). White solid; mp 184 ~ 186 °C (lit.[14] 191 ~ 192 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.39 (m, 6H, ArH), 7.11 (d, J = 7.5 Hz, 1H, ArH), 7.03 (t, J = 7.2 Hz, 1H, ArH), 2.66 (s, 3H, CH_3), 2.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 153.3, 150.7, 141.8, 140.6, 136.9, 131.1, 130.6, 126.7, 124.0, 122.6, 118.1, 112.0, 106.3, 21.5, 13.0; IR (KBr, cm^{-1}) : 3043, 2973, 1737, 1615, 1526, 1496, 1458, 1398, 1272, 1204, 1048, 969, 869, 829, 758 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{14}N_2O_2$ $[M]^+$ 290.1055; found 290.1053.

1-(4-Methoxyphenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (2c). White solid; mp 196 ~ 198 °C (lit.[15a] 199 ~ 200 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.38 (m, 4H, ArH), 7.10–7.02 (m, 4H, ArH), 3.92 (s, 3H, OCH_3), 2.66 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9, 158.3, 153.5, 150.8, 142.1, 132.3, 131.2, 128.4, 124.1, 122.7, 118.2, 115.2, 112.2, 106.3, 55.9, 13.1; IR (KBr, cm^{-1}) : 3065, 2966, 2940, 2840, 1737, 1609, 1523, 1459, 1304, 1245, 1212, 1049, 1026, 967, 850, 759 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{14}N_2O_3$ $[M]^+$ 306.1004; found 306.0999.

1-(4-Fluorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (2d). White solid; mp 202 ~ 204 °C (lit.[15a] 194 ~ 196 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56–7.52 (m, 2H, ArH), 7.46–7.39 (m, 2H, ArH), 7.29 (t, J = 8.4 Hz, 2H, ArH), 7.07 (s, 2H, ArH),

2.65 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6, 162.1, 157.9, 153.4, 151.0, 142.0, 135.6, 131.4, 129.2, 129.1, 124.2, 122.4, 118.3, 117.3, 1170, 111.8, 13.0; IR (KBr, cm^{-1}) : 3080, 1736, 1616, 1528, 1492, 1273, 1229, 1204, 1048, 970, 854, 756 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{11}F\ N_2O_2$ $[M]^+$ 294.0805; found 294.0801.

1-(3-Chlorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (2e). White solid; mp 210 ~ 212 °C (lit.[14] 213 ~ 215 °C); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.61–7.55 (m, 3H, ArH), 7.51–7.42 (m, 3H, ArH), 7.18–7.06 (m, 2H, ArH), 2.67 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 153.6, 151.4, 146.6, 142.1, 140.6, 135.8, 131.6, 131.1, 130.7, 127.5, 124.3, 122.6, 118.5, 111.8, 106.9, 13.1; IR (KBr, cm^{-1}) : 3080, 1743, 1652, 1593, 1521, 1482, 1208, 1046, 1023, 972, 875, 757 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{11}^{35}ClN_2O_2$ $[M]^+$ 310.0509; found 310.0509.

3-Methyl-1-(3-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2f). White solid; mp 190 ~ 192 °C (lit.[14] 202 ~ 203 °C); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.51–7.43 (m, 4H, ArH), 7.37–7.31 (m, 2H, ArH), 7.13 (d, J = 7.5 Hz, 1H, ArH), 7.07–7.01 (m, 1H, ArH), 2.69 (s, 3H, CH_3), 2.47 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.2, 153.5, 150.9, 141.8, 140.5, 139.5, 131.2, 131.1, 129.8, 127.6, 124.1, 124.0, 122.8, 118.2, 112.1, 106.5, 21.6, 13.1; IR (KBr, cm^{-1}) : 1746, 1671, 1648, 1616, 1522, 1490, 1047, 1020, 798, 756 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{14}\ N_2O_2$ $[M]^+$ 290.1055; found 290.1053.

1-Phenyl-3-propylchromeno[4,3-c]pyrazol-4(1H)-one (2g). White solid; mp 210 ~ 212 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.61–7.55 (m, 5H, ArH), 7.45–7.42 (m, 2H, ArH), 7.11–7.03 (m, 2H, ArH), 3.07–3.03 (m, 2H, CH_2), 1.90–1.84 (m, 2H, CH_2), 1.04 (t, J = 6.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.6, 154.7, 153.1, 141.6, 139.4, 131.0, 130.1, 130.0, 126.9, 123.9, 122.4, 117.9, 111.8, 105.8, 29.2, 21.9, 14.0; IR (KBr, cm^{-1}) : 3059, 2955, 2930, 2870, 1737, 1578, 1522, 1429, 1146, 1044, 1015, 761, 619 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}N_2O_2$ $[M+H]^+$ 305.1290; found 305.1294.

3-Propyl-1-(4-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2h). White solid; mp 134 ~ 136 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.42 (m, 6H, ArH), 7.11–7.03 (m, 2H, ArH), 3.05–3.01 (m, 2H, CH_2), 2.50 (s, 3H, CH_3), 1.89–1.83 (m, 2H, CH_2), 1.04 (t, J = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.5, 154.4, 152.9, 141.5, 140.2, 136.8, 130.8, 130.3, 126.6, 123.7, 122.4, 11.6, 111.7, 105.5, 29.1, 21.8, 21.3, 13.9; IR (KBr, cm^{-1}) : 3035, 2975, 2931, 2899, 1739, 1531, 1412, 1048, 880, 757 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ 319.1447; found 319.1444.

8-Chloro-3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-one (2i). White solid; mp 282 ~ 284 °C (lit.[20] 280~283 °C); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.63–7.53 (m, 5H, ArH), 7.37–7.33 (m, 2H, ArH), 7.01 (s, 1H, ArH), 2.66 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.4, 151.6, 150.9, 140.5, 138.8, 131.0, 130.5, 130.0, 129.2, 126.7, 122.1, 119.4, 112.9, 106.5, 12.9; IR (KBr, cm^{-1}): 3092, 3069, 1752, 1543, 1522, 1483, 1378, 1207, 981, 832, 776 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{11}^{35}ClN_2O_2$ $[M]^+$ 310.0509; found 310.0504.

8-Chloro-3-methyl-1-(4-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2j). White solid; m.p. 242 ~ 244 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.56–7.17 (m, 6H, ArH), 7.04 (s, 1H, ArH), 2.62 (s, 3H, CH_3), 2.48 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 151.7, 150.9, 141.0, 140.6, 136.5, 131.1, 130.7, 129.4, 126.6, 122.3, 119.5, 113.2, 106.5, 21.6, 13.0; IR (KBr, cm^{-1}): 3034, 1750, 1699, 1648, 1576, 1541, 1508, 1489, 1207, 1030, 824 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{13}^{35}Cl\ N_2O_2$ $[M]^+$ 324.0666; found 324.0666.

8-Chloro-1-(4-methoxyphenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (2k). White solid; mp 210 ~ 212 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.33 (m, 4H, ArH), 7.11 (d, J = 8.7Hz, 2H, ArH), 7.06–7.05 (m, 1H, ArH), 3.94 (s, 3H, OCH_3), 2.67 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.1, 157.6, 151.7, 150.8, 140.7, 131.7, 131.1, 129.4, 128.1, 122.2, 119.5, 115.2, 113.2, 108.4, 55.9, 13.0; IR (KBr, cm^{-1}): 3066, 2957, 2837, 1745, 1652, 1541, 1523, 1457, 1396, 1261, 1207, 1028, 983, 835, 820 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{13}^{35}ClN_2O_3$ $[M]^+$ 340.0615; found 340.0611.

8-Chloro-1-(4-chlorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (2l). White solid; mp 234 ~ 236 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.63–7.58 (m, 2H, ArH), 7.52–7.47 (m, 2H, ArH), 7.42–7.33 (m, 2H, ArH), 7.10 (s, 1H, ArH), 2.66 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.2, 151.7, 151.3, 146.1, 137.2, 136.6, 134.3, 131.2, 130.3, 129.5, 128.1, 121.8, 119.6, 112.8, 12.8; IR (KBr, cm^{-1}): 3096, 3044, 3002, 2976, 1762, 1577, 1521, 1410, 1206, 1095, 1025, 985, 836 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{11}^{35}Cl_2N_2O_2$ $[M+H]^+$ 345.0198; found 345.0197.

8-Chloro-1-(4-fluorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (2m). White solid; m.p. 218 ~ 220 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.56–7.52 (m, 2H, ArH), 7.40–7.30 (m, 4H, ArH), 7.00 (d, J = 2.1Hz, 1H, ArH), 2.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 161.9, 157.3, 151.7, 151.2, 140.8, 135.2, 135.1, 131.3, 129.5, 129.1, 129.0, 122.0, 120.0, 117.5, 117.2, 112.9, 112.7, 106.7, 12.9; IR (KBr, cm^{-1}): 3104, 3052, 1745, 1522, 1490, 1448, 1416, 1227, 1021, 986, 896, 834, 772 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{10}^{35}ClF\ N_2O_2$ $[M]^+$ 328.0415; found 328.0412.

8-Chloro-3-methyl-1-(2-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2n). White solid; mp 239 ~ 240 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, J = 6.0 Hz, 1H, ArH), 7.49–7.44 (m, 2H, ArH), 7.40–7.34 (m, 3H, ArH), 6.67 (s, 1H, ArH), 2.69 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.3, 151.5, 150.8, 146.0, 140.9, 137.7, 136.0, 131.7, 131.0, 129.4, 127.6, 121.3, 119.3, 118.1, 112.9, 105.9, 17.2, 12.9; IR (KBr, cm^{-1}): 3090, 3000, 2931, 1748, 1577, 1428, 1126, 1019, 980, 831, 771 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{14}^{35}ClN_2O_2$ $[M+H]^+$ 325.0744; found 325.0745.

8-Bromo-3-methyl-1-(3-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2o). White solid; mp 256 ~ 258 °C (lit.[22] 253 ~ 254 °C); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.56–7.44 (m, 3H, ArH), 7.37 (s, 1H, ArH), 7.33-7.29 (m, 2H, ArH), 7.26 (t, J = 3.9 Hz,1H, ArH), 2.69 (s, 3H, CH_3), 2.49 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 152.3, 151.1, 140.7, 140.4, 138.9, 134.0, 131.4, 130.0, 127.4, 125.4, 123.8, 119.9, 116.8, 113.7, 106.7, 21.5, 13.1; IR (KBr, cm^{-1}): 3095, 2925, 1756, 1609, 1519, 1487, 1455, 1208, 1018, 978, 877, 827, 770 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{13}^{79}Br\ N_2O_2$ $[M]^+$ 368.0160; found 368.0163.

8-Bromo-1-(4-chlorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (2p). White solid; mp 242 ~ 243 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.56–7.41 (m, 5H, ArH), 7.23–7.19 (m, 2H, ArH), 2.60 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.1, 152.0, 151.2, 140.3, 137.3, 136.4, 134.1, 130.2, 127.9, 124.8, 119.8, 116.7, 113.2, 106.7, 12.8; IR (KBr, cm^{-1}): 3095, 3001, 2976, 2935, 1761, 1578, 1520, 1439, 1095, 1026, 980, 837 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{11}^{79}Br\ ^{35}ClN_2O_2$ $[M+H]^+$ 388.9692; found 388.9692.

8-Bromo-1-(4-fluorophenyl)-3-methylchromeno[4,3-c]pyrazol-4(1H)-one (2q). White solid; mp 246 ~ 248 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55–7.52 (m, 3H, ArH), 7.35–7.27 (m, 3H, ArH), 7.17 (s, 1H, ArH), 2.65 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 161.9, 157.3, 152.2, 151.2, 140.7, 135.2, 135.1, 134.2, 129.1, 128.9, 125.1, 120.0, 117.5, 117.2, 116.9, 113.5, 106.8, 13.0; IR (KBr, cm^{-1}): 3101, 3048, 1750, 1522, 1489, 1379, 1268, 1228, 1210, 1023, 982, 836, 802 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{10}^{79}BrF\ N_2O_2$ $[M]^+$ 371.9910; found 371.9912.

8-Bromo-3-methyl-1-(2-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2r). White solid; mp 196 ~ 198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56–7.39 (m, 5H, ArH), 7.29 (d, J = 9.0Hz, 1H, ArH), 6.81 (s, 1H, ArH), 2.68 (s, 3H, CH_3), 2.04 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.3, 152.0, 150.8, 146.0, 140.7, 137.7, 136.0, 133.8, 131.7, 131.0, 127.6, 124.4, 119.6, 116.8, 113.4, 105.9, 17.2, 12.9; IR (KBr, cm^{-1}): 3090, 3068, 3000, 2980, 2932, 1752, 1578, 1426, 1127, 1018, 974, 830, 771 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{14}^{79}Br\ N_2O_2$ $[M+H]^+$ 369.0239; found 369.0236.

8-Methoxy-3-methyl-1-(4-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2s). Light yellow solid; mp 228 ~ 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.38 (m, 4H, ArH), 7.32 (d, J = 9.0 Hz, 1H, ArH), 6.99 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1H, ArH), 6.55 (s, 1H, ArH), 3.51 (s, 3H, OCH_3), 2.67 (s, 3H, CH_3), 2.49 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 155.7, 150.9, 147.9, 142.0, 140.8, 137.0, 130.6, 127.2, 119.2, 118.6, 112.3, 106.6, 105.9, 55.7, 21.7, 13.2; IR (KBr, cm^{-1}): 3113, 3052, 2960, 2929, 1735, 1531, 1463, 1337, 1273, 1240, 1199, 1148, 1031, 829, 770 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{16}N_2O_3$ $[M]^+$ 320.1161; found 320.1157.

8-Methoxy-3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-one (2t). Light yellow solid; mp 228 ~ 230 °C (lit.[20] 232 ~ 234 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62–7.55 (m, 5H, ArH), 7.28(d, J = 8.8 Hz, 1H, ArH), 6.97 (m, 1H, ArH), 6.48 (d, J = 2.4 Hz, 1H, ArH), 3.46 (s, 3H, OCH_3), 2.65 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.1, 155.3, 150.7, 147.5, 141.6, 139.2, 130.2, 129.8, 127.1, 118.9, 118.5, 111.8, 106.4, 105.1, 55.2, 12.9; IR (KBr, cm^{-1}): 3062, 2930, 1738, 1529, 1461, 1249, 1024, 824, 692 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_3$ $[M+H]^+$ 307.1083; found 307.1077.

3-Methyl-8-nitro-1-(4-methylphenyl)chromeno[4,3-c]pyrazol-4(1H)-one (2u). Light red solid; mp 250 ~ 252 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 (dd, J_1 = 9.0 Hz, J_2 = 2.7 Hz, 1H, ArH), 8.03 (d, J = 2.7 Hz, 1H, ArH), 7.53 (d, J = 9.3 Hz, 1H, ArH), 7.48–7.40 (m, 4H, ArH), 2.69 (s, 3H, CH_3), 2.54 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 156.4, 151.0, 143.4, 141.3, 140.0, 135.8, 130.8, 126.2, 125.7, 119.0, 118.6, 112.3, 106.3, 21.5, 12.8; IR (KBr, cm^{-1}): 3103, 1767, 1698, 1599, 1523, 1473, 1345, 1257, 1215, 1015, 986, 824 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{13}N_3O_4$ $[M]^+$ 335.0906; found 335.0905.

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[21] Crystal data for **2a**: $C_{17}H_{12}N_2O_2$; M = 276.29, colorless block crystals, 0.28 × 0.19 × 0.12 mm, Orthorhombic, space group Pna2(1), a = 20.204(4) Å, b = b = 7.0090(13) Å, c = 9.5281(18) Å, α = 90º, β = 90º, γ = 90º, V = 1349.3(4) Å^3, Z = 4, D_c = 1.360 g·cm^{-1}, F(000) = 576, μ (Mo$K\alpha$) = 0.091 mm^{-1}. Intensity data were collected on a diffractometer with graphite monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) using ω scan mode with 2.36 º< θ < 25.20 º. 9940 unique reflections were measured and 1324 reflections with $I>2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R = 0.0390 and wR = 0.1014.

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