An Efficient Synthesis of Tetracyclic Pyrano[2,3-*d*]pyrimidines

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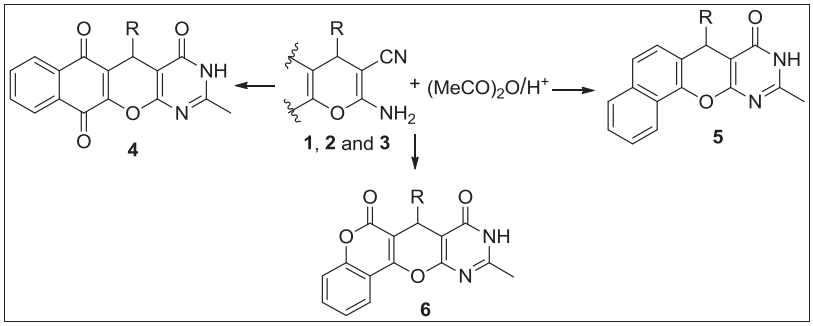
Received December 4, 2015
DOI 10.1002/jhet.2630
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



A series of pyrano[2,3-*d*]pyrimidine derivatives have been synthesized by the reaction of 2-amino-3-cyano-4*H*-pyrans and acetic anhydride with acid catalyst . This method is very efficient because of short reaction times and easy work-up, and it provides an efficient and promising synthetic strategy for the construction of the tetracyclic pyrano[2,3-*d*]pyrimidine skeleton. The X-ray crystal structures of products are confirmed, and the possible mechanism is provided in this paper.

J. Heterocyclic Chem., **00,** 00 (2016).

INTRODUCTION

Pyran scaffolds are an important class of heterocycles widely distributed in nature, including iridoids, polyether antibiotics, carbohydrates, pheromones, and alkaloids [1,2]. Moreover, pyran derivatives are well known for pharmacological and biological properties. They can be antitumor [3], antiallergic [4], antiviral [5], estrogenic [6], antibacterial [7], spasmolytic [8], and antifungal [9], as well as inhibit calcium signaling [10]. Fused pyrimidines, such as pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines, or pyrazo[3,4-*d*]pyrimidines, are also reported to have a wide range of biological activities [11–15]. The synthesis of compounds containing a pyran and a pyrimidine ring show significant synthetic challenges.

Of the many methods available for the synthesis of pyrano [2,3-*d*]pyrimidines, the most widely used is the one-pot reaction of aromatic aldehydes, compounds with active α-hydrogen (Meldrum's acid or Malononitrile), and compounds with the pyrimidinone skeleton (barbituric acid or 2-amino-4,6-dihydroxypyrimidine) [16–19]. However, less previous works have employed the tricyclic pyrans to build pyrano[2,3-*d*]pyrimidines skeleton directly. In recent work, we have studied the reaction of the 2-amino-3-cyano-4*H*-pyran derivatives with acetic anhydride in the presence of various catalysts [20]. Herein, we report a facile and rapid route for the synthesis of tetracyclic pyrano[2,3-*d*]pyrimidine derivatives with acid catalyst. As far as we know, there are no similar reports in the literature on the X-ray crystal structure of the corresponding products and the possible mechanism.

RESULTS AND DISCUSSION

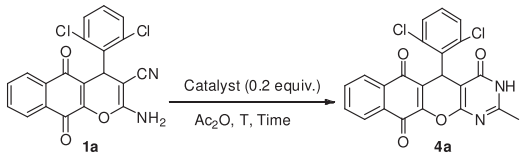
In initial experiments, the mixtures of 2-amino-4-(2-nitrophenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile **1a** and acetic anhydride were heated at the temperature in the range of 60–120°C for 30 min (Table 1, entry 1). Only trace amount of product **4a** was formed even extending the reaction time to 14 h (Table 1, entries 1 and 2). Referring to the literature [21], we next investigated the above reaction in the presence of 20 mol% of various acid catalysts in heated acetic anhydride. The results showed that the sulfuric acid-catalyzed reaction gave the highest yields, as illustrated in Table 1.

To further optimize the reaction conditions, the identical reaction was carried out at different temperatures ranging from 70°C to 110°C in the presence of 20 mol% of sulfuric acid. We found that the yield of product **4a** was improved and the reaction time was shortened as the reaction temperature was increased to 90°C from 70°C (Table 1, entries 6 and 7). Further increasing the temperature to 110°C could not improve the reaction outcome (Table 1, entry 8). So sulfuric acid as the catalyst in acetic anhydride at 90°C was identified as the optimal reaction conditions for the synthesis of product **4a**.

We then investigated the substrate scope of this synthesis by subjecting a series of aryl (R group) substituted compounds **1**, **2**, and **3** to the reactions with acetic anhydride under the optimal condition. As shown in Table 2, various aryl groups (R) bearing either electron-withdrawing or electron-donating functional groups on benzene ring, such

Table 1

Initial experiments and optimizations of reaction conditions[a] for the synthesis of **4a**.



Entry	Catalyst	T (°C)	Time (min)	Yield (%)[b]
1	None	60–120	30	Trace
2	None	60–120	14 h	Trace
3	Phosphorus pentoxide	95	30	39
4	Hydrochloric acid	90	35	21
5	Silica sulfuric acid	95	45	18
6	Sulfuric acid	70	15	56
7	Sulfuric acid	90	15	69
8	Sulfuric acid	110	15	69

[a]The mixture of **1a** (1 mmol), acetic anhydride (1 mL), and 0.2 equiv of catalyst was stirred at different temperatures.
[b]Isolated yield.

as nitro, chloro, bromo, or methyl, were all found to be suitable for the reaction (Table 2, entries 1–8).

To further expand the scope of the methodology, 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitrile **2** and 2-amino-5-oxo-4-aryl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile **3** were employed instead of compound **1** to react with acetic anhydride, respectively. These reactions occurred rapidly to give the desired products **5a–5g**, and **6a–6g** in 66–75%, and 67–78% yields, respectively (Table entries 9–15 and 16–22). The structures of all products have been confirmed by infrared (IR), ^{1}H nuclear magnetic resonance (NMR) spectroscopy, and elemental analysis. Additionally, the structure of products **4g**, **5a**, and **6b** were also determined by single crystal X-ray diffraction (Figs. 1–3).

The IR spectrum of compounds showed strong absorption peaks at 1684–1653 and 1395–1360 cm^{-1}, which attested to the presence of carbonyl and methyl groups, respectively. The cyano group, which would show absorption peak at 2260–2220 cm^{-1}, was disappeared. The ^{1}H NMR spectrum of compounds exhibited the singlet at δ 12.82–12.45 and 2.43–2.22, which are the characteristic representation of the secondary amino group and the methyl group protons, respectively.

As Figures 1–3 showed, we found that four contiguous heterocycles in the molecule structures of compounds were nearly coplanar. The dihedral angles between the plane of aryl ring and the plane of pyran ring in the molecules of compounds **4g**, **5a**, and **6b** were 82.94°, 77.18°, and 73.95°, respectively. The crystal data and structure refinement for **4g**, **5a**, and **6b** were given in Table 3.

Although the detailed mechanism of the previously mentioned reaction remains to be unclear, a possible mechanism was proposed in Scheme 1. Initially, the amino of compound **A** is acetylated to generate intermediate **C**. Then, cyan-hydrolysis of the intermediate **C** yields intermediate **F**, which undergoes keto-enol tautomerism to give the amide intermediate **G**. The intermediate **G** undergoes intramolecular dehydration–cyclization to afford the intermediate **H**, which is converted into the final product **I**.

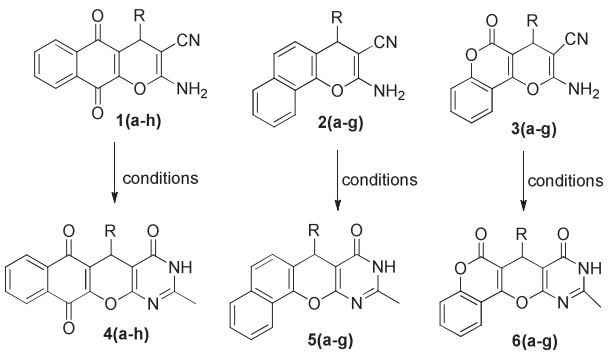
In conclusion, we have developed an efficient acid-catalyzed heterocyclization reaction, which allows us to build blocks of potentially bioactive tetracyclic pyrano[2,3-*d*]pyrimidines with a range of substituents. This method is very efficient because of the short reaction time and easy work-up.

EXPERIMENTAL

All reagents purchased from commercial sources were used as received. 2-Amino-4-aryl-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile **1**, 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitrile **2**, and 2-amino-5-oxo-4-aryl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile **3** were prepared according to literature procedures [22,23]. Melting points were determined with an X-4 apparatus and were uncorrected. IR spectra were recorded on a PerkinElmer Spectrum One Version B (PerkinElmer Inc., Waltham, MA) spectrometer with KBr pellets. ^{1}H NMR spectrum was obtained on a Varian Inova-400 MHz spectrometer with trimethylsilyl (TMS) as internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using an Elementar-vario EL cube elemental analysis instrument (Elementar Inc., Hanau, Germany). The reflection data of **4g**, **5a**, and **6b** were collected on a Rigaku Saturn724$^+$ (Rigaku Corp., Tokyo, Japan) charge coupling device (CCD) diffractometer with an area detector at 173(2) K.

Table 2

Synthesis of compounds **4**, **5**, and **6** under the optimized conditions[a].



Entry	Product	R	Time (min)	Yield (%)[b]
1	**4a**	2,6-$Cl_2C_6H_3$	15	76
2	**4b**	3,4-$(CH_3)_2C_6H_3$	10	68
3	**4c**	4-$CH_3C_6H_4$	13	69
4	**4d**	4-ClC_6H_4	13	70
5	**4e**	4-BrC_6H_4	15	71
6	**4f**	3-$CH_3C_6H_4$	13	65
7	**4g**	3-$NO_2C_6H_4$	10	64
8	**4h**	2-$NO_2C_6H_4$	13	71
9	**5a**	C_6H_5	10	67
10	**5b**	3-$NO_2C_6H_4$	12	75
11	**5c**	4-ClC_6H_3	10	72
12	**5d**	3-$(OCH_3)C_6H_4$	15	71
13	**5e**	3,4-$(OCH_3)_2C_6H_4$	14	66
14	**5f**	2,6-$Cl_2C_6H_4$	13	70
15	**5g**	4-$NO_2C_6H_4$	10	73
16	**6a**	C_6H_5	10	67
17	**6b**	4-MeC_6H_4	10	72
18	**6c**	4-ClC_6H_4	12	78
19	**6d**	3-$OCH_3C_6H_3$	15	68
20	**6e**	2,6-$Cl_2C_6H_4$	14	72
21	**6f**	4-BrC_6H_3	12	74
22	**6g**	4-$NO_2C_6H_4$	11	69

[a]The mixture of **1**, **2**, or **3** (1 mmol), acetic anhydride (1 mL), and 0.2 equiv of sulfuric acid was stirred at 90°C.
[b]Isolated yield.

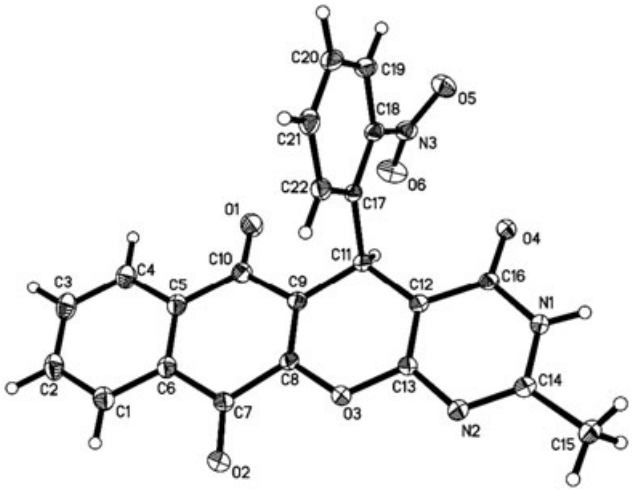


Figure 1. X-ray crystal structure of compound **4g** (CCDC: 1435232).

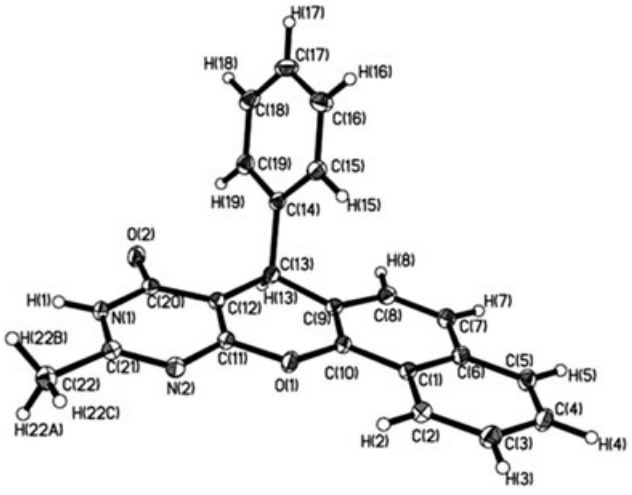


Figure 2. X-ray crystal structure of compound **5a** (CCDC: 1435230).

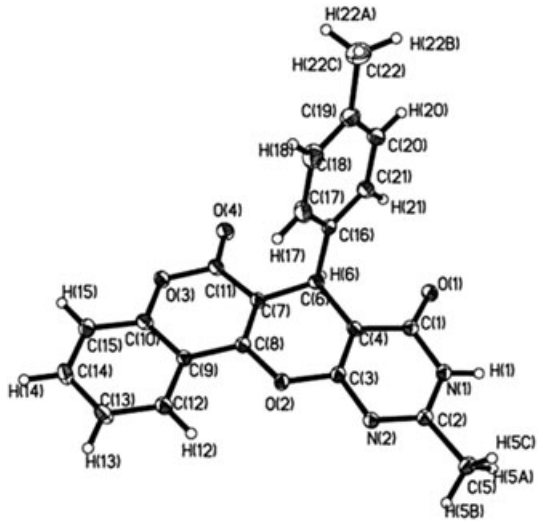


Figure 3. X-ray crystal structure of compound **6b** (CCDC:1435231).

Sample experimental. General procedure for the synthesis of **4**, **5**, or **6**:

In an oven-dried 25-mL flask, compounds **1**, **2** or **3** (1 mmol), acetic anhydride (1 mL), and sulfuric acid (0.2 mmol) were mixed and magnetically stirred at 90°C until thin-layer chromatography indicated total consumption of the starting material. Upon completion, the reaction mixture was cooled to room temperature and then poured into 250 mL water. The solid product was filtrated and purified by recrystallization from 95% ethanol to afford the pure product.

5-(2,6-Dichlorophenyl)-2-methyl-3H-benzo*[6,7]*chromeno[2,3-d]pyrimidine-4,6,11(5H)-trione (4a).

Brown crystal, mp >300°C

IR (KBr, ν, cm^{-1}): 1666, 1596, 1392.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.60 (s, 1H, NH), 8.09–8.06 (m, 1H, ArH), 7.91–7.85 (m, 3H, ArH), 7.51-7.48 (m, 1H, ArH), 7.26–7.22 (m, 2H, ArH), 5.93 (s, 1H, CH), 2.31 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{12}Cl_2N_2O_4$: C 60.16, H 2.75, N 6.38; found: C 60.17, H 2.73, N 6.39.

5-(3,4-Dimethylphenyl)-2-methyl-3H-benzo*[6,7]*chromeno[2,3-d]pyrimidine-4,6,11(5H)-trione (4b).

Yellow solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1670, 1594, 1394.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.66 (s, 1H, NH), 8.10–8.06 (m, 1H, ArH), 7.88–7.85 (m, 3H, ArH), 6.96 (s, 1H, ArH), 6.81–6.80 (m, 2H, ArH), 5.01 (s, 1H, CH), 2.89 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 2.30 (s, 3H, CH_3).

Anal. calcd for $C_{24}H_{18}N_2O_4$: C 72.35, H 4.55, N 7.03; found: C 72.37, H 4.58, N 7.05.

2-Methyl-5-(p-tolyl)-3H-benzo*[6,7]*chromeno[2,3-d]pyrimidine-4,6,11(5H)-trione (4c).

Yellow crystal, mp >300°C

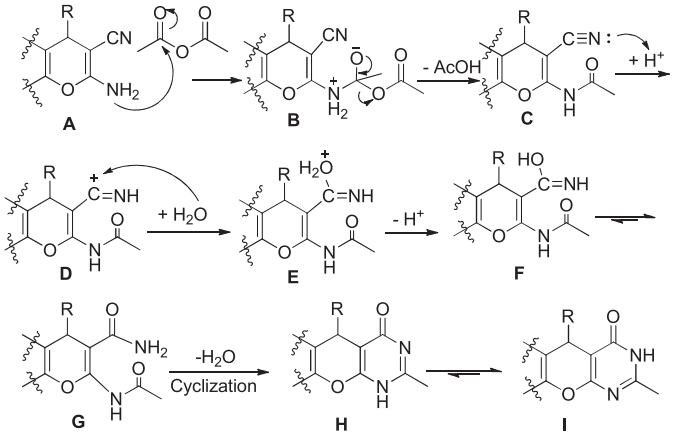
IR (KBr, ν, cm^{-1}): 1670, 1593, 1395.

Table 3

Crystal data and structure refinement for **4g**, **5a**, and **6b**.

Identification code	**4g**	**5a**	**6b**
Empirical formula	$C_{22}H_{13}N_3O_6$	$C_{22}H_{16}N_2O_2$	$C_{22}H_{16}N_2O_4$
Formula weight	415.35	340.37	372.37
Temperature (K)	173 (2)	173 (2)	173 (2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	C2/c	P2(1)/n	P2(1)/c
Unit cell dimensions	a = 15.519 (3) Å α = 90.00° b = 12.716 (3) Å β = 111.03 (3)° c = 19.369 (4) Å γ = 90.00°	a = 8.948 (4) Å α = 90.00° b = 11.278 (5) Å β = 98.982 (7)° c = 16.323 (7)Å γ = 90.00°	a = 13.764(3) Å α = 90.00° b = 8.8079 (18) Å β = 114.28 (3)° c = 16.517 (3) Å γ = 90.00°
Volume	3567.7 (13) $Å^3$	1627.0 (12) $Å^3$	1825.4 (6) $Å^3$
Z	8	4	4
Density (calculated) (mg/m^3)	1.547	1.390	1.355
Absorption coefficient (mm^{-1})	0.115	0.090	0.095
F(000)	1712	712	776
Crystal size (mm)	0.24 × 0.21 × 0.13	0.53 × 0.11 × 0.10	0.61 × 0.33 × 0.01
Theta range for data collection	2.71° to 27.47°	2.80° to 27.46°	2.83° to 27.49°
Index ranges	−19 ≤ h ≤ 19, −14 ≤ k ≤ 16, -17 ≤ 1 ≤ 25	−11 ≤ h ≤ 11, −14 ≤ k ≤ 14, -12 ≤ 1 ≤ 21	−17 ≤ h ≤ 14, −11 ≤ k ≤ 11, -13 ≤ 1 ≤ 21
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Reflections collected	7719	12816	12485
Independent reflections	3995 [*R*(int) = 0.0343]	3710 [*R*(int) = 0.0508]	4163 [*R*(int) = 0.0630]
Max. and min. transmission	1.0000 and 0.7239	1.0000 and 0.5910	0.9993 and 0.9445
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3995/0/281	3710/0/236	4163/0/255
Goodness-of-fit on F^2	1.149	1.211	1.234
Final *R* indices [I > 2sigma (I)]	*R*1 = 0.0685, *wR*2 = 0.1349	*R*1 = 0.0682, *wR*2 = 0.1341	*R*1 = 0.0841, *wR*2 = 0.1563
R indices (all data)	*R*1 = 0.0813, *wR*2 = 0.1422	*R*1 = 0.0778, *wR*2 = 0.1388	*R*1 = 0.1025, *wR*2 = 0.1656

Scheme 1. Possible reaction mechanism of the reaction.



^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.66 (s, 1H, NH), 8.09–8.06 (m, 1H, ArH), 7.93–7.90 (m, 1H, ArH), 7.87–7.84 (m, 2H, ArH), 7.23 (d, J = 8.02Hz, 2H, ArH), 7.04 (d, J = 8.02Hz, 2H, ArH), 5.03 (s, 1H, CH), 2.30 (s, 3H, CH_3), 2.20 (s, 3H, CH_3).

Anal. calcd for $C_{23}H_{16}N_2O_4$: C 71.87, H 4.20, N 7.29; found: C 71.89, H 4.23, N 7.31.

5-(4-Chlorophenyl)-2-methyl-3H-benzo*[6,7]*chromeno[2,3-d]pyrimidine-4,6,11(5H)-trione (4d).

Yellow solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1681, 1593, 1394.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.71 (s, 1H, NH), 8.09–8.07 (m, 1H, ArH), 7.93–7.84 (m, 3H, ArH), 7.41 (d, J = 8.61Hz, 2H, ArH), 7.30 (d, J = 8.61Hz, 2H, ArH), 5.06 (s, 1H, CH), 2.31 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{13}ClN_2O_4$: C 65.28, H 3.24, N 6.92; found: C 65.30, H 3.27, N 6.90.

5-(4-Bromophenyl)-2-methyl-3H-benzo*[6,7]*chromeno[2,3-d]pyrimidine-4,6,11(5H)-trione (4e).

Brown solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1681, 1594, 1393.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.71 (s, 1H, NH), 8.09–8.07 (m, 1H, ArH), 7.92–7.84 (m, 3H, ArH), 7.44 (d, J = 8.61Hz, 2H, ArH), 7.34 (d, J = 8.61Hz, 2H, ArH), 5.04 (s, 1H, CH), 2.31 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{13}BrN_2O_4$: C 58.82, H 2.92, N 6.24; found: C 58.87, H 2.97, N 6.26.

2-Methyl-5-(m-tolyl)-3H-benzo*[6,7]*chromeno[2,3-d]pyrimidine-4,6,11(5H)-trione (4f).

Red brown solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1670, 1595, 1392.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.66 (s, 1H, NH), 8.09–8.07 (m, 1H, ArH), 7.93–7.84 (m, 3H, ArH), 7.16–7.13 (m, 3H, ArH), 6.99–6.96 (m, 1H, ArH), 5.03 (s, 1H, CH), 2.31 (s, 3H, CH_3), 2.23 (s, 3H, CH_3).

Anal. calcd for $C_{23}H_{16}N_2O_4$: C 71.87, H 4.20, N 7.29; found: C 71.86, H 4.22, N 7.30.

2-Methyl-5-(3-nitrophenyl)-3H-benzo*[6,7]*chromeno[2,3-d]pyrimidine-4,6,11(5H)-trione (4g).

Green crystal, mp >300°C

IR (KBr, ν, cm^{-1}): 1671, 1593, 1393.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.73 (s, 1H, NH), 8.23 (t, 1H, ArH), 8.01–8.04 (m, 2H, ArH), 7.92–7.84 (m, 5H, ArH), 5.20 (s, 1H, CH), 2.32 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{13}N_3O_6$: C 63.62, H 3.15, N 10.12; found: C 63.64, H 3.17, N 10.16.

2-Methyl-5-(2-nitrophenyl)-3H-benzo*[6,7]*chromeno[2,3-d]pyrimidine-4,6,11(5H)-trione (4h).

Brown crystal, mp >300°C

IR (KBr, ν, cm^{-1}): 1670, 1597, 1387.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.62 (s, 1H, NH), 8.10–8.07 (m, 1H, ArH), 7.93 (dd, J = 8.22 Hz, 1H, ArH), 7.89–7.85 (m, 3H, ArH), 7.59–7.52 (m, 2H, ArH), 7.43–7.39 (m, 1H, ArH), 6.13 (s, 1H, CH), 2.30 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{13}N_3O_6$: C 63.62, H 3.15, N 10.12; found: C 63.61, H 3.13, N 10.14.

10-Methyl-7-phenyl-7H-benzo*[7,8]*chromeno[2,3-d]pyrimidin-8(9H)-one (5a).

Colorless crystal, mp >300°C

IR (KBr, ν, cm^{-1}): 1654, 1572, 1374.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.61 (s, 1H, NH), 8.34 (d, J = 7.98 Hz, 1H, ArH), 7.99 (d, J = 7.04 Hz, 1H, ArH), 7.74–7.67 (m, 3H, ArH), 7.41–7.23 (m, 6H, ArH), 5.35 (s, 1H, CH), 2.43 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{16}N_2O_2$: C 77.63, H 4.74, N 8.23; found: C 77.65, H 4.72, N 8.26.

10-Methyl-7-(3-nitrophenyl)-7H-benzo*[7,8]*chromeno[2,3-d]pyrimidin-8(9H)-one (5b).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1660, 1572, 1374.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.59 (s, 1H, NH), 8.29 (d, J = 8.25 Hz, 1H, ArH), 8.19 (t, 1H, ArH), 7.92 (d, J = 7.43 Hz, 1H, ArH), 7.73–7.53 (m, 5H, ArH),

7.33 (d, J = 8.59 Hz, 1H, ArH), 5.53 (s, 1H, CH), 2.35 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{15}N_3O_4$: C 68.57, H 3.92, N 10.90; found: C 68.60, H 3.89, N 10.92.

7-(4-Chlorophenyl)-10-methyl-7H-benzo[7,8]chromeno[2,3-d] pyrimidin-8(9H)-one (5c).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1655, 1566, 1375.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.55 (s, 1H, NH), 8.26 (d, J = 8.22 Hz, 1H, ArH), 7.92 (d, J = 8.41 Hz, 1H, ArH), 7.68–7.58 (m, 4H, ArH), 7.30–7.28 (m, 4H, ArH), 5.30 (s, 1H, CH), 2.34 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{15}N_2O_2Cl$: C 70.50, H 4.03, N 7.47; found: C 70.54, H 3.89, N 7.49.

7-(3-Methoxyphenyl)-10-methyl-7H-benzo[7,8]chromeno[2,3-d] pyrimidin-8(9H)-one (5d).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1654, 1570, 1374.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.53 (s, 1H, NH), 8.25 (d, J = 7.81 Hz, 1H, ArH), 7.91 (d, J = 6.93 Hz, 1H, ArH), 7.67–7.58 (m, 3H, ArH), 7.38–7.34 (m, 1H, ArH), 7.16–7.12 (m, 1H, ArH), 6.89–6.88 (m, 1H, ArH), 6.77–6.75 (m, 2H, ArH), 5.23 (s, 1H, CH), 3.69 (s, 3H, CH_3), 2.35 (s, 3H, CH_3).

Anal. calcd for $C_{23}H_{18}N_2O_3$: C 74.58, H 4.90, N 7.56; found: C 74.59, H 4.91, N 7.58.

7-(3,4-Dimethoxyphenyl)-10-methyl-7H-benzo[7,8]chromeno [2,3-d]pyrimidin-8(9H)-one (5e).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1658, 1571, 1373.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.59 (s, 1H, NH), 8.33 (d, J = 8.10 Hz, 1H, ArH), 7.99 (d, J = 8.05 Hz, 1H, ArH), 7.75–7.67 (m, 3H, ArH), 7.45 (d, J = 8.58 Hz, 1H, ArH), 7.09 (d, J = 2.02 Hz, 1H, ArH), 6.87 (d, J = 8.32 Hz, 1H, ArH), 6.71–6.69 (m, 1H, ArH), 5.29 (s, 1H, CH), 3.78 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 2.43 (s, 3H, CH_3).

Anal. calcd for $C_{24}H_{20}N_2O_4$: C 70.50, H 4.03, N 7.47; found: C 70.53, H 4.99, N 7.50.

7-(2,6-Dichlorophenyl)-10-methyl-7H-benzo[7,8]chromeno [2,3-d]pyrimidin-8(9H)-one (5f).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1655, 1566, 1375.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.45 (s, 1H, NH), 8.24 (d, J = 7.73 Hz, 1H, ArH), 7.90 (d, J = 7.87 Hz, 1H, ArH), 7.67–7.58 (m, 4H, ArH), 7.31–7.24 (m, 2H, ArH), 6.99(d, J = 8.60 Hz, 1H, ArH), 6.23 (s, 1H, CH), 2.34 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{14}Cl_2N_2O_2$: C 64.56, H 3.45, N 6.84; found: C 64.51, H 3.47, N 6.86.

10-Methyl-7-(4-nitrophenyl)-7H-benzo[7,8]chromeno[2,3-d] pyrimidin-8(9H)-one (5g).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1660, 1572, 1374.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.60 (s, 1H, NH), 8.28 (d, J = 8.26 Hz, 1H, ArH), 8.12 (d, J = 8.82Hz, 2H, ArH), 7.92 (d, J = 7.87 Hz, 2H, ArH), 7.66–7.57 (m, 5H, ArH), 7.29 (d, J = 7.43 Hz, 2H, ArH), 5.48 (s, 1H, CH), 2.35(s, 3H, CH_3).

Anal. calcd for $C_{22}H_{15}N_3O_4$: C 68.57, H 3.92, N 10.90; found: C 68.60, H 3.95, N 10.89.

10-Methyl-7-phenylchromeno[3',4':5,6]pyrano[2,3-d]pyrimidine-6,8(7H,9H)-dione (6a).

Colorless crystal, mp >300°C

IR (KBr, ν, cm^{-1}): 1663, 1597, 1372.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.74 (s, 1H, NH), 7.98–7.96 (m, 1H, ArH), 7.74–7.70 (m, 1H, ArH), 7.51–7.46 (m, 2H, ArH), 7.32–7.16 (m, 5H, ArH), 4.87 (s, 1H, CH), 2.33 (s, 3H, CH_3).

Anal. calcd for $C_{21}H_{14}N_2O_4$: C 70.39, H 3.94, N 7.82; found: C 70.43, H 3.97, N 7.79.

10-Methyl-7-(p-tolyl)chromeno[3',4':5,6]pyrano[2,3-d]pyr imidine-6,8(7H,9H)-dione (6b).

Colorless crystal, mp >300°C

IR (KBr, ν, cm^{-1}): 1665, 1596, 1371.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.73 (s, 1H, NH), 7.96–7.94 (m, 1H, ArH), 7.74–7.69 (m, 1H, ArH), 7.50–7.46 (m, 2H, ArH), 7.17 (d, J = 8.41 Hz, 2H, ArH), 7.05 (d, J = 8.41 Hz, 2H, ArH), 4.82 (s, 1H, CH), 2.33 (s, 3H, CH_3), 2.22 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{16}N_2O_4$: C 70.39, H 4.33, N 7.52; found: C 70.41, H 4.32, N 7.57.

7-(4-Chlorophenyl)-10-methylchromeno[3',4':5,6]pyrano[2,3-d]pyrimidine-6,8(7H,9H)-dione (6c).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1664, 1599, 1373.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.77 (s, 1H, NH), 7.97–7.95 (m, 1H, ArH), 7.75–7.71 (m, 1H, ArH), 7.49 (t, 2H, ArH), 7.36–7.30 (m, 4H, ArH), 4.85 (s, 1H, CH), 2.33 (s, 3H, CH_3).

Anal. calcd for $C_{21}H_{13}N_2O_4Cl$: C 64.21, H 3.34, N 7.13; found: C 64.91, H 3.37, N 7.15.

7-(3-Methoxyphenyl)-10-methylchromeno[3',4':5,6]pyrano [2,3-d]pyrimidine-6,8(7H,9H)-dione (6d).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1678, 1586, 1370.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.74 (s, 1H, NH), 7.96 (d, J = 7.87 Hz 1H, ArH), 7.72 (t, 1H, ArH), 7.49 (t, 2H, ArH), 7.17 (t, 1H, ArH), 6.87–6.76 (m, 3H, ArH), 4.85 (s, 1H, CH), 3.69 (s, 3H, CH), 2.33 (s, 3H, CH_3).

Anal. calcd for $C_{22}H_{16}N_2O_5$: C 68.04, H 4.15, N 7.21; found: C 68.07, H 4.18, N 7.17.

7-(2,6-Dichlorophenyl)-10-methylchromeno[3',4':5,6] pyrano[2,3-d]pyrimidine-6,8(7H,9H)-dione (6e).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1664, 1598, 1369.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.67 (s, 1H, NH), 7.95 (d, J = 8.81Hz 1H, ArH), 7.73 (t, 1H, ArH), 7.48

(t, 4H, ArH), 7.26 (t, 1H, ArH), 5.79 (s, 1H, CH), 2.34 (s, 3H, CH_3).

Anal. calcd for $C_{21}H_{12}N_2O_4Cl_2$: C 59.04, H 2.83, N 6.56; found: C 59.09, H 2.81, N 6.58.

7-(4-Bromophenyl)-10-methylchromeno[3',4':5,6]pyrano[2,3-d]pyrimidine-6,8(7H,9H)-dione (6f).

Colorless crystal, mp >300°C

IR (KBr, ν, cm^{-1}): 1664, 1597, 1371.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.77 (s, 1H, NH), 7.97–7.95 (m, 1H, ArH), 7.75–7.70 (m, 1H, ArH), 7.51–7.43 (m, 4H, ArH), 7.29–7.27 (m, 2H, ArH), 4.84 (s, 1H, CH), 2.33 (s, 3H, CH_3).

Anal. calcd for $C_{21}H_{13}N_2O_4Br$: C 57.69, H 3.00, N 6.41; found: C 57.69, H2.99, N 6.43.

10-Methyl-7-(4-nitrophenyl)chromeno[3',4':5,6]pyrano[2,3-d]pyrimidine-6,8(7H,9H)-dione (6g).

White solid, mp >300°C

IR (KBr, ν, cm^{-1}): 1664, 1599, 1360.

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 12.82 (s, 1H, NH), 8.12 (d, J = 8.81 Hz, 2H, ArH), 8.00–7.98 (m, 1H, ArH), 7.77–7.72 (m, 1H, ArH), 7.63 (d, J = 8.82Hz, 2H, ArH), 7.53–7.48 (m, 2H, ArH), 5.00 (s, 1H, CH), 2.34 (s, 3H, CH_3).

Anal. calcd for $C_{21}H_{13}N_3O_6$: C 62.53, H 3.25, N 10.42; found: C 62.50, H 3.22, N 10.40.

Acknowledgments. We are grateful for financial support from the National Natural Science Foundation of China (21402124).

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