Tetrahedron 67 (2011) 7426–7430

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Nickel chloride-catalyzed one-pot three-component synthesis of pyrazolophthalazinyl spirooxindoles

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ARTICLE INFO

Article history:
Received 25 May 2011
Received in revised form 26 June 2011
Accepted 1 July 2011
Available online 7 July 2011

Keywords:
Nickel chloride
Pyrazolophthalazinyl spirooxindoles
Multicomponent reaction
One-pot
Polyethylene glycol

ABSTRACT

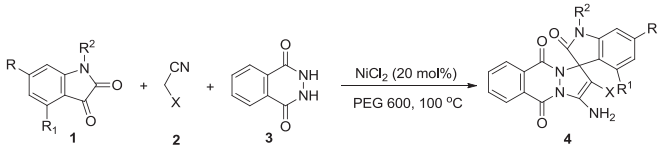
A direct and efficient approach for the preparation of pyrazolophthalazinyl spirooxindoles has been developed through one-pot three-component reaction of easily available isatin, malononitrile or cyanoacetic ester, and phthalhydrazide catalyzed by nickel chloride in polyethylene glycol 600. Desired products were obtained in high to excellent yields using a simple workup procedure.

1. Introduction

Multicomponent coupling reactions (MCRs), with high-throughput generate structurally complex molecules by the reaction of three or more readily accessible starting materials via a one-pot methodology, have become powerful tools in organic, combinatorial, and medicinal chemistry. They offer significant advantages over conventional stepwise strategies, by reducing waste production, saving energy, shortening reaction periods, and avoiding protection–deprotection of functional groups thus resulting in both economical and environmental benefits.[1]

Heterocyclic chemistry is one of the most important disciplines in organic synthesis and pharmaceutical chemistry.[2] Among the various heterocyclic systems discovered and developed, the nitrogen-containing heterocycles play a fundamental role in the context of both chemistry and biology. Spirooxindole is one of prevalent heterocycles found in numerous natural and synthetic products along with useful bio-, physio-, and pharmaceutical activities.[3] In addition, heterocyclic fused phthalazines have been found to posses cytotoxic, antimicrobial, anticonvulsant, antifungal, anticancer, anti-inflammatory, and cardiotonic activities.[4] They also exhibited good feature as new luminescence material or fluorescence probe.[5] Consequently, great efforts have been made to find efficient synthetic methods to gain access to spirooxindole and phthalazine derivatives. So far, only a few methods have been reported for the preparation of pyrazolophthalazinyl spirooxindoles.[6] Considering the above reports, the development of new synthetic methodologies for the construction of pyrazolophthalazinyl spirooxindole scaffold will be a beneficial and interesting challenge.

In recent years, the use of polyethylene glycol as a reaction medium has gained considerable interest in organic synthesis due to its many advantages from environmental, economical, and safety standpoints.[7] It is non-toxic, inexpensive, non-volatile, thermally stable, biologically acceptable, and eco-friendly, and allows many useful organic transformations to be performed under mild reaction conditions, such as coupling,[8] addition,[9] substitution,[10] condensation,[11] oxidation,[12] reduction,[13] and multicomponent reaction.[14] In a continuation of our interest in developing more efficient and environmental benign methodologies,[15] we report herein a simple and facile procedure for the synthesis of pyrazolophthalazinyl spirooxindoles through one-pot three-component reaction of isatin, malononitrile or cyanoacetic ester and phthalhydrazide catalyzed by $NiCl_2$ in PEG 600 (Scheme 1).



Scheme 1. Synthesis of pyrazolophthalazinyl spirooxindoles catalyzed by $NiCl_2$ in PEG 600.

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doi:10.1016/j.tet.2011.07.002

2. Results and discussion

First of all, the model reaction of isatin (1.0 mmol), malononitrile (1.0 mmol), and phthalhydrazide (1.0 mmol) was conducted to screen the optimal reaction conditions and the results were listed in Table 1. We attempted various conditions and found that the reaction gave satisfying result in the presence of $NiCl_2$ in PEG 600 at 100 °C (Table 1, entry 15). Other Lewis acids, such as $FeCl_3$, $ZnCl_2$, $InBr_3$, $CoCl_2$, $Cu(NO_3)_2$, and $Cu(SO_4)_2$, afforded **4a** in lower yields along with recovery of the starting material (Table 1, entries 9–14). Moreover, the results indicated that the yield was decreased to some extent when 10 mol % of $NiCl_2$ was used (Table 1, entry 21), and no reaction was observed even for longer time in the absence of a catalyst (Table 1, entry 1). No substantial improvement in the yield was observed by increasing the amount of $NiCl_2$ to 30 mol %. Also, the effect of the solvents on the reaction was investigated. As could be seen in Table 1, the solvent played a crucial role for this reaction. Water, acetonitrile, *N*,*N*-dimethyl formamide (DMF), and 1,4-dioxane (Table 1, entries 16–19) were found not suitable for this reaction, since no reaction took place. The target product was obtained in 60% yield in refluxing ethanol. To our surprise, we found that the yield of the desired product **4a** could be improved to 90% when PEG 600 was employed. Besides, the effect of temperature was studied by carrying out the model reaction in PEG 600 at different temperatures in the presence of $NiCl_2$. The results suggested that the optimized reaction temperature was 100 °C.

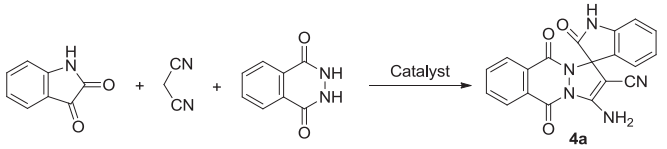
The scope and limitations of this new MCR process were further evaluated under optimized reaction conditions and the results are shown in Table 2. A variety of isatin, both electron-donating and electron-withdrawing groups on the aromatic ring, were reacted with malononitrile and phthalhydrazide to generate pyrazolophthalazinyl spir-3′-oxindoles (**4**) in good to high yields. In general, isatins with electron-withdrawing group on the aromatic ring reacted rapidly, while isatins bearing electron-donating group decreased the reactivity, requiring longer reaction times. In addition, the reactions were also found to be effective when less reactive cyanoacetic esters were employed in place of malononitrile. However, it is observed that the corresponding products were obtained in slightly lower yields than malononitrile.

The products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, and by elemental analysis. The structure of **4i** was further confirmed by X-ray diffraction analysis of single crystal and is shown below in Fig. 1.

In order to elucidate the reaction mechanism, we also conducted the reaction of 2-(2-oxoindolin-3-ylidene)malononitrile (**5**)[17] with phthalhydrazide in the presence of $NiCl_2$ under same condition. Interestingly, **4a** was obtained in high yield. In addition, when we tried to perform the reaction of phthalhydrazide with isatin or malononitrile in the above reaction conditions, no reaction was observed. On the basis of these findings, we propose a plausible mechanism for this three-component reaction (Scheme 2). The reaction may proceed in a stepwise manner. Firstly, we assume that the initial step is a Knoevenagel condensation between isatin and malononitrile, resulting the adduct **5**, which suffers a Michael addition of phthalhydrazide to the C=C bond of **5**, followed by cycloaddition and isomerization to afford the target product **4a**. The role of $NiCl_2$ probably would be Lewis acid for the activation of the nitrile to transform into amine.

Finally, the present route to pyrazolophthalazinyl spirooxindole was successfully applied to a large scale process. A typical reaction was performed for synthesis of **4a** with tenfold amounts of reactants and catalyst with respect to the one mentioned in the Experimental section. The result showed that the desired product **4a** was obtained in 88% yield.

Table 1
Screening on the reaction conditions for the synthesis of **4a**[a]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	No	PEG 600	100	5.0	0
2	$NaHCO_3$ (20 mol %)	EtOH	Reflux	2.5	0
3	NaOAc (20 mol %)	H_2O	Reflux	4.0	0
4	MgO (20 mol %)	EtOH	Reflux	5.5	0
5	CuO (20 mol %)	EtOH	Reflux	2.0	0
6	NaOAc (20 mol %)	PEG 600	100	2.0	0
7	K_2CO_3 (20 mol %)	EtOH	Reflux	5.5	12
8	β-CD (20 mol %)	H_2O	Reflux	2.0	15
9	$FeCl_3$ (20 mol %)	PEG 600	100	3.0	8
10	$ZnCl_2$ (20 mol %)	PEG 600	100	3.5	18
11	$InBr_3$ (20 mol %)	PEG 600	100	2.5	0
12	$CoCl_2$ (20 mol %)	PEG 600	100	3.5	12
13	$Cu(NO_3)_2$ (20 mol %)	PEG 600	100	3.0	20
14	$Cu(SO_4)_2$ (20 mol %)	PEG 600	100	3.0	10
15	$NiCl_2$ (20 mol %)	PEG 600	100	1.3	90
16	$NiCl_2$ (20 mol %)	H_2O	Reflux	3.0	0
17	$NiCl_2$ (20 mol %)	CH_3CN	Reflux	3.5	0
18	$NiCl_2$ (20 mol %)	DMF	Reflux	3.5	0
19	$NiCl_2$ (20 mol %)	1,4-Dioxane	Reflux	3.0	0
20	$NiCl_2$ (20 mol %)	EtOH	Reflux	2.5	60
21	$NiCl_2$ (10 mol %)	PEG 600	100	3.0	21
22	$NiCl_2$ (30 mol %)	PEG 600	100	1.0	90
23	$NiCl_2$ (20 mol %)	PEG 600	25	5.0	0
24	$NiCl_2$ (20 mol %)	PEG 600	60	3.0	0
25	$NiCl_2$ (20 mol %)	PEG 600	80	3.5	40
26	$NiCl_2$ (20 mol %)	PEG 600	110	1.5	85

[a] All reactions were run with isatin (1.0 mmol), malononitrile (1.0 mmol), and phthalhydrazide (1.0 mmol) in solvent (5 mL).
[b] Isolated yields.

3. Conclusion

In summary, we have developed a new strategy that provides an efficient synthesis of a class of structurally unique pyrazolophthalazinyl spirooxindoles via $NiCl_2$-catalyzed one-pot three-component condensation reaction from simple and readily available precursors. The simplicity, high yields of products, easy workup procedure, and avoidance of hazardous organic solvents are the major features of this methodology.

4. Experimental section

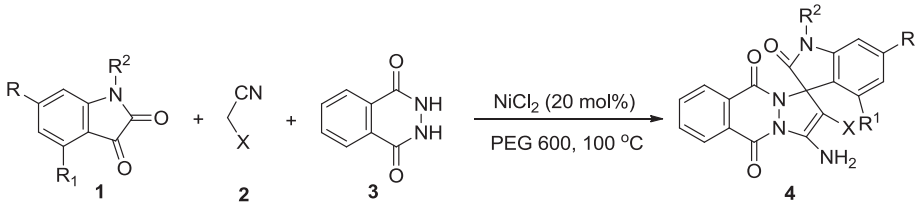
4.1. General

All solvents and chemicals were obtained commercially and were used as received. Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were recorded using a Bruker-TENSOR 27 spectrometer instrument. NMR spectra were taken with a Bruker DRX-500 spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C) using DMSO-d_6 as the solvent. Elemental analyses were obtained on a Vario EL III CHNOS elemental analyzer.

4.2. General procedure for synthesis of pyrazolophthalazinyl spirooxindoles

A mixture of isatin **1** (1.0 mmol), malononitrile or cyanoacetic ester **2** (1.0 mmol), phthalhydrazide (1.0 mmol), and $NiCl_2$ (0.2 mmol) in PEG 600 (5 mL) was stirred at 100 °C for the appropriate time (Table 2). After complete conversion as indicated by TLC, water was added and the product was extracted with ethyl

Table 2
Synthesis of pyrazolophthalazinyl spirooxindoles catalyzed by $NiCl_2$ in PEG 600



Entry	R	R^1	R^2	X	Products	Time (h)	Yield[a] (%)	Mp (°C)	lit. Mp (°C)
1	H	H	H	CN	**4a**	1.3	90	268–270	269–270[6]
2	H	H	Me	CN	**4b**	1.2	88	283–285	282–284[6]
3	H	H	$CH_2CH_2CH_2CH_3$	CN	**4c**	1.3	85	223–224	222–223[6]
4	H	H	CH_2=$CHCH_3$	CN	**4d**	1.1	86	278–279	276–277[6]
5	H	H	$PhCH_2$	CN	**4e**	1.0	83	265–266	266[6]
6	Me	H	H	CN	**4f**	2.3	84	278–279	
7	Me	Me	H	CN	**4g**	2.5	80	>350	
8	Cl	H	H	CN	**4h**	1.2	91	325–327	
9	Br	H	H	CN	**4i**	1.0	92	>350	
10	I	H	H	CN	**4j**	1.0	93	348–350	
11	NO_2	H	H	CN	**4k**	0.8	95	280–281	280–282[6]
12	H	H	H	COOMe	**4l**	2.5	82	318–320	
13	Cl	H	H	COOMe	**4m**	2.3	80	288–290	
14	Br	H	H	COOMe	**4n**	2.0	85	305–307	
15	I	H	H	COOMe	**4o**	3.0	90	308–310	
16	NO_2	H	H	COOMe	**4p**	1.5	93	340–342	
17	H	H	H	COOEt	**4q**	2.0	83	285–286	284–286[6]
18	H	H	$CH_2CH_2CH_2CH_3$	COOEt	**4r**	2.1	84	259–260	258–260[6]
19	H	H	CH_2=$CHCH_3$	COOEt	**4s**	2.2	85	255–256	254–256[6]
20	H	H	$PhCH_2$	COOEt	**4t**	2.5	86	291–292	290–291[6]
21	Cl	H	H	COOEt	**4u**	2.0	84	332–334	
22	Br	H	H	COOEt	**4v**	2.0	88	331–333	
23	I	H	H	COOEt	**4w**	2.3	83	340–342	
24	NO_2	H	H	COOEt	**4x**	1.7	91	320–322	
25	Cl	H	H	COO^iPr	**4y**	3.5	82	322–323	
26	Br	H	H	COO^iPr	**4z**	3.5	84	308–309	

[a] Yields refer to pure isolated products.

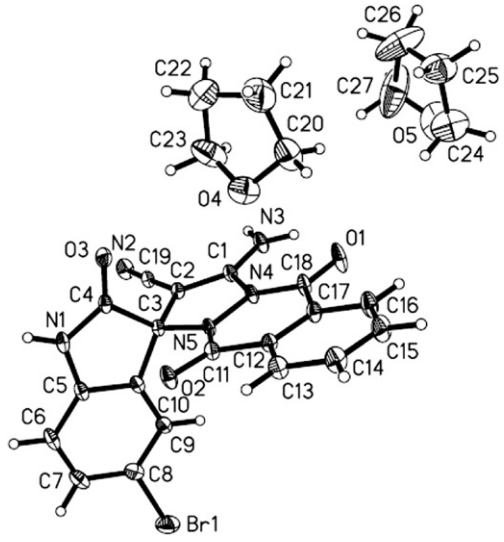
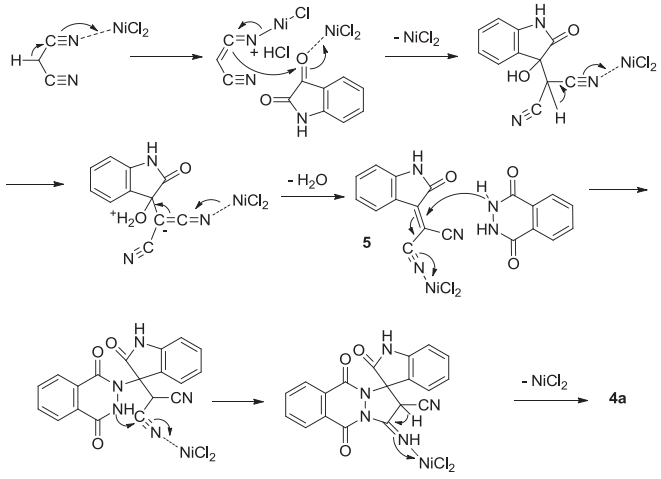


Fig. 1. X-ray crystal structure of **4i** (CCDC 825902).[16]



Scheme 2. A possible mechanism for the one-pot reaction for synthesis of **4a**.

acetate (2×10 ml). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was recrystallized from ethanol to afford the pure product.

4.3. Characterization data

*4.3.1. 3′-Amino-5-methyl-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (**4f**).* Yellow solid; IR (KBr) ν 3353, 3315, 2208, 1747, 1719, 1692, 1659, 1624, 1601, 1558, 1545, 1533, 1497, 1437, 1375, 1261, 1203, 1167, 1144, 824, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.22 (s, 3H, CH_3), 6.81 (d, J=8.0 Hz, 1H, ArH), 7.11 (d, J=8.0 Hz, 1H, ArH), 7.32 (s, 1H, ArH), 7.98–8.03 (m, 2H, ArH), 8.06 (d, J=7.5 Hz, 1H, ArH), 8.30 (d, J=8.0 Hz, 1H, ArH), 8.34 (s, 2H, NH_2), 10.83 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.6, 60.3, 69.9, 110.0, 114.5, 125.1, 125.5, 127.0, 127.6, 127.9, 128.7, 130.7, 131.8, 134.3, 135.0, 139.8, 151.7, 152.5,

156.3, 172.4; Anal. Calcd for $C_{20}H_{13}N_5O_3$: C, 64.69; H, 3.53; N, 18.86; found: C 64.85; H 3.38; N, 19.02.

*4.3.2. 3′-Amino-5,7-dimethyl-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (**4g**).* Yellow solid; IR (KBr) ν 3465, 3404, 2194, 1743, 1683, 1652, 1604, 1558, 1490, 1419, 1382, 1271, 1205, 1147, 1033, 866, 694 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.18 (s, 1H, CH_3), 2.23 (s, 3H, CH_3), 6.94 (s, 1H, ArH), 7.12 (s, 1H, ArH), 8.00–8.07 (m, 3H, ArH), 8.31 (d, J=8.0 Hz, 1H, ArH), 8.32 (s, 2H, NH_2), 10.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 16.1, 20.4, 60.4, 70.1, 114.5, 119.1, 122.3, 125.1, 126.9, 127.6, 127.9, 128.9, 131.3, 132.1, 134.3, 135.0, 138.3, 151.6, 152.4, 156.2, 172.8; Anal. Calcd for $C_{21}H_{15}N_5O_3$: C, 65.45; H, 3.92; N, 18.17; found: C 65.58; H 4.10; N, 17.98.

*4.3.3. 3′-Amino-5-chloro-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (**4h**).* Yellow solid; IR (KBr) ν 3358, 3249, 2208, 1762, 1705, 1662, 1643, 1622, 1558, 1473, 1411, 1363, 1257, 1167, 1134, 1115, 1029, 827, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 6.94 (d, J=8.0 Hz, 1H, ArH); 7.36 (dd, J=8.5, 2.0 Hz, 1H, ArH), 7.71 (d, J=2.0 Hz, 1H, ArH), 8.00–8.08 (m, 3H, ArH), 8.31 (d, J=8.0 Hz, 1H, ArH), 8.39 (s, 2H, NH_2), 11.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 59.5, 69.5, 111.7, 114.3, 124.9, 126.5, 127.0, 127.5, 127.6, 127.7, 128.8, 130.2, 134.4, 135.0, 141.0, 151.9, 152.5, 156.4, 172.2; Anal. Calcd for $C_{19}H_{10}ClN_5O_3$: C, 58.25; H, 2.57; N, 17.88; found: C 58.06; H 2.75; N, 17.70.

*4.3.4. 3′-Amino-5-bromo-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (**4i**).* Yellow solid; IR (KBr) ν 3394, 3354, 2212, 1751, 1693, 1658, 1618, 1602, 1577, 1558, 1477, 1440, 1379, 1272, 1257, 1166, 1147, 1122, 819, 800, 702 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 6.89 (d, J=8.5 Hz, 1H, ArH); 7.49 (dd, J=8.5, 2.0 Hz, 1H, ArH), 7.82 (d, J=2.0 Hz, 1H, ArH), 8.00–8.08 (m, 3H, ArH), 8.32 (dd, J=8.5, 2.0 Hz, 1H, ArH), 8.39 (s, 2H, NH), 11.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 59.5, 69.4, 112.2, 114.2, 114.3, 127.0, 127.5, 127.6, 127.7, 127.8, 128.8, 133.0, 134.4, 135.0, 141.4, 151.9, 152.5, 156.3, 172.1; Anal. Calcd for $C_{19}H_{10}BrN_5O_3$: C, 52.31; H, 2.31; N, 16.05; found: C 52.15; H 2.50; N, 15.88.

*4.3.5. 3′-Amino-5-iodo-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carbonitrile (**4j**).* Yellow solid; IR (KBr) ν 3392, 3303, 3180, 2212, 1751, 1691, 1658, 1616, 1602, 1577, 1473, 1440, 1379, 1274, 1257, 1291, 1166, 1147, 1124, 815, 800, 702 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 6.77 (d, J=8.0 Hz, 1H, ArH), 7.64 (d, J=8.5 Hz, 1H, ArH), 7.93 (s, 1H, ArH), 8.01–8.08 (m, 3H, ArH), 8.31 (d, J=8.0 Hz, 1H, ArH), 8.39 (s, 2H, NH_2), 11.05 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 59.6, 69.3, 85.4, 112.6, 114.3, 127.0, 127.5, 127.7, 127.9, 128.8, 133.0, 134.4, 135.0, 138.8, 141.8, 151.8, 152.4, 156.3, 171.9; Anal. Calcd for $C_{19}H_{10}IN_5O_3$: C, 47.23; H, 2.09; N, 14.49; found: C 47.40; H 1.92; N, 14.66.

*4.3.6. Methyl 3′-amino-2,5′,10′-trioxo-5′,10′-dihydrospiro [indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4l**).* Yellow solid; IR (KBr) ν 3415, 3352, 1758, 1701, 1670, 1652, 1616, 1508, 1465, 1407, 1382, 1305, 1290, 1290, 1267, 1240, 1164, 1139, 1095, 779, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.44 (s, 3H, CH_3), 6.83 (d, J=7.5 Hz, 1H, ArH), 6.88 (t, J=7.5 Hz, 1H, ArH), 7.21 (t, J=7.5 Hz, 1H, ArH), 7.30 (d, J=7.0 Hz, 1H, ArH), 7.98–8.06 (m, 3H, ArH), 8.30–8.32 (m, 1H, ArH), 10.74 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 51.0, 70.6, 81.2, 109.9, 122.2, 124.2, 127.1, 127.4, 127.9, 128.6, 129.0, 130.0, 134.6, 135.5, 143.8, 150.9, 151.0, 152.5, 157.1, 163.8, 173.8; Anal. Calcd for $C_{20}H_{14}N_4O_5$: C, 61.54; H, 3.62; N, 14.35; found: C 61.38; H 3.45; N, 14.52.

*4.3.7. Methyl 3′-amino-5-chloro-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4m**).* Yellow solid; IR (KBr) ν 3454, 3350, 1751, 1701, 1666, 1647, 1602, 1521, 1477, 1448, 1394, 1315, 1267, 1168, 1145, 1116, 823, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.47 (s, 3H, CH_3), 6.79–6.85 (m, 1H, ArH), 7.25–7.40 (m, 1H, ArH), 7.52–7.64 (m, 1H, ArH), 8.00–8.05 (m, 3H, ArH), 8.30–8.32 (m, 1H, ArH), 10.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 51.1, 70.2, 70.3, 111.2, 111.8, 113.9, 124.2, 126.2, 127.3, 127.5, 127.9, 128.4, 129.2, 129.8, 134.7, 135.5, 152.6, 157.2, 173.2, 173.3; Anal. Calcd for $C_{20}H_{13}ClN_4O_5$: C, 56.55; H, 3.08; N, 13.19; found: C 56.72; H 2.90; N, 13.02.

*4.3.8. Methyl 3′-amino-5-bromo-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4n**).* Yellow solid; IR (KBr) ν 3404, 3292, 1751, 1705, 1670, 1647, 1618, 1533, 1477, 1448, 1382, 1309, 1265, 1217, 1168, 1143, 1116, 1031, 810, 704 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.47 (s, 3H, CH_3), 6.80 (d, J=8.5 Hz, 1H, ArH), 7.39 (dd, J=8.5, 2.0 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 8.00–8.07 (m, 3H, ArH), 8.30–8.32 (m, 1H, ArH), 10.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 50.5, 69.7, 80.3, 111.2, 113.4, 126.8, 126.9, 127.4, 128.0, 128.7, 129.0, 132.1, 134.2, 134.9, 142.6, 152.1, 156.7, 163.1, 163.1, 172.6; Anal. Calcd for $C_{20}H_{13}BrN_4O_5$: C, 51.19; H, 2.79; N, 11.94; found: C 51.02; H 2.98; N, 12.13.

*4.3.9. Methyl 3′-amino-5-iodo-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4o**).* Yellow solid; IR (KBr) ν 3446, 3354, 1739, 1701, 1666, 1647, 1635, 1616, 1602, 1521, 1473, 1394, 1313, 1267, 1217, 1168, 1143, 1118, 823, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.47 (s, 3H, CH_3), 6.68 (d, J=8.0 Hz, 1H, ArH), 7.54 (dd, J=8.0, 1.5 Hz, 1H, ArH), 7.75 (d, J=1.5 Hz, 1H, ArH), 8.00–8.07 (m, 3H, ArH), 8.30–8.32 (m, 1H, ArH), 10.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 50.6, 69.6, 80.4, 84.5, 111.8, 127.0, 127.4, 128.0, 128.8, 129.2, 132.1, 134.2, 135.0, 137.9, 143.1, 150.6, 152.1, 156.7, 163.2, 172.4; Anal. Calcd for $C_{20}H_{13}IN_4O_5$: C, 46.53; H, 2.54; N, 10.85; found: C 46.35; H 2.72; N, 10.68.

*4.3.10. Methyl 3′-amino-5-nitro-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4p**).* Yellow solid; IR (KBr) ν 3421, 3313, 1751, 1701, 1662, 1608, 1558, 1473, 1456, 1382, 1338, 1309, 1265, 1211, 1141, 1083, 1033, 839, 774, 702 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.46 (s, 3H, CH_3), 7.05 (d, J=7.5 Hz, 1H, ArH), 7.73 (br s, 2H, NH_2), 8.00–8.03 (m, 3H, ArH), 8.20 (d, J=8.0 Hz, 1H, ArH), 8.32 (d, J=7.5 Hz, 1H, ArH), 8.46 (s, 1H, ArH), 11.49 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 51.0, 70.6, 81.2, 109.9, 122.2, 124.2, 127.1, 127.4, 127.9, 128.6, 129.0, 130.0, 134.6, 135.5, 143.8, 151.0, 152.5, 157.1, 163.8, 173.4; Anal. Calcd for $C_{20}H_{13}N_5O_7$: C, 55.18; H, 3.01; N, 16.09; found: C 54.99; H 2.83; N, 16.25.

*4.3.11. Ethyl 3′-amino-5-chloro-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4u**).* Yellow solid; IR (KBr) ν 3442, 3332, 1751, 1705, 1662, 1647, 1602, 1533, 1481, 1400, 1298, 1265, 1164, 1145, 1112, 819, 773, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 0.92 (t, J=7.0 Hz, 3H, CH_3), 3.84–3.94 (m, 2H, CH_2), 6.84 (d, J=8.5 Hz, 1H, ArH), 7.27 (dd, J=8.5, 2.0 Hz, 1H, ArH), 7.51 (d, J=2.0 Hz, 1H, ArH), 8.00–8.06 (m, 3H, ArH), 8.31–8.32 (m, 1H, ArH), 10.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 13.7, 58.8, 69.8, 80.3, 110.6, 124.1, 125.7, 127.0, 127.4, 128.0, 128.7, 128.9, 129.2, 134.2, 135.0, 142.3, 150.8, 152.2, 156.6, 163.0, 172.8; Anal. Calcd for $C_{21}H_{15}ClN_4O_5$: C, 57.48; H, 3.45; N, 12.77; found: C 57.65; H 3.28; N, 12.60.

*4.3.12. Ethyl 3′-amino-5-bromo-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4v**).* Yellow solid; IR (KBr) ν 3438, 3330, 1747, 1705, 1662, 1620, 1602, 1529, 1477, 1398, 1300, 1265, 1219, 1167, 1145, 1118, 1064, 821, 702 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 0.92 (t, J=6.5 Hz, 3H, CH_3), 3.84–3.94 (m, 2H, CH_2), 6.80 (d, J=8.0 Hz, 1H, ArH), 7.40 (dd, J=8.0, 2.0 Hz, 1H,

ArH), 7.63 (d, *J*=2.0 Hz, 1H, ArH), 7.98–8.08 (m, 3H, ArH), 8.30–8.32 (m, 1H, ArH),10.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 13.7, 58.9, 69.8, 80.3, 111.2, 113.3, 126.8, 127.0, 127.4, 128.0, 128.7, 129.2, 132.0, 134.2, 134.9, 142.7, 150.8, 152.1, 156.6, 163.0, 172.7; Anal. Calcd for $C_{21}H_{15}BrN_4O_5$: C, 52.19; H, 3.13; N, 11.59; found: C 52.01; H 2.98; N, 11.76.

*4.3.13. Ethyl 3′-amino-5-iodo-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4w**).* Yellow solid; IR (KBr) ν 3439, 3331, 1739, 1701, 1662, 1616, 1604, 1525, 1473, 1429, 1398, 1386, 1357, 1299, 1265, 1165, 1145, 1120, 821, 777, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.92 (t, *J*=7.5 Hz, 3H, CH_3), 3.85–3.94 (m, 2H, CH_2), 6.69 (d, *J*=8.0 Hz, 1H, ArH), 7.55 (dd, *J*=8.0, 2.0 Hz, 1H, ArH), 7.74(d, *J*=2.0 Hz, 1H, ArH), 8.00–8.06 (m, 3H, ArH), 8.30–8.32 (m, 1H, ArH), 10.84 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.2, 59.3, 70.1, 80.9, 84.9, 112.2, 127.5, 127.9, 128.5, 129.2, 129.9, 132.6, 134.7, 135.4, 138.3, 143.6, 151.3, 152.6, 157.1, 163.5, 172.9; Anal. Calcd for $C_{21}H_{15}IN_4O_5$: C, 47.57; H, 2.85; N, 10.57; found: C 47.38; H 3.01; N, 10.60.

*4.3.14. Ethyl 3′-amino-5-nitro-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4x**).* Yellow solid; IR (KBr) ν 3442, 3330, 1757, 1708, 1664, 1652, 1612, 1533, 1481, 1429, 1400, 1382, 1340, 1296, 1265, 1211, 1145, 1085, 702 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.89 (t, *J*=7.5 Hz, 3H, CH_3), 3.86 (q, *J*=7.5 Hz, 2H, CH_2), 7.03 (d, *J*=8.5 Hz, 1H, ArH), 7.96–8.04 (m, 3H, ArH), 8.20 (dd, *J*=8.5, 2.0 Hz, 1H, ArH), 8.31 (d, *J*=7.0 Hz, 1H, ArH), 8.44 (d, *J*=2.0 Hz, 1H, ArH), 11.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 13.7, 59.0, 69.3, 79.8, 109.5, 120.2, 126.8, 127.0, 127.5, 127.8, 128.0, 128.9, 134.3, 134.9, 142.5, 149.6, 151.1, 152.3, 156.7, 162.9, 173.8; Anal. Calcd for $C_{21}H_{15}N_5O_7$: C, 56.13; H, 3.36; N, 15.58; found: C 55.98; H 3.52; N, 15.40.

*4.3.15. Isopropyl 3′-amino-5-chloro-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4y**).* Yellow solid; IR (KBr) ν 342, 3313.5, 2980, 2853, 1751, 1701, 1662, 1647, 1622, 1558, 1533.3, 1481, 1398, 1296, 265.2, 1166.9, 1145, 1105, 1076, 1043, 896, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.78 (d, *J*=6.5 Hz, 3H, CH_3), 1.09 (d, *J*=6.5 Hz, 3H, CH_3), 4.76–4.83 (m, 1H, CH), 6.90 (d, *J*=8.5 Hz, 1H, ArH), 7.34 (dd, *J*=8.5, 2.0 Hz, 1H, ArH), 7.57 (d, *J*=2.0 Hz, 1H, ArH), 8.05–8.09 (m, 2H, ArH), 8.12–8.14 (m, 1H, ArH), 8.37–8.39 (m, 1H, ArH), 10.95 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 21.2, 21.5, 66.1, 70.0, 80.6, 110.7, 124.2, 125.8, 127.1, 127.5, 128.1, 128.8, 129.2, 129.2, 134.3, 135.1, 142.4, 151.0, 152.3, 156.6, 162.9, 173.0; Anal. Calcd for $C_{22}H_{17}ClN_4O_5$: C, 58.35; H, 3.78; N, 12.37; found: C 58.52; H 3.96; N, 12.20.

*4.3.16. Isopropyl 3′-amino-5-bromo-2,5′,10′-trioxo-5′,10′-dihydrospiro[indoline-3,1′-pyrazolo[1,2-b]phthalazine]-2′-carboxylate (**4z**).* Yellow solid; IR (KBr) ν 3751, 3425, 3313, 2852, 1747, 1701, 1683, 1662, 1647, 1618, 1604, 1570, 1533, 1508, 1400, 1296, 1265, 1222, 1167, 1145, 1103, 1031, 821, 775, 702 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.72 (d, *J*=6.0 Hz, 3H, CH_3), 1.03 (d, *J*=6.0 Hz, 3H, CH_3), 4.69–4.77 (m, 1H, CH), 6.80 (d, *J*=8.0 Hz, 1H, ArH), 7.41 (dd, *J*=8.5, 2.0 Hz, 1H, ArH), 7.63 (d, *J*=2.0 Hz, 1H, ArH), 8.00–8.03 (m, 2H, ArH), 8.06–8.08 (m, 1H, ArH), 8.31–8.32 (m, 1H, ArH), 10.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 21.2, 21.5, 66.1, 69.9, 111.3, 113.4, 126.9, 127.1, 127.6, 128.1, 128.8, 129.5, 132.1, 134.4, 135.1, 142.8, 151.0, 152.3, 152.5, 156.7, 162.9, 172.9; Anal. Calcd for $C_{22}H_{17}BrN_4O_5$: C, 53.13; H, 3.45; N, 11.27; found: C 52.96; H 3.62; N, 11.08.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (20872025 and 21072042) and the Nature Science Foundation of Hebei Province (B2011205031) for the financial support.

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