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One-pot four-component synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives

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ABSTRACT

The synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives by $NiCl_2$-catalyzed novel one-pot four-component condensation reaction of phthalimide, hydrazine, malononitrile (or ethyl cyanoacetate), and aromatic aldehydes was reported. This work provides a simple, efficient, and eco-friendly method for the construction of pyrazolo[1,2-*b*]phalazine-5,10-dione derivatives.

Introduction

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications in biologically active pharmaceuticals, agrochemicals, and functional materials are getting more and more important.[1–4] Furthermore pyrazoles are usually the core fragment of many biologically active compounds, such as Celecoxib, Viagra, Pyrazofurine, and so on.[5–8] Recently, heterocycles containing a phthalazine moiety have attracted extensive attentions. Phthalazine derivatives have been reported to possess anticonvulsant,[9] cardiotonic,[10] vasorelaxant,[11] cytotoxic,[12] antimicrobial,[13] antifungal,[14] anticancer,[15] and anti-inflammatory activities.[16] In addition, the titled compounds, pyrazolo[1,2-*b*]phthalazine-diones, were also found to have analgesic, antihypoxic, and anti-pyretic activities.[17] Therefore, the development of simple methods for the synthesis of pyrazolo[1,2-*b*]phthalazine-5,10-diones is very important. Multicomponent reactions were employed as a powerful tool to synthesize diverse and complex heterocyclic compounds due to their advantages of the intrinsic atom economy, simpler procedures, structural diversity, energy savings, and reduced waste.[18–20] To our knowledge, there are only several literatures about the multicomponent synthesis for 1*H*-pyrazolo [1,2-*b*] phthalazine-5,10-dione derivatives, which were synthesized by a one-pot three-component reaction of phthalhydrazide, aromatic aldehydes, and malononitrile or ethyl cyanoacetate catalyzed by *p*-TSA,[21] Et_3N[4] or [Bmim]OH.[22] However, the present methods have more or less shortcomings. For example, the use of strong acid probably results in pollution discharge and flammable, explosive, and expensive catalysts were employed. Herein we wish to report the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives by a one-pot four-component condensation reaction of phthalimide, hydrazine hydrate, aromatic aldehydes, and malononitrile or ethyl cyanoacetate catalyzed by Lewis acid $NiCl_2{\cdot}6H_2O$.

Results and discussion

Initially, we carried out the one-pot four-component reaction of phthalimide (**1**), hydrazine hydrate (**2**), malononitrile (**3a**), and 4-nitrobenzaldehyde (**4**) in refluxing ethanol as a model reaction. Different Lewis acids were tested, and results are listed in Table 1. As shown in Table 1, all tested Lewis acids had catalytic effects on the four-component condensation reaction. Under the same experimental conditions, $NiCl_2{\cdot}6H_2O$ showed an excellent catalytic activity, which gave product **5a1** in a yield of 94% (Table 1, entry 6). When using $MnCl_2$ and $SnCl_2{\cdot}2H_2O$ as catalysts, we got **5a1** in moderate yields of 76% and 70%, respectively (Table 1, entries 2 and 5). The reactions catalyzed by ZnI_2 or $CoCl_2{\cdot}6H_2O$ could give product **5a1** in 80% or 81% yield, respectively (Table 1, entries 1 and 4). However, only 65% yield of product was obtained from the reaction catalyzed by $FeCl_2{\cdot}4H_2O$ (Table 1, entry 3). Therefore, $NiCl_2{\cdot}6H_2O$ was chosen as the catalyst for the further study. Meanwhile, water was tested as a reaction medium of model reaction catalyzed by $NiCl_2{\cdot}6H_2O$, but just 75% yield of product was isolated (Table 1, entry 7). The effect of temperature on the reaction was also investigated (Table 1, entries 6, 8 and 9). After examining the reaction in ethanol at 30 °C, 50 °C and at the boiling point of

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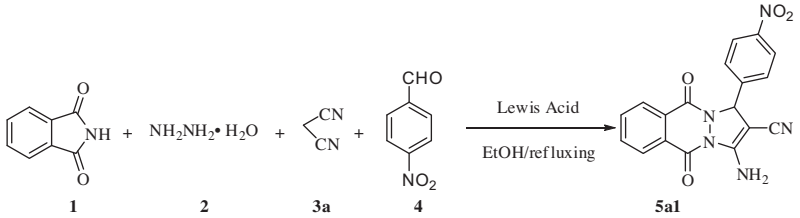
Table 1
The effect of different conditions on the model reaction[a]

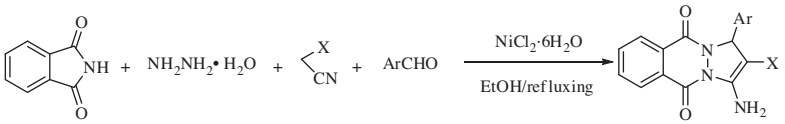


1 2 3a 4 5a1

Entry	Cat.	Cat. (mol %)	Solvent	T/°C	Yield[b] (%)
1	ZnI_2	10	EtOH	Refluxing	80
2	$MnCl_2$	10	EtOH	Refluxing	76
3	$FeCl_2·4H_2O$	10	EtOH	Refluxing	65
4	$CoCl_2·6H_2O$	10	EtOH	Refluxing	81
5	$SnCl_2·2H_2O$	10	EtOH	Refluxing	70
6	$NiCl_2·6H_2O$	10	EtOH	Refluxing	94
7	$NiCl_2·6H_2O$	10	H_2O	Refluxing	75
8	$NiCl_2·6H_2O$	10	EtOH	30	N.D.
9	$NiCl_2·6H_2O$	10	EtOH	50	56
10	$NiCl_2·6H_2O$	5	EtOH	Refluxing	70
11	$NiCl_2·6H_2O$	15	EtOH	Refluxing	93

[a] Reaction conditions: phthalimide (1.0 mmol), hydrazine hydrate (1.0 mmol), Lewis acid, solvent (3.0 mL), 2 h; then adding 4-nitrophenylaldehyde (1.0 mmol), malononitrile (1.0 mmol), 2 h.
[b] Isolated yields.

Table 2
$NiCl_2·6H_2O$ catalyzed synthesis of phthalazinetrione derivatives[a]



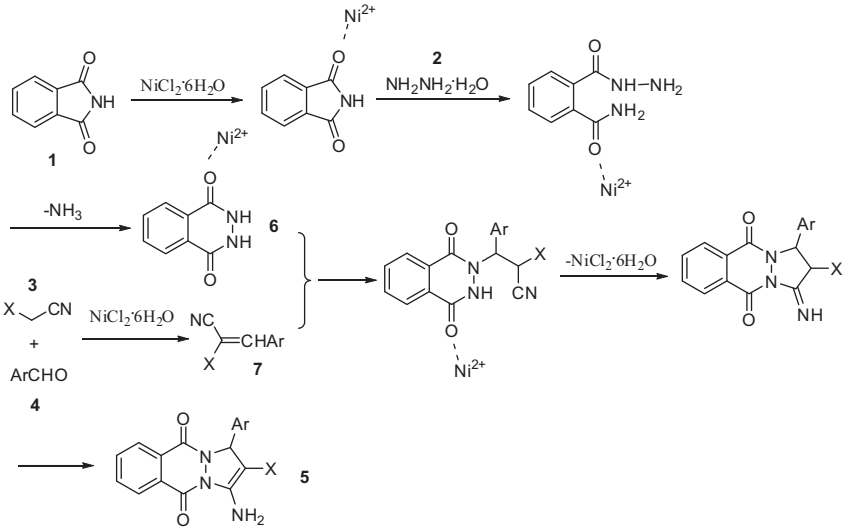
1 2 **3a** X=CN **3b** X=CO_2Et 4 5

Entry	X	Ar	Product	Time/h	Yield[b] (%)
1	CN	4-$NO_2C_6H_4$	**5a1**	2	94
2	CN	3-$NO_2C_6H_4$	**5a2**	4	90
3	CN	2-$NO_2C_6H_4$	**5a3**	4	85
4	CN	4-FC_6H_4	**5a4**	4	82
5	CN	4-ClC_6H_4	**5a5**	6	80
6	CN	3-ClC_6H_4	**5a6**	5	85
7	CN	2-ClC_6H_4	**5a7**	5	80
8	CN	4-BrC_6H_4	**5a8**	6	91
9	CN	3-BrC_6H_4	**5a9**	6	82
10	CN	C_6H_5	**5a10**	3	87
11	CN	4-MeC_6H_4	**5a11**	6	81
12	CN	4-$MeOC_6H_4$	**5a12**	6	92
13	CO_2Et	4-$NO_2C_6H_4$	**5b1**	4	84
14	CO_2Et	4-FC_6H_4	**5b2**	5	71[c]
15	CO_2Et	3-ClC_6H_4	**5b3**	5	83
16	CO_2Et	4-BrC_6H_4	**5b4**	6	80
17	CO_2Et	C_6H_5	**5b5**	5	84

[a] Reaction conditions: phthalimide (1.0 mmol), hydrazine hydrate (1.0 mmol), $NiCl_2·6H_2O$ (0.1 mmol), ethanol (3.0 mL), refluxing 2 h; then adding aromatic aldehyde (1.0 mmol), malononitrile or ethyl cyanoacetate (1.0 mmol), refluxing. For general procedure, please see ref. 23.
[b] Isolated yields.
[c] Reaction conditions: phthalimide (1.0 mmol), hydrazine hydrate (1.0 mmol), $NiCl_2·6H_2O$ (0.1 mmol), ethanol (3.0 mL), refluxing 2 h; then adding ethanol (3.0 mL) in order to stir smoothly, 4-fluoro benzaldehyde (1.0 mmol), ethyl cyanoacetate (1.0 mmol), refluxing 5 h.

ethanol, it was found that the best result was obtained from the reaction in refluxing ethanol. Then the catalyst loading on the model reaction was investigated. When 5 mol % of catalyst was used, the product **5a1** was obtained only in 70% yield (Table 1, entry 10). The catalyst loading of 10 mol % led to an excellent yield of 94 % (Table 1, entry 6), however no obvious improvement was observed by further increasing the catalyst loading to 15 mol %, which gave a yield of 93% (Table 1, entry 11). Therefore, 10 mol % of $NiCl_2·6H_2O$ was used as the optimized catalyst for further research.

The generality of this four-component reaction was studied under optimal conditions by varying the structures of aldehydes. The results are summarized in Table 2. Generally, the reactions that employed aromatic aldehydes bearing electron-withdrawing or electron-donating functional groups at different positions produced the corresponding products **5** in good to excellent yields within 6 h. The steric and electronic properties of the aldehydes affected the reaction yields obviously. For example, reacting with phthalimide, hydrazine hydrate, and malononitrile, 4-nitrobenzaldehyde gave an excellent yield of 94% (Table 2,



Scheme 1. A plausible reaction mechanism.

entry 1); while 3-nitrobenzaldehyde and 2-nitrobenzaldehyde provided the product in 90% and 85% yields, respectively (Table 2, entries 2 and 3). The decrease of yields was likely that the steric effect of nitro group increased from *para* position to *ortho* position. Similarly, 3-chlorobenzaldehyde gave a better yield than 2-chlorobenzaldehyde (Table 2, entries 6 and 7). This trend also was found using 4-bromobenzaldehyde and 3-bromobenzaldehyde (Table 2, entries 8 and 9). However there was an exception that 4-chlorobenzaldehyde provided a relatively low yield of 80% (Table 2, entry 5) than 3-chlorobenzaldehyde. Overall this procedure was applicable to various F, Cl, and Br substituted benzaldehydes which gave satisfactory yields (Table 2, entries 4–9). The high yields of products could be obtained from benzaldehyde and aromatic aldehydes bearing electron-donating groups as well. In addition, the four-component reactions using ethyl cyanoacetate (Table 2, entries 13–17) instead of malononitrile generally gave good yields except reacting with 4-fluorobenzaldehyde (Table 2, entry 14).

A plausible mechanism was proposed for the formation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones from the four-component condensation reaction of phthalimide, hydrazine hydrate, malononitrile, and aromatic aldehydes (Scheme 1). In the presence of a catalyst, phthalimide **1** reacts with hydrazine hydrate **2** to generate phthalhydrazide **6**. Meanwhile, the Knoevenagel condensation of malononitrile or ethyl cyanoacetate **3** with aldehyde **4** produces intermediate **7**. Subsequently, Michael-type addition of phthalhydrazide **6** and intermediate **7** followed by cyclization affords the corresponding product **5**.

Conclusion

In summary, we have developed a one-pot four-component reaction for the synthesis of pyrazolo[1,2-*b*]phthalazine-5,10-diones from readily available starting materials. This method has the advantages of being concise, highly efficient, friendly to the environment, and inexpensive.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.063.

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23. *General procedure for the synthesis of phthalazine derivatives* ***5***: A mixture of phthalimide (1.0 mmol), hydrazine hydrate (1.0 mmol), and $NiCl_2{\cdot}6H_2O$ (0.1 mmol) in ethanol (3.0 mL) was stirred under reflux for 2 h. Then aromatic aldehyde (1.0 mmol), malononitrile, or ethyl cyanoacetate (1.0 mmol) were added, and the mixture was refluxed for a specified time. The reaction was monitored by TLC. After the reaction completed, the reaction mixture was allowed to cool to rt. The residue precipitated during the process was separated from the solution by filtration, and the filter cake was washed with ethanol to yield NMR pure **5**.