$InCl_3$-Catalyzed green synthesis of 1H-pyrazolo[1,2-b] phthalazine-5,10-diones under solvent-free conditions

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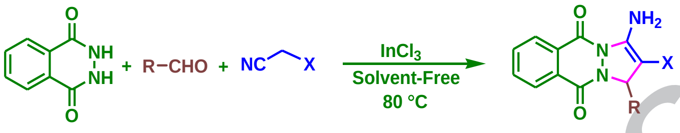

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ABSTRACT

A simple, efficient and green practical approach to 1H-pyrazolo[1,2-b]phthalazine-5,10-diones from phthalhydrazide, aldehydes, and malononitrile/ ethyl cyanoacetate has been developed that uses inexpensive and readily available $InCl_3$ as a catalyst in solvent-free one-pot three-component cyclo condensation reaction. This method should provide high yields, shorter reaction time, easy work-up, purification of products by non-chromatographic method and cleaner reaction. It's a new strategy for N-fused heterocycles synthesis, whose are having a wider applications in organic and medicinal chemistry.

1. Introduction

The molecules which are containing heterocyclic unit(s) have profound interest in medicinal chemistry because their wide range of biological activities.[1] These potential drug candidates synthesis with privileged heterocycles are a crucial issue in diversity oriented synthesis (DOS), and combinatorial chemistry. Most of the nitrogen-containing fused pyrazolo[1,2-b] phthalazines heterocycles are showing multiple biological activities.[2-7] Even though establishing various methodologies for these important biologically active pharmaceuticals, agrochemicals, and functional materials which are resemblances with naturally occurring nitrogen-containing heterocyclic (N-heterocyclic) compounds, still there is challenging to development of new methodologies for modern synthetic organic chemists. Only a few methods have been reported the one-pot synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones, based on catalysts such as Et_3N,[8] Mesoporous solid acid catalysts (Al-KIT-6),9 [bmim]Br/PTSA,[10] [Bmim]OH[11] and $NiCl_2$•6H2O.[12] However, these procedures also are limited in scope, because of relatively long reaction times and the use of an organic solvent, expensive ionic liquids and catalysts. Therefore, the development of an easy and efficient method for the preparation of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones is still a challenging task.

Now-a-days from the view point of green and sustainable chemistry[13-16] solvent-free organic synthesis is the best eco-friendly methodology to overcome the problems[17-20] in green chemical synthesis of various biologically active compounds by considering fewer or no toxic substances and greatly removing the ecologically harmful and flammable organic solvents which are create a large quantities of wastage. Reduction of these global warming now-a-days explorations of solvent-free reactions has gained an important role in synthetic organic chemistry[21-31] by virtue of experimental simplicity, less energy requirement, and producing high yields of products by almost quantitative reactivity of the substrates.

literature feedback the merits of readily availability, non-toxicity, inexpensiveness, moisture stability, air and water compatibility, and Lewis acidic nature of indium chloride ($InCl_3$) as catalyst in synthetic organic chemistry for various organic transformations to get highly selective products.[32-36] Because of its acidic nature enhance this usage towards catalytic amount from stoichiometric. In addition to these numerous advantages it also has merits of recyclability, operational simplicity, and remarkable ability to suppress side reactions in acid sensitive substrates are encouraging as eco-friendly catalyst in green chemistry and supporting for a wide variety of reactions.[37-41] Moreover, solvent-free and $InCl_3$ combination reactions are well known in organic transformation.[42-45] Solvent-free reaction endorsed $InCl_3$ reactions are well known as environmentally benign methods that also usually provide improved selectively, enhanced reaction rates, cleaner products and manipulative simplicity. This area has also attracted considerable attention in recent years.[42-45] We therefore became interested in devising more general and green methods for the synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones.

Our literature survey at this stage revealed that there are no reports on the synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones under solvent-free at 80 °C mediated by $InCl_3$. Our main target is to develop a green organic reaction methodology. As part of our ongoing research program on the development of

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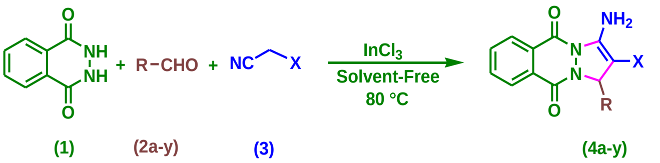
green protocols,[46-48] herein, we report a facile one-pot synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones via three-component coupling of phthalhydrazide, aldehydes and malononitrile/ ethyl cyanoacetate in the presence of catalytic amount (10 mol %) of $InCl_3$ under solvent-free at 80 °C (Scheme 1).



Scheme-1 Solvent-free synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones.

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2. Result and Discussions

In this letter, we have presented a new and efficient method for the synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones using $InCl_3$ (**Schemes 1**).[49]

In order to optimize the reaction conditions, firstly, we investigated the effect of different solvents on the reaction rate and as well as yields of the products. As a model reaction, the reaction of phthalhydrazide (**1**, 1 mmol), 3-fluorobenzaldehyde (**2b**, 1 mmol) and malononitrile (**3**,1 mmol) catalyzed by 10 % $InCl_3$ in various solvents including ethanol (EtOH), *n*-propanol (*n*-C_3H_7OH), benzene (C_6H_6), chloroform ($CHCl_3$), tetrahydrofuran (THF), acetonitrile (CH_3CN) and water was investigated at 80 °C (**Table 1**). In aprotic solvents such as benzene, chloroform, THF and CH_3CN, the reaction were very slow and resulted in lower product yield (**Table 1 entries 1-4**). Conducting the reactions in protic solvents improved both the reaction rates as well as product yields (**Table 1 entry 5-7**). Water has been identified as an ideal solvent because it is inexpensive, non-flammable, abundant and environmentally benign. However, when the same reaction was carried out in water, the expected product was obtained only in low yield even after 10 h (**Table 1 entry 8**). Furthermore, we also conducted this $InCl_3$ catalyzed condensation reaction under solvent-free conditions at 80 °C. As shown in **Table** 1 entry 13, the yields of the reaction under solvent-free conditions were higher and the reaction times were shorter than under solvent conditions. The better yield in solvent-free conditions could be explained by a uniform distribution of the eutectic mixture of reactants, being in closer proximity to react than in conditions using ethanol as the solvent.

To optimize the reaction temperature, the mixture was heated at different temperatures ranging from 20 to 100 °C (**Table 1 entries 9-14**). The yield of product **4b** was increased when the reaction was raised from 20 to 80 °C. However, no more increments were found for product **4b** when the reaction temperature was raised from 80 to 100 °C. Therefore, 80 °C was chosen as the reaction temperature for all further reactions.

Table 1. Influence of the solvent and temperature on the 3-amino-1-(3-fuorophenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (4b)[a]

Entry	Solvent	Temperature °C	Time (min)	Yield[b] (%)
1	THF	80	180	42
2	CH_3CN	80	180	55
3	$CHCl_3$	80	180	51
4	C_6H_6	80	180	62
5	Ethanol	80	180	85
6	*n*-Propanol	80	180	86
7	*n*-Propanol	100	160	82
8	H_2O	80	600	40
9	Solvent-free	20	180	30
10	Solvent-free	40	150	40
11	Solvent-free	60	90	70
12	Solvent-free	70	45	85
13	Solvent-free	80	25	94
14	Solvent-free	100	25	94

[a]Reaction of 3-fluorobenzaldehyde (1 mmol), phthalhydrazide (1 mmol) and malononitrile (1 mmol) catalyzed by $InCl_3$ (mol 10 %) .

Because of the important role of catalyst in a reaction, we investigated the effects of various catalysts by manipulating the reaction conditions on the representative of model reaction under solvent-free conditions. In the absence of the catalyst, the reaction could be carried out but the product was obtained in very low yield after prolonged reaction time. Therefore, our efforts focused on the search for a suitable catalyst. Initially, $GaCl_3$ was chosen as the catalyst to carry out this reaction. As a result, long reaction times were needed and low transformation rates were observed. Attempts with different catalysts at 80 ºC, under solvent-free conditions, and the results are listed in **Table 2**. It was found that $InCl_3$ showed better catalytic activity among these catalysts. Most excitingly, when $InCl_3$ was used, the reaction proceeded very smoothly and gave the product in 94% yield (**Table 2**, **entry 8**). Moreover, we found that the yields were obviously affected by the amount of $InCl_3$ loaded. When 2 mol %, 5 mol %, 10 mol %, and 20 mol % of $InCl_3$ were used, the yields were 40, 70, 94, and 95%, respectively (**Table 2**, **entries 8–11**). Therefore, 10 mol % of $InCl_3$ was sufficient and excessive amount of catalyst did not increase the yields significantly (**Table 2**, **entries 8**).

Table 2. Influence of the catalyst on the amino-1-(3-fluorophenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**4b**)[a]

Entry	Catalyst	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	NO	-	180	20
2	$GaCl_3$	10	150	38
3	$AlCl_3$	10	150	52
4	$GaBr_3$	10	170	40
5	$FeCl_3$	10	150	62
6	$InBr_3$	10	80	65
7	InF_3	10	55	75
8	$InCl_3$	10	25	94
9	$InCl_3$	2	60	40
10	$InCl_3$	5	40	70
11	$InCl_3$	20	25	95

[a]Reaction of 3-fluorobenzaldehyde (1 mmol), phthalhydrazide (1 mmol) and malononitrile (1 mmol) under solvent-free conditions at 80 °C. [b]Isolated yield

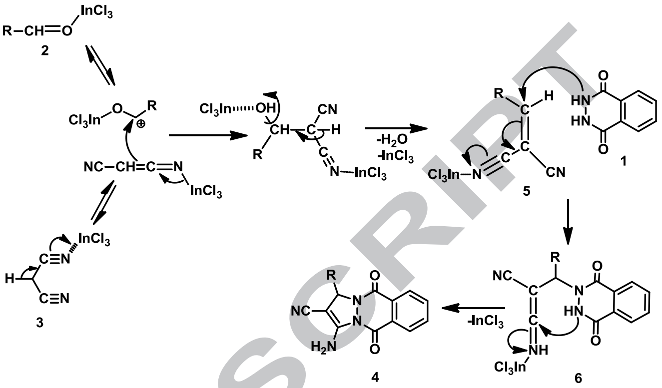
In order to extend the above reaction (**Scheme 1**) to a library system, various kinds of aldehydes (**2a-y**), (**Table 3**) were subjected to react with 1 and 3 to give the corresponding 1H-pyrazolo [1,2-b] phthalazine-5,10-diones (**4a-y**) (**Table 3**). All of **2a-y** gave the expected products at high yields, either bearing electron-withdrawing groups or electron-donating groups under the same reaction condition. The heterocyclic/aliphatic aldehydes were also obtained in good yields. Comparatively with aromatic aldehydes the aliphatic aldehydes showed significant yields even though their inertness. It is noteworthy that there are no reports of the synthesis of 1H-pyrazolo[1,2- b]phthalazine-5,10-diones from aliphatic aldehydes. Now we are also tested the model reaction with cinnamaldehyde and α,β-unsaturated butanal. But we could not found significant amount of the title product from these unsaturated aldehydes. Various functional groups were found to be compatible under the reaction conditions. In addition, malononitrile acts well in comparison with ethyl cyanoacetate in the mentioned reaction. In general, the reactions were clean and no side products were detected. In all cases, the reactions proceeded efficiently at 80 °C under solvent-free and $InCl_3$ (10 mol %) catalytic conditions. The simplicity, together with the use of inexpensive, non-toxic, and environmentally benign nature of $InCl_3$ catalyst under solid state reaction condition is another remarkable feature of the protocol. All of the structures were characterized by ^1H NMR, ^{13}C NMR and HRMS. **4n** and **4y** compounds data coincide with reported compounds.

Table 3. $InCl_3$ catalyzed multi-component synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones

Entry	Aldehyde R	X	Yield[a] (%)	Time (min)	mp (°C)
4a	2-F-C_6H_4	CN	92	25	268-270
4b	3-F-C_6H_4	CN	94	25	264-266
4c	3-NO_2-4-F-C_6H_3	CN	90	30	258-260
4d	3-F-4-Me-C_6H_3	CN	90	26	261-263
4e	2-F-4-OMe-C_6H_3	CN	91	28	232-234
4f	4-OEt-C_6H_4	CN	90	29	258-260
4g	4-OH-C_6H_4	CN	92	26	270-272
4h	4-IsoPropyl-C_6H_4	CN	93	24	264-266
4i	3,4-5-OMe-C_6H_2	CN	89	28	253-255
4j	6-nitrobenzo[d][1,3]dioxole ($C_7H_5NO_4$)	CN	85	35	251-253
4k	C_2H_5	CN	85	32	238-240
4l	C_3H_7	CN	88	30	220-222
4m	$CH(CH_3)_2$	CN	88	30	228-230
4n	2-thiophene (C_4H_3S)	CN	90	31	244-246
4o	2-F-C_6H_4	COOEt	90	28	235-237
4p	3-F-C_6H_4	COOEt	89	27	228-230
4q	2-Br-4-F-C_6H_3	COOEt	88	30	238-240
4r	3-F-4-Me-C_6H_3	COOEt	87	35	222-224
4s	2-F-4-OMe-C_6H_3	COOEt	89	32	227-229
4t	4-OEt-C_6H_4	COOEt	90	28	210-212
4u	4-IsoPropyl-C_6H_4	COOEt	89	35	231-233
4v	C_2H_5	COOEt	83	35	165-167
4w	C_3H_7	COOEt	85	33	150-152
4x	$CH(CH_3)_2$	COOEt	84	40	160-162
4y	2-thiophene (C_4H_3S)	COOEt	88	35	228-230

[a]Isolated yield

A schematic mechanism for the catalytic activity of $InCl_3$ in the synthesis of titled compounds (**4a-y**) should be postulated as shown in **Scheme 2**. The reaction is thought to proceed in a stepwise manner. Firstly, we assumed that the reaction occurs via a Knoevenagel condensation between malononitrile, **3** and aldehyde, **2** to form the intermediate **5** on the acidic activity of $InCl_3$, which suffers immediate Michael addition of phthalhydrazide, **1** to the C=C bond of 5 forms iminomethylene derivative intermediate **6**. Finally the titled compounds (**4a-y**) were formed by intramolecular concerted cyclisation by tautomerization of Michael adduct, **6**. The role of $InCl_3$ probably would be Lewis acid for the activation of the nitrile to transform into amine.



Scheme 2: Schematic mechanism for the catalytic activity of$InCl_3$ in the synthesis of titled compounds (**4a-y**)

3. Conclusion

In conclusion, an efficient, environmentally benign, atom economical, and simple methodology for the preparation of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones in a three-component reaction in the presence of $InCl_3$ under solvent-free condition is reported. The procedure offers several advantages including cleaner reaction profiles, use of easily available, cheap, high yields, and simple experimental and work-up procedures. These $InCl_3$ catalyzed one-pot, multi-component reactions provide a rapid and efficient route to the preparation of a variety of unusual heterocycles.

Supplementary data

All Compounds NMR spectra were provided as Supplementary data.

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(49) **General procedure for the synthesis of 3-amino-1-(3-fluorophenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile 4b**. A mixture of phthalhydrazide (**1**, 1 mmol), 3-fluorobenzaldehyde (**2b**, 1 mmol), malononitrile (**3**, 1 mmol) and $InCl_3$ (10 mol %) was stirred at 80 °C under solvent-free condition for 25 min (**Table 3, entry 2**). The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was washed with water and ethanol and residue recrystallized from ethanol to afford the pure product **4b** (94%).