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Clean and facile synthesis of 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives catalyzed by Neodymium (III) chloride hexahydrate as an efficient Lewis acidic catalyst under solvent-free conditions

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ABSTRACT

A clean and simple synthesis of 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives via one-pot four-component condensation reaction of phthalimide, hydrazine monohydrate, aromatic aldehydes derivatives and malononitrile in the presence of neodymium (III) chloride hexahydrate ($NdCl_3.6H_2O$) as an efficient and eco-friendly Lewis acidic catalyst under thermal and solvent-free conditions with good yields and short reaction times is developed. This present methodology has notable benefits such as highly efficient, non-toxic catalyst, one-pot, solvent-free conditions, simplicity of operation with no necessity of chromatographic purification steps and eco-friendly. And all products have been characterized by melting points and ^{1}H NMR spectroscopy.

Keywords: *Neodymium (III) chloride hexahydrate ($NdCl_3.6H_2O$), 1H-pyrazolo[1,2-b] phthalazine-5,10-dione derivatives, solvent-free conditions, Multi-component reaction, Clean synthesis, Eco-friendly.*

1. INTRODUCTION

In recent years, multi-component domino reactions (MCRs) [1-4] has become to one of the best approach for economical and efficient synthesis of organic compounds. The special advantages of multi-component reactions are including simple work-up, atom-economy, mild and environmentally-friendly, low-cost, one-pot for the synthesis of organic compounds. Therefore, our recent studies focused on developing of multi-component reactions.

Recently, the study for the synthesis of nitrogen-containing heterocyclic compounds such as 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives has attracted considerable interest in organic chemists because of their special biological [5] (Figure1) and pharmacological (Figure2) properties for example antibacterial (inhibitory activity against *Escherichia coli* FabH) [6], anticancer [7], anti-inflammatory [8], anti-microbiological [9] and they have been reported to possess cardiotonic [10]. Some of the phtahlazines derivatives have found application in clinical medicine due to their pronounced antipyretic, analgesic and cardiovascular activity while others have shown interesting vasodilator and antihypertensive properties [11-14]. Phtahlazines bearing a substitution represent key intermediates in the synthesis of various compounds with highly interesting pharmacological properties. Phtahlazines has been found to be a selective phosphodiesterase (PDE) inhibitor or the thromboxane synthetase inhibitor and bronchodilator. The phthalazine nucleus has been proved to be a versatile system in medicinal chemistry. Moreover, a number of established drug molecules [15-19] are accessible starting from the corresponding phthalazinones. A number of established phthalazines drug molecules like Hydralazine, Budralazine, Azelastine, Ponalrestat or Zopolrestat etc. The phthalazine derivative azelastine **1**(Figure 2) is an antihistamine used in the treatment of allergic rhinitis. Newer agents are more selective inhibitors of the cGMP-inhibited phosphor diesterase (PDE), phthalazine derivatives like MY5445 **2** (Figure II) [20, 21].

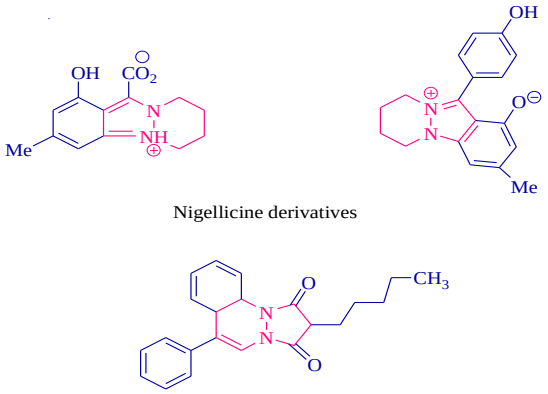
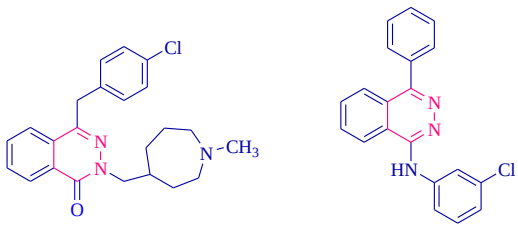


Figure1. Biologically active compounds with two ring junction nitrogen atom.



1 **2**

Figure 2. Some of the phtalazine derivatives have found applications in clinical medicine.

Thus, recently, a number of procedures for the synthesis of 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives have been reported that is including Lewis and Brønsted acid catalysts for example $Ce(SO_4)_2.4H_2O$ [22], SBA-Pr-SO3H [23], $InCl_3$[24], $NiCl_2.6H_2O$ [25], [Bmim] OH [26], Ultrasound-assisted [27],

PTSA/[Bmim]Br [28], STA [29], CuI nanoparticles [30], P-TSA [31], TBBAD [32]. Some of these methodologies have limitations such as long time reactions, low yields, toxic and expensive catalysts, difficulty work-up, use of strongly acidic conditions. Because of specially pharmaceutical and biological activities 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives, the study of efficient and environmental friendly catalyst for multi-component synthesis of these heterocyclic compounds is an important goal in our recent researches and finally, we have reported neodymium (III) chloride hexahydrate ($NdCl_3.6H_2O$) as a mild, economical and efficient Lewis acidic catalyst for the one-pot four-component synthesis of 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives via reaction of phthalimide, hydrazine monohydrate, aromatic aldehydes derivatives and malononitrile under thermal and solvent-free conditions. The advantages of neodymium (III) chloride hexahydrate ($NdCl_3.6H_2O$) as catalyst in organic compounds synthesis are mild, non-toxic, eco-friendly, high catalytic activity. We carried out the one-pot multi-component condensations by neodymium (III) chloride hexahydrate ($NdCl_3.6H_2O$) catalyst in good yields and short reaction times. Furthermore, one of the source of environmental pollutions is the usage of organic solvents under reflux conditions and the need for column chromatography to purity the products. In this present work, the products were obtained through simple filtering with no need column chromatographic separation.

2. EXPERIMENTAL SECTION

2.1. General. Melting points all compounds were determined using an Electro thermal 9100 apparatus. Also, nuclear magnetic resonance, ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with DMSO-d_6 as solvents. In this article, all reagents and solvents were purchased from Merck, Fluka and Acros chemical companies were used without further purification.

2.2. General procedure for preparation of pyrazolo[1,2-b]phthalazine-5,10-dione derivatives (5a-k). A mixture of phthalimide (**1**, 1.0 mmol), hydrazine monohydrate (**2**, 1.0 mmol) and neodymium (III) chloride hexahydrate ($NdCl_3.6H_2O$) (15 mol %) was heated for 2h at 90 °C. then aromatic aldehyde (**3**, 1.0 mmol) and malononitrile (**4**, 1.0 mmol) were added and the mixture was heated for the appropriate time. After completion of the reaction (by Thin layer chromatography TLC) the mixture was cooled to rt the solid products were filtered and then were be recrystallized from ethanol to give pure compounds (**5a-k**). All products have been characterized by melting points and ^{1}H NMR spectroscopy. Spectra data all products are represented below:

*3-Amino-1-(phenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5a**):*

Solid powder; Yield: 79; M.p. 271-273 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.14 (1H, s, CHAr), 7.33-7.48 (5H, m, ArH), 7.97-8.29 (6H, m, NH_2 and ArH).

*3-Amino-1-(3,4,5-trimethoxyphenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**5b**):*

Solid powder; Yield: 85; M.p. 255-257 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 3.66 (3H, s, OCH_3), 3.76 (6H, s, 2 OCH_3), 6.07 (1H, s, CHAr), 6.78 (2H, s, ArH), 7.89- 8.29 (6H, m, NH_2 and ArH).

*3-Amino-1-(3-methoxyphenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**5c**):*

Solid powder; Yield: 82; M.p. 249-251 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 3.34 (3H, s, OCH_3), 6.09 (1H, s, CHAr), 6.88-7.30 (4H, m, ArH), 7.83- 8.26 (6H, m, NH_2 and ArH).

*3-Amino-1-(2-chlorophenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5d**):*

Solid powder; Yield: 79; M.p. 258-260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.47 (1H, s, CHAr), 7.39-7.65 (4H, m, ArH), 7.91-8.31 (6H, m, NH_2 and ArH).

*3-Amino-1-(4-bromophenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5e**):*

Solid powder; Yield: 78; M.p. 267-269 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.14 (1H, s, CHAr), 7.46 (2H, d, *J*=11.2 Hz, ArH), 7.58 (2H, d, *J*=11.2 Hz, ArH), 7.70-8.29 (6H, m, NH_2 and ArH).

*3-Amino-1-(3-nitrophenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5f**):*

Solid powder; Yield: 83; M.p. 268-270°C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.35 (1H, s, CHAr), 7.57-7.90 (4H, m, ArH), 7.95-8.51 (6H, m, NH_2 and ArH).

*3-Amino-1-(4-fluorophenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5g**):*

Solid powder; Yield: 82; M.p. 266-268 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.17 (1H, s, CHAr), 7.20 (2H, t, *J*=8.8 Hz, ArH), 7.53-7.57 (2H, m, ArH), 7.96-8.26 (6H, m, NH_2 and ArH).

*3-Amino-1-(3-methylphenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5h**):*

Solid powder; Yield: 78; M.p. 251-253 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.30 (3H, s, CH_3), 6.08 (1H, s, CHAr), 7.14 (1H, s, ArH), 7.26 (3H, d, *J*=11.2 Hz, ArH), 7.97-8.29 (6H, m, NH_2 and ArH).

*3-Amino-1-(2-nitrophenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5i**):*

Solid powder; Yield: 81; M.p. 265-267 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.62 (1H, s, CHAr), 7.61 (1H, t, *J*=9.6 Hz, ArH), 7.73 (1H, t, *J*=9.6 Hz, ArH), 7.85-7.91 (2H, m, ArH), 7.97-8.30 (6H, m, NH_2 and ArH).

*3-Amino-1-(4-methylphenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5j**):*

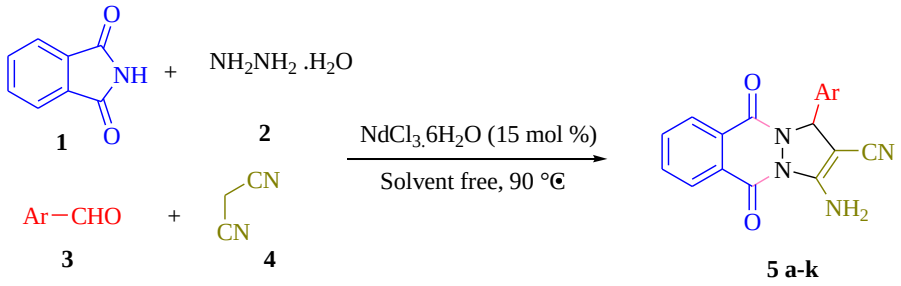
Solid powder; Yield: 82; M.p. 253-255 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.30 (3H, s, CH_3), 6.10 (1H, s, CHAr), 7.18 (2H, d, *J*=8.0 Hz, ArH), 7.34 (2H, d, *J*=8.0 Hz, ArH), 7.97-8.28 (6H, m, NH_2 and ArH).

*3-Amino-1-(3-fluorophenyl)-5, 10-dihydro-5, 10-dioxo-1H-pyrazolo [1, 2-b] phthalazine-2-carbonitrile (**5k**):*

Solid powder; Yield: 79; M.p. 264-266 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.16 (1H, s, CHAr), 7.16-7.20 (1H, m, ArH), 7.33 (1H, d, *J*=9.6 Hz, ArH), 7.39-7.46 (2H, m, ArH), 7.84-8.29 (6H, m, NH_2 and ArH).

3. RESULTS SECTION

A mild and eco-friendly Lewis acidic catalyst for one-pot, clean and simple protocol to diverse synthesis of 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives via phthalimide (**1**, 1.0 mmol), hydrazine monohydrate (**2,** 1.0 mmol), aromatic aldehydes derivatives (**3,** 1.0 mmol) and malononitrile (**4**, 1.0 mmol) in the present of neodymium (III) chloride hexahydrate ($NdCl_3.6H_2O$) under thermal and solvent-free conditions is reported.

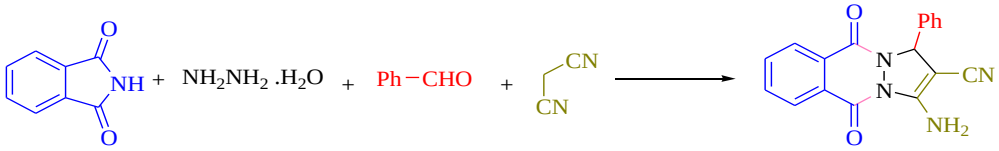


Scheme1. Synthesis of 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives.

In order to optimized the reaction conditions, the synthesis of compound **5a** (Table 3, entry 1) was used as a model reaction. The effect of different amount of catalyst on the reaction has been studied in this protocol. No product could be detected in the absence of the catalyst even after 12h (Table 1, entry 1). Good yields were obtained in the presence of catalyst. The best amount of catalyst was 15 mol % (0.037 g) (Table 1, entry 4). The higher amount of catalyst did not increase the yields products (Table 1, entry 5).

However, the higher yield of product is obtained with 15mol% of catalyst and the results are summarized in Table 1.

Table1. Optimization of the reaction condition for the synthesis of pyrazolo[1,2-b]phthalazine-5,10-dione **5a** [a]

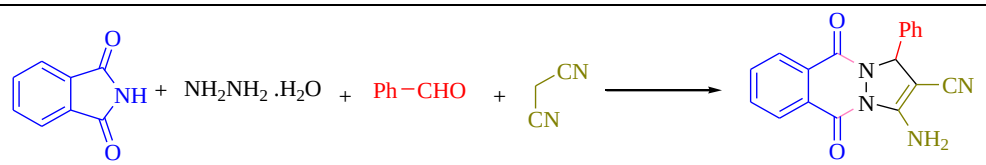


Entry	$NdCl_3.6H_2O$ (mol %)	Time (h)	Product	Isolated Yields (%)
1	Catalyst free	12	5a	Not product
2	5	9	5a	38
3	10	6	5a	63
4	**15**	**4**	**5a**	**79**
5	20	4	5a	81

[a] Reaction conditions: phthalimide, hydrazine monohydrate, aromatic aldehydes derivatives and malononitrile(1:1:1:1) and neodymium (III) chloride hexahydrate was heated at 90 °C for the appropriate time.

Also, the effect of temperature on the reaction has been investigated. No product could be detected at room temperature conditions (Table2, entry1). The reaction was investigated by changing temperature from 40-110 °C and the high yield of product was obtained at 90 °C temperature (Table 2, entry 5). The yields of product at different temperature are reported in Table 2.

Table 2. Effect of the reaction temperature on the synthesis of **5a** [a]



Entry	Temperature (°C)	Time (h)	Isolated Yields (%)
1	r.t.	12	Not product
2	40	12	27
3	60	7	48
4	80	4	65
5	**90**	**4**	**79**
6	110	4	82

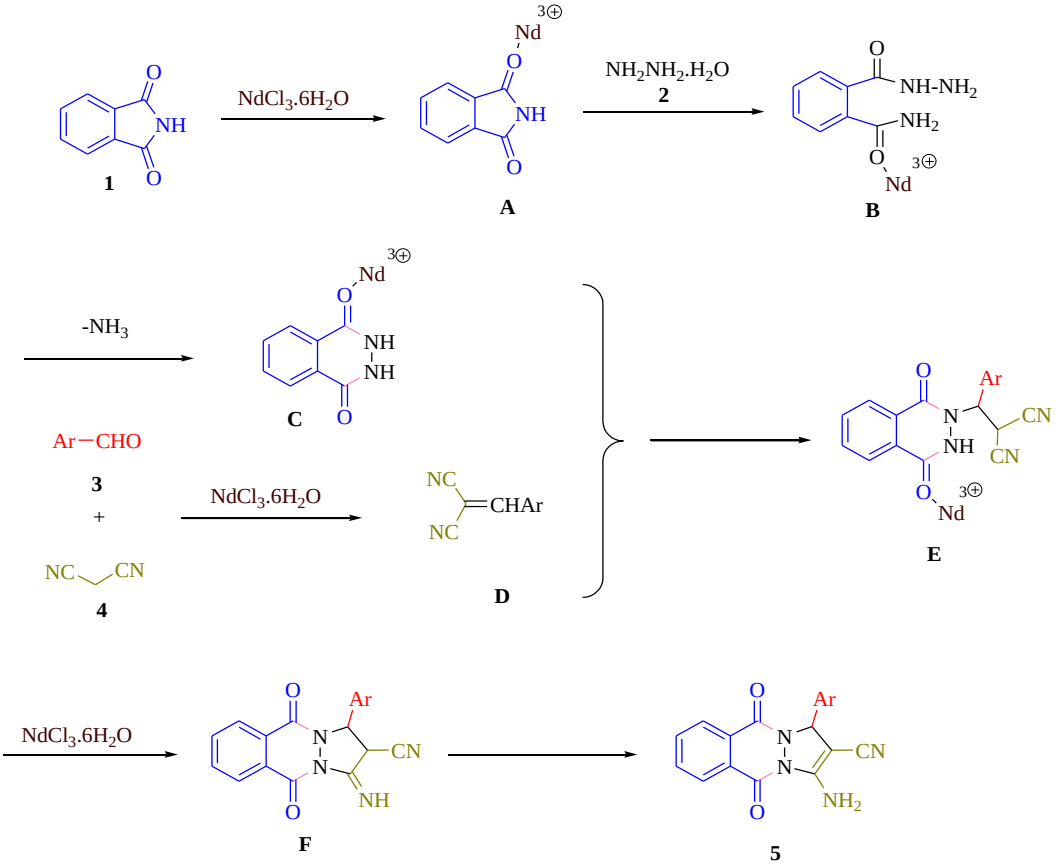
[a] Reaction conditions: phthalimide, hydrazine monohydrate, aromatic benzaldehye and malononitrile (1:1:1:1) with neodymium (III) chloride hexahydrate (15 mol%) was heated under various temperatures for the appropriate time [b] yields.

In order to study of this procedure, we have synthesized a series of compounds with the type of electron-donating and electron-withdrawing aldehydes derivatives such as Cl, Br, NO_2, Me, OMe, substituted benzaldehydes which gave excellent yields and the generality of this four condensation reaction was studied by using of neodymium (III) chloride hexahydrate (15 mol %) via phthalimide (1.0 mmol), hydrazine monohydrate (1.0 mmol) and the type of aldehydes derivatives (1.0 mmol), malononitrile (1.0 mmol) under thermal and solvent-free conditions and the results are shown in Table 3. The proposed mechanistic route for the synthesis of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives in the presence of $NdCl_3.6H_2O$ are shown in scheme 2.

Also, ^{1}HNMR data of products have been compared with literature for synthesis of 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives are shown in Table 4.

Table 3. $NdCl_3.6H_2O$ catalyzed synthesis of pyrazolo[1,2-b]phthalazine-5,10-dione derivatives under solvent free conditions

Entry	Ar	Product	Time (h)	Isolated Yields (%)	M.p. °C	Lit. M.p. °C
1	C_6H_5	**5a**	4	79	271-273	270-272[30]
2	3,4,5-$(OMe)_3$-C_6H_2	**5b**	4.5	85	255-257	253-255[24]
3	3-OMe- C_6H4	**5c**	4	82	249-251	248-251[27]
4	2-Cl- C_6H4	**5d**	5	79	258-260	257-259[29]
5	4-Br- C_6H4	**5e**	6	78	267-269	265-267[23]
6	3-O_2N-C_6H_4	**5f**	4	83	268-270	269-271[28]
7	4-F- C_6H4	**5g**	4.5	82	266-268	263-265[23]
8	3-Me-C_6H4	**5h**	5	78	251-253	250-252[30]
9	2-O_2N-C_6H_4	**5i**	5	81	265-267	265-266[23]
10	4-Me- C_6H4	**5j**	5	82	253-255	253-255[30]
11	3-F- C_6H4	**5k**	5.5	79	264-266	263-265[29]



Scheme2. Proposed mechanistic route for the synthesis of pyrazolo[1,2-b]phthalazine-5,10-dione derivatives.

Table 4. Comparison of ^{1}HNMR data for synthesis of 1*H*-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives

Entry	Product	H Shift (found)	H Shift (lit)	Ref.
1	**5a**	6.14 (1H, s, CHAr) 7.33-7.48 (5H, m, ArH) 7.97-8.29 (6H, m, NH_2 and ArH)	6.12 (1H, s, CHAr) 7.29-7.47 (5H, m, ArH) 7.80-8.3 (6H, m, NH_2 and ArH)	32
2	**5b**	3.66 (3H, s, OCH_3) 3.76 (6H, s, 2 OCH_3) 6.07 (1H, s, CHAr) 6.78 (2H, s, ArH) 7.89- 8.29 (6H, m, NH_2 and ArH).	3.64-3.73 (9H, s, OCH_3) 6.05 (1H, s, CHAr) 6.75 (2H, s, ArH) 7.94- 8.26 (6H, m, NH_2 and ArH).	32

3	**5d**	6.47 (1H, s, CHAr) 7.39-7.65 (4H, m, ArH) 7.91-8.31 (6H, m, NH_2 and ArH)	6.46 (1H, s, CHAr) 7.33-7.62 (4H, m, ArH) 7.87-8.30 (4H, m, ArH) 8.15 (2H, s, NH_2)	28
4	**5j**	2.30 (3H, s, CH_3) 6.10 (1H, s, CHAr) 7.18 (2H, d, *J*=8.0 Hz, ArH) 7.34 (2H, d, *J*=8.0 Hz, ArH) 7.97-8.28 (6H, m, NH_2 and ArH)	2.28 (3H, s, CH_3) 6.07 (1H, s, CHAr) 7.14-7.33 (4H, m, ArH) 7.94-8.25 (6H, m, NH_2 and ArH)	30

Comparison of catalytic ability some of catalysts reported in the literature for the synthesis of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives are shown in Table5. This study reveals that $NdCl_3.6H_2O$ has shown its extraordinary potential to be an alternative mild and eco-friendly catalyst for the synthesis of these biologically active compounds. In addition to the use of solvent-free conditions with excellent yield and short reaction times are the notable advantages this present methodology.

Table 5. Comparison of catalytic ability some of catalysts reported in the literature for the synthesis of 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives [a]

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	$InCl_3$	Water, Reflux	1.5h/85	[24]
2	$NiCl_2.6H_2O$	EtOH, Reflux	3h/87	[25]
3	PTSA	[Bmim]Br, 100 °C	3h/94	[28]
4	STA	Solvent-free, 70 °C	20 min/94	[29]
5	CuI nanoparticles	MeCN, Reflux	27 min/91	[30]
6	$NdCl_3.6H_2O$	Solvent-free, 90 °C	4h/79	This work

[a]Based on the four-component reaction of benzaldehyde, phthalimide, hydrazine monohydrate and malononitrile.

4. CONCLUSIONS

In summary, neodymium (III) chloride hexahydrate ($NdCl_3.6H_2O$) as an efficient and eco-friendly Lewis acidic catalyst for the clean one-pot four-component synthesis of pyrazolo[1, 2-b] phthalazine-5,10-dione derivatives by means of phthalimide (1.0 mmol), hydrazine monohydrate (1.0 mmol) and the type of aldehydes derivatives (1.0 mmol), malononitrile (1.0 mmol) under thermal and solvent-free conditions with excellent yields and short reaction times was studied. The notable advantages of the present methodology are low-cost, non-toxic catalyst, eco-friendly, high catalytic activity, mild, one-pot, highly efficient, simplicity of operation with no necessity of chromatographic purification steps and solvent-free conditions.

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6. ACKNOWLEDGEMENTS

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