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A Simple, Solvent-free Four-component Domino Synthesis of 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione Derivatives Catalyzed by Copper (II) oxide

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Abstract

An eco-safe and facile multi-component domino reaction has been described for the synthesis of 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione derivatives. The products were obtained by a four-component condensation reaction between phthalimide, hydrazine monohydrate, aromatic aldehyde derivatives and malononitrile in the presence of a catalytic amount of copper (II) oxide (CuO) under solvent-free conditions in high yields. The advantages of this one-pot procedure is environmentally friendly, efficient and economic availability of the catalyst, short reaction times, solvent-free conditions and clean reaction profiles.

Keywords: 1H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives, Copper (II) oxide (CuO), Economical process, One-pot synthesis, Solvent-free conditions.

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Introduction

In the recent years, the 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione derivatives have attracted considerable attention in organic synthesis because the show some biological activities [1, 2] and pharmacological properties such as anticancer [3], anti-inflammatory [4] and they have been reported to possess vasorelaxant [5], cardiotonic [6], anticonvulsant [7], antifungal [8]. Due to the importance of 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione derivatives, various methodologies for the preparation of these compounds have developed that is including various catalysts for example $Ce(SO_4)_2.4H_2O$ [9], SBA-Pr-SO_3H [10], $InCl_3$[11], $NiCl_2.6H_2O$ [12], [Bmim]OH [13], Ultrasound-assisted [14], P-TSA [15], STA [16], CuI nanoparticles [17], PTSA/[Bmim]Br [18], TBBAD [19], NZF@HAP-Cs [20], potassium carbonate [21], [bmim]OH [22] and [Pyrr][HCOO] [23]. Some of limitation these methodologies are low yields, toxic catalyst, long time reactions, harsh reaction conditions and expensive materials. Also, the major source of environmental pollutions is the usage of organic solvents in organic synthesis. Therefore, we had interested work in developing on multi-component reactions [24-27] with reduction of the amount of organic solvents and the developing of designing multi-component reactions under solvent-free conditions have become the chief of the goal our researches. During the past decades, the use of copper compounds as environmental safe catalysts in organic synthesis have attracted great interest due to their notable advantages such as non-toxic, environmentally-friendly, easy to handle, highly efficient and low-cost [28-30]. Based on the above considerations and our interest in the development of environmental benign synthetic methodologies [31-35], attempts were described to synthesize biologically active 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione derivatives by using copper (II) oxide (CuO) as catalyst *via* four-component condensation of phthalimide, hydrazine monohydrate, aromatic aldehyde derivatives and malononitrile under solvent-free conditions with high yields. Short reaction times, high yields, eco-friendly, one-pot and highly efficient procedure, readily available, low-cost and non- toxic catalyst that makes our protocol alternative in comparison to some of the earlier reported methods. Furthermore, one of the sources 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 and then were being recrystallized from ethanol with no need column chromatographic separation.

Experimental

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 instrument 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.

General procedure for preparation of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives ***(5a-p)***

A mixture of phthalimide (**1**, 1.0 mmol), hydrazine monohydrate (**2**, 1.0 mmol) and CuO (20 mol %) was heated for 2h at 80 °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 being recrystallized from ethanol to give pure compounds (**5a-p**). Products have been characterized by melting points and ^{1}H NMR spectroscopy. Spectra data some of products are represented below:

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

Yield: 86%; m.p. 268-270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.14 (1H, s, $H_{benzylic}$), 7.33-7.48 (5H, m, H_{Ar}), 7.97-8.29 (6H, m, NH_2 and H_{Ar}).

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

Yield: 89%; m.p. 252-254 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.30 (3H, s, CH_3), 6.08 (1H, s, $H_{benzylic}$), 7.14-7.26 (4H, m, H_{Ar}), 7.97-8.29 (6H, m, NH_2 and H_{Ar}).

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

Yield: 77%; m.p. 257-259 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 6.47 (1H, s, $H_{benzylic}$), 7.39-7.65 (4H, m, H_{Ar}), 7.91-8.31 (6H, m, NH_2 and H_{Ar}).

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

Yield: 87%; m.p. 251-253 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.30 (3H, s, CH_3), 6.10 (1H, s, $H_{benzylic}$), 7.18 (2H, d, *J*= 8.0 Hz, H_{Ar}), 7.34 (2H, d, *J*= 8.0 Hz, H_{Ar}), 7.97-8.28 (6H, m, NH_2 and H_{Ar}).

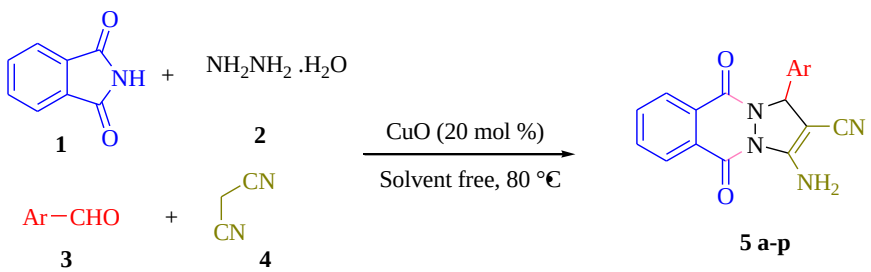
3-Amino-1-(3,4,5-trimethoxyphenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2 carbonitrile ***(5f)***

Yield: 82%; m.p. 254-255 °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, $H_{benzylic}$), 6.78 (2H, s, ArH), 7.89- 8.29 (6H, m, NH_2 and ArH).

^{13}C NMR (100 MHz, DMSO-d_6): 56.5, 60.3, 61.7, 63.8, 104.6, 116.1, 127.1, 127.7, 129.2, 129.4, 134.1, 134.6, 135.0, 137.7, 151.0, 152.8, 153.9, 157.2.

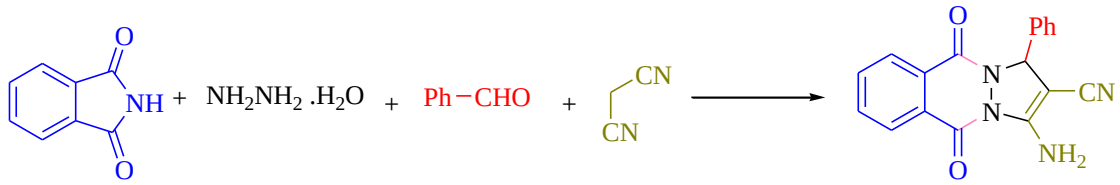
Results and discussion

To optimize the reaction conditions under conventional thermal conditions, at first, the condensation of phthalimide, hydrazine monohydrate, benzaldehyde and malononitrile was selected as a model reaction to provide the desired 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione derivatives, and it was examined in the presence of 20 mol% of CuO at range of rt-90 ºC in the absence of solvent (Table 1). As Table 1 indicates, the reasonable results were observed when the reaction was performed at 80 °C. The Increment of the temperature up to 90 °C didn't significantly improve the reaction results. In another study, the reaction of phthalimide, hydrazine monohydrate, benzaldehyde and malononitrile was tested in the presence of different molar ratios of CuO at 80 ºC under solvent-free conditions (Table 1). As it is shown in Table 1, 20 mol% of the catalyst was sufficient to promote the reaction efficiently at 80 °C. After optimization of the reaction conditions, the efficiency and generality of the method were evaluated by the reaction of phthalimide (**1**, 1.0 mmol), hydrazine monohydrate (**2**, 1.0 mmol) and malononitrile (**4**, 1.0 mmol) with arylaldehydes bearing electron withdrawing substituents, electron-donating substituents (**3**, 1.0 mmol) (Scheme1). The results are summarized in Table 2. As it can be seen in Table 2, the method was general and efficient, all reactions were performed successfully to furnish the corresponding 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione derivatives in high yields and in relatively short reaction times.



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

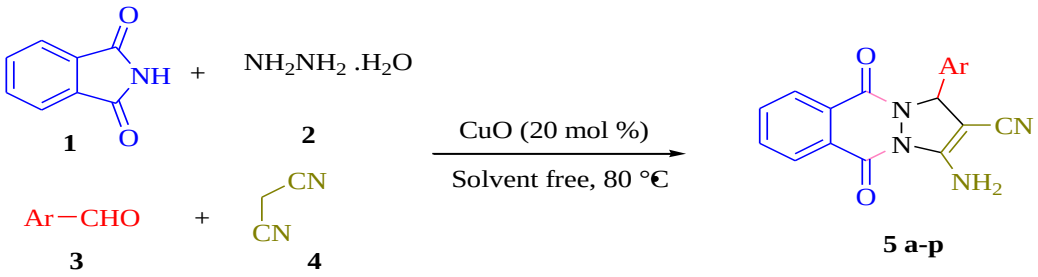
Table 1. Optimization of the reaction condition [a].



Entry	CuO (mol %)	Temperature (^{0}C)	Time (h)	Isolated Yields (%)
1	Catalyst free	80	12	No product
2	5	80	6	21
3	10	80	5	45
4	15	80	3.5	67
5	**20**	**80**	**3**	**86**
6	20	rt	12	No product
7	20	40	7	24
8	20	50	5.5	36
9	20	60	4	57
10	20	70	3	71
11	20	90	3	86
12	25	80	3	88

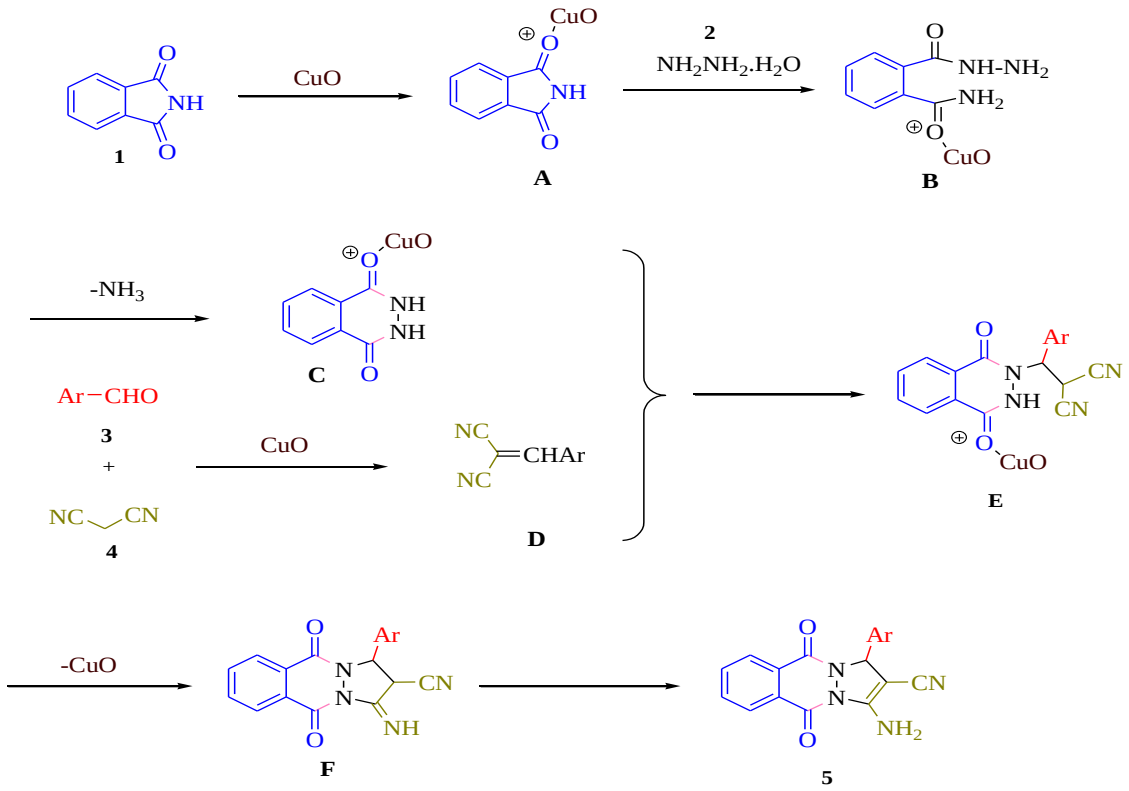
[a] Reaction conditions: phthalimide, hydrazine monohydrate, benzaldehyde and malononitrile (1:1:1:1) and CuO was heated at various temperatures.

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



Entry	Ar	Product	Time (h)	Isolated Yields (%)	m.p.˚C	Lit. m.p.˚C
1	C_6H_5	**5a**	3	86	268-270	265-268 [21]
2	3-Me-C_6H_4	**5b**	3	89	252-254	250-252 [17]
3	2-Cl- C_6H_4	**5c**	4	77	257-259	258-260 [21]
4	3-Br- C_6H_4	**5d**	4.5	74	274-276	273-275 [22]
5	4-Me- C_6H_4	**5e**	3	87	251-253	253-255 [17]
6	3,4,5-$(OMe)_3$-C_6H_2	**5f**	4	82	254-255	253-255 [11]
7	3-O_2N-C_6H_4	**5g**	2.5	86	267-269	269-271 [23]
8	3,4-$(OMe)_2$-C_6H_3	**5h**	4	85	151-153	150-152 [20]
9	2,4-Cl_2-C_6H_3	**5i**	5	73	258-260	259-261 [21]
10	3-F-C_6H_4	**5j**	2	91	265-267	264-266 [11]
11	3-OMe- C_6H_4	**5k**	3.5	86	250-252	248-251 [23]
12	4-Br- C_6H_4	**5l**	5	72	263-265	265-267 [14]
13	2-OMe- C_6H_4	**5m**	3.5	88	155-157	153-155 [20]
14	4-F- C_6H_4	**5n**	2	93	264-266	263-265 [14]
15	2-O_2N-C_6H_4	**5o**	2	89	263-265	265-266 [14]
16	C_4H_3S	**5p**	3.5	84	246-248	245-247 [16]

The proposed mechanistic route for the synthesis of 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione derivatives in the presence of CuO are shown in scheme 2. Here, the catalyst can facilitate active hosting site for the reactant molecule (phthalimide **1**) and accelerate the reaction rate. The formation of product **5** can be rationalized by initial formation of intermediate **D** by standard Knoevenagel condensation of the aldehyde **3** and malononitrile **4**. Then, the subsequent Michael-type addition of the phthalhydrazide **C** to the intermediate **D**, followed by cyclization and tautomerization affords the corresponding products **5**.



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

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives is shown in Table 3. This study reveals that CuO has shown its extraordinary potential to be an alternative, inexpensive, readily available and highly efficient catalyst for synthesis of these biologically active nitrogen-containing heterocyclic compounds, in addition to the use of solvent-free conditions with high yield and short reaction times in the reaction are the notable advantages this present methodology.

Table 3. Comparison of catalytic ability some of catalysts reported in the literature for 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	[11]
2	$NiCl_2.6H_2O$	EtOH, Reflux	3h/87	[12]
3	*p*-TSA	[Bmim]Br, 100 °C	3h/94	[15]
4	STA	Solvent-free, 70 °C	20 min/94	[16]
5	CuI nanoparticles	MeCN, Reflux	27 min/91	[17]
6	TBBAD	Solvent-free, 80-100 °C	15 min/89	[19]
7	CuO	Solvent-free, 80 °C	3h/86	This work

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

Conclusion

In summary, we have explored the use of copper (II) oxide (CuO) as a catalyst for the synthesis of 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-dione derivatives. The advantages of this method are high yields, short reaction times, one-pot and economical procedure, low-cost, readily available and highly efficient catalyst, solvent-free conditions, clean reaction profiles, simple experimental and work-up procedure.

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