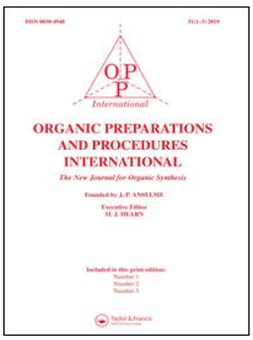

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OPPI BRIEF

Theophylline as a Green Catalyst for the Synthesis of 1*H*-Pyrazolo[1,2-b]phthalazine-5,10-diones

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1*H*-Pyrazolo[1,2-b]phthalazine-5,10-diones are a significant class of heterocyclic compounds and represent an interesting template in medicinal chemistry. Many of these compounds are known for their biological and pharmacological activities. These include anticancer,[1] anti-inflammatory,[2] vasorelaxant,[3] cardiotonic,[4] anticonvulsant[5] and antifungal[6] properties.

For the preparation of these important materials, a number of methods have been developed and include the use of such catalysts as $Ce(SO_4)_2{\cdot}4H_2O$,[7] sulfonic acid functionalized nanoporous silica,[8] $InCl_3$,[9] $NiCl_2{\cdot}6H_2O$,[10] [Bmim] OH,[11] ultrasound,[12] PTSA,[13] STA,[14] CuI nanoparticles,[15] PTSA/[Bmim]Br,[16] TBBAD,[17] $Ni_{0.5}Zn_{0.5}Fe_2O_4$,[18] K_2CO_3[19] and $Zn(OAC)_2{\cdot}2H_2O$.[20] Although each of these methods has its own value, many also have disadvantages, such as cost or the use of environmentally unfriendly reagents and solvents or lack of convenience. Therefore, it seemed desirable to seek a convenient and eco-friendly protocol.

There are several advantages of using theophylline (Figure 1) as a green and bio-based catalyst.[21–23] It is inexpensive, readily available, non-toxic and biodegradable. We now report the theophylline-catalyzed preparation of the title compounds in a one-pot four-component reaction of phthalimide, hydrazine monohydrate, aromatic aldehydes and malononitrile. The reaction occurs under solvent-free conditions in high yields.

As a model reaction, we studied the one-pot reaction of phthalimide (1.0 mmol), hydrazine monohydrate (1.0 mmol), benzaldehyde (1.0 mmol) and malononitrile (1.0 mmol). We used varying amounts of theophylline as a catalyst and the results are presented in Table 1. The best result (Entry 4, Table 1) was achieved by carrying out the reaction with 15 mol% of catalyst at 70 °C for 2.5 hours. The success of the reaction appeared to be a balance among catalyst loading, reaction temperature and time. For example, in the absence of catalyst no product was formed even at higher temperature and prolonged reaction time (Entry 1). A high loading of catalyst and prolonged reaction time were not enough to compensate for working at a lower temperature (Entry 5). Use of a higher amount of catalyst did not improve the yield while a decrease in the amount of catalyst decreased the yield. The effect of temperatures was studied under

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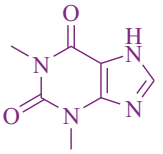
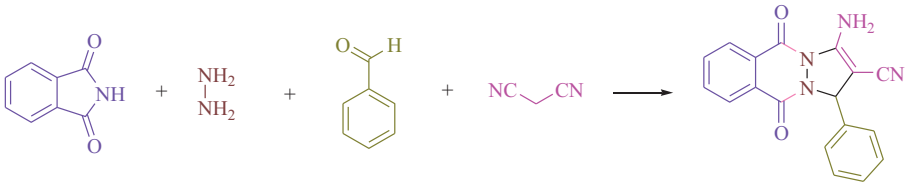


Figure 1. Structure of theophylline.

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



Entry	Theophylline (mol %)	Temperature (0C)	Time (h)	Isolated Yields (%)
1	Catalyst free	70	8	No product
2	5	70	6.5	47
3	10	70	4	65
4	**15**	**70**	**2.5**	**88**
5	15	rt	8	No product
6	15	40	7	39
7	15	50	5	55
8	15	60	3.5	70
9	15	80	2.5	88
10	20	70	2.5	89

[a]Reaction times determined by tlc (see experimental section).

solvent-free conditions (rt, 40, 50, 60, 70 and 80 °C) and the best results were obtained at 70 °C (Entry 4, Table 1).

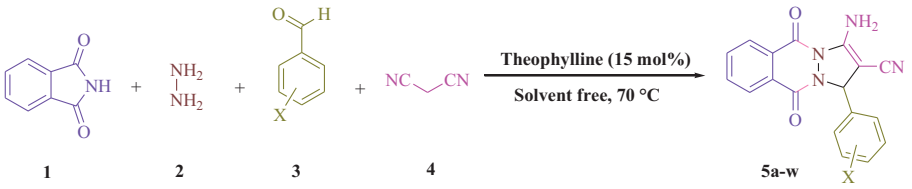
To study the generality of this process, it was carried out using a good range of aldehydes. The related 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives were obtained without observation of any by-products in high to excellent yields (Table 2).

A comparison of catalysts reported in the literature for the synthesis of the title compounds is shown in Table 3. As can be seen, theophylline catalysis offers yields comparable to other methods, but has the advantage of being green, readily available, and inexpensive. Our study suggests that theophylline has shown significant potential to be an alternative green catalyst for the synthesis of these valuable heterocyclic compounds. Its use permits solvent-free conditions with very good yields. We hope that our results will lead to increased research into this worthwhile catalyst.

Experimental section

Melting points of all compounds were determined using an Electro thermal 9100 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instrument with DMSO-d_6 as solvents. All reagents and solvents were purchased from Merck, Fluka and Acros chemical companies and were used without further purification.

Table 2. Theophylline catalyzed synthesis of 1*H*-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[References]
1	4-F-C_6H_4	**5a**	2	91	264-266	263-265[12]
2	3-Cl-C_6H_4	**5b**	3.5	80	265-267	266-267[12]
3	2-O_2N-C_6H_4	**5c**	2	88	263-265	265-266[12]
4	3-Br-C_6H_4	**5d**	3.5	78	272-274	270-272[12]
5	2,4-Cl_2-C_6H_3	**5e**	4	75	255-257	257-258[11]
6	3-OMe-C_6H_4	**5f**	3	86	249-251	248-251[20]
7	4-OH-C_6H_4	**5g**	4	79	272-274	270-272[15]
8	3,4,5-$(OMe)_3$-C_6H_2	**5h**	3.5	82	251-253	253-255[9]
9	2-F-C_6H_4	**5i**	2	93	267-268	268-270[9]
10	4-OMe-C_6H_4	**5j**	3	88	265-267	264-266[11]
11	4-Br-C_6H_4	**5k**	4	76	263-265	265-267[12]
12	2-Cl-C_6H_4	**5l**	3	83	259-261	261-262[11]
13	3-F-C_6H_4	**5m**	2	90	263-265	263-265[14]
14	4-Cl-C_6H_4	**5n**	4	78	271-273	270-272[15]
15	C_6H_5	**5o**	2.5	88	268-270	265-268[19]
16	2-Me-C_6H_4	**5p**	2	92	249-251	248-250[15]
17	4-Me-C_6H_4	**5q**	2.5	87	255-257	253-255[15]
18	3-OH-C_6H_4	**5r**	3.5	82	269-271	270-272[18]
19	C_4H_3S	**5s**	3	90	242-244	244-246[15]
20	4-O_2N-C_6H_4	**5t**	3	85	272-274	272-274[11]
21	3-O_2N-C_6H_4	**5u**	2	84	257-259	258-260[18]
22	2-OMe-C_6H_4	**5v**	2	89	155-157	153-155[18]
23	3-Me-C_6H_4	**5w**	2.5	90	249-251	250-252[15]

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[9]
2	$NiCl_2{\cdot}6H_2O$	EtOH, Reflux	3h/87[10]
3	*p*-TSA	[Bmim]Br, 100 °C	3h/94[13]
4	STA	Solvent-free, 70 °C	20 min/94[14]
5	CuI nanoparticles	MeCN, Reflux	27 min/91[15]
6	TBBAD	Solvent-free, 80-100 °C	15 min/89[17]
7	Theophylline	Solvent-free, 70 °C	2.5h/88[This work]

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

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

A mixture of phthalimide (**1**, 1.0 mmol), hydrazine monohydrate (*Caution! Hydrazine hydrate is corrosive. All workers should be thoroughly trained in its use prior to undertaking experiments, to include eye protection, gloves and ventilation*) (**2**, 1.0 mmol) and theophylline (15 mol%) was heated for 2h at 70 °C. Then an aromatic aldehyde (**3**, 1.0 mmol) and malononitrile (**4**, 1.0 mmol) were added and the mixture was heated for the time specified to complete the reaction as determined by TLC (*n*-hexane:ethyl acetate (8:3)). After

completion of the reaction the mixture was cooled to ambient temperature, the solid products were filtered and were recrystallized from ethanol to give pure compounds (**5a-w**). All of the compounds are known, and their melting points matched those in the literature references cited in Table 2. For the sake of completeness, some representative ^{1}H-NMR data are given below along with the appropriate references.

3-Amino-1-(3,4,5-trimethoxyphenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5h)[9]

^{1}H NMR (400 MHz, DMSO-d_6): 3.66 (3H, s, OCH_3), 3.76 (6H, s, $2 \times OCH_3$), 6.07 (1H, s, $H_{benzylic}$), 6.78 (2H, s, H_{Ar}), 7.89- 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-2-carbonitrile (5l)[11]

^{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-chlorophenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5n)[15]

^{1}H NMR (400 MHz, DMSO-d_6): 6.15 (1H, s, $H_{benzylic}$), 7.43 (2H, d, $J = 11.2$ Hz, H_{Ar}), 7.54 (2H, d, $J = 11.2$ Hz, H_{Ar}), 7.88-8.28 (6H, m, NH_2 and H_{Ar}).

3-Amino-1-(phenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5o)[19]

^{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-(4-methylphenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5q)[15]

^{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-methylphenyl)-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (5w)[15]

^{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}).

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