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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2015, Vol. 31, No. (4):
Pg. 2153-2158

An Efficient and High-yielding One-pot Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones Catalyzed by Sodium Hydrogen Carbonate under Solvent-free Conditions

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http://dx.doi.org/10.13005/ojc/310437

(Received: June 24, 2015; Accepted: August 06, 2015)

ABSTRACT

Sodium hydrogen carbonate, $NaHCO_3$, efficiently catalyzes the one-pot, three-component reaction of phthalhydrazide, an aromatic aldehyde, and malononitrile or ethyl cyanoacetate under solvent-free conditions, to afford the corresponding 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones in high yields. Easy work up, inexpensive and readily available catalyst and avoiding the use of harmful organic solvents are other advantages of this simple procedure.

Key words: 1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-diones, Sodium hydrogen carbonate, $NaHCO_3$, Solvent-free.

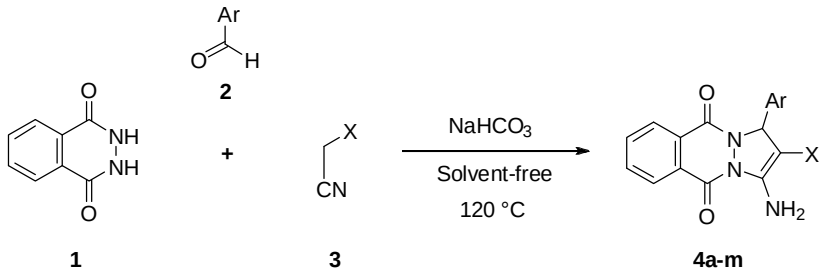
INTRODUCTION

The presence of pyrazole and phthalazine ring systems, either alone or as a fused ring with other heterocyclic moieties, in a number of pharmacologically significant molecules have made them prime targets for scientific research. Literature reports had already established pyrazoles and phthalazines as anticancer[1,2], antifungal[3,4], anti-inflammatory[5], antiviral[6], antidepressant[7], antibacterial[8], antipyretic[9], and anticonvulsant[10] agents. Some substituted pyrazoles also act as inhibitors of COX-2 and B-Raf kinases[11,12]. On the other hand, pyrazoles are of interest as efficient analytical regents in the complexation of transition-metal ions[13] and are the core structure of blockbuster drugs such as celecoxib, viagra, pyrazofurine, and many others[14-17]. In addition, recently, the titled compounds, 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones containing two active pharmacophores pyrazole and phthalazine, attracted organic chemists because of their antiinflammatory, analgesic, antihypoxic, and antipyretic activities[18].

A perusal of literature reveals that there are only a few methods for the one-pot, three-component synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones which involve the cyclocondensation of phthalhydrazide, aldehyde, and malononitrile or

ethyl cyanoacetate in the presence of *P*-TSA[19], nano ZnO[20], $InCl_3$[21], and Al-KIT-6[22] as catalyst. Syntheses of these compounds using [bmim]OH or Et_3N under microwave[23] or ultrasonic irradiation[24], respectively, have also been reported. In addition, they can also be accessed by the one-pot, four-component reaction of phthalimide or phthalic anhydride, hydrazine hydrate, aldehyde, and an active methylene component[25-28]. Each of these methods has its own merit, however, many of them suffer from disadvantages such as the use of halogenated solvent or catalyst, long reaction time and using microwave irradiation for accelerated synthesis. Therefore, the development of a new greener and more convenient method using a new readily available catalyst with high catalytic activity for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones is highly desirable.

Inspired by these facts and due to our interest in the synthesis of heterocyclic compounds with potential biological activities[29-33], and as part of our research on the development of environmentally friendly methods for the synthesis of organic compounds using catalysts[34-43], we report here our results from efficient solvent-free synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones by one-pot, three-component cyclocondensation reaction of phthalhydrazide, aromatic aldehyde, and malononitrile or ethyl cyanoacetate using $NaHCO_3$ as catalyst (Scheme 1).



Scheme 1: $NaHCO_3$ catalyzed synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

EXPERIMENTAL

All chemicals were available commercially and used without additional purification. Melting points were recorded using a Stuart SMP3 melting point apparatus. The FT-IR spectra of the products were obtained with KBr disks, using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR and ^{13}C-NMR spectra were recorded using a Bruker 400 spectrometer at 400 and 100 MHz frequencies, respectively.

General Procedure for the Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones 4a-m catalyzed by $NaHCO_3$

A mixture of phthalhydrazide (1 mmol), an aromatic aldehyde (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol), and $NaHCO_3$ (1 mmol) was heated in an oil bath at 120 °C for 15-50 min. The reaction was monitored by TLC. Upon completion of the transformation, the reaction mixture was cooled to room temperature and warm water was added. This resulted in the precipitation of the product, which was collected by filtration. The crude product was washed with warm water repeatedly and then with warm ethanol to give compounds 4a-m in high yields.

Selected spectral data

3-Amino-5,10-dioxo-1-phenyl-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile ***4a*** ^{1}H NMR (400 MHz, d_6-DMSO): ä (ppm) 6.14 (s, 1H, CH), 7.30-7.50 (m, 5H, arom-H), 7.95-8.30 (m, 6H, arom-H & NH_2); IR (KBr disc): *õ* (cm^{-1}) 3361 & 3260 (NH_2), 2198 (CN), 1682 & 1661 (C=O).

3-Amino-1-(furan-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile 4f ^{1}H NMR (400 MHz, d_6-DMSO)

δ (ppm) 6.32 (s, 1H, CH), 6.45-6.50 (m, 1H, arom-H), 6.34 (d, *J* = 3.2 Hz, 1H, arom-H), 7.65-

7.68 (m, 1H, arom-H), 7.96-8.30 (m, 6H, arom-H & NH_2); IR (KBr disc): υ (cm^{-1}) 3362 & 3256 (NH_2), 2204 (CN), 1651 (C=O).

Ethyl 3-amino-1-(3-bromophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate 4h ^{1}H NMR (400 MHz, d_6-DMSO)

δ (ppm) 1.06 (t, *J* = 7.2 Hz, 3H, CH_3), 3.90-4.06 (m, 2H, diastereotopic protons in CH_2), 6.07 (s, 1H, CH), 7.26 (t, *J* = 7.6 Hz, 1H, arom-H), 7.45 (dd, *J* = 8.0, 1.6 Hz, 2H, arom-H), 7.67 (t, *J* = 1.6 Hz, 1H, arom-H), 7.87-8.32 (m, 6H, arom-H & NH_2); ^{13}C-NMR (100 MHz, d_6-DMSO): δ (ppm) 15.7, 60.3, 64.3, 82.6, 122.7, 128.1, 128.3, 128.8, 130.3, 130.6, 131.7, 131.8, 132.0, 135.2, 136.2, 144.1, 151.5, 154.9, 158.5, 165.5; IR (KBr disc): *õ* (cm^{-1}) 3450 & 3339 (NH_2), 1705 & 1660 (C=O).

Ethyl 3-amino-1-(3-hydroxyphenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate 4l ^{1}H NMR (400 MHz, d_6-DMSO)

δ (ppm) 1.07 (t, *J* = 7.2 Hz, 3H, CH_3), 3.95-4.08 (m, 2H, diastereotopic protons in CH_2), 6.00 (s, 1H, CH), 6.34 (d, *J* = 8.0 Hz, 1H, arom-H), 6.79 (d, *J* = 1.6 Hz, 1H, arom-H), 6.83 (d, *J* = 8.0 Hz, 1H, arom-H), 7.09 (t, *J* = 8.0 Hz, 1H, arom-H), 7.68 (br., 2H, NH_2), 7.95-8.35 (m, 4H, arom-H), 9.32 (s, 1H, OH); ^{13}C-NMR (100 MHz, d_6-DMSO): δ (ppm) 15.8, 60.3, 64.6, 83.3, 115.7, 116.1, 119.6, 128.3, 128.9, 130.2, 130.4, 135.2, 136.3, 142.7, 151.2, 154.7, 158.3, 158.4, 158.6, 165.7; IR (KBr disc): υ (cm^{-1}) 3436 & 3324 (NH_2), 3274 (OH), 1703 & 1655 (C=O).

RESULTS AND DISCUSSION

The one-pot synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones was achieved by the three-component cyclocondensation of phthalhydrazide, aromatic aldehydes and malononitrile or ethyl cyanoacetate using $NaHCO_3$ as catalyst. At first, the synthesis of compound **4a** was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by heating a mixture of phthalhydrazide (1 mmol), benzaldehyde (1 mmol), and malononitrile (1 mmol) under various conditions. We decided to investigate the efficiency of $NaHCO_3$ in the model reaction under solvent-free conditions, which offers

Table 1: Synthesis of compound 4a in the presence of the $NaHCO_3$ catalyst under different reaction conditions

Entry	Catalyst (mmol)	Solvent	T (°C)	Time (min)	Isolated yield (%)
1	-	-	120	120	-
2	0.1	-	80	120	12
3	0.1	-	100	120	13
4	0.1	-	120	120	15
5	0.1	-	130	120	16
6	0.5	-	80	120	34
7	0.5	-	100	120	37
8	0.5	-	120	120	40
9	0.5	-	130	120	40
10	1.0	-	80	60	74
11	1.0	-	100	45	80
12	1.0	-	120	35	88
13	1.0	-	130	40	86
14	1.5	-	120	35	87
15	1.0	H_2O	Reflux	120	25
16	1.0	MeOH	Reflux	120	45
17	1.0	EtOH	Reflux	120	47
18	1.0	CH_3CN	Reflux	120	trace
19	1.0	CH_2Cl_2	Reflux	120	-

Reaction conditions: phthalhydrazide (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol).

several advantages such as being environmentally friendly, simpler work ups, cleaner products, enhanced selectivity, reduction of by products, and faster reactions. To find the optimum reaction conditions, different parameters were studied for the formation of compound **4a**. The results are summarized in Table 1. No product was obtained in the absence of the catalyst at 120 °C under solvent free conditions even after 120 min (entry 1), indicating that the catalyst is necessary for the reaction. We were pleased to see that the reaction was efficiently catalyzed by $NaHCO_3$ under solvent-free conditions at elevated temperature leading to a high yield of product **4a**. Then, the reaction was performed in the presence of various amounts of the catalyst and also in different temperatures under solvent-free conditions. As can be seen, the efficiency of the reaction is affected mainly by the amount of $NaHCO_3$ and reaction temperature. The best result was obtained when the reaction was run at 120 °C in the presence of 1 mmol of $NaHCO_3$ (entry 12). For showing the effect of solvent, the same model reaction was also carried out in different solvents including H_2O, MeOH, EtOH, CH_3CN and CH_2Cl_2 in the presence of 1 mmol of the catalyst (entries 15-19). As shown, the yield of the reaction under solvent-free conditions was greater and the reaction time was considerably shorter than the

Table 2: $NaHCO_3$ catalyzed synthesis 1*H*-pyrazolo[1,2-*b*] phthalazine-5,10-diones 4a-m under the optimized conditions

Entry	Ar	X	Product	Time (min)	Isolated yield (%)	Melting point (°C)	
						Found	Reported
1	C_6H_5	CN	4a	35	88	274-276	276-278[19]
2	4-BrC_6H_4	CN	4b	30	92	262-264	265-267[24]
3	4-ClC_6H_4	CN	4c	30	98	268-270	270-272[19]
4	4-$O_2NC_6H_4$	CN	4d	15	85	267-269	264-266[20]
5	4-$MeOC_6H_4$	CN	4e	50	90	240-242	240-242[27]
6	2-furyl	CN	4f	35	86	288-290	290-292[27]
7	3-pyridyl	CN	4g	40	91	264-266	267-270[20]
8	3-BrC_6H_4	CO_2Et	4h	40	87	235-237	New
9	4-ClC_6H_4	CO_2Et	4i	40	86	275-276	276-278[27]
10	4-FC_6H_4	CO_2Et	4j	45	87	230-232	230-232[27]
11	4-MeC_6H_4	CO_2Et	4k	50	86	205-207	204-206[19]
12	3-HOC_6H_4	CO_2Et	4l	50	85	245-247	New
13	3-$O_2NC_6H_4$	CO_2Et	4m	35	85	238-240	239-240[19]

Reaction conditions: phthalhydrazide (1 mmol), aromatic aldehyde (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol), $NaHCO_3$ (1 mmol), 120 ºC, solvent-free.

Table 3: Comparison of the efficiencies of various catalysts for the one-pot, three-component synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

Catalyst	Conditions			Time (min)	Yield (%)	Ref.
	Solvent	T/ºC	Other			
P-TSA	[bmim]Br	100	-	140-300	73-97	19
nano ZnO	-	100	-	8-45	86-93	20
$InCl_3$	-	60	-	240	79-93	22
[bmim]OH	[bmim]OH	45	MW	4-5	89-98	23
Et_3N	EtOH	50	ultrasonic	60	85-98	24
$NaHCO_3$	-	120	-	15-50	85-98	this work

conventional methods. Therefore, our optimized conditions are 1 mmol of $NaHCO_3$ at 120 °C under solvent free conditions. All subsequent reactions were carried out using these conditions.

Encouraged by the remarkable results obtained with the above reaction conditions, and to show the generality and scope of this new protocol, a range of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones were prepared in the presence of $NaHCO_3$ under optimized conditions, with the results shown in Table 2. Most of the reactions proceeded very efficiently and no side products were observed. As can be seen from Table 2, aromatic aldehydes bearing either electron donating or electron withdrawing substituents reacted successfully with phthalhydrazide and malononitrile or ethyl cyanoacetate to give the corresponding 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione products in high yields over short reaction time.

To show the merit of the present methodology, the results have been compared with the other methods reported for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones. This comparison is shown in Table 3. As can be seen, our method gave the desired products in high yields over short reaction times.

CONCLUSION

In conclusion, we have successfully developed an easy and efficient method to prepare a variety of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones from the reaction of phthalhydrazide, aromatic aldehydes, and malononitrile or ethyl cyanoacetate in the presence of $NaHCO_3$ under solvent-free conditions. Short reaction times, simple performance and work-up procedure, high yields, low cost of the catalyst, and the absence of any hazardous organic solvents are some of advantages of this procedure.

ACKNOWLEDGEMENTS

The authors express their gratitude to the Islamic Azad University, Mashhad Branch for its financial support.

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