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Ultrasound-assisted one-pot, three-component synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

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ABSTRACT

Triethylamine was found to be an efficient catalyst for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones by one-pot reaction of phthalhydrazide, aromatic aldehydes, and malononitrile or ethyl cyanoacetate in ethanol under ultrasonic irradiation. The advantages of this method are the use of an inexpensive and readily available catalyst, easy workup, improved yields, and the use of ethanol as a solvent that is considered to be relatively environmentally benign.

1. Introduction

Multi-step reactions usually produce significant amount of waste, principally due to a series of complex isolation procedures which often involves toxic, hazardous and expensive solvents after each step. Thus, multi-component reactions (MCRs) constitute an efficient synthetic strategy for the rapid and effective libratory organic transformations. Because, products are prepared in a one-pot and single step and the diversity can be obtained directly by changing the reacting components [1,2]. On the other hand, polyfunctionalized heterocycles play considerable roles in the drug discovery process, and analysis of drugs shows that most of them are polyfunctionalized heterocycles [3]. Therefore, research on the multi-components synthesis of polyfunctionalized heterocyclic compounds is an interesting challenge.

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important [4–6]. The development of new efficient methods to synthesize *N*-heterocycles with structural diversity is one major interest of modern synthetic organic chemists [7–9]. Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing bridgehead hydrazine have received considerable attention because of their pharmacological properties and clinical applications [10–17]. Similarly, pyrazoles are important compounds that have many derivatives with a wide range of interesting properties, such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, and anti-viral activities [18].

Considering the important biological properties of heterocycles containing bridgehead hydrazine, a number of methods have been reported for the synthesis of these heterocycles [19–23].

2. Experimental

2.1. Chemicals and apparatus

The chemical used in this work were obtained from Fluka and Merck and were used without purification. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102 MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in DMSO-d_6 using TMS. Ultrasonication was performed in a EUROSONIC® 4D ultrasound cleaner with a frequency of 50 kHz and an output power of 350 W. The reactions were performed in open vessels. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

2.2. Typical procedure for the preparation of 3-amino-5,10-dioxo-1-phenyl-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**4a**)

A mixture of malononitrile (0.07 g, 1 mmol), benzaldehyde (0.12 g, 1 mmol), phthalhydrazide (0.16 g, 1 mmol), and Et_3N

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(0.02 g, 20% mol) in EtOH (5 ml) was sonicated at 50 °C for 60 min (TLC). After completion of reaction, the reaction mixture was filtered and the precipitate washed with ethanol to afford the pure product **4a**.

*2.2.1. 3-Amino-1-(3-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**4c**)*

Yellow powder; mp = 266–267 °C. IR (KBr) (ν_{max}/cm^{-1}): 3363, 3255, 2192, 1665, 1658. MS, m/z (%): 350 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 6.13 (1H, s, CH), 7.38–8.25 (10H, m, H–Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 61.2, 62.8, 117.5, 122.6, 126.0, 127.1, 127.7, 128.7, 129.0, 129.5, 130.8, 133.7, 134.2, 135.0, 140.5, 151.2, 153.0, 157.2. Anal. Calcd. for $C_{18}H_{11}ClN_4O_2$: C, 61.64; H, 3.16; N, 16.97%. Found: C, 61.60; H, 3.11; N, 16.90%.

*2.2.2. 3-Amino-1-(2-nitrophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**4e**)*

Yellow powder; mp = 265–266 °C. IR (KBr) (ν_{max}/cm^{-1}): 3378, 3173, 2207, 1694, 1658. MS, m/z (%): 361 (M^+).^1H NMR (300 MHz, DMSO-d_6): δ_H 6.61(1H, s, CH), 7.59–8.28 (10H, m, H–Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 58.6, 60.3, 16.1, 124.7, 127.1, 127.8, 128.7, 129.3, 129.5, 130.1, 133.7, 134.4, 134.8, 135.2, 148.7, 152.1, 154.3, 157.1. Anal. Calcd. for $C_{18}H_{11}N_5O_4$: C, 59.84; H, 3.07; N, 19.38%. Found: C, 59.89; H, 3.03; N, 19.30%.

*2.2.3. 3-Amino-1-(4-fluorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**4h**)*

Yellow powder; mp = 263–265 °C. IR (KBr) (ν_{max}/cm^{-1}): 3373, 3260, 2182, 1683, 1663. MS, m/z (%): 334 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 6.15(1H, s, CH), 7.15–8.26 (10H, m, H–Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 61.6, 62.7, 115.6, 115.9, 116.5, 127.1, 127.7, 129.0, 129.3, 129.5, 129.6, 134.2, 135.1, 151.1, 154.1, 157.1, 160.8, 164.0. Anal. Calcd. for $C_{18}H_{11}FN_4O_2$: C, 64.67; H, 3.32; N, 16.76%. Found: C, 64.61; H, 3.27; N, 16.70%.

*2.2.4. 3-Amino-1-(3-bromophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**4k**)*

Yellow powder; mp = 270–272 °C. IR (KBr) (ν_{max}/cm^{-1}): 3363, 3248, 2187, 1683, 1663. MS, m/z (%): 396 (M^++2), 394 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 6.12 (1H, s, CH), 7.32–8.24 (10H, m, H–Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 61.3, 62.7, 116.5, 122.3, 126.5, 127.1, 127.7, 129.0, 129.5, 129.9, 131.1, 131.7, 134.2, 135.0, 141.7, 151.2, 154.2, 157.2. Anal. Calcd. for $C_{18}H_{11}BrN_4O_2$: C, 54.70; H, 2.81; N, 14.18%. Found: C, 54.74; H, 2.85; N, 14.26%.

*2.2.5. 3-Amino-1-(4-bromophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (**4l**)*

Yellow powder; mp = 265-267 °C. IR (KBr) (ν_{max}/cm^{-1}): 3420, 3310, 2202, 1693, 1660. MS, m/z (%): 396 (M^++2), 394 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 6.13 (1H, s, CH), 7.44–8.24 (10H, m, H–Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 61.3, 62.8, 116.5, 122.0, 127.1, 127.7, 129.0, 129.3, 129.6, 132.0, 134.2, 135.0, 138.3, 151.2, 154.1, 157.1. Anal. Calcd. for $C_{18}H_{11}BrN_4O_2$: C, 54.70; H, 2.81; N, 14.18%. Found: C, 54.76; H, 2.75; N, 14.11%.

*2.2.6. Ethyl 3-amino-1-(3-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate (**4o**)*

Yellow powder; mp = 211–213 °C. IR (KBr) (ν_{max}/cm^{-1}): 3450, 3347, 1706, 1658, 1642. MS, m/z (%): 397 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.03(3H, bs, CH_3), 3.96 (2H, bs, OCH_2), 6.05 (1H, s, CH), 7.29–8.26 (10H, m, H–Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 14.6, 59.1, 63.2, 81.5, 122.1, 123.2, 126.6, 127.1, 127.7, 127.8, 128.0, 129.5, 130.2, 133.0, 134.1, 135.1, 142.7, 147.2, 153.4, 164.4. Anal. Calcd. for $C_{20}H_{16}ClN_3O_4$: C, 60.38; H, 4.05; N, 10.56%. Found: C, 60.32; H, 4.0; N, 10.61%.

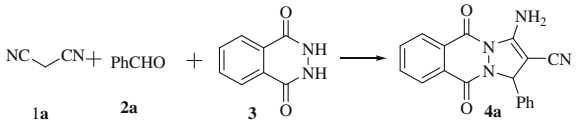
*2.2.7. Ethyl 3-amino-1-(2-nitrophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate (**4q**)*

Yellow powder; mp = 235–237 °C. IR (KBr) (ν_{max}/cm^{-1}): 3460, 3342, 1707, 1658, 1647. MS, m/z (%): 408 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.93(3H, m, CH_3), 3.90 (2H, m, OCH_2), 6.97 (1H, s, CH), 7.47–8.27 (10H, m, H–Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 14.5, 59.1, 64.7, 81.2, 124.4, 127.2, 127.7, 129.0, 129.1, 129.4, 129.5, 131.2, 133.9, 134.2, 135.2, 149.4, 153.7, 157.3, 164.2. Anal. Calcd. for $C_{20}H_{16}N_4O_6$: C, 58.82; H, 3.95; N, 13.72%. Found: C, 58.88; H, 3.89; N, 13.79%.

*2.2.8. Ethyl 3-amino-1-(4-bromophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate (**4u**)*

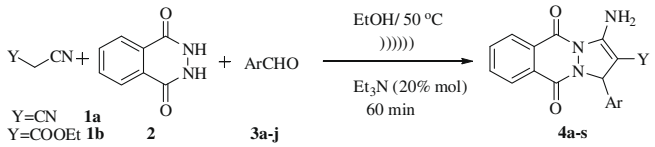
Yellow powder; mp = 205–206 °C. IR (KBr) (ν_{max}/cm^{-1}): 3424, 3306, 1699, 1663, 1637. MS, m/z (%): 443 (M^++2), 441 (M^+). ^1H

Table 1
Effect of reaction conditions.[a]



Entry	Conditions	Method	Catalyst (mol%)	Time (min)	Yield (%)
1	EtOH/50 °C	Ultrasound	None	180	Trace
2	EtOH/50 °C	Ultrasound	Et_3N (10)	60	60
3	EtOH/50 °C	Ultrasound	Et_3N (20)	60	90
4	EtOH/50 °C	Ultrasound	Et_3N (30)	60	91
5	EtOH/40 °C	Ultrasound	Et_3N (30)	60	75
6	EtOH/30 °C	Ultrasound	Et_3N (30)	60	50
7	EtOH/50 °C	High speed stirring	Et_3N (20)	180	Trace
8	H_2O/50 °C	Ultrasound	Et_3N (20)	60	48
9	H_2O/50 °C	High speed stirring	Et_3N (20)	180	Trace
10	THF/50 °C	Ultrasound	Et_3N (20)	60	85
11	THF/50 °C	High speed stirring	Et_3N (20)	180	<30
12	$CHCl_3$/50 °C	Ultrasound	Et_3N (20)	60	50
13	$CHCl_3$/50 °C	High speed stirring	Et_3N (20)	180	40
14	CH_3CN/50 °C	Ultrasound	Et_3N (20)	60	78
15	CH_3CN/50 °C	High speed stirring	Et_3N (20)	180	<30

[a] Malononitrile (1 mmol), benzaldehyde (1 mmol), phthalhydrazide (1 mmol).



Scheme 1.

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

Product **4**	Ar	Y	Yield[a] (%)
a	Ph	CN	92
b	2-ClC_6H_4	CN	93
c	3-ClC_6H_4	CN	91
d	4-ClC_6H_4	CN	96
e	2-$NO_2C_6H_4$	CN	95
f	3-$NO_2C_6H_4$	CN	97
g	4-$NO_2C_6H_4$	CN	98
h	4-FC_6H_4	CN	89
i	4-$CH_3C_6H_4$	CN	87
j	4-$MeOC_6H_4$	CN	85
k	3-BrC_6H_4	CN	90
l	4-BrC_6H_4	CN	89
m	Ph	CO_2Et	93
n	2-ClC_6H_4	CO_2Et	91
o	3-ClC_6H_4	CO_2Et	91
p	4-ClC_6H_4	CO_2Et	90
q	2-$NO_2C_6H_4$	CO_2Et	94
r	3-$NO_2C_6H_4$	CO_2Et	95
s	4-$NO_2C_6H_4$	CO_2Et	97
t	4-$CH_3C_6H_4$	CO_2Et	88
u	4-BrC_6H_4	CO_2Et	89

[a] Isolated yields.

NMR (300 MHz, DMSO-d_6): δ_H 1.04(3H, bs, CH_3), 3.98(2H, bs, OCH_2), 6.05 (1H, s, CH), 7.24–8.28 (10H, m, H–Ar and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 14.8, 59.8, 62.2, 81.0, 123.1, 123.8, 126.7, 126.8, 128.1, 127.1, 126.9, 127.7, 130.8, 132.7, 135.1, 135.4, 142.4, 146.1, 155.4, 164.0. Anal. Calcd. for $C_{20}H_{16}BrN_3O_4$: C, 54.31; H, 3.65; N, 9.50%. Found: C, 54.27; H, 3.59; N, 9.42%.

3. Results and discussion

Very recently [24], we have prepared 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones via a novel approach. This was done by the reaction of phthalhydrazide, malononitrile or ethyl cyanoacetate and aromatic aldehydes in the presence of *p*-TSA at 100 °C in [bmim]Br within 130–300 min. In order to obtain mild reaction conditions, lower temperatures as well as speeding up the reaction for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones, other catalysts and various reaction conditions have been investigated in the reaction of malononitrile **1a**, phthalhydrazide **2**, and benzaldehyde **3a** as a model reaction (Table 1). As could be seen in Table 1, the best result was obtained with a 20 mol% of Et_3N as the catalyst in ethanol at 50 °C under ultrasonic irradiation. Using lower amount of catalyst resulted in lower yields, while higher amount of catalyst did not affected reaction times and yields (Table 1).

To study the effect of temperature on this synthesis, we also performed three experiments in 30, 40, and 50 °C under sonication (Table 1). It was observed that a lower reaction temperature leads to a lower yield. To delineate the role of ultrasound and solvent effect, the reaction was investigated with and without ultrasonic irradiation at the same temperature (50 °C) in various solvents. In all reactions it was found that the use of ultrasound irradiation leads to a faster reaction and a higher yield. Table 1 demonstrates that absolute EtOH was the best choice of solvent and the use of ultrasound radiation in ethanol improves the rate of the reaction and also the yield of the product.

Encouraged by this success, we extended the reaction of aromatic aldehyde **3a–j**, malononitrile **1a** or ethyl cyanoacetate **1b** and phthalhydrazide under similar conditions (EtOH/NEt_3/ultrasound), furnishing the respective 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives **4a–s** in excellent yields for 60 min (Scheme 1). The results were excellent in terms of yields and product purity using Et_3N, while, without this catalyst the yields of products were low even after 5 h (<30%).

The optimized results are summarized in Table 2. The results were excellent in yields using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents.

Compounds **4a–s** are stable solids whose structures are fully supported by IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.

4. Conclusion

In conclusion, we have described a rapid and efficient method for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione in high yield and short reaction time by a cyclo-condensation reaction of aldehyde, malononitrile or ethyl cyanoacetate and phthalhydrazide in ethanol using Et_3N as an inexpensive and readily available catalyst under ultrasonic irradiation.

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