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Preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones using ZrO_2 nanoparticles as a catalyst under solvent-free conditions

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Abstract: Zirconium oxide nanoparticles are an efficient catalyst for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones via a three-component reaction of phthalhydrazide, aromatic aldehydes and malononitrile under solvent-free conditions.

Keywords: aromatic aldehydes; multicomponent reaction; nanoparticles; phthalhydrazide; solvent-free; zirconium oxide.

Introduction

Multi-component reactions (MCRs) have become a powerful, fast and convenient approach for the synthesis of complex heterocyclic compounds from simple and readily available starting materials [1]. MCRs have advantages over classical reaction strategies including greater efficiency and shorter reaction time [2, 3]. Nanometer-sized particles have recently been considered as an alternative matrix for supporting catalytic reactions. Reusable nanoscale heterogeneous catalysts show high catalytic activity due to a high specific surface area and low-coordination sites [4].

1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives containing fused hydrazine are an important class of pharmaceutical compounds that exhibit a wide spectrum of biological activities [5–7]. Such compounds are relatively difficult to synthesize [8–17].

Therefore, the development of simple methods for the synthesis of pyrazolo[1,2-*b*]phthalazine-5,10-diones is important. In continuation of our efforts to develop a new methodology for the synthesis of heterocyclic compounds [18–21], we now report the use of ZrO_2 nanoparticles as an efficient catalyst for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **4a–g** from phthalhydrazide, aromatic aldehydes and malononitrile (Scheme 1).

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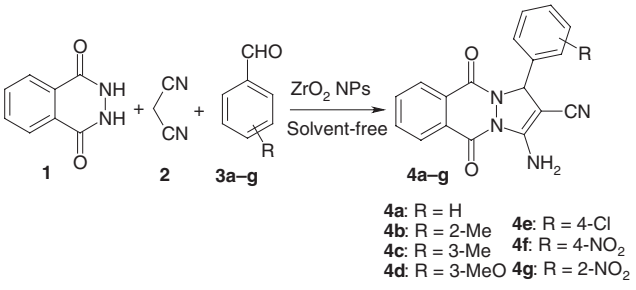
Results and discussion

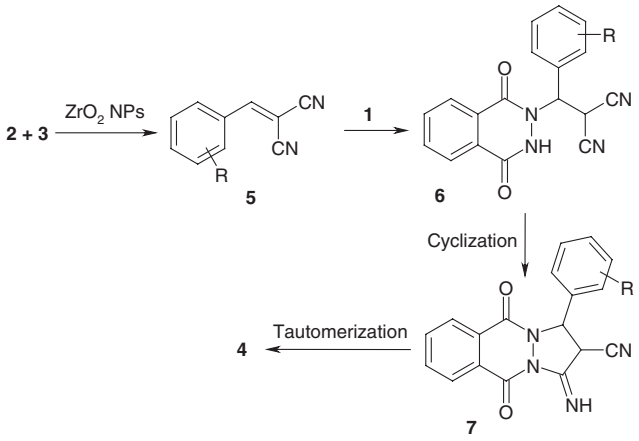
Initially, different reaction parameters for the synthesis of compound **4a** by the three-component condensation reaction using benzaldehyde as a model reaction were optimized. The scrutinized parameters were temperature, time of reaction solvents, including ethanol, tetrahydrofuran, acetonitrile, dichloromethane and water, and solvent-free conditions. The best results were obtained under solvent-free conditions. When 10 mol%, 15 mol% and 20 mol% of ZrO_2 nanoparticles were used, the yields of **4a** were 82%, 91% and 91%, respectively, and the yields were much lower in any solvent. Only 20% of **4a** was obtained in the absence of a catalyst. Under optimized solvent-free conditions, the reaction was conducted with 15 mol% of the catalyst at 100°C for 45 min and furnished **4a** with a 91% yield. The reactions with other aromatic aldehydes conducted using this optimized procedure were also similarly effective. All reactions were completed within 35–45 min and afforded good yields of products **4b–g**. The aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and afforded the products in good yields. As seen from Table 1, the method compares well with other known preparations of the model product **4a**. The suggested mechanism for the formation of products **4** involves generation of the intermediate compounds **5–7**, as shown in Scheme 2.



Scheme 1 Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **4a–g**.

Table 1 Comparison of the results of different preparations of **4a**.

Entry	Catalyst	Conditions	Time (min)	Yield (%) [Ref]
1	p-TSA (30 mol%)	[Bmim]Br/100°C	180	94 [8]
2	TBBDA/PBBS	EtOH, 100°C	15/40	89/65 [9]
3	Et_3N (20 mol%)	EtOH, 50°C, ultrasound	60	90 [10]
4	[Bmim]OH (20 mol%)	MW, 100 W, 45°C	4	96 [11]
5	CuI NPs	Solvent-free, 70°C	27	91 [12]
7	APTES-MNPs (10 mol%)	Solvent-free, rt	19	92 [14]
8	$NiCl_26H_2O$	EtOH, reflux	180	87 [16]
9	AL-KIT-6	EtOH, 60°C	240	93 [17]
10	ZrO_2 NPs	Solvent-free, 100°C	40	91 (present work)



Scheme 2 A plausible mechanism for the formation of compounds **4**.

Conclusions

The reaction between phthalhydrazide, malononitrile and aromatic aldehydes in the presence of nano-ZrO_2 offers a simple one-pot access to pyrazolo[1,2-*a*][1,2,4]triazole-1,3-dione derivatives of potential synthetic and pharmacological interest. The simplicity, easy workup, as well as the safety and reusability of the catalyst are advantages of this method.

Experimental

Melting points were determined on an Electrothermal 9100 apparatus and are not corrected. Infrared (IR) spectra were recorded in KBr pellets on a Shimadzu 460 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AVANCE 400 spectrometer using DMSO-d_6 as a solvent. Electron impact mass spectra were obtained at 70 eV on a Finnigan MAT 8430 mass spectrometer. Elemental analyses for C, H and N were obtained on a Heraeus CHNO Rapid analyzer. All commercially available chemicals and reagents were used without further purification. In all experiments, ZrO_2 (5–25 nm, Plasma Chem GmbH) was used.

General procedure for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones 4a–g

A mixture of phthalhydrazide (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol) and ZrO_2 nanoparticles (15 mol%) was stirred at 100°C under solvent-free conditions for 35–45 min. After completion of the reaction, the resultant precipitate was crystallized from MeOH to afford pure product **4**.

3-Amino-1-phenyl-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4a) Yellow powder; yield 0.29 g (91%); mp 276–278°C; IR: 3361, 3292, 3248, 2198, 1659, 1567 cm^{-1}; ^{1}H NMR: δ 6.12 (s, 1H, CH), 7.31–7.46 (m, 5H, ArH), 7.92–8.26 (m, 6H, ArH and NH_2); ^{13}C NMR: δ 61.8, 62.8, 116.3, 126.6, 126.7, 127.1, 128.2, 128.5, 128.7, 129.1, 133.7, 134.6, 138.4, 149.8, 153.6, 156.8; EI-MS: *m/z* 316. Anal. Calcd for $C_{18}H_{12}N_4O_2$ (316.32): C 68.35, H 3.82, N 17.71. Found: C 68.28, H 3.75, N 17.78.

3-Amino-1-(2-methylphenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4b) Yellow powder; yield 0.29 g (88%); mp 247–249°C; IR: 3383, 3300, 2207, 1659, 1603 cm^{-1}; ^{1}H NMR: δ 2.43 (3H, s, CH_3), 6.30 (1H, s, CH), 7.17–7.28 (4H, m, Ar), 7.96–8.25 (6H, m, Ar and NH_2); ^{13}C NMR: δ 20.1, 61.2, 62.9, 122.0, 126.7, 127.2, 127.7, 128.1, 128.3, 128.5, 129.0, 130.3, 133.8, 134.8, 135.2, 136.5, 153.7, 154.2, 156.9; EI-MS: *m/z* 330. Anal. Calcd for $C_{19}H_{14}N_4O_2$ (330.35): C 69.09, H 4.27, N 16.95. Found: C 68.95, H 4.25, N 16.96.

3-Amino-1-(3-methylphenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4c) Yellow powder; yield 0.29 g (89%); mp 250–252°C; IR: 3361, 3259, 2194, 1658, 1570 cm^{-1}; ^{1}H NMR: δ 2.25 (3H, s, CH_3), 6.08 (1H, s, CH), 7.11–7.22 (4H, m, Ar), 7.97–8.26 (6H, m, Ar and NH_2); ^{13}C NMR: δ 21.0, 61.2, 62.8, 122.0, 122.3, 127.0, 127.4, 127.9, 128.4, 128.6, 128.9, 131.4, 134.2, 134.7, 135.8, 136.4, 154.1, 154.4, 157.3; EI-MS: *m/z* 330.

Anal. Calcd for $C_{19}H_{14}N_4O_2$ (330.35): C 69.09, H 4.27, N 16.95. Found: C 69.12, H 4.18, N 16.85.

3-Amino-1-(3-methoxyphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4d) Yellow powder; yield 0.30 g (87%); mp 247–249°C; IR: 3363, 3260, 2189, 1655, 1567 cm^{-1}; ^{1}H NMR: δ 3.76 (s, 3H, OCH_3); 6.15 (s, 1H), 6.90 (d, ^3J = 8.0 Hz, 1H), 6.96–6.99 (m, 2H), 7.26 (t, ^3J = 7.5 Hz, 1H), 7.65–7.99 (m, 2H), 8.09–8.12 (m, 3H, NH_2, CH), 8.25–8.28 (m, 1H); ^{13}C NMR:

δ 55.7, 61.2, 62.6, 112.8, 114.5, 119.2, 124.3, 126.8, 127.2, 128.9, 129.1, 129.2, 129.6, 134.3, 137.6, 150.6, 153.2, 157.1, 160.0; EI-MS: *m/z* 346. Anal. Calcd for $C_{18}H_{11}N_5O_4$ (346.35): C 65.89, H 4.07, N 16.18. Found: C 65.78, H 4.15, N 16.24.

3-Amino-1-(4-chlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4e) Yellow powder; yield 0.33 g (93%); mp 273–275°C; IR: 3362, 3256, 2188, 1661, 1652 cm^{-1}; ^1H NMR: δ 6.17 (1H, s, CH), 7.43–7.54 (4H, m, Ar), 7.94–8.18 (6H, m, Ar and NH_2); ^{13}C NMR: δ 61.7, 62.6, 116.7, 126.8, 127.7, 128.2, 128.7, 129.3, 129.4, 133.3, 134.0, 134.7, 137.4, 150.2, 154.1, 157.3; EI-MS: *m/z* 350. Anal. Calcd for $C_{18}H_{11}N_4O_2Cl$ (350.77): C 61.64, H 3.16, N 15.97. Found: C 61.53, H 3.13, N 16.03.

3-Amino-1-(4-nitrophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo-[1,2-*b*]phthalazine-2-carbonitrile (4f) Yellow powder; yield 0.35 g (96%); mp 226–228°C; IR: 3371, 3301, 3079, 2185, 1662, 1554 cm^{-1}; ^1H NMR: δ 6.30 (s, 1H); 7.81 (d, ^3J = 8.6 Hz, 2H), 7.97–8.09 (m, 3H), 8.22 (brs, 2H, NH_2), 8.24 (d, ^3J = 8.6 Hz, 2H), 8.26–8.29 (m, 1H); ^{13}C NMR δ 61.5, 62.9, 116.5, 126.1, 127.9, 128.1, 128.8, 129.1, 129.4, 134.5, 134.9, 146.4, 147.6, 150.8, 154.0, 157.2; EI-MS: *m/z* 361. Anal. Calcd for $C_{18}H_{11}N_5O_4$ (361.32): C 59.84, H 3.07, N 19.38. Found: C 60.13, H 3.13, N 19.23.

3-Amino-1-(2-nitrophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo-[1,2-*b*]phthalazine-2-carbonitrile (4g) Yellow powder; yield 0.34 g (95%); mp 261–263°C; IR: 3380, 3165, 2192, 1694, 1655 cm^{-1}; ^1H NMR: δ 6.64 (1H, s, CH), 7.59–8.28 (10H, m, Ar and NH_2); ^{13}C NMR δ 61.1, 62.8, 106.5, 124.1, 126.8, 127.3, 128.1, 128.9, 129.2, 129.7, 133.4, 134.0, 134.6, 135.0, 148.4, 151.8, 154.2, 157.0; EI-MS: *m/z* 361. Anal. Calcd for $C_{18}H_{11}N_5O_4$ (361.32): C 59.84, H 3.07, N 19.38. Found: C 59.98, H 3.15, N 19.16.

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