An Efficient One-Pot Synthesis of 1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-dione Derivatives

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Abstract: An efficient, three-component, one-pot condensation reaction between phthalhydrazide, aromatic aldehydes, and malononitrile or ethyl cyanoacetate for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives in excellent yields is reported.

Key words: malononitrile, ethyl cyanoacetate, phthalhydrazide, pyrazolo[1,2-*b*]phthalazine-5-dione

After the discovery of multicomponent reactions (MCR) in 1850 by Strecker,[1] the concept has stimulated substantial interest in organic chemistry because it provides useful products in a single step by the creation of several new bonds in one pot. In drug discovery as well as 'green chemistry', MCR are the preferred techniques due to high throughput synthesis of compounds in a cost- and time-effective manner.[2,3]

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds,[4–7] among them such prominent drug molecules as celecoxib (**1**), pyrazofurine (**2**), and many others. Similarly, heterocycles containing a phthalazine moiety are of interest because they show some pharmacological and biological activities.[8–10] For example, pyrazolo[1,2-*b*]phthalazine-dione derivatives **3** were reported as anti-inflammatory, analgesic, antihypoxic, and antipyretic agents.[8] Phthalazine derivatives were reported to possess anticonvulsant,[11] cardiotonic,[12] and vasorelaxant[13] activities (Figure 1).

So far, only a few methods have been reported for the synthesis of pyrazolo[1,2-*b*]phthalazine-dione.[14] Despite the available methods, the development of new synthetic methods for the efficient preparation of heterocycles containing a phthalazine ring fragment is therefore an interesting challenge.

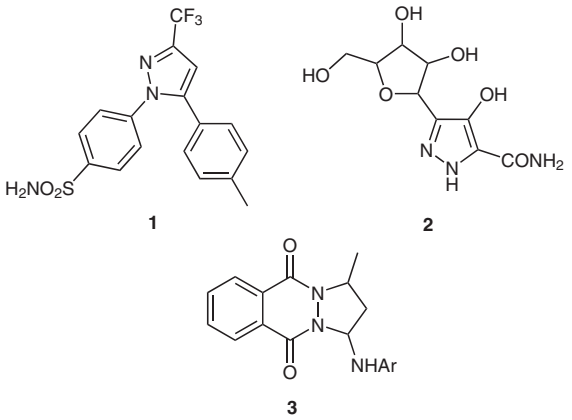
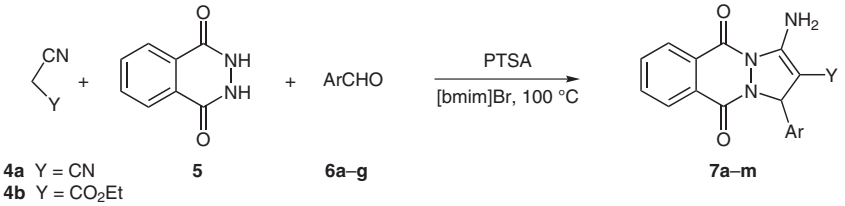


Figure 1

Multicomponent reactions of malononitrile or alkyl cyanoacetate, an aldehyde, and nucleophilic compounds have recently attracted the interest of the synthetic community because the formation of different condensation products can be expected depending on the specific conditions and structure of the building blocks.[15–19]

Considering the above reports and in continuation of our previous works on synthesis of heterocyclic compounds,[20] we report the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives via the simple, efficient, one-pot, and three-component condensation reaction of malononitrile (**4a**) or ethyl cyanoacetate (**4b**), phthalhydrazide (**5**) and aldehydes **6a–g** in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) in ionic liquid 1-butyl-3-methylimidazolium bromide {[bmim]Br} as solvent at 100 °C (Scheme 1).[21]

To achieve suitable conditions for the above transformation, we investigated the reaction of malononitrile (**4a**), benzaldehyde (**6a**), and phthalhydrazide (**5**) in various



Scheme 1

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solvents, ionic liquids (IL), and under solvent-free classical heating conditions. In refluxing various solvents or under solvent-free conditions, the reaction was very slow and the yield of product was very low. We found that the best result was obtained in the presence of PTSA at 100 °C in [bmim]Br (Table 1).

Table 1 Effect of Reaction Conditions[a]

Conditions	Time (h)	Yields (%)[b]
[bmim]Br, 100 °C, PTSA	3	94
[bmim]Br, 100 °C	6	<40
[bmim]Br, 80 °C, PTSA	5	65
solvent-free, 100 °C, PTSA	6	55
EtOH (reflux), PTSA	10	<40
DMF (reflux), PTSA	10	54
MeCN (reflux), PTSA	10	<40

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

To explore the scope and limitation of this reaction, we have extended the reaction of phthalhydrazide **5** with a range of aromatic aldehydes **6a**–**g** and malononitrile (**4a**) or ethyl cyanoacetate (**4b**) under similar conditions {using [bmim]Br and PTSA}, furnishing the respective 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **7b**–**m** in high yields. The optimized results are summarized in Table 2. The results were excellent in terms of yields and product purity using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents in the presence of PTSA, while without it for a long period of time (8 h) the yields of products were low (<40%). Under the same conditions {using [bmim]Br, PTSA}, this reaction almost could not be observed when the aliphatic aldehyde was used as a starting material.

The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m/z* values. Compounds **7a**–**m** are stable solids whose structures are fully supported by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.

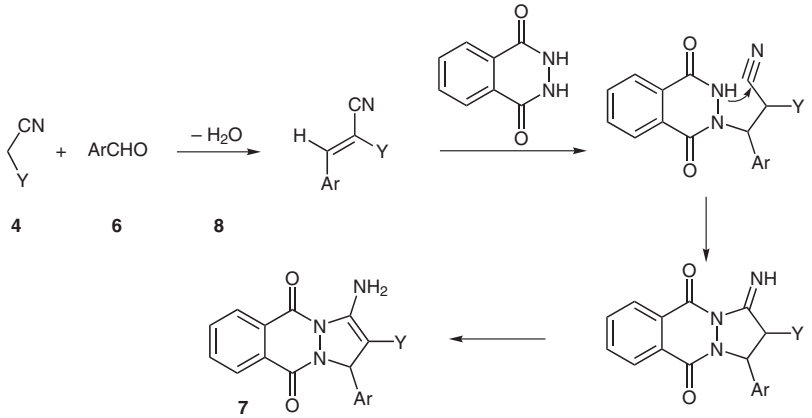
Table 2 Synthesis of 1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-diones **7a**–**m**[22]

Product	Ar	Y	Time (h)	Yield (%)[a]
7a	Ph	CN	3	94
7b	2-ClC_6H_4	CN	3.2	88
7c	4-ClC_6H_4	CN	2.8	91
7d	3-$O_2NC_6H_4$	CN	3.8	92
7e	4-$O_2NC_6H_4$	CN	2.2	97
7f	4-MeC_6H_4	CN	5	78
7g	4-$MeOC_6H_4$	CN	5	75
7h	Ph	CO_2Et	3.5	91
7i	2-ClC_6H_4	CO_2Et	5	89
7j	4-ClC_6H_4	CO_2Et	3.3	90
7k	3-$O_2NC_6H_4$	CO_2Et	3	93
7l	4-$O_2NC_6H_4$	CO_2Et	2.7	95
7m	4-MeC_6H_4	CO_2Et	5	73

[a] Isolated yields.

The formation of products **7a**–**m** can be rationalized by initial formation of intermediate **8** by standard Knoevenagel condensation of the malonitrile or ethyl cyanoacetate **4** and aldehyde **6**. Then, the subsequent Michael-type addition of the phthalhydrazide (**5**) to the intermediate **8**, followed by cyclization and tautomerization affords the corresponding products **7** (Scheme 2).

In summary, we have described an efficient and one-pot synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones via a cyclocondensation reaction of malonitrile or ethyl cyanoacetate, phthalhydrazide, and aromatic aldehydes in [bmim]Br. The novelty and synthetic usefulness of these methodologies were demonstrated by the efficient synthesis of phthalazine derivatives.



Scheme 2

Acknowledgment

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(21) **Typical Procedure for the Preparation of 3-Amino-5,10-dihydro-5,10-dioxo-1-phenyl-1*H*-pyrazolo[1,2-*b*]phthalazin-2-carbonitrile (7a)**
A mixture of malononitrile (1 mmol), phthalhydrazide (1 mmol), benzaldehyde (1 mmol), PTSA (0.3 mmol), and [bmim]Br (0.30 g) was heated at 100 °C for 3 h (TLC). After cooling, the reaction mixture was washed with H_2O (15 mL) and residue recrystallized from MeOH to afford the pure product **7a**. Yellow powder (94%); mp 276–278 °C. IR (KBr): ν_{max} = 3359, 3190, 2197, 1690, 1658 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 316 (20) [M^+], 299 (42), 239 (100). ^1H NMR (300 MHz, DMSO-d_6): δ = 6.13 (1 H, s, CH), 7.29–7.47 (5 H, m, ArH), 7.93–8.26 (4 H, m, ArH), 8.09 (2 H, s, NH_2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 62.4, 63.6, 116.1, 127.2, 127.3, 127.7, 128.7, 128.9, 129.2, 134.1, 135.1, 138.7, 151.2, 154.2, 157.1 ppm. Anal. Calcd (%) for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.41; H, 3.87; N, 17.78.
(22) **Selected Characterization Data**
3-Amino-1-(2-chlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (7b)
Yellow powder (88%); mp 259–262 °C. IR (KBr): ν_{max} = 3370, 3176, 2207, 1695, 1658 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 350 (17) [M^+], 333 (44), 239 (100). ^1H NMR (300 MHz, DMSO-d_6): δ = 6.46 (1 H, s, CH), 7.33–7.62 (4 H, m, ArH), 7.87–8.30 (4 H, m, ArH), 8.15 (2 H, s, NH_2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 60.2, 61.0, 116.2, 127.2, 127.8, 128.3, 128.8, 129.2, 130.2, 130.4, 131.7, 134.3, 135.2, 135.8, 151.6, 154.0, 157.1 ppm. Anal. Calcd (%) for $C_{18}H_{11}ClN_4O_2$: C, 61.64; H, 3.16; N, 15.97. Found: C, 61.57; H, 3.11; N, 15.91.
3-Amino-1-(4-chlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (7c)
Yellow powder (91%); mp 270–272 °C. IR (KBr): ν_{max} = 3375, 3264, 2200, 1662, 1655 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 350 (8) [M^+], 333 (27), 239 (100). ^1H NMR (300 MHz, DMSO-d_6): δ = 6.15 (1 H, s, CH), 7.41–7.53 (4 H, m, ArH), 7.93–8.26 (4 H, m, ArH), 8.13 (2 H, s, NH_2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 61.3, 62.7, 116.4, 127.1, 127.7, 128.9, 129.3, 133.3, 134.2, 135.1, 137.9, 151.2, 154.1, 157.1 ppm. Anal. Calcd (%) for $C_{18}H_{11}ClN_4O_2$: C, 61.64; H, 3.16; N, 15.97. Found: C, 61.56; H, 3.09; N, 15.92.
Ethyl 3-Amino-5,10-dihydro-1-(3-nitrophenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (7k)
Yellow powder (93%); mp 239–240 °C. IR (KBr): ν_{max} = 3360, 3249, 1693, 1651, 1613 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 408 (23) [M^+], 286 (100), 240 (40), 162 (85). ^1H NMR (300 MHz, DMSO-d_6): δ = 0.99 (3 H, t, $^3J_{HH}$ = 9.2 Hz, CH_3), 3.94 (2 H, q, $^3J_{HH}$ = 7.8 Hz, OCH_2), 6.22 (1 H, s, CH), 7.56–8.30 (10 H, m, NH_2 and ArH), 8.26–8.27 ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.51, 59.19, 63.10, 81.12, 122.58, 123.12, 127.14, 127.69, 129.09, 129.49, 129.99, 134.17, 134.56, 135.05, 142.61, 147.95, 150.52, 153.93, 157.39, 164.31 ppm. 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, 13.66.
Ethyl 3-Amino-5,10-dihydro-1-(4-nitrophenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (7l)
Yellow powder (95%); mp 241–243 °C. IR (KBr): ν_{max} = 3386, 3210, 1694, 1655, 1630 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 408 (13) [M^+], 286 (81), 240 (17), 162 (100). ^1H NMR (300 MHz, DMSO-d_6): δ = 1.03 (3 H, t, $^3J_{HH}$ = 6.8 Hz, CH_3), 3.95 (2 H, q, $^3J_{HH}$ = 6.7Hz, OCH_2), 6.18 (1 H, s, CH), 7.73–8.29 (10 H, m, NH_2 and ArH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.61, 59.27, 63.04, 81.18, 123.59, 125.58, 127.16, 127.73, 129.02, 129.25, 133.04, 134.22, 135.12, 147.34, 147.77, 153.81, 157.32, 164.26 ppm. Anal. Calcd (%) for $C_{20}H_{16}N_4O_6$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.75; H, 3.90; N, 13.78.
Ethyl 3-Amino-5,10-dihydro-5,10-dioxo-1-p-tolyl-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (7m)
Yellow powder (73%); mp 204–206 °C. IR (KBr): ν_{max} = 3447, 3333, 1706, 1658, 1624 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 377 (27) [M^+], 286 (100), 240 (25), 162 (10). ^1H NMR

(300 MHz, DMSO-d_6): δ = 1.04 (3 H, t, $^3J_{HH}$ = 8.9 Hz, CH_3), 2.25 (3 H, s, CH_3), 3.96 (2 H, q, $^3J_{HH}$ = 9.0 Hz, OCH_2), 6.04 (1 H, s, CH), 7.07–7.38 (4 H, m, ArH), 7.69 (2 H, br s, NH_2), 7.92–8.27 (4 H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.66, 21.17, 59.12, 63.45, 82.17, 127.11, 127.71, 128.93, 129.18, 129.34, 134.05, 135.11, 137.23, 137.26, 150.13, 153.49, 157.22, 164.55. Anal. Calcd (%) for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.88; H, 5.01; N, 11.19.

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