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One-Pot Four Component Synthesis of 3-Amino-1-(1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine Derivatives Mediated by [DBUH][OAc][1]

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Abstract—One-pot, four component, green, and efficient synthesis of 3-amino-1-(5-nitro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine derivatives by reaction of phthalic anhydride with hydrazine hydrate, 5-nitro-1*H*-indole-3-carboxaldehyde–indole-3-carboxaldehydes and malononitrile–ethyl cyanoacetate in the presence of [DBUH][OAc] at 60–65°C is developed. The method is characterized by short reaction time, high yields, and purity of products formed.

Keywords: [DBUH][OAc], green synthesis, one-pot reaction

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INTRODUCTION

Phthalazines are heterocycles that possess multiple biological activities such as antimicrobial [1], anticonvulsant [2], antifungal [3], anticancer [4], and anti-inflammatory [5]. Therefore, a number of methods of synthesis of phthalazine derivatives [6, 7] has been developed. Recently, synthesis of 1-aryl-1*H*-pyrazolo-[1,2-*b*]phthalazine-5,10-diones by one-pot, three component condensation of phthalhydrazide with malononitrile–ethyl cyanoacetate and benzaldehydes was reported [8–10]. 1-Aryl-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones were synthesized in a four component process of phthalic anhydride with hydrazine, malononitrile/ethyl cyanoacetate and benzaldehydes using basic ionic liquids, such as 1,8-diazabicyclo-[5.4.0]-undec-7-en-8-ium acetate [11], pyrrolidinium acetate [11] and TEA as a catalyst under ultrasound-sonication [12].

Ionic liquids (ILs) have attracted close attention due to their distinctive properties such as negligible vapour pressure, high thermal stability, wide liquid temperature range, easy recyclability, excellent chemical stability, and strong solvent power for a wide range of organic and inorganic compounds. By modification of cations and/or anions, the properties of ILs can be turned in many ways for various applications in organic synthesis [13–17]. DBU is a strong organic base and has been extensively applied in the base-induced reactions with excellent catalytic activity. However, separation of DBU from a reaction mixture is generally difficult. DBU-based ILs (DBU-ILs) overcome this drawback and exhibit the basicity similar to that of DBU accompanied by the general features of ILs [18].

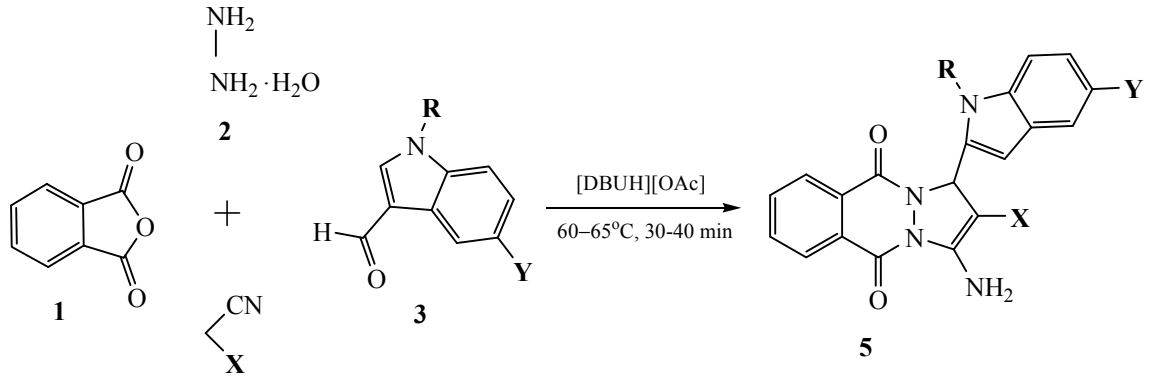
Based on the above, we report herein synthesis of 3-amino-1-(5-nitro/chloro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine derivatives by reaction of phthalic anhydride with hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate in the presence of [DBUH][OAc] at 60–65°C.

RESULTS AND DISCUSSION

Initial optimization of the one-pot four component reaction started with the reaction of phthalic anhydride **1** with hydrazine hydrate **2** in-situ and formation of phthalhydrazide as an intermediate in the presence of the ionic liquid. Addition of 5-nitroindole-3-carboxaldehyde **3a** and malononitrile **4a** to the above

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 3-amino-1-(1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine derivatives **5a–5h.**



Y = NO_2 (**3a, 5a, 5e**), H (**3b–3d, 5b–5d, 5f–5h**), R = H (**3a, 3b, 5a, 5b, 5e, 5f**), CH_3 (**3c, 5c, 5g**), C_2H_5 (**3d, 5d, 5h**), X = CN (**5a–5d**), COOEt (**5e, 5f–5h**).

reaction mixture in the presence of different ionic liquids ([DBUH][OAc], [bmim][Br] or [bmim][OH]) at room temperature led to formation of 3-amino-1-(5-nitro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile **5a.** This process was used in the following studies as a simple model method (see Table 1).

Following optimization of the process was carried out by using different ratio of the reagents in the range of temperature 20–80°C over various reaction time (Table 1). This approach allowed to work out the most favorable conditions of the synthesis (Scheme 1) that were the one-pot reaction of compound **1** (1 equiv.) with compounds **2** (1 equiv.), **3a** (1 equiv.) and **4a** (1 equiv.) in the presence of [DBUH][OAc] as a medium (5 equiv.), the reaction time 30 min and temperature range 60-65°C. These led to the highest yield (85%) of the product 3-amino-1-(5-nitro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile **5a** (see Table 1).

The structure of **5a** has been elucidated from ^1H and ^{13}C NMR, IR, and Mass spectroscopic data.

This newly developed synthetic method was successfully extended to malononitrile, indole-3-carboxaldehyde **3b** and its *N*-methyl and *N*-ethyl derivatives **3c, 3d** (Table 2).

The plausible mechanism of the process can be presented as follows (Scheme 2). In the first step, formation of phthalhydrazide X_1 is achieved by nucleophilic addition of hydrazine hydrate **2** to phthalic anhydride **1**, which is followed by dehydration. The second step involves formation of heterodiene Y_1 by the standard Knoevenagel condensation of indole-3-carboxaldehyde **3** with malononitrile or ethyl cyanoacetate **4**. In the third step, the Michael-type addition of phthalhydrazide X_1 to the heterodiene Y_1 leads to formation of the intermediate iminomethylene derivative which undergoes cyclisation affording **5**.

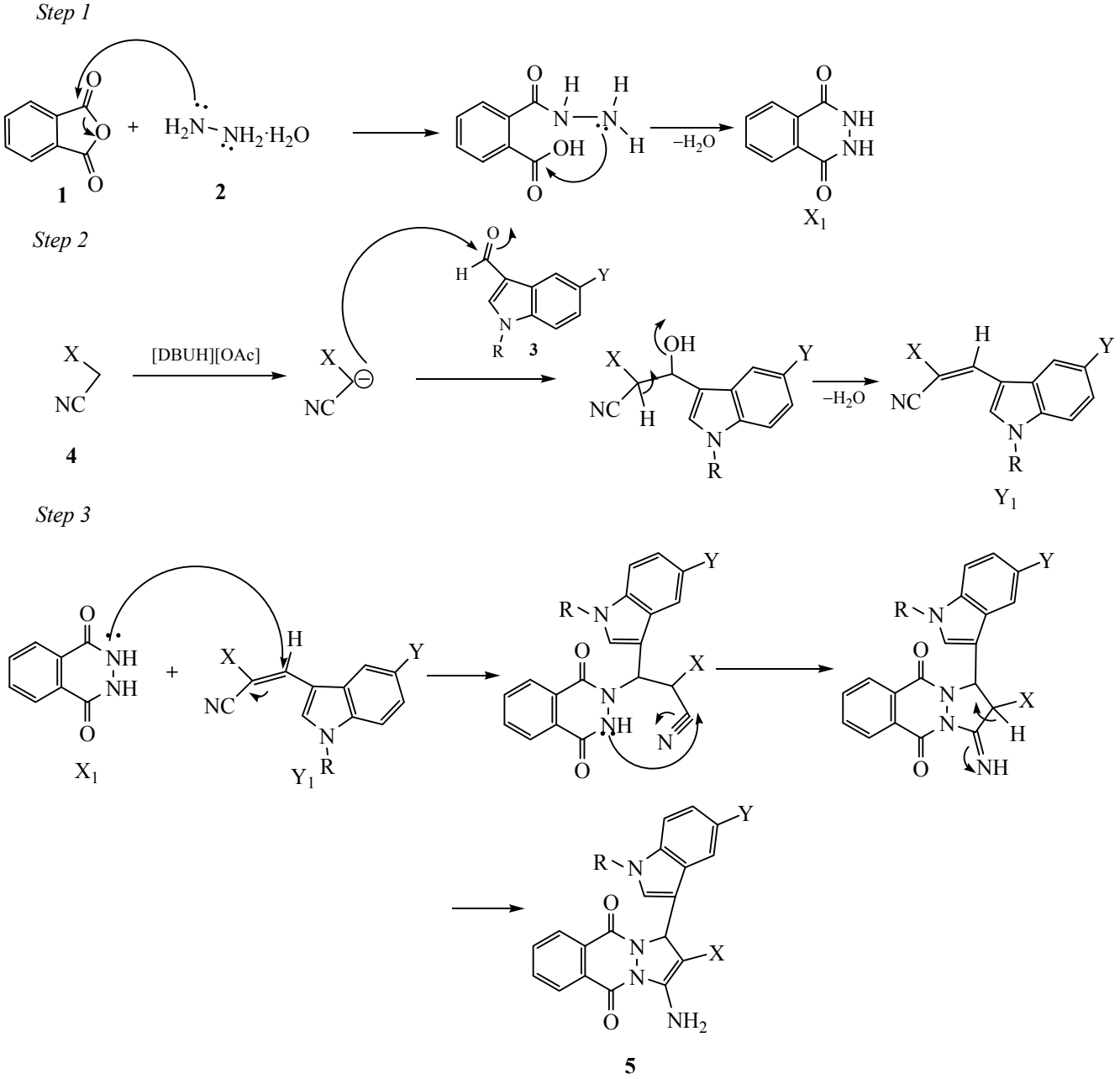
EXPERIMENTAL

Melting points were determined in open capillary tubes. TLCs were carried out on silica gel G and visualized by iodine vapour or under UV light. IR

Table 1. Effects of ionic liquids and the reaction conditions upon the yield of the compound **5a**

[Ionic liquid]/equiv.	Temprature, °C	Time, min	Yield of **5a,** %	[Ionic liquid/ equiv.	Temprature, °C	Time, min	Yield of **5a,** %
[DBUH][OAc]/5	Room temperature	120	65	[DBUH][OAc]/5	60	30	85
[bmim][Br]/5	Room temperature	240	60	[DBUH][OAc]/5	80	30	60
[bmim][OH]/5	Room temperature	180	55	[DBUH][OAc]/2	60	90	70
[DBUH][OAc]/5	40	90	75	[DBUH][OAc]/10	60	30	80

Scheme 2. Plausible mechanism for 3-amino-1-(1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine derivatives **5**.



spectra were recorded on a Perkin Elmer 1000 spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard at 400 MHz operating frequency. Mass spectra were measured on an Agilent-LCMS instrument.

General procedure of synthesis of 3-amino-1-(1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo-[1,2-*b*]phthalazine derivatives (5). Phthalic anhydride (**1**) (10 mM) and hydrazine hydrate (**2**) (10 mM) were added to [DBUH][OAc] (50 mM) and heated for 10 min at 60–65°C to form phthalhydrazide as an intermediate. Then, to this reaction mixture were added 5-nitroindole-3-carboxaldehydes (**3a**) (10 mM) and malanonitrile/ethylcyano acetate (**4**) (10 mM). The reaction mixture was heated for 20–35 min until no starting materials could be detected by TLC. Upon completion of the process, cold water was added and

Table 2. Synthesis data for compounds **5a–5h**

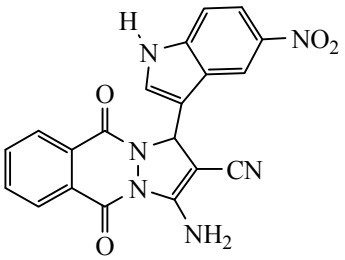
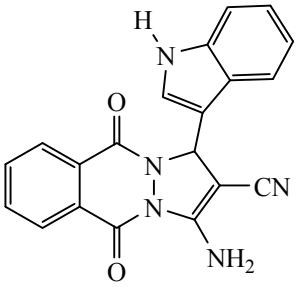
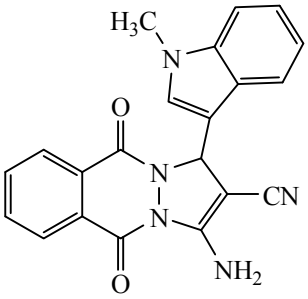
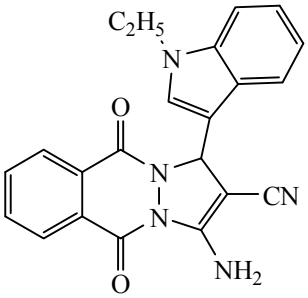
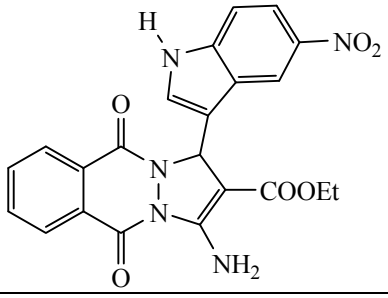
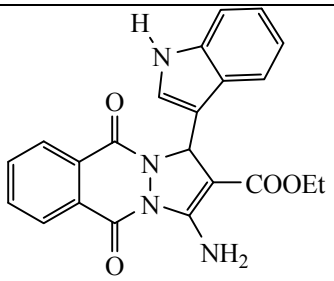
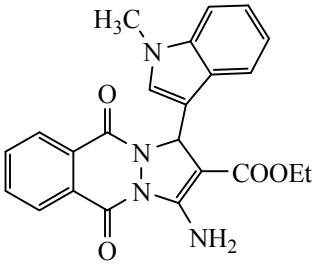
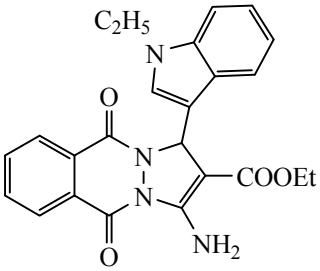
Comp. no.	Reagents				Product	Time, min	Yield, %
5a	**1**	**2**	**3a** (R = H, Y = NO_2)	**3a** (R = H, Y = NO_2)		30 30	30
5b	**1**	**2**	**3b** (R = H, Y = H)	**4a** (X = CN)		40	82
5c	**1**	**2**	**3c** (R = CH_3, Y = H)	**4a** (X = CN)		45	78
5d	**1**	**2**	**3d** (R = C_2H_5, Y = H)	**4a** (X = CN)		40	81
5e	**1**	**2**	**3a** (R = H, Y = NO_2)	**4b** (X = COOEt)		30	83

Table 2. (Contd.)

Comp. no.	Reagents				Product	Time, min	Yield, %
5f	**1**	**2**	**3b** (R = H, Y = H)	**4b** (X = COOEt)		45	82
5g	**1**	**2**	**3c** (R = CH_3, Y = H)	**4b** (X = COOEt)		45	82
5h	**1**	**2**	**3d** (R = C_2H_5, Y = H)	**4b** (X=COOEt)		40	81

thevsolid residue was filtered off. The corresponding product **5** was recrystallized from ethanol.

3-Amino-1-(5-nitro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5a). mp >220°C. IR spectrum, ν, cm^{-1}: 3116–3440 br.m (NH), 2218 s (CN), 1669 s (CO, amide), 1686 s (CO, amide). ^{1}H NMR spectrum, δ, ppm: 5.67 s (1H, CH), 7.26–8.68 m (10H, Ar-H, NH_2), δ 11.87 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 61.5, 69.1, 110.6, 111.5, 115.8, 115.9, 119.2, 122.9, 123.6, 127.6, 134.6, 135.6, 138.4, 144.6, 145.8, 161.6, 164.5. MS: *m/z*: 400 $[M + H]^+$.

3-Amino-1-(1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5b). mp >220°C. IR spectrum, ν, cm^{-1}: 3116–3440 br.m (NH), 2218 s (CN), 1669 s (CO, amide), 1686 s (CO, amide). ^{1}H NMR spectrum, δ, ppm: 5.67 s (1H, CH), 7.26–8.68 m (11H, Ar-H, NH_2), δ 11.87 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 61.0, 69.0, 110.1, 111.5, 115.9, 119.2, 122.9, 123.9, 127.3, 134.6, 135.8, 138.4, 144.6, 145.8, 161.0, 164.5. MS: *m/z*: 356 $[M + H]^+$.

3-Amino-1-(1-methyl-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5c). mp >220°C. IR spectrum, ν, cm^{-1}: 2213 s (CN), 1668 s (CO, amide), 1682 s (CO, amide). ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 5.30 s (1H, CH), 7.21–8.68 m (11H, Ar-H, NH_2). ^{13}C NMR spectrum, δ, ppm: 23.4, 60.1, 68.1, 111.3, 111.4, 114.8, 118.1, 122.9, 123.6, 127.4, 133.5, 134.7, 138.3, 144.2, 145.9, 161.4, 164.4. MS: *m/z*: 370 $[M + H]^+$.

3-Amino-1-(1-ethyl-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5d). mp >220°C. IR spectrum, ν, cm^{-1}: 2216 s (CN), 1663 s (CO, amide), 1678 s (CO, amide). ^{1}H NMR spectrum, δ, ppm: 1.81 t (3H, CH_3) 2.22 q (2H, CH_2), 5.26 s (1H, CH), 7.21–8.94 m (11H, Ar-H, NH_2). ^{13}C NMR spectrum, δ, ppm: 19.2, 23.2, 60.4, 68.5, 111.2, 111.5, 114.2, 118.2, 122.4, 123.2, 127.1,

133.0, 134.3, 138.2, 144.0, 145.2, 161.5, 164.9. MS: *m/z*: 384 $[M + H]^+$.

Ethyl-3-amino-1-(5-nitro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5e). mp >220°C. IR spectrum, ν, cm^{-1}: 3076–3360 m (NH), 2297 s (CN), 1660 s (CO, amide), 1666 s (CO, amide). ^1H NMR spectrum, δ, ppm: 1.32 t (3H, CH_3), 4.46 q (2H, CH_2), 6.02 s (1H, CH), 7.20–8.69 m (10H, Ar-H, NH_2), 11.79 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 14.0, 61.9, 69.1, 74.0, 110.6, 111.1, 115.8, 115.9, 119.1, 122.9, 123.6, 127.1, 134.6, 135.7, 140.6, 143.7, 151.6, 155.6. MS: *m/z*: 402 $[M + H]^+$.

Ethyl-3-amino-1-(1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5f). mp >220°C. IR spectrum, ν, cm^{-1}: 3112–3453 m (NH), 2204 s (CN), 1668 s (CO, amide), 1672 s (CO, amide). ^1H NMR spectrum, δ, ppm: 1.24 t (3H, CH_3), 4.18 q (2H, CH_2), 5.42 s (1H, CH), 7.22–8.68 m (11H, Ar-H, NH_2), 11.78 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 15.3, 55.2, 60.5, 68.1, 110.3, 111.4, 115.0, 117.2, 122.0, 123.5, 127.2, 133.0, 134.9, 137.3, 142.5, 144.5, 150.1, 156.4. MS, *m/z*: 403 $[M + H]^+$.

Ethyl-3-amino-1-(1-methyl-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5g). mp >220°C. IR spectrum, ν, cm^{-1}: 2213 s (CN), 1664 s (CO, amide), 1683 s (CO, amide). ^1H NMR spectrum, δ, ppm: 1.12 t (3H, CH_3), 2.24 s (3H, CH_3), 4.00 q (2H, CH_2), 5.42 s (1H, CH), 7.22–8.64 m (11H, Ar-H, NH_2). ^{13}C NMR spectrum, δ, ppm: 15.3, 22.5, 56.3, 61.4, 67.0, 111.4, 113.5, 114.7, 118.0, 122.0, 122.7, 125.0, 132.4, 134.6, 138.0, 144.1, 143.5, 152.2, 153.5. MS: *m/z*: 417 $[M + H]^+$.

Ethyl-3-amino-1-(1-ethyl-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (5h). mp >220°C. IR spectrum, ν, cm^{-1}: 2215 s (CN), 1666 s (CO, amide), 1673 s (CO, amide). ^1H NMR spectrum, δ, ppm: 1.18 t (3H, CH_3), 1.69 t (3H, CH_3) 2.39 q (2H, CH_2), 4.15 q (2H, CH_2), 5.26 s (1H, CH), 7.22–8.93 m (11H, Ar-H, NH_2). ^{13}C NMR spectrum, δ, ppm: 15.2, 19.4, 23.6, 54.3, 60.2, 68.4, 111.5, 111.7, 114.0, 118.1, 122.3, 124.1, 126.8, 133.4, 134.9, 138.1, 144.2, 145.5, 151.6, 154.6. MS: *m/z*: 431 $[M + H]^+$.

CONCLUSIONS

In summary, a novel method of synthesis of 3-amino-1-(5-nitro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine derivatives has been developed by the reaction of phthalic anhydride with hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate in the presence of [DBUH][OAc] at 60–65°C. This one-pot process is characterized by short reaction time, high yields and purity of products isolated.

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CONFLICT OF INTERESTS

No conflict of interests was declared by the authors.

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