HETEROCYCLES, Vol. 94, No. 8, 2017, pp. 1567 - 1572. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 8th May, 2017, Accepted, 8th June, 2017, Published online, 10th June, 2017
DOI: 10.3987/COM-17-13690

ONE-POT FOUR COMPONENT REACTION FOR THE SYNTHESIS OF 1-(1*H*-INDOL-2-YL)-1*H*-PYRAZOLO[1,2-*b*]PHTHALAZINE-5,10-DIONE DERIVATIVES BY SELF-CATALYSIS

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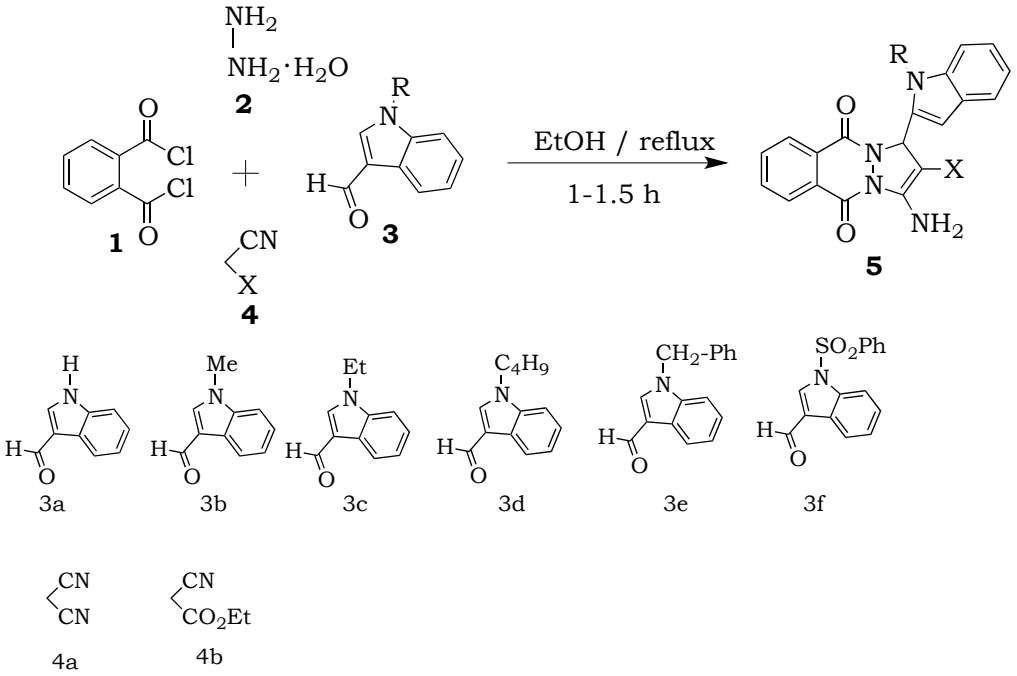
Abstract – In this, we performed a four component domino reaction of phthaloyl dichloride, hydrazine hydrate, indole-3-carboxaldehydes and malononitrile/ethyl cyanoacetate to form 1-(1*H*-indol-2-yl)-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives by *in situ* generation of HCl as catalyst in refluxing ethanol for 1 h in good yields. This four component domino reaction transformation presumably proceeds via addition/dehydrohalogenation/condensation/cyclization of reactions. The material was thoroughly characterized at various stages of its formation by means of FTIR, NMR spectroscopic and Mass spectrometric analysis and is confirmed to be the derivative of 1-(1*H*-indol-2-yl)-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione.

Phthalazines are important heterocycles that are known to possess multiple biological activities such as antimicrobial,[1] anticonvulsant,[2] antifungal,[3] anticancer,[4] and anti-inflammatory.[5] Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives.[6,7] Recently, the synthesis of 1-aryl-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives was reported by one-pot, three component condensation of phthalhydrazide, malononitrile/ethyl cyanoacetate and benzaldehydes using one of the following conditions:- a) In the presence of catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in ionic liquid, 1-butyl-3-methylimidazolium bromide ([bmim]Br), as solvent at 100 °C;[6a] b) using triethylamine (0.02 g, 20% mol) as catalyst in EtOH (5 mL) at 50 °C for 60 min under ultrasonication with a frequency of 50 kHz and an output power of 350 W;[6b] c) using 1-butyl-3-methylimidazolium hydroxide ([Bmim]OH) under irradiation in a single-mode microwave synthesis system at 100 W power and 45 °C.[8] The synthesis of 1-aryl-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives were also reported by one-pot, four component synthesis of phthalic anhydride, hydrazine, malononitrile/ethyl cyanoacetate and

benzaldehydes, using basic ionic liquids such as 1,8-diazabicyclo[5.4.0]undec-7-en-8-ium acetate,[9] pyrrolidinium acetate[9] and triethylamine as catalyst under ultrasound-sonication.[6b] The latter synthesis (i.e. four component reaction) is very similar to the previous synthesis (i.e. three component reaction) except for the fact that the phthalhydrazide has been prepared from phthalic anhydride and hydrazine hydrate *in situ*. By keeping in view of these facts and in continuation to the work on phthalic anhydride by other groups,[10] we now wish to report intensive and extensive study of the four component domino reaction of 1-(1*H*-indol-2-yl)-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives from phthaloyl dichloride, hydrazine hydrate, indole-3-carboxaldehydes and malanonitrile/ethyl cyanoacetate by in situ generation of HCl as a catalyst in ethanol.

In this letter, we have developed an efficient method for the synthesis of 1-(1*H*-indol-2-yl)-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives in the presence of ethanol. In order to optimize the reaction conditions, firstly, we investigated the effect of different solvents at different temperatures on the reaction rate and also products yield. As a model reaction, the reaction of phthaloyl dichloride (**1**), hydrazine hydrate (**2**) was stirred in refluxing ethanol at rt (room temperature) for 10 min to form phthalhydrazide as intermediate by dehydrochlorination (HCl) which was very useful as a catalyst to proceed further reaction. Then, to this reaction mixture were added indole-3-carboxaldehyde (**3a**) and malanonitrile (**4a**) and further stirred for 1 h in refluxing ethanol to form 1-(1*H*-indol-2-yl)-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione (**5a**) (**Table 1**, entry 1). The structure of the product was assigned on the basis of its spectral properties -IR, NMR and Mass spectra (for details, please see the experimental section). Then, this domino reaction was done in various solvents (EtOH, MeOH, DMF and DMSO). However, it was found that the four-component domino reaction of **1**, **2**, **3a** and **4a** in refluxing ethanol gave reasonably high yield (90%) of the product **5a** (**Table 1**, entry 1).

In the following step, the scope and efficiency of the process was explored under the optimized conditions for the synthesis of title compounds (**Table 2**). For this purpose, structurally diverse indole-3-carboxaldehyde (**3a-3f**) and malanonitrile/ethyl cyanoacetate (**4a-4b**) were condensed with phthaloyl dichloride (**1**) and hydrazine hydrate **(2**) in refluxing ethanol for 1-2 h (**Scheme 1**) and the results were displayed in **Table 2**. The structures of the products were assigned on the basis of its spectral properties, FTIR (**Figure S1** in Supporting Information), ^{1}H NMR (**Figure S2**), ^{13}C NMR (**Figure S3**) and Mass spectrometry (**Figure S4**) (for details, please see the experimental section).

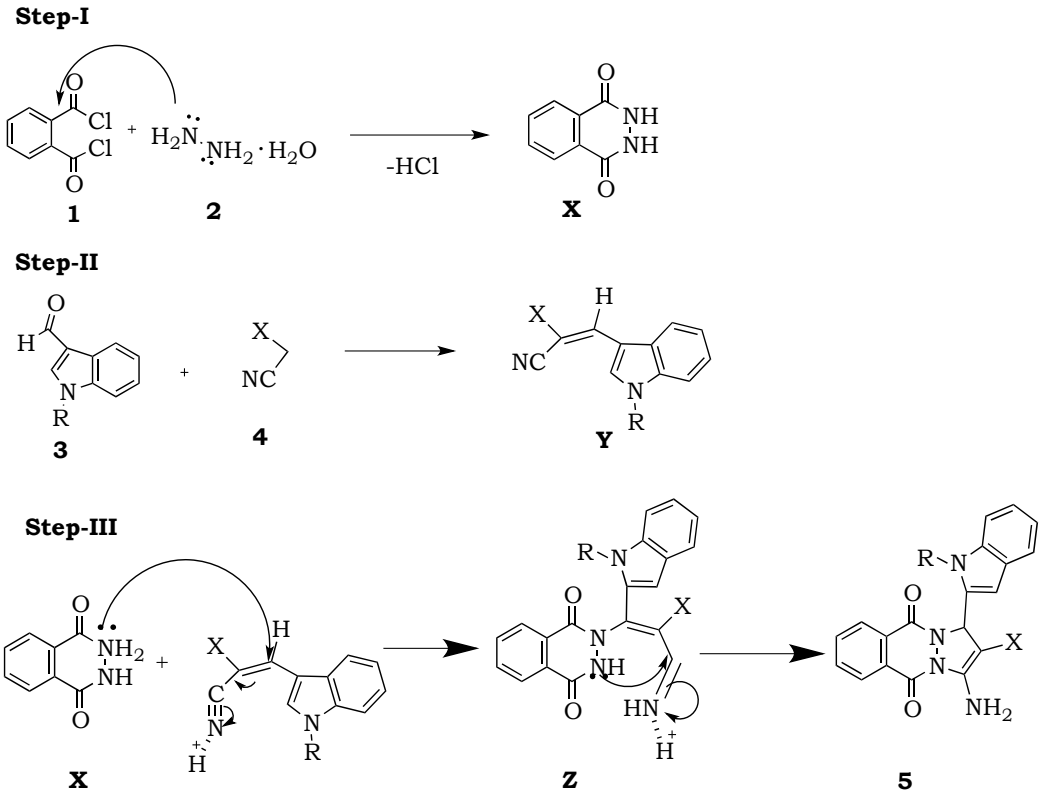


Scheme 1

Table 1. Effect of solvent on the reaction of **1**, **2**, **3a** and **4a** at rt yielding **5a**

Entry	Solvent	Temperature	Time (h)	5a (%)
1	EtOH	reflux	1	90
2	MeOH	reflux	1.5	85
3	DMF	100 ºC	2	70
4	DMF	140 ºC	1.5	65
5	DMSO	100 ºC	2	70
6	DMSO	140 ºC	1.5	65
7	MeCN	reflux	2	75
8	THF	reflux	2	30
9	$CHCl_3$	reflux	2	35

A schematic representation of reaction mechanism for the synthesis of titled compounds (**5**) is shown in **Scheme 2**. This mechanism contains three steps. In the first step, the formation of phthalhydrazide (**X**) by the nucleophilic addition of hydrazine hydrate (**2**) to phthaloyl dichloride (**1**) followed by dehydrochlorination (HCl) was very useful as the catalyst to proceed further reaction. The second step involves the formation of heterodiene (**Y**) by standard Knoevenagel condensation of indole-3-carboxaldehyde (**3**) and malanonitrile/ethyl cyanoacetate (**4**) in the presence of HCl. Then, in the third step, Michael-type addition of the phthalhydrazide (**X**) to heterodiene (**Y**) to form intermediate i.e. iminomethylene derivative (**Z**) which undergoes cyclisation to afford the corresponding product **5** (**Scheme 2**).



Scheme 2. Plausible mechanism for **5** from **1**, **2**, **3** and **4**

Table 2. Characterization data, reaction time and yields of **5** obtained from **1**, **2**, **3** and **4** via one-pot, four component synthesis

Entry	Starting materials				Product	Yield
1	**1**	**2**	**3a**	**4a**	**5a**	85
2	**1**	**2**	**3b**	**4a**	**5b**	85
3	**1**	**2**	**3c**	**4a**	**5c**	80
4	**1**	**2**	**3d**	**4a**	**5d**	80
5	**1**	**2**	**3e**	**4a**	**5e**	75
6	**1**	**2**	**3f**	**4a**	**5f**	75
7	**1**	**2**	**3a**	**4b**	**5g**	80
8	**1**	**2**	**3b**	**4b**	**5h**	80
9	**1**	**2**	**3c**	**4b**	**5i**	80
10	**1**	**2**	**3d**	**4b**	**5j**	80
11	**1**	**2**	**3e**	**4b**	**5k**	75
12	**1**	**2**	**3f**	**4b**	**5l**	75

In summary, we have developed novel 1-(1*H*-indol-2-yl)-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives by one-pot, multi-component synthesis in a practical and green synthetic method with good yields.

EXPERIMENTAL

Phthaloyl chloride (**1**) and hydrazine hydrate (**2**) was refluxed in EtOH for 10-15 min to form phthalhydrazide as intermediate and HCl. Now, to this reaction mixture, indole-3-carboxaldehyde (**3**) and malanonitrile/ethyl cyanoacetate (**4**) were added and again refluxed for 50-60 min. The completion of the reaction was checked by TLC. After that, ice-cold water (50 mL) was added to the reaction mixture, the solid that separated out was filtered, washed with water (10 mL) and dried. The product was recrystallized from suitable solvent to obtain **5**. Physicochemical properties (mp, ^{1}H and ^{13}C NMR, MS) of **5a-l** were summarized as Supporting Information.

The melting points were determined in open capillary tubes in sulfuric acid bath. TLC was run on silica gel–G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin–Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO-d_6 using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 values only.

ACKNOWLEDGEMENTS

The authors are grateful to the Deanship of Scientific Research, King Saud University for funding through Vice Deanship of Scientific Research Chairs program.

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