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ONE-POT SYNTHESES OF 1H-PYRAZOLO[1,2-B]PHTHALAZINE-5,10-DIONES IN MOLTEN TBAB

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Abstract
One-pot, four component syntheses for the preparation of 1-H Pyrazolo[1,2-b]phthalazine-5,10-diones **(5a-5h)** have been achieved from phthaloyl dichloride **(1)** , hydrazine hydrate **(2)**, benzaldehydes **(3)** and malononitrile **(4a)** or ethyl cynoacetate **(4b)** in molten Tetrabutylammonium Bromide as medium at 100-105 ^{o}C for 20-30 min by in-situ generation of HCl as a catalyst. These reactions have an easy workup, provide excellent yields, and use TBAB as the reaction medium.

Keywords: TBAB, phthaloyl dichloride, one-pot syntheses, green syntheses.

Introduction:

Multi component reactions were known for over 100 years[I]. They are playing efficient role in modern and combinatorial chemistry because of their potential to prepare small drug like molecules with several degree of structural diversity [II-III]. Multi-component reaction is a reaction in which either three or more different components react at a time to form a final product where most, if not all of the atoms are take part in the final product. This reaction tool allows heterocyclic molecules to be prepared in a few steps and usually in a multi component reaction[IV].

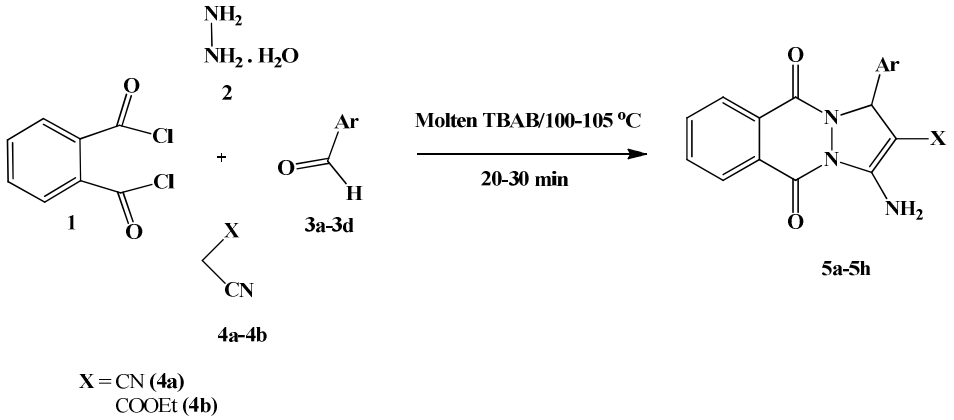
Phthalazines are important heterocyclic compounds that are known to possess biological activities such as antimicrobial[V], anticonvulsant[VI], antifungal[VII], anticancer[VIII] and anti-inflammatory[IX]. Therefore, a number of methods have been reported for the preparation of phthalazine derivatives[X-XI]. Recently, syntheses of 1-aryl-1H-Pyrazolo[1,2-b]phthalazine-5,10-diones were reported by one-pot, three component condensation of phthalhydrazide, malononitrile/ ethyl cynoacetate and benzaldehydes by using following reaction conditions:- a) By using a catalytic amount of p-toluenesulfonic acid and in ionic liquid [bmim]Br as a solvent at 100 ^{o} C [XII] ; b) Using triethylamine as a catalyst in ethanol at 50 ^{o} C for 60 min under ultrasonication with a frequency of 50 kHz and an output power of 350 W [XIII] c) using

[bmim]OH as ionic liquid under irradiation in a single-mode microwave oven at 100Wpower and 45 ^{o}C [XIV] .The syntheses of 1-aryl-1H-Pyrazolo[1,2-b]phthalazine-5,10-diones also were reported by one-pot, four component synthesis phthalic anhydride, hydrazine, malononitrile/ ethyl cynoacetate, benzaldehydes using basic ionic liquids such as 1,8-diazabicyclo[5,4,0]-undec-7-en-8-ium[XV] acetate,pyrrolidinium acetate[XI] and triethylamine[XII] as catalyst under ultrasound-sonication[XIII] .The latter syntheses (i.e. four component reaction) are very similar to the previous syntheses (i.e. three component reaction) except for the fact that phthalhydrazide has been prepared from phthalic anhydride and hydrazine hydrate in situ in this reaction.

Keeping these results in our mind and in continuation of earlier work on phthalic anhydride[XVI], we now report intensive and extensive study of the four component domino reaction of 1-H-Pyrazolo[1,2-b]phthalazine-5,10-diones **(5a-5h)** from phthaloyl dichloride **(1)** , hydrazine hydrate **(2)**, benzaldehydes **(3)** and malononitrile **(4a)** / ethylcyanoacetate **(4b)** by in-situ generation of HCl as a catalyst in molten TBAB for 20-30 min.

Results and Discussion:

As illustrated in **Scheme -1**, the reaction of phthaloyl dichloride **(1)** with hydrazine hydrate **(2)** in TBAB heated to melt at 100-105 ^{o}C for 5 min led to the in-situ formation of phthalhydrazide as intermediate by dehydrochloronation (HCl) which was very useful as a catalyst to proceed with the further reaction. Then, benzaldehyde **(3a)** and malononitrile **(4a**) were added and maintained the reaction mixture at same temperature in molten TBAB for 10 min. Processing the reaction mixture led to the isolation of 1-H-Pyrazolo[1,2-b]phthalazine-5,10-dione **(5a) (Table-1 entry-1)** as the final product. Then, this reaction was examined by carrying out the multi component reaction with **1, 2, 3a** and **4a** in the presence of different solvents (Glycerol, PEG-600, ethylene glycol, DMF& DMSO) at 100 ^{o}C **(Table 1)**. However, multi component reaction of **1, 2, 3a & 4a** in molten TBAB at 100 ^{o}C for 20 min was found to be the best method giving **5a** in purity with good yield (≥ 90%) (**Table-1, entry1)**. Therefore, Molten TBAB was chosen as the reaction medium for the further study at 100 ^{o}C.



Scheme-1. Syntheses of 1-H Pyrazolo[1,2-b]phthalazine-5,10-diones **(5a-5h)**

Table-1. Effect of solvent on reaction of **1**, **2, 3a & 4a** at 100^{o}C yielding **5a.**

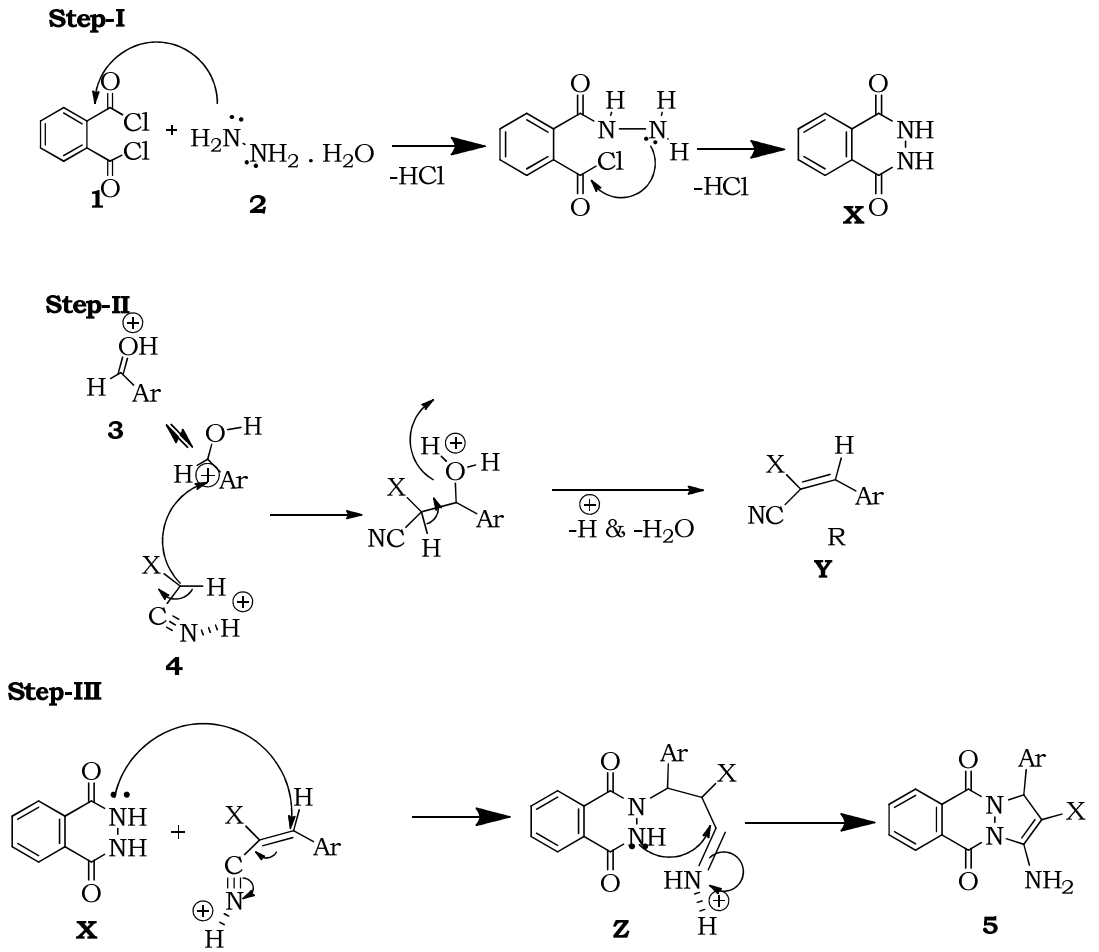
Entry	**Solvent**	**Temperature ^{o}C**	**Time (min)**	**5a (%)**
1	**Molten TBAB**	**100**	**20**	**90**
2	Glycerol	100	120	73

3	PEG-600	100	120	76
4	Ethylene glycol	100	150	69
5	DMF	100	150	72
6	DMSO	100	150	64

% Refers isolated yields only

The generality of this four-component reaction was examined by optimized conditions with benzaldehydes and active methylenes to obtain **5a-5h**. The results have been summarized in **Table 2.** Generally, the reactions that employed aromatic aldehydes containing electron-withdrawing or electron donating groups at different positions produced the corresponding products **5** in good yields. Electron donating groups at aromatic aldehydes produced less yields compared to electron-withdrawing groups at aromatic aldehydes . The structures of the products have been established from their spectral properties. (^{1}H- NMR, ^{13}C-NMR) and also by comparison with reported[XIII,XV&XVII] literature.

A schematic mechanism for the synthesis of titled compounds **5** can be postulated as shown in **Scheme 2**. This mechanism contains three steps. In the first step, formation of phthalhydrazide **X** by nucleophilic addition of hydrazine hydrate **(2)** to phthaloyl dichloride (**1)** followed by dehydrochloronation (HCl) which was used as a catalyst to proceed further reaction. The second step consists in the formation of olefin **(Y)** by standard Knoevenagel condensation of benzaldehydes and malononitrile ethyl cyanoacetate . Then, in the third step, Michael-type addition of the phthalhydrazide **X** to activated olefin **Y** takes place forming the intermediary enamine derivative **Z** which undergoes cyclisation affording **5**. **(Scheme-2)**



Scheme-2. Plausible mechanism for the synthesis of 5.

Table-2

Entry	Starting Materials				Product	Yield≠	M.P (Lit M.P)
1	1	2	3a (Ar= -Ph)	4a (X= CN)	**5a**	90	275-276 (276-278)[13]
2	1	2	3b (Ar = 2-Cl-Ph)	4a (X= CN)	**5b**	87	259-260 (259-261)[13]
3	1	2	3c (Ar = 4-Br-Ph)	4a (X= CN)	**5c**	87	263-265 (265-267)[9]
4	1	2	3d (Ar = 2-NO_2-Ph)	4a (X= CN)	**5d**	88	229-230 (228-230)[11]
5	1	2	3a (Ar= -Ph)	4b (X=COOEt)	**5e**	89	230-231 (232-234)[11]
6	1	2	3b (Ar = 2-Cl-Ph)	4b (X=COOEt)	**5f**	84	265-267 (266-267)[9]
7	1	2	3c (Ar = 4-Br-Ph)	4b (X=COOEt)	**5g**	86	207-208 (205-206)[9]
8	1	2	3d (Ar = 2-NO_2-Ph)	4b (X=COOEt)	**5h**	88	232-233 (230-232)[11]

≠ Refers to yields of isolated products only.

Conclusion

In summary, we have developed title compounds by one-pot, four-component syntheses in practical and green synthetic method with good yields. This method contain short reaction time, mild conditions with simple work-up procedure and environmentally benign process.

Experimental section

Melting points were uncorrected and determined in sulphuric acid bath in open capillary tubes.TLC was run on silica gel –G and visualization were done by using iodine or UV light.IR spectra were recorded using Perkin-Elmer 1000 instrument. ^{1}HNMR and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as internal standard. Mass spectra were recorded on Agilent-LCMS instrument.

General procedure for the synthesis of 5a-5h.

Phthaloyl chloride **(1)** (10 mM) and hydrazine hydrate **(2)** (10 mM) was heated at 100-105 ^{o}C in TBAB for 10 min to form phthalhydrazide as intermediate and in-situ generate the HCl. Then, substituted benzaldehydes **(3)** (10 mM) and malononitrile **(4a)** or ethyl cynoacetate **(4b)** (10 mM) in succession, and the mixture maintained at same temperature for 10-20 min. After completion of the reaction, ice-cold water (50ml) was added to the reaction mixture and neutralized with 10% sodium bicarbonate solution; the solid that separated out was filtered, washed with water (10 ml) and dried. The product was recrystallized from suitable solvent to obtain final compounds.

5a: IR (KBr) : 3191-3360 cm^{-1} (-NH- group), 2197 (-CN- group),, 1681 cm^{-1} (-CO- group), 1660 cm^{-1} (-CO- group); ^{1}H- NMR (DMSO-d_6, 400 MHz): δ 6.12 (s, 1H, -C**H**), 7.32 (m, 3H, Ar-**H**), 7.44 (s, 2H, N**H$_2$**), 7.95 (d, 2H, Ar-**H**), 8.03 (m, 3H, Ar-**H**), 8.26 (m, 1H, Ar-**H**); ^{13}C-NMR (DMSO- d $_6$, 100 MHz): δ 61.4, 62.9, 115.9, 126.6, 126.7, 127.2, 128.2, 128.4, 128.6, 128.7, 133.6, 134.6, 138.3, 150.5, 153.6, 156.6; HRMS calcd for $C_{18}H_{12}N_4O_2$ $[M+H]^+$: 317.09652. Found: 317.09380.

5b: IR (KBr) : 3181-3370 cm^{-1} (-NH- group), 2190 (-CN- group), 1683 cm^{-1} (-CO- group), 1662 cm^{-1} (-CO- group) ; ^{1}H- NMR (DMSO- d $_6$, 400 MHz): δ 6.20 (s, 1H, -C**H**), 7.22 (m, 2H, Ar-**H**), 7.32 (s, 2H, N**H$_2$**), 7.82 (d, 2H, Ar-**H**), 8.13 (m, 3H, Ar-**H**), 8.23 (m, 1H, Ar-**H**); ^{13}C-NMR (DMSO- d $_6$, 100 MHz): δ 61.3, 62.8, 115.3, 126.2, 126.5, 127.3, 128.1, 128.5, 128.7, 128.8, 133.3, 134.2, 138.2, 150.4, 153.5, 156.8; HRMS calcd for $C_{18}H_{11}ClN_4O_2$ $[M+H]^+$: 351.18653. Found: 351.18967.

5c: IR (KBr) : 3190-3390 cm^{-1} (-NH- group), 2180 (-CN- group), 1689 cm^{-1} (-CO- group), 1669 cm^{-1} (-CO- group) ; ^{1}H- NMR (DMSO- d $_6$, 400 MHz): δ 6.10 (s, 1H, -C**H**), 7.12 (d, 2H, Ar-**H**), 7.40 (s, 2H, N**H$_2$**), 7.92 (d, 2H, Ar-**H**), 8.13 (m, 3H, Ar-**H**), 8.23 (m, 1H, Ar-**H**); ^{13}C-NMR (DMSO- d $_6$, 100 MHz): δ 61.0, 62.3, 115.5, 126.1, 126.2, 127.3, 128.2, 128.8, 128.9, 128.9, 133.4, 134.1, 138.3, 150.2, 153.4, 156.6; HRMS calcd for $C_{18}H_{11}BrN_4O_2$ $[M+H]^+$: 395.28423. Found: 395.28034.

5d: IR (KBr) : 3200-3410 cm^{-1} (-NH- group), 2210(-CN- group), 1680 cm^{-1} (-CO- group), 1668 cm^{-1}(-CO- group); ^{1}H- NMR (DMSO- d $_6$, 400 MHz): δ 6.21 (s, 1H, -C**H**), 7.31 (m, 2H, Ar-**H**), 7.34 (s, 2H, N**H$_2$**), 7.65 (d, 2H, Ar-**H**), 8.23 (m, 3H, Ar-**H**), 8.29 (m, 1H, Ar-**H**); ^{13}C-NMR (DMSO- d $_6$, 100 MHz): δ 61.1, 62.4, 115.3, 126.0, 126.0, 127.2, 128.0, 128.5, 128.8, 128.9, 133.4, 134.0, 138.2, 150.1, 153.2, 156.5; HRMS calcd for $C_{18}H_{11}N_5O_3$ $[M+H]^+$: 362.13310. Found: 362.13612.

5e: IR (KBr) : 3180-3390 cm^{-1} (-NH- group), 1732 (-CO- group), 1680 cm^{-1} (-CO- group), 1670 cm^{-1} (-CO- group) ; ^{1}H- NMR (DMSO- d $_6$, 400 MHz): δ 1.22 (t, 3H, -C**H$_3$**), δ 3.88 (q,

2H, -C**H$_2$**), δ 6.13 (s, 1H, -C**H**), 7.22 (m, 3H, Ar-**H**), 7.24 (s, 2H, N**H$_2$**), 7.93 (d, 2H, Ar-**H**), 8.02 (m, 3H, Ar-**H**), 8.28 (m, 1H, Ar-**H**); ^{13}C-NMR (DMSO- d $_6$, 100 MHz): δ 14.0, 58.9, 61.3, 61.8, 114.8, 124.5, 125.1, 128.0, 128.3, 128.3, 128.7, 128.8, 133.4, 134.3, 138.0, 150.2, 153.2, 156.5, 162.2; HRMS calcd for $C_{20}H_{17}N_3O_4$ $[M+H]^+$: 364.13041. Found: 364.13441.

5f: IR (KBr) : 3162-3370 cm^{-1} (-NH- group), 1722(-CO- group), 1685 cm^{-1} (-CO- group), 1674 cm^{-1}(-CO- group); ^{1}H- NMR (DMSO- d $_6$, 400 MHz): δ 1.12 (t, 3H, -C**H$_3$**), δ 3.98 (q, 2H, -C**H$_2$**), δ 6.03 (s, 1H, -C**H**), 7.31 (m, 2H, Ar-**H**), 7.43 (s, 2H, N**H$_2$**), 7.94 (d, 2H, Ar-**H**), 8.02 (m, 3H, Ar-**H**), 8.36 (m, 1H, Ar-**H**); ^{13}C-NMR (DMSO- d $_6$, 100 MHz): δ 14.2, 58.5, 61.5, 61.9, 114.3, 124.0, 124.2, 125.1, 126.2, 127.2, 127.4, 128.3, 132.3, 133.4, 137.1, 151.3, 153.3, 155.1, 160.2; HRMS calcd for $C_{20}H_{16}ClN_3O_4$ $[M+H]^+$: 398.24039. Found: 398.24339.

5g: IR (KBr) : 3012-3360 cm^{-1} (-NH- group), 1713 (-CO- group), 1675 cm^{-1} (-CO- group), 1670 cm^{-1}(-CO- group); ^{1}H- NMR (DMSO- d $_6$, 400 MHz): δ 1.30 (t, 3H, -C**H$_3$**), δ 3.76 (q, 2H, -C**H$_2$**), δ 6.04 (s, 1H, -C**H**), 7.24 (m, 3H, Ar-**H**), 7.32 (s, 2H, N**H$_2$**), 7.86 (d, 2H, Ar-**H**), 8.24 (m, 3H, Ar-**H**), 8.28 (m, 1H, Ar-**H**); ^{13}C-NMR (DMSO- d $_6$, 100 MHz): δ 14.4, 56.6, 61.4, 61.7, 113.2, 120.3, 124.3, 124.9, 126.1, 126.7, 126.9, 128.2, 132.0, 133.3, 136.0, 150.2, 153.2, 154.0, 161.3; HRMS calcd for $C_{20}H_{16}BrN_3O_4$ $[M+H]^+$: 442.13242. Found: 442. 13642.

5h: IR (KBr) : 3100-3364 cm^{-1} (-NH- group), 1712 (-CO- group), 1679 cm^{-1}(-CO- group), 1672 cm^{-1} (-CO- group) ; ^{1}H- NMR (DMSO- d $_6$, 400 MHz): δ 1.20 (t, 3H, -C**H$_3$**), δ 3.86 (q, 2H, -C**H$_2$**), δ 6.02 (s, 1H, -C**H**), 7.30 (m, 2H, Ar-**H**), 7.40 (s, 2H, N**H$_2$**), 7.90 (d, 2H, Ar-**H**), 8.13 (m, 3H, Ar-**H**), 8.25 (m, 1H, Ar-**H**); ^{13}C-NMR (DMSO- d $_6$, 100 MHz): δ 14.2, 56.4, 61.2, 61.5, 113.1, 120.2, 124.4, 124.8, 126.4, 126.6, 126.8, 128.1, 132.1, 133.3, 136.0, 150.2, 153.1, 154.0, 161.0; HRMS calcd for $C_{20}H_{16}N_4O_5$ $[M+H]^+$: 409.12567. Found: 409.12867.

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