

DABCO Catalyzed One Step Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione in aqueous medium

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Abstract:

The green and sustainable approach for one step multicomponent synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione by using malononitrile, phthalhydrazide and arylaldehyde in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) as catalyst in aqueous medium. The present synthetic methodology have several advantages like mild reaction condition, operational simplicity, short reaction time, high yield of the product easy work-up procedure and environment sustainable protocol.

Keywords: Multicomponent reactions, DABCO catalyst, 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione aqueous medium.

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I. INTRODUCTION:

Multicomponent reactions (MRC) play an important role in modern synthetic organic chemistry. It is most efficient tools which have significant features that contribute an ideal strategy for synthetic methodology. As compared with classic reaction strategies, MRCs have significant advantages like greater efficiency, high yield of product with short reaction time, irreversible product. All the above mentioned features of MRCs, it acts as a powerful synthetic tool for the synthesis of heterocyclic compounds [1-2]. Aqueous medium for organic transformation have several advantages such as a safe, cheap, non-toxic and environmentally friendly alternative. Breslow in 1980 represents a number of various organic transformations have been takes place in aqueous medium with special properties like outstanding enhancements such as grater selectivity and faster reaction rate in number of organic synthesis [3]. Recently 1,4-diazabicyclo[2.2.2]octane (DABCO) has been used in variety of organic transformation in the form of solid catalyst. It has received considerable attention due to their significant features like high reactivity, inexpensive, easy to handle, non-toxic and ecofriendly. This catalyst used in organic synthesis which affording the corresponding products in excellent yield within short reaction time with high selectivity [4-5]. Heterocyclic compounds are important class of organic chemistry which is widely occur in nature and these are essential for life [6-8]. Number of heterocyclic compounds containing phthalazine moiety and they shows important biological and pharmacological properties [9-11]. The phthalazine moiety has considerable attention due to their biological activities such as cardiotoxic, vasorelaxant, cytotoxic, anticancer, antimicrobial, antifungal, anti-inflammatory and anticonvulsant activities [12-19].

II. RESULT AND DISCUSSION:

Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione achieved by mixture of malononitrile, phthalhydrazide and arylaldehyde in the presence of DABCO as catalyst in aqueous medium at 60°C. The catalytic utility of DABCO is excellent for the synthesis of heterocyclic compounds. For this synthetic methodology, a solution of aldehyde, malononitrile and phthalhydrazide catalyzed by catalytic amount of DABCO (10 mol %) by stirring at room temperature. After certain period of time, the reaction took place exclusively and white compound was found to thrown out. By observing the product by TLC, it was found that the only first step of Knoevenagel condensation had taken place and phthalhydrazide remained as it is. When we keep the reaction for prolonged time, after five to six hours a small amount of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione was found on TLC. Then we explore this protocol for prolonged time but satisfactory yield was not obtained even after increasing the catalytic load of DABCO. It is because of high energy of activation required for proceeding the reaction or insolubility of phthalhydrazide in aqueous medium. Then we decide to change the reaction condition and set up reaction for different temperature such as 50°C, 55°C 60°C and we found that, at 60°C as usual the first Knoevenagel condensation took place rapidly between an aldehyde and malononitrile and corresponding cyanoolefin formed rapidly and after 10 min. of heating immediately a yellow coloured Phthalazine-dione were formed in good to excellent yield. Based on this methodology we have reported the synthesis of variety of its derivatives by varying different aliphatic as well as aromatic aldehydes.

For this organic transformation we have screened different solvents such as ethanol, methanol, isopropanol and water. It is observed that, there is not tremendous effect of solvent on the in yield and reaction time as compared with water as a solvent (Table 1.1).

Table 1.1 Effect of solvent on synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione

Solvent	Time (Min.)	Yield %
Water	20	95
Methanol	25	88
Ethanol	30	80

For the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione, We have screened the catalytic efficiency of the different base, and we found that, the organic base like piperidine the reaction mixture turns immediately into yellow coloured solution. The solidified compound did not obtain in liquid organic base. In case of MgO, reaction drives towards the product formation with low yield but the DABCO catalyze the reaction efficiently within short reaction time with high yield of product (Table 1.2).

Table 1.2 Effect of base on % yield.

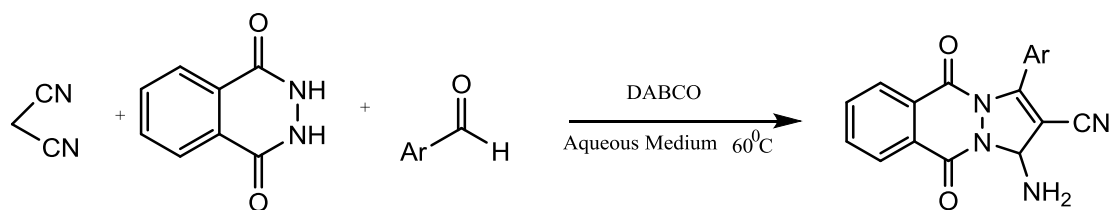
Base	Solvent	Time (Min.)	Yield (%) c
Piperidine	Water	10	-
Triethylamine	Water	10	-
Diethylamine	Water	10	-
Morpholine	Water	10	-
MgO	Water	20	60
DABCO	Water	20	95

As per Table 1.3 we have also screened different amount of catalyst load for this organic transformation. We have carried out this synthesis from 2mol % to 15mol % and we observed that, the increment in the catalyst amount over 10 mol % does not affect yield of the product (Table 1.3).

Table 1.3 Effect of catalyst DABCO on % yield of the product.

DABCO (mol %)	Yield (%)
2	62
5	70
10	95

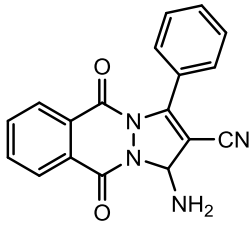
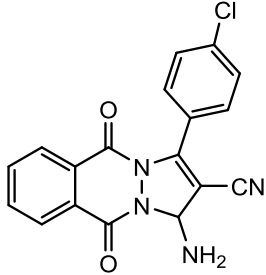
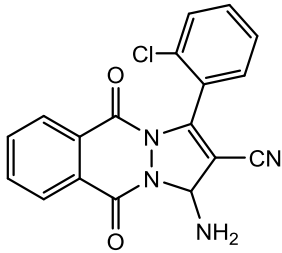
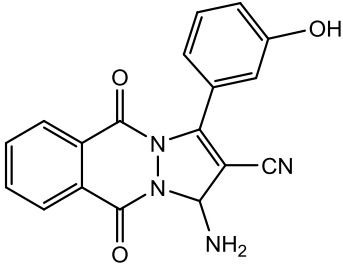
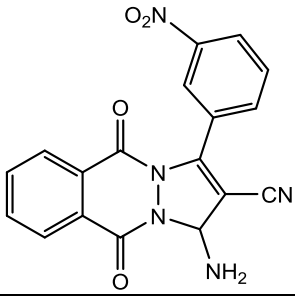
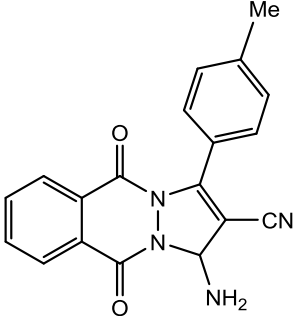
Due to dynamic catalytic efficiency of DABCO, we planned to explore the catalytic utility of DABCO for heterocycle synthesis. Herein we reported a greener one step multicomponent synthesis of pyrazolo[1,2-b]phthalazine- dione by using malononitrile, phthalhydrazide and arylaldehyde in the presence of 1, 4-diazabicyclo[2,2,2]octane (DABCO) as catalyst in water. (Scheme 1.1).

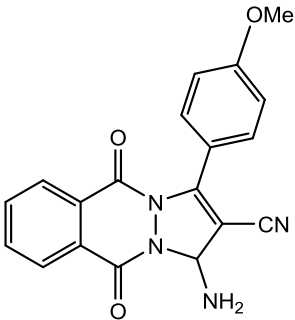
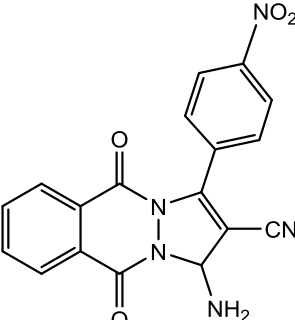
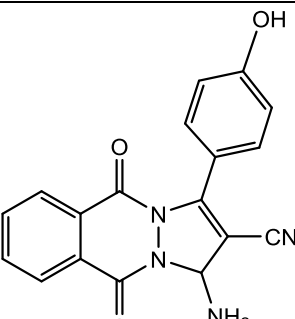
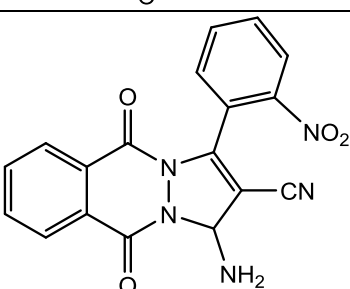
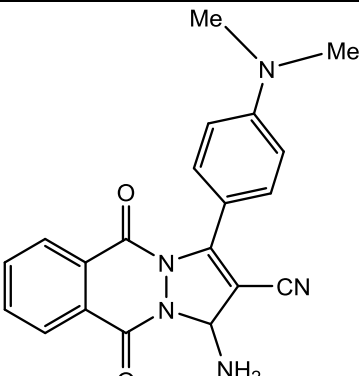


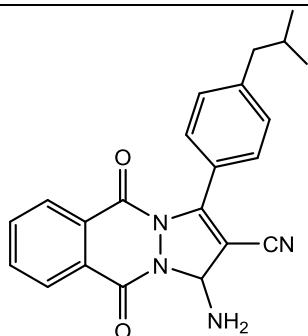
Scheme 1.1: Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione in aqueous medium

With this synthetic methodology we successfully prepared 1H-pyrazolo[1,2-b]phthalazine-5,10-dione in aqueous medium catalyzed by DABCO. This synthetic protocol have significant advantages such as greener and sustainable approach for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione, short reaction time, high yield of product, easy work-up procedure and mild reaction condition. For this transformation we have select number of aldehydes like aliphatic and aromatic but we observed that, aryl aldehydes containing both electron withdrawing and donating groups reacts with same affinity to give good yield of product within short reaction time (Table 1.4).

Table 1.4: Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione catalyzed by DABCO in aqueous medium.

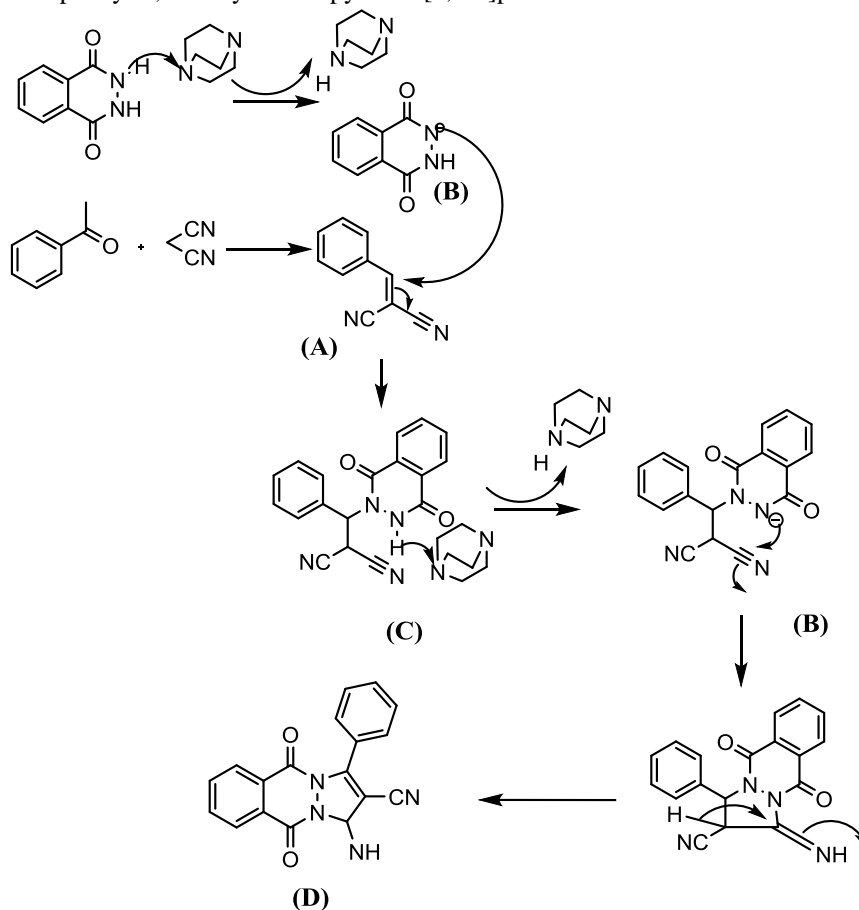
Entry	Product	Time (Min.)	Yield (%)
1		20	95
2		28	92
3		25	90
4		25	92
5		25	90
6		30	85

7		42	90
8		28	90
9		25	88
10		20	90
11		30	85



Plausible Mechanism

The plausible mechanism involves aryl aldehyde and malononitrile undergo Knoevenagel condensation to form cyanoolefin (A). The catalyst DABCO removes acidic N-H proton of phthalhydrazidetoform negatively charged species (B), which shows subsequent Michael addition on an electron deficient carbon atom of cyanoolefin gives a Michael adduct (C). Further nucleophilic addition of (B) across cyano group finally forms 3-amino-5,10-dioxo-1-phenyl-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile formed (D).



Experimental:

All chemicals were purchased from Loba and Sigma Aldrich chemical companies and used for the synthesis without further purification. Melting points were determined in a melting point apparatus and are uncorrected. The purity of compound observed by the TLC. The Fourier transform infrared spectroscopy was performed by FTIR, Lambda, Australia, in the form of diluted sample (10 wt.%) pressed into KBr pellets. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avon 300 MHz spectrometer using CDCl_3 as solvent and TMS as internal standard.

Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione:

A mixture of malononitrile (1 mmol), phthalhydrazide (1mmol), benzaldehyde (1 mmol) and DABCO (10 mol%) in water was heated at 60°C for 20 min. on an oil bath. The completion of reaction monitored by TLC. After cooling, the reaction mixture was filtered under vacuum and the residue recrystallized from methanol to afford pure product. The reaction mixture was poured on ice cold water and crude product obtained was filtered and recrystallized from ethanol.

Spectral Data:

1-Amino-5,10-dioxo-3-phenyl-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (Table 1.4, entry 1),

IR 3363, 3262, 2199, 1680 cm^{-1} , $^1\text{H NMR}$ δ 6.10(s, CH), δ 7.30-7.42(m, Ar-H) δ 8.05-8.25 (m, Ar-H) δ 7.90 (s, 2H), $^{13}\text{C NMR}$ δ 61, 63, 116, 127, 128, 129, 134, 135,138, 151, 154, 157 **Mass Spectra: (m/z)** 316 (M+).

1-amino-3-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (Table 1.4, entry 2)

IR 3362, 3304, 2196, 1658 cm^{-1} , $^1\text{H NMR}$ δ 6.12 (s, CH), δ 7.44-7.54 (m, Ar-H, J= 8.4 Hz) δ 7.90 (s,2NH), $^{13}\text{C NMR}$ (300 MHz) δ 60, 61, 110, 114, 117, 118, 126, 127, 128, 129, 132, 134, 136, 140, 152, 156,158, **Mass spectrum (m/z)** 351 (M+).

1-Amino-3-(2-chlorophenyl)-5,10-dioxo-5,10dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile(Table 1.4, entry 3)

IR 3372, 3298, 2210, 1659 cm^{-1} , $^1\text{H NMR}$ δ 6.43(s, CH), δ 7.30-7.41 (m,Ar-H), δ 8.30(s,2NH) $^{13}\text{C NMR}$ δ 60, 116, 124, 126, 127.17, 127, 128, 134, 148, 146, 151.62, 154. **Mass spectrum (m/z)** 351 (M+).

1-Amino-3-(3-hydroxyphenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (Table 1.4, entry 4)

IR 3372, 3304, 3268, 2192 1681 cm^{-1} , $^1\text{H NMR}$ 1H δ 3.45(s,OH), 5.97(s,CH), δ 6.65-7.10 (m,4Ar-H), δ 7.84-8.10 (m,4Ar-H), δ 8.24 (s,2NH), $^{13}\text{C NMR}$ δ 61, 63, 113, 115, 116, 117, 127, 127, 128, 128, 129, 133, 134, 150, 153, 156, 157 ppm, **Mass spectrum (m/z)** 333 (M)

1-Amino-3-(3-nitrophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (Table 1.4, entry 5)

IR 3365, 3292, 2192, 1651 cm^{-1} , $^1\text{H NMR}$ δ 6.30 (s,CH), δ 7.61-8.35 (m,Ar-H), $^{13}\text{C NMR}$ δ 61, 62, 116, 122, 123, 127, 127, 128, 129, 130, 134, 134, 140, 148, 151, 154, 157 ppm, **Mass spectrum (m/z)** 361 (M+).

III. CONCLUSION

We have demonstrated environmental sustainable a simple, ecofriendly and elegant protocol for the synthesis of pyrazolo[1,2-b]phthalazinedione using DABCO as catalyst in aqueous medium. This methodology proceeds with good efficiency in aqueous medium without use of any volatile organic solvent. Use of DABCO (1,4-diazabicyclo[2,2,2]octane) as a catalyst renders this method environmentally benign.

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