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ONE POT SYNTHESIS OF PYRAZOLO PHTHALAZINE DIONE DERIVATIVES UNDER MICROWAVE IRRADIATION

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ABSTRACT

In this method, we have reported the catalytic ability of boric acid as a green, eco-friendly catalyst for one-pot four component condensation reaction of phthalic anhydride, Monohydrate hydrazine, Malononitrile and substituted aromatic aldehyde was reported. The major synthetic protocol is the use of inexpensive, nontoxic, avoiding the use of harmful organic solvent, short reaction time, mild condition reaction, simple procedure, excellent yield and environmentally benign.

Keywords: Multicomponent Reaction, Green Synthesis, Pyrazolo Phthalazine Dione, Microwave Irradiation.

INTRODUCTION

Multicomponent condensation reactions (MCR) are more important in the synthesis of heterocyclic molecules. In presence of phthalazine and pyrazole heterocyclic ring system or fused ring with a different heterocyclic moiety, are in a number of pharmacologically emphasis molecules. In many cases, use of the classical method for the synthesis of heterocyclic compounds, however, these are simply no longer reaction time acceptable by current environmental and safety standard. All these reasons, the various possibilities offered by microwave synthesis are attractive high yield, fast or minimum time and environmentally benign are important advantages.

Nitrogen-containing bridgehead hydrazine heterocyclic compounds have attracted prominent interest due to their pharmacological properties, biological activities and clinical applications[1,2,3,4,5,6]. The pyrazolo phthalazine derivative expands in nature and their applications of biologically active pharmaceuticals, functional materials as well as agrochemicals.[7-10] Pyrazolo phthalazine dione derivatives show various biological activities such as Anticonvulsant[11], Cardiotonic[12], vasorelaxant[13], Cytotoxic[14], Anticancer[15], Antifungal[16], Anti-inflammatory[17], Antiviral[18], Antitumor[19], Anticoagulant[20], Antibacterial[21]and Ant hypoglycemic activity[22]. To develop a simple method for synthesis of pyrazolo phthalazine dione is important in organic synthesis.

Earlier reports revealed that one-pot four component synthesis of pyrazolo phthalazine dione derivatives have been prepared by using different catalytic system such as Et_3N[23] ,AL-KIT-6[23], [bmim] Br/PTSA[24], [bmim]OH[25], $NiCl_2.6H_2O$[26], $InCl_3$[27], CAN[28], $[(DBU)CH_3COO]$ [29], CuI NPs[30],$Zn(OAc)_2$[31] and $NiFe_2O_4$[32]. However, these strategies show different disadvantages related to green synthesis. The present method has less drawbacks such as short reaction time, use of a cheap catalyst and easy workup procedure.

Herein, we report the use of a catalyst as a boric acid non-toxic, inexpensive, easily available catalyst, for organic transformations to give excellent yield because of new numerous advantages associate with ecofriendly compound. The synthesis of pyrazolo phthalazine dione derivatives by one-pot four component condensation reaction of phthalic anhydride, Monohydrate hydrazine, substituted aromatic aldehyde and malononitrile (Scheme-1).

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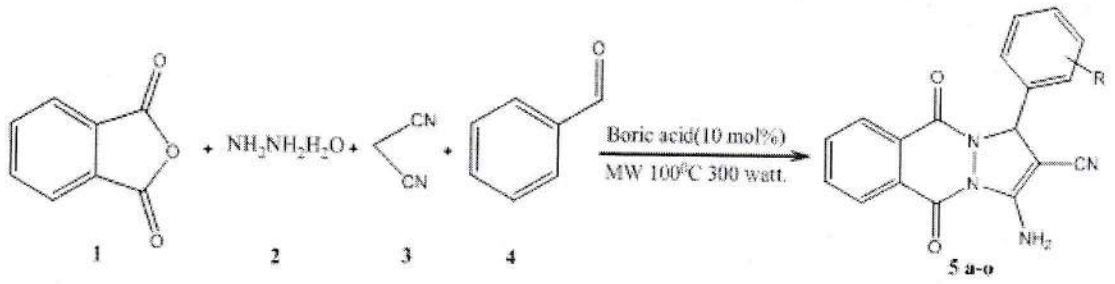


Scheme-1: Synthesis of Pyrazolo Phthalazine Dione Derivatives.

EXPERIMENTAL

Materials and Methods

All chemicals, solvents and reagents purchased from commercial sources.Melting points were taken in open capillary and are uncorrected. The reaction was carried out microwave synthesizer, mass-II, Sineo.^{1}H NMR spectra were recorded on a Bucker 300 instrument and IR was recorded in KBr pellets on a Nicolet impact.

General Reaction Procedure for Pyrazolo Phthalazine Dione Derivatives

A mixture of phthalic anhydride **1** (1 mmol) and monohydrate hydrazine **2**(1 mmol) were mixed at 80^{0}C for 15 min. then added Malononitrile**3** (1 mmol), aromatic aldehyde **4** (1 mmol) and boric acid (10 mol%) as a catalyst in round bottom flask were microwave irradiation at power 300 watt. At 100^0 C for 10 min. after completion of the reaction, the reaction mixture was added ice cold water then it filtered and recrystallized from methanol.

Spectral Data for Representative Compound

3-Amino-1-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (Yellow powder) (5b):MP 271-274^{0}C, IR (KBr, cm^{-1}); 3376, 3260, 2195, 1660, 1656; ^{1}H NMR ($CDCl_3$, 300MHz); 6.15 (1H, s, CH), 7.40-7.51 (4H, m, Ar), 7.95-8.25(6H, m, Ar & NH_2), ^{13}CNMR ($CDCl_3$, 100MHz): 61.4, 62.9, 116.4, 127.3, 127.8, 128.9, 129.4, 133.4, 134.4, 125.2, 137.01, 151.3, 154.2, 157.3.

3-Amino-1-(4-hydroxyphenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (Yellow powder)(5d):MP 270-273^{0}C, IR (KBr, cm-1); 3373, 3260, 2198, 1664, 1569,^{1}H NMR ($CDCl_3$, 300MHz); 6.03 (1H, s), 6.71-6.73 (2H, d, J=8 Hz, Ar), 7.23-7.25 (2H, d, J=8Hz, Ar), 7.96-8.25 (6H, m, Ar & NH_2), 9.52 (1H, s,), ^{13}CNMR ($CDCl_3$, 100MHz): 61.5, 62.7, 115.01, 116.3, 126.7, 127.4, 128.4, 128.7, 128.9, 133.5, 134.6, 150.6, 153.6, 156.5, 157.7.

3-Amino-5,10-dioxo-1-p-tolyl-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile(Yellow Powder)(5e): MP 252-254^{0}C, IR(KBr, cm-1) 3362,3260,2197,1657,1570, ^{1}H NMR ($CDCl_3$, 300 MHz); 2.29(3H, S, CH3), 6.08(1H, S,CH), 7.15-7.34(4H, m, Ar), 7.95-8.26(6H, m, Ar & NH_2),
^{13}C NMR ($CDCl_3$, 100 MHz); 121.3,62.4,64.01,123.2,123.5,127.5,127.7,127.9,128.2,128.8,130.3,130.9, 133.4,134.7,135.01,136.6,153.01,154.8,157.01

RESULTS AND DISCUSSION

The one-pot synthesis of pyrazolo phthalazine dione was possible by the one-pot four component cyclocondensation of phthalic anhydride (1), monohydrate hydrazine (2), aromatic aldehyde (3), and malononitrile (4) using boric acid as a catalyst. To optimized reaction condition using various solvents effects such as ethanol, tetrahydrofuran, dichloromethane, acetonitrile, methanol, ethylene glycol, PEG-200, PEG-400, toluene, water and solvent-free condition. We examined the reaction proceed in ethanol and tetrahydrofuran the product was obtained with a lower yield which took it more time (Table-1, entry 1-2). Then other solvents were uses like as dichloromethane and acetonitrile, they gave the low yield and consumed more time. (Table-1, entry 3-4). The solvents are toluene and ethylene glycol take more time in

complete reaction with less 48% and 67% yield respectively (Table-1, entry 5-6). The Solvents are PEG-200 and PEG-400 give good yields but in increasing long time reaction (Table-1, entry 7-8). The water and methanol used in reaction as a solvent which takes more time and obtained low yield (Table 1, entry 9-10). Therefore, we decided the reaction goes to solvent-free condition and give excellent yield with lesser time.

Table-1:Synthesis of Compound 5a in the Presence of Different Solvents.

Entry	Solvents	Time (Min.)	Yield[b](%)
1	EtOH	45	60
2	THF	120	40
3	CH_2Cl_2	50	53
4	CH_3CN	60	55
5	Toluene	480	48
6	Ethylene Glycol	300	67
7	PEG-200	80	87
8	PEG-400	90	89
9	H_2O	120	20
10	MeOH	60	50
11	Solvent-free	15	91

[a]Phthalic anhydride (1mmol), hydrazine monohydrate (1mmol), benzaldehyde (1mmol) and malononitrile (1mmol).
[b]Isolated yield.

To optimize all Lewis acid catalytic effect on multicomponent condensation reaction. The reaction was carried out in the same conditions, boric acid shows good catalytic role, which gave in product yield of 95% (Table-1, entry14). When used $FeCl_2$ and MgO as a catalyst, we observed5a in reasonably corresponding yield of 40% and 50% (Table-2, entry1-2). The reaction carried by Et_3N and CuBr they give the product in 45% and 61 % yields (Table-2, entry 3-4). The use of catalyst CuCl and $GaCl_3$ take the same reaction time and product obtained 55% and 35 % yield respectively (Table-2, entry5-6). Another catalyst ZnI_2, $MnCl_3$, Al-KIT-6, $InCl_3$, CAN, [bmim] Br/PTSA and these catalyst give low yield product and prolong reaction time 80%, 76%, 87%, 85%, 88%, 89%, yields respectively (Table-2, entry 7-12).
We determine the synthesis of pyrazolo phthalazine dione derivatives using boric acid using 10 mol% give large amount of yields. (Table-2, entry 14). When 5 mol% of boric acid was used to give 85% of yield. Hence, using 10 mol% of boric acid was suitable with an excess amount of catalyst which shows and no improvement, no increase in the yield was observed.

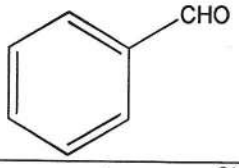
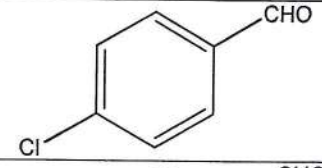
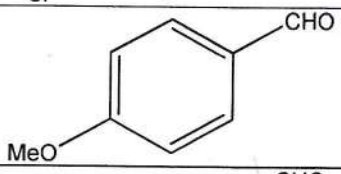
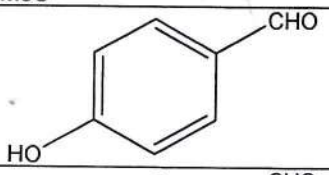
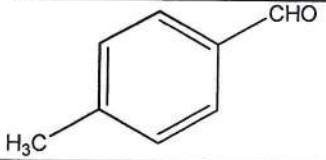
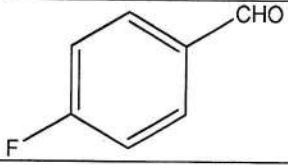
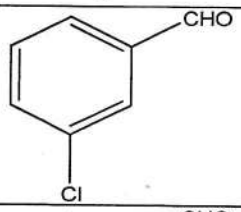
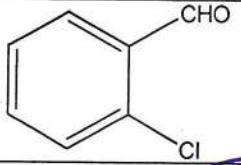
Table-2: Comparison of Synthesis for Pyrazolo Phthalazine Dione Derivatives Using Boric Acid and Different Catalyst.

Entry	Catalysts	Mol%	Time(Min.)	Yield[b](%)
1	$FeCl_2$	15	80	40
2	MgO	10	80	50
3	Et_3N	20	180	45
4	CuBr	10	45	61
5	CuCl	10	45	55
6	$GaCl_3$	10	100	35
7	ZnI_2	10	160	80
8	$MnCl_2$	10	180	76
9	Al-KIT-6	10	240	87
10	$InCl_3$	10	90	85
11	CAN	5	80	88
12	[bmim]Br/PTSA	10	180	89
13	Boric acid	5	20	85
14	Boric acid	10	15	91

[a]Phthalic anhydride (1mmol), hydrazine monohydrate (1mmol), benzaldehyde (1mmol) and malononitrile(1mmol).
[b]Isolated yield.

To investigate the various substituted aromatic aldehyde containing an electron donating or electron withdrawing groups reacted with phthalic anhydride, hydrazine monohydrate and malononitrile using boric acid as a catalyst. Almost all reaction with different aromatic aldehyde and obtained product with desired high yield within lesser reaction time. Aromatic substituted aldehyde reacts faster and higher yield compared to aliphatic aldehyde (Table-3).

Table-3: Synthesis of Pyrazolo Phthalazine Dione Derivative[a].

Entry	Aldehydes	Time (min.)	Yield[b](%)
5a		10	91
5b		12	93
5c		13	90
5d		11	90
5e		15	91
5f		10	93
5g		11	94
5h		13	92

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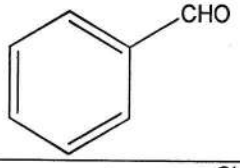
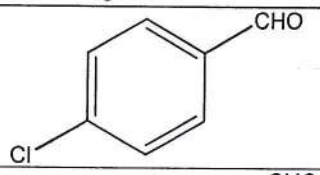
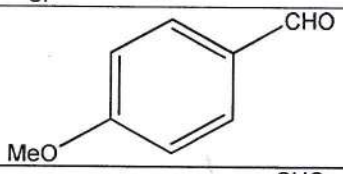
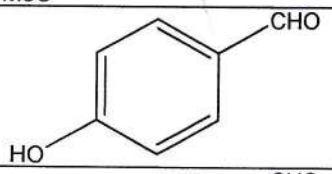
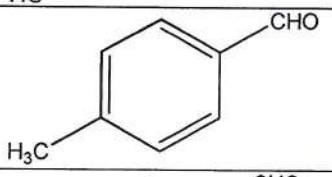
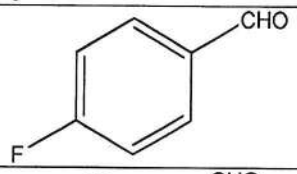
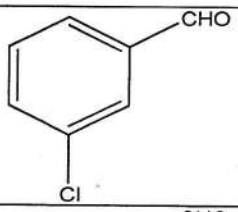
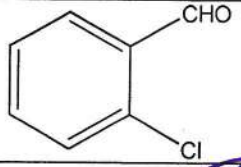
5a		10	91
5b		12	93
5c		13	90
5d		11	90
5e		15	91
5f		10	93
5g		11	94
5h		13	92

REFERENCES

1. W. R. Vaughan, *Chem. Rev.,* **43**, 447 (1948). **DOI:** 10.1021/cr60136a003
2. R.A. Clement, *J. Org. Chem.,***25**, 1724 (1960)
3. H.W. Heine, R. Henrie, L. Heitz, S.R. Kovvali, *J. Org. Chem.,***39**, 3187 (1974)
4. H.W. Heine, L.M. Aclawski, S.M. Bonser, G.D. Wachob, *J. Org. Chem.,***41**, 3229(1976), **DOI:** 10.1021/jo008829002
5. T. Sheradsky, R. Moshenberg, *J. Org. Chem.,***51**, 3123(1986), **DOI:** 10.1021/jo00366a008
6. L.N. Jungheim, S.K. Sigmund, *J. Org. Chem.,***52**, 4007 (1987)
7. E.C. Franklin, *Chem. Rev.,***16**, 305(1935) , **DOI:**10.1021/cr600559001
8. F.W. Bergstrom, *Chem. Rev.,***35**, 77(1944) , **DOI:**10.1021/cr601119001
9. F.W. Lichtenthaler, *Acc. Chem. Res.,***35**, 728(2002) , **DOI:**10.1021/ar010071i
10. M.R. Nabid, S.J.Tabatabaie, R. Gahremanzadeh, A. Bazgir, *Ultrason. Sonochem.,***17**, 159(2010), **DOI:**10.1016/j.ultsonch.2009.06.012
11. S. Grasso, G. DeSarro, N. Micale, M. Zappala, G. Puja, M. Baraldi, C.Demicheli, *J. Med. Chem.,***43**, 2851(2000) , **DOI:**10.1021/jm001002x
12. Y. Nomoto, H. Obase, H. Takai, M. Teranishi, J. Nakamura, K. Kubo, *Chem. Pharma. Bull.,***38**, 2179(1990) , **DOI:** 10.1248/cpb.38.2179
13. N. Watanabe, Y. Kabasawa, Y. Takase, M. Matsukura, K. Miyazaki, H. Ishihara, K. Kodama, H. Adachi, *J. Med. Chem.,***41**, 3367(1998) , **DOI:**10.1021/jm970815r
14. J.S. Kim, H.K. Rhee, H.J. Park, S.K. Lee, C. Lee, H.P. Choo, *Bioorg. Med. Chem.,***16**, 4545(2008) , **DOI:**10.1016/j.bmc.2008.02.049
15. S.S. El-Saka, A.H. Soliman, A.M. Imam, *Afinidad,* **66**, 167(2009)
16. C. Ryu, R. Park, M. Ma, J. Nho, *Bioorg. Med.Chem. Lett.,* **17**, 2577(2007), **DOI:** 10.1016/j.bmcl.2007.02.003
17. T. Nakamura, M. Sato, H. Kakinuma, *J. Med. Chem.,* **46**, 5416(2003) , **DOI:** 10.1021/jm020557k
18. M.J. Genin, C. Biles, B.J. Keiser, J. *Med. Chem.,* **43**, 1034(2000) , **DOI:**10.1021/jm990383f
19. F.Wei, B.X. Zhao, B. Huang, *Bioorg. Med. Chem. Lett.,* **16**, 6342(2006), **DOI:** 10.1016/j.bmcl.2006.09.008
20. Y. Xia, Z.W. Dong, B.X. Zhao, *Bioorg. Med. Chem.,* **15**, 6893(2007), **DOI:** 10.1016/j.bmc.2007.08.021
21. P.C. Lu, J. Sun, Y. Yang, H.L. Zhu, *Bioorg. Med. Chem. Lett.,* **15**, 4657(2010), **DOI:** 10.1016/j.bmcl.2010.05.105
22. N. Cho, M. Kamaura, T. Yogo, H. Imoto, WO 2009139340
23. G. Karthikeyana, A. Pandurangan, *J. Mol. Catal. A: Chem.,* **361-362**, 58(2012), **DOI:** 10.1016/j.molcata.2012.05.003
24. R. Ghahremanzadeh, G. Imani Shakibaei, A. Bazgir, *Synlett.,* **8**, 1129(2008), **DOI:** 10.1021/cc900130a
25. D.S. Raghuvanshi, K.N. Singh, *Tetrahedron Lett.,* **52**, 5702(2011) , **DOI:** 10.1039/c7ra02350b
26. S. Song, J. Zhong, Y. He, Z. Guan, *Tetrahedron Lett.,* **53**, 7075(2012), **DOI:** 10.1016/j.tetlet.2012.10.063
27. Y. D. Reddy, B. Suryanarayana, Ch. V.R. Reddy, P.K. Dubey, *Heterocyclic Lett.,* **4(3)**341(2014)
28. M. Kidwai, R. Chauhan, *J. Heterocyclic Chem.,* **51**, 1689(2014), **DOI:** 10.1002/jhet.1809
29. H.R. Shaterian, M. Mohammadnia, *J. Mol. Liq.,* **173**, 55(2012), **DOI:** 10.1016/j.molliq.2012.06.007
30. J. Safaei-Ghomi, H. Shahbazi-Alavi, A. Ziarati, R. Teymuri, M.R. Saberi, *Chin. Chem. Lett.,* **25**, 401(2014) , **DOI:**10.1016/j.cclet.2013.11.046
31. F. Mohamadpour, M. Lashkari, R. Heydari, N. Hazeri. *Indian Journal of Chemistry,* **57-B** 843(2017)
32. V.V. Dabholkar, S.K. Kurade, K.S. Badhe, *Der PharmaChemica.,* **10(6),** 135(2018)

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