Green and efficient phosphate fertilizers DAP, MAP and TSP as catalysts for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones under solvent-free condition

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(Received: 26 July 2016, accepted 25 October 2016)

Abstract: Phosphate fertilizers (Mono-Ammonium Phosphate: MAP, Di-Ammonium Phosphate: DAP and Triple Super Phosphate: TSP) have been used as efficient catalysts for the preparation of 1H-pyrazolo[1,2-b]phthalazine-5,10 -diones in one-pot cyclo-condensation reaction of phthalhydrazide, aromatic aldehyde and malononitrile or ethyl cyanoacetate under solvent free condition in good to excellent yields.This work provides a simple, efficient, and eco-friendly method for the construction of pyrazolo [1,2-b]phthalazine-5,10-dione derivatives.

Keywords: 1H-pyrazolo[1,2-b]phthalazine-5,10-diones; phosphate fertilizers; catalysts; Solvent-free; MAP, DAP and TSP.

INTRODUCTION

Multi-component reactions (MCRs) constitute a very powerful tool to synthesize diverse and complex heterocyclic compounds. They are considered to be superior synthetic strategies, with highly efficient atom economy compared to other organic reactions. Their advantages in terms of one pot multi-component reaction time, product yield, minimization of waste production, energy consumption and reproducibility have been repeatedly exploited in various efficient syntheses of heterocyclic compounds [1-11].

Their presence in the reaction of the bridgehead hydrazine has attracted considerable attention because the target products show a number of interesting pharmacological properties and biological activities [12]. For example, pyrazole derivatives are acknowledged to possess a wide range of bioactivities and exhibit important biological properties such as anti-inflammatory [13], antifungal [14], anticancer [15], antiviral [16], antitumor [17], anticoagulant [18], antibacterial (inhibitory activity against Escherichia coli FabH) [19] and antihypoglycemic activity [20-21]. In addition, phthalazine derivatives were reported to possess a multiplicity of pharmacological properties including antimicrobial [22], anticonvulsant [23], antifungal [24], anticancer [25], cardiotonic [26], vasorelaxant [27] activities. Pyrazolo[1,2-b] phthalazinedione derivatives have also been described as anti-inflammatory, analgesic, antihypoxic, and antipyretic agents [28]. The development of simple methods for the synthesis of pyrazolo[1,2-b]phthalazine-5,10-diones is therefore considered very important.

The synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones derivatives via the three-component coupling of aldehyde, malononitrile/ ethyl cyanoacetate and phthalhydrazide has been reported in the presence of diverse catalysts such as PTSA/[Bmim]Br (100°C, 3h) [29], Et_3N/EtOH [30], [Bmim]OH/MW [31], 1,8-diazabicyclo[5,4,0] -undec-7-en-8-ium acetate, (DBU[CH_3CO_2], (solvent-free) [32], Al-KIT-6 [33], $NiCl_2$,6 H_2O (ethanol/reflux) [34], $InCl_3$ [35], CuINP$_S$ [36], TBBDA or PBBS [37], CAN PEG 400 [38], and $Ni_{0.5}Zn_{0.5}Fe_2O_4$ Nano crystallites [39].

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Table I: Comparison between some catalysts described in the literature and ours.

Entry	Catalyst	Time (min)	Yield %
1	Neat	600	Trace
2	$NiCl_2$,6 H_2O	120	94[34]
3	$InCl_3$	25	94 [35]
4	$CuINP_S$	25	93 [36]
5	Fe-MCM-22	45	85 [41]
6	MAP	10	95
7	DAP	3	98
8	TSP	12	97

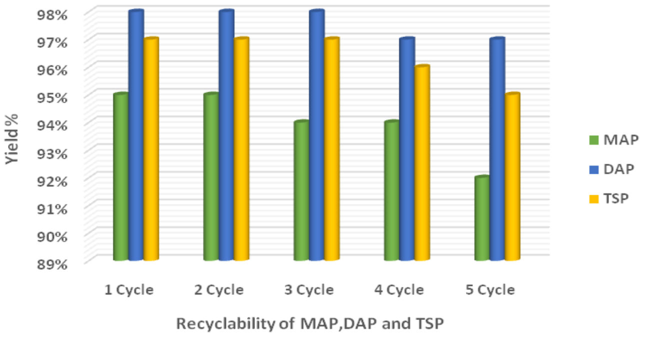


Fig. 1: Recyclability of catalysts for the synthesis of 1H-pyrazolo [1,2-b]phthalazine-5,10-dione.

In this work, we explored the possibility of synthesizing 1H-pyrazolo[1,2-b]phthalazine-5,10-diones using MAP, DAP or TSP as green catalysts [40] by the three component condensation reactions of phthalhydrazide, aromatic aldehydes and malononitrile or ethyl cyanoacetate under solvent-free condition.

EXPERIMENTAL

Material and methods

All chemicals were purchased from Merck or Fluka Chemical Companies. The known products were identified by comparison of their melting points and spectral data with those reported in the literature. TLC using silica gel SIL G/UV 254 plates monitored progress of the reactions. Infrared spectra were carried out on a Tensor 27 spectrometer using KBr pellets. Melting points were determined using a Kofler hot stage apparatus and are uncorrected.

General procedure of synthetic 1H-pyrazolo [1,2-b]phthalazine-5,10-diones

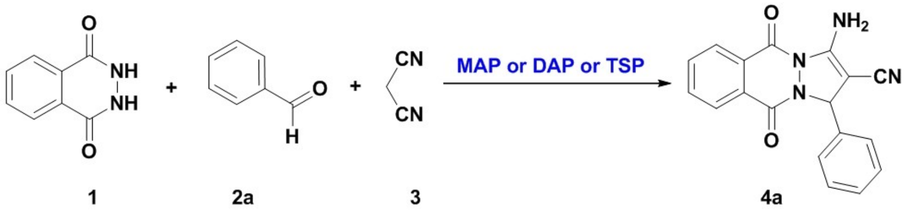
To a mixture of aromatic aldehyde (1 mmol), malononitrile or ethyl acetocetate (1 mmol) and phthalhydrazide (1 mmol) was added 1 mol% of catalyst (MAP, DAP or TSP). The mixture was stirred at 80 °C under solvent-free condition for a specific time, after completion of the reaction (monitored by TLC).The resulting crude solid residue was recrystallized from MeOH to afford the pure product.

RESULTS AND DISCUSSION

Initially we have synthesized 1H-pyrazolo[1,2-b] phthalazine-5,10-dione by the one-pot condensation of phthalhydrazide (1), benzaldehyde (2a) and malononitrile (3) in the presence of MAP, DAP or TSP as catalyst under solvent-free condition at 80°C. This reaction was selected as a model system for the optimization study (Scheme 1).

First, a series of comparative experiments were performed to compare the effectiveness of the catalysts MAP, DAP or TSP versus other catalysts in the formation of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione (Table I) .

Then, we examined the effect of the solvents on the above reaction. The results in Table II indicate that the different solvents affected the efficiency of the reaction. Yields were poor for DMF, butanol, isopropanol, dioxane and tetrahydrofuran (Entries 3, 4, 5 and 8). Better yields were obtained using more polar solvents like methanol, ethanol and acetonitrile (Entries 1, 2 and 6). However, the best results were obtained under solvent-free condition.



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

Table II: Influence of the solvent on the reaction[a].

Entry	Solvent (1 mL)	Time (min)			Yield %[b]		
		MAP	**DAP**	**TSP**	**MAP**	**DAP**	**TSP**
1	Ethanol	60	45	35	80	82	89
2	Methanol	60	45	35	83	86	90
3	Butanol	45	40	30	40	32	56
4	Isopropanol	90	60	50	60	56	50
5	DMF	180	120	60	38	40	44
6	Acetonitrile	55	45	35	77	81	76
7	THF	75	70	40	68	70	53
8	Dioxane	120	90	55	52	66	48
9	Solvent-free	25	12	20	84	90	90

[a] Reaction of benzaldehyde (1 mmol), phthalhydrazide(1 mmol) and malononitrile (1 mmol) catalysts MAP, DAP or TSP under solvent-free condition at 80 °C.

[b] Isolated yield.

Recently, organic synthesis involving multicomponent reactions under solvent-free condition has attracted much attention. We therefore explored the possibility of obtaining the target compounds under solvent-free condition. We found that the condensation reaction proceeds smoothly in much shorter time and at moderate temperature to synthesize products in high yields, while minimizing the amount of organic waste generated in each process.

The results obtained from the reaction to determine the optimum amount of catalyst are presented in Table II. As can be seen from this Table, the best results were obtained by using 1 mol% of MAP, DAP or TSP as catalyst (Table III, entry 1).

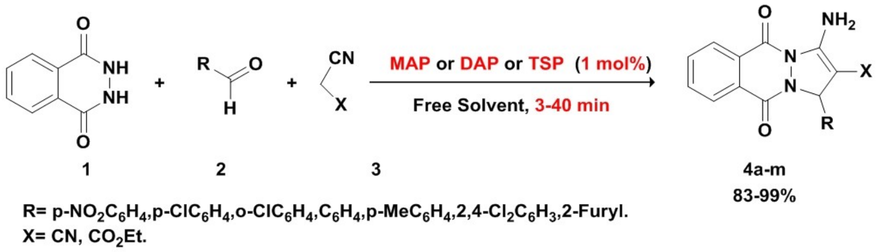
One of the most important features of the present protocol is the recyclability and reusability of the catalyst. The reusability was also investigated after the completion of the same model reaction under optimized conditions. For this purpose, hot ethanol

Table III: Optimization of amount of catalyst[a].

Entry	Amount of catalyst	Time (min)			Yield %[b]		
		MAP	**DAP**	**TSP**	**MAP**	**DAP**	**TSP**
1	1 mol%	10	3	12	95	98	97
2	2 mol%	12	3	12	95	98	97
3	3 mol%	15	5	12	93	96	97
4	4 mol%	15	5	12	93	96	97
5	5 mol%	15	5	12	90	94	97
6	6 mol%	20	6	15	89	94	96
7	7 mol%	20	10	15	89	91	96
8	8 mol%	24	10	20	84	90	95
9	9 mol%	30	15	20	80	89	95
10	10 mol%	35	20	20	79	87	95

[a] Reaction of benzaldehyde (1 mmol), phthalhydrazide(1 mmol) and malononitrile (1 mmol) catalysts MAP, DAP or TSP (1 mol%) under solvent-free condition at 80 °C.

[b] Isolated yield.



Scheme 2. Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives using MAP, DAP or TSP as catalysts.

was added to the mixture reaction and the solid catalyst was filtered. Then, the catalyst was washed with acetone two times,and then dried in the oven for the further reactions. It is interesting to note that the supported catalyst could be recycled five consecutive times without any significant loss of activity (Fig. 1).

Encouraged by these remarkable results, we then investigated the scope and versatility of the process. Substituted aromatic aldehydes (electron-donating or -withdrawing groups) reacted successfully with malononitrile or ethyl cyanoacetate and phthalhydrazide to provide 1H-pyrazolo [1,2-b]phthalazine-5,10-dione derivatives (scheme 2) in high yields. The results listed in Table IV indicated clearly that the reaction can be generalized and the nature of the reactants does not significantly modify the contact time in the mentioned conditions.

CONCLUSION

Attractive features of this method using phosphate fertilizers as catalysts are a simple procedure, a cleaner reaction, and the use of a reusable catalyst. Furthermore, this procedure allows easy workup and easy multicomponent reactions performed under solvent-free condition.

Table IV: Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives[a].

Entry	R	X	Time (min)			Yield %[b]			Mp°C	
			MAP	**DAP**	**TSP**	**MAP**	**DAP**	**TSP**	**Found**	**Reported**
4a	C_6H_5	CN	10	3	12	95	98	97	>260	275-277 [41]
4b	4-MeC_6H_4	CN	20	15	18	87	91	90	253-255	253-255 [36]
4c	2-ClC_6H_4	CN	12	10	10	96	99	98	>260	259-261 [41]
4d	4-ClC_6H_4	CN	6	3	5	95	99	98	>260	272-274 [41]
4e	4-$NO_2C_6H_4$	CN	8	5	5	89	93	90	228-230	228-229 [41]
4f	2-Furyl	CN	30	12	15	83	90	87	>260	288-290 [43]
4g	2,4-$Cl_2C_6H_3$	CN	20	11	15	90	94	92	242-244	242-244 [44]
4h	C_6H_5	CO_2Et	25	15	20	87	90	89	113-115	113-115 [42]
4i	4-MeC_6H_4	CO_2Et	30	10	12	90	97	95	205-207	205-207 [43]
4j	2-ClC_6H_4	CO_2Et	15	8	10	87	96	92	236-238	236-238 [42]
4k	4-ClC_6H_4	CO_2Et	25	10	12	91	96	94	116-168	116-168 [42]
4l	4-$NO_2C_6H_4$	CO_2Et	10	5	7	89	92	91	230-232	230-232 [42]
4m	2-Furyl	CO_2Et	40	25	30	86	93	90	>260	272-274 [38]

[b] Isolated yield.

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