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A Green and Efficient Process for the Synthesis of Benzothiazinones using Phosphate Fertilizers MAP, DAP and TSP as Heterogeneous Catalysts

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Abstract: The aim of this work is to demonstrate the efficiency of the phosphate fertilizers mono-ammonium phosphate (MAP), di-ammonium phosphate (DAP), and triple-super phosphate (TSP) as a "green" heterogeneous catalyst for the synthesis of 2-aryl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones *via* the C-S and C-N coupling process of *gem*-dicyano epoxide with α-aminothiophenol. To optimize the reaction conditions, the synthesis was conducted with a range of solvents, catalyst amounts, and particle sizes of the catalyst. Also, the recyclability potential of the catalysts was confirmed by using the recycled catalyst.

Keywords: Heterogeneous catalyst, phosphate fertilizer, MAP, DAP, TSP, Benzothiazinone.

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INTRODUCTION

To date, benzothiazinone (BTZ) skeleton have been extensively used as pharmacophore group for the construction of numerous biologically active compounds such as anti-tubercular (1), antimicrobial (2), allosteric modulator (3), inhibitor of glycogen synthase kinase 3β (3), monoamine oxidase B inhibitors (4), adenosine A2A receptor antagonists (4), antioxidant (5), anti-candida (6) and antitumor agents (7).

Currently, BTZ compounds were identified as a possible new class of acetylcholinesterase inhibitors for curing the symptoms of Alzheimer's disease (8).

In continuation of evaluation of BTZ's properties, Ghailane et al. (9) were able to classify some BTZ derivatives as anticorrosive agents for mild steel in 1M HCl based on quantum chemical studies and electrochemical measurements.

Given the importance of BTZ heterocyclic systems, they have been the object of several synthetic studies. For example, BTZ derivatives were successfully synthesized by the condensation of α-aminothiophenol with aryltrichlorocarbinol (10), or dibromonitroacrylates (11), from methyl 2-iodobenzoate and cyclic thiourea (12) or 2-mercaptoacetate and substituted 2-iodoanilines (13) via the Cu-catalyzed coupling processes. In attempts to establish a green approach to elaborate new derivatives of BTZ, Sharifi et al. (14) developed a green synthesis of various benzothiazinones via the condensation of 2-bromoalkanoates with α-aminothiophenol using ball milling and KF-Al_2O_3 support. Recently, new, facile, and regio-controlled methods to obtain BTZ derivatives by reacting α-aminothiophenol with different electron acceptor epoxides were reported (15). Therefore, the improvement of these methods in terms of reaction time, product purity and yield is highly desirable given environmental considerations.

MAP, DAP, and TSP are ones of the most important and popular members of phosphate fertilizers family due to their composition rich in nitrogen (from NH_4^+ (MAP, DAP)), phosphorus (from PO_4^{3-} (MAP, DAP, TSP)) and calcium (from Ca (TSP)). Nowadays, they prove to be eco-friendly, economically and highly active heterogeneous catalysts for Knoevenagel condensation (16), 2,3-dihydroquinazolin-4(1H)-one synthesis (17) and synthesis of 1-(benzothiazolylamino) methyl-2-naphthol derivatives (18).

As part of our previous efforts to valorize phosphate fertilizers (16) we describe herein a 'green' optimization of the one-pot synthesis of BTZ derivatives from *gem*-dicyano epoxide **1** as described by Ghailane et al. (15) using MAP, DAP and TSP fertilizers as novel heterogeneous and reusable catalysts.

EXPERIMENTAL

Chemicals and instruments

Chemicals were purchased from Fluka or Aldrich Companies. Catalysts MAP, DAP and TSP, were purchased from OCP group. They are marked as mention in our previous work (16). Mono-Ammonium Phosphate: MAP 11-52-00 - Binary Fertilizer, complex granule with Nitrogen: 11% N and Phosphorus: 52% P_2O_5. Di-Ammonium Phosphate: DAP 18-46-00 - Binary Fertilizer, complex granule with Nitrogen: 18% N and Phosphorus: 46% P_2O_5.Triple Super Phosphate: TSP 00-46-00 - Simple granule Fertilizer with Phosphorus: 46% P_2O_5.

All known compounds were identified by comparing their melting points with literature data. Melting points were recorded on a Wagner & Munz HEIZBANK Kofler bench.

Separation of catalyst's particles according to their size

The catalyst was crushed and sieved on a mechanical sieve shaker to provide different size of catalyst particles. Three different powders of catalysts MAP, DAP and TSP were tested in this work. The first (designated F_1) comprised catalyst powder in size range of 36-71 µm. The second (designated F_2) was of the size range between 71 and 90 µm. The last powder tested (designated F_3) comprised between 91 and 120 µm.

General experimental procedure for the phosphate fertilizers MAP, DAP and TSP catalyzed the one-pot synthesis of 2-(*p*-tolyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one, 3a

Into a 25 mL round-bottomed flask equipped with a reflux condenser and mechanical stirrer were placed 2 mmoles of epoxide **1**, 2 mmoles of α-aminothiophenol **2** dissolved in 3 mL of acetonitrile. 10 mol% of catalyst was then added to the mixture. The latter was stirred for an appropriate time. The progress of the reaction was monitored by TLC, eluted with chloroform/petroleum ether (2:1). After completion of the reaction, the mixture was filtered to separate the catalyst. Then, the solvent of the filtrate was removed under vacuum, and the oily residue obtained was triturated with a mixture of diethyl ether and petroleum ether (9:1) to give 2-arylbenzothiazin-3-one as a solid which was collected and crystallized from ethanol.

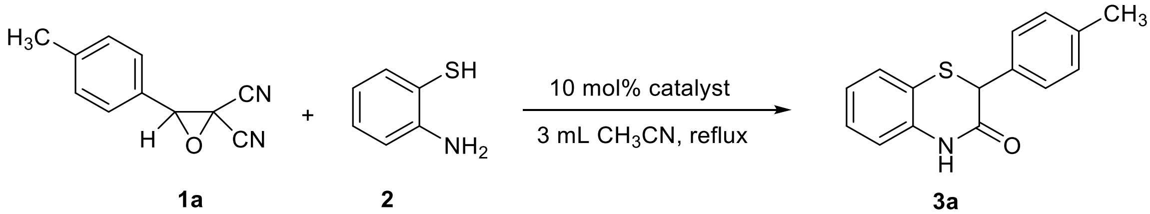
Recyclability studies on the catalysts

The catalyst separated from the mixture was rinsed with EtOH (2×5 mL), dried at 70 °C for 6 hours and reused for subsequent catalytic reactions.

RESULTS AND DISCUSSION

Catalytic synthesis of BTZ

To obtain the optimal reaction conditions, one-pot synthesis of BTZ was carried out using MAP, DAP and TSP as heterogeneous catalysts. The reaction of epoxide **1a** with α-aminothiophenol was selected as a model reaction to produce 2-(*p*-tolyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (**3a**). In the preliminary studies, the reaction was conducted following the conventional synthesis conditions earlier described (12) in the presence of 10 mol% of catalyst from fraction 1 (F_1) (Scheme 1).



Scheme 1: Synthesis of compounds **3a** in the presence of MAP, DAP or TSP catalysts.

Table 1: Catalytic test runs.

Entry	Catalyst	Time	Yield (%)
1	Neat	22 h	80
2	MAP	1 h 20	87
3	DAP	1 h	85
4	TSP	2 h	82

Influence of reaction parameters

Effects of reaction solvent

After screening the potential activity of phosphate fertilizers MAP, DAP, and TSP, an optimized procedure for the preparation of 2-(*p*-tolyl)-2*H*-benzo[*b*]1,4]thiazin-3(4*H*)-one (**3a**) over these heterogeneous catalysts were therefore developed. Initially, the reaction was carried out in several solvents including MeCN, EtOH, AcOEt, $CHCl_3$ using 10 mol% of catalyst (F_1) (Table 2). As shown, the three catalysts tested were highly active and gave the desired BTZ **3a** in high yields within short reaction time in EtOH (Table 2, entries 4, 5 and 6). These results can be explained by the fact that EtOH contains polar molecules and an acidic hydrogen atom which is liable to establish a hydrogen bond with the oxygen atom of epoxide to facilitate the bi-nucleophilic attack of α-aminothiophenol.

Effects of catalysts' amount

The catalytic activities were then tested with a range of catalyst amounts (F_1), from 10 mol% up to 40 mol%, to determine the optimal catalyst loading for each catalyst. The reaction was conducted under otherwise identical reaction conditions in the presence of EtOH as a solvent. As can be seen, MAP, DAP and TSP catalysts exhibited high activities under a catalyst loading of 10 mol% and afforded the desired product within 40, 35, and 55 minutes, respectively, in high yields (Table 3, entries 1, 5 and 9). A further increase in the catalysts' amounts up to 40 mol% resulted in an extension of the reaction time with a slight decrease in the product yield, indicating the catalyst amount of 10 mol% to be optimal. This observation established the excellent catalytic activity of the recently developed catalysts.

Table 2: Optimization of the reaction solvent using MAP, DAP and TSP catalysts.

Entry	Catalyst (10 mol %)	Solvent (3 mL)	Time	Yield (%)
1	MAP	MeCN	1 h 20	87
2	DAP	MeCN	1h	85
3	TSP	MeCN	2h	82
4	MAP	EtOH	40 min	92
5	DAP	EtOH	35 min	89
6	TSP	EtOH	55 min	90
7	MAP	AcOEt	3 h 30	75
8	DAP	AcOEt	3 h	73
9	TSP	AcOEt	2h 50	65
10	MAP	$CHCl_3$	3 h 10	63
11	DAP	$CHCl_3$	3 h 40	60
12	TSP	$CHCl_3$	4 h	55

Table 3: Optimization of the catalysts amount for the synthesis of 2-(*p*-tolyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one **3a**.

Entry	Catalyst	Catalyst loading (%)	Time	Yield (%)
1	MAP	10	40 min	92
2	MAP	20	55 min	91
3	MAP	30	1 h 10	85
4	MAP	40	1 h 25	82
5	DAP	10	35 min	89
6	DAP	20	45 min	88
7	DAP	30	1 h	85
8	DAP	40	1 h 15	83
9	TSP	10	55 min	90
10	TSP	20	1 h 05	85
11	TSP	30	1 h 20	83
12	TSP	40	1 h 35	79

Effects of catalysts' particle size

In the current study, we also focused on determining the effect of the catalysts' particle size in an attempt to compare the results with those obtained in our previous work (18). No remarkable influence of the catalyst particle size on the catalysts activities was observed. The results prove our previous findings that the three phosphate fertilizers MAP, DAP and TSP can constantly show high catalytic activities even when their particle size increases.

Table 4: Screening of the effects of catalyst particle size on the catalytic activities of MAP, DAP and TSP for the synthesis of 2-(*p*-tolyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one **3a**.

Entry	Catalyst (10 mol%)	Particle size range	Time (min)	Yield (%)
1	MAP	36-71 µm	40	92
2	MAP	71-90 µm	40	93
3	MAP	90-120 µm	40	91
4	DAP	36-71 µm	35	89
5	DAP	71-90 µm	35	89
6	DAP	90-120 µm	40	88
7	TSP	36-71 µm	55	90
8	TSP	71-90 µm	55	88
9	TSP	90-120 µm	55	91

Control of the generality of the catalysts

To further screen the scope and the generality of our new catalysts, the reaction of α-aminothiophenol with various substituted epoxides for the synthesis of BTZ derivatives was studied under the optimized conditions using catalyst from fraction 1 (F_1). As shown in Table 5, almost all of the epoxide substrates with either electron-withdrawing or electron-donating substitution furnished the corresponding adducts in high yields. It is noteworthy that the reaction time was extended to 45 min for MAP, 50 min for DAP and 1h for TSP when the epoxide was substituted with the nitro group (Table 5, Entries 7, 8 and 9).

Table 5. Synthesis of BTZ derivatives over phosphate fertilizers MAP, DAP and TSP under the optimized conditions.

Entry	**R**	**1**	**Catalyst**	**Product**	**Time (min)**	**Mp (°C)**	**Yield (%)**
1	CH_3	**1a**	MAP	**3a**	40	198-199	92
2	CH_3	**1a**	DAP	**3a**	35	198-199	89
3	CH_3	**1a**	TSP	**3a**	55	198-199	90
4	Cl	**1b**	MAP	**3b**	25	186-187	96
5	Cl	**1b**	DAP	**3b**	30	186-187	93
6	Cl	**1b**	TSP	**3b**	40	186-187	94
7	NO_2	**1c**	MAP	**3c**	45	202-203	92
8	NO_2	**1c**	DAP	**3c**	50	202-203	85
9	NO_2	**1c**	TSP	**3c**	60	202-203	90

Recyclability studies on the catalysts

In another study, the reaction of epoxide **1a** and α-aminothiophenol **2** was tested in the presence of recovered MAP, DAP and TSP to establish the reusability of the three catalysts developed for the synthesis of 2-(p-tolyl)-2H-benzo[b][1,4]thiazin-3(4H)-one **3a**, the results are displayed in Table 6. To our delight, MAP, DAP and TSP catalysts were found to be reusable with consistency in activity up to four times.

Table 6. Recyclability of MAP, DAP and TSP catalysts.

Entry	**Catalyst**	**Run number**	**Time(min)**	**Yield (%)**
1	MAP	1	40	92
2	MAP	2	40	92
3	MAP	3	40	91
4	MAP	4	40	90
5	DAP	1	35	89
6	DAP	2	35	88
7	DAP	3	35	88
8	DAP	4	35	87
9	TSP	1	55	90
10	TSP	2	55	88
11	TSP	3	55	88
12	TSP	4	55	87

CONCLUSIONS

Through this study, we demonstrated the catalytic efficiency of the phosphate fertilizers MAP, DAP and TSP for the C-S and C-N coupling reactions. A "green" optimized procedure was therefore designed for the synthesis of 2-aryl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones from α-aminothiophenol and *gem*-dicyano epoxide.

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