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Mediterranean Journal of Chemistry **2017**, 6(2), 53-59

Green and efficient method for the synthesis of 1,5-benzodiazepines using phosphate fertilizers as catalysts under solvent-free conditions

Sarra Sibous, Touriya Ghailane, Serrar Houda, Rachida Ghailane, Said Boukhris and Abdelaziz Souizi *

Laboratory of Organic, Organometallic and Theoretical Chemistry, University of IbnTofail,
B.P. 133, 14000 Kenitra, Morocco

Abstract: Three-component reaction in one pot transformation of aldehydes, ethylacetoacetate and *o*-phenylenediamine was employed for the synthesis, under solvent-free, of 1,5-benzodiazepine derivatives using fertilizers mono-ammonium phosphate (MAP), di-ammonium Phosphate (DAP) and triple super phosphate (TSP) as safe, clean, and recyclable catalysts. The synthesis method seems to be operationally simple and provides access to a variety of 1,5-benzodiazepines with excellent yields in a short reaction time.

Keywords: 1,5-benzodiazepine derivatives, recyclable catalysts, phosphate fertilizers, MAP, DAP, TSP.

Introduction

Benzodiazepines form an important class of heterocyclic compounds containing nitrogen atoms. They have attracted special attention due to their important biological or pharmacological properties [1-8] and their wide field of application in different areas of medicine [9-12] and agriculture [13]. It was reported that the 1,5-benzodiazepines and its derivatives present interesting pharmacological and therapeutic properties. Their use has been extended to treat various diseases such as cancer, viral infection (non-nucleoside inhibitors of HIV-1 reverse transcriptase), and cardiovascular disorders. For this reason, their synthesis has received great attention, especially in the field of medicinal chemistry [10,14]. Therefore, the research on synthetic methods for 1,5-benzodiazepines has become one of the hot issues.

It is known that the most classical synthesis method for 1,5-benzodiazepines is the condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds in the presence of a wide variety of Lewis-acid catalysts [15-26].

In order to develop environmentally friendly organic reactions, the synthesis of benzodiazepines using different solid acid catalysts [27-29] and heteropolyacid catalysts using THF or acetonitrile as reaction solvent [30-31] has also been investigated. Recently, a crystalline iron-based metal-organic framework MOF-235 was synthesized, characterized by different techniques and used as a heterogeneous catalyst for the synthesis of 1,5-benzodiazepines by the cyclo-condensation of 1,2-diamines with ketones [32].

However, developing an efficient and recyclable heterogeneous catalyst system for the synthesis of 1,5-benzodiazepines still needs to be explored.

On the other hand, the solvents used in organic synthesis are obviously harmful to environment; the solvent-free organic reactions have attracted the attention of organic chemists in order to reduce the pollution and to bring down the experimental cost. Indeed, it has been established that multicomponent reactions (MCRs) are a powerful tool for the synthesis of a wide variety of compounds in a single pot assuring good yields and low costs, short reaction times, minimizing energy, and avoiding expensive purification procedures. Moreover, the MCRs are generally much more environmentally friendly than the multi-step reactions and allow a rapid access to various molecules [33-44].

According to our interest in the green protocols in organic synthesis, the aim of this work is to use the fertilizers mono-ammonium phosphate (MAP), di-ammonium phosphate (DAP) and triple super phosphate (TSP) [45] as solid heterogeneous catalysts for the synthesis of 1,5-benzodiazepines (Scheme 1).

These fertilizers are produced in industrial quantities and are used mainly in agriculture as nutrient sources for nitrogen and phosphorus.

**Corresponding author: Abdelaziz Souizi*
Email address: souizi@yahoo.com
DOI: http://dx.doi.org/10.13171/mjc61/01701181035/souizi

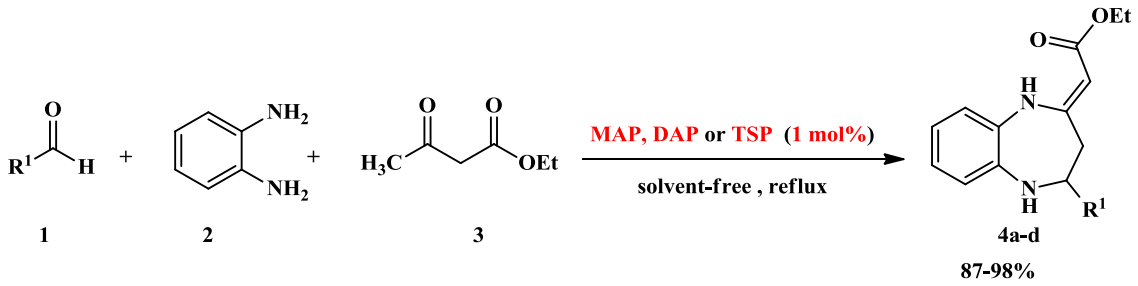
Received December 9th, 2016
Accepted December 29st, 2016
Published January 18th, 2017

Morocco has the most important phosphate worldwide reserves and is thus a major country for the production of phosphate fertilizers whose physicochemical characteristics are shown on the website of the OCP (Office Cherifien des Phosphates) [46], the first Moroccan company.

Furthermore, these fertilizers are widely available and their use as catalysts is undoubtedly an added value for Moroccan phosphates.

Results and Discussion

Herein we focus our interest on the synthesis of 1,5-benzodiazepine derivatives using phosphate fertilizers as catalysts which have been employed as promoters of the reaction to achieve higher yields. This synthesis was accomplished by three-component reaction in one pot cyclocondensation of aldehydes, ethylacetoacetate and *o*-phenylenediamine in the presence of catalytic amount (1mol%) of phosphate fertilizers (Scheme 1).



Scheme 1. Synthesis of 1,5-Benzodiazepines 1 a-d.

We envisage to evaluate the catalytic activity of the mentioned fertilizers [45] as solid heterogeneous catalysts in the synthesis of 1,5-benzodiazepine derivatives. Initially, in order to optimize the reaction conditions, we chose *o*-phenylenediamine, ethylacetoacetate and benzaldehyde as the model reaction which occurs in the presence of the three catalysts (MAP, DAP and TSP). Considering that the reaction medium is one of the most important factors influencing any process, several solvents are used to accomplish further insight at the solvent effect on the synthesis of 1,5- benzodiazepines. Thus, the synthesis of 1,5-benzodiazepine derivative **4b**, in various organic solvents and under solvent-free, is performed. The yields and the reaction times are summarized in Table 1.

Table 1. The solvent effect on the synthesis of 1,5-benzodiazepines [a].

Entry	Solvent	Time (min)			Yield %[b]		
		MAP	**DAP**	**TSP**	**MAP**	**DAP**	**TSP**
1	Ethanol	180	120	90	89	86	80
2	Methanol	110	90	120	90	91	94
3	Isopropanol	210	65	110	50	61	72
4	Butanol	90	60	70	51	42	49
5	DMF	60	55	90	47	61	57
6	Acetonitrile	120	80	180	77	67	71
7	THF	180	120	190	50	73	62
8	AcOEt	250	233	240	57	58	79
9	Dioxane	130	150	210	52	61	37
10	CH_2Cl_2	180	184	240	41	44	56
11	CH_3Cl	270	230	250	67	45	57
12	Cyclohexane	310	240	350	39	55	54
13	Solvent-free	60	55	90	92	91	96

[a] Reaction of *o*-phenylenediamines (**1 mmol**) b-keto esters (**1 mmol**) and benzaldehyde (**1 mmol**) catalyzed MAP or DAP or TSP under reflux conditions.
[b] Isolated yield.

The results indicate that the best yields are obtained in the solvent-free (92, 91 and 96%) or in the presence of methanol (90, 91 and 94%) using respectively MAP, DAP and TSP as catalysts. Although methanol is the most appropriate solvent for this transformation which is accomplished with

high yields compared to the other solvents. The reaction under solvent-free conditions is carried out in the shortest times which are 60, 55 and 90 min relative to those obtained with methanol (110, 90 and 120 min). This result is interesting as it is taking into account the requirements of green chemistry and minimizing the risk accompanied by the use of organic solvents such as toxicity and flammability.

The efficiency of the reaction is mainly affected by the amount of catalyst; therefore we propose to optimize this amount for the model reaction under solvent free conditions. For this purpose, we vary the amount of catalyst from 1 to 10 mol% by a step of 1mol%. The obtained yields and reaction times are reported in Table 2.

It is noticeable that the great yields of 94, 96 and 97% of the reaction are obtained for the amount of 1mol% in presence of three catalysts MAP, DAP and TSP respectively. At this amount of catalyst, the reaction time is estimated by 60, 45 and 65 min with the MAP, DAP and TSP catalysts respectively, thus theses values are also the shortest ones. In conclusion 1mol% of catalyst is sufficient to afford the best results with high yields in short reaction time.

Furthermore, it is interesting to notice that the yields of the reaction diminish when the amount of the catalyst increase, that is probably due to the dispersion effect of the reagents on the catalyst's surface.

Table 2. Effect of catalytic amount on synthesis of 1,5-benzodiazepines[a].

Entry	Amount of catalyst Mol%	Time (min)			Yield %[b]		
		MAP	**DAP**	**TSP**	**MAP**	**DAP**	**TSP**
1	1	60	45	65	94	97	96
2	2	60	45	65	94	97	96
3	3	60	50	80	94	94	96
4	4	60	55	85	92	92	96
5	5	60	55	90	92	91	96
6	6	90	60	90	90	91	94
7	7	120	70	95	87	89	90
8	8	120	90	110	82	77	88
9	9	130	120	120	79	72	80
10	10	130	180	120	79	65	80

[a] Reaction of o-phenylenediamines (**1 mmol**) b-keto esters (**1 mmol**) and benzaldehyde (**1 mmol**) catalyzed MAP or DAP or TSP under solvent-free conditions at reflux .[b] Isolated yield.

In addition, the principal disadvantage of most of the existing methods is that the catalysts are destroyed in work- up procedure and could not be recovered or reused whereas their reusability is central to their utility. It is well known that the reusability of the heterogeneous catalyst is one of the major significant parameters and is of great importance in industrial uses. In order to study the reusability of the three catalysts used in this work, regeneration experiments were carried out. Thereby, the recovery and reusability of the supported catalyst using ethyl acetoacetate, *o*-phenylenediamine and benzaldehyde as model substrates were studied.

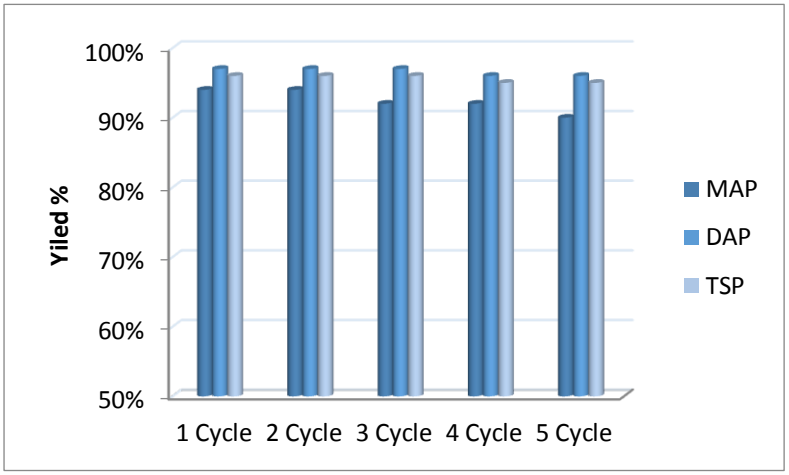


Figure 1. Reusability of MAP, DAP and TSP catalysts in synthesis of 1,5-benzodiazepine **4b**

To point out the advantages of DAP, MAP and TSP catalysts used in the synthesis of 1,5-benzodiazepine derivatives, we opt to compare their catalytic activity with that of other catalysts given in the literature. The reaction times and the yields of the isolated product are collected in Table 3. These previous studies have shown that organic and inorganic catalysts [26,46,47] were used for 1, 5-benzodiazepine derivatives synthesis by a one-pot three-component reaction in solvents leading to low yields and long reaction times compared to the ones obtained with DAP, MAP and TSP catalysts used in the present work. These catalysts were found to be prominent catalysts and provided the highest yield and short reaction times for the model reaction. Thus, they are proved to be effective catalysts for the synthesis of 1, 5-benzodiazepine derivatives.

Table 3. Optimum conditions for 1, 5- benzodiazepine **4b** synthesis catalyzed by MAP; DAP, TSP and for other derivatives synthesis using various catalysts given in previous studies.

Catalyst	**Catalyst amount**	**Solvant**	**Time (min)**	**Yield %**	**Ref.**
MAP	1 mol%	Solvant-free	60	94	This work
DAP	1 mol%)	Solvant-free	45	97	This work
TSP	1 mol%	Solvant-free	65	96	This work
BDMS	10 mol%	DCE	270	72	46
Benzoic acid	20 mol%	DCE	480	21	26
2-Nitrobenzoic acid	20mol%)	DCE	480	26	26
2,6-Pyridinedicarboxylic acid	20 mmol%	DCE	300	70	26
p-TsOH	10 mmol%	EtOH	480	85	47
HOAc (acetic acid)	10 mmol%	EtOH	390	79	47
STA (silicotungstic acid)	10 mmol%	EtOH	720	70	47
PMA(phosphomolybdic acid)	10 mmol%	EtOH	420	89	47
$CeCl_3 \cdot 7H_2O$	10 mmol%	EtOH	600	85	47
$NiCl_2 \cdot 6H_2O$	10 mmol%	EtOH	600	86	47
I_2	10 mmol%	EtOH	420	75	47

[a] Reaction conditions: o-phenylenediamine(**1 mmol**), b-keto esters (**1 mmol**) and benzaldehyde (**1 mmol**).
[b] Isolated yields.

Next, under the optimized conditions, we examined the generality and scope of this reaction using ethyl acetoacetate, *o*-phenylenediamine, and various substituted aromatic aldehydes, which smoothly underwent the one-pot reaction to afford the corresponding products **4a-4d** in good to excellent yields (Table 4).

Table 4. One pot three-component synthesis of 1,5-benzodiazepines **4a-4d** catalyzed by MAP, DAP and TPS

Entry	**R^1**	**Time (min)**			**Yield %[b]**			**Mp°C**	
		MAP	**DAP**	**TSP**	**MAP**	**DAP**	**TSP**	**Found**	**Reported**
4a	4-ClC_6H_4	60	45	65	94	97	96	176-178	176-180[46]
4b	4-MeC_6H_4	150	120	90	87	90	94	95-97	95-98[46]
4c	C_6H_5	240	180	90	89	95	98	73-75	73-77[46]
4d	2-Furyl	300	240	180	92	96	97	84-86	84-88[46]

[b] Isolated yield.

Conclusion

To sum up, we described the three-component one-pot transformation of ethyl acetoacetate, *o*-phenylenediamine, and various substituted aromatic aldehydes in solvent-free conditions using three phosphate fertilizers as catalysts to synthesize four 1,5-benzodiazepine derivatives. It is found that the strategy developed in this work is an efficient procedure for the synthesis of these derivatives. The advantages of this method are easy work-up procedure, good yields, short reaction times, contribution to the green chemistry development, gain on the cost of the experiment since phosphate fertilizers are very cheap and are available everywhere. Further applications of this method for various syntheses using these catalysts are in progress in our laboratory.

Experimental Section

Materials and methods

All reagents were obtained commercially 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 [46]. The purity determination of the substrates and reactions monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates. Melting points were detected on a Kofler hot stage apparatus and are uncorrected.

Typical experimental procedure

To a mixture of 1,2-phenylenediamine (1 mmol) and ß-keto esters (1 mmol), 1 mol% of catalyst (MAP, DAP or TSP) was added. The mixture was stirred for 15 min under solvent-free conditions at room temperature. Then, the aromatic aldehyde (1 mmol) was added and the mixture was stirred under reflux for the specific times indicated in Table 4. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, the catalyst was separated from the mixture by filtration and washed several times with ethyl acetate and dried for a later use. The filtrate was evaporated and the obtained 1,5-benzodiazepines were recrystallized from ethanol. The structures of compounds 4a-d were confirmed by the comparison of their melting points and spectral data with those reported in the literature [26,46].

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