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Iron (III) Phosphate as an Efficient and Reusable Catalyst for the Synthesis of 1,5-Benzodiazepines

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Abstract

Iron (III) phosphate was used as an efficient catalyst for the preparation of 1,5-benzodiazepines in excellent yields. This method is applicable for the reaction of o-phenylenediamines with cyclic or acyclic ketones. The salient features of the present methodology are cheaper process and catalyst and in addition, the catalyst can be easily recovered after completion of the reaction and reusable without affecting its activity.

Keywords: ***1,5-benzodiazepines; o-phenylenediamines; Ketones; Iron(III) phosphate***

Introduction

Iron is one of the most numerous and environmentally friendly metals on the earth. Several groups have reported various iron metal-catalyzed organic transformations during the past decades [1]. Iron catalysts in organic reactions have recently received much attention in view of their cheapness and environmental friendliness. Among them iron (III) phosphate is ranked as powerful Lewis acid for affecting various organic transformations such as one-pot synthesis of 1,2,4,5-tetraarylated imidazoles [2], synthesis of polyhydroquinoline derivatives through the hantzsch four component [3], one-pot three component synthesis of 2,4,5-triarylated imidazoles [4] and L-proline-catalyzed synthesis of functionalized unsymmetrical dihydro-1H-indeno[1,2-b]pyridines [5]. Also, 1,5-benzodiazepines are an important category of heterocyclic compounds that own a wide range of therapeutic and pharmacological properties. They are widely used as anticonvulsant, antianxiety, analgesic, sedative, anti-depressive, and hypnotic agents [6]. Due to their wide applications, several methods for the synthesis of benzodiazepines have been reported by reaction between *o*-phenylenediamines (OPDAs) and ketones [7], enones [8] or β-haloketones [9], using ionic liquids [10], under microwave irradiation [11], $SbCl_3$–Al_2O_3 [12], $HClO_4$ [13], acetic acid [14], polyphosphoric acid or SiO_2 [15], $TiCl_4$ [16], $Yb(OTf)_3$ [17], $H_{14}[NaP_5W_{30}O_{110}]$ [18] and $Fe(ClO_4)_3$ [19]. Some of these methods suffer from restrictions such as hard reaction conditions, expensive reagents, low yields, relatively long reaction time and the formations of side products. As a result, introducing a new methodology for the synthesis of 1,5-benzodiazepines in terms of being simple, eco-friendly and economically viable is still of prime importance. In this communications, herein, $FePO_4$ was used as a catalyst in the condensation reaction between various *o*-phenylenediamines

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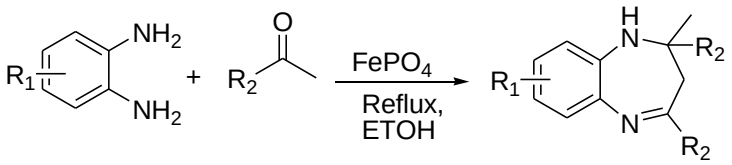
(OPDAs) and ketones for synthesis of 1,5-benzodiazepines in good to excellent yields under mild reaction conditions SCHEME 1. To the best of our knowledge, this is the first report of the application of $FePO_4$ as a heterogeneous catalyst in the synthesis of 1,5-benzodiazepine derivatives.



SCHEME 1. **Synthesis of 1,5-benzodiazepines using iron (III) phosphate.**

Results and Discussion

To investigate the catalytic activity of iron (III) phosphate in the synthesis of 1,5-benzodiazepine derivatives, initially, to optimize the reaction conditions, the reaction of OPDA (1.0 mmol) and acetophenone (2.0 mmol) was subjected as a simple model reaction in the presence of different catalytic amounts of catalyst in ethanol as a green solvent under reflux conditions. It was found that 10 mol% of the catalyst efficiently catalyzed the model reaction in high yields and short reaction times TABLE 1. The reaction was not successful in the absence of the catalyst (Entry 1). The increase of the amount of the catalyst improves neither the reaction times nor yields.

TABLE 1. **Optimizing of catalytic amount of the catalyst in the synthesisof 2-methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine.**

Entry	$FePO_4$ (mol%)	Time (h)	Yield %
1	-	48	10
2	2	35	40
3	5	10	60
4	10	3	94
5	15	3	94

Reaction condition: OPDA (1.0 mmol), acetophenone (2.0 mmol), ethanol (5.0 ml) under reflux condition.

The role of solvent and temperature in the reaction was also screened. As shown in TABLE 2, it was found that ethanol is a suitable solvent to give the target products in high to excellent yields and relatively short reaction time in comparison with solvent-free conditions. Selecting ethanol is acknowledged as a green solvent as it is produced from agricultural feed stocks. Under solvent-free conditions low yields of the product was obtained respectively.

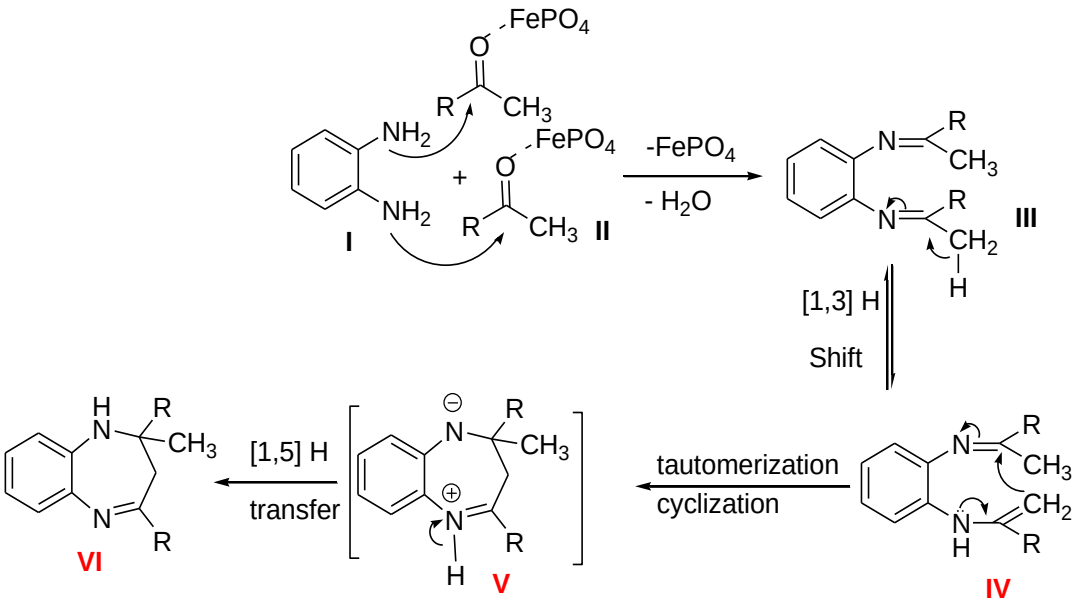
After optimization of the reaction conditions, this protocol was generalized using different kinds of ketones were reacted with OPDAs to produce the corresponding benzodiazepines under mild reaction conditions in high to excellent yields. As illustrated in TABLE 3, linear, cyclic and aromatic ketones react with 1,2-phenylenediamine derivatives to obtain various benzodiazepines.

TABLE 2. **Optimizing of the solvent type in the synthesis of 2-methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine.**

Entry	Solvent (mml)	Temp. (°C)	Yield %[a]
1	Free	25	20
2	Free	50	55
3	Free	70	75
4	Ethanol	25	30
5	“	50	75
6	“	reflux	94
7	H_2O	reflux	-

Reaction condition: OPDA (1.0 mmol), acetophenone (2.0 mmol), $FePO_4$ (10 mol%).

The suggested mechanism for the formation of 1,5-benzodiazepines have been shown in SCHEME 2. The first event is the formation of diimine III from the condensation reaction between OPDA I and two moles of ketones II in the presence of the $FePO_4$. The oxygen atoms of II are adsorbed through their lone pair electrons on the surface acid sites of the catalyst, and the amino groups of I attack to the carbonyl groups of II to give compound III. Then, an intramolecular imine-enamine tautomerization-cyclization of intermediate IV and proton abstract V promoted to yield the products VI.



SCHEME 2. **Proposed mechanism for the preparation of 1,5-benzodiazepines.**

The reusability of the composite catalyst was also investigated on the model reaction. An important feature of $FePO_4$ catalyst was its easy and reliable separation from the reaction mixture. The heterogeneous nature of the catalyst allowed its facile recovery by simple filtration, washing with ethanol and drying at 50ºC to provide an opportunity for recycling experiments.

The separated catalyst was reused in the mentioned reaction for the synthesis of four times without considerable loss of its catalytic activity TABLE 4.

TABLE 3. **Synthesis of 1,5-benzodiazepines using iron phosphate (III).**

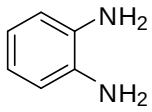
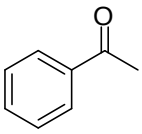
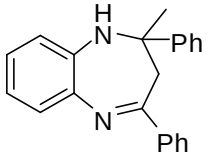
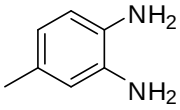
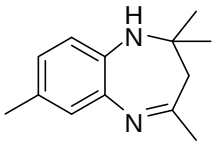
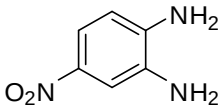
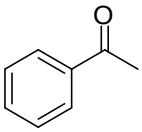
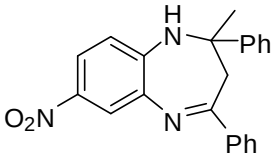
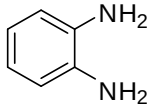
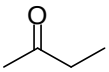
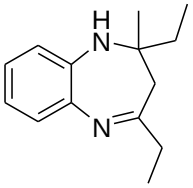
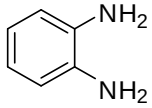
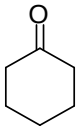
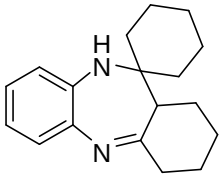
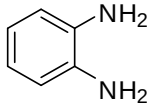
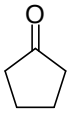
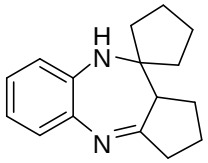
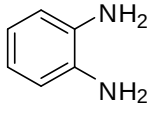
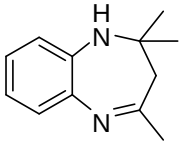
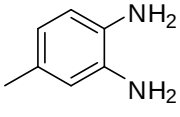
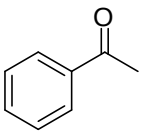
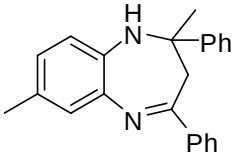
Entry	Amine	Ketone	Product Structure	Time (h)	Yield (%)	Mp (ºC) Found & Reported [ref.]
1				3	94	153-156:150-152 [17]
2				2:30	92	122-125:127-128 [18]
3				2:45	90	137-140:136-138 [20]
4				2:45	94	134-136:137-139 [17]
5				3	94	135-138:136-137 [17]
6				3	95	135-137:138-139 [20]
7				2:45	91	131-134:136-138 [17]
8				2:30	92	97-99:92-93 [18]

TABLE 4. **Reusability of the catalyst.**

Runs	1	2	3	4
Yield%	94	92	92	90

Reaction condition: OPDA (1.0 mmol), acetophenone (2.0 mmol), $FePO_4$ (10 mol%) and ethanol (5.0 ml) under reflux condition.

Experimental

General procedure for the synthesis of benzodiazepine derivatives using iron (III) phosphate

A mixture of OPDA (1.0 mmol), ketone (2.0 mmol) and $FePO_4$ (10 mol%) in 5.0 mL of ethanol was stirred under reflux condition in appropriate times according to TABLE 3. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 3/1), the catalyst was filtrated off and, the reaction solution was evaporated and the residue was purified by recrystallization from ethanol to give pure compounds.

Physical and spectral data

2-Methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry 1): Yellow crystal; Yield (94%, ethanol); MP (ºC): 150-152; IR (KBr, cm^{-1}): 3406 (NH), 3057 (C–H), 1613 (C=N), 1475 (Aromatic C=C), 1215 (C–N), 1141, 755. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 2.85 (br d, J=12.9 Hz, 2H, CH_2), 3.66 (brs, 1H, NH), 6.84-7.92 (m, 14H, ArH) ppm.

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1H-1,5-benzodiazepine (Entry 2): Yellow solid; Yield (92%, ethanol); MP (ºC): 122-125; IR (KBr, cm^{-1}): 3387 (NH), 1618 (C=N), 1513 (Aromatic C=C), 1215 (C–N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 6H, $–CH_3$), 1.35 (s, 3H, $–CH_3$), 2.30-2.32 (m, 5H, $–CH_3$, $–CH_2$), 3.31 (brs, 1H, -NH), 6.51 (s, 1H, ArH), 6.79 (d, J=7.4, 1H, ArH), 7.0 (d, J=8.7, 1H, ArH) ppm.

2-Methyl-2, 4-diphenyl-2,3-dihydro-8-nitro-1H-1,5-benzodiazepine (Entry 3): Dark yellow solid; Yield (90%, ethanol); MP (ºC): 137-140; IR (KBr, cm^{-1}): 3435 (NH), 1640 (C=N), 1471 (Aromatic C=C), 1248 (C–N), 1091, 951, 880. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 3.05-3.15 (d, J=12.6 Hz, 1H), 3.35 (d, J=12.6 Hz, 1H), 4.40 (brs, 1H), 6.80-7.95 (m, 13H) ppm.

2,4-Diethyl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry 4): Yellow; Yield (94%, ethanol); MP (ºC): 134-136; IR (KBr, cm^{-1}): 3407 (NH), 3056 (Aromatic C–H), 2968 (Aliphatic C–H), 1614 (C=N), 1475 (Aromatic C=C), 1216 (C–N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, 3H, $–CH_3$), 1.31 (m, 6H, $–CH_3$, $–CH_3$), 1.72 (q, 2H, $–CH_2$), 2.21 (m, 2H, $–CH_2$), 2.60 (q, 2H, $–CH_2$), 3.32 (brs, 1H, -NH), 6.55-7.31 (m, 4H, ArH) ppm.

10-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-1H-dibenzo[1,5]diazepine (Entry 5): Pale yellow; Yield (91%, ethanol); MP (ºC): 136-137; IR (KBr, cm^{-1}): 3421 (NH), 2931(C–H), 1617 (C=N), 1477 (Aromatic C=C), 1138 (C–N), 814. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23-1.66 (m, 18H), 2.81 (s, 1H), 4.09 (brs, 1H), 7.07-7.75 (m, 4H, ArH) ppm.

10-Spirocyclopentane-1,2,3,9,10,10a-hexahydro-1H-dibenzo[b]-cyclopenta[e][1,4]-diazepine (Entry 6): Yellow solid; Yield (95%, ethanol); MP (ºC): 135-137; IR (KBr, cm^{-1}): 3394 (NH), 2953 (Aliphatic C–H), 1640 (C=N), 1479 (Aromatic C=C), 1050 (C–N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.92 (m, 12H), 2.30-2.61 (m, 3H), 4.54 (brs, 1H), 6.60-7.39 (m, 4H) ppm.

2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (Entry 7): Pale Yellow solid; Yield (91%, ethanol); MP (ºC): 131-134; IR (KBr, cm^{-1}): 3407 (NH), 2968 (Aliphatic C–H), 1614 (C=N), 1477 (Aromatic C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 6H, $–CH_3$), 2.20 (s, 2H, $–CH_2$), 2.40 (s, 3H, $–CH_3$), 3.23 (brs, 1H, –NH), 6.70-7.21 (m, 4H, ArH) ppm.

2-Methyl-2,4-diphenyl-2,3-dihydro-8-methyl-1H-1,5-benzodiazepine (Entry 8): Yellow solid; Yield (92%, ethanol); MP (ºC): 97-99; IR (KBr, cm^{-1}): 3413 (NH), 2972 (Aliphatic C–H), 1593 (C=N), 1445 (Aromatic C=C), 1210 (C–N). ^{1}H NMR (300 MHz, $CDCl_3$): 1.80 (s, 3H), 2.41(s, 3H), 3.00 (d, J=13 Hz, 1H), 3.15 (d, J=13 Hz, 1H), 3.50 (brs, 1H, NH), 6.70-7.69 (m, 13H) ppm.

Conclusion

In summary in this paper has demonstrated that iron (III) phosphate acts as a highly efficient solid acid catalyst in the preparation of 1,5-benzodiazepines. The cheaper process, available catalyst, simple work-up procedure, mild reaction conditions, versatility, recyclability of the catalyst make this method a valid contribution to the existing methodologies.

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