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RECYCLABLE HETEROGENEOUS NANOCRYSTAL PROMOTED CASADE REACTION IN WATER: AN ACCESS TO GREEN SYNTHESIS OF HIGHLY FUNCTIONALIZED 4*H*-PYRANS CONTAINING PHOSPHONATE MOTIF

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Abstract – A green and environmentally friendly cascade reaction of diethyl (2-phenylacetyl)phosphonate with benzylidenemalononitrile promoted by Zr-Ce-SBA-15-NH_2 in water was developed, and a wide range of highly functionalized 4*H*-pyrans containing phosphonate motif were obtained in up to 89% yield. Moreover, SBA-15-NH_2 also showed good catalytic activity for this transformation in acetonitrile.

Pyran derivatives belong to one of the most important classes of natural products and pharmaceuticals.[1] Among different pyran derivatives, 2-amino-3-cyano-4*H*-pyrans and their derivatives are the core skeleton of many biological molecules and pharmaceuticals.[2] For example, compounds **i-iii** exhibit anti-bacterial, anti-viral and anti-tumor activities (Figure 1).[3] Therefore, it is of great importance to synthesize those compounds, and organic chemists have made considerable efforts to develop efficient approaches for the synthesis of those molecules.[3c,4] However, most of the established methods are mainly focused on the construction of simple 2-amino-3-cyano-4*H*-pyrans or 4*H*-chromene derivatives. On the other hand, phosphonate frameworks usually exhibit ubiquitous biological activities in medicines and agriculture chemicals.[5] To the best of our knowledge, the synthesis of 2-amino-3-cyano-4*H*-pyrans containing phosphonate motifs has scarcely been reported except our group's work on the DBU promoted cascade reaction of diethyl (2-phenylacetyl)phosphonate with benzylidenemalononitrile.[6] In this context, it is still desirable to develop more simple, green and environmentally friendly catalytic systems for the synthesis of those compounds.

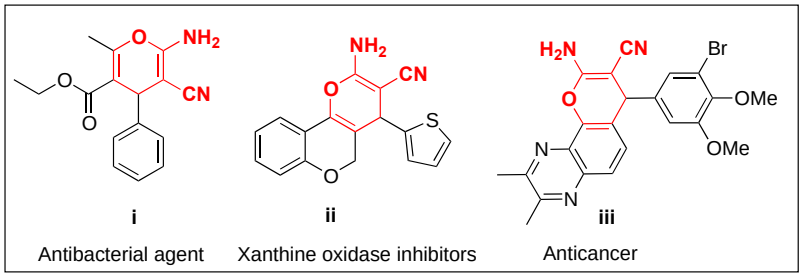
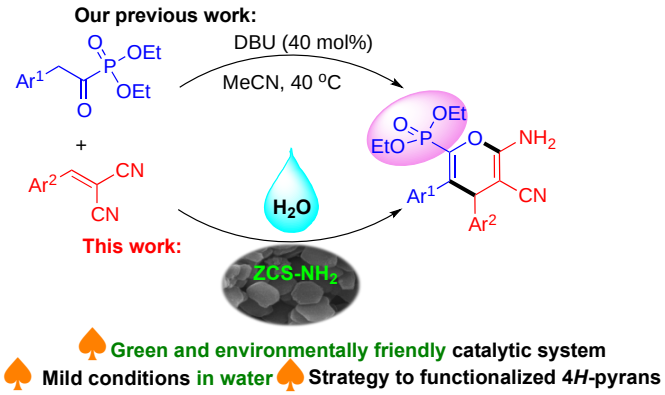


Figure 1. The examples of bioactive compounds contaning 4*H*-pyrans

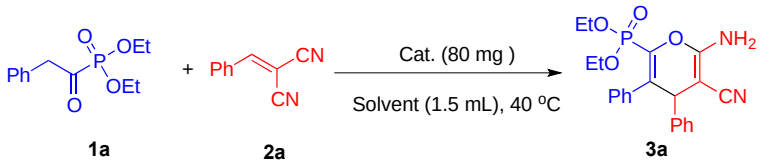
The heterogeneous catalysts have attracted great interest due to their unique advantages of catalyst recovery and reuse.[7] Hence, nanoparticles have recently been widely used to immobilize the homogeneous nitrogenous organic bases.[8] The nanoparticles supported nitrogenous organic bases, which combine the advantages of heterogeneous catalysts, nano-supports and organic bases, including excellent catalytic activity and simple separation and recycling. In our previous work, our group successfully synthesized a Zr-Ce-SBA-15-NH_2 (ZCS-NH_2) supported nitrogenous organic bases nanocrystals which demonstrates catalytic properties and recyclability.[9] So, remarkable attention has been focused on the further development of the catalytic properties of these nanocrystals.



Scheme 1. Synthesis of 4*H*-pyrans containing phosphonate and our strategy in this work

Based on this background and our continuing interesting in the development of environmentally friendly methodologies for the synthesis of 2-amino-3-cyano-4*H*-pyrans containing phosphonate motifs, herein, we achieved the green synthesis of 2-amino-3-cyano-4*H*-pyrans in water using the Zr-Ce-SBA-15-NH_2 nanocrystals as the heterogeneous catalysts.

Table 1. Optimization of the reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Solvent	Yield (%)[b]
1	ZCS-NH_2	H_2O	69
2	SBA-15-NH_2	H_2O	53
3	ZCS-NH_2	H_2O	60
4	ZCS-NH_2	H_2O	35
5[c]	ZCS-NH_2	H_2O	62
6[d]	ZCS-NH_2	H_2O	59
7	ZCS-NH_2	MeCN	32
8	SBA-15-NH_2	MeCN	70
9	SBA-15-NH_2	toluene	39
10	SBA-15-NH_2	CH_2Cl_2	61
11	SBA-15-NH_2	THF	12
12	SBA-15-NH_2	DMF	26
13	SBA-15-NH_2	MeOH	0
14[e]	SBA-15-NH_2	MeCN	40

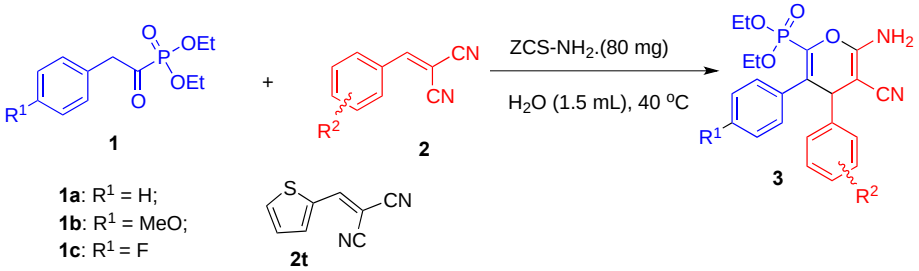
[a] Unless otherwise specified, all reaction carried out with **1a** (0.225 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.0 equiv.) and catalyst (80 mg) in solvent (1.5 mL) at 40 °C. [b] Isolated yields. [c] 60 mg catalyst Loading was used. [d] 40 mg catalyst Loading was used. [e] Carried out at 60 °C.

We synthesized Zr-Ce-SBA-15-NH_2 supported primary amine according to our reported method.[10] To estimate its catalytic activity, in the presence of those nanocrystals, the reaction of diethyl (2-phenylacetyl)phosphonate **1a** with benzylidenemalononitrile **2a** was carried out in water. To our delighted, the desired product **3a** 2-amino-3-cyano-4*H*-pyran containing phosphonate motifs was produced in 69% yield (Table1, entry 1). Then, SBA-15-NH_2 was used as comparative experiment. Predictably, product **3a** was obtained in inferior yield, which might be because that the shorter channelled ZCS-NH_2 possesses higher catalytic activity than SBA-15-NH_2. To improve the synthetic efficiency, other reaction conditions including temperature and catalyst loading were screened. With the increase of reaction temperature, the yield was decreased obviously (Table 1, entries 1 vs 3 and 4). Decreasing the catalyst loading resulted in a slightly lower yield of **3a** (Table 1, entries 1 vs 5 and 6). In order to further improve the yield, the reaction was conducted in organic solvent acetonitrile, unfortunately, no better

result was obtained (Table 1, entry 7). However, the reaction which carried out in the presence of SBA-15-NH_2 in acetonitrile could give almost the same results as in the presence of ZCS-NH_2 in water (Table 1, entries 1 vs 8). Thus, using SBA-15-NH_2 as catalyst, other organic solvents were examined. Of the various solvent, acetonitrile was found to be the best solvent for the catalytic system of SBA-15-NH_2 (70% yield). When the temperature was increased to 60 °C, the yield decreased from 70% to 40% (Table 1, entries 8 vs 14). Based on the comprehensive screenings, it was found that the reaction could produce **3a** in satisfactory yield whether promoted by ZCS-NH_2 in water (69% yield) or promoted by SBA-15-NH_2 in acetonitrile (70% yield). In order to develop a greener and environment-friendly methodology for the synthesis of compounds **3**, the optimal reaction conditions were recommended: 0.225 mmol **1** and 0.15 mmol **2** with 80 mg ZCS-NH_2 in water at 40 °C (Table 1, entry 1).

Under the optimized reaction condition, the substrate scope was investigated using various diethyl (2-phenylacetyl)phosphonates **1** and 2-benzylidenemalononitriles **2**, and the results were summarized in Table 2. As shown in Table 2, substituents on aryl rings of diethyl phosphonates **1** and 2-benzylidenemalononitriles **2** were tolerated, affording the desired product in up to 89% yields. A range of 2-benzylidenemalononitriles **2** were studied. The electronic and steric properties of the substituents on the aromatic ring of **2** showed evident effects on the yields (Table 2, entries 2-19). When 2-benzylidenemalononitrile **2** with an electron-withdrawing substituent on the aromatic ring at *para*-position was used, this transformation gave higher yields than those with electron-donating substituents (Table 2, entries 2 and 3 vs 4-8). In addition, this phenomenon was also observed when the substituents were located at *ortho*-position (Table 2, entries 14 and 15 vs 16-19). As for 2-benzylidenemalononitriles **2** with substituents at *meta*-position, the reaction delivered the desired product in good yields except substrate **2l** (Table 2, entries 9-13).

Table 2. Substrate scope of the cascade reactions[a]



Entry	**1**	**2**	Time (h)	Yield[b] (%)
1	**1a**	**2a:** R^2 = H	6 (48)[c]	**3a:** 69 (70)[c]
2	**1a**	**2b:** R^2 = 4-MeO	48 (48)	**3b:** 10 (63)
3	**1a**	**2c:** R^2 = 4-Me	72 (72)	**3c:** 14 (68)

4	**1a**	**2d:** R^2 = 4-F	18 (36)	**3d:** 47 (73)
5	**1a**	**2e:** R^2 = 4-Cl	12 (24)	**3e:** 55 (73)
6	**1a**	**2f:** R^2 = 4-Br	12 (12)	**3f:** 62 (82)
7	**1a**	**2g:** R^2 = 4-CF_3	7 (12)	**3g:** 57 (78)
8	**1a**	**2h:** R^2 = 4-NO_2	7 (12)	**3h:** 89 (76)
9	**1a**	**2i:** R^2 = 3-MeO	18 (72)	**3i:** 74 (59)
10	**1a**	**2j:** R^2 = 3-Me_3	24 (72)	**3j:** 63 (65)
11	**1a**	**2k:** R^2 = 3-Cl	24 (12)	**3k:** 56 (85)
12	**1a**	**2l:** R^2 = 3-Br	24 (48)	**3l:** 26 (66)
13	**1a**	**2m:** R^2 = 3-NO_2	18 (12)	**3m:** 76 (70)
14	**1a**	**2n:** R^2 = 2-MeO	18 (72)	**3n:** 15 (57)
15	**1a**	**2o:** R^2 = 2-Me	48 (72)	**3o:** 30 (58)
16	**1a**	**2p:** R^2 = 2-F	24 (24)	**3p:** 47 (75)
17	**1a**	**2q:** R^2 = 2-Cl	18 (12)	**3q:** 50 (77)
18	**1a**	**2r:** R^2 = 2-Br	18 (12)	**3r:** 46 (79)
19	**1a**	**2s:** R^2 = 2-NO_2	48(48)	**3s:** 66 (64)
20	**1a**	**2t**	48 (48)	**3t:** 31 (68)
21	**1b**	**2a:** R^2 = H	6 (48)	**3u:** 72 (69)
22	**1c**	**2a:** R^2 = H	6 (24)	**3v:** 75 (76)

[a] Unless otherwise specified, all reaction carried out with **1** (0.225 mmol, 1.5 equiv.), **2** (0.15 mmol, 1.0 equiv.) and ZCS-NH_2 (80 mg) in H_2O (1.5 mL) at 40 °C. [b] Isolated yields. [c] Data in brackets refer to the time and yields of the reaction of **1** (0.225 mmol, 1.5 equiv.) with **2** (0.15 mmol, 1.0 equiv.) in the presence of SBA-15-NH_2 (80 mg) in MeCN (1.5 mL) at 40 °C.

Remarkably, when the heterocyclic substituted **2s** was employed, the product was obtained in 31% yield (Table 2, entry 20). Furthermore, the different *para*-substituted aromatic rings of diethyl phosphonate had slightly effects on the yields, and all the cases gave good results regardless bearing electron-withdrawing or electron-donating substituents (69-75% yields, Table 2, entries 1, 21 and 22).

Meanwhile, for comparison, the reaction generalities were also studied with the SBA-15-NH_2 as the catalyst and acetonitrile as the solvent and the results were listed in brackets in Table 2. As indicated in Table 2, substrates with electron-withdrawing substituents on the aromatic ring could give higher yields than those with electron-donating substituents regardless of the position of the substituents (Table 2, entries 2 and 3 vs 4-8, 9 and 10 vs 11-13, 14 and 15 vs 16-19). Except for nitro-substituted **2h**, **2m**, **2s**,

and 3-methoxy-substituted **2i**, all the reactions with the SBA-15-NH_2 as the catalyst in acetonitrile produced higher yields than that the reaction promoted by ZCS-NH_2 in water.

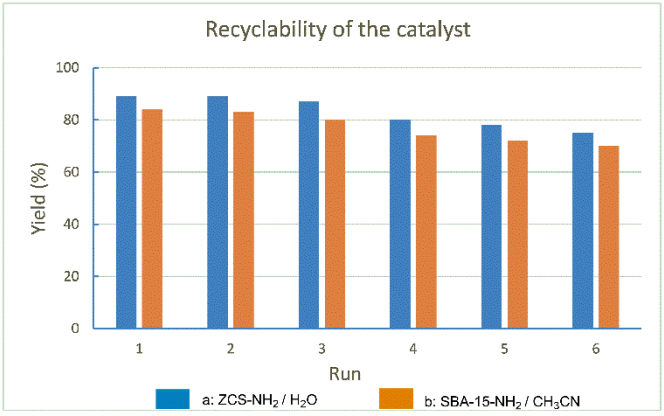


Figure 2. Recyclability of the catalyst. Reaction conditions a: **1a** (0.225 mmol, 1.0 equiv.), **2h** (0.15 mmol, 1.0 equiv.), ZCS-NH_2 (80 mg), in H_2O at 40 °C; b: **1a** (0.225 mmol, 1.0 equiv.), **2k** (0.15 mmol, 1.0 equiv.), SBA-15-NH_2 (80 mg), in MeCN at 40 °C.

To test the catalyst reusability, the reaction of **1a** with **2h** was carried out in the presence of ZCS-NH_2 under the optimized conditions and monitored by TLC. After the reaction being completed on each run, the catalyst was separated from the reaction mixture by filtrating, washed with methanol and directly reused in the next run. The results indicated that the isolated yield of the product was almost consistent after six runs and the catalyst could be reused at least six times (Figure 2a). Under the same treatment for the above to examine the catalyst reusability of SBA-15-NH_2, the catalyst could be also reused six times on being consistent in yield Figure 2b).

In conclusion, we have developed a greener and environmentally friendly cascade reaction of diethyl (2-phenylacetyl)phosphonate with benzylidenemalononitrile promoted by ZCS-NH_2 in water, and a wide range of highly functionalized 4*H*-pyrans containing phosphonate motif were obtained in up to 89% yield. Moreover, SBA-15-NH_2 also showed good catalytic activity for this transformation in acetonitrile. This work provides an efficient method for the greener synthesis of highly functionalized 4*H*-pyrans containing phosphonates.

EXPERIMENTAL

1. General information

NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra of $CDCl_3$ solutions were recorded either at 400 or 300 MHz (Bruker Avance), respectively. ^{1}H NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) with the solvent signal as the internal standard ($CDCl_3$ at 7.26 ppm). Data are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (double

of doublet), br (broad) or m (multiplets), coupling constants (Hz) and integration. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. Reactions were monitored by TLC and visualized with ultraviolet light. All reagents were obtained from commercial supplier without further purification.

2. The preparation of nanocrystal ZCS-NH_2 and SBA-15-NH_2

Procedure for the preparation of ZCS-NH_2[9a]

Pluronic P123 (0.01015 equiv.) was dissolved in water (170 equiv.) and the solution was stirred at 35 ^oC to form micellar solution. To the solution, ethyl orthosilicate (1 equiv.), zirconium oxychloride (0.05 equiv.) and cerium nitrate (0.05 equiv.) were added. The reaction mixture was stirred at 35 ^oC for 20 h, swiched to the autoclave with PTFE liner and crystallized at 100 ^oC for 24 h. The reaction solution was cooled, filtered, washed with water and dried at 60 ^oC, and then roasted at 550 ^oC for 6 h controlling the heating rate at 1 ^oC/ min to remove the template. The product white powder solid ZCS was obtained. The sample of calcined ZCS (1.0 g) was dried in vacuum at 120 ^oC for 12 h, then dispersed in anhydrous toluene (60 mL). To the reaction solution, AAPTS (8 mmol/g) was added. And the reaction mixture was refluxed at 65 ^oC for 24 h. After the reaction completed, the reaction mixture was filtered and the filter cake was washed repeatedly with anhydrous toluene and isopropanol. The resulting solid was dried in an oven at 60 ^oC for overnight. Then, the dried sample was dispersed in HCl solution (0.2 M), stirred at room temperature for 6 h. The reaction mixture was filtered and dried at 50 ^oC for 12 h. Then, the sample ZCS-NH_2 was obtained.

Procedure for the preparation of SBA-15-NH_2[11]

SBA-15 was prepared by traditional method according to reported method.[11] The sample of calcined SBA-15 (1.0 g) was dried in vacuum at 120 ^oC for 12 h, then dispersed in anhydrous toluene (60 mL). To the reaction solution, AAPTS (8 mmol/g) was added. And the reaction mixture was refluxed at 65 ^oC for 24 h. After the reaction completed, the reaction mixture was filtered and the filter cake was washed repeatedly with anhydrous toluene and isopropanol. The resulting solid was dried in an oven at 60 ^oC for overnight. Then, the dried sample was dispersed in HCl solution (0.2 M), stirred at room temperature for 6 h. The reaction mixture was filtered and dried at 50 ^oC for 12 h. Then, the sample SBA-15-NH_2 was obtained.

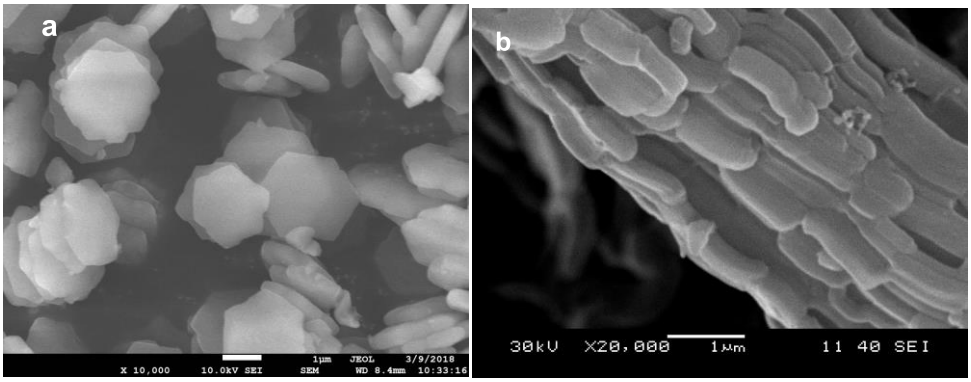


Figure 3. SEM images of samples. a) ZCS-NH_2; b) SBA-15-NH_2

3. General procedure for the synthesis of 2-amino-3-cyano-4*H*-pyrans 3

A solution of ZCS-NH_2 (80 mg), diethyl (2-phenylacetyl)phosphonates **1** (0.225 mmol) and 2-benzylidenemalononitriles **2** (0.15 mmol) in H_2O (1.5 mL) was stirred at 40 ^oC for the time indicated in Table 2. After the 2-benzylidenemalononitriles was consumed as indicated (monitored by TLC), the reaction solution was filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (eluent PE:EtOAc = 10:1) to afford pure products 2-amino-3-cyano-4*H*-pyrans **3**.

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SUPPORTING INFORMATION

Supplementary (synthesis of the catalysts and compounds **3**, ^1H NMR spectra) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27196/102/6.

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