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Short communication

Synthesis of tetrahydro-4*H*-indol-4-one derivatives catalyzed by carbonaceous material

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ABSTRACT

An efficient, high yielding method has been developed for the synthesis of diversity tetrahydro-4*H*-indol-4-one derivatives via a three component, one pot domino reaction from cyclohexane-1,3-diones, amines and nitrostyrenes using carbon functionalized with sulfonic acid group carbonaceous material as catalyst for the first time. The reaction was carried out in water, affording good to excellent yields in short time. The advantages of atom and step economy, green, and scope make this reaction a powerful tool for assembling heterocyclic scaffolds of general chemical and biomedical interest.

1. Introduction

Since the pioneering work of Scharff who opened up the field of 'new forms of carbonaceous materials' [1] e.g. fullerenes [2] and carbyne-like one-dimensional structures [3], tremendous advances have been achieved with wide variety of applications, which include adsorbents, catalysts [4], electrode materials [5], stationary phases in liquid chromatography [6], and so on. Recently, sulfonated carbonaceous materials have received more and more attention for their potential substitute for the traditional homogeneous acid catalysts [7–11]. Very recently, a novel carbon functionalized with sulfonic acid group carbonaceous material ($C–SO_3H$) has been synthesized by our group using one-step hydrothermal carbonization of furaldehyde and hydroxyethylsulfonic acid aqueous solution [12]. The sulfonic acid groups were introduced to the carbonaceous material during the carbonization process (Fig. 1). Furthermore, the carbonaceous material showed comparable catalytic activities to Brønsted acid in esterification and oxathioketalization [12].

Organic synthesis in water is a rapidly growing area of research in modern organic chemistry since it holds great promise for the future in terms of the cheaper and less hazardous production of chemicals [13–15]. It is clear that for the full potential of water as reaction solvent to be realized aqueous metal catalysts are required that can at least match the efficacy of traditional metal catalysts developed for non-aqueous media [16–19]. Accordingly, we began an investigation aimed at developing carbonaceous material catalysts for synthesis in water.

Recently, we developed an efficient and mild method for the synthesis of tetrahydro-4*H*-indol-4-one derivatives with cyclohexane-1,3-diones, amines and (*E*)-(2-nitroprop-1-en-1-yl)benzenes catalyzed by *L*-proline [20]. Besides aryl-substituted amines, alkyl-substituted amines also could be applied in this transformation, providing variation on the C-1 position of tetrahydro-4*H*-indol-4-one derivatives. In addition, this reaction could proceed well and be applied to various available (*E*)-(2-nitroprop-1-en-1-yl)benzenes, giving different choices of substituents on the C-3 position. However, under the similar conditions, (*E*)-(2-nitrovinyl)benzenes, which could give different choices of substituents on the C-2 position, did not work well with cyclohexane-1,3-diones and amines. Following our interest in the field, we decided to investigate the possibility of synthesis of tetrahydro-4*H*-indol-4-one derivatives under heterogeneous conditions with (*E*)-(2-nitrovinyl) benzene.

2. Experimental

All reagents were commercial products without further purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck silica gel GF254 plates. Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were measured on an X-4 melting point apparatus. ^1H NMR spectra were recorded on a 400 MHz instrument (Bruker Avance 400 Spectrometer). Chemical shifts (δ) are given in ppm relative to TMS as the internal reference, with coupling constants (J) in Hz. ^{13}C NMR spectra were recorded at 100 MHz. Chemical shift were reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Elemental analysis was carried out on EuroEA elemental analyzer. ESI-MS was

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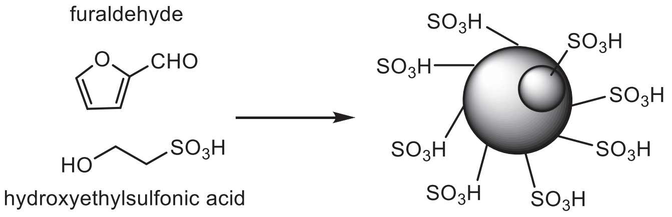


Fig. 1. The synthesis of the carbon functionalized material with sulfonic acid groups.

determined by using the LCQ Fleet HPLC/MS instrument (Thermo Finnigan). HRMS (ESI) was measured with a Bruker Daltonics APEXII instrument.

2.1. Synthesis and property of the carbonaceous material

According to literature method [12], the mixture of the 10 g furaldehyde, 5 g hydroxyethylsulfonic acid and 80 mL deionized water was placed in 100 mL Teflon-lined stainless steel autoclaves, which were heated in an oven at 200 °C for 5 h. The resulting products were filtered, washed with water and methanol, and dried in a vacuum oven at 110 °C for 5 h. The acidity of the carbonaceous material was 2.4 mmol/g, which was determined through the neutralization titration. This carbonaceous material owned much higher acidity than that of the sulfonated carbonaceous materials, which were obtained via the sulfonation of the inactive carbon. The acid strength of the catalyst was determined by thermodesorption of chemisorbed ammonia (NH_3-TPD). The result showed that the catalyst had great acid strength in which ammonia was desorbed at 400 to 600 °C.

2.2. The preparation of tetrahydro-4*H*-indol-4-one derivatives **4**

In a 10-mL reaction vial, nitroolefin (0.5 mmol), cyclohexane-1,3-dione (0.5 mmol), amine (0.5 mmol), carbonaceous material (10 mg) and water (3.0 mL) were mixed and then capped. The mixture was stirred for a given time (Table 2) at 50 °C. Upon completion as shown by TLC monitoring, the reaction mixture was cooled at room temperature and exacted with ethyl acetate (5 mL × 3). The resulting residue was purified by column chromatography on silica gel with the eluent (ethyl acetate/petroleum ether = 1:20–1:5) to give the pure product.

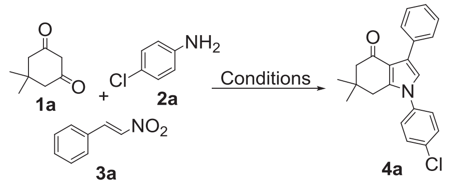
3. Results and discussion

3.1. Optimization of the reaction conditions

In order to find an efficient and sustainable method to synthesize tetrahydro-4*H*-indol-4-one derivatives, various reaction conditions were investigated, including solvent, temperature and catalysts. To choose the optimum solvent, the reaction of 5,5-dimethylcyclohexane-1,3-dione (**1a**), 4-chloroaniline (**2a**) and (*E*)-(2-nitrovinyl)benzene (**3a**) was examined in the presence of carbonaceous material (10 mg) at 50 °C in different solvents, such as MeOH, EtOH, THF, toluene and DMF. The results of the screening of solvents are presented in Table 1 (entries 1–6). As shown in Table 1, the reaction in water gave the best results (Table 1, entry 6). Moreover, to further optimize the reaction temperature, the reaction was carried out in water at the temperature ranging from 30 °C to 80 °C with an increment of 10 °C. As shown in Table 1, when the temperature was increased from 30 °C to 50 °C, the yield of product **4** improved from 42% to 89% (entries 6–11). However, no significant increase in the yield of product **4** was observed as the reaction temperature was raised from 60 °C to 80 °C. Therefore, the temperature of 50 °C was chosen for all further reactions.

For further screening of the reaction conditions, several catalysts were evaluated for their catalytic efficiency in the reaction (Table 1, entries 12–17). However, none of the tested catalysts proved better than carbonaceous material. Next, the effect of catalyst loading on the reaction was evaluated in water. Similar reactions were attempted in the presence of 3, 5 and 20 mg of carbonaceous material. The results from Table 1 (entries 18–20) showed that carbonaceous material (10 mg) was sufficient to push the reaction forward in water. Higher loading of the catalyst (20 mg) did not improve the reaction to a great extent.

Table 1
Optimization of the reaction conditions.[a]



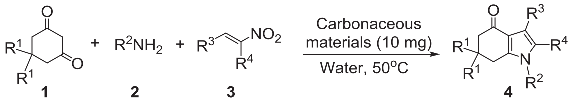
Entry	Solvent	Catalyst (mg)	T (°C)	Time (h)	Yield (%)[b]
1	MeOH	C–SO_3H (10)	50	6	85
2	EtOH	C–SO_3H (10)	50	6	75
3	THF	C–SO_3H (10)	50	6	79
4	C_7H_8	C–SO_3H (10)	50	6	67
5	DMF	C–SO_3H (10)	50	6	56
6	Water	C–SO_3H (10)	50	6	89
7	Water	C–SO_3H (10)	30	24	42
8	Water	C–SO_3H (10)	40	24	73
9	Water	C–SO_3H (10)	60	6	89
10	Water	C–SO_3H (10)	70	6	85
11	Water	C–SO_3H (10)	80	6	84
12	Water	HOAc (10)	50	6	37
13	Water	TFA (10)	50	6	21
14	Water	*p*-TsOH (10)	50	6	45
15	Water	H_2SO_4 (10)	50	6	35
16	Water	Amberlyst-15 (10)	50	6	50
17	Water	Zeolite (10)	50	6	13
18	Water	C–SO_3H (20)	50	6	90
19	Water	C–SO_3H (5)	50	12	71
20	Water	C–SO_3H (3)	50	12	33

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.50 mmol), **3a** (0.50 mmol), catalyst (X mg), and solvent (3.0 mL).
[b] Isolated yields.

3.2. Reaction scope of substrates

With the optimal reaction conditions established, we next investigated the substrate scope of the reaction by employing a variety of nitroolefins and amines. The results are summarized in Table 2. As revealed in Table 2, a range of invaluable tetrahydro-4*H*-indol-4-one derivatives can be synthesized in good to excellent yields. Firstly, the different aromatic amines and aliphatic amines were employed to react with 5,5-dimethylcyclohexane-1,3-dione (**1a**) and (*E*)-(2-nitrovinyl)benzene (**3a**). To our delight, these reactions proceeded smoothly to give tetrahydro-4*H*-indol-4-one derivatives in good to excellent yields (Table 2, entries 1–9). Then, we employed dimethylcyclohexane-1,3-dione (**1a**) and aniline (**2a**) as model substrates and examined various different nitroolefins. The results indicate that a wide range of substituted groups of nitroolefins all gave the desired products in good to excellent yields, which include fluoro, chloro, bromo, methyl, or methoxy groups (Table 2, entries 10–16). It is worth noting that less reactive heterocyclic nitroolefin such as (*E*)-2-(2-nitrovinyl)thiophene (Table 2, entry 17) still displayed high reactivity and led to tetrahydro-4*H*-indol-4-one derivative with excellent yield (90%). Finally, with a broad scope of nitroolefins and amines examined, our attention turned to using other ketones, such as cyclohexane-1,3-dione (**1b**). When cyclohexane-1,3-dione (**1b**) was used under the optimized conditions with different amines and nitroolefins, the reactions also could be carried out smoothly to give the desired products with high yields (Table 2, entries 18–21). In addition, the substrate scope of this transformation was further investigated and a variety of (*E*)-(2-

Table 2
Reaction scope of substrates.[a]



Entry	4	R^1	R^2	R^3	R^4	Time (h)	Yield (%)[b]	Mp (°C)
1	**4a**	Me	4-ClC_6H_4	C_6H_5	H	6	89	Oil
2	**4b**	Me	2-MeC_6H_4	C_6H_5	H	6	86	Oil
3	**4c**	Me	2-$OMeC_6H_4$	C_6H_5	H	6	86	Oil
4	**4d**	Me	2-OHC_6H_4	C_6H_5	H	8	77	Oil
5	**4e**	Me	1-Naphthyl	C_6H_5	H	8	89	Oil
6	**4f**	Me	2-Naphthyl	C_6H_5	H	8	81	Oil
7	**4g**	Me	Bn	C_6H_5	H	6	90	Oil [21]
8	**4h**	Me	$(CH_2)_4Me$	C_6H_5	H	6	88	Oil
9	**4i**	Me	Cy	C_6H_5	H	6	87	75–76
10	**4j**	Me	C_6H_5	4-FC_6H_4	H	6	86	106–108
11	**4k**	Me	C_6H_5	4-BrC_6H_4	H	6	88	Oil
12	**4l**	Me	C_6H_5	4-MeC_6H_4	H	6	81	Oil
13	**4m**	Me	C_6H_5	4-$OMeC_6H_4$	H	6	81	Oil
14	**4n**	Me	C_6H_5	2-ClC_6H_4	H	6	90	Oil
15	**4o**	Me	C_6H_5	2,4-ClC_6H_3	H	6	91	Oil
16	**4p**	Me	C_6H_5	2,6-ClC_6H_3	H	6	83	Oil
17	**4q**	Me	C_6H_5	2-Thienyl	H	6	90	98–100
18	**4r**	H	C_6H_5	C_6H_5	H	6	88	Oil
19	**4s**	H	2-MeC_6H_4	C_6H_5	H	6	91	Oil
20	**4t**	H	2-$OMeC_6H_4$	C_6H_5	H	6	84	Oil
21	**4u**	H	Cy	C_6H_5	H	6	83	Oil
22	**4v**	Me	C_6H_5	C_6H_5	Me	6	85	138–140 [20]
23	**4w**	Me	C_6H_5	4-$NO_2C_6H_4$	Me	6	77	110–112 [20]
24	**4x**	Me	4-ClC_6H_4	C_6H_5	Me	6	80	116–118 [20]
25	**4y**	H	1-Naphthyl	C_6H_5	Me	6	81	128–130 [20]
26	**4z**	H	2,4-MeC_6H_3	C_6H_5	Me	6	82	124–126 [20]

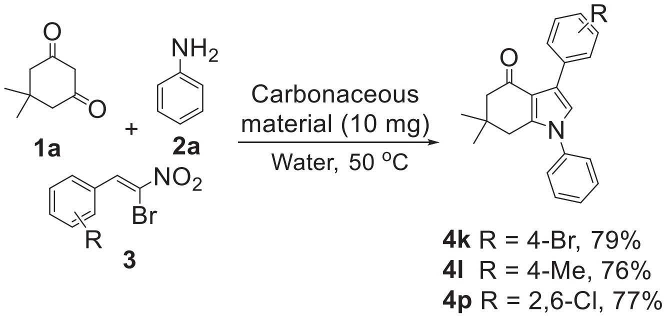
[a] Reaction conditions: **1** (0.50 mmol), **2** (0.50 mmol), **3** (0.50 mmol), carbonaceous material (10 mg) and water (3.0 mL).
[b] Isolated yields.

nitroprop-1-en-1-yl)benzenes was also found to be suitable for this multicomponent reaction (Table 2, entries 22–26).

In addition, our attention focused on finding further application of this catalytic system. Inspired by the structural similarity between the nitrostyrene derivatives and bromonitrostyrene derivatives, we envisaged that the reaction between bromonitrostyrenes, 5,5-dimethylcyclohexane-1,3-dione and amines to give tetrahydro-4*H*-indol-4-one derivatives could take place using the same catalytic system. To our delight, the tetrahydro-4*H*-indol-4-one derivatives also could be given with bromonitrostyrenes instead of nitrostyrenes under the similar cascade process but with different yields (Scheme **1**).

3.3. The recycle of carbonaceous material

One property of carbonaceous material is the reusability. The recovery of the catalyst was very convenient. After reactions, the reaction mixture was filtered with MeOH and water and the solid, dried in vacuum oven at 120 °C for 4 h, could be reused easily. The recovered activities were investigated through the model reaction of 5,5-dimethylcyclohexane-1,3-dione (**1a**), 4-chloroaniline (**2a**) and (*E*)-(2-nitrovinyl)benzene (**3a**) carefully. The yields remained almost unchanged even after the catalyst had been recycled for six times (Fig. 2).



Scheme 1. Synthesis of compounds **4** with (*Z*)-bromonitrostyrenes.

3.4. Mechanism for the domino reaction

The carbonaceous material (C–SO_3H) has been successfully used as acidic catalyst for the esterification of acetic and butanol and the oxathioketalization of cyclohexanone and mercaptoethanol [12]. The domino reaction of cyclohexane-1,3-diones, amines and nitrostyrenes follows the regular mechanism of acid-catalyzed condensations [22,23]. We assumed that the mechanism of the domino reaction probably involves the reaction of C–SO_3H with the cyclohexanone by acting as an acid and playing a complex role in promoting the imine-enamine tautomerization to give radical intermediate [20] as shown in Scheme 2. It is conceivable that, the initial event is the formation of enaminones **B** from an activated **A** and an amine **2**. The intermediate **B** further undergoes a conjugate addition of the nitroolefin **3** to give intermediate **C**. Intermediate **C** undergoes imine-enamine tautomerization to give radical intermediate **D** and C–SO_3H. Finally, intramolecular cyclization followed by elimination of H_2O and HNO from the intermediate **E** afford the desired product **4**.

4. Conclusions

In conclusion, a novel, mild, and environmentally-friendly, one pot synthetic protocol was developed for obtaining a variety of tetrahydro-4*H*-indol-4-one derivatives directly from cyclohexane-1,3-diones, anilines and nitroolefins in aqueous medium in the presence of carbonaceous material. This system could be applied to various available substrate synthetic procedures in good to excellent yields. Therefore, this work not only provides plenty of novel tetrahydro-4*H*-indol-4-one compounds with structural diversity for further bioassay, but also enriches the research contents of carbonaceous material fields.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2014.12.026.

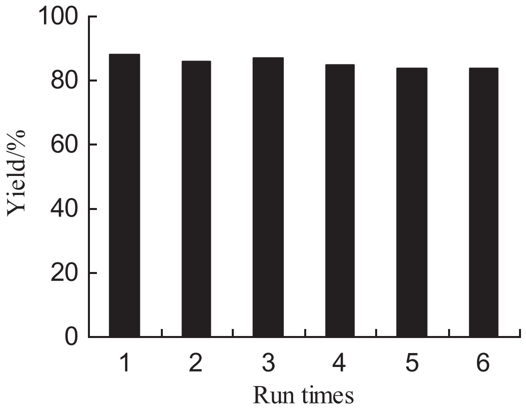
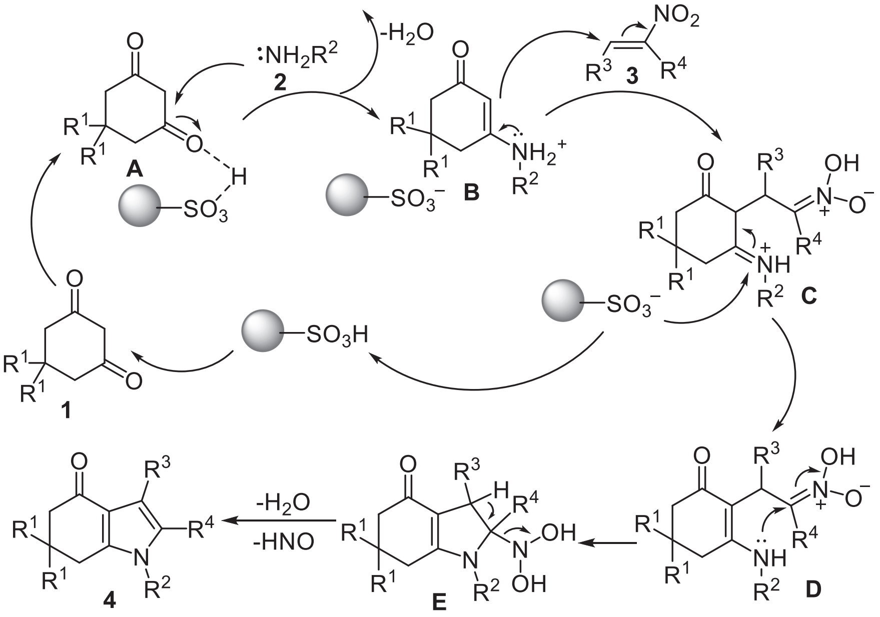


Fig. 2. The recycle of the carbonaceous material.



Scheme 2. Proposed mechanism for the domino reaction catalyzed by carbonaceous material.

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