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PAPER

Catalyst-free Synthesis of 3-Sulfone Nitrile from Sulfonyl Hydrazides and Acrylonitrile in Water

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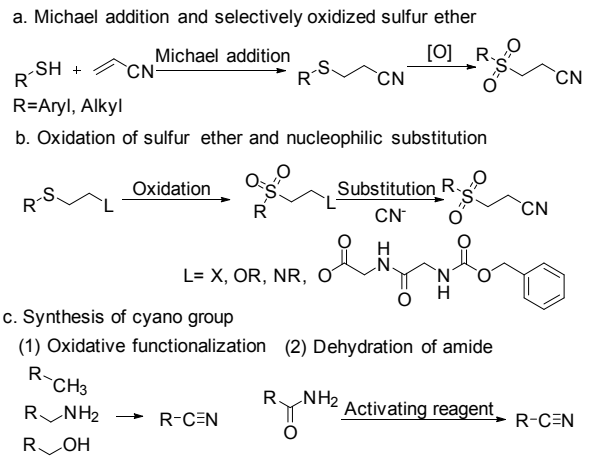
A novel catalyst-free sulfonation reaction of synthesizing 3-sulfone nitrile compounds was demonstrated from sulfonylhydrazides and acrylonitriles in water, without any metal catalyst, ligand or organic solvent. The catalyst-free protocol provides a new synthetic method for the construction of 3-sulfone nitrile compounds with excellent yields. The D_2O experiment sufficiently proved that the catalyst-free sulfonation reaction pass a Michael addition mechnism and the hydrogen of 3-sulfone nitrile come from water.

Introduction

As a starting substrate in the synthesis of sulfur compounds, sulfones have been paid attention[1]. Specially, the sulfone compounds are of broad-spectrum biological activity, thus exhibiting wide application in the production of agricultural chemicals[2] and pesticide[3]. Meanwhile, it is noteworthy that the key step for the construction of sulfoneis the formation of C-S bonds,[6] for which the shorter synthetic steps with available reagents and less toxic waste were desired. On the other hand, nitriles are important unsaturated organic compounds with unsaturated carbon and nitrogen triple bond[4] which could be easily converted to esters[5a], amides[5b], amines[5c], imines[5d] and heterocyclic compounds[5e]. In view of the important roles of sulfone and nitrile compounds, it is of great significance to develop simple method for the construction of sulfone and nitrile compounds, which would provide more efficient and powerful tool for constructing biomedical molecules.

The traditional dominant synthesis of sulfone and nitrile compounds was realized by addition and oxidation of toxic mercaptan or thiophenol[7] (Scheme 1a). The common drawbacks is that a variety of toxic and expensive reagents are often required in those protocols. As shown in Scheme 1b, thioether compounds synthesized from the nucleophilic substitution reaction are easily oxidized to sulfone compounds[8]. Then, the leaving groups, such as halogen, alkoxy group, amidogen or ester groups, were displaced by cyano group, thus finally leading to the formation of sulfone and nitrile compounds. However, some metal catalysts or oxidants, such as $Cu(OAc)_2$[9], tert-butyl hydroperoxide (TBHP)[10] or palladium salt[11] were desired across the reaction process. Meanwhile, various side-products are formed along with the reactions.



Scheme 1. Typical pathways for constructing of sulfone and cyano group

As for the synthesis of nitrile, the main synthesis methods involve direct oxidation functionalization of amines[12a], hydrocarbons[12b], alcohols[13] (Scheme 1c, 1). Besides, the dehydration reaction of amide is also important for the formation of nitrile. However, across those reaction processes, various Lewis acid activating reagents were adopted. Furthermore, α-hydroxyl cyano compounds[14] could also be obtained from aldehydes and ketones by nucleophilic addition. What's more, the selective reduction of α, β-unsaturated nitrile is applied for the synthesis of nitrile as well.[15] In recent

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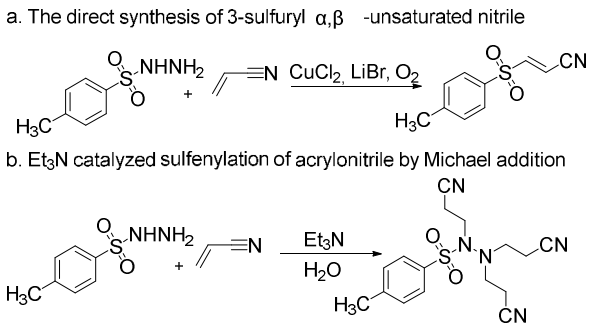
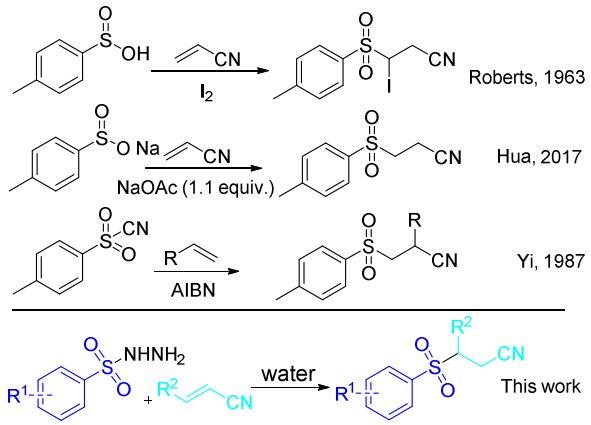
decades, transition metal-catalysed coupling reaction also supplied a serious of new protocols to construct aryl cyano compounds[16].



Scheme 2. The reported reaction of benzenesulfonyl hydrazide and acrylonitrile.

The reaction of benzenesulfonyl hydrazide and acrylonitrile is rare reported. In 2014, Huanfeng Jiang[17] reported that $CuCl_2$ could catalyse the oxidation of benzenesulfonyl hydrazide and acrylonitrile to 3-sulfuryl α, β-unsaturated nitriles under the atmosphere of O_2 (Scheme 2a). The new method shown that benzenesulfonyl hydrazide could generate the nucleophilic reagent to attack the double bond. In 1967, Novacek developed a method that the two nitrogen atoms of benzenesulfonoylhydrazide as nucleophilic reagent attack three double bonds of acrylonitriles by Michael addition reaction (Scheme 2b).[18]



Scheme 3. Synthesis method for the3-sulfone nitriles

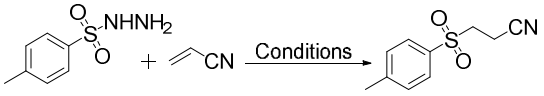
The synthesis methodology of 3-sulfone nitrile compounds are important. The traditional synthetic method was selectively oxidized to cyano group[19a]. In 1963, Robert et al. reported an iodine promoted reaction of *p*-benzene sulfinic acid and acrylonitrile for the construction of 3-iodo-3-tosylpropanenitrile (Scheme 3).[19b] In 2017, Hua reported the reaction of benzene sulfinic acid sodium and acrylonitrile in the promotion of 1.1 equiv. NaOAc for 15 h. In the report, only acrylonitrile was involved.[19c] Next year, the protocol for constructing 3-sulfone nitrile from 4-methylbenzenesulfonyl cyanide and olefin catalysed by AIBN was revealed by Yi.[19d]

With continuous interest in the concepts of "green chemistry"[20], we developed a green catalyst-free chemical methodology to synthesize 3-sulfone nitrile compounds in water (Scheme 3). We reported herein a novel water smoothly promoted sulfonation reaction from sulfonyl hydrazides and α, β-unsaturated nitriles.

Results and discussion

Initially, we chose 4-methylbenzenesulfonohydrazide and acrylonitrile as substrates, and a series of lewis acids as catalyst, such as $Pd(OAc)_2$, $FeCl_3$, $Cu(OAc)_2$ and binol phosphonic acid in water solvent under air atmosphere to optimize the reaction conditions (Table 1, entries 1–4). However, all the attempts only produced a trace amount of 3-tosylpropanenitrile (**3aa**) (Table 1, entries 1-4). Unexpectedly, when in the absence of any catalyst, the corresponding product 3-tospropanenitrile was obtained in 44% yield in water at 100 °C (Table 2, entry 8). And then, when some organic solvents were applied to the reaction, such as alcohol, ester, ether, CH_3CN, DMF and DMSO, the solvents could not promote the reaction at all (Table S1). It is clearly that water played a key role in the reaction. Additionally, when the reaction time was extended to 24 h, the yield decreased to 69% for the hydrolysis of 3-tospropanenitrile (Table 2, entry 6).

Table 1 Optimization of the reaction conditions[a]



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

Entry	Catalyst	Solvent	T/°C	Yield[b]/%
1	$Pd(OAc)_2$	H_2O	100	Trace
2	$FeCl_3$	H_2O	100	Trace
3	$Cu(OAc)_2$	H_2O	100	Trace
4	Binol phosphonic acid	H_2O	100	Trace
5	-	H_2O	80	95
6[e]	-	H_2O	80	69
7[c]	-	H_2O	80	82
8[d]	-	H_2O	80	88

Reaction conditions: [a]**1a** (0.5 mmol, 96.1 mg), **2a** (1 mmol, 0.065 mL), water (1 mL), catalyst (2 mol%), 80 °C, 10 h. [b]Yield of isolated product is based on the sulfonyl hydrazine. [c]H_2O (0.5 mL). [d]H_2O (2 mL). [e] reaction time 24 h.

The influence of reaction time was carefully studied. Along with the reducing of the reaction time, the substrates could not completely transform (Table 2, entries 1-4). Extending the reaction time, hydrolysis of 3-tospropanenitrile leads to a lower yield. (Table 2, entries 4 and 5). The reaction yield could be enhanced to 95% at 80 °C for 10 h. Especially, worthy of our attention is that the occurrence of elevated temperature is unfavourable to the reaction for the hydrolysis of 3-

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tospropanenitrile. (Table 2, entries 8 and 9). Beyond that, lower reaction temperature gave only a lower yield (Table 2, entries 6 and 7).

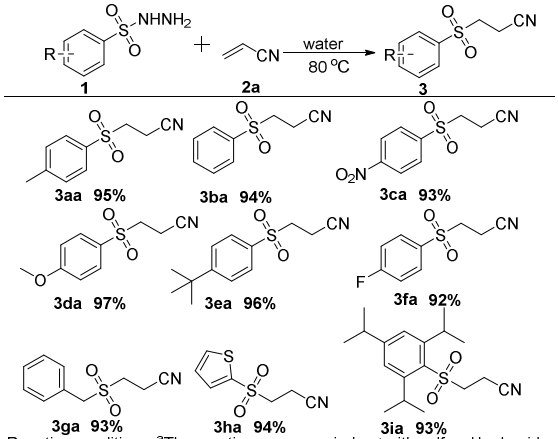
Table 2 Optimization of the reaction time and temperature[a]

Entry	t/h	Solvent	T/°C	Yield[b]/%
1	2	H_2O	80	—
2	4	H_2O	80	39
3	6	H_2O	80	42
4	10	H_2O	80	95
5	24	H_2O	80	69
6	10	H_2O	40	Trace
7	10	H_2O	60	37
8	10	H_2O	100	44
9	10	H_2O	140	49

Reaction conditions: [a]The reactions were carried out with **1a** (0.5 mmol，96.1 mg, 1 eqiv.), **2a** (1 mmol，0.065 mL, 2 eqiv.), solvent water (1 mL). [b]Yield of isolated product is based on the sulfonyl hydrazine.

With the optimal conditions in hand, the scope of this transformation of sulfonylation was examined. The instances of the reaction between acrylonitrile and benzenesulfonohydrazides were shown in Table 3. The optimized reaction conditions could be applicable to a list of substituted sulfonyl hydrazides and acrylonitrile. First, we investigated a variety of arylsulfonylhydrazides to be carried out in the water at the optimized conditions. Regardless of the electron-donating groups (R=Me, tBu, OMe, 2,4,6-trimethyl) or electon-withdrawing groups (R=NO_2, F) on the phenyl ring could be presented to the desired product **3aa**-**3ia** in excellent yields of over 92% (Table 3). However, the arylsulfonyl hydrazides with electron-donating groups gave slightly better yields than that with electron-withdrawing groups. In addition, the steric hindrance 4-tert-Butylbenzensulfonyl hydrazides had slightly effect on the reaction.

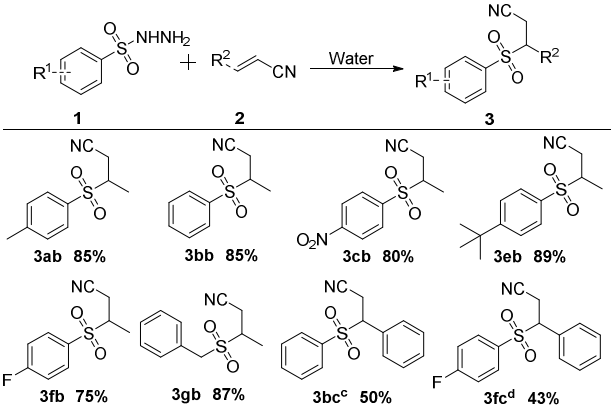
Table 3. Substrate scope of substituted sulfonyl hydrazides with acrylonitrile [a, b]



Reaction conditions: [a]The reactions were carried out with sulfonyl hydrazides (96.1 mg, 0.5 mmol, 1 eq.), acrylonitrile (1 mmol, 0.065 mL, 2eq.), H_2O (1 mL), 80 °C, 10 h. [b]Yield of isolated product is based onsulfonyl hydrazides.

To further establish the generalization of the transformation, β-substitutional acrylonitriles were applied in the transformation. It is noteworthy that the reaction could only be carried out, when temprature was elevated to 120 °C as shown in table 4. When 2-buteneolefine was chosen the substrates, the sulfonation reaction could proceed smoothly with good yields. It is simple to acrylonitrile. 2-buteneolefine with arylsulfonyl hydrazides gave more than 80% of yields (Table 4, **3ab**-**3gb**). Unexpected, the reaction of cinnamonitrile with arylsulfonyl hydrazides only gave moderate yields (Table 4, **3bc**-**3fc**). These experimental results showed that the steric hindrance from the acrylonitrile had obvious inhibitory effect on the reaction.

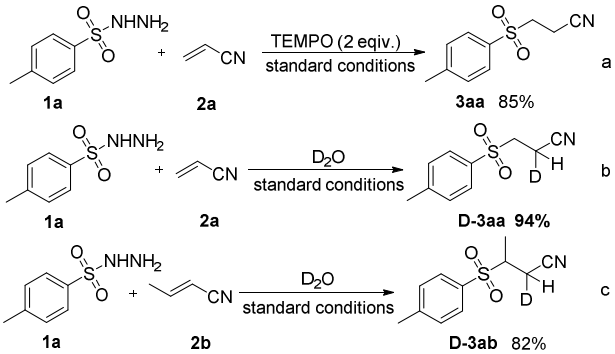
Table 4. Substrate scope of substituted sulfonyl hydrazides with 2-buteneolefine and cinnamonitrile.[a,b]



Reaction conditions: [a]sulfonyl hydrazides (186.1 mg, 1 mmol), and 2-butenenitrile (2 mmol, 0.16 mL), H_2O (1 mL), 120 °C, 10 h. [b]Yield of isolated based on sulfonyl hydrazides. [c] benzenesulfonyl hydrazides (172.2 mg, 1 mmol), and cinnamonitrile (2 mmol, 0.25 mL), H_2O (1 mL), 130 °C, 10 h. [d]4-fluorine benzenesulfonylhydrazine (190.1 mg, 1 mmol), and cinnamonitrile (2 mmol, 0.25 mL), H_2O (1 mL),130 °C, 10 h.

Studies on the reaction mechanisms

To get an insight into the mechanism for the synthesis of sulfonylation process, three control experiments were conducted. Radical trapping experiments were carried out to illustrate whether the reaction involves radical species. The scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 2 equiv.) was introduced under standard conditions to afford **3aa** in 85% yield (Scheme 3a), which implied that the reaction did not occur via a free-radical pathway[21].



Scheme 3. Control experiments to investigate the mechanism.

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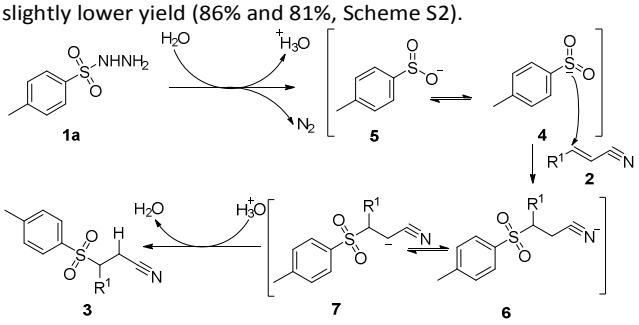
Secondly, to get an insight the hydrogen source of the product **3**, D_2O was applied as the solvent. The reaction afforded a deuterium generation product **D-3aa** and **D-3ab**. (Scheme 3, b). The ^{1}HNMR indicated that the origin of the α-hydrogen atom of 3-sulfone nitrile derived from water. On the other hand, NaOAc or Na_2CO_3 was adopted as base in the standard conditions were added in the revised manuscript. As prediction, the reaction of 4-methylbenzenesulfonohydrazide and acrylonitrile gave the corresponding products with a slightly lower yield (86% and 81%, Scheme S2).



Scheme 4 The proposed mechanism for the reaction

On the basis of our investigations and previous reports, we proposed a possible mechanism, which was shown in Scheme 4. Initially, sulfonylhydrazide is deprotonated catalyzed by water and quickly transformed into a sulphinyl anion **4**, which resonate with the sulfur-centered anion **5** in water. And then, the sulfur-centered anion **5** is selectively added **1a** via Michael addition process, leading to the nitrogen-centered anion **6**, which can resonate with the carbon-centered anion **7**, which affords **3aa** by a subsequent proton transfer (PT) from hydronium ions of the water.

Conclusions

In summary, with the solvent of water, the reaction of sulfonylation and acrylonitrile, 2-buteneolefine, cinnamonitrile were developed, affording 3-sulfone nitrile with excellent yields. The sulfonylation reaction was carried out without any catalyst, additive, ligand or organic solvent and moreover toxic by-products. Mechanism study demonstrated that the hydrogen of 3-sulfone nitrile is from water. In addition, a broad scope of reaction substrates illustrated the wide application of this reaction. The catalyst-free sulfonation reaction pass a Michael addition mechanism and further studies to clearly understand the mechanism are ongoing in our laboratory.

Experimental section

General information Unless otherwise indicated, all commercially available reagents and solvents were used directly from the supplier without further purification.^{1}HNMR and ^{13}CNMR were recorded at ambient temperature in $CDCl_3$ (7.27 ppm). Chemical shift values are expressed as parts per million (ppm) and J values are in Hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet or combination, br. s broad singlet or m: multiplet. Infrared samples were recorded on a Perkin-Elmer 2000FTIR spectrometer. HRMS were recorded on the TOF-HRMS-EI at University of Ji Nan. All reactions were carried out in thick wall pressure pipe unless otherwise indicated.

General procedure for the preparation of 3-sulfone nitrile 1a-1i. To a stirred solution of tetrahydrofuran (5 mL) at 0 °C, 0.5 g benzene sulfonyl chloride was added. The resultant mixture was stirred for 2 minutes. Then 2 mL hydrazine hydrate was dropwise added at 0 °C. The solution was stirred for 25 minutes. The mixed solution was extracted. Organic phase was collected and dried with anhydrous sodium sulfate and concentrated under reduced pressure to get white solid.

General procedure for the preparation of 3-sulfone nitrile 3aa-3ia. benzenesulfoyl hydrazide (0.5 mmol), acrylonitrile (1 mmol, 0.065 mL) and water (1 mL) were added in a thick wall pressure pipe. The resultant mixture was stirred at 80 °C under magnetic stirring for 10 h. After the reaction was completed, the reaction solution was cooled to room temperature. The mixture was extracted with EtOAc (2 × 50 mL) and then the combined organic phase was washed with brine for three times (3 × 10 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc: petroleum ether =1: 2), getting a light white solid.

General procedure for the preparation of 3-sulfone nitrile 3ab-3fc. benzenesulfoyl hydrazide (0.5 mmol), 2-buteneolefine or (1 mmol, 0.065 mL) and water (1 mL) were added in a thick wall pressure pipe. The resultant mixture was stirred at 80 °C under magnetic stirring for 10 h. After the reaction was completed, the reaction solution was cooled to room temperature. The mixture was extracted with EtOAc (2 × 50 mL) and then the combined organic phase was washed with brine for three times (3 × 10 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc: petroleum ether =1: 2), getting a light white solid.

Acknowledgements

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