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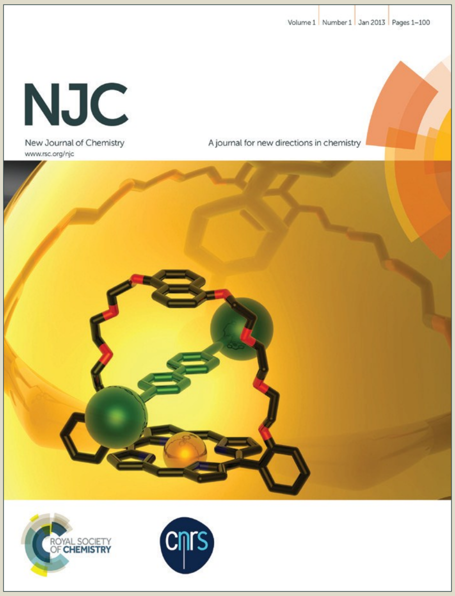

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Metal-Free Catalytic Synthesis of Diaryl Thioethers under Mild Conditions

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Abstract: A novel method to synthesize diaryl thioethers from aryl halides and carbon disulfide catalyzed by 1, 8-diazabicyclo [5, 4, 0] undec-7-enium acetate [DBUH][OAc] ionic liquid (IL) under solvent-free conditions has been developed. This metal-free catalytic system displayed high efficiency for coupling aryl halides by CS_2 to deliver thioethers. Compared to the conventional methods, no any metal catalyst was needed, instead of which the DBU-based ILs played the catalyst and solvent roles simultaneously. Some reactions were carried out at mild conditions (55 °C, 0.5 h), giving moderate to high yields. Moreover, compared with the rare reports, the reaction of the aryl chlorides and fluorides with CS_2 could smoothly react in this catalytic system. The products were easily separated from the ILs which could be reused at least three times. The present method provides an efficient and environment-friendly catalytic approach to synthesize diaryl thioethers.

Introduction

Sulfur-containing functional groups are very important motifs, particularly, diaryl thioethers and their derivatives are common structural features in pharmacologically active compounds and in material sciences.[1] Therefore, the carbon-sulfur (C-S) bond forming methodology is of strategic importance in synthetic chemistry, which has received much attention. Traditional methods for C-S bond formation often require harsh reaction conditions, such as the use of toxic and high boiling polar solvents quinoline, HMPA, or N,N-dimethylacetamide and at elevated temperatures as high as 200 °C.[2] In order to overcome these shortcomings, transition-metal-catalyzed coupling systems were developed. A variety of metals, such as Pd,[3] Co,[4] In,[5] Cu,[6] Fe,[7] and Ni [8] were applied in the synthesis of diaryl thioethers. However, these metal-catalyzed reactions require, odorous, expensive, and less available arenethiols, which are prone to undergo oxidative homocoupling to produce disulfides as byproducts. Alternative sulfur sources have been developed based on aryl halides or pseudo halides, yielding thiourea,[9] thiolates,[10] thioacetamide,[11] potassium ethyl xanthogenate,[12] thiocyanate,[13] metal sulfides,[14] and carbon disulfide.[15] These approaches, however demand higher temperature, excess amount of reagents (>1.0 equiv) and long reaction time(>10 h) with the involvement of metal catalysis, protection of N_2 and usage of organic solvents. Following the guidance of green chemistry, designing an environment-friendly way to synthesize diaryl thioethers is considered of high practical value, particularly for the pharmaceutical companies who

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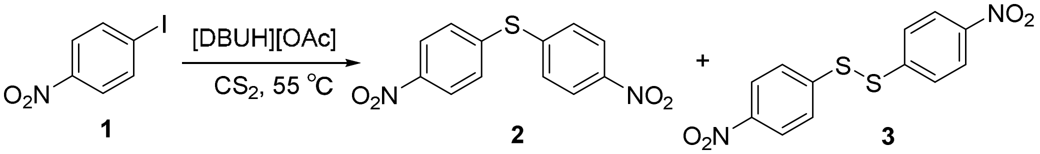
herald for environmental awareness to reduce or even to avoid metal residues. Hence, the metal-free catalytic systems for preparing diary thioethers are highly in demand. Initially, we focus on the green synthetic method to capture CO_2 and CS_2, and convert it into valuable chemicals *via* DBU-based reversible ionic liquid. We found it is effective to fix CX_2 (O, S) in DBU-based IL to construct C-C and C-S bond. [16] To screen the catalytic effect of this type IL, we synthesized different ILs, such as [DBUH][OAc], [DBUH][Cl], [DBUH][HSO_4], [DBUH][PhCOO] and [DBUH] [EtCOO] etc. While other ILs are solid except [DBUH][OAc] at room temperature. Herein, we report a simple, metal-free green method for the synthesis of the diaryl thioethers based on the novel recyclable catalytic systems via reaction of CS_2 and aryl halides by employing ionic liquid [DBUH][OAc] as catalyst and solvent at the same time, and it is a part of our continuous effort toward C−S bond formation using CS_2.[16]

Result and discussion

The influence of the amount of CS_2 on the reaction was initially investigated. When 0.25 equiv of CS_2 (relative to 1-iodo-4-nitrobenzene **1**) was introduced to the model reaction at the presence of [DBUH][OAc], **2** was obtained in 76% yield (Table 1, entry 1). The best yield (91%, Table 1, entry 2) was obtained when 0.5 equiv of CS_2 was used. Both conditions yielded non-observable compound **3**. However, when the amount of CS_2 was increased to 1.0, 2.0 and 3.0 equiv, the ratio of disulfide products **3** was gradually increasing (Table 1, entries 3, 4 and 5). It might be caused that excess CS_2 reacted with reactant **1**, forming 4-nitrobenzenethiol which can produce by-product **3** by coupling reaction. The results showed that 0.5 equiv of CS_2 was the optimal condition to synthesize diaryl thioethers.

Table 1. The influence of the amount of CS_2 on the reaction.[a]



Entry	Equiv of CS_2	Yield of **2** (%)[b]	Yield of **3** (%)[b]
1	0.25	76	0
2	**0.5**	**91**	**0**
3	1.0	48	36
4	2.0	44	40
5	3.0	33	45

[a] Reaction conditions: 1-iodo-4-nitrobenzene (1 mmol), [DBUH][OAc] (5 mmol) at 55 °C. [b] Isolated yield.

Generally, the organic solvents are necessary in this type reaction of synthesizing diaryl thioethers.[2-8] However, some high boiling point organic solvents are hardly

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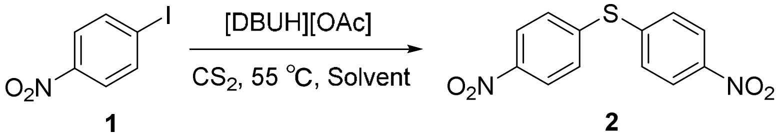
removed during the post-treatment if they are employed in reaction, which will pollute the products. Especially for the medicine industry, the residual solvents in pharmaceuticals are strictly limited. Development of a solvent-free green method would minimize the residual solvent problems. In our study, the influence of different solvents and solvent-free on the reaction were investigated. The non-polar solvents acetonitrile, toluene and ethyl acetate were used in this system and good yields were obtained (Table 2, entry 2-4). However, the polar solvents (alcohols, acetic acid and water) tended to give yields between low to trace amount, presumably due to the low solubility of the substrate in polar solvents. Surprisingly, the solvent-free condition yielded the best yield of 91% in our reaction (Table 2, entry 1). We speculated that [DBUH][OAc] played both solvent and catalytic roles at the same time and formed a highly efficient catalytic system for this coupling reaction. For this model, we screened the temperature ranging from room temperature to 100℃. It was found that the best temperature was 55℃, and the reaction cannot go through completely at lower temperature and has by-product at higher temperature, so we selected 55℃ as the optimum temperature.

Table 2. The reaction of 1-iodo-4-nitrobenzene and CS_2 in different solvents with [DBUH][OAc].[a]



Entry	Solvent	Yield [b] (%)
1	Solvent-free	91
2	CH_3CN	72
3	$PhCH_3$	71
4	$CH_3COOCH_2CH_3$	71
5	CH_3CH_2OH	59
6	CH_3OH	23
7	CH_3COOH	Trace
8	H_2O	Trace

[a] Reaction conditions: 1-iodo-4-nitrobenzene (1 mmol), CS_2 (0.5 mmol), [DBUH][OAc] (5 mmol), solvent (5 mmol) at 55 °C. [b] Isolated yield.

In order to expand the scope of this catalytic system, various aryl halides were then examined. The common samples of different aryl iodides and bromides were tested firstly (Table 3). The experimental results disclosed that the substrates bearing electron-withdrawing groups have higher reactivity, which reacted smoothly to render the corresponding symmetric diaryl thioethers in moderate to high yileds (60-91%). The nitro group on the substrates are especially favorable for increasing the reactivity, the reaction of which could be carried out in mild conditions (55 °C, 0.5 h) (Table 3,

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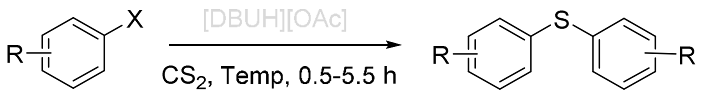
entries 1, 2, and 6). The coupling of heteroaryl bromides with CS_2 also performed well (Table 3, entries 10 and 11). Nonetheless, the substrates without substituent group or with the electron-donating groups gave relatively low yields (Table 3, entries 8 and 9).

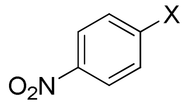
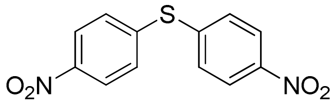
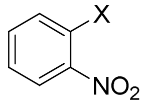
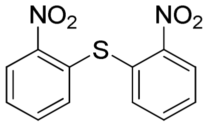
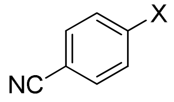
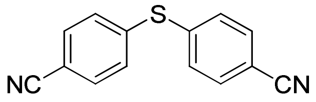
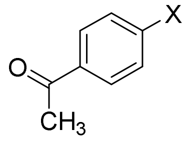
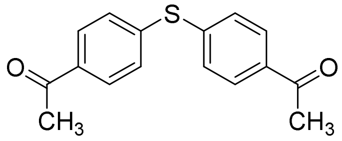
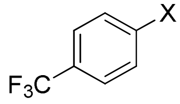
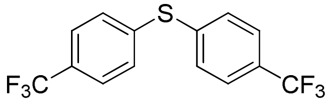
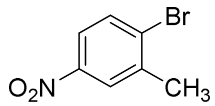
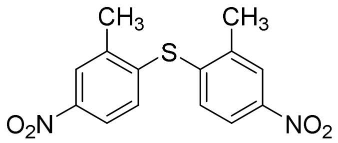
Significantly, the catalyst [DBUH][OAc] used in this reaction was found to remain catalytic ability after being three times. Yet the product yields only decline slightly (reducing from 91% in the first run to 81% in the third run). This result indicated that this catalytic system was recyclable for catalyzing the coupling reaction of CS_2 with aryl halides.

Table 3. Synthesis of various diaryl thioethers from aryl iodides and bromides.[a]



4

5

Entry	Substrate	Product	Temp (°C)	Time (h)	Yield (%)[b]
1	 X = I, Br		55	0.5	91, 87[c], 81[d] (X = I) 87 (X = Br)
2	 X = I, Br		55	0.5	88 (X = I) 87 (X = Br)
3	 X = I, Br,		95	5.5	78 (X = I) 72 (X = Br)
4	 X = I, Br		95	5.5	68 (X = I) 65 (X = Br)
5	 X = I, Br		120	5.5	68 (X = I) 60 (X = Br)
6			55	1.5	81

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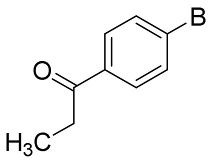
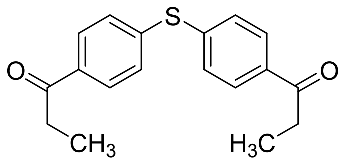
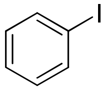
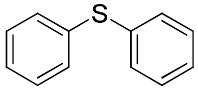
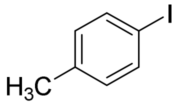
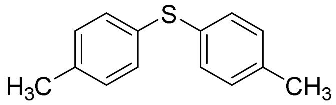
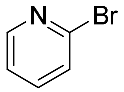
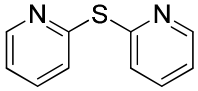
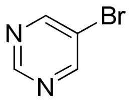
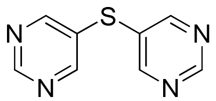
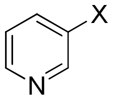
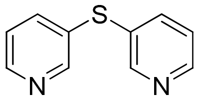
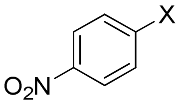
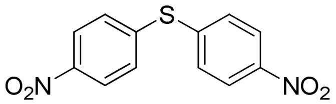
7			95	5.5	73
8			145	5.5	35
9			145	5.5	30
10			100	5.5	80
11			100	5.5	70
12	 X = I, Br		120	5.5	72 (X = I) 65 (X = Br)

[a] Reaction conditions: aryl halides (1 mmol), CS_2 (0.5 mmol), [DBUH][OAc] (5 mmol); [b] Isolated yield, [c] Yield of the product (runs: 2), [d] Yield of the product (runs: 3).

In the cross-coupling reactions, aryl chlorides and fluorides, particularly the latter, are often much less reactive than the corresponding iodides and bromides.[17] In order to demonstrate the generality of substrates and further expand the application of this catalytic system, we employed aryl chlorides and fluorides as the substrates (Table 4). It was fortunately found that both aryl chlorides and fluorides could also react well with CS_2 in this catalytic system to furnish diaryl thioethers in considerably high yields. Some substrates could even react and achieve good yields at as low temperature as 55 °C (Table 4, entries 1 and 2). Our catalytic system do not need special metal catalysts and higher temperature as the previous literatures illustrated for the coupling reaction of aryl chlorides and fluorides.[18]

Table 4. Synthesis of various diaryl thioethers from aryl chlorides and fluorides.[a]

Entry	Substrate	Product	Temp(°C)	Time(h)	Yield (%)[b]
1			55 (X =Cl) 60 (X = F)	0.5	85 (X = Cl) 92 (X = F)

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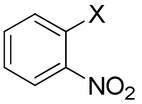
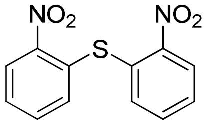
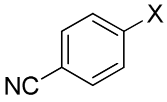
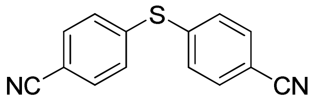
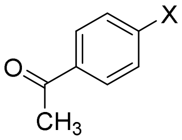
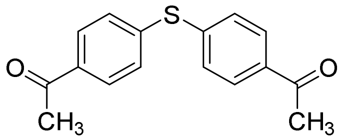
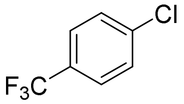
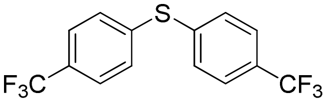
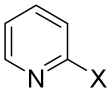
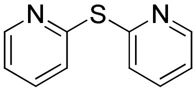
	X = Cl, F				
2	 X = Cl, F		55	1.0	82 (X = Cl) 80 (X = F)
3	 X = Cl, F		95 (X =Cl) 100 (X =F)	5.5	60 (X = Cl) 65 (X = F)
4	 X = Cl, F		95	5.5	55 (X = Cl) 50 (X = F)
5			120	5.5	40
6	 X = Cl, F		120	5.5	70 (X = Cl) 62 (X = F)

[a] Reaction conditions: aryl halides (1 mmol), CS_2 (0.5 mmol), [DBUH][OAc] (5 mmol), [b] Isolated yield.

A plausible pathway was outlined in Scheme 1. The ILs [DBUH][OAc] **6** reacted with CS_2 to give intermediate **7** and **8,** which was reported by literature,[15] and then the nucleophilic substitution reaction occurred between the substrates and **8** to yield intermediate **9** which was detected by GC/MS (Fig. 1). The key intermediate **10**, was formed by the reaction of [DBUH][OAc] and **9**, which then reacted with aryl halides via nucleophilic substitution, resulted the product **5** and another ILs [DBUH][X] (X= I, Br, Cl, F). Acetic acid reacted with [DBUH][X] and yielded **6**, becoming a recyclable catalytic system.

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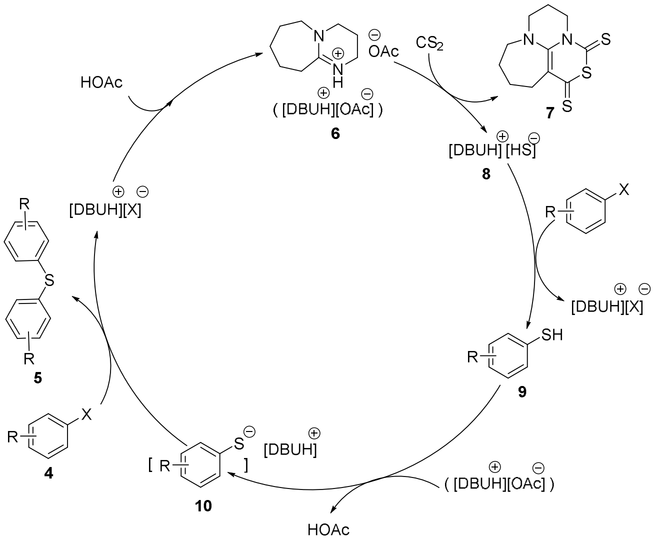

Scheme 1. The possible reaction pathway

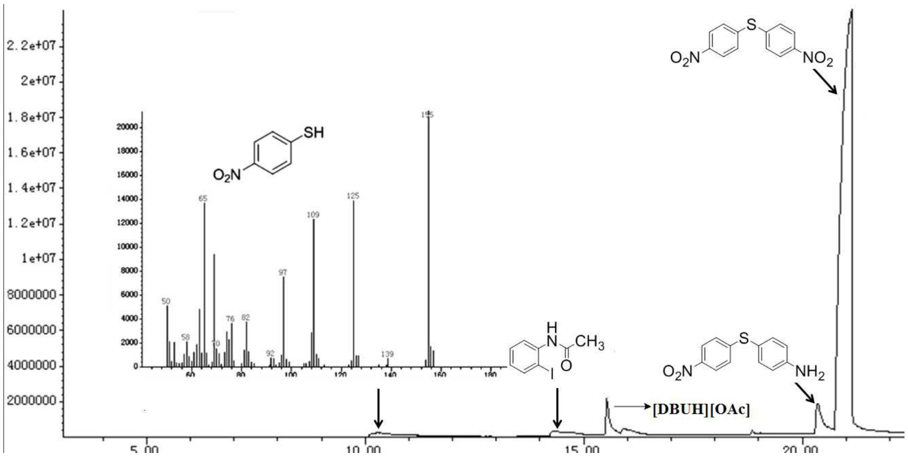

Figure 1. The GC/MS data of the intermediate **9**.

Conclusion

In summary, we have developed an efficient [DBUH][OAc]-promoted coupling reaction of different aryl halides with CS_2 as an inexpensive, conveniently available and easy-to-handle sulfide surrogate under solvent-free conditions. The generated products were easily separated from the ILs which could be reclaimed at least three times. The C-S bond formation is readily accomplished to afford symmetrical thioethers in moderate to high yields under mild conditions. The operational simplicity and environmental friendliness of this method highlights its potential application in organic synthesis and pharmaceutical industry.

Experimental

General procedure for preparation of ionic liquid [DBUH][OAc]: To a 150 mL three-necked flask was added 20 mmol of DBU. Acetic acid (20 mmol) was then added slowly dropwise in ice bath. After dropwise addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 24 h. The oil residue was

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dried in vacuo at 60℃ for 24 h to afford [DBU][OAc] as a light yellow, viscous liquid. The characteristic data is accord with the literature.[19]

The general procedure of preparing all products is similar. Taking the model reaction as an example (Table 3, entry 1): 1-Iodo-4-nitrobenzene (1 mmol) and [DBUH][OAc] (5 mmol) were added into a 10 mL bottle. The reactor was placed in a heating apparatus at 55 °C. After 0.5 h, the residue was suspended in Et_2O, and the mixture was purified by column chromatography. An example was presented in supporting materials.

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