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DBSA-catalyzed Friedel–Crafts alkylation of cyclic ketene dithioacetals with alcohols in water

Haifeng Yu [a,*], Peiqiu Liao [b]

[a] School of Chemistry and Life Science, Anshan Normal University, Anshan, Liaoning 114007, China
[b] Department of Chemistry, Northeast Normal University, Changchun, Jilin 130024, China

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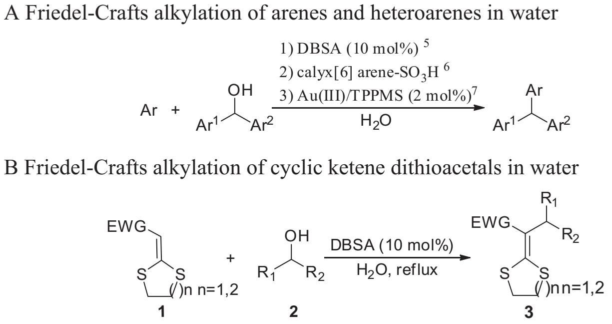
ABSTRACT

A novel DBSA-catalyzed Friedel–Crafts alkylation of cyclic ketene dithioacetals, internal alkenes with highly nucleophilic carbon atom adjacent to the electron-withdrawing group, with alcohols in water has been developed. The reaction is efficient in the presence of catalyst loading as low as 10 mol % in water at reflux, and a wide range of alkylated ketene dithioacetals are synthesized in excellent yields.

Introduction

Over the past decade, organic reaction in water without the use of organic solvents is regarded as an important research topic in green chemistry since the use of water can remarkably reduce the discharge of harmful organic solvents.[1] Friedel–Crafts alkylation is one of the most prominent C–C bonds-forming reactions, and has been widely applied in the synthesis of many natural products and biologically active compounds.[2] Among them, the alkylation of alcohols as green alkylating reagents has attracted considerable attention because water is the exclusive by-product, which establishes an environmentally benign alkylation process.[3] Friedel–Crafts alkylation of arenes or heteroarenes with alcohols had been well documented in the past years,[4] and their alkylations catalyzed by dodecylbenzenesulfonic acid (DBSA),[5] calyx[6] arene sulfonic acids,[6] or Au(III)/TPPMS[7] in water have been realized successfully in recent years (Scheme 1A). Nevertheless, the letters on the alkylation of olefins with alcohols are rare, owing to the lower nucleophilicity.



Scheme 1. Friedel–Crafts alkylation in water.

Ketene dithioacetals, which are versatile and significant reagents in organic synthesis,[8–12] are considered as polarized internal olefins with highly nucleophilic carbon atom adjacent to the electron-withdrawing group (EWG) due to the push–pull effect of the alkylthio group and the EWG at either side of the double bond.[8] Recently, the high nucleophilic nature of ketene dithioacetals grabbed the attention for the alkylations with alcohols and a few letters have appeared.[13] These Letters include $BF_3 \cdot OEt_2$-mediated alkylation of ketene dithioacetals with various alcohols,[13a] $CuBr_2$ (30 mol %)-catalyzed alkylation of ketene dithioacetals with benzylic alcohols,[13b] and $FeBr_3$ (30 mol %)-catalyzed the Friedel–Crafts alkylation between ketene dithioacetals and propargyl alcohols.[13c] However, all the reported reactions are performed in organic medium such as acetonitrile and dichloromethane, which can lead to serious environmental and safety problems. Therefore, from the green chemistry point of view, the development of environmental compliant alkylation of ketene dithioacetals and alcohols is a great importance and

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* Corresponding author. Tel.: +86 412 2960076; fax: +86 412 2960065.
E-mail address: yuhf68105@sina.com (H. Yu).

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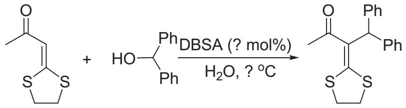
Table 1
Screening of the reaction conditions[a]



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

Entry	DBSA (mol %)	*T* (°C)	Time (h)	Yield[b] (%)
1	0	Reflux	20	0
2	10	Reflux	20	95
3	7.5	Reflux	20	77
4	7.5	Reflux	36	82
5	10	90	20	81
6	10	90	40	87

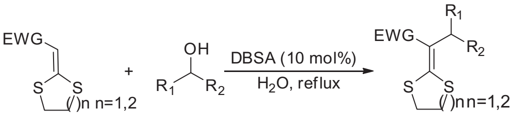
[a] Reagents and conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), H_2O solvent (1 mL).
[b] Isolated yield.

necessity. Recently, we have been interested in the organic reaction of ketene diacetals in water, and reported dodecylbenzenesulfonic acid (DBSA) efficiently catalyzes thioacetalization and synthesis of dithianes utilizing ketene dithioacetals as odorless thiol equivalent in water.[14] As part of our continuing research in the context, we more recently investigated DBSA-catalyzed Friedel–Crafts alkylation of cyclic ketene dithioacetals with alcohols in water to gain an environmental compliant alkylation process. Herein, we would like to report our finding (Scheme 1B).

Results and discussion

According to our previous work,[14] we selected a surfactant-type Brønsted acid DBSA as catalyst to investigate Friedel–Crafts alkylation of cyclic ketene dithioacetals and alcohols in water. The reaction of 1-(1,3-dithiolan-2-ylidene)-propan-2-one **1a** (0.25 mmol)

Table 2
DBSA catalyzed Friedel–Crafts alkylation of cyclic ketene dithioacetals **1** with alcohols **2** in water[15]



1 **2** **3**

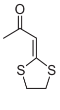
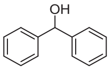
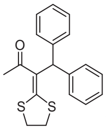
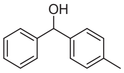
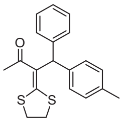
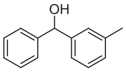
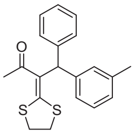
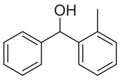
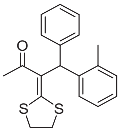
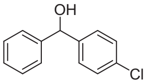
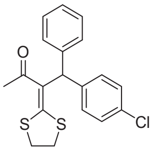
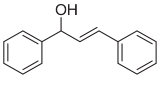
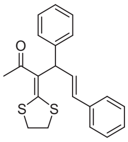
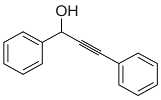
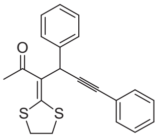
Entry	1	2	Time (h)	3	Yield[a] (%)
1	 **1a**	 **2a**	20	 **3a**	95
2		 **2b**	20	 **3b**	93
3		 **2c**	20	 **3c**	92
4		 **2d**	20	 **3d**	94
5		 **2e**	20	 **3e**	93
6		 **2f**	20	 **3f**	92
7		 **2g**	20	 **3g**	90

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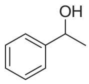
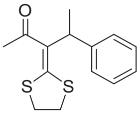
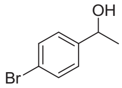
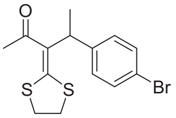
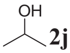
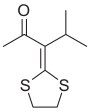
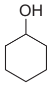
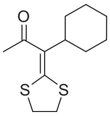
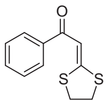
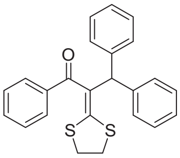
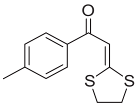
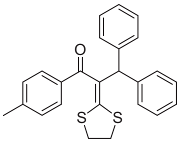
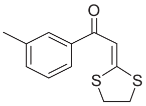
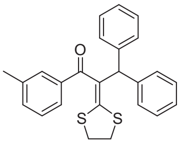
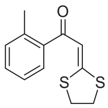
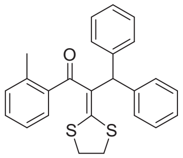
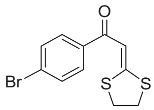
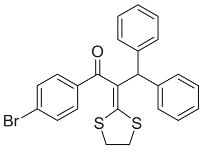
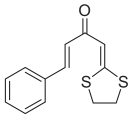
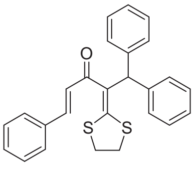
Table 2 (*continued*)

Entry	**1**	**2**	Time (h)	**3**	Yield[a] (%)
8		 **2h**	36	 **3h**	85
9		 **2i**	36	 **3i**	87
10		 **2j**	20	 **3j**	0(93)[b]
11		 **2k**	20	 **3k**	0(95)[b]
12	 **1b**	**2a**	20	 **3l**	96
13	 **1c**		20	 **3m**	95
14	 **1d**		20	 **3n**	93
15	 **1e**		20	 **3o**	92
16	 **1f**		20	 **3p**	94
17	 **1g**		20	 **3q**	90

(*continued on next page*)

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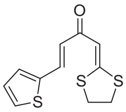
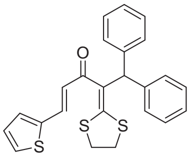
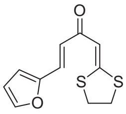
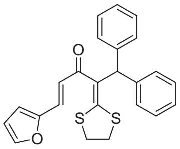
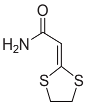
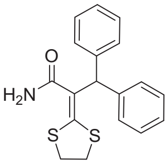
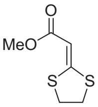
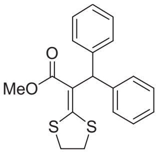
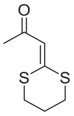
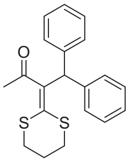
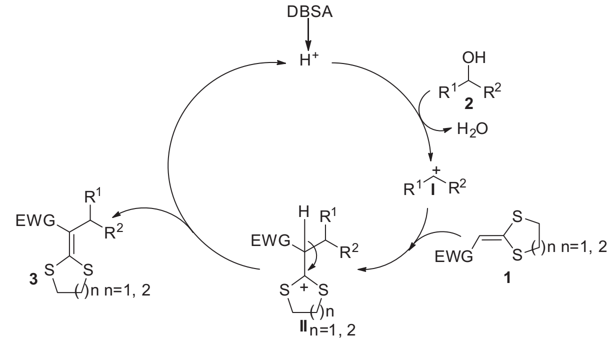
Table 2 (*continued*)

Entry	1	2	Time (h)	3	Yield[a] (%)
18	 **1h**		20	 **3r**	91
19	 **1i**		20	 **3s**	90
20	 **1j**		36	 **3t**	89
21	 **1k**		30	 **3u**	89
22	 **1l**		40	 **3v**	86

[a] Isolated yield.
[b] Recovery yield of **1a**.

with diphenylmethanol **2a** (0.30 mmol) was selected as model reaction to optimize the catalyst loading and reaction temperature. The results are summarized in Table 1. Apparently, the catalyst loading and reaction temperature have a dramatic influence on this reaction. We initially examined the reactions in the presence of various catalysts loading in water at reflux (Table 1, entries 1–4). It is found that using 10 mol % of DBSA, the reaction proceeded efficiently, affording the desired product 3-(1,3-dithiolan-2-ylidene)-4,4-diphenylbutan-2-one **3a** in excellent yields (Table 1, entries 2). It is noteworthy that **3a** is easily obtained after being filtered and washed with water since it is a white solid and deposits from the reaction system once formed. However, on changing the amount of DBSA from 10 mol % to 7.5 mol %, the reaction efficiency is markedly diminished even prolonging reaction time (Table 1, entries 3 and 4). With this, we select 10 mol % of DBSA as catalyst. Next, we tested the influence of reaction temperature in the presence of 10 mol % of DBSA, and found the reaction proceeded less efficiently below 100 °C (Table 1, entries 5 and 6). Accordingly, the optimal reaction conditions are 10 mol % of DBSA as catalyst and at reflux.

With the optimal reaction conditions in hand, we next investigate the scope of the reaction. The results are summarized in Table 2. Initially, we checked the scope of the Friedel–Crafts alkylation in terms of alcohols. We found that a variety of alcohols such as diarylmethanols **2a–e**, allylic alcohols **2f**, propargylic alcohol **2g**, and benzylic alcohols **2h** or **2i** are efficiently reacted with ketene dithioacetal **1a**, thereby afforded the alkylated ketene dithioacetals **3a–i** in quantitate yields (Table 2, entries 1–9). However, propan-2-ol **2j** or cyclohexanol **2k** and **1a** showed no reaction under the selected reaction conditions, and **1a** was recovered in nearly quantitative yields (Table 2, entries 10 and 11). Later, we explored the reaction outcome with different ketene dithioacetals (Table 2, entries 12–21). We found that a divergent ketene dithioacetals such as 2-(1,3-dithiolan-2-ylidene)-1-aryl-ethanones **1b–f**, (*E*)-1-(1,3-dithiolan-2-ylidene)-4-aryl-but-3-en-2-ones **1g–i**, 2-(1,3-dithiolan-2-ylidene)-acetamides **1j**, and methyl 2-(1,3-dithiolan-2-ylidene) acetate **1k** are suitable for the Friedel–Crafts alkylation with alcohols. The reactions with diphenylmethanol **2a** gave the corresponding alkylated ketene dithioacetals **3l–u** in excellent yields. It is noteworthy that the reaction of heteroaryl–



Scheme 2. Proposed mechanism for DBSA-catalyzed Friedel–Crafts alkylation of **1** with **2** in water.

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alkenoyl ketene dithioacetals **1h** and **1i** with diphenylmethanol **2a** exclusively formed the desired products **3r** and **3s** respectively in good yields. In these reactions, the by-product of Friedel–Crafts alkylation occurring in hetero-arylates was not detected (Table 2, entries 18 and 19). Furthermore, we examined the reaction outcome with 1-(1,3-dithian-2-ylidene)propan-2-one **1l** by reacting with alcohols **2a**, and found that the reaction proceeded successfully under the optimal conditions, thereby delivered the target products **3v** in high yields (Table 2, entry 22).

Based on our previous Letters[14] and the current experimental results, we proposed a possible mechanism (Scheme 2). It is clear that the reaction of **1** and **2** is presumably initiated by formation of carbocation **I** from alcohol **2**, by removal of hydroxyl group of **2** activated by hydrion. Nucleophilic attack at the cationic carbon atom of **I** by α-carbon of **1** forms the more stable intermediate **II** stabilized by the adjacent two alkylthio groups. α-Hydrogen elimination of **II** occurs to afford the desired **3** as well as hydrion which can complete the catalytic cycle.

Conclusions

In summary, we developed the first DBSA-catalyzed Friedel–Crafts alkylation of activated internal olefins i.e., ketene dithioacetals **1** with alcohols **2** in water, leading to the synthesis of alkylated ketene dithioacetals **3** in excellent yields, which is one of the most efficient and environmentally friendly synthetic strategies for alkylation of olefins.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05.062.

References and notes

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15. General procedure (the reaction of **1a** and **2a** as example): The mixture of **1a** (40 mg, 0.25 mmol), **2** (55.2 mg, 0.30 mmol), and DBSA (8.18 mg, 0.025 mmol) in water (1 mL) in round-bottom flask was stirred at reflux until **1a** was completely consumed by TLC monitoring. After the mixture was allowed to cool down to ambient temperature, some white solid deposited from the reaction system. The white solid was collected by filtration and washed with aqueous $NaHCO_3$ (10%, 3 × 25 mL) and water (3 × 25 mL) to give alkylation product **3a** 77.4 mg (Yield: 95%).

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