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## H<sub>2</sub>O-controlled selective thiocyanation and alkenylation of ketene dithioacetals under electrochemical oxidation†

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Efficient and H<sub>2</sub>O-controlled selective thiocyanation and alkenylation of internal olefins, to afford tetra-substituted olefins under electrochemical oxidation, has been successfully developed. This transformation can present a critical feature wherein neither exogenous oxidants nor catalysts are required. Notably, such an electrochemical oxidation-based synthetic strategy exhibits excellent tolerance towards functional groups and can be easily scaled up with good efficiency.

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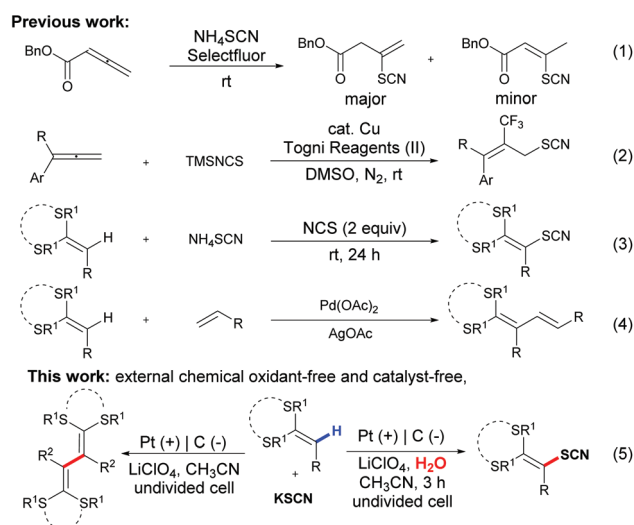
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### Introduction

The functionalization of olefins, especially the thiocyanation and alkenylation of internal alkenes, has been recognized as one of the most efficient approaches toward the construction of structurally diverse polysubstituted alkene molecules.<sup>1</sup> As ubiquitous building blocks for various polysubstituted alkenes, the structural units of thiocyanate olefins have been proven to be key synthetic intermediates toward a wide variety of sulfur-containing compounds such as sulfides,<sup>2</sup> thioesters<sup>3</sup> and sulfur heterocycles.<sup>4</sup> A wide range of applications has stimulated the development of new approaches to obtain organic thiocyanate compounds.<sup>5</sup> During the past few decades, the methodologies concerning the thiocyanation of functionalized olefins have been extensively studied for the construction of aryl thiocyanate and diene compounds. For example, in 2014, Laali's group reported a Selectfluor-mediated thiocyanation of allenes yielding thiocyanated alkene derivatives in low to moderate yields (Scheme 1, eqn (1)).<sup>6</sup> Subsequently, Liu and coworkers provided a convenient bifunctional strategy to obtain CF<sub>3</sub>-containing allyl thiocyanates by copper catalyzed –SCN group nucleoaddition of allenes (Scheme 1, eqn (2)).<sup>7</sup> Recently, Wang's group disclosed the thiocyanation of ketene dithioacetals under stoichiometric chemical oxidation conditions (Scheme 1, eqn (3)).<sup>8</sup> Moreover, Yu's group reported a palladium-catalyzed direct cross-coupling

of α-oxoketene dithioacetals with terminal alkenes (Scheme 1, eqn (4)).<sup>9</sup> In spite of the above developments achieved, the effective methods towards the thiocyanation and alkenylation of internal alkenes are scarce and remain a challenge under catalyst-free and oxidant-free conditions.

During the past few decades, the transition-metal-catalyzed and stoichiometric chemical oxidant-mediated thiocyanation of heteroatom compounds, such as indoles<sup>10</sup> and imidazoles,<sup>11</sup> have been intensively studied for the construction of C–S bonds.<sup>10,11</sup> However, the direct coupling of internal alkenes with thiocyanation reagents to construct the C–S bonds under transition-metal-free and exogenous oxidant-free conditions has not yet been disclosed. In recent years, the



Scheme 1 Thiocyanation and alkenylation of alkenes.

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electrochemical-aided synthesis route, as an extremely powerful tool, has become an interesting and widely applied green preparation method, wherein simply by using an anode electrons are removed to realize the C–S bond construction.<sup>12</sup> In continuation of our efforts on the functionalization of alkenes<sup>13</sup> and construction of sulfone-containing compounds,<sup>14</sup> here we wish to report a novel and highly selective thiocyanation and alkenylation of internal alkenes regulated by water under constant current conditions. Neither metal catalysts nor external chemical oxidants are required in this transformation.

In terms of substrate scope, various ketene dithioacetals can be compatible in the present protocol, generating the desired products in up to 98% yields. More notably, the so-developed synthesis protocol can be scaled up to gram quantities of the desired products in favourable yields at room temperature. To the best of our knowledge, this is the first success on the H<sub>2</sub>O-controlled selective thiocyanation and alkenylation of ketene dithioacetals *via* electrochemical oxidation under metal- and oxidant-free conditions.

## Results and discussion

Initially, 2-(1,3-dithiolan-2-ylidene)-1-phenylethan-1-one (**1a**) and potassium thiocyanate (KSCN) were chosen as the model substrates to optimize the reaction conditions (Table 1). Upon optimizing key reaction parameters, the best results were obtained by performing the electrolysis at room temperature with a constant current of 5 mA cm<sup>-2</sup> in an undivided cell equipped with a platinum plate as the anode, a graphite rod as the cathode and lithium perchlorate (LiClO<sub>4</sub>) as the electrolyte in the solvent of CH<sub>3</sub>CN. Under these conditions, the desired

product **3aa** was obtained in 96% yield (Table 1, entry 1). Both increasing and decreasing the constant current would lead to decreased reaction yields and faradaic efficiency under the same reaction conditions (Table 1, entries 2 and 3).

In order to demonstrate that the cathodic depolarizer is not lithium ions but water, ammonium salts such as <sup>n</sup>Bu<sub>4</sub>NClO<sub>4</sub>, <sup>n</sup>Bu<sub>4</sub>NBF<sub>4</sub>, and <sup>n</sup>Bu<sub>4</sub>NPF<sub>6</sub> can also be used as electrolytes to obtain the desired products, which decreases the reaction efficiency compared with lithium perchlorate (Table 1, entries 4–6). This indicates that the cathodic depolarizer is not affected by the lithium ions but water. Moreover, the effects of the electrode materials were also investigated. Lower reaction yields were obtained when the platinum plate (anode) or graphite rod (cathode) was replaced by the graphite rod (anode) or platinum plate (cathode) (Table 1, entries 7 and 8). Undoubtedly, the control experiments have shown that no desired product was obtained without electricity and water (Table 1, entries 9 and 10). In addition, when the reaction was carried out under the O<sub>2</sub> atmosphere, the yield of the desired product was severely reduced to 45% (Table 1, entry 11). Furthermore, the desired product was not formed when oxygen was directly used as the oxidant in the absence of electricity (Table 1, entry 12). These results indirectly indicate that water cannot serve as the potential oxidant when it is split to generate oxygen and hydrogen even after several hours of electrochemical processing.

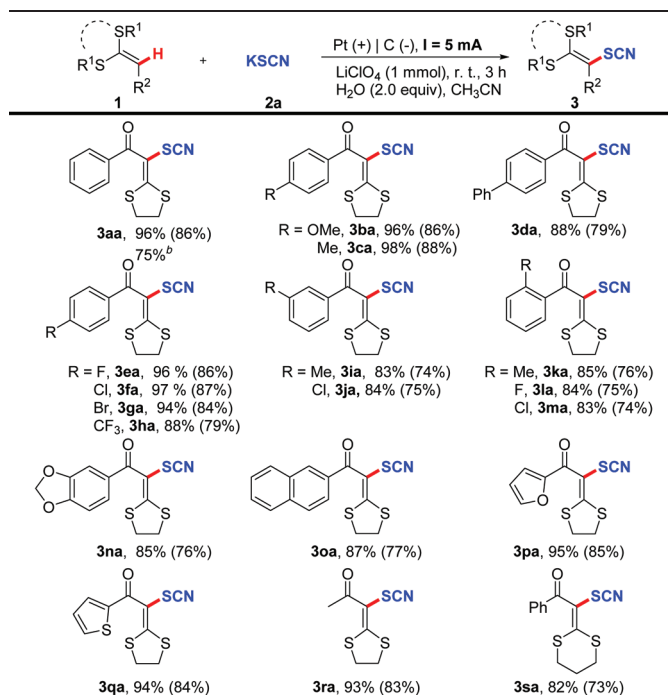
Interestingly, the home-coupling product **4a** was obtained in 81% yield when the reaction was carried out at 5 mA cm<sup>-2</sup> without water (Table S1,† entry 1), which otherwise may be considerably difficult to realize by the selective cross-coupling using the conventional chemical oxidation methods. The control experiments showed that no product was detected in the absence of electricity or KSCN or in the presence of water (Table S1,† entries 2–4). Moreover, ammonium salts such as <sup>n</sup>Bu<sub>4</sub>NClO<sub>4</sub>, <sup>n</sup>Bu<sub>4</sub>NBF<sub>4</sub>, and <sup>n</sup>Bu<sub>4</sub>NPF<sub>6</sub> can also be used as electrolytes to obtain the desired products, which decreases the reaction efficiency compared with lithium perchlorate (Table S1,† entries 5–7). This indicates that the home-coupling process is not affected by lithium ion reduction. Cyclic voltammetry experiments demonstrate that ketene dithioacetals and potassium thiocyanate are more susceptible to oxidation in the presence of water under electrochemical conditions, which should play a key role in the selective thiocyanation and alkenylation of the internal olefins.

Under the optimized conditions described above, the scope and limitations of the reactions of various internal alkene substrates were explored, and the results are summarized in Table 2. The benzoyl alkenes containing electron-donating or electron-withdrawing substituents on the aryl groups are more suitable for the present protocol (**3aa–3ha**). It is noteworthy that various substituted functional groups such as Ph, F, Cl, Br and CF<sub>3</sub> are more compatible with this protocol affording corresponding products (**3da–3ha**), which may be used for further functionalization to synthesize other kinds of important complex molecules. Moreover, when the hydrogen at the *O*- or *m*-position of the benzene ring was substituted separately

**Table 1** Optimization of the reaction conditions<sup>a</sup>

Entry	Deviation from standard conditions	Yield <sup>b</sup> (%)
1	None	96 (86)
2	7 mA instead of 5 mA, 3 h	85 (76)
3	3 mA instead of 5 mA, 3 h	60 (54)
4	<sup>n</sup> Bu <sub>4</sub> NClO <sub>4</sub> instead of LiClO <sub>4</sub>	54 (48)
5	<sup>n</sup> Bu <sub>4</sub> NBF <sub>4</sub> instead of LiClO <sub>4</sub>	72 (64)
6	<sup>n</sup> Bu <sub>4</sub> NPF <sub>6</sub> instead of LiClO <sub>4</sub>	63 (56)
7	C (+) Pt (-) instead of Pt (+) C (-)	75 (67)
8	Pt (+) Pt (-) instead of Pt (+) C (-)	78 (70)
9	Without H <sub>2</sub> O	Trace
10	Without current	n.d.
11	O <sub>2</sub> instead of N <sub>2</sub>	45 (40)
12	Without current in O <sub>2</sub>	n.d.

<sup>a</sup> Standard conditions: Pt anode, C cathode, constant current = 5 mA, **1a** (0.25 mmol), **2a** (0.5 mmol), LiClO<sub>4</sub> (4 equiv.), H<sub>2</sub>O (2.0 equiv.), MeCN (10.0 mL), r. t., N<sub>2</sub>, 3 h. n.d. = not detected. <sup>b</sup> Isolated yields (faradaic efficiency).

Table 2 Scope of thiocyanation of ketene dithioacetals<sup>a</sup>

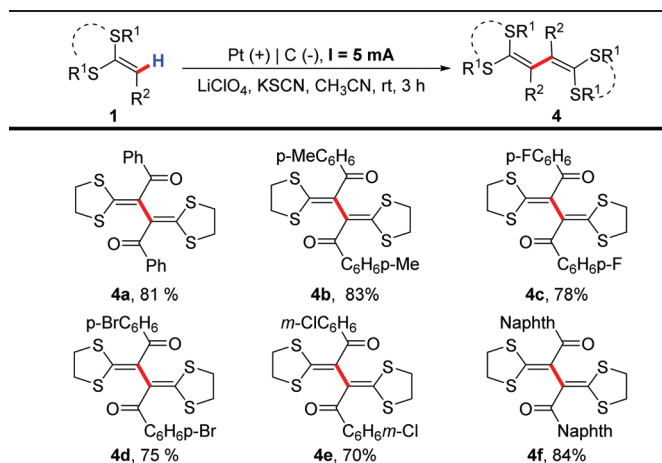
<sup>a</sup> Standard conditions: Pt anode, C cathode, constant current = 5 mA, **1a** (0.25 mmol), **2a** (0.5 mmol), LiClO<sub>4</sub> (4 equiv.), H<sub>2</sub>O (2.0 equiv.), MeCN (10.0 mL), r. t., N<sub>2</sub>, 3 h. n. d. = not detected. Isolated yields shown (faradaic efficiency). <sup>b</sup> NH<sub>4</sub>SCN instead of KSCN.

by methyl, F, and Cl groups, the activation reactions were not negatively affected (**3ia–3ma**). It should be noted that the ketene dithioacetals substituted by the steric hindrance, heterocyclic or alkyl groups can still react smoothly under the established conditions (**3na–3ra**). To our delight, altering the dithioalkyl moiety to –S(CH<sub>2</sub>)<sub>3</sub>S– could also lead to the desired product in a moderate yield (**3sa**).

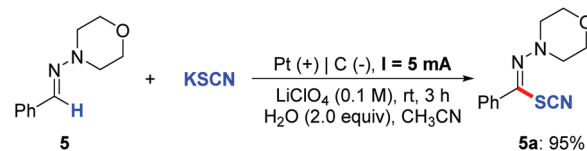
Later, the scope of the electrochemical home-coupling of ketene dithioacetals was investigated, and the results are summarized in Table 3. The experimental results show that the electron effect and steric hindrance cannot adversely affect the progress of the reactions, and the desired corresponding products could be obtained in moderate yields (**4a–4f**). In addition, the reaction scope could also be extended to the carbon–nitrogen  $\pi$  bonds, in which the aldehyde-derived hydrazone **5** underwent the thiocyanation process smoothly, achieving the corresponding product **5a** in 95% yield under the developed reaction conditions (Scheme 2).

Furthermore, the synthetic applicability of this method was investigated on a gram-scale reaction between **1f** and KSCN. As shown in Scheme 3, the reaction could afford **3fa** in 80% yield. The results confirm that the present protocol can serve as a practical and efficient strategy to obtain products *via* the thiocyanation of ketene dithioacetals.

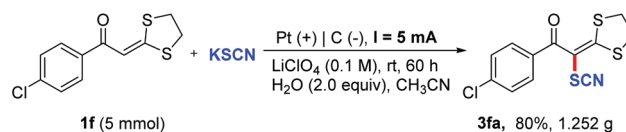
To gain further insights into the transformation mechanism, control experiments and cyclic voltammetry (CV) experiments were carried out. Firstly, cyclic voltammetry experiments

Table 3 Scope of home-coupling of ketene dithioacetals<sup>a</sup>

<sup>a</sup> Standard conditions: Pt anode, C cathode, constant current = 5 mA, **1a** (0.25 mmol), KSCN (0.5 mmol), LiClO<sub>4</sub> (4 equiv.), MeCN (10.0 mL), r. t., N<sub>2</sub>, 3 h. n. d. = not detected. Isolated yields shown.

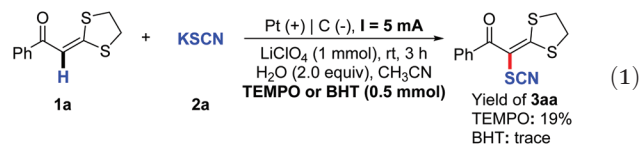


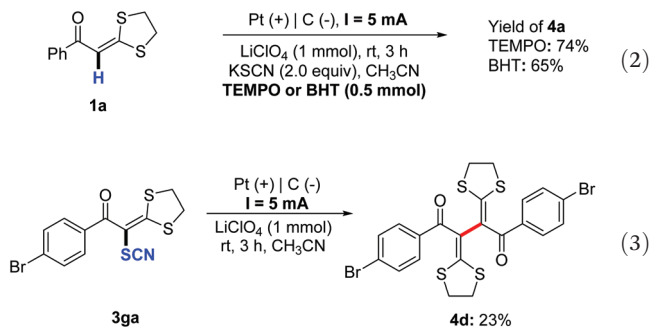
Scheme 2 The thiocyanation of hydrazones.



Scheme 3 Gram-scale experiment.

were carried out in order to explain the selectivity of the internal olefin thiocyanation and alkenylation. When LiClO<sub>4</sub> was used as the electrolyte in 0.1 M CH<sub>3</sub>CN solution, the oxidation potential of substrate **1a** was 1.57 V (*vs.* Ag/AgCl), whereas the peak potential of **1a** was decreased to 1.45 V (*vs.* Ag/AgCl) when two equivalents of water were added. Subsequently, the peak potential of KSCN could also significantly reduce from 0.79 V to 0.73 V in the presence of water (Fig. S1†). These results indicate that substrate **1a** and KSCN should be more easily oxidized on the surface of the electrode under electrochemical conditions in the presence of water, and the thiocyanation of ketene dithioacetals can be selectively achieved.<sup>15</sup>





Moreover, several control experiments were performed to gain a deeper insight into the reaction mechanism. The thiocyanation reaction was almost inhibited when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-tertbutyl-4-hydroxytoluene (BHT) was added into the present reaction system, suggesting that the reaction presumably adopted a radical pathway (eqn (1)). At the same time, under the described conditions, the alkenylation reaction was not affected when the inhibitor TEMPO or BHT was added into the system (eqn (2)).

Furthermore, in order to investigate the role of KSCN in home-coupling of ketene dithioacetals, the desired product could be initially obtained in 24% yield when the stoichiometric amount of KSCN was changed to 10 mol%. Also, when KOAC was used instead of KSCN, a trace amount of the product was also obtained (Table S1,<sup>†</sup> entries 8 and 9). Subsequently, the home-coupling product **4d** could be obtained in a 23% yield when the thiocyanation product **3ga** was carried out under the alkenylation conditions (eqn (3)). The data demonstrate that the thiocyanation products may be an intermediate of the home-coupling reaction. Based on the above experimental results, we speculate that KSCN may play a dual role in home-coupling of ketene dithioacetals, one as a base and the other as a leaving group, similar to pseudohalogens.<sup>16</sup>

On the basis of the above results and previous reports,<sup>12d,e,13e,15,16</sup> a possible reaction pathway was outlined and is described in Scheme 4. Initially, KSCN could be oxidized to (SCN)<sub>2</sub>, and then converted to thiocyanyl radical **A** by the electrochemical anodic oxidation in the presence of water. Subsequently, radical addition of thiocyanyl radical **A** to ketene dithioacetal **1a** afforded the radical intermediate **B**,

from which a proton might be abstracted by another thiocyanyl radical **A** to furnish the desired product **3aa** (path A). Moreover, ketene dithioacetal **1a** was oxidized to form a radical cation intermediate **C** on the surface of the anode in the absence of water, and then reacted with alkaline electrophile KSCN to obtain intermediate **D**, which loses an electron and a proton to yield intermediate **3aa**. Finally, the home-coupling product **4d** is obtained by the removal of the pseudohalogen group SCN (path B).

## Conclusions

In conclusion, we have disclosed a highly selective and H<sub>2</sub>O-controlled thiocyanation and alkenylation of ketene dithioacetals under electrochemical oxidation. Compared with the previously reported methods for functionalizing internal olefins, this electrochemical oxidation-based synthetic strategy can avoid the usage of transition metals and external oxidants. A series of new drug candidate products can be obtained in good to high yields with excellent tolerance towards functional groups under electrochemical oxidation conditions. Especially, this H<sub>2</sub>O-controlled synthesis strategy of anodic oxidation can be easily scaled up, which is beneficial for a wide range of practical applications. Studies on using green thiocyanation and alkenylation to synthesize other bioactive compounds are currently underway in our laboratory.

## Conflicts of interest

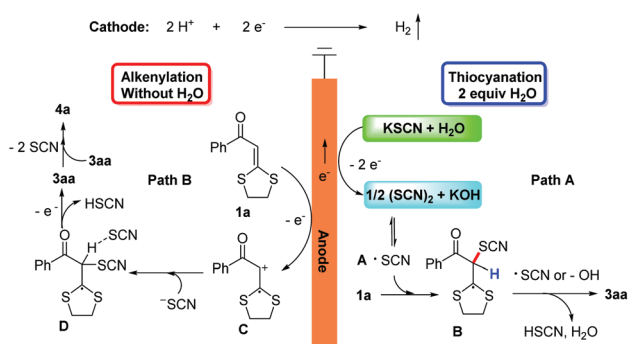
There are no conflicts to declare.

## Acknowledgements

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Scheme 4 Postulated reaction pathway.

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