

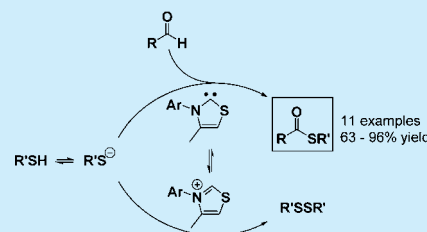
## Organocatalyzed Anodic Oxidation of Aldehydes to Thioesters

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## S Supporting Information

**ABSTRACT:** A method has been developed for the direct conversion of aldehydes to thioesters via integration of organocatalysis and electrosynthesis. The thiazolium precatalyst was found to facilitate oxidation of thiolate anions, leading to deleterious formation of disulfide byproducts. By circumventing this competing reaction, thioesters were obtained in good-to-excellent yields for a broad range of aldehyde and thiol substrates. This approach provides an atom-efficient thioesterification that circumvents the need for stoichiometric exogenous oxidants, high cell potentials, or redox mediators.



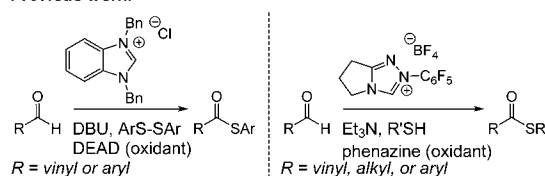
Oxidative transformations of aldehydes are excellent methods for efficient functional group interconversion, and organocatalyzed methods using *N*-heterocyclic carbenes (NHCs) in particular have received considerable attention.<sup>1</sup> In general, NHCs facilitate aldehyde oxidations via nucleophilic attack on the aldehyde to ultimately give an electron-rich Breslow intermediate<sup>2</sup> or pseudobenzyl alcohol. These intermediates are readily oxidized to give an electrophilic acyl azolium species capable of acyl transfer to various nucleophiles.

Although direct aldehyde-to-ester conversions have received the greatest focus,<sup>3</sup> access to a range of other functional groups have also been reported.<sup>4</sup> Among them, direct thioesterification of aldehydes has received relatively little attention, which is unfortunate considering the importance of thioesters as synthetic intermediates and biologically active compounds.<sup>5,6</sup> Herein, we describe the development of a direct aldehyde-to-thioester synthesis via organocatalyzed anodic oxidation of aldehydes that circumvents the need for stoichiometric oxidants, high electrochemical cell potentials, or redox mediators.

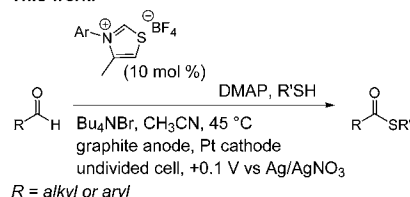
Despite the superficial similarities with the more familiar NHC-catalyzed oxidative esterification of aldehydes, thioester formation poses unique challenges due to the potentially deleterious formation of disulfides. This not only consumes the thiol coupling partner but also may lead to rapid irreversible sulfenylation of NHC catalysts, as reported by Rastetter.<sup>7</sup> While Yadav recently reported the successful use of diaryl disulfides in NHC-catalyzed aldehyde thioesterifications (Scheme 1); it is unclear if moderate-to-good yields are attainable with lower than 30 mol % catalyst loadings.<sup>5d</sup> The delicate reactivity of thiols and thiolates signifies the importance of selecting a compatible oxidant. This task was highlighted in the report by Takemoto, in which phenazine emerged as an optimal stoichiometric oxidant after screening several candidates (Scheme 1).<sup>5c</sup> Notably, each reported general method for NHC-catalyzed aldehyde thioesterification requires a *stoichiometric* exogenous oxidant. This reduces overall efficiency, can limit chemoselectivity, and may give deleterious byproducts

## Scheme 1. Representative Methods for Conversion of Aldehydes to Thioesters Using NHC Catalysts and Stoichiometric Oxidants, in Comparison with the Present Work

## Previous work:



## This work:

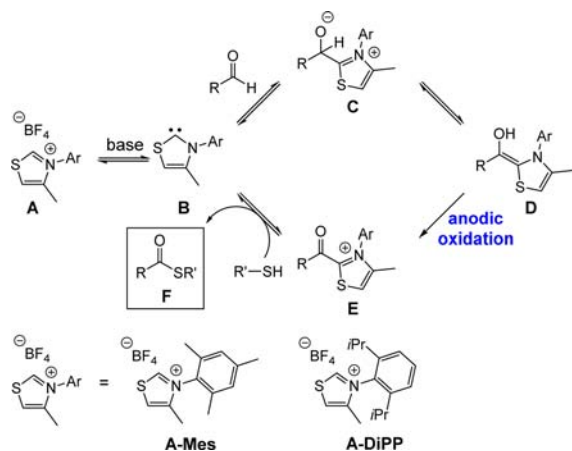


(e.g., hydrazides are produced from hydrazobenzenes when azobenzene is used as an oxidant).<sup>5f</sup>

We recently demonstrated a highly atom-efficient method of NHC-catalyzed oxidative esterification via integration of organocatalysis and electrosynthesis.<sup>8–11</sup> This approach enables one-pot oxidative couplings without the need for stoichiometric oxidants, which we speculated would provide an improved method of thioester synthesis. The catalytic cycle (Figure 1) involves *in situ* deprotonation of a thiazolium precatalyst (A) to give the active NHC catalyst B. Reaction of the NHC with aldehyde substrates leads to an equilibrium mixture strongly favoring the addition adduct C over the electroactive Breslow intermediate D.<sup>12</sup> While oxidations of (pseudo)benzyl alcohols such as C have been demonstrated,<sup>1b</sup> the oxidation

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**Figure 1.** Proposed catalytic cycle for NHC-catalyzed anodic oxidation of aldehydes to thioesters.

potentials measured via cyclic voltammetry and used herein for potentiostatic oxidation are consistent with oxidation of the Breslow intermediate **D**.<sup>8,13,14</sup> The irreversible anodic oxidation of **D** provides acyl thiazolium species **E**, which is intercepted by the thiol substrate to give the thioester product **F** and regenerate the active catalyst **B**. Notably, oxidations at the anode are balanced by the formation of H<sub>2</sub> gas at the cathode.

We began our attempts at direct thioesterification by applying the conditions we previously developed for esterifications.<sup>8</sup> Specifically, reactions were conducted in an undivided cell using a graphite anode and Pt basket cathode, with DBU and CH<sub>3</sub>CN as the base and solvent, respectively. After screening a series of azolium precatalysts, we found 4-methyl-3-(2,4,6-trimethylphenyl)thiazolium tetrafluoroborate (**A-Mes**) and 4-methyl-3-(2,6-diisopropylphenyl)thiazolium tetrafluoroborate (**A-DiPP**) to be most effective (see Supporting Information). Unfortunately, these conditions gave only a 26% yield of thioester when *p*-tolualdehyde and butanethiol were used in the initial screenings.

Analysis of the reaction mixture revealed that the remainder of the butanethiol had been oxidized to the corresponding disulfide. We speculated that electrochemical oxidation of either the thiol or thiolate anion was a likely cause. Notably, the Breslow intermediates display two one-electron oxidations clustered around  $-1.0$  V and  $-0.8$  V vs SCE; butanethiol and the butanethiolate anion display oxidation potentials at  $+1.12$  and  $-0.85$  V vs SCE, respectively. This suggested to us that cell potentials capable of oxidizing the Breslow intermediate would also be capable of oxidizing thiolates, but that thiols would not be readily oxidized.

Interestingly, our investigations also revealed results consistent with an azolium-mediated oxidation of thiolates. Specifically, in the absence of an applied voltage, the combination of a thiazolium cation and thiolate anion resulted in efficient formation of disulfides (Table 1). In the absence of either reactant, no disulfide was observed (entries 1 and 2). DBU was found to be a sufficiently strong base to facilitate thiolate and thus disulfide formation (entry 3). Similarly, sodium butanethiolate was easily oxidized in the presence of the thiazolium salt (cf. entries 4 and 5). In an attempt to minimize thiolate formation, we investigated DMAP and found that disulfide was formed to a much lesser extent (entry 7).

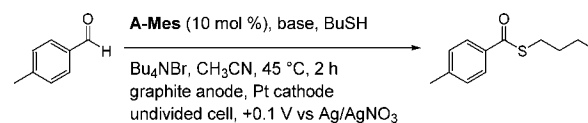
We further investigated the influence of base strength and concentration during the anodic oxidation to form thioesters

**Table 1.** Investigation into Disulfide Formation<sup>a</sup>

$\text{MSBu} \xrightarrow[\text{CD}_3\text{CN, rt, 2 h}]{\text{additive, base}} \text{BuSSBu}$				
entry	additive	MSBu	base	% BuSSBu <sup>b</sup>
1	<b>A-Mes</b>	HSBu	none	0
2	none	HSBu	DBU	0
3	<b>A-Mes</b>	HSBu	DBU	25
4	none	NaSBu	none	0
5	<b>A-Mes</b>	NaSBu	none	15
6	none	HSBu	DMAP	0
7	<b>A-Mes</b>	HSBu	DMAP	4

<sup>a</sup>Reactions conducted at rt in a screw cap NMR tube under N<sub>2</sub> with 0.150 M **A-Mes** (as indicated), 0.150 M MSBu, and 0.150 M base in CD<sub>3</sub>CN. <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

**Table 2.** Base Screen for NHC-Catalyzed Anodic Oxidation of Aldehydes to Thioesters<sup>a</sup>



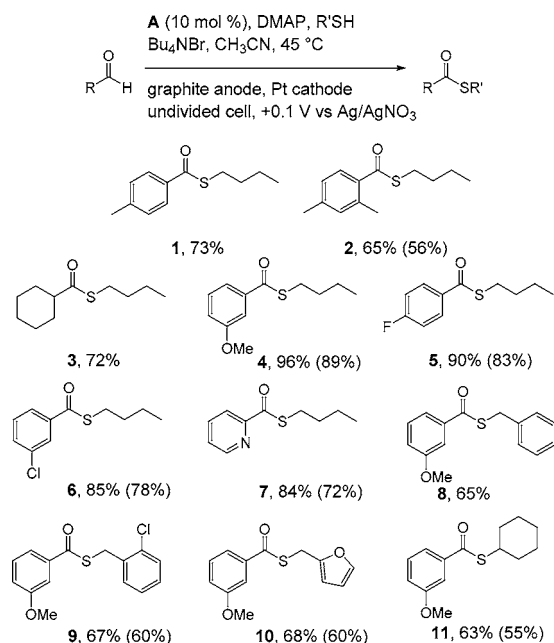
entry	base (M)	% thioester <sup>b</sup>	% BuSSBu <sup>b</sup>
1	DBU (0.15)	<1	57
2	K <sub>2</sub> CO <sub>3</sub> (0.15)	15	15
3	DMAP (0.15)	21	10
4	DMAP (0.075)	11	4
5	DBU (0.075)	3	58
6	pyridine (0.075)	0	0
7	K <sub>2</sub> CO <sub>3</sub> (0.075)	5	3
8	DIPEA (0.075)	20	13
9	DABCO (0.075)	15	10
10	NEt <sub>3</sub> (0.075)	30	12

<sup>a</sup>Reactions conducted at 45 °C in a three-neck flask under N<sub>2</sub> with a graphite anode, Pt basket cathode, 0.045 M Bu<sub>4</sub>NBr, 0.150 M aldehyde, 0.300 M R'SH, and constant cell potential of  $+0.1$  V (vs Ag/AgNO<sub>3</sub>). <sup>b</sup>Determined by GC-MS and <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

(Table 2). After 2 h, DBU (100 mol % relative to aldehyde) gave a 57% yield of disulfide (entry 1) and only trace amounts of thioester. Use of K<sub>2</sub>CO<sub>3</sub> or DMAP each resulted in improved yields of thioester (entries 2 and 3, respectively), with DMAP giving a 21% yield of thioester while producing a 10% yield of disulfide. To further minimize thiolate formation, we reduced the amount of DMAP to 50 mol % (entry 4). Although the yield of thioester dropped to only 11% in the 2-h run, the ratio of thioester to disulfide (2.75:1) was improved in comparison with those having higher base loadings. With the exception of pyridine (entry 6), which was found to be completely ineffective, we continued to observe a greater yield of thioester than disulfide when maintaining a 50 mol % base loading (entries 7–10).

We next explored the aldehyde and thiol substrate scope; key results are depicted in Scheme 2. Unactivated and *ortho*-substituted aldehydes gave good yields of thioester, as did cyclohexane carboxaldehyde. In general, electron-deficient aldehydes proceeded in good-to-excellent yields, including heteroaromatic 2-pyridinecarboxaldehyde. Attempts with  $\alpha,\beta$ -unsaturated aldehydes were met with limited success. In addition to butanethiol, we found that other primary thiols such

## Scheme 2. Substrate Scope of NHC-Catalyzed Anodic Oxidation of Aldehydes to Thioesters<sup>a</sup>



<sup>a</sup>Reactions conducted at 45 °C in a three-neck flask under N<sub>2</sub> with a graphite anode, Pt basket cathode, 0.045 M Bu<sub>4</sub>NBr, 0.150 M aldehyde, 0.300 M R'SH, 0.075 M DMAP, and constant cell potential of +0.1 V (vs Ag/AgNO<sub>3</sub>). For 1–5 and 6–11 precatalysts, A-Mes and A-DiPP were used, respectively. Reaction times ranged from 8 to 44 h and were monitored by <sup>1</sup>H NMR spectroscopy and GC-MS until production of thioester had ceased. Yields were determined by GC-MS using 1,3,5-trimethoxybenzene as the internal standard (average of two runs); isolated yields in parentheses. See Supporting Information for experimental details.

as benzyl, 2-chlorobenzyl, and 2-furfuryl each gave good yields of the desired thioester. Additionally, cyclohexanethiol gave the secondary thioester in 63% yield.

In summary, we have demonstrated a direct conversion of aldehydes to thioesters. This integrated organocatalyzed electrochemical approach achieves efficient anodic oxidation of catalytically generated species and circumvents the need for stoichiometric exogenous oxidants, high cell potentials, or redox mediators while producing minimal byproducts. Optimization of the strength and concentration of the base was essential for minimizing unwanted disulfide formation and achieving efficient thioesterification. This thioesterification reaction provides good-to-excellent yields for a broad range of aldehyde and thiol substrates.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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