The NHC-catalyzed thioesterification of aromatic or aliphatic aldehydes with a range of thiols was developed in the presence of a stoichiometric amount of an organic oxidant. Among the oxidants examined, phenazine was shown to give the best results in terms of chemical yield and compatibility with thiols.

Thioesters are important compounds from both synthetic and biological perspectives. They have frequently been used as synthetic intermediates for acyl transfer reactions, including native chemical ligation, functional group transformations into ketone and aldehyde, and the formation of carbon-carbon bonds such as in the aldol and Michael reactions. In nature, acetyl-CoA, a biologically important thioester, plays a pivotal role in fatty acid and polyketide biosynthesis. To synthesize such versatile thioesters, various methods have been developed: (1) condensation of carboxylic acid and thiol with dehydrating reagents, (2) transthioesterification of active carboxylic acid derivatives with thiol, (3) palladium-catalyzed thiocarbonylation of iodoarenes and thiol with carbon monoxide, and (4) radical-mediated coupling of aldehyde with disulfide or thiol. However, the discovery of efficient catalytic methods for thioesters remains an important synthetic challenge in organic chemistry.

(i) Internal redox reaction

(ii) External redox reaction

Scheme 1 NHC-Catalyzed thioesterification of aldehydes by the internal and external redox activations.

On the other hand, N-heterocyclic carbene (NHC)\textsuperscript{10}-catalyzed redox reactions have been applied to the concise synthesis of esters\textsuperscript{11,12} and amides\textsuperscript{13,14} from aldehydes through the use of internal or external redox protocols. In contrast, there have been fewer studies on NHC-catalyzed thioesterification. In fact, there have been only two previous reports to date, in which either cyclopropyl aldehyde\textsuperscript{15}c was used as a substrate or azobenzene\textsuperscript{16} was used as an oxidant for the internal or external redox reaction (Scheme 1). However, each reaction has its own limitations in terms of substrate scope or the formation of side-products. In particular, the choice of an appropriate external oxidant is the key to success in external redox thioesterification. In this paper, we describe a new efficient and practical method for the one-step conversion of aldehyde into the corresponding thioesters using phenazine as an external oxidant.

Table 1 Screening of Oxidants

As a model reaction for thioesterification, we examined the reaction of benzaldehyde 1a and phenylmethanethiol 2a with catalyst A (10 mol%) and triethylamine (10 mol%) in the presence of...
of several oxidants (Table 1). The use of oxidants such as 
MnO₂,¹²⁻¹⁴ quinone 3a¹²⁻¹⁶ and riboflavin 3b,¹⁷ which were used
for NHC-catalyzed esterification, gave thioester 4a in low to
moderate yields due to the formation of disulfide 5 (entries 1-3).
Other oxidants such as diethyl azodicarboxylate (DEAD), o-
iodoxybenzoic acid (IBX)¹⁸ and Phl(OAc)₂ gave disulfide 5 as
the major product along with a trace amount of 4a (entries 4-6).
We then examined heterocyclic compounds 3c and 3d as
hydrogen acceptors (entries 7 and 8). To our delight, phenazine
3c was shown to be a sufficiently mild oxidant to afford the
desired product 4a in high yield without the formation of any
disulfide.

Table 2 Thioesterification of Aromatic Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>A¹</th>
<th>R²</th>
<th>Yield of 4 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC₆H₄</td>
<td>Bn</td>
<td>98 (4b)</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄</td>
<td>Bn</td>
<td>84 (4c)</td>
</tr>
<tr>
<td>3</td>
<td>4-CIC₆H₄</td>
<td>Bn</td>
<td>90 (4d)</td>
</tr>
<tr>
<td>4</td>
<td>3-CIC₆H₄</td>
<td>Bn</td>
<td>&gt;99 (4e)</td>
</tr>
<tr>
<td>5</td>
<td>2-CIC₆H₄</td>
<td>Bn</td>
<td>92 (4f)</td>
</tr>
<tr>
<td>6</td>
<td>4-NO₂C₆H₄</td>
<td>Bn</td>
<td>83 (4g)</td>
</tr>
<tr>
<td>7</td>
<td>4-MeOCOC₆H₄</td>
<td>Bn</td>
<td>91 (4h)</td>
</tr>
<tr>
<td>8</td>
<td>2-furyl</td>
<td>Bn</td>
<td>&gt;99 (4i)</td>
</tr>
<tr>
<td>9</td>
<td>3-pyridyl</td>
<td>Bn</td>
<td>68 (4j)</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>(2-furyl)methyl</td>
<td>88 (4k)</td>
</tr>
<tr>
<td>11</td>
<td>Ph</td>
<td>c-hexyl</td>
<td>82 (4l)</td>
</tr>
<tr>
<td>12</td>
<td>Ph</td>
<td>'Bu</td>
<td>72 (4m)</td>
</tr>
<tr>
<td>13</td>
<td>Ph</td>
<td>Ph</td>
<td>67 (4n)</td>
</tr>
<tr>
<td>14</td>
<td>Ph</td>
<td>4-MeOC₆H₄</td>
<td>62 (4o)</td>
</tr>
<tr>
<td>15</td>
<td>Ph</td>
<td>4-FC₆H₄</td>
<td>57 (4p)</td>
</tr>
</tbody>
</table>

* Conditions: 1 (0.3 mmol), 2 (1.1 equiv), 3c (1.2 equiv), A (10 mol%), NEt₃ (10 mol%), THF (0.5 M), Ar, rt. a Isolated yields. b 1.5 equiv of 2 and 3c: 24 h.

Table 3 Screening of Reaction Conditions for Thioesterification of Aliphatic Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield of 7a (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>Et₃N</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>DBU</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>Et₃N</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>DBU</td>
<td>12</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>DBU</td>
<td>12</td>
<td>86</td>
</tr>
</tbody>
</table>

* Conditions: 6a (0.3 mmol), 2b (1.1 equiv), 3c (1.2 equiv), catalyst A or B (10 mol%), Base (10 mol%), THF (0.5 M), rt. a Isolated yields. b 1.5 equiv of 2b and 3c were used.

After establishing the optimized reaction conditions, we
investigated the generality of this thioesterification (Table 2). A
wide range of aryl and heteroaryl aldehydes bearing electron-
donating and electron-withdrawing groups could be used
regardless of their substituted position, to give the corresponding
thioesters 4b-j in good to high yields (entries 1-9). With regard to
the thiol used, both alkyl and aryl thiols were tolerated under
these conditions, while products 4n-p were obtained in slightly
lower yields even with 1.5 equiv of both thiols and 3c in the case
of aryl thiols (entries 10-15).

Table 4 Thioesterification of Aliphatic Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₁₂H₂₅</td>
<td>C₁₂H₂₅</td>
<td>83 (7b)</td>
</tr>
<tr>
<td>2</td>
<td>BnO</td>
<td>Bn</td>
<td>71 (7c)</td>
</tr>
<tr>
<td>3</td>
<td>c-hexyl</td>
<td>C₁₂H₂₅</td>
<td>96 (7d)</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>C₁₂H₂₅</td>
<td>80 (7e)</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>NH₂Boc</td>
<td>79 (7f)</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>'Bu</td>
<td>71 (7g)</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>'Bu</td>
<td>83 (7h)</td>
</tr>
<tr>
<td>8</td>
<td>PhCH₂CH₂-</td>
<td>Bn</td>
<td>91 (7I)</td>
</tr>
<tr>
<td>9</td>
<td>PhCH₂CH₂-</td>
<td>(2-furyl)methyl</td>
<td>81 (7j)</td>
</tr>
<tr>
<td>10</td>
<td>PhCH₂CH₂-</td>
<td>c-hexyl</td>
<td>88 (7k)</td>
</tr>
<tr>
<td>11</td>
<td>PhCH₂CH₂-</td>
<td>'Bu</td>
<td>63 (7l)</td>
</tr>
</tbody>
</table>

* Conditions: 6 (0.3 mmol), 2 (1.5 equiv), 3c (1.5 equiv), B (10 mol%), DBU (10 mol%), THF (0.5 M), Ar, rt. a Isolated yields. c Racemic product was obtained. d S-tert-butyl 3-(tert-butylthio)-2-methyl-phenylpropane-
thiolate was formed in 11% yield. e Run for 24 h.

We next explored the thioesterification of aliphatic aldehydes
(Table 3). When the reaction of 3-phenylpropionaldehyde 6a with
an odorless dodecanethiol 2b was carried out under the same
reaction conditions, the yield of 7a significantly decreased (entry
We finally applied the optimal reaction conditions to a variety of aliphatic aldehydes (Table 4). Primary and secondary aliphatic aldehydes bearing functional groups such as an isolated olefin, ether, and carbamate were converted into the corresponding thiosteres 7b-f in good yields without any problems (entries 1-5). The reaction of chiral α-amino aldehyde derivative 6f was accompanied by racemization to provide the racemic thiostere 7f in 79% yield. Although α,β-unsaturated aldehyde 6g underwent a redox reaction to give thiostere 7g as a major product together with the Michael adduct in 11% yield, β,β-disubstituted unsaturated aldehyde 6h only gave the desired product 7h in 83% yield (entries 6 and 7). In a similar manner, several alky1 and aryl thiois could be introduced to 3-phenylpropionaldehyde 6a in good yields (entries 8-12).

In summary, we found that phenazine was the best oxidant for the NHC-catalyzed direct thioesterification of aldehydes, and did not lead to the formation of any disulfides. Furthermore, the appropriate combination of a NHC precatalyst and base (catalyst A/Et3N, catalyst B/DBU) was shown to be important for the efficient thioesterification of aromatic and aliphatic aldehydes by redox activation.

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Notes and references


