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ARTICLE TYPE

NHC-catalyzed Thioesterification of Aldehydes by External Redox Activation

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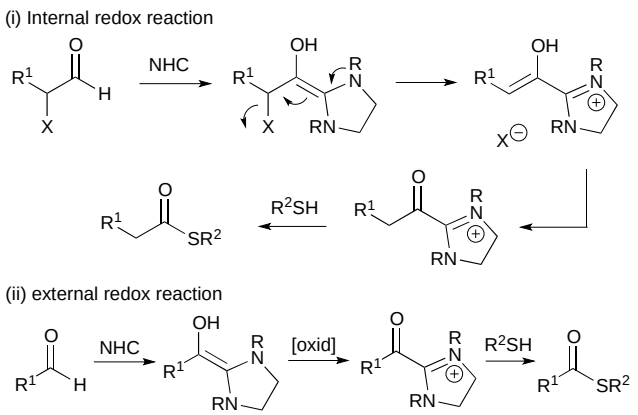
The NHC-catalyzed thioesterification of aromatic or aliphatic aldehydes with a range of thiols was developed in the presence of a stoichiometric amount of an organic oxidant. Among the oxidants examined, phenazine was shown to give the best results in terms of chemical yield and compatibility with thiols.

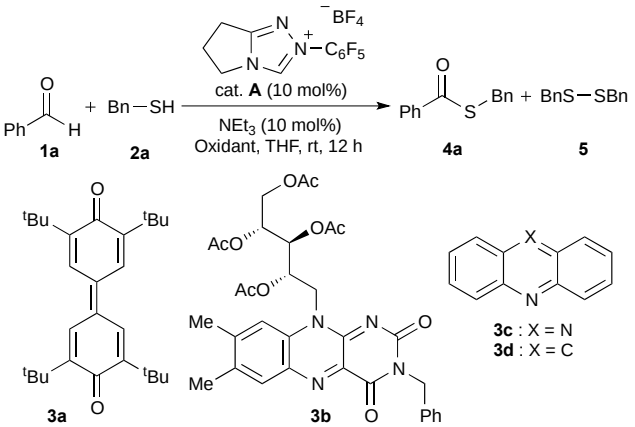
Thioesters are important compounds from both synthetic and biological perspectives. They have frequently been used as synthetic intermediates for acyl transfer reactions,[1] including native chemical ligation,[2] functional group transformations[3] into ketone and aldehyde, and the formation of carbon-carbon bonds[4] 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.[5] To synthesize such versatile thioesters, various methods have been developed: (1) condensation[6] of carboxylic acid and thiol with dehydrating reagents, (2) transthioesterification[7] of active carboxylic acid derivatives with thiol, (3) palladium-catalyzed thiocarbonylation[8] of iodoarenes and thiol with carbon monoxide, and (4) radical-mediated coupling[9] of aldehyde with disulfide or thiol. However, the discovery of efficient catalytic methods for thioesters remains an important synthetic challenge in organic chemistry.



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

On the other hand, N-heterocyclic carbene (NHC)[10]-catalyzed redox reactions have been applied to the concise synthesis of esters[11,12] and amides[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[11c] was used as a substrate or azobenzene[15] 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[a]

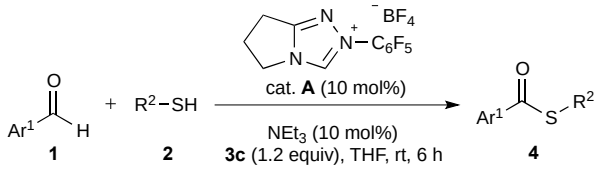


Entry	Oxidant	Yield of **4a** (%)[b]	Yield of **5** (%)[b]
1	MnO_2[c]	21	70
2	**3a**	59	27
3[d]	**3b**, O_2	67	23
4	DEAD	trace	88
5	IBX[e]	10	82
6	$PhI(OAc)_2$[e]	trace	90
7[f]	**3c**	94	trace
8	**3d**	6	33

[a] Conditions: **1a** (0.3 mmol), **2a** (1.1 equiv), oxidant (1.2 equiv), **A** (10 mol%), NEt_3 (10 mol%), THF (0.5 M), Ar, rt. [b] Isolated yields. [c] 5.0 equiv of MnO_2 was used. [d] Conditions: **1a** (2.0 equiv), **2a** (0.3 mmol), **3b** (10 mol%), **A** (10 mol%), NEt_3 (50 mol%), $CHCl_3$, MS4Å, O_2, rt. [e] 2.0 equiv of oxidant was used. [f] Run for 6 h.

As a model reaction for thioesterification, we examined the reaction of benzaldehyde **1a** and phenylmethanethiol **2a** with catalyst **A** (10 mol%) and triethyamine (10 mol%) in the presence

Table 2 Thioesterification of Aromatic Aldehydes[a]



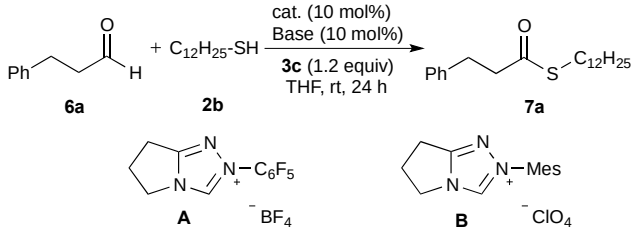
1 2 4

Entry	Ar^1	R^2	Yield of **4** (%)[b]
1	4-MeC_6H_4	Bn	98 (**4b**)
2	4-$MeOC_6H_4$	Bn	84 (**4c**)
3[d]	4-ClC_6H_4	Bn	90 (**4d**)
4	3-ClC_6H_4	Bn	>99 (**4e**)
5	2-ClC_6H_4	Bn	92 (**4f**)
6	4-$NO_2C_6H_4$	Bn	83 (**4g**)
7[f]	4-$MeOCOC_6H_4$	Bn	91 (**4h**)
8	2-furyl	Bn	>99 (**4i**)
9	3-pyridyl	Bn	68 (**4j**)
10	Ph	(2-furyl)methyl	88 (**4k**)
11	Ph	*c*-hexyl	82 (**4l**)
12	Ph	^{t}Bu	72 (**4m**)
13[c]	Ph	Ph	67 (**4n**)
14[c]	Ph	4-$MeOC_6H_4$	62 (**4o**)
15[c]	Ph	4-FC_6H_4	57 (**4p**)

[a] Conditions: **1** (0.3 mmol), **2** (1.1 equiv), **3c** (1.2 equiv), **A** (10 mol%), NEt_3 (10 mol%), THF (0.5 M), Ar, rt. [b] Isolated yields. [c] 1.5 equiv of **2** and **3c**, 24 h.

of several oxidants (Table 1). The use of oxidants such as MnO_2,[12d,e] quinone **3a**[12c,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 $PhI(OAc)_2$ 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 3 Screening of Reaction Conditions for Thioesterification of Aliphaitc Aldehyde[a]



6a 2b 7a

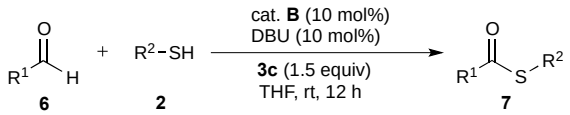
A B

Entry	Catalyst	Base	Time (h)	Yield of **7a** (%)[b]
1	**A**	Et_3N	24	55
2	**A**	DBU	24	71
3	**B**	Et_3N	24	trace
4	**B**	DBU	12	74
5[c]	**B**	DBU	12	86

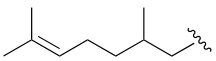
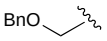
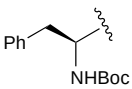
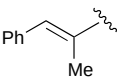
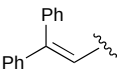
[a] Conditions: **6a** (0.3 mmol), **2b** (1.1 equiv), **3c** (1.2 equiv), catalyst **A** or **B** (10 mol%), Base (10 mol%), THF (0.5 M), rt. [b] Isolated yields. [c] 1.5 equiv. of **2b** and **3c** were used.

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[a]



6 2 7

Entry	R^1	R^2	Yield (%)[b]
1		$C_{12}H_{25}$	83 (**7b**)
2		Bn	71 (**7c**)
3	*c*-hexyl	$C_{12}H_{25}$	96 (**7d**)
4		$C_{12}H_{25}$	80 (**7e**)
5		Bn	79 (**7f**)[c]
6		^{t}Bu	71 (**7g**)[d]
7		^{t}Bu	83 (**7h**)
8	$PhCH_2CH_2$-	Bn	91 (**7i**)
9	$PhCH_2CH_2$-	(2-furyl)methyl	81 (**7j**)
10	$PhCH_2CH_2$-	*c*-hexyl	88 (**7k**)
11	$PhCH_2CH_2$-	^{t}Bu	63 (**7l**)
12[e]	$PhCH_2CH_2$-	4-$MeOC_6H_4$	60 (**7m**)

[a] 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. [b] 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

1). This could probably be attributed to the sluggish reaction due to the low reactivity of the aliphatic aldehyde. The use of DBU instead of Et_3N improved the chemical yield from 55 to 71% (entry 2). Replacement of the NHC precatalyst **A** by more nucleophilic *N*-mesityl triazolium salt **B**, along with an increase in the amounts of the thiol and base, led to a further increase in yield, and gave the thioester **7a** in 86% yield (entries 3-5).

We finally applied the optimal reaction conditions to a variety of aliphatic aldehydes (Table 4). Primary and secondary alkyl aldehydes bearing functional groups such as an isolated olefin, ether, and carbamate were converted into the corresponding thioesters **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 thioester **7f** in 79% yield. Although α,β-unsaturated aldehyde **6g** underwent a redox reaction to give thioester **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 alkyl and aryl thiols 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**/Et_3N, 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

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