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PAPER

Conjugate reduction and reductive aldol cyclization of α,β-unsaturated thioesters catalyzed by (BDP)CuH†

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A conjugate reduction of α,β-unsaturated thioesters catalyzed by copper hydride using PMHS as stoichiometric reductant has been developed. 1,2-Bis(diphenylphosphino)benzene (BDP) was the most effective ligand for this reduction. Saturated thioesters could be produced in excellent yields when the substituent on the thiol is not sterically-demanding. This protocol was applied to induce the reductive aldol cyclization of keto-enethioates, which could offer β-hydroxythioesters in moderate to good yields.

Introduction

The thioester is a versatile functional group in organic chemistry, undergoing a range of reactions effectively as an electrophile and as a nucleophile. Mediated by soft metal salts such as Hg(II), Ag(I), Cu(I), and Cu(II),[1] thioesters are acylating agents for alcohols and amines in peptide synthesis.[2] They can be selectively reduced by silane in the presence of palladium using the Fukuyama reduction to yield aldehydes,[3] and alkylated by palladium-catalyzed coupling with organozinc[4] and organoindium reagents,[5] organostannanes[6] and boronic acids[7] to produce ketones. As precursors for carbon nucleophiles, thioesters have been used extensively as enol ether precursors in chiral crossed aldol reactions[8] and enol precursors in direct aldol reactions, both in the laboratory[9] and in nature.[10] The generation of thioester enolate derivatives for carbon–carbon bond formations have been realized also from α,β-unsaturated thioesters by conjugate addition[11] and Morita–Baylis–Hillman reactions.[12]

While the reductive generation of enolates from unsaturated ketones and esters has seen enormous success for catalytic diastereoselective and enantioselective carbon–carbon bond formation,[13] the corresponding reductive generation of enolates from unsaturated thioesters has never been reported. In fact, upon searching the literature, there have only been a handful of examples of even simple reductions of α,β-unsaturated thioesters. Whereas the reduction of unsaturated thioester derivatives, such as crotonyl ACP, is a transformation in the fatty acid biosynthesis pathway, a general, bench-top corollary of this reduction has yet to be reported. One reason is probably because sulfur-rich compounds are well-known poisons of many metal catalysts.

Conjugate reductions mediated by copper hydrides have been reported for many electron-deficient olefins,[14] including enones,[15] enoates,[16] nitroalkenes,[17] 2-alkenylheteroarenes,[18] and unsaturated sulfones,[19] nitriles,[20] phosphonates.[21] Due to the paucity of examples of reductions of unsaturated thioesters, and in line with our interest in reductions mediated by copper hydride,[22] we undertook a study examining the reduction of enethioates. Herein we report that (BDP)CuH catalyzes the conjugate reduction of α,β-unsaturated thioesters, as well as the reductive aldol cyclization of these substrates.

Results and discussion

Using α,β-unsaturated thioester **1a** as a model substrate for examining the conjugate reduction, we were initially surprised that the treatment with a stoichiometric amount of Stryker's reagent ($[Ph_3PCuH]_6$) afforded the saturated thioester **2a** in a very low yield (3–22%), along with numerous by-products. The reduction using a catalytic amount of $[Ph_3PCuH]_6$ and silane utterly failed to proceed (Table 1, entry 1). This result was initially unexpected, because both enones and enoates, *i.e.* olefins conjugated with more and less electron-withdrawing groups respectively, underwent reductions with stoichiometric or catalytic amounts of Stryker's reagent readily and without incident. The affinity of copper for sulfur could account for the anomalous behaviour of Stryker's reagent with the enethioate.

Recent studies have demonstrated the profound effect of ligands on the chemistry of the resultant copper hydride, including the modulation of reactivity and chemoselectivity.[23,24] Thus we undertook a screening of ligands to find one which would minimize the copper–sulfur interaction and would promote the desired catalytic reduction to furnish **2a** in high yield. The copper hydride catalysts were prepared *in situ* using $Cu(OAc)_2$–H_2O (**3**) as the copper source. The results are summarized in Table 1.

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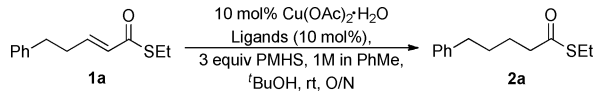
† Electronic supplementary information (ESI) available: Detailed experimental procedures and ^1H and ^{13}C NMR spectra of **1a–1q**, **2a–2p**, **4a–c**. See DOI: 10.1039/c1ob05352c

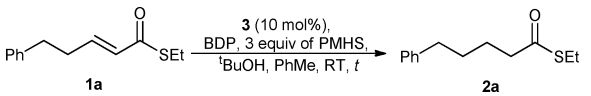
Table 1 Screening of ligands



Entry	Ligand	Conversion (%)[a]	Yield of **2a** (%)[b]
1	Ph_3P	0	0
2	dppm	0	0
3	dppe	82	78
4	dppf	95	90
5	BDP	100	92
6	*rac*-BINAP	70	65

[a] Conversion was determined by the ^{1}H NMR spectrum of the crude reaction mixture. [b] Isolated yield.

Table 2 Optimization of the conjugate reduction of **1a**



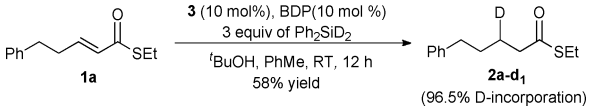
Entry	BDP (mol%)	M	*t* (h)	Yield of **2a** (Recovered **1a**)
1	10	1.0	4	91% (0)
2	10	0.5	7	92% (0)
3	5	1.0	7	90% (0)
4	5	0.5	9	88% (0)
5[a]	5	1.0	12	83% (12)
6[b]	5	1.0	12	78% (5)

[a] 5 mol% of **3** used. [b] 2.0 equiv of PMHS was used.

As the copper hydride of the monodentate triphenylphosphine failed to induce catalytic reduction, a range of bisphosphines were examined as ligands. The activities of the catalysts were compared by conducting the reduction with 10 mol% of each of **3** and the ligand, 3 equivalents of PMHS, and in the presence of ^{t}BuOH to increase the reaction rate. Bis(diphenylphosphino)methane (dppm) produced a very unreactive copper hydride (Table 1, entry 2). However, the use of bis(diphenylphosphino)ethane (dppe) and bis(diphenylphosphino)ferrocene (dppf) offered significantly higher conversion rates over dppm. 1,2-Bis(diphenylphosphino)benzene (BDP) afforded the copper hydride with the highest activity among the ligands tried,[24] resulting in complete conversion and the highest yield of **2a**. On the other hand, *rac*-BINAP exhibited an inferior activity.

Using BDP as the ligand, we examined the optimization of the reaction conditions (Table 2). Using 10 mol% **3** and 10% BDP, the reaction at 1.0 M concentration is complete in 4 h in good yield (Table 2, entry 1). Lowering the concentration of the reaction to 0.5 M, or the amount of BDP to 5 mol% results in complete conversion in about 7 h (Table 2, entries 2–3). The lowering of both the concentration of the reaction and the amount of BDP used still resulted in full conversion over a longer reaction time (Table 2, entry 4), but limiting **3** to 5 mol% resulted in incomplete conversion even after reaction overnight (Table 2, entry 5). Reducing the amount of PMHS to 2 equivalents also resulted in incomplete conversion (Table 2, entry 6).

The reduction occurs by the 1,4-addition of copper hydride to the conjugated system, which is clearly shown by deuteration when Ph_2SiD_2 is used as the stoichiometric reductant (Scheme 1). Presumably, the copper enolate formed from reduction is subsequently quenched by ^{t}BuOH. The CuO^tBu thus formed undergoes metathesis with silane to regenerate the copper hydride.



Scheme 1 Reduction of **1a** using Ph_2SiD_2.

The scope of the reaction was examined by subjecting a range of α,β-unsaturated thioesters to (BDP)CuH-catalyzed conjugate reduction, and the results are shown in Table 3. The unsaturated thioester substrates were synthesized by three methods: the esterification of unsaturated acids using EDCI and alkanethiols, the Wittig reaction of aldehydes with *S*-ethyl 2-(triphenylphosphoranylidene)ethanethioate,[25] and zinc-activated acylation of alkanethiols with acid chlorides.[26]

Unsaturated thioesters of unhindered alkanethiols, such as **1a** (R^1 = Et) or **1b** (R^1 = ^{n}Bu) were reduced readily (Table 3, entries 1, 2). However, as R^1 increased in length (**1c**, R^1 = $^n C_{12}H_{25}$)[27] and steric hindrance (**1d**,**e** R^1 = ^{t}Bu, Ph), the reduction became sluggish (Table 3, entries 3, 4). Thus even with this highly active copper hydride, some unsaturated thioesters remain quite unreactive toward reduction. Therefore, this reaction should be chemoselective for the reduction of ethyl or butyl enethioates in the presence of phenyl enethioates. The monoreduction of substrates **1f** and **1j** demonstrate that the (BDP)CuH-catalyzed reduction is chemoselective for electron-deficient alkenes (Table 3, entry 6, 10).

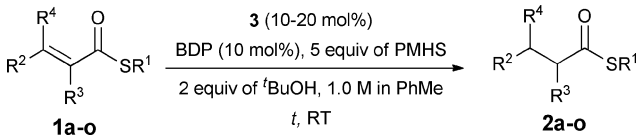
Unsaturated thioesters (**1g**) with α-substituents ($R^3 \neq H$) are reduced in good yield, but require a higher loading of copper catalyst (Table 3, entry 7). However, thioesters **1h** and **1i** derived from cyclohex-1-ene carboxylic acid underwent reaction very slowly. β-Substitution (**1j**) is also tolerated, albeit using a higher catalyst loading as well.

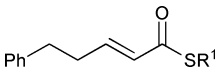
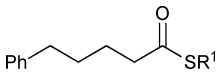
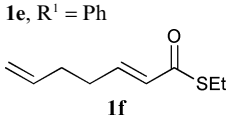
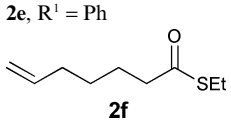
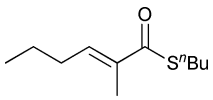
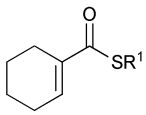
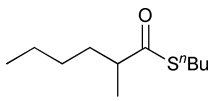
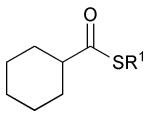
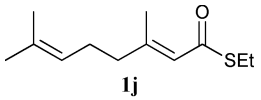
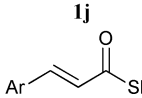
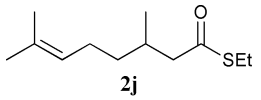
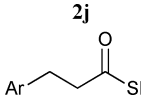
Thioesters of cinnamic acid derivatives (**1k–1o**) are stabilized by the extended conjugated system. Nevertheless, they were successfully reduced, but the reactions generally required longer reaction times, additional copper and/or PMHS (Table 3, entries 11–13). Electron-withdrawing substituents on the aromatic ring greatly increase the reactivity of these substrates (Table 3, entries 15, 16).

The (BDP)CuH-catalyzed reduction using PMHS as stoichiometric reductant is a much more effective method for the reduction of unsaturated thioesters compared with other protocols.[28] Moreover, the copper-catalyzed reduction also permits reductive aldol cyclizations if ^{t}BuOH was omitted to prevent the quenching of the enolate.[13,29] But to be able to continue to an aldol reaction, the rate of the intramolecular aldol reaction of the copper thioester enolate must be faster than transmetallation with the silane.

Indeed, in the presence of ^{t}BuOH, the simple reduction of keto-enethioate **1p** occurred to solely generate **2p** in good yield (Scheme 2). Gratifyingly, however, in the absence of ^{t}BuOH, a single diastereomeric β-hydroxythioester **4a** having three contiguous stereocentres was obtained from reductive aldol cyclization as the major product (Scheme 2). In the reduction of **1q**, hydroxythioester **4b** and its β-lactone derivative **4c** could be obtained as major products even in the presence of a proton source (Scheme 2).

Table 3 Conjugate reduction of unsaturated thioesters **1a–o**



Entry	Substrate	Product	**3** (mol%)	*t* (h)	Yield of **2** (Recovered **1**)
					
1[a]	**1a**, R^1 = Et	**2a**, R^1 = Et	10	4	91%
2[a]	**1b**, R^1 = ^{n}Bu	**2b**, R^1 = ^{n}Bu	10	5	90%
3	**1c**, R^1 = $^n C_{12}H_{25}$	**2c**, R^1 = $^n C_{12}H_{25}$	10	12	60% (18%)
4	**1d**, R^1 = ^{t}Bu	**2d**, R^1 = ^{t}Bu	10	12	52% (34%)
5	**1e**, R^1 = Ph	**2e**, R^1 = Ph	20	12	8% (82%)
6[a]	 **1f**	 **2f**	10	6	87%
7	 **1g** 	 **2g** 	20	12	97%
8	**1h**, R^1 = Et	**2h**, R^1 = Et	10	12	25% (69%)
9	**1i**, R^1 = ^{n}Bu	**2i**, R^1 = ^{n}Bu	10	12	22% (68%)
10	 **1j** 	 **2j** 	20	12	88% (4%)
11[a]	**1k**, Ar = Ph	**2k**, Ar = Ph	10	12	82% (12)
12[a]	**1k**	**2k**	20	12	85% (6%)
13	**1k**	**2k**	20	12	90%
14	**1l**, Ar = *o*-Cl-C_6H_4	**2l**, Ar = *o*-Cl-C_6H_4	20	12	86% (3%)
15[a,b]	**1m**, Ar = *m*-NO_2-C_6H_4	**2m**, Ar = *m*-NO_2-C_6H_4	10	5	81% (4%)
16[b]	**1n**, Ar = *p*-NO_2-C_6H_4	**2n**, Ar = *p*-NO_2-C_6H_4	10	4	90%
17	**1o**, Ar = *m*-MeO-C_6H_4	**2o**, Ar = *m*-MeO-C_6H_4	10	12	86% (3%)

[a] 3.0 equiv. of PMHS used. [b] 0.5 M in PhMe.

This is probably due to the facility for cyclization to form a five-membered ring. Without ^{t}BuOH, aldol cyclization was the only observed outcome. At a higher catalyst loading, hydroxythioester **4b** was produced in 81% yield as a single diastereomer. The relative structures of **4a–c** were determined by NOESY 2D-NMR, and the stereochemical outcomes are similar to those obtained from the copper-mediated reductive aldol cyclizations of the analogous enones and enoates.[22]

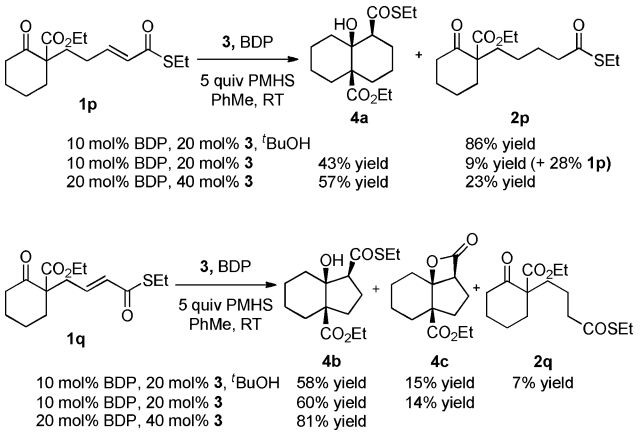
Conclusion

In summary, a range of α,β-unsaturated thioesters could be reduced in a conjugate fashion, in good to excellent yields under catalysis by (BDP)CuH with PMHS as stoichiometric reductant. Under similar conditions but by omitting the proton source, intramolecular reductive aldol cyclizations of keto-enethioates were effected to afford the corresponding β-hydroxythioesters in moderate to good yield. We are continuing our work to examine the enantioselective variants of this reduction.

Experimental section

Typical procedure for reductions catalyzed by (BDP)CuH

A solution of **3** (39.4 mg, 0.197 mmol) and BDP (89.1 mg, 0.199 mmol) in 1.0 mL PhMe was stirred at room temperature for 5 min. PMHS (360 μL, 6.0 mmol) was added and the reaction



Scheme 2 Reductive aldol cyclization catalyzed by (BDP)CuH.

mixture became greenish-yellow. Thioester **1a** (440.5 mg, 1.999 mmol) in 1.0 mL PhMe and ^{t}BuOH (380 μL, 3.97 mmol) were added sequentially. The reaction was monitored by TLC and quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was filtered through a pad of silica gel. The filtrate was extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash chromatography using 1.5% EtOAc in hexane to afford **2a** (403.8 mg, 91%) as a pale yellow oil. **2a**: R_f (5% EtOAc in hexane): 0.56; IR (CH_2Cl_2): 3035, 2938, 2857, 1684 (C═O), 1449, 1264 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.29 (m, 2H), 7.16–7.20 (m, 3H), 2.87 (q, J = 7.4 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.56 (m, 2H), 1.63–1.73 (m, 4H), 1.24 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 142.1, 128.42, 128.37, 125.8, 43.9, 35.6, 30.7, 25.3, 23.3, 14.8 ppm; LRMS (ESI): m/z 245 ([M$^+$ + Na]$^+$, 32), 161 (100), 162 (13); HRMS (ESI): calcd for $C_{13}H_{18}OS$ ([M$^+$ + Na]$^+$), 245.0976, found 245.0983.

Typical procedure for reductive aldol reactions

A solution of **3** (23.4 mg, 0.119 mmol) and BDP (26.6 mg, 0.0596 mmol) in 2.0 mL PhMe was stirred for 5 min. PMHS (90 μL, 1.5 mmol) was added and the reaction mixture turned greenish yellow. Thioester **1p** (93.1 mg, 0.298 mmol) in 1.0 mL PhMe was added. The reaction was monitored by TLC and quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was filtered through a pad of silica gel. The filtrate was extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **4a** (53.9 mg, 57%) as a pale yellow oil and **2p** (21.5 mg, 23%). **4a**: R_f (10% EtOAc in hexane): 0.53; IR (CH_2Cl_2): 3468, 2937, 2870, 1695 (thioester C═O), 1655 (ester C═O), 1456, 1236 cm^{-1}; ^{1}H NMR (500 MHz, toluene-d_8, 80 °C): δ 4.33 (s, 1H), 3.96–3.86 (m, 2H), 2.95 (dd, J = 11.9, 3.8 Hz, 1H), 2.70 (dq, J = 7.4, 0.7 Hz, 2H), 2.32–2.08 (m, 2H), 1.98–1.92 (m, 2H), 1.71–1.67 (m, 1H), 1.60–1.53 (m, 4H), 1.52–1.32 (m, 4H), 1.31–1.22 (m, 1H), 1.06 (t, J = 7.4 Hz, 3H), 0.98 (m, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, toluene-d_8, 80 °C): δ 200.7, 177.1, 73.3, 60.5, 55.4, 51.8, 35.7, 31.6, 31.0, 26.1, 23.7, 23.5, 23.2, 20.9, 14.8, 14.2 ppm; LRMS (EI, 20 eV): m/z 253 (M$^+$ − C_2H_4, 11), 179 (54), 135 (100); HRMS (EI, 20 eV): calcd for $C_{14}H_{21}O_4$ (M$^+$ − C_2H_4), 253.1434, found 253.1441.

Acknowledgements

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