New Odorless Protocols for the Synthesis of Aldehydes and Ketones from Thiol Esters

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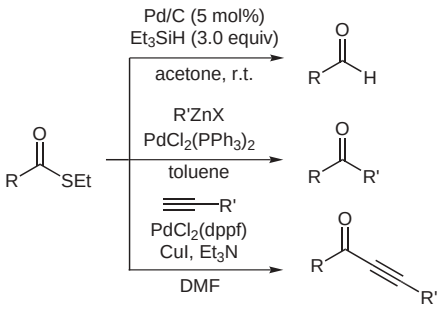
Received 2 December 2003

Abstract: Dodecanethiol esters derived from odorless dodecanethiol proved to be suitable substrates for Pd-catalyzed reduction with triethylsilane, coupling with organozinc reagents, and coupling with terminal acetylenes.

Key words: odorless dodecanethiol, thiol esters, palladium-catalyzed reaction, aldehyde, ketone

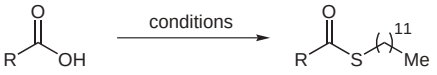
Conversion of carboxylic acids to aldehydes[1] or ketones[2] is an important transformation in synthetic organic chemistry. Among the numerous protocols for these transformations, thiol ester derivatives display highly useful reactivity, i.e., ketone formation by addition of Grignard reagents to (*S*)-(2-pyridyl) thiol esters[3] and selective reduction of 2-thiazoline-2-thiol esters by DIBAL.[4] In addition, transition metal-catalyzed cross-coupling reactions of thiol ester derivatives have also been investigated.[5] Against this background, we have established a palladium-mediated reduction of ethanethiol esters with triethylsilane,[6] an extension of which enabled us to develop a versatile ketone[7] and alkynyl ketone synthesis[8] from ethanethiol esters (Scheme 1). The practical utility of our protocol was demonstrated by its application to the total synthesis of complex natural products.[9,10] However, despite their many advantages over other methods, ethanethiol and its by-products are particularly unpleasant compounds to work with because of their offensive odor. In this paper, we describe an improvement of our protocol using dodecanethiol, which is surprisingly odorless**,** as reported by Node and co-workers.[11]



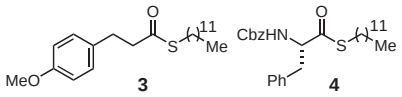
Scheme 1

The preparation of dodecanethiol esters was examined using 3-(4-methoxyphenyl) propionic acid (**1**) and *N*-Cbz-phenylalanine (**2**) as the substrates. As shown in Table 1, the desired dodecanethiol ester **3** could be synthesized in high yields by using the mixed anhydride method, conversion to the acid chloride, or by using a condensation reagent.[12] In the case of *N*-Cbz-phenylalanine (**2**), two equivalents of dodecanethiol were needed to suppress epimerization. The reaction with two equivalents of dodecanethiol provided **4** in 83% yield (96% ee) by using the mixed anhydride method and in 89% yield (98% ee) using WSCD.[13]

Table 1 Preparation of Dodecanethiol Esters



Conditions



	Time, Yield	Time, Yield
1) $ClCO_2i$-Bu, Et_3N 2) $HS(CH_2)_{11}Me$ (1.2 equiv) Et_3N, DMAP	1) 30 min 2) 70 min 88%	1) 20 min 2) 90 min 83%, 96% ee[a]
$HS(CH_2)_{11}Me$ (1.2 equiv) WSCD, DMAP	40 min 95%	20 min 89%, 98% ee[a]
1) $(COCl)_2$, cat. DMF 2) $HS(CH_2)_{11}Me$ (1.2 equiv) Et_3N	1) 30 min 2) 20 min 87%	–

[a] 2.0 equiv of dodecanethiol were used.

First, we subjected the dodecanethiol esters to palladium-catalyzed reduction conditions with triethylsilane[6] (Table 2). Although a prolonged reaction time was required to complete the reaction, the desired aldehydes were obtained in yields comparable to those obtained with their corresponding ethanethiol esters.[14] In the case of the optically active dodecanethiol esters (entries 3 and 4) derived from *N*-Cbz-phenylalanine and proline, respectively, the optical purity of the starting dodecanethiol esters was preserved after reduction.[16] In this procedure, the separation of the product from the reaction mixture could be carried out rather easily. After removal of the palladium

SYNLETT 2004, No. 3, pp 0477–0480
Advanced online publication: 26.01.2004
DOI: 10.1055/s-2004-815427; Art ID: U26603ST

catalyst using filtration through a pad of Celite, and concentration of the filtrate, the less polar co-product, $Et_3SiS(CH_2)_{11}Me$, could be separated effectively by passing the material through a short column of silica gel with hexanes as eluent.

Second, we applied dodecanethiol esters to the palladium-mediated coupling reaction with an organozinc reagent[7,6c] (Table 3). As expected, the substrates, including the optically active dodecanethiol esters, entries 3 and 4, provided the corresponding ketones in slightly better yields than those obtained from the ethanethiol esters.[17] No loss of optical purity was observed during ketone formation with optically active substrates (entries 3 and 4).

Finally, we examined the alkynyl ketone synthesis[8] with dodecanethiol esters (Table 4). As observed in the two reactions above, the dodecanethiol esters proved to be suitable substrates for this reaction as well, and coupling with terminal alkynes took place smoothly to provide the desired ynones in high yields.[18] Remarkably, the use of dodecanethiol ester generally provided better yields than ethanethiol ester. This is due to a suppression of the Michael addition of the thiol to the ynone products, which was the primary reason for the decreased yields in the original protocol when using ethanethiol esters.[8]

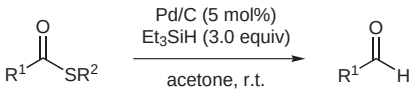
We also applied our protocol to the Evans chiral auxiliary[19,9d,f] controlled aldol chemistry (Scheme 2). A nucleophilic addition of lithium dodecanethiolate[20] took place regioselectively at the imide carbonyl to generate pivotal dodecanethiol ester in good yield, which can then be converted to the aldehyde or a range of ketones under our conditions. For example, the standard reduction conditions afforded the corresponding aldehyde, which would be used again as the substrate for the aldol reaction. Repetition of this protocol would make it possible to elongate the carbon chain with control of the stereochemistry.

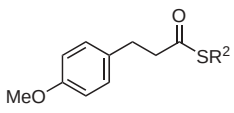
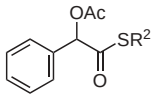
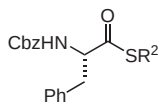
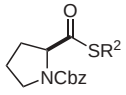
In summary, we have demonstrated that dodecanethiol esters are suitable substrates for palladium-mediated reduction to aldehyde and ketone synthesis. Replacement of ethanethiol with dodecanethiol provided not only a solution for eliminating the unpleasant odor throughout the entire process, but also created a superior feature in ketone synthesis. Thus, we expect that these three odorless transformations using dodecanethiol esters will find many useful applications in organic synthesis.

Acknowledgment

This work was supported in part by the Ministry of Education, Culture, Sports, Science, and Technology, Japan. H.T. thanks PRESTO, JST for financial support.

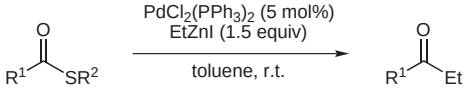
Table 2 Reduction of Dodecanethiol Esters to Aldehydes

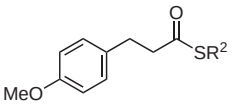
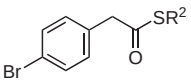
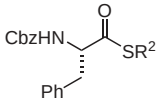
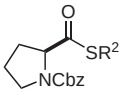


Entry	Substrate	$R^2 = (CH_2)_{11}Me$		$R^2 = Et$	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1		40	89	10	90[c]
2		60	86	50	84[a,c]
3		40	71[b]	10	91[a,d]
4		30	82[b]	5	96[a,d]

[a] Ref.[6b]
[b] The enantiomeric excess of the starting dodecanethiol esters was determined to be 98% ee (entry 3) and >99% ee (entry 4),[15] and preserved in the course of these reactions.[16]
[c] 2 mol% of Pd/C was used.
[d] 2.5 equiv of Et_3SiH was used.

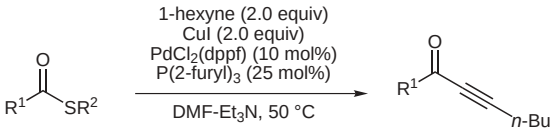
Table 3 Coupling Reaction of Dodecanethiol Esters with Ethylzinc Iodide

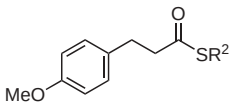
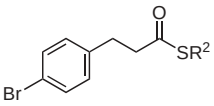
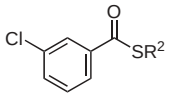
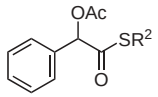


Entry	Substrate	$R^2 = (CH_2)_{11}Me$		$R^2 = Et$[a]	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1		15	95	5	91[c]
2		60	91	5	91
3		25	94[b–d]	15	88[c,e]
4		210	88[b–d]	180	73[c,f]

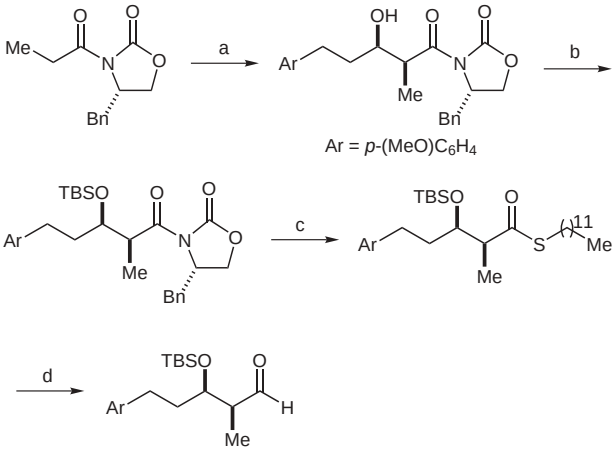
[a] Ref.[7]
[b] The enantiomeric excess of the substrate was preserved.[15]
[c] 0.1 equiv of $PdCl_2(PPh_3)_2$ was used.
[d] 3.0 equiv of EtZn I was used.
[e] 2.5 equiv of EtZn I was used.
[f] 2.0 equiv of of EtZn I was used.

Table 4 Coupling of Dodecanethiol Esters with 1-Hexyne



Entry	Substrate	$R^2 = (CH_2)_{11}Me$		$R^2 = Et$[a,b]	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1		3.0	99	2.0	94
2		1.5	82	1.0	81
3		1.0	85	0.6	74[c]
4		17	83	5.0	53[d]

[a] Ref.[8]
[b] 1.7 Equiv of CuI was used.
[c] 12% of the by-product, i.e., the Michael adduct of ethyl thiolate to the product, was obtained.
[d] 45% of starting material remained.



Scheme 2 *Reagents and conditions*: (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C; *p*-$MeOC_6H_4(CH_2)_2CHO$, 83%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 67%; (c) *n*-BuLi, dodecanethiol, THF, 0 °C, 87%; (d) Et_3SiH, 10% Pd/C, acetone, r.t., 77%.

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(10) (a) Hayashi, Y.; Itoh, T.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 2235. (b) Mori, Y.; Seki, M. *Heterocycles* **2002**, *58*, 125.

(11) (a) Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett.* **2001**, *42*, 9207. (b) Nishide, K.; Ohsugi, S.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 5177. (c) 1-Dodecanethiol is available from Aldrich at $22.90 (500 mL).

(12) **3-(4-Methoxyphenyl)-thiopropionic Acid (*S*)-dodecyl Ester (3).** (a) Via mixed anhydride: To a solution of 3-(4-methoxyphenyl)propionic acid (**1**; 1.02 g, 5.66 mmol) in CH_2Cl_2 (23 mL) was added isobutyl chloroformate (0.880 mL, 6.79 mmol) and Et_3N (0.780 mL, 5.66 mmol). After stirring for 30 min at r.t., 1-dodecanethiol (1.60 mL, 6.79 mmol), Et_3N (0.780 mL, 5.66 mmol), and DMAP (35.0 mg, 0.283 mmol) were added successively and the resulting mixture was stirred for 70 min at r.t. The reaction was quenched by addition of H_2O (50 mL). The mixture was partitioned, and the aqueous layer was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography on silica gel (66 g, 0–2% EtOAc/hexanes) gave the thiol ester **3** (1.82 g, 4.99 mmol, 88%) as a white crystalline solid: mp: 31–32 °C. IR(film): 2925, 2853, 1693, 1612, 1514, 1465, 1248, 1178, 1040, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 3.78 (s, 3 H), 2.94–2.79 (m, 6 H), 1.58–1.51 (m, 2 H), 1.25 (br, 18 H), 0.88 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.8, 158.2, 132.3, 132.3, 129.3, 129.3, 113.9, 55.2, 45.8, 31.9, 30.7, 29.6, 29.6, 29.5, 29.5, 29.3, 29.1, 28.9, 28.8, 22.7, 14.1. Anal. Calcd for $C_{22}H_{36}O_2S$: C, 72.48; H, 9.95. Found: C, 72.38; H, 9.67. (b) With water-soluble carbodiimide (WSCD): To a solution of acid (**1**; 1.05 g, 5.83 mmol), WSCD (1.34 g, 6.99 mmol), and DMAP (36.0 mg, 0.292 mmol) in CH_2Cl_2 (23 mL) was added 1-dodecanethiol (1.67 mL, 6.99 mmol). The solution was stirred for 40 min at r.t., and the reaction was quenched by addition of H_2O (50 mL). A similar purification procedure as above afforded the thiol ester **3** (2.01 g, 5.51

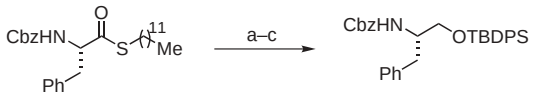
mmol, 95%). (c) Via acid chloride: To a solution of acid (**1**; 104 mg, 0.577 mmol) in CH_2Cl_2 (2.0 mL) was added oxalyl chloride (0.050 mL, 0.58 mmol) and DMF (2.3 μL, 0.029 mmol). The solution was stirred for 30 min at r.t., and concentrated. The residue was dissolved in CH_2Cl_2 (2.0 mL) and to this solution was added 1-dodecanethiol (0.160 mL, 0.692 mmol), followed by Et_3N (0.160 mL, 1.15 mmol). After stirring for 20 min at r.t., the reaction was quenched by addition of water (2 mL). A similar purification procedure as above gave the thiol ester **3** (183 mg, 0.502 mmol, 87%).

(13) The enantiomeric excess of the dodecanethiol ester **4** was determined by HPLC (DAICEL Chiral-OD, 4.6 mm I.D. × 250 mm, 10% 2-propanol/*n*-hexane, 0.3 mL/min, 25 °C).

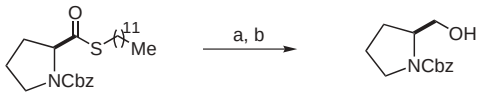
(14) It is essential to carry out the reaction using 0.5 M or higher concentration of the substrate in order to complete the reaction.
A Typical Procedure for Reduction of (*S*)-Dodecyl Thioester: To a mixture of the thioester **4** (521 mg, 1.08 mmol) and 10% Pd/C (57.5 mg, 0.0540 mmol) in acetone (2.2 mL) was added triethylsilane (0.518 mL, 3.24 mmol). After being stirred for 40 min at r.t., the mixture was diluted with Et_2O (11 mL) and filtered through a pad of Celite. The filtrate was concentrated and the residue was treated with hexane (5 mL). The precipitate was collected by filtration and washed twice with hexane. Additional amount of the product was recovered from the filtrate by the same manner to give the desired aldehyde[6b] as a white crystalline solid (217 mg, 0.766 mmol, 71%).

(15) The enantiomeric excess of dodecanethiol ester prepared from proline was determined by HPLC (DAICEL Chiral-OD, 4.6 mm I.D. × 250 mm, 10% 2-propanol/*n*-hexane, 0.5 mL/min, 25 °C).

(16) The enantiomeric excesses of the aldehydes prepared in entries 3 and 4 were determined by HPLC analysis after conversion of these aldehydes as described below (DAICEL Chiral-OD, 4.6 mm I.D. × 250 mm, 10% 2-propanol/*n*-hexane, 0.3 mL/min, 25 °C, Scheme 3).



(a) Et_3SiH, 10% Pd/C, acetone, r.t.; (b) $NaBH_4$, MeOH, r.t.; (c) TBDPSCl, Im, DMF, r.t.



(a) Et_3SiH, 10% Pd/C, acetone, r.t; (b) $NaBH_4$, MeOH, r.t.

Scheme 3

(17) **A Typical Procedure for Coupling with Ethylzinc Iodide:** To a solution of the thiol ester **4** (509 mg, 1.05 mmol) and $PdCl_2(PPh_3)_2$ (73.8 mg, 0.105 mmol) in toluene (3.5 mL) was added ethylzinc iodide (3.95 mL, 3.15 mmol, 0.80 M solution in THF). The reaction mixture was stirred for 25 min at r.t., then quenched with 1 M HCl (10 mL). The mixture was partitioned and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (Florisil on 20 g of silica gel, 20–40% EtOAc/hexanes) gave the desired ethyl ketone[7,6c] (307 mg, 0.986 mmol, 94%) as a yellow oil.

(18) **A Typical Procedure for Coupling with 1-Hexyne:** To a solution of the thiol ester (**3**; 202 mg, 0.554 mmol), $PdCl_2$(dppf) (45.2 mg, 0.0554 mmol), CuI (211 g, 1.11 mmol) and tri-2-furylphosphine (32.2 mg, 0.139 mmol) in DMF (1.0 mL) and Et_3N (0.2 mL) was added 1-hexyne (126 μL, 1.11 mmol). The reaction mixture was stirred for 3 h at 50 °C, diluted with Et_2O (5 mL), and quenched with 5 × H_2O (5 mL). The mixture was filtered through a pad of Celite and the filtrate was partitioned. The aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography on silica gel (5 g, 5–10% Et_2O/hexanes) gave the alkynyl ketone (134 mg, 0.548 mmol, 99%) as a brown oil. IR (film): 2958, 2871, 2214, 1671, 1513, 1247, 1178, 1036, 825 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.3 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 3.78 (s, 3 H), 2.92 (t, *J* = 6.8 Hz, 2 H), 2.83 (t, *J* = 7.1 Hz, 2 H), 2.37 (t, *J* = 6.8 Hz, 2 H), 1.58–1.52 (m, 2 H), 1.46–1.40 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.1, 158.0, 132.4, 129.2, 113.9, 94.8, 80.8, 55.2, 47.3, 29.7, 29.1, 21.9, 18.6, 13.5. HR-MS (FAB): *m/z* calcd for $C_{16}H_{20}O_2$: 244.1463. Found: 244.1458.

(19) Gage, J. R.; Evans, D. A. *Org. Synth., Coll. Vol. VIII*; Wiley and Sons: New York, **1993**, 339.

(20) For removal of the auxiliary with benzyl mercaptan, see: (a) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849. (b) With 1-octanethiol, see: Narasaka, K.; Saitou, M.; Iwasawa, N. *Tetrahedron: Asymmetrie* **1991**, *2*, 1305.