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Thiol-Catalyzed Acyl Radical Cyclization of Alkenals

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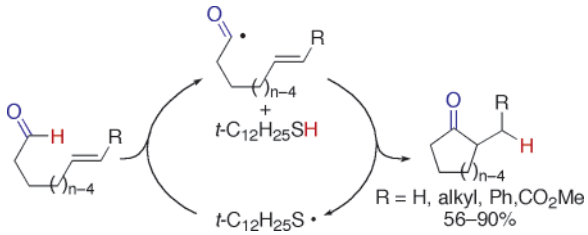


Thiol-catalyzed direct generation of acyl radicals and their intramolecular addition to olefins of alkenals gave 2-substituted five- and six-membered cyclic ketones in reasonably good yields. The combination of odorless *tert*-dodecanthiol and AIBN or V-40 was the initiator of choice among surveyed radical generators for the cyclization of alkenals. Aldehydes having electron-deficient olefins cyclized more easily than those having unactivated olefins.

Development of atom economical transformation is an important strategy in synthetic organic chemistry.[1] A good example of an atom economical transformation is an addition reaction, in which all elements in the starting substrates remain in the products. Herein, we describe the formation of various 2-substituted cyclic ketones via thiol-catalyzed addition reactions of acyl radicals to internal olefins.

We have already reported cyclization reactions of ω-oxo-α,β-unsaturated esters through a tandem conjugate addition−intramolecular aldol reaction initiated by lithium thiolate.[2,3] The reaction of **1a** with lithium phenylmethanethiolate **2** gave stereoselectively cyclic β-hydroxy-β'-thioalkanoate **3** in 95% yield (Scheme 1, path A). We then expected that the chemistry of S-centered radical **4** might enable the same transformation with a catalytic amount of an initiator.[4] However, the reaction of **1a** with phenylmethanethiol (1.2 equiv) and AIBN (0.6 equiv) in refluxing toluene did not give the expected product **3** but ketoester **5a** in 74% yield (Scheme 1, path B). The reaction seemed to proceed via acyl radical intermediate **6**.[5,6] This type of cyclization has been achieved with acyl radicals[7] generated by a homolytic cleavage of C−S,[8] C−Se,[9] and other carbon−heteroatom bonds[10] and by coupling of carbon-centered radicals with

SCHEME 1. Cyclization of ω-Oxo-alkenoate 1a in an Anionic (Path A) and a Radical (Path B) Mode

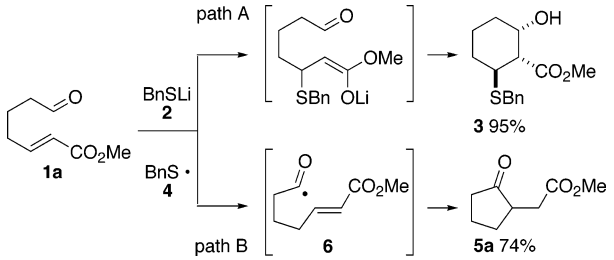
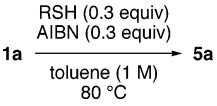


TABLE 1. The Radical Cyclization Reaction of 1a with Various Thiols Initiated by AIBN



entry	thiol/RSH	time (h)	yield (%)[a]
1[b]	Bn	4	63 (18)
2	Ph	6	16 (76)
3	*t*-Bu	6	74 (16)
4	2,4,6-$(Me)_3C_6H_2CH_2$	6	44 (53)
5	Ph_3C	6	2 (96)
6[b]	*t*-$C_{12}H_{25}$	19	89 (<3)
7[b]	none	22	trace (98)
8	NHPI[c]	23	20 (17)

[a] The numbers in parentheses are the recovery yields of **1a**. [b] In refluxing benzene (1 M). [c] *N*-Hydroxyphthalimide (NHPI) was used instead of a thiol.

(1) Trost, B. M. *Science* **1991**, *254*, 1471−1477.

(2) (a) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **2001**, *66*, 8199−8203. (b) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 6979−6982.

(3) Our previous studies on the catalytic asymmetric Michael reaction of thiols: (a) Nishimura, K.; Tsubouchi, H.; Ono, M.; Hayama, T.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **2003**, *44*, 2323−2326. (b) Nishimura, K.; Tomioka, K. *Yakugaku Zasshi* **2003**, *123*, 9−18. (c) Nishimura, K.; Tomioka, K. *J. Org. Chem.* **2002**, *67*, 431−434. (d) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 440−442. (e) Tomioka, K.; Okuda, M.; Nishimura, K.; Manabe, S.; Kanai, M.; Nagaoka, Y.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 2141−2144. (f) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974−12975. (g) Tomioka, K. *Synthesis* **1990**, 541−549.

(4) A dramatic inversion of cis/trans selectivity in a cyclization reaction was observed by changing an ionic reaction to a radical one: Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4043−4046.

(5) An intermolecular acyl radical reaction was reported: Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 67−75.

(6) For a review of acyl radicals: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991−2069.

(7) For polarity reversal catalysis of hydrogen atom abstraction: Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25−35.

(8) (a) Ozaki, S.; Adachi, M.; Sekiya, S.; Kamikawa, R. *J. Org. Chem.* **2003**, *68*, 4586−4589. (b) Crich, D.; Hao, X. *J. Org. Chem.* **1997**, *62*, 5982−5988. (c) Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308−310.

(9) (a) Evans, P. A.; Roseman, J. D. *J. Org. Chem.* **1996**, *61*, 2252−2253. (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429−1443. (c) Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272−9284. (d) Bachi, M. D.; Denenmark, D. *Heterocycles* **1989**, *28*, 583−588. (e) Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1986**, *27*, 641−644.

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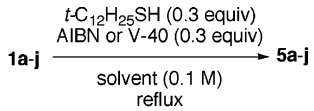
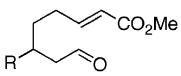
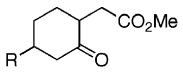
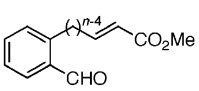
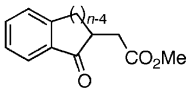
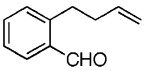
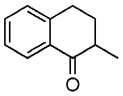
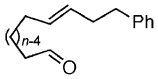
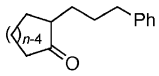
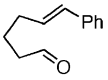
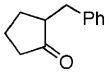
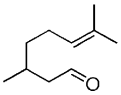
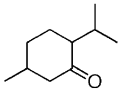
TABLE 2. The Acyl Radical Cyclization Reaction of 1, Using *tert*-Dodecanethiol and AIBN or V-40[a]



entry	substrate		solvent	time (h)	product		yield (%)[b]
1	**1a**		PhCl[c]	19	**5a**		90
2		**1b** (R = H)	PhMe	19		**5b**	85
3		**1c** (R = Me)	C_6H_6[c]	20		**5c**	78 (12)[d]
4[e,f]		**1d** (*n* = 5)	PhMe	23		**5d**	73 (6)
5[e,f,g]		**1e** (*n* = 6)	PhCl	19		**5e**	76 (5)
6[e,f]		**1f**	PhMe	19		**5f**	58
7[e,f]		**1g** (*n* = 5)	C_6H_6[c]	40		**5g**	81
8[f,h]		**1h** (*n* = 6)	PhMe	24		**5h**	56
9[f,i]		**1i**	PhMe	21		**5i**	64
10		**1j**	PhMe	21		**5j**	86 (6)[j]

[a] In toluene or PhCl, V-40 was used as an initiator, whereas AIBN was used in benzene. [b] The numbers in parentheses are the recovery yields of **1**. [c] In 1 M solution. [d] Cis:trans = 5:6. [e] With 1.5 equiv of the initiator. [f] With 3.0 equiv of the thiol. [g] At 100 °C. [h] With 0.6 equiv of V-40. [i] V-40 was added in two portions (0.3 equiv each). [j] Cis:trans = 2:3.

carbon monooxide.[11] However, there is no example of this cyclization[12,13] through direct generation of acyl radicals from formyl alkenoates.[14,15]

We first examined the reaction of ω-oxo-alkenoate **1a** in benzene or toluene (1 M) with several thiols using AIBN (0.3 equiv) as a radical initiator (Table 1). The reaction with a catalytic amount of phenylmethanethiol gave **5a** in 63% yield (entry 1). The use of benzenethiol reduced the yield to 16% probably because phenylthiyl radical is too stable (bond dissociation energy (BDE) in kJ/mol: RS−H = 366, PhS−H = 349, Ac−H = 374)[16] to abstract hydrogen from the formyl group efficiently (entry 2). Bulkier 2-methyl-2-propanethiol improved the yield to 74% (entry 3), but the results with 2,4,6-trimethylphenylmethanethiol and triphenylmethanethiol were less satisfactory (entries 4 and 5). Finally, bulky *tert*-dodecanethiol,[5] which has a much higher boiling point (227−248 °C) than the reaction temperature, gave the best result to provide **5a** in 89% yield (entry 6). Without thiols and under thoroughly deoxygenated conditions no reaction proceeded and **1a** was recovered in high yield (entry 7).[17] With *N*-hydroxyphthalimide (NHPI)[14a,b] instead of a thiol, the yield of **5a** was poor (entry 8). It is also important to note that bulky and stench-free[18] thiols prevent formation of hemithioacetals with the aldehyde

(10) (a) Bath, S.; Laso, N. M.; Lopez-Ruiz, H.; Quinclet-Sire, B.; Zard, S. Z. *Chem. Commun.* **2003**, 204−205. (b) Crich, D.; Chen, C.; Hwang, J.-T.; Yuan, H.; Papadatos, A.; Walter, R. I. *J. Am. Chem. Soc.* **1994**, *116*, 8937−8951. (c) Coveney, D. J.; Patel, V. F.; Pattenden, G.; Thompson, D. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2721−2728. (d) Curran, D. P.; Liu, H. *J. Org. Chem.* **1991**, *56*, 3463−3465. (e) Cekovic, Z. *Tetrahedron Lett.* **1972**, *13*, 749−752.

(11) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018−1019.

(12) A chiral carbene-catalyzed cyclization of this type: (a) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934−1936. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299.

(13) Rhodium-catalyzed asymmetric intramolecular 5-endo hydroacylation of alkenals: Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806−5816.

(14) Direct generation of an acyl radical and its intermolecular addition to an olefin: (a) Tsujimoto, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 5601−5604. (b) Tsujimoto, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2001**, 2352−2353. (c) Gottschalk, P.; Neckers, D. C. *J. Org. Chem.* **1985**, *50*, 3498−3502. See also ref 4.

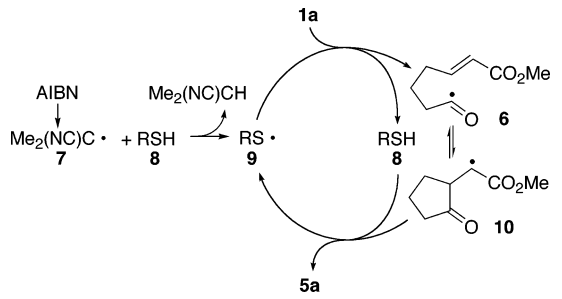
(15) A similar cyclization of dithioalkyl radicals: Nishida, A.; Kawahara, N.; Nishida, M.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 9713−9734.

(16) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2002.

(17) Under the standard argon atmosphere carboxylic acids were obtained along with **5a** in poor yield.

(18) Nishide, K.; Patra, P. K.; Matoba, M.; Shanmugasundaram, K.; Node, M. *Green Chem.* **2004**, *6*, 142−146.

SCHEME 2. Plausible Radical Chain Mechanism for the Cyclization Reaction



as well as conjugate addition to the α,*β*-unsaturated ester. Dimethylzinc or triethylborane-initiated radical reaction[19] was not applicable in this thiol-catalyzed acyl radical cyclization.[20]

Full conversion of **1a** was achieved when the reaction was conducted in refluxing chlorobenzene (bp 132 °C) to give **5a** in 90% yield (Table 2, entry 1). At higher temperature, 1,1′-azobis(cyclohexanecarbonitrile) (V-40), which has a much longer half-life (2 h/100 °C) than AIBN (7 min/100 °C),[21] was the initiator of choice. Other formylalkenoates also underwent this cyclization reaction. Six-membered cyclic alkanoates **5b** and **5c** were obtained from **1b** and **1c** in 85% and 78% yield, respectively (entries 2 and 3). Formation of benzene-fused rings was also possible to give **5d** and **5e** from **1d** and **1e** in 73% and 76% yield, respectively (entries 4 and 5). In contrast to the brilliant, carbene-catalyzed cyclization reactions,[12] an electron-withdrawing methoxycarbonyl group is not essensial for the cyclization reaction to proceed. Mono-, di- and trialkyl-substituted alkenes **1f**−**j** can be utilized as an acyl radical acceptor to give the corresponding cyclized products in good yields (entries 6−10). It is noteworthy that a relatively high concentration for an intramolecular reaction (1−0.1 M) is applicable to obtain the products in good yields without formation of any byproducts from an intermolecular reaction.

The reaction seems to proceed through a radical chain process shown in Scheme 2.[5] The thermal decomposition of AIBN initiates the reaction by the formation of cyanoalkyl radical **7**, which abstracts a hydrogen from thiol **8** to give thiyl radical **9**. Hydrogen abstraction from **1a** by **9** produces acyl radical **6** which cyclizes to give **10**.[22] Hydrogen exchange with thiol **8** gives product **5a** and thiyl radical **9** to propagate the chain reaction.

Table 2 shows that the stability of cyclized radical intermediate **10** strongly influences the yields of the products. Thus, alkenes **1a**−**e** and **1j** having good radical stabilizing substituents (BDE in kJ/mol: α-C−H of ethyl propanoate = 400, *t*-Bu−H = 400)[16] gave the products in better yields (entries 1−5 and 10) than **1f**−**h**, which give less stable primary or secondary alkyl radicals (BDE in kJ/mol: Et−H = 421, *i*Pr−H = 411) as intermediates (entries 6−8). The hydrogen abstraction from thiol **8** by more stable benzylic radical (BDE in kJ/mol: α-C−H of PhPr = 366) is probably so slow that the reaction of **1i** is less efficient (entry 9).

In conclusion, we have developed a thiol-catalyzed intramolecular addition reaction of a formyl group to an olefin to give a variety of 2-substituted cyclic ketones in reasonably good yields. Because the aldehyde hydrogen atom is transferred to the product via a thiol, this reaction is quite atom economical.

Experimental Section

The General Procedure for Cyclization of Alkenal (Table 2, Entry 2). Methyl (2-oxocyclohexane)acetate (5b): V-40 (37 mg, 0.15 mmol) was added to a solution of alkenal **1b** (85 mg, 0.50 mmol) and *tert*-dodecanethiol (30 mg, 0.15 mmol) in dry toluene (5 mL). The solution was degassed three times by the freeze−thaw procedure. The mixture was then refluxed under argon atmosphere for 19 h. The crude reaction mixture was directly purified by silica gel column chromatography (hexane/ether 4/1) to give cyclic ketone **5b** (73 mg, 85%)[23] as a colorless oil.

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Supporting Information Available: The preparation methods of alkenals **1** and the characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048275A

(19) (a) Yamamoto, Y.; Maekawa, M.; Yamada, K.; Tomioka, K. *Tetrahedron* **2005**, *61*, 379−384. (b) Yamada, K.; Yamamoto, Y.; Tomioka, K. *J. Synth. Org. Chem., Jpn.* **2004**, *62*, 1158−1165. (c) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Chen, J.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 6595−6597. (d) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tomioka, K. *J. Org. Chem.* **2004**, *69*, 1531−1534. (e) Yamamoto, Y.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 795−797. (f) Yamada, K.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797−1799. (g) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509−3511.

(20) Davies, A. G.; Roberts, B. P. *J. Chem. Soc. B* **1971**, 1830−1837.

(21) Walling, C.; Huyser, E. S. Free Radical Additions to Olefins to Form Carbon−Carbon Bonds. In *Organic Reactions*; Adams, R., Blatt, A. H., Boekelheide, V., Cairns, T. L., Cope, A. C., Curtin, D. Y., Niemann C., Eds.; Willey & Sons: New York, 1963; Vol. 13, pp 113−116.

(22) The generation of acyl radicals from aldehydes via hydrogen abstraction by thiyl radicals and their reaction with a disulfide: Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Commun.* **2002**, 1082−1083.

(23) Ebinger, A.; Heinz, T.; Umbricht, G.; Pfaltz, A. *Tetrahedron* **1998**, *54*, 10469−10480.