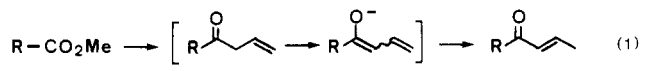
Reaction of Ester Enolates with Nucleophiles. Stereocontrolled Formation of Ketone and Aldehyde Enolates[1]

Summary: Lithium enolates of carboxylic and thiocarboxylic esters react with nucleophiles [RLi, RMgX, $NaAl(OC_2H_4OCH_3)_2H_2$] to afford ketone and aldehyde enolates and subsequently their enol silyl ethers diastereoselectively. This reaction is applied to the synthesis of γ-damascone, α-damascone, β-safranal, and artemisia ketone.

Sir: Recently we published an efficient procedure for converting nonenolizable or slowly enolizable carboxylic esters or amides into ketones, with allylmagnesium chloride/LDA as reagent.[2] This reaction (eq 1) succeeds,

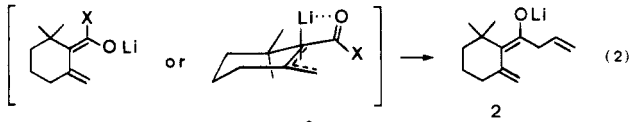


(1)

because the initially formed ketones are protected from further reaction by rapid enolate formation.

Whereas the scope of this transformation (eq 1) is limited to readily deprotonated ketones (e.g., reactions of allylmagnesium halides), we now report a general conversion of structurally diverse ester (or thiol ester) enolates into ketone and aldehyde enolates.[3,4]

This reaction sequence (eq 2 and Table I) constitutes a perfect protection against double addition of the nucleophile independent of the organometallic reagent used

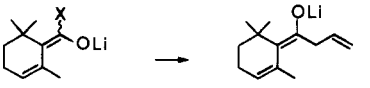


(2)

1a X = OMe react. temp. ⩾ 25°C
1b X = S Ph " " ⩾-50°C

and works for a wide range of nucleophiles [e.g., RLi, RMgX (R = alkyl, alkenyl, allyl, phenyl), $LiAlH_4$, Vitride] and esters, either α-branched or not. Thus deprotonation of methyl β-cyclogeranate with *n*-BuLi[5] (1.3 equiv, THF, 15 °C, 5 min) and reaction of the resultant ester *E* enolate **1a**[6] with allylmagnesium chloride in THF (1.3 equiv, 25–35 °C, 20 min) afforded selectively the ketone *E* enolate **2** (*E*/*Z*, 19:1). In situ silylation of the latter (TMSCl, 3 equiv, −20 to 20 °C, 30 min) gave the enol silyl ether (Table I, entry 1).

Selective kinetic protonation of the same ketone enolate **2** (NH_4Cl, aqueous) followed by isomerization of the vinyl double bond (Al_2O_3, Et_2O, 20 °C)[7] led to an expeditious synthesis of γ-damascone[8] (76% yield) (entry 5). A similar Grignard reaction on deprotonated isopropyl β-cyclogeranate required a higher reaction temperature (≥35 °C), whereas the enolate **1b** obtained from deprotonation of β-cyclothiogeranate (*n*-BuLi, −78 °C) reacted already at −50 °C with allylmagnesium chloride. An analogous relationship between reactivity and nucleofugal properties of the leaving group was observed in the preparation of α-damascone[9] from the enolate of methyl α-cyclogeranate **3a** (≥25 °C) and from the phenylthio enolate **3b** (≥−78 °C)[10] (eq 3 and Table I, entries 4 and 8).



(3)

3a X = OMe react. temp. ⩾ 25°C
3b X = SPh " " ⩾-78°C

Application of this reaction sequence to the synthesis of γ-damascenone[11] from methyl β-safranate[12] was equally successful (entry 11), as was the synthesis of artemisia ketone[9a,13] via reaction of prenylmagnesium chloride with

(1) Part of this work was presented at the Swiss Chemical Society Meeting in Berne, October 10, 1986.

(2) Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1986**, *69*, 228. Fehr, C. (Firmenich SA) Eur. Pat. A1 0093840 (prior. 20.4.1982); *Chem. Abstr.* **1984**, *100*, 102816*w*.

(3) (a) For the related reaction of organolithium reagents with ketenes, generated in situ from suitable α-branched BHT alkanoates, see: Häner, R.; Laube, T.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396. (b) For a related formal Dieckmann condensation supposed to proceed via an in situ generated ketene, see: Corey, E. J.; Su, W.; Houpis, I. N. *Tetrahedron Lett.* **1986**, *27*, 5951. (c) For in situ generation and trapping of ketenimines, see: Meyers, A. I.; Smith, E. M.; Ao, M. S. *J. Org. Chem.* **1973**, *38*, 2129, 2136. Meyers, A. I.; Knaus, G.; Kamata, Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567. Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. Dubois, J. E.; Lion, C. *Bull. Soc. Chim. Fr.* **1973**, *2673*; **1976**, 1875. El Jazouli, M.; Masson, S.; Thuillier, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1598. For the reaction of organometallic reagents with ketenes, see, e.g.: (d) Naef, F.; Decorzant, R. *Tetrahedron* **1986**, *42*, 3245. (e) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391.

(4) (a) For examples of organometallic nucleophilic additions to carbonyl groups possessing partial negative charge, see: Jorgensen, M. J. *Org. React. (N.Y.)* **1970**, *18*, 1. Barabas, A.; Balaban, A. T. *Tetrahedron* **1971**, 27, 5495. Boudjouk, P.; Ohrbom, W. H.; Woell, J. B. *Synth. Commun.* **1986**, *16*, 401. Peterse, A. J. G. M.; de Groot, Ae, van Leeuwen, P. M.; Penners, N. H. G.; Koning, B. H. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 124. In a synthesis of nezukone: Wenkert, E.; Greenberg, R. S.; Kim, H.-S. *Helv. Chim. Acta* **1987**, *70*, 2159. (b) For examples and discussions of pyramidalized carbanion centers in preference to planar enolates, see: Bongini, A.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1986**, 50. Ndibwami, A.; Deslongchamps, P. *Can. J. Chem.* **1986**, *64*, 1788. Takahashi, O.; Saka, T.; Mikami, K.; Nakai, T. *Chem. Lett.* **1986**, 1599. Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572. Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. Lochmann, L.; Lim, D. *J. Organomet. Chem.* **1973**, *50*, 9. Häner, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1655. Häner, R.; Olano, B.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1676.

(5) Analogous deprotonations of α,β-unsaturated esters are well documented; e.g.: (a) Wilson, S. R.; Myers, R. S. *J. Org. Chem.* **1975**, *40*, 3309. (b) Gesson, J. P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron Lett.* **1980**, *21*, 2509. Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1333. Baumann, J. G.; Hawley, R. C.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1569. See also ref 6.

(6) The corresponding trimethylsilyl ketene acetal undergoes 1,5 (O → C) silicon migration at 20 °C. For analogies, see: Adams, A. D.; Schlessinger, R. H.; Tata, J. R.; Venit, J. J. *J. Org. Chem.* **1986**, *51*, 3069. Bell, S. H.; Cameron D. W.; Fentrill, G. I.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **1985**, *26*, 6519. See also ref 5a.

(7) Reetz, M. T.; Wenderoth, B.; Urz, R. *Chem. Ber.* **1985**, *118*, 348.

(8) (a) Schulte-Elte, K. H.; Rautenstrauch, V.; Ohloff, G. *Helv. Chim. Acta* **1971**, *54*, 1805. Schulte-Elte, K. H.; Muller, B. L.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 310. Näf, F.; Decorzant, R. *Helv. Chim. Acta* **1974**, *57*, 1317. Takazawa, O.; Saigo, K.; Narasaka, K. *Chem. Lett.* **1977**, 757. Gosselin, P. *Tetrahedron Lett.* **1986**, *27*, 5495. Amrollah-Madjdabadi, A.; Stella, L. *Bull. Soc. Chim. Fr.* **1987**, 350. Snowden, R. L.; Linder, S. *Helv. Chim. Acta* **1987**, *70*, 1858. (b) Zaidlewicz, M. *Tetrahedron Lett.* **1986**, *27*, 5135.

(9) (a) Ohloff, G. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1978; Vol. 35, p 431. (b) References cited in ref 2, 3d, and 8b.

(10) This outstanding reactivity of thiol esters has not been exploited, although it is found in many biological transformations, e.g., *S*-acetylcoenzyme A in acetyl transfer reactions: Douglas, K. T. *Acc. Chem. Res.* **1986**, *19*, 186.

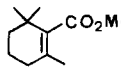
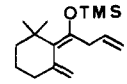
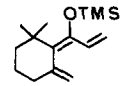
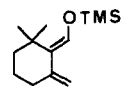
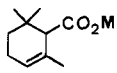
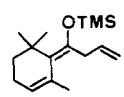
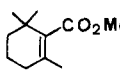
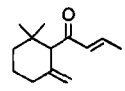
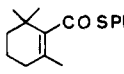
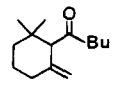
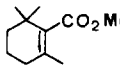
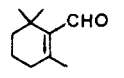
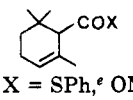
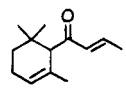
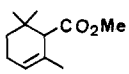
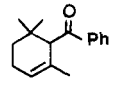
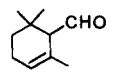
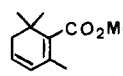
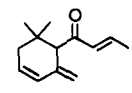
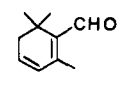
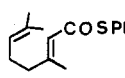
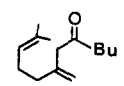
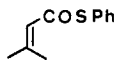
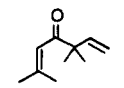
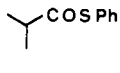
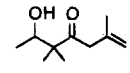
(11) Hogyoku Koryo Co. Ltd. J. P 81,128,727; *Chem. Abstr.* **1982**, *96*, 34694*b*.

(12) Schulte-Elte, K. H.; Muller, B. L.; Egger, B. (Firmenich SA) Eur. Pat. Appl. 46606 (prior. 26.8.1980); *Chem. Abstr.* **1982**, *97*, 24036*v*.

(13) For recent syntheses, see: Dubois, J. E.; Lion, C.; Arouisse, A. *Bull. Soc. Chim. Belg.* **1984**, *93*, 1083. Stella, L.; Amrollah-Madjdabadi, A. *Synth. Commun.* **1984**, 1083. Hendrickson, J. B.; Boudreaux, G. J.; Palumbo, P. S. *J. Am. Chem. Soc.* **1986**, *108*, 2358. Fehr, C.; Galindo, J.; Perret, R. *Helv. Chim. Acta* **1987**, *70*, 1745.

0022-3263/88/1953-1828$01.50/0

Table I. Reaction of Ester Enolates with Nucleophiles (RM)

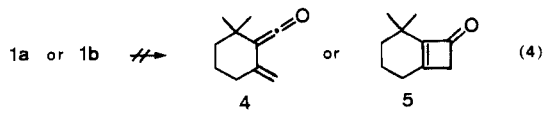
entry	substrate + THF	base (equiv; °C; min) RM in THF (equiv; °C; min) electrophile (equiv; °C; min)	product	isolated yield (%) E/Z
1		*n*-BuLi (1.3; 15; 5) CH_2CHCH_2MgCl (1.3; 25→35; 20) TMSCl (3.0; −20→20; 30)		(76) 19:1[a]
2		*n*-BuLi (1.3; 15; 5) $CH_2CHMgBr$ (1.3; 25→35; 45) TMSCl (3.0; −20→20; 30)		(70) 9:1[a]
3		*n*-BuLi (1.3; 15; 5) $LiAlH_4$ (0.5; 45; 90) NEt_3 (1.3)/TMSCl (4.0; −78→0; 60)		(70) 6:1[a]
4		*n*-BuLi (1.0; −78→15; 45) CH_2CHCH_2MgCl (1.2; 15→35; 30) TMSCl (5.0; −20→20; 30)		(75)[b] 9:1
5		*n*-BuLi (1.3; 15; 5) CH_2CHCH_2MgCl (1.3; 25→35; 20) NH_4Cl, aqueous; Al_2O_3[c]		(76)[d]
6		*n*-BuLi (2.0; −78→20; 30) NH_4Cl, aqueous		(60)
7		*n*-BuLi (1.3; 15; 5) Vitride (1.0; 40; 45)[f] *sec*-BuOH (5.0; 15; 1); HCl, aqueous		(70)
8	 X = SPh,[e] OMe	*n*-BuLi (1.0; −78; 30)[g] CH_2CHCH_2MgCl (1.2; −78→−50; 60)[g] NH_4Cl, aqueous; Al_2O_3[c]		(80)[h]
9		*n*-BuLi (1.0; −78→15; 45) PhLi (1.1; 25→30; 150) NH_4Cl, aqueous		(64)
10		*n*-BuLi (1.1; −78→15; 45) Vitride (1.0; 40; 45) NH_4Cl, aqueous		(65)
11		*n*-BuLi (1.05; −78→15; 45) CH_2CHCH_2MgCl (1.05; 15→35; 20) NH_4Cl, aqueous; Al_2O_3[c]		(81)[i]
12		*n*-BuLi (1.05; −78→15; 45) Vitride (1.0; 40; 45) TMSCl (2.5; −15→20; 45); HCl, aqueous		(85)[j]
13		LDA (1.05; −78; 30) *n*-BuLi (2.15; −78→30; 120)[k] NH_4Cl, aqueous		(30)[l]
14		LDA (1.05; −78; 30) *n*-BuLi (1.05; −78; 5)[k] CMe_2CHCH_2MgCl (1.2; −78→20; 240) NH_4Cl, aqueous; Al_2O_3[c]		(56)[m]
15		LDA (1.1; −78; 30) *n*-BuLi (1.05; −78; 10)[k] CH_2CMeCH_2MgCl (1.1; −78→40; 45) MeCHO (1.05; −78; 30); HCl, aqueous		(54)[l,n,o]

[a] The stereochemistry was assigned on the basis of ^1H NMR NOE measurements. [b] Reference 3d. [c] Reference 7. [d] Reference 8. [e] Prepared from acid chloride [PhSLi (1.0 equiv) or PhSH/NEt_3 in THF, 20 °C, 1–15 h]. [f] Vitride = Red-Al (Aldrich) = $NaAlH_2(OCH_2CH_2OMe)_2$ 70% in toluene. [g] X = SPh; for X = OMe, see entry 4. [h] Reference 9. [i] Reference 11. [j] Reference 14. [k] For deprotonation of generated diisopropyl amine. [l] Contains minor amounts (~10%) of isomeric α,β-unsaturated enone. [m] Reference 13. [n] Was converted into artemisia ketone (Ac_2O, pyridine; 445 °C; Al_2O_3; 45%). [o] Illustrative procedure (entry 15): Phenylthio isobutyrate (3.0 g, 16.7 mmol) in THF (20 mL) was successively treated with LDA (in THF/hexane), *n*-BuLi (in hexane), methallylmagnesium chloride (in THF), and acetaldehyde (for equivalents, reaction temperature, and times, see table). The cold (−78 °C) solution was poured into a vigorously stirred solution of 5% aqueous HCl and extracted with Et_2O. The organic phase was washed with 5% aqueous NaOH (16.7 mmol; for removal of thiophenol), H_2O, and brine, dried (Na_2SO_4), evaporated, and distilled (100–110 °C, 4 Torr) to afford 1.53 g (54%) of 6-hydroxy-2,5,5-trimethyl-1-hepten-4-one.

the enolate derived from *S*-phenyl 3,3-dimethylthioacrylate (entry 14). An important extension of this reaction sequence involves direct reduction of the ester enolates by using Vitride or $LiAlH_4$ to afford aldehyde *E* enolates (entry 3), thus opening a simple access to α- and β-cyclocitral (entries 7 and 10) and β-safranal (entry 12).[14]

Finally, trapping of the intermediate ketone enolates with acetaldehyde (entry 15) allows regiocontrolled formation of two C,C-bonds in one operation as exemplified in the direct construction of the artemisia ketone skeleton.[15]

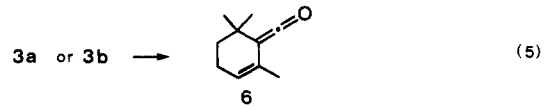
The course of the reaction described herein is dependent on substrate structure and leaving group (steric and stereoelectronic factors), metal counterions, and nucleophilic reactivity of the organometallic reagent. In order to elucidate the potential intermediacy of a ketene, we have focused on the reactivity of ester enolates with or without added nucleophile. The *s*-cis *E* dienolates **1a** and **1b** are stabilized by lithium ion complexation,[6] and all experiments directed toward the synthesis and detection of ketene **4** or its valence tautomer **5** starting from either the dienolate **1a** or **1b** have failed (eq 4). Presumably, the



COX group of these enolates is twisted out of the allyl π-system for steric reasons.[4b,16] Therefore it is probable that these ester anions lead to the formation of ketone enolates **2** via species that possess carbanionic character and whose COX groups still retain residual electrophilicity.[4]

Next, in an attempt to trap a putative ketene intermediate by intramolecular [2 + 2] cycloaddition, we heated the enolate (entry 13) with or without added nucleophile; however, no 2-methylene-7,7-dimethylbicyclo[3.1.1]heptan-7-one[17] or derived products thereof were isolated. In addition, the enolates (entries 13 and 14) both undergo acylation reactions and thus do not provide support for a putative ketene intermediate in these cases.[18]

In contrast, the α-cyclogeranate enolates **3a** and **3b** are thermally unstable and are converted to ketene **6**[3d] above 10 and −78 °C respectively (eq 5).



In order to account for these observations, we propose the following mechanistic rationale: the nucleophile RM, bonded by complexation or aggregation to the ester enolate, contributes to the weakening of the C–X bond; in a second stage, RM then attacks the COX group to afford the ketone or aldehyde enolate.[19] Only in certain cases is the C–X bond cleaved completely to give rise to an elimination–addition reaction type via a ketene intermediate.[20]

(14) For recent β-safranal syntheses, see: Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1128. Könst, W. M. B.; van der Linde, L. M.; Boelens, H. *Tetrahedron Lett.* **1974**, 3175. For the reduction of ynolates, see: Kowalski, C. J.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 1325.

(15) For a related trapping with aldehydes, see ref 3a.

(16) For analogous cases, see ref 6 and: Büchi, G.; Wüest, H. *Helv. Chim. Acta* **1971**, *54*, 1767. MNDO calculations (Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899; 4907) on **1a** (Boschung, A. F., unpublished) further indicate that the carbonyl C has a substantial partial positive charge and that the COX group is not coplanar with the allyl π-system (dihedral angle between the two planes ≈80°).

(17) Kulkarni, Y. S.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 2809.

(18) BHT ester enolates possessing H atoms at the α-position are reported not to afford ketones when treated with organometallic reagents, possibly because the intermediate ketenes are deprotonated to ynolates.[3a] Indeed, the reaction (entry 13) on *n*-BuLi on the corresponding BHT ester enolate failed to give any of the corresponding butyl ketone.

(19) For a discussion on lithium enolate aggregates, see: Seebach, D. *Proc. R. A. Welch Found. Conf.* **1984**, *27*, 93. For interaction between organolithium compounds and esters or ketones, see: Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715. The importance of complexation of organometallic reagents with the substrate which imparts some intramolecular character to the transformation has been recently emphasized; see, e.g., ref 2 and: Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016 ("lithium bridging promotes reaction between two species which would normally be considered to repel each other"). Rachon, J.; Goedken, V.; Walborsky, H. M. *J. Am. Chem. Soc.* **1986**, *108*, 7435. Meyers, A. I.; Barner, B. A. *J. Org. Chem.* **1986**, *51*, 120. Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7115. Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025.

(20) For mechanistic investigations which distinguish between a tetragonal $B_{AC}2$ mechanism and an E1cB pathway, see: Douglas, K. T. *Acc. Chem. Res.* **1986**, *19*, 186. In an intramolecular ester condensation implicating a cumulated enolate, a pathway involving a ketene intermediate is discarded for steric reasons: Corey, E. J., synthesis of C_{15}-gingkolide; conference presented at ETH Zürich, 20 March, 1987.

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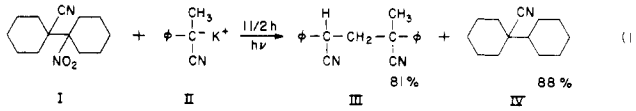
Received October 9, 1987

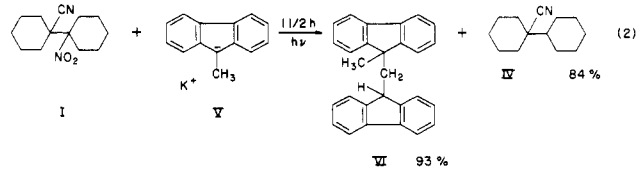
Carbanions That Function Both as Electron Transfer Agents and as Hydrogen Atom Donors: A New Electron Transfer Chain Reaction[1]

Summary: New reactions are described in which carbanions function both as one electron transfer agents and as hydrogen atom donors; a novel feature of these reactions is the generation of a radical anion by hydrogen atom abstraction.

Sir: We have discovered a new reaction in which carbanions function both as one electron transfer agents and as hydrogen atom donors. Thus β-nitro nitrile I reacts completely with α-methylbenzyl cyanide anion (II) in $1^1/_2$ h (eq 1).[2] In contrast, the potassium salt of benzyl cyanide under the same conditions does not react at all with β-nitro nitrile I.



Furthermore, β-nitro nitrile I when treated with the anion of 9-methylfluorene (V) reacts rapidly as shown in eq 2. On the other hand the potassium salts of fluorene and 9-phenylfluorene fail to react.



(1) Paper 33 in the series "Substitution Reactions Which Proceed *via* Radical Anion Intermediates". For preceding paper, see: Kornblum, N.; Ackermann, P.; Manthey, J. W.; Musser, M. T.; Pinnick, H. W.; Singaram, S.; Wade, P. A. *J. Org. Chem.*, in press.

(2) This and the other reactions reported here were carried out with exposure to two 110-V, 20-W white fluorescent lights. They proceed at a slightly slower rate if simply exposed to room light.

0022-3263/88/1953-1830$01.50/0