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Convenient synthesis of a reactive ester homoenolate

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Abstract

Reaction between methyl 3-phenyl-3-trimethylsilylpropionate (8) and catalytic quantities of tetrabutylammonium triphenyldifluorosilicate (TBAT) effects desilylation to the corresponding homoenolate, which can be trapped by a variety of electrophiles. Rearrangement of the homoenolate to the more stable enolate was not observed. The reaction amounted to overall umpolung of methyl cinnamate, the α , β -unsaturated ester from which 8 was prepared. © 1999 Elsevier Science Ltd. All rights reserved.

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Considerable effort has been invested in attempts to produce so-called homoenolates 1, in which the charge resides at the beta carbon to the carbonyl group.^{1,2} Because these species derive little if any resonance stabilization from the carbonyl group, they are frequently postulated to exist in solution in a tautometric form 2 in which the charge resides on oxygen. They are also considerably more difficult to produce than conventional enolates. Nickon and Lambert subjected bicyclic ketones to harsh basic conditions (potassium t-butoxide in t-butanol for many hours at high temperature) and were able to demonstrate the formation of homoenolates under these conditions. For example, optically active camphenilone (3) racemized and underwent deuterium exchange to produce 4 and 5 (Eq. 1), consistent with the intermediacy of symmetrical intermediate 6.3 Consistent with the postulate of the intermediates such as 2 and 6 in such reactions, treatment of notricyclyl acetate with t-butoxide afforded norcamphor.⁴ Homoketonization of oxyanions generated by: (a) base treatment of cyclopropanols;⁵ (b) nucleophilic attack on trialkylsilyloxycyclopropanes;⁶ or (c) alkoxide attack upon cyclopropanones,⁷ has remained the most popular method for generating homoenolates. Open chain precursors of homoenolate equivalents include β -haloketones (reaction with lithium),⁸ β -haloacetals (reaction with magnesium),⁹ N,β -dilithio derivatives of amides, 10-13 and β -metallo enol silvl ethers. ¹⁴ Nakamura prepared zinc homoenolates of alkyl propionates by reaction of ZnCl₂ with 1-trimethylsilyloxy-1-alkoxycyclopropanes.¹⁵ Although these species are relatively stable and do react with a variety of electrophiles, they are only moderately nucleophilic and fail to react with less active electrophiles. Furthermore, reaction with some electrophiles

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affords cyclopropane derivatives by reaction at oxygen via 2.¹⁵ Nudelman has reported that reaction of two equivalents of phenyllithium with cinnamaldehyde affords a dianion homoenolate equivalent which can be alkylated at the β -position by a variety of alkyl halides.¹⁶ We report here formation of an ester homoenolate under mild conditions and its reaction at carbon with a variety of electrophiles.



Nishiguchi has shown that electrochemical or magnesium-promoted silulation of methyl cinnamate (7) results in silulation at the β -position to afford methyl β -trimethylsilul propionate (8) (Eq. 2).¹⁷

$$C_{6}H_{5} \xrightarrow{\text{OMe}} OMe \xrightarrow{\text{Mg or } 2 \text{ e}^{-}, \text{ Mg anode}} Me_{3}S_{1} \xrightarrow{\text{OMe}} OMe$$

$$C_{6}H_{5} \xrightarrow{\text{OMe}} OMe$$

$$(2)$$

$$R_{6}H_{5} \xrightarrow{\text{OMe}} S_{1}$$

We reacted 8 with the fluoride source tetrabutylammonium triphenyldifluorosilicate $(TBAT, 9)^{18}$ in the presence of a variety of electrophiles (Scheme 1; Table 1). Presumably the initial step in this process is fluoride-induced desilylation of 8 to afford benzylic carbanion 10. A question of concern at this point was the possibility of rearrangement of 10 to the more stable enolate 11. Although intramolecular rearrangement of 10 to 11 is forbidden on orbital symmetry grounds, presumably it could still take place by a multi-step sequence involving adventitious proton sources in the medium or even by a symmetry-allowed concerted exchange of protons between two molecules of 10. It was therefore deemed necessary to establish which carbanion, 10 or 11, the reaction products would be derived from.



Scheme 1.

The first electrophile examined was benzaldehyde (13). Two diastereomeric substances, mp 98–100 and 86–88°C, respectively, were formed in 52:48 ratio and total yield of 88%. The product should be either 14 or 15, depending whether rearrangement of 10 to 11 had taken place. Inspection of structures

Electrophile	Time	Electrophile : 8 molar ratio	Mol eq TBAT	Product	Yield %
13	1 hr	2:1	0.1	14	88
16	3 hr	3:1	0.1	17, 18	82
7	24 hr	2:1	0.5	19	22
20	14 hr	1:1	0.2	21a	55
22	4 hr	1.2:1	0.2	23	47

Table 1 TBAT-induced desilylative electrophilic substitution on β -trimethylsilyl ester 8

14 and 15 suggested that their spectral properties should be very similar; indeed, it was not possible to determine from either their 300 MHz ¹H (both 1D and COSY) and ¹³C NMR spectra or their mass spectra whether they represented 14 or 15. The problem was solved in favor of 14 by converting methyl dihydrocinnamate to its enol silyl ester, followed by Mukaiyama condensation¹⁹ of the latter with benzaldehyde and SnCl₂ to afford a 3:2 mixture of diastereomers of authentic 15,¹⁹ whose spectral properties were similar but not identical to those of the reaction products. Thus, the products were the two diastereomers of 14 and were derived from 10, not 11.

Electrophilic trapping by *N*-benzylidene aniline (16) afforded a mixture of adducts 17 (22%) and 18 (60%). Compound 17 was isolated as a single diastereomer, whereas 18 was obtained as a roughly 1:1 mixture of diastereomers. The ¹H NMR spectra of 17 and 18 were identical with those of the authentic substances,^{10,13} once again ruling out the possibility that they are derived from enolate 11. We tentatively assigned the *erythro* stereochemistry to 17 since it should cyclize slower to 18 than would the *threo* diastereomer.



Electrophilic trapping by methyl cinnamate (7) (*trans*) afforded a single diastereomeric adduct (19), mp 168–170°C, in low yield. The symmetry of the ¹H (1D and COSY) and ¹³C NMR spectra of this substance demonstrated that it was 19 and therefore was formed from 10, not 11. Comparison of the mp and NMR spectrum with literature data²⁰ established the fact that this material was the *meso* diastereomer of 19. The reaction, therefore, complements the cathodic hydrodimerization of cinnamates,^{21,22} which affords only the *dl* diastereomer. Condensation of dimethyl maleate (20) under similar conditions afforded a 1:1 mixture of diastereomers, assigned structure 21a by analogy to the previous experiments. The high resolution NMR spectra of these substances were identical (except for differences in the alkoxy region) to those of the known diethyl analog 21b;²³ they were, therefore, also homoenolate-derived. Cyclohexenone (22) afforded an 89:11 diastereomeric mixture of conjugate adducts, to which we assigned structure 23 by analogy to the other adducts, all of which corresponded to reaction by homoenolate 10. Also isolated from this reaction was cyclohexenone dimer 24, which has previously been isolated from base-promoted reactions of cyclohexenone.²⁴

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In conclusion, we note that the sequence $7 \rightarrow 8 \rightarrow 12$ amounts to overall umpolung of the α,β unsaturated ester moiety. The ease of preparation of homoenolate 10 in these reactions and its failure to rearrange to the more stable enolate 11 are surprising. The dominant species in solution is very likely a cyclopropane analogous to 2 in equilibrium with the more reactive 10. We are exploring the generality of this synthetic approach to homoenolates.

Typical procedure: A 50 ml r.b. flask containing activated molecular sieves and fitted for reflux was flushed with N₂. Benzaldehyde (0.43 ml, 4.23 mmol), **8** (500 mg, 2.12 mmol), and TBAT (110 mg, 0.212 mmol) were added to the flask together with 15 ml of dry THF. After 1 h reflux, the mixture was poured into H₂O, extracted with hexane, and dried over MgSO₄. After evaporation of solvent, the crude product was purified by flash chromatography, eluting with EtOAc–hexane (10–20–30% EtOAc, successively) to afford both diastereomers of **14**. One diastereomer was isolated as a white solid: mp 98–100°C (255 mg, 44.5%); ¹H NMR (300 MHz): δ 7.4–7.7 (m, 10H), 5.7 (d, 1H), 3.8 (q, 1H), 3.6 (s, 3H), 3.35 (d, 1H), 3.2 (d, 1H); its COSY spectrum shows that δ 5.7 is coupled to 3.8, while 3.8 is also coupled to 3.35 and 3.2, which are coupled to each other. The other diastereomer was a pale orange solid: mp 86–88°C (249 mg, 43.5%); ¹H NMR: δ 7.0–7.8 (m, 5H), 6.1 (d, 1H), 4.3 (q, 1H), 3.8 (s, 3H), 3.35 (d, 1H), 3.2 (d, 1H); the COSY spectrum was similar to that of the first diastereomer.

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