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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.

Keywords: carbanions; fluorine; fluorine compounds; mechanisms; silicon; silicon compounds.

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 tautomeric 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 silyl ethers.[14] Nakamura prepared zinc homoenolates of alkyl propionates by reaction of $ZnCl_2$ 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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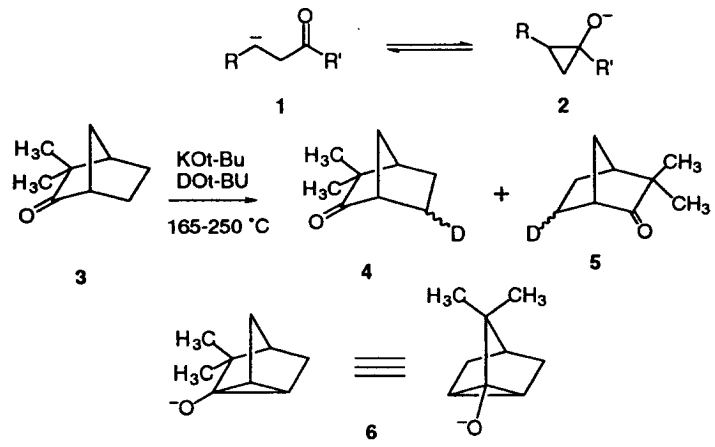
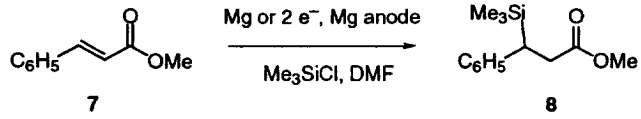
affords cyclopropane derivatives by reaction at oxygen via **2**.[15] Nudelman has reported that reaction of two equivalents of phenyllithium with cinnamaldehyde affords a dianion homoenolate equivalent which can be alkylated at the β-position by a variety of alkyl halides.[16] We report here formation of an ester homoenolate under mild conditions and its reaction at carbon with a variety of electrophiles.



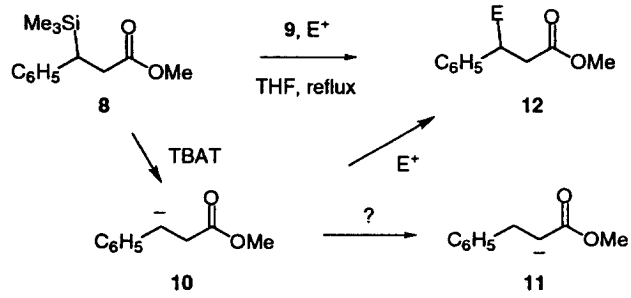
(1)

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



(2)

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.

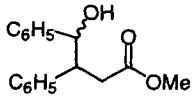
The first electrophile examined was benzaldehyde (**13**). Two diastereomeric substances, mp 98–100 and 86–88°C, respectively, were formed in 52:48 ratio and total yield of 88%. The product should be either **14** or **15**, depending whether rearrangement of **10** to **11** had taken place. Inspection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

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

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

14 and **15** suggested that their spectral properties should be very similar; indeed, it was not possible to determine from either their 300 MHz ^{1}H (both 1D and COSY) and ^{13}C 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 condensation[19] of the latter with benzaldehyde and $SnCl_2$ 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 ^{1}H 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.



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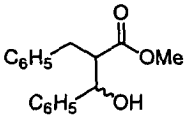

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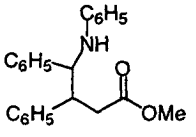

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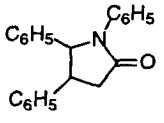
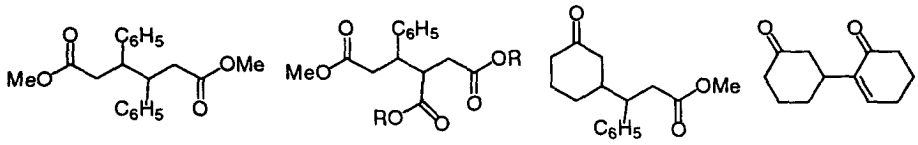


18

Electrophilic trapping by methyl cinnamate (**7**) (*trans*) afforded a single diastereomeric adduct (**19**), mp 168–170°C, in low yield. The symmetry of the ^{1}H (1D and COSY) and ^{13}C 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 data[20] 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]



19 21 a, R = Me b, R = Et 23 24

In conclusion, we note that the sequence **7**→**8**→**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 N_2. 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 H_2O, extracted with hexane, and dried over $MgSO_4$. 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%); ^{1}H 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%); ^{1}H 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.

Acknowledgements

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