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Fluoride-promoted reactions of unsaturated carbonyl compounds. Dimerization by a non-Baylis–Hillman pathway

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Abstract—Fluoride ion acts as a base toward α,β -unsaturated esters and cyclohexenone to induce self-condensation and/or double-bond isomerization. © 2001 Elsevier Science Ltd. All rights reserved.

We previously found that fluoride anion can convert benzylic silanes to the corresponding benzylic carbanions in the presence of an unactivated silyl group and that such carbanions can be trapped in good yield by a variety of electrophiles.^{1,2} The electrophiles included the esters dimethyl maleate, dimethyl fumarate, and methyl cinnamate. Conjugate addition took place in good yields with all of these esters. We report here, however, that esters bearing γ -protons follow a different reaction course. When a dry THF solution containing methyl crotonate (1) was refluxed in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT)^{3,4} for 4 h, dimer **2** was formed in 74% yield. This reaction is



superficially reminiscent of the well-studied Baylis–Hillman condensation of acrylate esters with aldehydes in the presence of DABCO or related catalysts.^{5,6} Acrylate esters, alkyl and aryl vinyl ketones, and acrylonitrile do afford such dimers under Baylis–Hillman conditions.^{7,8} The mechanism of Baylis–Hillman dimerization appears to be of addition–elimination type, in which the first step is addition of DABCO at the β-position of the activated alkene.^{5,6} However, conversion of **2** must take place by a different mechanism than that by which acrylates dimerize, for the following reasons: (a) acrylate esters such as 1 bearing alkyl groups at the β -position do not undergo dimerization at all under typical Baylis-Hillman conditions; even under forcing conditions (10 kbar pressure) 1 affords a dimer in only very low yield in contrast to the relative ease with which it is converted into 2; (b) as noted above, no fluorideinduced dimerization took place with several more electrophilic unsaturated esters not bearing such β -alkyl groups.^{1,2} Conversion of **1** to **2** is very likely initiated by γ -proton abstraction from **1** by fluoride ion to produce the resonance-stabilized anion 3. Nucleophilic attack of 3 upon 1, followed by a series of prototropic shifts, would then lead ultimately to 2 (Scheme 1).

We were interested in the possibility of an intramolecular version of this dimerization. We therefore prepared the doubly unsaturated ester 4^9 by double Horner– Emmons condensation^{10,11} of methyl triphenylphosphoranylideneacetate with succindialdehyde. Treatment of 4 with TBAT in dry THF at 40°C for 40 min resulted in complete conversion into an isomeric diester (5) as a ca. 6:1 mixture of geometric isomers. No further reaction was observed when the reaction mixture was heated at 40°C for a further 12 h. We assign structure 5 to this isomeric diester on the basis of its ¹H



Scheme 1.

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and COSY NMR spectra and its ultraviolet spectrum $(\lambda_{\text{max}} 260 \text{ nm}, \log \varepsilon = 4.2 \text{ in EtOH})$, which closely resembles that of roridin D, a naturally occurring $\alpha,\beta,\gamma,\delta$ -bis-unsaturated lactone.¹² The 1D and 2D proton NMR spectra of 5 in fact closely resemble those of methyl sorbate and other $\alpha, \beta, \gamma, \delta$ -unsaturated esters¹³ and are considerably different from those of the remaining double-bond positional isomers dimethyl 3,5-octadienoate $(6)^{9,14}$ and dimethyl 2,5octadienoate (7).¹⁵

> OMe 6

pounds. Indeed, we have found that cyclohexenone undergoes a similar condensation in the presence of fluoride to afford dimer 8.20 Finally, it should be noted that the fluoride-induced dimerization of ethyl crotonate involves considerably milder conditions than the literature procedure involving a substantial excess of very strong base such as potassium or benzylpotassium.^{21–26} Fluoride has recently been reported to be an efficient basic catalyst in another context.27



Acknowledgements

We believe that fluoride again acts as a base to effect this isomerization by a series of prototropic shifts involving the unconjugated ester 7 as an intermediate. The alternate Baylis-Hillman-type mechanism involving nucleophilic addition of fluoride ion to the β -position of one of the unsaturated ester units of 4 seems even more unlikely than for the dimerization of 1, since it provides little driving force for conversion of 4 to 7.

It is particularly interesting to note, in contrast to this result, that 2,4-alkadienoic esters are deconjugated to the corresponding 3,5-dienoic esters under the influence of strong bases such as lithium dialkylamides ^{14,16,17} and that α , β -unsaturated esters are converted to β , γ -unsaturated esters under these same conditions.^{18,19} Such isomerization reactions are typically effected by conversion of the unsaturated ester to a conjugated anion, followed by rapid addition of a proton donor. The final step in this sequence presumably involves kinetic protonation of the respective pentadienyl or allyl anion. Isomerization of 4 to 5, on the other hand, apparently proceeds under thermodynamic conditions, presumably because of the weaker basicity of fluoride ion and the presence of starting ester as a proton source to mediate equilibration. The importance of the latter point is demonstrated by the fact that deconjugation of α , β unsaturated esters does not take place if less than a full equivalent of LDA is employed.¹⁹



Reactions such as these might be expected to take place with other α,β -unsaturated carbonyl com-

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- 24. Ethyl 3-methyl-4-carboethoxy- $\Delta^{4,5}$ -hexenoate (2). Ethyl *trans*-crotonate (1.7 mL, 13.7 mmol) and tetratetrabutylammonium triphenyldifluorosilicate (0.16 g, 3 mmol) were dissolved in dry THF containing 0.5 g of activated molecular sieves. The clear colorless solution was heated to 75°C for 4 h under N₂. Flash chromatography (hexane/ethyl acetate) afforded 4 (1.15 g, 74%) as a 7:1 *E:Z* mixture [deduced from the relative heights of the vinyl proton quartets at δ 6.83 (*E*) and 5.96 (*Z*)].
- 25. Dimethyl octa-2,6-dienoate (4). Dimethylsulfoxide (19.6 mL, 277 mmol) was added over 5 min to a solution of oxalyl chloride (12.4 mL, 139.4 mmol) in 50 mL of dry dichloromethane at -70°C. The solution was stirred for 15 min and then to it was added over 5 min a suspension of 1,4-dihydroxybutane (5.23 g, 58 mmol) in 30 mL of dichloromethane. After stirring for 2.5 h at -10°C, triethylamine (80.3 mL, 576 mmol) was added slowly and the reaction mixture was allowed to warm to 0°C. Methylene chloride (400 mL) was added and to the dark yellow suspension methyl triphenylphosphoranylideneacetate was added in one portion. After 21 h reflux, the clear yellow solution was concentrated in vacuo to a volume of 600 mL. It was then poured into 500 mL of satd NaCl, extracted with methylene chloride (5×200 mL)

and dried over $MgSO_4$. Concentration afforded a brown oil, which was purified by flash chromatography over silica gel. Elution with 20% ethyl acetate-hexane afforded 0.97 g (8%) of 4⁹ as a colorless oil.

- 26. Dimethyl octa-2,4-dienoate (5). Dimethyl octa-2,6dienoate (4) (0.15 g, 0.75 mmol) and tetrabutylammonium triphenyldifluorosilicate (0.2 g, 0.34 mmol) were dissolved in 20 mL of dry THF containing 1 g of activated molecular sieves. A trace of 5 was produced upon standing at room temperature overnight. Heating for 40 min at 40°C under N₂ resulted in complete conversion of dimethyl octa-2,4-dienoate (5), as determined by GC-mass spectral analysis. After removal of the molecular sieves by filtration, the THF was removed by an aspirator and the residue redissolved in ether. It was washed with 1 M HCl, water, and 5% NaHCO3 and concentrated. Flash chromatography (hexane/ethyl acetate) afforded 7 (0.145 g, 97%) as a clear colorless oil whose properties suggested it to be a ca. 6:1 mixture of double-bond isomers: ¹H NMR (CDCl₃) (major isomer): δ 6.0–6.1 (m, 1H), 4.0 (s, 3H), 3.9 (s, 3H), 2.7 (m, 4H); the COSY spectrum showed one cross-peak between δ 6.0 and the 7.5 multiplet, another cross-peak between the 7.5 and 6.3–6.5 multiplets, and another within the latter multiplet, as well as a cross-peak between the δ 2.7 and δ 6.3–6.5 resonances; ¹³C NMR (CDCl₃) (major isomer): δ 29, 36, 51.8, 51.9, 120.5, 130.5, 142.3, 146.5, 168.2, 173.6; MS (EI): *m*/*z* 167, 138, 107, 99, 79, 68, 59; UV (EtOH): λ_{max} 260 nm (log ε =4.2); HRMS calcd for C₁₀H₁₄O₄: 198.0892. Found: 198.0891.
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