

DECONJUGATIVE ALKYLATION OF THE ENOLATE ANION DERIVED FROM ETHYL CROTONATE

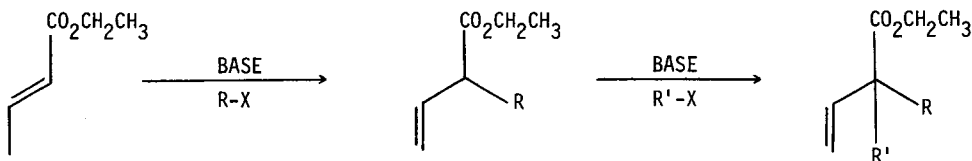
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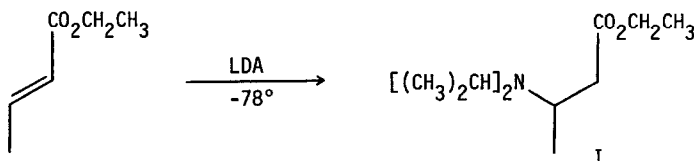
A recent communication by Rathke and coworkers¹ on the reactions of lithium enolates derived from α , β -unsaturated esters has prompted us to report our own efforts in this area. For some time, we have been intrigued with the supposition that the enolate anion derived from a simple α , β -unsaturated ester such as ethyl crotonate might undergo reaction predominantly at the α -carbon atom. Were this found to be the case, we felt that it might be possible *via* a two step alkylation process to create, adjacent to the ester functionality, a quaternary carbon atom bearing a vinyl substituent. Quaternary carbon atom centers of this type exist in a number of natural products, our particular interest being the potent cytotoxic sesquiterpene, vernolepin.²



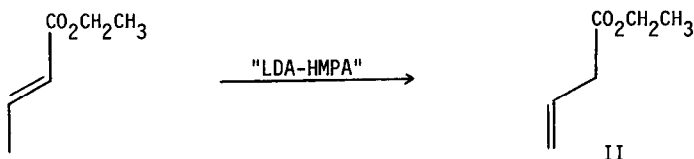
Some credence for the proposed reactivity of crotonate esters was found in the observation that enolates derived from enone systems react for the most part at their α -carbon atoms.³ Furthermore, simple MO calculations carried out on the lithium enolates of ethyl crotonate and ethyl 2-methyl crotonate indicated the maximum negative charge in both cases would reside on the α -car-

bon atom.⁴

A major experimental concern to us in generating crotonic enolates was the possibility that the base employed for these reactions might also act as a nucleophile and conjugatively add to the unsaturated ester at a rate competitive with proton abstraction. Indeed, this concern proved justified, for when ethyl crotonate (1 equivalent) was added to a 1 molar THF solution of lithium diisopropylamide (LDA)⁵ at -78° the Michael adduct I was rapidly formed (10 minutes) in nearly quantitative yield.⁶ Variations in temperature (-40° to -110°) did not significantly alter the Michael addition behavior of LDA towards the crotonate as well as a variety of other unsaturated esters.⁷



We now wish to report an essentially non-nucleophilic form of lithium diisopropylamide which only acts as a base towards ethyl crotonate and permits high yield mono- and dialkylation at the α -carbon atom of this ester. This modification of LDA is an apparent 1:1 complex of the nitrogenous base with hexamethylphosphoramide (HMPA). Formation of this presumed complex is carried out by simply adding, at -78° , 1.1 equivalents of HMPA to a 1 molar THF solution of LDA (1 equivalent) and allowing the mixture to stir 30 minutes (-78°) before use. No Michael addition to ethyl crotonate is observed with this base mixture at -78° even after a period of 3 hours and the only product isolated (92%) is the unconjugated ester II.⁸



Alkylation of ethyl crotonate is conveniently carried out by preparing, as described, 1 equivalent of the LDA-HMPA complex at -78° (1 molar in THF), adding 1 equivalent of the ester followed, after 10 minutes, by 1.1 to 1.3 equivalents of the desired alkylating agent. A summary of some of our results is given in Table I.⁹

TABLE I

| Ester | Alkylating Agent | R | Product | Yield, % |
|-----------------|---------------------------------------|--------------------------------------|---|----------|
| Ethyl Crotonate | CH ₃ I | CH ₃ - | CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | 94% |
| Ethyl Crotonate | CH ₃ CH ₂ I | CH ₃ CH ₂ - | CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | 96% |
| Ethyl Crotonate | (CH ₃) ₂ CHI | (CH ₃) ₂ CH- | CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | 96% |
| Ethyl Crotonate | Br(CH ₂) ₃ Br | Br(CH ₂) ₃ - | CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | 94% |
| Ethyl Crotonate | CH ₂ =CHCH ₂ Br | CH ₂ =CHCH ₂ - | CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | 90% |
| Ethyl Crotonate | HC≡CCH ₂ Br | HC≡CCH ₂ - | CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | 94% |
| Ethyl Crotonate | CH ₃ OCH ₂ Cl | CH ₃ OCH ₂ - | CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | 92% |

A second alkylation leading to the formation of a quaternary α -carbon atom also may be carried out in high yield on these systems.¹⁰ A series of typical examples using the product derived from ethyl crotonate and isopropyl iodide, CH₂=CHCH(R)CO₂CH₂CH₃ where R = (CH₃)₂CH-, are given in Table II.

TABLE II

| Ester | Alkylating Agent | R' | Product | Yield, % |
|---|---------------------------------------|--------------------------------------|--|-------------------|
| CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | CH ₃ CH ₂ I | CH ₃ CH ₂ - | CH ₂ =CHC(R)(R')CO ₂ CH ₂ CH ₃ | 98% |
| CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | (CH ₃) ₂ CHI | (CH ₃) ₂ CH- | CH ₂ =CHC(R)(R')CO ₂ CH ₂ CH ₃ | 96% ¹¹ |
| CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | Br(CH ₂) ₃ Br | Br(CH ₂) ₃ - | CH ₂ =CHC(R)(R')CO ₂ CH ₂ CH ₃ | 97% |
| CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | CH ₂ =CHCH ₂ Br | CH ₂ =CHCH ₂ - | CH ₂ =CHC(R)(R')CO ₂ CH ₂ CH ₃ | 92% |
| CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | HC≡CCH ₂ Br | HC≡CCH ₂ - | CH ₂ =CHC(R)(R')CO ₂ CH ₂ CH ₃ | 95% |
| CH ₂ =CHCH(R)CO ₂ CH ₂ CH ₃ | CH ₃ OCH ₂ Cl | CH ₃ OCH ₂ - | CH ₂ =CHC(R)(R')CO ₂ CH ₂ CH ₃ | 88% |

It should be noted that all of the above alkylation experiments were done under nearly ideal stoichiometry. Furthermore, they are convenient to carry out on both a small and large scale. These manifold aspects imply that deconjugative alkylation, especially when applied to the creation of quaternary carbon atoms, may be a powerful tactical method within the context of complex synthetic strategies.

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REFERENCES

1. M. W. Rathke and D. Sullivan, *Tetrahedron Letts.*, 4249 (1972). These authors report only methylation and benzylation reactions and apparently did not attempt to dialkylate esters of this type.
2. S. M. Kupchan, *Ann. N. Y. Acad. Sci.*, **32**, 85 (1970).
3. H. E. Zimmerman in "Molecular Rearrangements" ed. P. de Mayo, Interscience, New York, 1963 page 345.
4. We thank Professor K. Morokuma of this department for the program used.
5. Lithium diisopropylamide (LDA) was prepared by treatment of diisopropylamine with *n*-butyllithium at 4° for 15 minutes. This reagent when properly prepared is colorless to faintly yellow.
6. The yields given are for isolated products and are based on the amount of ester used. All compounds exhibited satisfactory spectral and physical properties. The reactions described herein were worked-up in the usual manner using saturated ammonium chloride which is sufficiently acidic to remove the diisopropylamine.
7. A number of 2-substituted acrylates also show this Michael addition behavior with LDA.
8. The stoichiometry of this complex follows from the observation that a mixture of LDA, 1 equivalent, and HMPA, 0.5 equivalents, when treated with 1 equivalent of ethyl crotonate gives a 1:1 mixture of I and II (94% combined yield). That a complex is involved is suggested by the fact that HMPA (1 equivalent) is not soluble, at -78°, in a 1 molar THF solution of diisopropylamine (1 equivalent), whereas, 1 equivalent of HMPA rapidly dissolves, at -78°, in the same quantity of LDA solution. We are currently developing a number of other uses for this LDA-HMPA complex along with attempting to further characterize this material.
9. Gamma alkylation with these reactions is always less than 3% as determined by GLC and Mass Spectra.
10. Gamma alkylation is not detectable in these cases.
11. This reaction was carried out at -20°.