

β -LACTAM FORMATION VIA ENOLATE ADDITION: AN UNEXPECTED METHYLENATION REACTION¹ 祝古稀

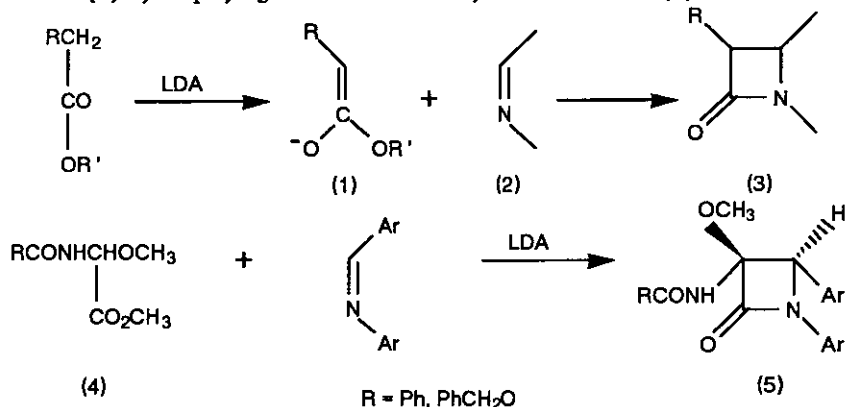
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Abstract—The condensation of ethyl phenylacetate or ethyl β -hydroxybutyrate with
Schiff bases in presence of an excess of lithium diisopropylamide or lithium
hexamethyldisilazide leads to unsaturated amides instead of the expected β -lactams.

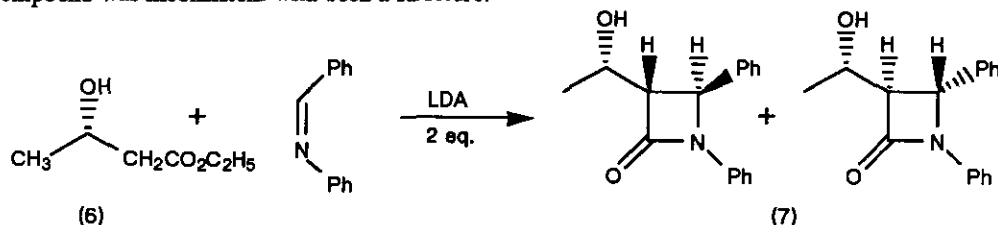
祝古稀 Dedicated to Prof. Edward C. Taylor on the occasion of his 70th birthday.

Formation of β -lactams (3) by the addition of ester enolates (1) to Schiff bases (2) has become a widely used
method since its introduction in 1980 by Bergbreiter *et al.*² Manhas and coworkers³ have prepared 3-amido-3-
methoxy-2-azetidinones (5) by employing α -amido- α -methoxyacetic acid esters (4).



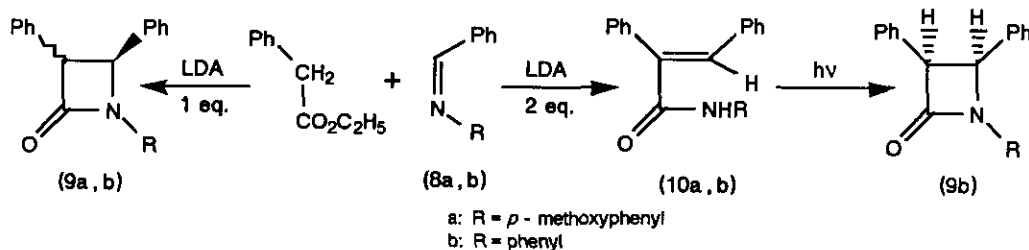
Hart *et al.*,⁴ Georg and Kant,⁵ Ojima *et al.*,⁶ and others⁷ have used the dianion from ethyl β -hydroxybutyrate
(6) in this reaction for the synthesis of β -lactams (7) with a thienamycin side chain. Such β -lactams are
intermediates for penem antibiotics.⁸ Other examples of this reaction have been summarized in a recent review.⁹

In the course of our ongoing research on β -lactams, we tested the suitability of this reaction for the preparation of 3-phenyl-2-azetidinones (**9**) using the enolate from ethyl phenylacetate. In an experiment in which benzylidene-*p*-anisidine (**8a**) and ethyl phenylacetate were inadvertently treated with an excess (instead of one equiv.) of the base LDA, a pale yellow crystalline compound, mp 132-134 °C, was obtained in 60% yield. The chemical ionization mass spectrum showed the pseudomolecular ion expected of the β -lactam (**9a**), but the color of the compound was inconsistent with such a structure.



The proton nmr spectrum revealed the absence of β -lactam protons; instead, a singlet at δ 8.1 indicated the presence of a vinyl proton conjugated with a carbonyl group. The infrared spectrum showed an amide carbonyl (1640 cm^{-1}) rather than a β -lactam carbonyl (1745-1760 cm^{-1}). We were thus led to assign the α, β -unsaturated amide structure (**10a**) to this compound. This structural assignment was verified and the stereochemistry at the double bond was established as (E) by synthesis of this compound by reacting (E)- α -phenylcinnamic acid with *p*-anisidine using dicyclohexylcarbodiimide as the condensing agent.

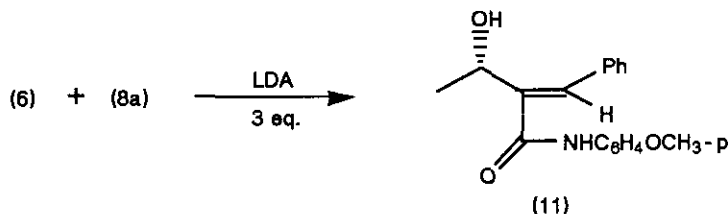
When ethyl phenylacetate and **8a** were reacted in the presence of only one mole of LDA, a mixture of *cis* and *trans* β -lactams (**9a**) was formed in about 60% yield with the *trans* isomer as the major product. Examination of the crude reaction product by thin layer chromatography and by nmr spectroscopy did not reveal the presence of any unsaturated amide.



In an investigation of the scope of this process, we reacted ethyl phenylacetate with *N*-benzylideneaniline. When 2 molar equivalents of LDA were used, the α, β -unsaturated amide (**10b**) was isolated in 58% yield, whereas with one equivalent of LDA the β -lactam (**9b**) was formed in 55% yield. In the latter case, examination of the crude reaction mixture gave no indication of the presence of any α, β -unsaturated amide.

In a further probe of the scope of the methylenation reaction, ethyl β -hydroxybutyrate (**6**) was treated with 3

moles of LDA at -78°C . Addition of the Schiff base (**8a**) led to the isolation of the α,β -unsaturated amide (**11**), mp $98-101^{\circ}\text{C}$, in 58% yield. It is of interest to note that Georg, Gill and Gerhardt¹⁰ obtained a diastereomeric mixture of β -lactams (**7**) when **6** and **8a** were reacted together in the presence of 2 equivalents of LDA.



We have also found that LHMDs can be substituted as a base in this methylenation reaction and the yield of the unsaturated amide is comparable to that obtained with LDA. Mild bases such as triethylamine did not afford either the β -lactam or the α,β -unsaturated amide.

Chapman and Adams¹¹ have reported that photochemical isomerization of **10b** leads almost exclusively to the *cis* β -lactam (**9b**). This observation, combined with the methylenation reaction reported here, affords a stereospecific route to *cis* β -lactams, while the corresponding *trans* β -lactams can be obtained by the ester condensation with one mole of LDA.

We have conducted a few experiments aimed at elucidating the mechanism of the methylenation reaction. When the β -lactam (**9a**) is treated with one mole of LDA under the condensation reaction conditions, it is recovered unchanged. The β -lactam (or its mono-anion) therefore cannot be an intermediate in the formation of the α,β -unsaturated amide. This is consistent with reported *cis* to *trans* isomerization,¹² alkylation,¹³ and aldol addition reactions¹⁴ of β -lactams at C-3 occurring by way of the monoanion, without ring cleavage. All of our observations are consistent with the hypothesis that β -lactam and the α,β -unsaturated amide are formed by two distinct mechanistic pathways which are not interconnected. It appears that the latter is formed when the dianion of the ester is present while the β -lactam arises from reaction with the monoanion. In confirmation of this, we find that the reaction of ethyl phenylacetate with *N*-benzylidene-*p*-anisidine in the presence of 1.5 equivalents of LDA gives a mixture of β -lactam (**9a**) and α,β -unsaturated amide (**10a**) in approximately 1:1 ratio. Findings from further studies on the applications of this reaction and its mechanism will be presented in future publications.

GENERAL EXPERIMENTAL¹⁵ Under nitrogen atmosphere 2.0 molar equiv. of diisopropylamine in 25 ml of freshly dried and distilled THF were placed in a 250 ml flame-dried flask. The flask was cooled to -78°C

and 2.0 molar equiv. of *n*-butyllithium in hexane were added slowly. The mixture was stirred for 30 min at -78 °C and one equiv. of ethyl phenylacetate in 25 ml of THF was added over 10-15 min at -78 °C. After stirring for 20 min the Schiff base (1 equiv. in 25 ml of THF) was added slowly. The reaction was stirred for an additional 3 h at -78 °C and then at room temperature overnight. After the usual workup, the product was purified by column chromatography on alumina, using hexane-ethyl acetate as the eluent.

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