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Conjugate propargylation of α,β-unsaturated lactones: a solution via 1,4-addition of (*Z*)-2-ethoxyvinyl anion

Samir Bennabi, Kesavaram Narkunan, Laurence Rousset†, Denis Bouchu† and Marco A. Ciufolini*

Laboratoire de Synthèse et Méthodologie Organiques (LSMO, UMR 5078), Université Claude Bernard Lyon 1 et Ecole Supérieure de Chimie, Physique, Electronique de Lyon, 43, Boulevard du 11 Novembre 1918, 69622 Villeurbanne cedex, France

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Abstract

Conjugate addition of (*Z*)-2-ethoxyvinyl anion to α,β-unsaturated lactones is best effected via Noyori-type organocopper reagents. The resulting adducts may be advanced to β-propargyllactones or utilized in the preparation of functionalized pyridines. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: aldehydes; conjugate addition; cuprates; propargylation; pyridines.

In connection with ongoing work, we needed to effect the conjugate propargylation of an α,β-unsaturated lactone. Apparently, no methods to achieve this transformation have been described, even though the analogous reaction of enones is well documented.[1] Propargyl cuprate reagents seem to be unknown, probably due to their instability. Corey's 1-(triisopropylsilyl)propargyllithium[2] undergoes conjugate addition to enones, but we were unable to cause it to add to a conjugated lactone (no reaction). Less encumbered 1,3-bis-(trimethylsilyl) propargyllithium[3] did react, but in no higher than 10–15% yield. Lithiated 3-phenylthio-1-trimethylsilylpropyne[4] underwent conjugate addition in about 40% yield, but a subsequent desulfurization, in a manner consonant with survival of other functionalities, was problematic. A solution to these difficulties was sought in the form of a two-stage approach involving formal conjugate addition of acetaldehyde enolate, followed by conversion of the emerging alkanal to an alkyne (cf. **1**→**3**, Scheme 1). We chose to explore (*Z*)-2-ethoxyvinyllithium[5] as an equivalent of acetaldehyde enolate. Organocopper reagents derived from this substance undergo 1,4-additions to enones,[5b] but, surprisingly, we were unable to find a precedent for a similar reaction with α,β-unsaturated lactones. This warranted a brief investigation of the conjugate ethoxyvinylation of these substrates. An ordinary dialkyl cuprate proved to be unsatisfactory in this reaction, but a Noyori organo-Cu complex[6] produced from equimolar amounts of $Cu(PBu_3)_2I$ and the vinyllithium species, obtained from commercial (*Z*)-2-ethoxyvinylbromide by halogen–

* Corresponding author.

† Mass spectral facility of the LSMO.

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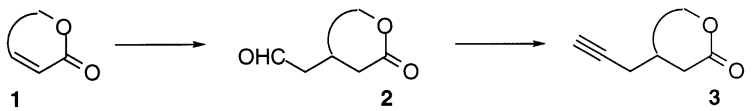
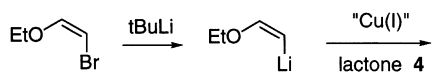
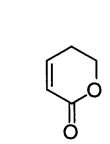
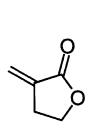
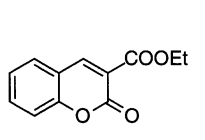
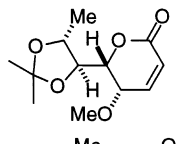
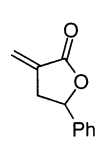
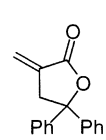
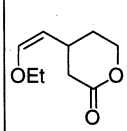
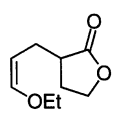
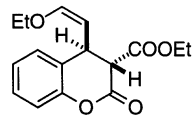
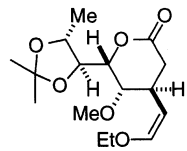
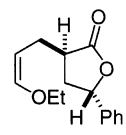
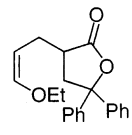
metal exchange, was generally successful (Table 1). The addition process was completely stereoselective, (300 MHz ^{1}H NMR), with substrates **4c–e**. However, C-5 substituted α-methylenebutyrolactones[7] reacted more efficiently with species of formal stoichiometry $R_2Cu(PBu_3)_2Li$, resulting from an increase in the ratio of organo-Li agent to CuI from 1:1 to 2:1. For instance, reaction of lactone **4e** with 1.5 molar equivalents of a true Noyori complex gave **6** in 95% yield (Scheme 2). The enolate formed through an initial conjugate addition evidently had itself undergone 1,4-addition to an intact molecule of substrate. The problem vanished with the modified Noyori-type cuprate, in accord with the principle that the behavior of organo-Cu reagents in 1,4-additions may be modulated by varying the stoichiometry of lithium organometallic relative to Cu salt. A particularly useful discussion in this area has been provided by Alexakis.[8] Butenolides **7** (Scheme 2) were poor substrates for the reaction, presumably due to facile enolization to an aromatic furan under basic conditions ($R^1=H$, $R^2=H$, Me, Ph), or to excessive hindrance at the reaction site ($R^1=R^2=Me$). Likewise, no conjugate addition with either type of organo-Cu agent occurred with plain coumarin, even though the more highly activated 3-carbethoxy coumarin **4c** reacted efficiently.



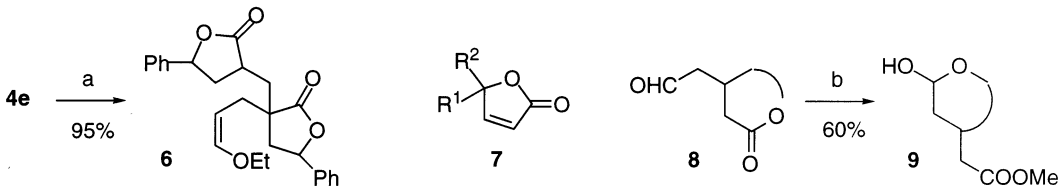
Scheme 1.

Table 1
Representative conjugate additions of (*Z*)-2-ethoxyvinyl anion to lactones



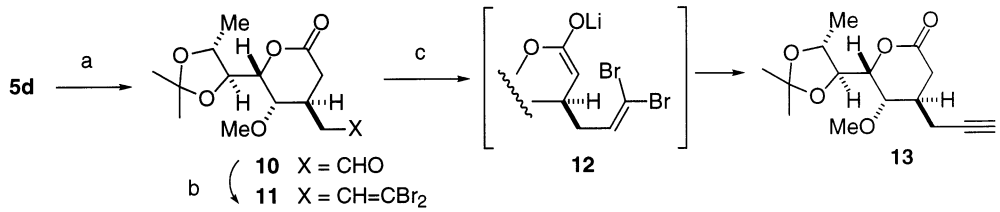
entry	a	b	c	d	e	f
lactone **4**						
product **5**						
%yield[a]	92	90	89	85	75	65
method[b]	**A**	**A**	**A**	**A**	**B**	**B**

a. Yields of pure, chromatographed **5**. b. Method **A**: *t*-BuLi (3 mmol) was added to a cold (–78°C) solution of *cis*-1-bromo-2-ethoxyethylene (1.5 mmol) in ether (4 mL) at -78°C. After stirring at –78°C for 30 min, a freshly prepared solution of CuI (1.5 mmol) and Bu_3P (3.75 mmol) in ether (4 mL) was injected dropwise, and the resulting mixture was stirred at -78°C for 1 h. Finally, a solution of unsaturated lactone (1 mmol) in ether (2 mL) was injected dropwise. After stirring at -78°C for 30 min, the reaction was quenched at –78°C by addition of satd. NH_4Cl solution (15 mL) at -78°C and allowed to warm to rt. The crude product was extracted with ether and purified by silica gel column chromatography using 10-20 % ethyl acetate in hexane. Method **B**: similar to **A**, except that the reagents were employed in the following proportions: *t*-BuLi: 8 mmol; *cis*-1-bromo-2-ethoxyethylene: 4 mmol; CuI: 2 mmol; Bu_3P: 5 mmol; unsaturated lactone: 1 mmol.



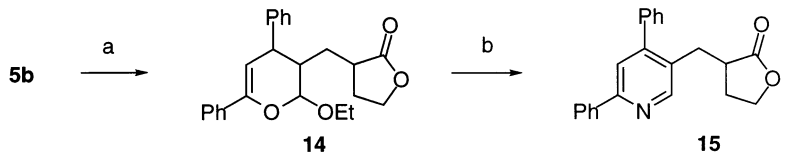
Scheme 2. (a) 2 equiv. (*Z*)-(EtOCH=CH)Cu(PBu_3)$_2$, THF, −78°C, 95%; (b) K_2CO_3, MeOH, acetyldiazophosphonate

Mild hydrolysis[9] of vinyl ethers **5** gave aldehydes of structure **8** (>95%). Attempts to convert these to alkynes by reaction with dimethyl diazomethylphosphonate[10] resulted in formation of complex mixtures containing modest amounts of desired acetylenes. Materials of structure **9** were the sole identifiable products obtained by reaction of representative aldehydes **8** with acetyldiazophosphonate[11] and K_2CO_3/MeOH (Scheme 2). An efficient propargylation sequence ultimately emerged as exemplified in Scheme 3 with lactone **5d**. Selective vinyl ether cleavage in the presence of the acetonide was achieved by reaction with catalytic TsOH in acetone. A modified[12] Corey–Fuchs[13] reaction advanced **10** to **11**. The lactone was protected from the action of BuLi, required to convert the dibromomethylene group to an alkyne, by enolate formation (LDA, cf. **12**) prior to same-pot treatment with additional BuLi. Propargyl lactone **13** was thus obtained in 84% yield.



Scheme 3. (a) 10 mol% TsOH in acetone, 40°C, 5 min, 96%; (b) CBr_4 (2 equiv.), PPh_3 (2 equiv.), Et_3N (1 equiv.), CH_2Cl_2, −20°C, 80%; (c) LDA (1.1 equiv.), THF, −78°C, then BuLi (2 equiv.), 84%

On a final note, the vinyl ether functionality present in compounds **5** may participate in a range of other useful reactions. For instance, the Yb(fod)$_3$-promoted cyclocondensation of **5b** with chalcone yielded functionalized dihydropyran **14**, which advanced to pyridine **15** in excellent yield upon reaction with hydroxylamine hydrochloride (Scheme 4).[14] The techniques just described are thus likely to find application in various other areas of synthetic, medicinal and heterocyclic chemistry.



Scheme 4. (a) Chalcone, 10 mol% Yb(fod)$_3$, $(CH_2Cl)_2$, reflux, 24 h, 58%; (b) HO–NH_2·HCl, MeCN, reflux, 3 h, 90%

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