



A Synthesis of Ynolates via the Cleavage of Ester Dianions

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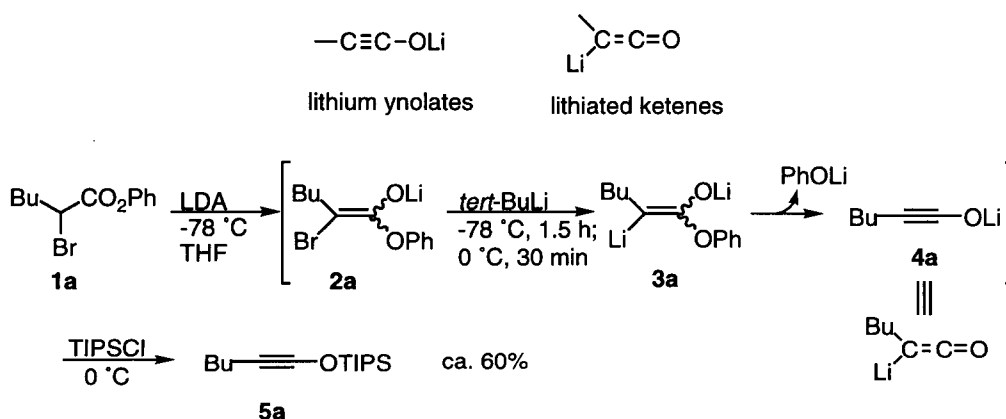
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Abstract: A new method for ynolate synthesis via the cleavage of ester dianions has been developed. The key intermediates, ester dianions, generated from α -bromocarboxylic acid ester enolates via lithium-halogen exchange turned out to be so labile that they were cleaved rapidly to give ynolates.

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Enolates are important, widely used, and well-established carbanions.¹ On the other hand, ynolates have received little attention in synthetic organic chemistry, although their chemistry should be no less interesting than that of enolates. Synthetic methods for ynolates have been reported by several groups,² but these have not been established well as general methodology. In view of the highly useful properties of ynolates, development of a more conventional synthetic approach to these species is highly desirable. Herein we describe a new method for ynolate synthesis via the cleavage of ester dianions derived from α -bromocarboxylic acid ester enolates.



Lithium ynolates are regarded as lithiated ketenes. The thermally-induced cleavage of lithium ester enolates has been reported to provide the corresponding ketenes and lithium alkoxides.³ On the basis of these facts, if ester dianions (e.g., **3a**), where ester enolates are metalated at the vinylic position, can be generated,

they would provide metalated ketenes (i.e., ynoates) via the thermally induced cleavage. Since the ester dianions are considered as vinyl lithium bearing alkoxy groups, they would be generated via lithium-halogen exchange from the α -bromocarboxylic acid ester enolates and *tert*-BuLi.

The ynoate forming process is exemplified by the following (Scheme 1): To a solution of lithium enolate (**2a**), prepared from the phenyl 2-bromocaproate (**1a**, 1.0 mmol) and LDA (1.0 mmol) in THF (5 ml), was added *tert*-BuLi (3.2 mmol, 1.4 M in pentane)⁴ at $-78\text{ }^\circ\text{C}$ to undergo metal-halogen exchange. After the mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1.5 h and then $0\text{ }^\circ\text{C}$ for 30 min, it was treated with triisopropylsilyl chloride (TIPSCl, 10 mmol) at $0\text{ }^\circ\text{C}$ for 3 h. Usual workup, followed by bulb-to-bulb distillation (bp. $200\text{ }^\circ\text{C}/1.5\text{ mmHg}$), afforded TIPS yno ether (**5a**)⁵ in ca. 60% yield together with minor amounts of by-products. While we were encouraged by this successful result, **5a** could not be further purified because of its sensitivity towards silica gel. In order to trap ynoates efficiently as stable products which can be easily purified for subsequent studies, we selected β -lactones^{2a,b,d} as targets for testing the generality of this new synthetic approach. Thus, the lithium ynoates were reacted with benzaldehyde (4 eq) at $-78\text{ }^\circ\text{C}$ for 15 min to give β -lactones (**6**).⁶ As shown in Table, **6a-c** were obtained in good yields. It is noteworthy that not only phenyl esters but also ethyl esters gave **6** in good yields, although ethoxide is a poorer leaving group than phenoxide. Phenyl α -bromophenylacetate (**1f**) did not give **6d** but a complex mixture (entry 6) since carbenes might be formed, while the bromoenolate monoanions of the other alkyl esters appear to be not prone to loss of bromide.

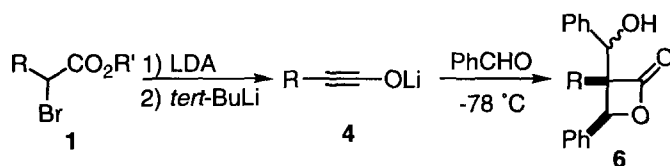


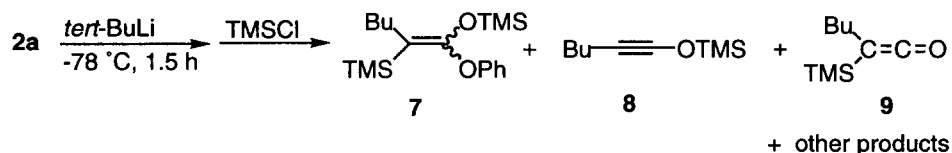
Table Trapping of **4** with Benzaldehyde to Form **6**^a

entry	1		6		
	R	R'		yield, % ^b	
1	1a	Bu	Ph	6a ^c	69
2	1b	Bu	Et	6a ^c	74
3	1c	Me	Ph	6b ^c	81
4	1d	Me	Et	6b ^c	69
5	1e	cyclohexyl	Et	6c ^c	85
6	1f	Ph	Ph	6d	0

a) The reaction procedure is described in the text. b) Yields refer to purified product by column chromatography. c) Mixture of diastereomers (~1:1).

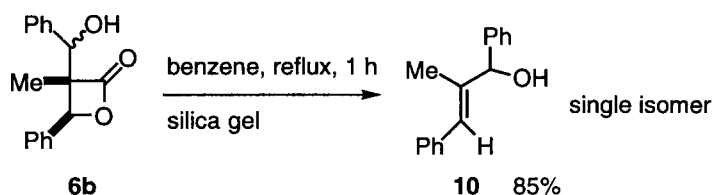
The ester dianions (**3**), which have not been reported so far to the best of our knowledge, would be the key intermediates in the course of this process. We attempted to trap **3a** with TMSCl at $-78\text{ }^\circ\text{C}$ before warming to $0\text{ }^\circ\text{C}$. But this reaction resulted in a complex mixture which could not be separated because of its high sensitivity to silica gel. Based on the ^1H -, ^{13}C -NMR, IR, and MS spectra of this crude mixture, it can be presumed that it consists of keteneacetal (**7**),⁷ TMS yno ether (**8**) (IR: 2279 cm^{-1}), TMS substituted ketene (**9**) (IR: 2087 cm^{-1}) and other products (Scheme 2). The existence of **7** suggests the generation of an ester dianion, albeit in small amount.⁸ It should be noted that the ynoate, precursor of **8** and **9**, also exists together

with the dianion at $-78\text{ }^{\circ}\text{C}$. This means that the electron-rich ester dianions decompose rapidly even at $-78\text{ }^{\circ}\text{C}$ to give the ynoles,⁹ while ketene formation from ester enolates (monoanions) requires warming above $-20\text{ }^{\circ}\text{C}$.



Scheme 2.

In order to confirm the stereochemistry of the β -lactones, **6b** was converted to an alkene via thermal decarboxylation, which is known to proceed via a stereospecific *cis*-elimination.¹⁰ From the result, since only (*E*)-alkene (**10**)¹¹ was produced, the relative configuration of **6b** was confirmed as shown in Scheme 3.¹² On the basis of this, we assigned the other β -lactones (**6a**, **6c**) as having the same relative configuration.¹³



Scheme 3.

In conclusion, we have developed a new and convenient method for lithium ynoles synthesis via the cleavage of ester dianions from readily available α -bromoesters. The ester dianions, novel intermediates, are so labile that they are rapidly cleaved to give ynoles. Further studies on this method and synthetic application of ynoles are in progress.

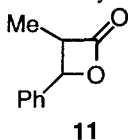
Acknowledgement

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References and Notes

- (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Inc.: California, 1972; p 492-628. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 99-319.
- Syntheses and reactions of ynoles. (a) Schollkopf, U. Hoppe, I. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 765. (b) Hoppe, I., Schollkopf, U. *Liebigs Ann. Chem.* **1979**, 219-226. (c) Woodbury, R. P. Long, N. R. Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 376. (d) Kowalski, C. J., Fields, K. W. *J. Am. Chem. Soc.* **1982**, *104*, 7321-7323. (e) Kowalski, C. J., Haque, M. S., Fields, L. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429-1430. (f) Kowalski, C. J., Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140-5142. (g) Kowalski, C. J., Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 1325-1327. (h) Kowalski, C. J., Lal, G. S. *J. Am. Chem. Soc.* **1986**, *108*, 5356-5357. (i) Kowalski, C. J., Lal, G. S., Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127-7128.

- (j) Kowalski, C. J., Lal, G. S. *Tetrahedron Lett.* **1987**, *28*, 2463-2466. (k) Kowalski, C. J., Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 7194-7208. (l) Reddy, R. E., Kowalski, C. J. *Org. Synth.* **1993**, *71*, 146. (m) Stang, P. J., Roberts, K. A. *J. Am. Chem. Soc.* **1986**, *108*, 7125-7127. (n) Julia, M., Saint-Jalmes, V. P., Verpeaux, J. N. *Synlett* **1993**, 233-234. (o) Kai, H., Iwamoto, K., Chatani, N., Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 7634-7635.
3. (a) Sullivan, D. F., Woodbury, R. P., Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038-2039. (b) Haner, R., Laube, T., Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396-5403. In this article, the authors described that addition of alkyllithium to monosubstituted ketenes generated from ester enolates was unsuccessful because ynoates might be formed. (c) Tomioka, K., Shindo, M., Koga, K. *J. Org. Chem.* **1990**, *55*, 2276-2277. (d) For zinc enolate: Pratt, R. F., Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956-5964.
4. Since LDA was regenerated by *tert*-BuLi, 3.2 equivalents of *tert*-BuLi was required.
5. $^1\text{H-NMR}$ (400 M, CDCl_3) δ : 0.89 (t), 1.13 (d), 1.26 (m), 1.40 (m), 2.07 (t). IR (neat) 2280 cm^{-1} . CI-MS (NH_3) m/z : 255 (MH^+).
6. Under these conditions, lithium ynoates reacted with two equivalents of benzaldehyde to give **6**. Since β -lactone enolates would be more reactive than ynoates, no disubstituted β -lactone (**11**) was observed, even if only one equivalent of benzaldehyde was added.



7. EI-MS spectra (m/z : 336 (M^+)) is identical with this compound.
8. Attempts at quenching **3a** with AcOD at $-78\text{ }^\circ\text{C}$ gave a small amount of α,α -dideuterioester, 30 % of α -bromo- α -deuterioester derived from the monoanion of a ester enolate, and complex products. This result also indicates the generation of the dianion.
9. The cleavage of ester dianions can also be considered as β -elimination of alkoxy (phenoxy) vinylolithium. With this regard to this kind of reactions, Schlosser reported that while (*Z*)-2-ethoxyvinylolithium and 2,2-diethoxyvinylolithium were stable, (*E*)-2-ethoxyvinylolithium decomposed to afford lithium ethoxide and acetylene at $-80\text{ }^\circ\text{C}$: (a) Lau, K. S. Y., Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595-1598. (b) Schlosser, M., Wei, H.-x. *Tetrahedron* **1997**, *53*, 1735-1742.
10. (a) Danheiser, R. L., Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176-1185. For reviews of the chemistry of β -lactones, see: (b) Pons, J.-M., Pommier, A. *Synthesis* **1993**, 441-459. (c) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, **1991**; Vol. 6, p 342-350.
11. Takai, K., Kimura, K., Kuroda, T. *Tetrahedron Lett.* **1983**, *24*, 5281-5284.
12. Aldol addition reactions of β -lactone enolates to aldehyde: Mulzer, J., Chucholowski, A. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 777-778, and references cited therein.
13. The possibility of the formation of (*E*)-alkene (**10**) from one of the diastereomers (**6b**) via the silica gel-mediated translactonization (internal transesterification) followed by decarboxylation cannot be ruled out.

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