

A Novel Tandem [2 + 2] Cycloaddition–Dieckmann Condensation: Facile One-Pot Process To Obtain 2,3-Disubstituted-2-cycloalkenones from Ynolates

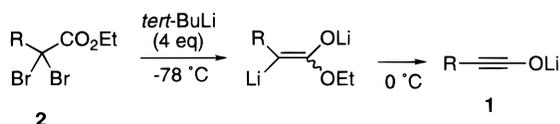
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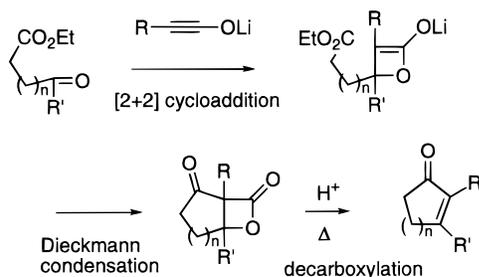
Ynolate anions (**1**) are ketene anion equivalents, and their chemistry is very attractive.¹ Recently, we have developed a novel and useful method for the generation of lithium ynolates via the cleavage of ester dianions prepared from readily available α,α -dibromo esters (**2**) (Scheme 1)² and have demonstrated new

Scheme 1



reactions using ynolates.³ It has been known that the [2 + 2] cycloaddition⁴ of ynolates with aldehydes affords highly reactive intermediates, β -lactone enolates.^{2,3a,5} This suggests that a well-designed reaction using ynolates could make one-pot multistep synthesis possible via intermediate β -lactone enolates, including those not available via enolization of the corresponding β -lactones. Herein, we describe a novel methodology of tandem [2 + 2] cycloaddition–Dieckmann condensation, taking advantage of these characteristics of ynolates, and demonstrate a facile one-pot synthesis of synthetically useful 2,3-disubstituted-2-cycloalkenones as an application for the described methodology (Scheme 2).

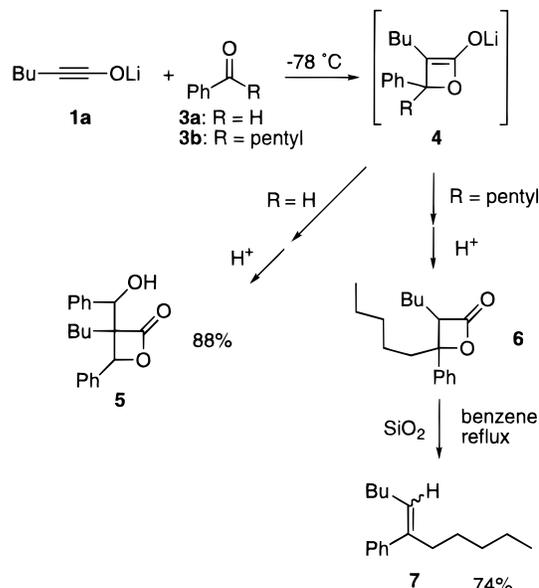
Scheme 2



- (1) Review: Shindo, M. *Chem. Soc. Rev.* **1998**, 27, 367–374.
 (2) (a) Shindo, M. *Tetrahedron Lett.* **1997**, 38, 4433–4436. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, 54, 2411–2422.
 (3) (a) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, 39, 4857–4860. (b) Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **1998**, 49, 113–116.
 (4) Stepwise mechanism cannot be ruled out, but in this manuscript, [2 + 2] cycloaddition is used as a matter of convenience.
 (5) (a) Schöllkopf, U.; Hoppe, I. *Angew. Chem., Int. Ed. Engl.* **1975**, 14, 765. (b) Hoppe, I.; Schöllkopf, U. *Liebigs Ann. Chem.* **1979**, 219–226. See also ref 1. For examples of β -lactone chemistry, see: (c) Mulzer, J.; Chucholowski, A. *Angew. Chem., Int. Ed. Engl.* **1982**, 21, 777–778. For reviews see: (d) Pons, J.-M.; Pommier, A. *Synthesis* **1993**, 441–459. (e) Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 342–350.

We previously described the reactions of alkyl-substituted ynolates with aldehydes at -78 °C which give 2:1 adducts (e.g., **5**), due to the nucleophilicity of the intermediate enolate **4a** higher than that of the ynolate (Scheme 3).² This result would indicate

Scheme 3



the difficulty of tandem reactions utilizing **4a** in this system because the β -lactone enolates would be immediately trapped by the aldehyde. To achieve a tandem reaction of β -lactone enolates derived from ynolates, the reactivity of the enolates (**4**) should be less than that of the ynolates. After surveying a range of electrophiles, we have found that ketones (e.g., pentyl phenyl ketone, **3b**) provide β -lactones (**6**) by the reaction with alkyl-substituted ynolates at -78 °C, followed by protonation with saturated aqueous NH_4Cl (Scheme 3). This product could be easily decarboxylated to form olefin **7**, as a 2:1 mixture of isomers, in good overall yield from **3b**.⁶ If the ketone **3** possessed another electrophilic center in the molecule, an intramolecular cyclization would proceed to provide bicyclic β -lactones, leading to the formation of synthetically useful disubstituted cycloalkenes.

On the basis of this concept, we selected γ - or δ -keto esters as substrates, expecting the realization of the tandem [2 + 2] cycloaddition–Dieckmann condensation. This process is exemplified by the following: To a solution of ynolate (**1a**), prepared from α,α -dibromo ester (1.0 mmol) and a solution of *t*-BuLi (4.0 mmol, 1.4 M in pentane) at -78 °C for 3 h and 0 °C for 0.5 h in THF, was added a solution of ethyl 5-oxo-5-phenylpentanoate (**8a**, 0.8 mmol) in THF, and the mixture was then stirred for 5 h at -78 °C. After the usual workup, acid-catalyzed decarboxylation (refluxing in benzene in the presence of a catalytic amount of silica gel: method A)⁷ was conducted without purification of β -lactone (**10aa**). After filtration and concentration, 2-butyl-3-phenyl-2-cyclohexenone (**11aa**) was isolated in a 74% yield along with 6% of ethyl 5-phenyl-5-decenoate (**12**), which was derived from uncyclized β -lactone (**9aa**) (Scheme 4). This is the first example of the tandem [2 + 2] cycloaddition–Dieckmann condensation⁸ (Table 1).

(6) Mechanistic investigations: Morao, I.; Lecea, B.; Arrieta, A.; Cossio, F. P. *J. Am. Chem. Soc.* **1997**, 119, 816–825 and references therein.

(7) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, 56, 1176–1185.

Scheme 4

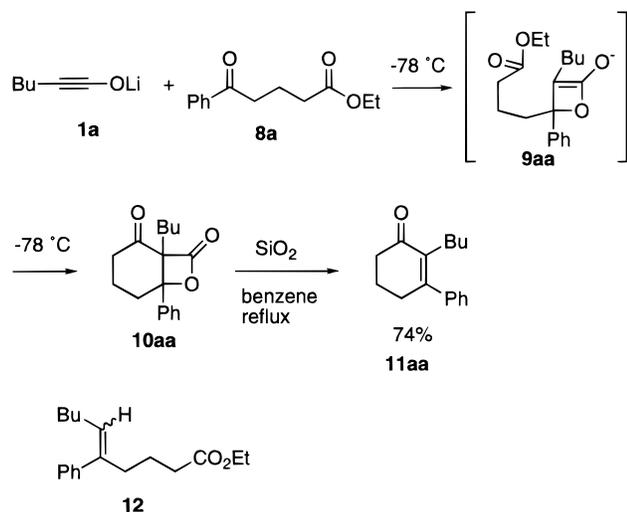


Table 1. Tandem [2 + 2] Cycloaddition–Dieckmann Condensation: Synthesis of 2,3-Disubstituted-2-cycloalkenones

| entry | ynolate | | keto ester | | <i>n</i> | tandem reaction | | decarboxylation ^a | 11 | yield/% |
|-------|-----------|--------|------------|--|----------|-----------------|--------|------------------------------|--------------------------|---------|
| | 1 | R | 8 | R' | | temp/ °C | time/h | | | |
| 1 | 1a | Bu | 8a | Ph | 2 | -78 | 5 | A | 11aa | 74 |
| 2 | 1b | Me | 8a | Ph | 2 | -78 | 3 | A | 11ba | 89 |
| 3 | 1a | Bu | 8b | Me | 2 | -78 | 1.5 | A | 11ab | 78 |
| 4 | 1a | Bu | 8b | Me | 2 | -78 | 1.5 | B | 11ab | 89 |
| 5 | 1b | Me | 8b | Me | 2 | -78 | 1.5 | A | 11bb | 54 |
| 6 | 1a | Bu | 8c | Ph | 1 | -40 | 1.5 | A | 11ac | 63 |
| 7 | 1a | Bu | 8c | Ph | 1 | -78 | 1.5 | B | 11ac | 89 |
| 8 | 1a | Bu | 8d | Me | 1 | -78 | 1.5 | A | 11ad | 83 |
| 9 | 1b | Me | 8c | Ph | 1 | -78 | 1.5 | B | 11bc | 84 |
| 10 | 1b | Me | 8e | Tol | 1 | -78 | 1.5 | B | 11be | 76 |
| 11 | 1e | pentyl | 8d | Me | 1 | -78 | 1.5 | A | 11ed ^b | 80 |
| 12 | 1b | Me | 8f | EtO ₂ C-(CH ₂) ₂ | 1 | -78 | 2 | B | 11bf | 60 |

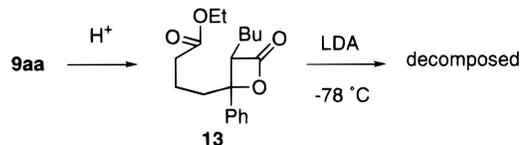
^a Method A: A solution of **10** in benzene was refluxed in the presence of silica gel. Method B: A reaction mixture of **10** was quenched with 3% HCl–EtOH and the resulting solution was refluxed.
^b Dihydrojasmane.

To establish the generality of the tandem reaction, we examined reactions using a variety of δ -keto esters (**8**). As shown in the table, they can serve as substrates and yield 2,3-disubstituted 2-cyclohexenones in good yields (entry 1–5). When γ -keto esters were used, 2,3-disubstituted cyclopentenones were also obtained in high yields (entry 6–11). Since some of the bicyclic intermediates (e.g., **10bc**, **10be**) were decomposed during the workup, the reaction mixture of the Dieckmann condensation was quenched

with 3% HCl–EtOH, followed by immediate refluxing of the resulting bicyclic β -lactones (decarboxylation method B). As a result, the desired products (**11**) were successfully obtained in higher yields (entry 4, 7, 9, 10). By this improved procedure, a facile one-pot synthesis of 2,3-disubstituted cycloalkenones was achieved. The utility of this transformation has been demonstrated by the accomplishment of the concise syntheses of dihydrojasmane (**11ed**)⁹ and a potential intermediate of α -cuparenone (**11be**).¹⁰ A keto-diester (**8f**) also gave the desired cyclopentenone (**11bf**), which demonstrates that the method will work with substrates having other ester functions.

β -Lactone **13**, obtained by protonation of the lactone enolate **9aa**, did not give **10aa** by treatment with LDA at -78 °C, but decomposed (Scheme 5). This indicates that the direct generation

Scheme 5



of the enolate **9aa** from the β -lactone **13** is very difficult. Use of the ynone anion has indeed solved this problem, however, allowing regioselective formation of the enolate via [2 + 2] cycloaddition, prior to Dieckmann condensation.

In conclusion, we have developed a novel tandem [2 + 2] cycloaddition–Dieckmann condensation via ynone anions and achieved a facile synthesis of 2,3-disubstituted-2-cycloalkenones in good yields. The salient feature of ynone anions as a ketene anion equivalent includes the selective formation of reactive intermediates such as enolate anions via a course different from enolization of the corresponding carbonyl compounds. This result demonstrates that ynone anions have much potential as players in new reaction sequences, especially tandem reactions.

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Supporting Information Available: Synthetic procedures and characterization data for **11aa**–**11bf** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA990656W

(8) A review for Dieckmann condensation: Davis, D. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 795–863. Recent examples for tandem Michael addition–Dieckmann condensation: Tatsuta, K.; Yamazaki, T.; Mase, T.; Yoshimoto, T. *Tetrahedron Lett.* **1998**, *39*, 1771–1772. Kobayashi, K.; Maeda, K.; Uneda, T.; Morikawa, O.; Konishi, H. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 443–446. Maiti, S.; Bhaduri, S.; Achari, B.; Banerjee, A. K.; Nayak, N. P.; Mukherjee, A. K. *Tetrahedron Lett.* **1996**, *44*, 8061–8062. Groth, U.; Halfang, W.; Köhler, T.; Kreye, P. *Liebigs Ann. Chem.* **1994**, 885–890. Honda, T.; Mori, M. *Chem. Lett.* **1994**, 1013–1016. Periasamy, M.; Reddy, M. R.; Radhakrishnan, U.; Devasagayaram, A. *J. Org. Chem.* **1993**, *58*, 4997–4999. Bunce, R. A.; Harris, C. R. *J. Org. Chem.* **1992**, *57*, 6981–6985.

(9) For recent examples of synthesis of dihydrojasmane, see: Shono, T.; Yamamoto, Y.; Takigawa, K.; Maekawa, H.; Ishifune, M.; Kashimura, S. *Chem. Lett.* **1994**, 1045–1048. Mathew, J. *J. Org. Chem.* **1990**, *55*, 5294–5297. Ho, T.-L. *Chem. Ind.* **1988**, 762.

(10) Cossy, J.; Gille, B.; Bouzbouz, S.; Bellosta, V. *Tetrahedron Lett.* **1997**, *38*, 4069–4070.