ORGANIC LETTERS

2001
Vol. 3, No. 13
2029−2031

# The First Tandem [2 + 2] Cycloaddition–Michael Reaction Using Ynolates: Facile Construction of Substituted Carbocycles

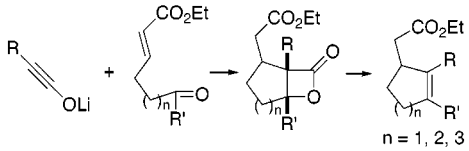
**Mitsuru Shindo,* Kenji Matsumoto, Yusuke Sato, and Kozo Shishido**

*Institute for Medicinal Resources, University of Tokushima, and TOREST, Japan Science and Technology Corporation (JST), Sho-machi 1, Tokushima 770-8505, Japan*

*shindo@fc.ph2.tokushima-u.ac.jp*

**Received April 17, 2001**

## ABSTRACT

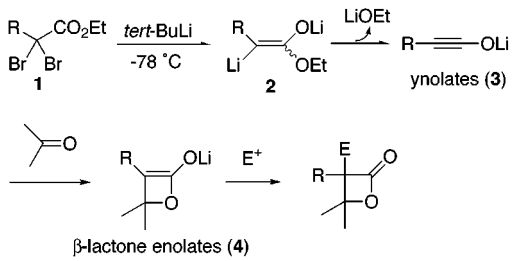



**A tandem [2 + 2] cycloaddition–Michael reaction using ynolate anions followed by decarboxylation produced polysubstituted five-, six-, and seven-membered cycloalkenes.**

We have developed a novel method for the generation of ynolate anions (**3**)[1] via cleavage of ester dianions (**2**)[2] and demonstrated their unique characteristics as multifunctional carbanions (Scheme 1).[3] Since ynolate anions react with ketones to give strongly nucleophilic $\beta$-lactone enolates,[2,4] we decided to take advantage of this to design tandem reactions for use in efficient syntheses of complicated carbon skeletons. Recently, we reported an example of a tandem reaction, [2 + 2] cycloaddition−Dieckmann condensation, utilizing keto esters as substrates.[5] If electrophilic functionalities other than esters are introduced in the substrate, a new type of tandem reaction could be developed.[6] Herein, we report the first tandem [2 + 2] cycloaddition−Michael reaction of ynolate anions, followed by decarboxylation, furnishing substituted cycloalkenes.

The readily available (*E*)-ethyl 6-oxo-6-phenyl-2-hexenoate (**5a**, R′ = phenyl, $n$ = 1) was used as the substrate. A typical procedure is as follows. To a solution of the ynolate

**Scheme 1.** Tandem Reaction of Ynolates




(1) For reviews, see: Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367−374. Shindo, M. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 1155−1166. Shindo, M. *Yakugaku Zasshi* **2000**, *120*, 1233−1246.

(2) Shindo, M. *Tetrahedron Lett.* **1997**, *38*, 4433−4436. Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411−2422.

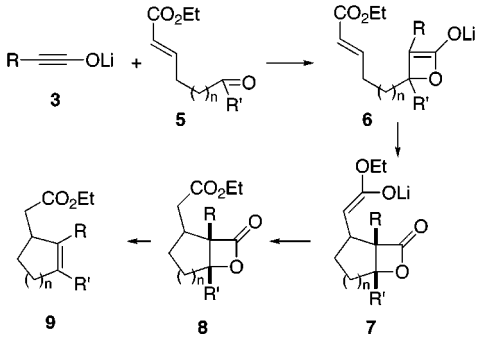
(3) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857−4860. Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **1998**, *49*, 113−116. Shindo, M.; Oya, S, Murakami, M. Sato, Y.; Shishido, K. *Tetrahedron Lett*. **2000**, *41*, 5943−5946. Shindo, M.; Oya, S, Murakami, M. Sato, Y.; Shishido, K. *Tetrahedron Lett*. **2000**, *41*, 5947−5950. Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2000**, *65*, 5443−5445.

(4) Schölkopf, U.; Hoppe, I. *Angew. Chem., Int. Ed. Engl*. **1975**, *14*, 765. Hoppe, I.; Schölkopf, U. *Liebigs Ann. Chem.* **1979**, 219−226. Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc*. **1982**, *104*, 321−323. Akai, S.; Kitagaki, S.; Naka, T.; Yamamoto, K.; Tsuzuki, Y.; Matsumoto, K.; Kita, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1705−1709. For examples of $\beta$-lactone chemistry, see: (a) Multzer, J.; Chucholowski, A. *Angew. Chem., Int. Ed. Engl*. **1982**, *21*, 777−778. For reviews, 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, pp 342−350.

10.1021/ol0159928 CCC: $20.00 
**Published on Web 06/07/2001**

(**3,** R = Me), prepared from the 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 **5** (0.8 mmol) in THF. The mixture was stirred for 30 min at −78 °C. After the addition of saturated aqueous $NH_4Cl$ and the usual workup, acid-catalyzed decarboxylation (refluxing in benzene in the presence of a catalytic amount of silica gel) was carried out without purification of the *β*-lactone (**8**). After filtration, concentration, and purification by silica gel column chromatography, the desired ethyl 2-methyl-3-phenyl-2-cyclopentenylacetate (**9**) was isolated in 84% yield (Scheme 2).

**Scheme 2.** Synthesis of Cycloalkenylacetates via Ynolates




To establish the generality of this process, we examined reactions using several kinds of keto-α,*β*-unsaturated esters (**5**). As shown in Table 1, the 2,3-disubstituted 2-cyclopentenylacetates were obtained in good yields (entries 1−6). In these reactions, the intermediate *β*-lactones (**8**) were mixtures of diastereomers with ratios from 1:1 to 4:1, determined from $^1$H NMR spectra. 2,3-Disubstituted 2-cyclohexenylacetates were also synthesized in good yields (entries 7−10). In these cases, the $^1$H NMR spectra of the *β*-lactones (**8**) showed a single isomer.[7] It is noteworthy that a seven-membered carbocycle was successfully obtained by this tandem reaction (entry 11), although this type of cyclization could not be achieved by the tandem [2 + 2] cycloaddition−Dieckmann condensation.[8]

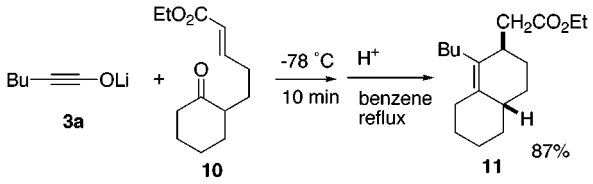
**Table 1.** Synthesis of Ethyl 2,3-Disubstituted-2-cycloalkenylacetates via a Tandem Reaction

| entry | R | R′ | *n* | yield (%) |
|---|---|---|---|---|
| 1 | Me | Me | 1 | 64 |
| 2 | Bu | Me | 1 | 74 |
| 3 | cyclohexyl | Me | 1 | 75 |
| 4 | Me | Ph | 1 | 84 |
| 5 | Bu | Ph | 1 | 94 |
| 6 | cyclohexyl | Ph | 1 | 97 |
| 7 | Me | Me | 2 | 75 |
| 8 | Bu | Me | 2 | 79 |
| 9 | cyclohexyl | Me | 2 | 93 |
| 10 | Bu | Ph | 2 | 78 |
| 11[a] | Bu | Me | 3 | 63 |

[a] −40 °C, 1 h.

The synthesis of bicyclic carbocycles was more challenging. As shown in Scheme 3, the ynolate anion (**3a**) reacted smoothly with the keto ester **10** to provide the desired octahydronaphthalene in excellent yield as a single stereoisomer. The stereochemistry was determined by a single-crystal X-ray analysis of the corresponding carboxylic acid (**11′**), which was produced by hydrolysis of compound **11**.

**Scheme 3.** Synthesis of Octahydronaphthalene **11**




The stereoselectivity of this tandem reaction can be explained by the assumption that the cycloaddition proceeded by equatorial attack, followed by Michael addition, through the proposed transition state model (Figure 1). As the stereochemistry of the intermediate *β*-lactone has not been determined, the detailed mechanism is unclear.

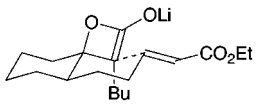



**Figure 1.** Proposed transition state model of Michael addition.

This tandem reaction was applied to the synthesis of polysubstituted naphthalenes. The ynolates anion **3b** reacted with (*E*)-4-(2-acetylphenyl)-2-butenoic acid ethyl ester (**12**) at −78 °C (Scheme 4), and the resulting *β*-lactone was decarboxylated by acid to give the dihydronaphthalene (**13**), which was oxidized with DDQ to furnish the desired ethyl 3,4-dimethyl-2-naphthalenylacetate (**14**).

In conclusion, we have developed an efficient synthesis of highly substituted carbocycles via a tandem [2 + 2] cycloaddition−Michael reaction using ynolates, taking advantage of the high nucleophilicity of *β*-lactone enolates

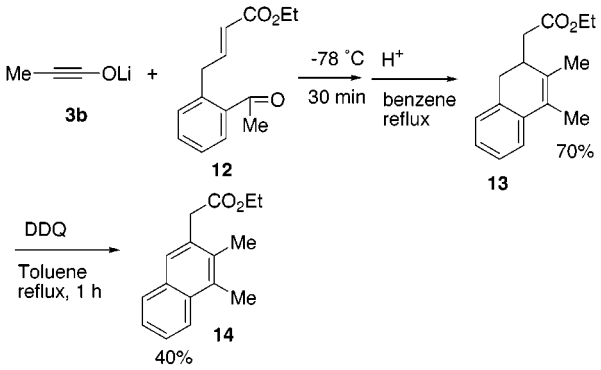
(5) Shindo, M.; Sato, Y.; Shishido, K. *J. Am. Chem. Soc.* **1999**, *121*, 6507−6508.

(6) For recent reviews on tandem reactions, see: Chapdelaine, M. J.; Hulce, M. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1990; pp 225−653. Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York; 1992. Bunce, R. A. *Tetrahedron*, **1995**, *51*, 13103−13159. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. Denmark, S. E.; Thrarensen, A. *Chem Rev.* **1996**, *96*, 137−165. Winkler, J. D. *Chem Rev.* **1996**, *96*, 167−176. Ryu, I.; Sonoda, N.; Curran, D. *Chem. Rev.* **1996**, *96*, 177−194. Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem Rev.* **1996**, *96*, 195−206.

(7) The relative configurations have not been determined.

(8) Shindo, M.; Sato, Y.; Shishido, K. Manuscript in preparation.

**Scheme 4.** Synthesis of Ethyl 3,4-Dimethyl-2-naphthalenylacetate **14**




derived from the reaction of ynolates with ketones. Since polysubstituted carbocycles, e.g., cycloalkenes, are not easy to synthesize via short routes using conventional methods, this approach should be very useful for organic synthesis. These results again demonstrate the broad utility of ynolates in organic synthesis.

**Acknowledgment.** This work was partially supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and the Asahi Glass Foundation. We thank Mr. Masahiko Bando, Otsuka Pharmaceutical Co., Ltd., for obtaining the single-crystal X-ray.

**Supporting Information Available:** General experimental procedures, characterization data of new compounds, and X-ray crystallographic data of **11′**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0159928