Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 47 (2006) 861–864

Tetrahedron Letters

Synthesis of alicyclic esters via an intramolecular conjugate addition reaction. New method for generating (*Z*)-vinylcopper species from 1,1-dibromoalkenes

Keiji Tanino,* Keisuke Arakawa, Mikiya Satoh, Yasuhiro Iwata and Masaaki Miyashita*

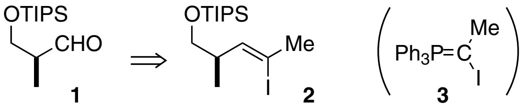
Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan

Received 13 November 2005; revised 28 November 2005; accepted 1 December 2005
Available online 19 December 2005

Abstract—A novel cyclization reaction of a 1,1-dibromoalkene derivative having an α,β-unsaturated ester moiety was developed. Under the influence of Me_2CuLi, the 1,1-dibromoalkene was converted into a (*Z*)-vinylcopper species which in turn underwent an intramolecular conjugate addition reaction with the α,β-unsaturated ester moiety. Five-, six-, and seven-membered carbocycles were constructed by the present method. The substrate having an epoxide moiety also afforded a five-membered product via a 5-*exo* type intramolecular cyclization reaction.

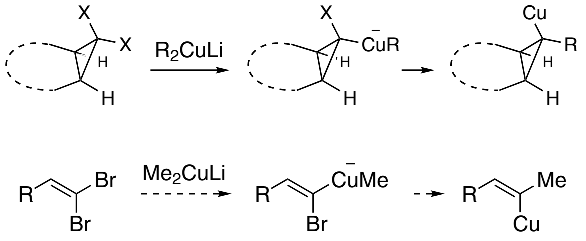
Conjugate addition reactions of an organocopper species with an α,β-unsaturated carbonyl compound have found widespread use in organic synthesis.[1] The intramolecular version of this type of reaction leads to formation of a carbocyclic compound, and there have been reported several methods for generating an organocopper species possessing a Michael acceptor moiety.[2] Transmetalation reactions of organozinc,[3] organotin,[2,4] and organosilicon[5] derivatives are particularly advantageous for this purpose, because these organometallic compounds tolerate the presence of a wide range of functional groups. While organozinc compounds can be prepared from the corresponding organohalides by treating with activated zinc metal, there are several reports on a halogen–metal exchange reaction giving rise to an organocopper species directly.[6]

In the course of our studies toward the asymmetric total synthesis of zincophorin,[7] it was required to convert optically active aldehyde **1** to tri-substituted vinyl iodide **2** with (*Z*)-configuration (Scheme 1).



Scheme 1. Synthetic plan of vinyl iodide **1** from aldehyde **2**.

Since the Wittig reaction using phosphorane **3** failed to give a satisfactory result, we planned to develop a new method on the basis of a halogen–metal exchange reaction using an organocopper reagent. It is well known that treatment of a 1,1-dihalocyclopropane derivative with R_2CuLi leads to stereoselective formation of an *endo* cyclopropyl copper species (Scheme 2).[8] The transformation is initiated by a halogen–metal exchange reaction at the less hindered *exo* halogen atom giving rise to an α-halo organocopper intermediate, which in turn undergoes 1,2-shift of the alkyl group with inversion of the configuration at the α-carbon. We expected that



Scheme 2. Stereoselective formation of an organocopper species from a 1,1-dihalo compound.

Keywords: Cyclobutanone; Organocopper; Conjugate addition; Cyclization; Dihaloalkene.

* Corresponding authors. Tel.: +81 117062703; fax: +81 117064920 (K.T.); tel.: +81 117062705; fax: +81 117064920 (M.M.); e-mail addresses: ktanino@sci.hokudai.ac.jp; miyasita@sci.hokudai.ac.jp

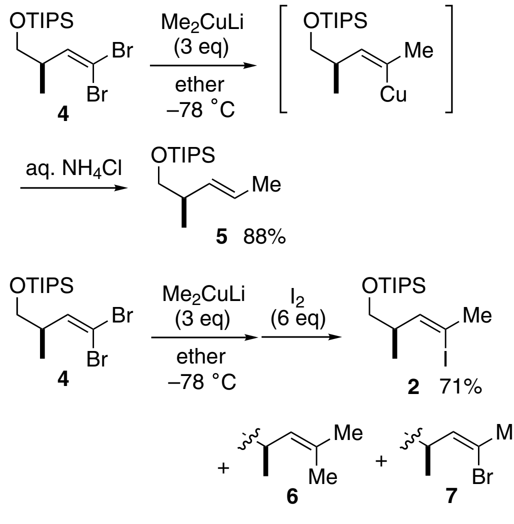
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.002

a 1,1-dibromoalkene might undergo an analogous reaction with Me_2CuLi giving rise to a tri-substituted vinylcopper with (*Z*)-configuration.

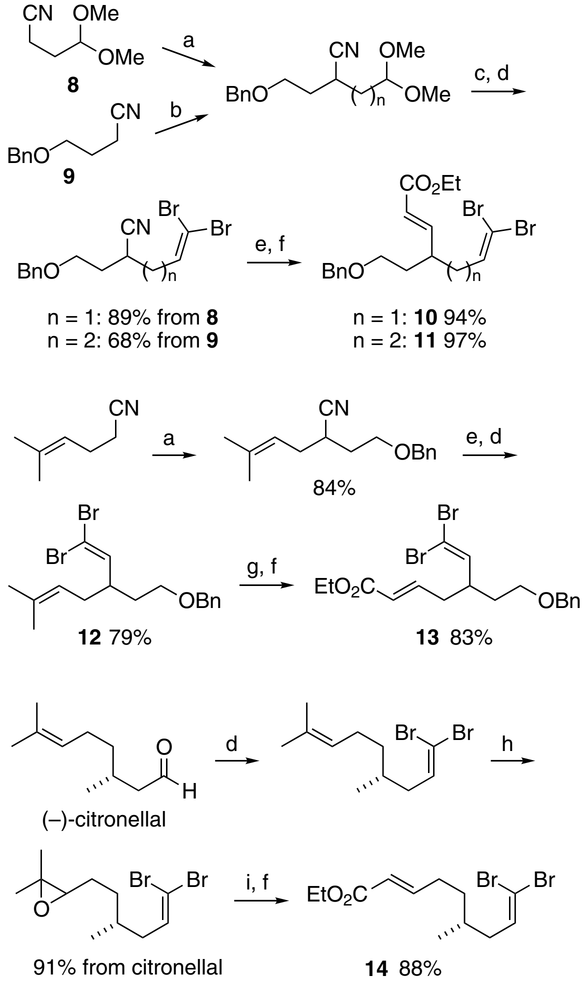
Dibromoalkene **4** was prepared from aldehyde **1** via a conventional method[9] and reactions with an excess amount of Me_2CuLi were examined (Scheme 3). Although a reaction in THF followed by quenching with an aqueous NH_4Cl solution gave a mixture of several products, use of diethyl ether as a solvent led to selective formation of (*E*)-alkene **5** in 88% yield. Further, addition of iodine to the reaction mixture gave rise to (*Z*)-vinyl iodide **2** in 71% yield along with a small amount of 1,1-dimethylalkene **6** and bromide **7**.

These results indicate that a vinylcopper species is generated smoothly from **4** in diethyl ether with high stereoselectivity. It is noteworthy that 1,1-dibromoalkenes derived from ketones are known to undergo replacement of both bromine atoms by methyl groups under the influence of Me_2CuLi.[10] Interestingly, Harada and Oku reported a similar transformation of a 1,1-dibromoalkene using an organozincate, which afforded a vinylzinc species as a mixture of geometrical isomers.[11]

The present method for generating a (*Z*)-vinylcopper species led us to develop an intramolecular cyclization reaction of 1,1-dibromoalkene derivatives having a Michael acceptor moiety. Since an α,β-unsaturated ketone was expected to undergo a rapid conjugate addition reaction with Me_2CuLi, we chose an α,β-unsaturated ester that generally exhibits lower reactivity as a Michael acceptor. Several cyclization precursors were prepared from nitriles having an acetal group or a prenyl group as shown in Scheme 4.



Scheme 3. Selective synthesis of a vinyl iodide with (*Z*)-configuration from a 1,1-dibromoalkene.

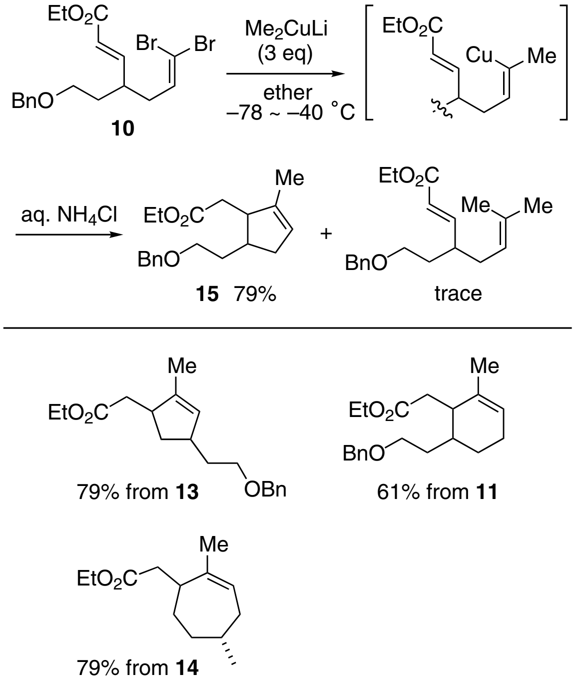


Scheme 4. Synthesis of 1,1-dibromoalkene derivatives. Reagents and conditions: (a) LDA, ICH_2CH_2OBn, THF; (b) LDA, $BrCH_2CH_2CH(OMe)_2$, THF; (c) aq HCl, acetone; (d) CBr_4, Ph_3P, pyridine, CH_2Cl_2; (e) DIBAL, hexane then aq HCl; (f) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (g) O_3, MeOH then Me_2S; (h) *m*CPBA, CH_2Cl_2; (i) $NaIO_4$, THF.

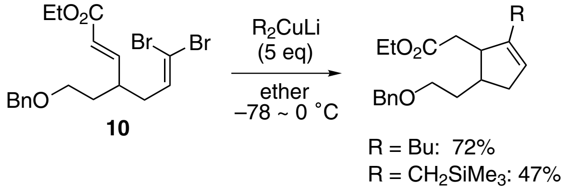
The cyclization reaction was performed by treating the 1,1-dibromoalkene derivative with an excess amount of Me_2CuLi at −78 °C followed by warming up to −40 °C (Scheme 5). The desired products possessing a five-, six-, or seven-membered ring were obtained in good yield along with a small amount of an acyclic α,β-unsaturated ester arising from a dimethylation reaction of the 1,1-dibromoalkene moiety. Cyclopentene and cyclohexene derivatives were obtained as an inseparable 10:1–2:1 mixture of diastereomers, while the cycloheptene derivative was found to be a single isomer, though the configuration of these products was not determined.

Use of Bu_2CuLi instead of Me_2CuLi also effected a smooth cyclization reaction of **10** giving rise to an ester having a butyl group, while the corresponding (silylmethyl)copper reagent afforded an allylsilane in lower yield (Scheme 6).

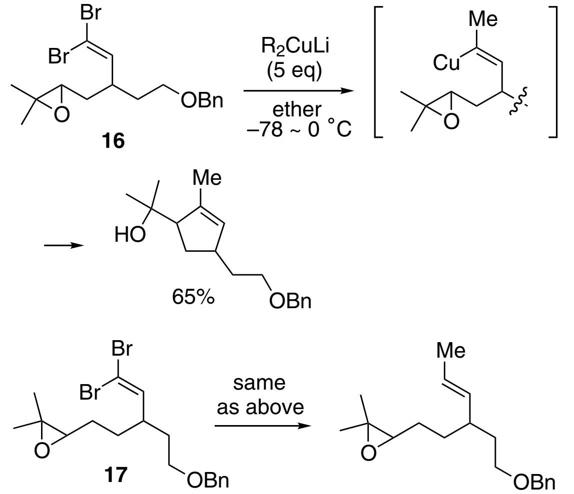
Finally, an intramolecular cyclization reaction of an epoxide was briefly examined. Under the influence of Me_2CuLi, epoxide **16** derived from diene **12** underwent a cyclization reaction to afford an alcohol in moderate yield. On the other hand, the corresponding homologue **17** failed to form a six-membered ring, and acyclic epoxide was detected as the major product (Scheme 7).



Scheme 5. Cyclization reactions of 1,1-dibromoalkene derivatives mediated by Me_2CuLi.



Scheme 6. Synthesis of cyclopentene derivatives having other substituents.



Scheme 7. Reactions of 1,1-dibromoalkene derivatives having an epoxide moiety.

In conclusion, we have developed a novel cyclization reaction of a 1,1-dibromoalkene derivative having an α,β-unsaturated ester moiety.[12] Under the influence of Me_2CuLi, the 1,1-dibromoalkene was converted into a (*Z*)-vinylcopper species which in turn underwent an intramolecular conjugate addition reaction with the α,β-unsaturated ester moiety. Five-, six-, and seven-membered carbocycles were constructed by the present method. The substrate having an epoxide moiety also afforded a five-membered product via a 5-*exo* type intramolecular cyclization reaction. Applications to a total synthesis of a natural product are currently under investigation in our laboratory.

Acknowledgements

Financial support from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (a Grant-in-Aid for Scientific Research on Priority Areas (No. 16073201), and a Grant-in-Aid for Scientific Research (B) (No. 16350049)) is gratefully acknowledged.

References and notes

1. (a) Posner, G. H. *Org. React.* **1972**, *19*, 1; (b) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225; (c) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135; (d) *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VHC: Weinheim, 2002.
2. For an example, see: Piers, E.; McEachern, E. J.; Burns, P. A. *Tetrahedron* **2000**, *56*, 2753.
3. Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417.
4. Behling, J. R.; Babiak, K. A.; Ng, S. J.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.
5. Miura, K.; Hosomi, A. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VHC: Weinheim, 2004; Vol. 2, pp 541–543.
6. (a) Corey, E. J.; Kuwajima, I. *J. Am. Chem. Soc.* **1970**, *92*, 395; (b) Corey, E. J.; Narisada, M.; Hiraoka, T.; Elljson, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 396; (c) Yamamoto, H.; Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 5816; (d) Szymoniak, J.; Thery, N.; Möise, C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 85.
7. Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4341.
8. Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1600; See also: Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911; Dauben, W. G.; Welch, W. M. *Tetrahedron Lett.* **1971**, 4531; Descoins, C.; Julia, M.; van Sang, H. *Bull. Soc. Chim. Fr.* **1971**, 4087.
9. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
10. Posner, G. H.; Loomis, G. L.; Sawaya, S. *Tetrahedron Lett.* **1975**, 1373.
11. Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaiji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897.
12. Typical procedure: To a suspension of CuI (114 mg, 0.60 mmol) in diethyl ether (1.2 mL) was added a 1.2 M diethyl ether solution of MeLi (1.0 mL, 1.20 mmol) at 0 °C. The resulting clear solution of Me_2CuLi was cooled to −78 °C, and a solution of ester **10** (89 mg, 0.20 mmol) in diethyl ether (0.8 mL) was added. After being stirred for 30 min at −78 °C and for 30 min at −40 °C, saturated aqueous NH_4Cl solution was added. The aqueous layer was extracted with diethyl ether and the combined organic

layer was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel column chromatography afforded the desired ester **15** (48 mg, 79%) as a 10:1 mixture of diastereomers: IR (neat) 2854, 1732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.24 (t, $J = 7.2$ Hz, 3 H), 1.55–1.71 (m, 4H, involving a singlet at 1.64), 1.76–1.97 (m, 2H), 2.02–2.13 (m, 1H), 2.25 (d, $J = 14.7$ Hz, 1H), 2.39–2.53 (m, 2H, involving a doublet at 2.45, $J = 14.7$ Hz), 2.53–2.63 (m, 1H), 3.48 (t, $J = 7.4$ Hz, 3H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.48 (d, $J = 11.8$ Hz, 1H), 4.50 (d, $J = 11.8$ Hz, 1H), 5.25–5.30 (m, 1H), 7.25–7.32 (m, 5H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 14.32, 15.00, 35.86, 37.31, 38.23, 41.05, 51.15, 60.25, 68.98, 72.80, 124.35, 127.31, 127.45, 128.18, 138.53, 140.69, 172.94.