Novel Synthesis of Functionalized Cyclobutane Derivatives via Intramolecular Conjugate Addition of Alkenyltrimethylstannane Functions to α,β-Alkynic Esters Mediated by Copper(I) Chloride

Edward Piers,* Eva M. Boehringer, and James G. K. Yee

Department of Chemistry, University of British Columbia, 2036 Main Mall, University Campus, Vancouver, British Columbia V6T 1Z1, Canada

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Due to their inherent reactivity and the consequent possibility of a variety of further synthetic manipulations, the discovery of new methods for the construction of functionalized four-membered carbocycles continues to be an active area of research.[1] In connection with ongoing investigations into the intramolecular conjugate addition of alkenyl functions to Michael acceptors,[2] we report herein a new method to form highly strained, functionalized cyclobutane derivatives via the copper(I) chloride-mediated internal conjugate addition of alkenyltrimethylstannanes to α,β-alkynic ester units.

The substrates utilized in the ring closure reactions were synthesized as outlined in Scheme 1. Treatment of the diester **1**[3] with lithium (trimethylstannyl)(cyano)cuprate[4] yielded the diester stannane **2**.[5] Reduction of the ester **3**[4] with DIBALH, followed by oxidation of the resultant alcohol with *n*-Pr_4NRuO_4 (TPAP)[6] in the presence of *N*-methylmorpholine *N*-oxide (NMO), provided the corresponding aldehyde, which, upon reaction with methyl 3-lithiopropynoate[7] (**14**), yielded the functionalized enynoate **4**. Swern oxidation[8] of **5**,[9] conversion[10] of the acquired aldehyde into 5-(trimethylstannyl)hex-5-en-1-yne, and sequential treatment of the latter substance with LDA and ethyl chloroformate produced the substrate **6**. A deconjugation−alkylation operation[11] involving the ester **7**[12] and methyl 3-bromopropynoate (**15**)[13] provided the diester **8**. A sequence of reactions similar to that involved in the transformation **3** → **4** served to convert substances **9**[14] and **11**[15] into the hydroxy esters **10** and **12**, respectively. Finally, subjection of the ester **11**[15] to alkylation with **15** (cf. **7** → **8**) furnished the cyclization precursor **13**. It should be noted that the yields reported in Scheme 1 have not been extensively optimized.

Scheme 1

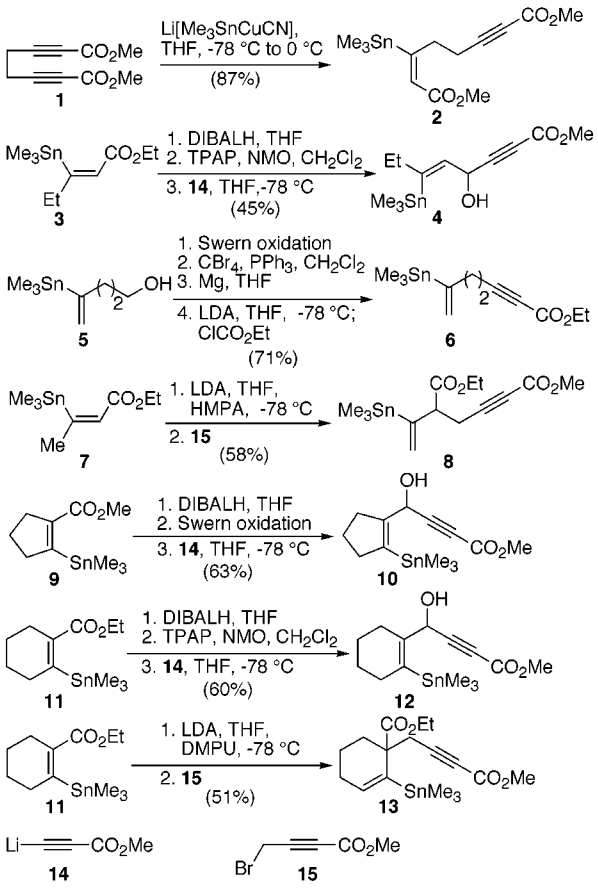
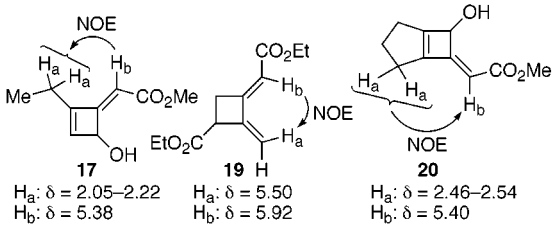


Chart 1. NOE Experiments



Collectively, the substrates **2**, **4**, **6**, **8**, **10**, **12**, and **13** (Scheme 1) display a variety of carbon skeletons and functionality.

Treatment of the acyclic substrate **2** with 2.5 equiv of commercial CuCl (99.995+%, stored in a glovebox under a dry, argon atmosphere) in dry DMF (∼10 mL/mmol of substrate) at 0 °C for 5 min furnished (95% yield) a single product, the monocyclic cyclobutane derivative **16** (Scheme 2). The intramolecular conjugate additions involving substrates **4**, **10**, and **12** were accomplished using an essentially identical protocol and provided the corresponding products **17**, **20**, and **21** in very good yields. When a similar procedure was employed for the structurally simpler substrate **6**, the expected product **18** (64% yield) was accompanied by lesser amounts of the trimethylstannyl product **26** (18%). A rationale for this result is outlined in Scheme 3. Reversible copper−tin transmetalation[16] involving **6** and CuCl would produce **23** and Me_3SnCl (**24**). Intramolecular cis addition[17] of the alkenylcopper function in **23** across the alkynoate

* To whom correspondence should be addressed. Tel: (604)822-3219. Fax: (604)822-2847. E-mail: epier@unixg.ubc.ca.

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(5) All new compounds reported herein exhibit spectra in accord with assigned structures and gave satisfactory elemental (C, H) analyses and/or molecular mass determinations (high-resolution mass spectrometry).

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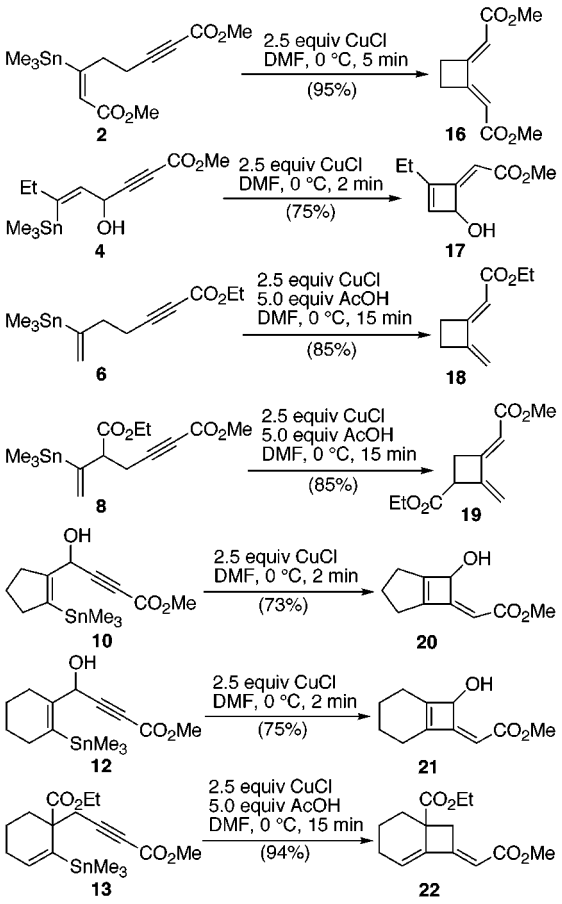
Scheme 2



triple bond would provide the intermediate **25**. Protonation of **25** during workup would give **18**, while, alternatively, reaction of **25** with **24** prior to workup would furnish, presumably reversibly,[16] the other observed product **26**. Longer reaction times decreased the amount of **26** in the product mixture but also reduced the yield of **18**. Further experimentation showed that the production of **26** could be completely curtailed and that, concomitantly, the yield of **18** could be increased by carrying out the cyclization in the presence of 5 equiv of HOAc. Presumably, under these conditions, the intermediate **25** is protonated (to furnish **18**) faster than it reacts with Me_3SnCl (**24**), and thus, the formation of **26** is precluded. It must also be concluded that

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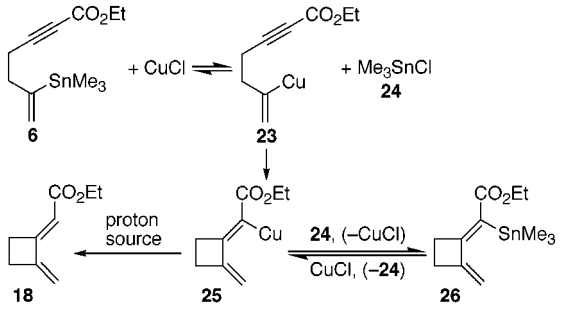
Scheme 3



the intermolecular protonation of **23** by HOAc is slow compared to the cyclization process (**23** → **25**). It was found that the use of HOAc in the conversions **8** → **19** and **13** → **22** also resulted in reactions that were cleaner and more efficient than those carried out in the absence of this additive.

The configuration of α,β-unsaturated ester functions in each of the conjugate addition products **17**−**22** was confirmed by suitable ^{1}H NMR NOE difference experiments. Representative examples are summarized in Chart 1. Irradiation at δ 5.38 (H_b singlet) in the spectrum of **17** increased the intensity of the multiplet (δ 2.05−2.22) due to the methylene protons H_a, while, in the ^{1}H NMR spectra of **19** and **20**, irradiation at δ 5.92 (H_b) and 2.50 (H_a), respectively, caused enhancement of the resonances due to the protons indicated in the structural formulas (Chart 1). Similar experiments provided conclusive evidence for the configurational assignments of the products **18**, **21**, and **22**.

The results presented herein show clearly the efficacy of the new methodology for the synthesis of diversely functionalized cyclobutane derivatives. Especially impressive is the fact that each of the highly strained products is produced under very mild reaction conditions, and it is clear that structurally novel substances such as these would not be easily accessible via alternative (known) synthetic routes. The transformations employed to make the substrates, as well as the reactions involved in effecting the intramolecular conjugate additions, are experimentally relatively straightforward. Several extensions to and applications of this chemistry are currently being investigated.

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Supporting Information Available: Typical experimental procedures for the preparation of compounds **6**, **12**, **13**, **18**, **21**, and **22** and characterization data for compounds **6**, **12**, **13**, and **16**−**22** (11 pages).

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