Pergamon

Tetrahedron Letters 39 (1998) 1521–1524

TETRAHEDRON LETTERS

IODOCYCLOPROPANES AS VERSATILE INTERMEDIATES FOR THE SYNTHESIS OF SUBSTITUTED CYCLOPROPANES

Stephen F. Martin* and Michael P. Dwyer

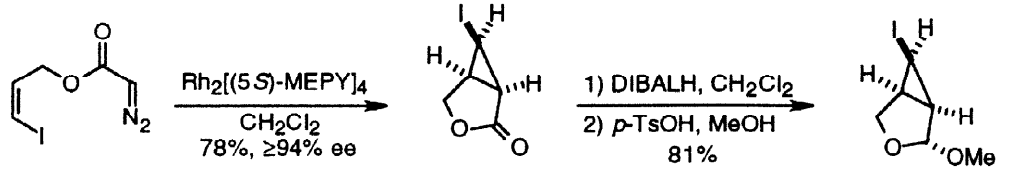
Department of Chemistry and Biochemistry, The University of Texas, Austin, TX 78712 USA

Received 26 November 1997; revised 2 January 1998; accepted 5 January 1998

Abstract. Iodocyclopropanes are versatile synthetic intermediates that have been used to prepare a variety of alkyl, aryl and acyl substituted cyclopropanes via organometallic reactions. © 1998 Elsevier Science Ltd. All rights reserved.

As part of a program directed toward the synthesis and evaluation of novel cyclopropane-containing peptidomimetics,[1] we required general methods for the asymmetric synthesis of diversely substituted cyclopropyl subunits from common intermediates. In order to explore one possible strategy, we envisioned that the iodocyclopropyl lactone **2**, which may be prepared in high optical purity by the asymmetric cyclization of allylic diazoacetate **1** (Scheme 1),[2-4] might be readily elaborated by selected organometallic reactions to afford the corresponding alkyl, aryl, and acyl cyclopropanes. Because the lactone moiety in **2** might not be compatible with some organometallic reagents, it was first converted into the acetal **3** as a prelude to exploratory reactions.[5] Herein, we report exemplary work detailing the utility of iodocyclopropane **3** for the synthesis of a variety of substituted cyclopropanes.

Scheme 1

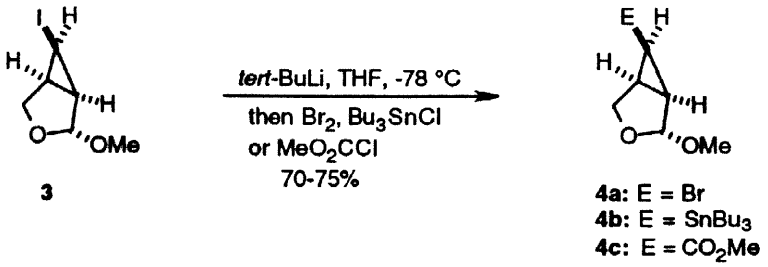


1 **2** **3**

In the first series of experiments, the methyl acetal **3** was treated with *tert*-BuLi (2.1 equiv) at -78 °C in THF and the intermediate cyclopropyllithium allowed to react with a number of electrophiles such as Br_2, Bu_3SnCl, and MeO_2CCl at -78 °C to afford the corresponding cyclopropanes **4a-c** in 70–75% yields (Scheme 2). No epimeric products were detected by ^1H NMR analysis of the crude reaction mixtures, indicating that the intermediate cyclopropyl anion was configurationally stable under the reaction conditions.[6]

0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00072-0

Scheme 2

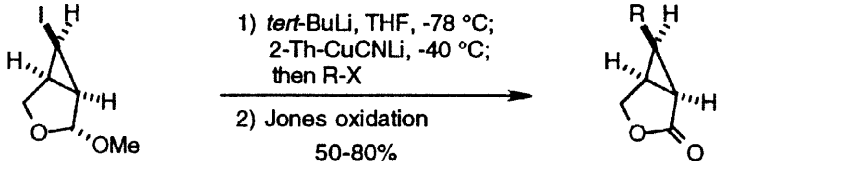


3

4a: E = Br
4b: E = $SnBu_3$
4c: E = CO_2Me

Having established that the iodocyclopropane **3** could be stereoselectively trapped with electrophiles, we turned our attention to introducing a variety of alkyl and functionalized alkyl substituents on the cyclopropane ring. However, several initial experiments using traditional alkylation methods were unsuccessful.[7] For example, lithiation of **3** by metal-halogen exchange with *tert*-BuLi as before followed by reaction of the intermediate cyclopropyllithium reagent with alkylating agents such as methyl iodide and 2-bromopropane yielded only complex mixtures, thereby prompting examination of the reactivity of cyclopropyl cuprate reagents.[8] In several exploratory experiments, **3** was converted to the corresponding cuprate by reaction with excess *n*-Bu_2CuLi (4 equiv).[9] However, the subsequent reaction of this cuprate with several alkylating agents (*e.g.*, CH_3I, $CH_2{=}CHCH_2Br$, and $C_6H_5CH_2Br$) afforded epimeric mixtures (3–10:1) of alkylated products,[10] the major of which resulted from retention of configuration at the reacting center. After some experimentation, we discovered that a mixed, higher-order cuprate derived from **3** underwent facile and clean alkylation. Thus, the higher-order, 2-thienyl cyanocuprate derived from **3**, which was prepared by the method of Lipschutz,[11,12] underwent stereoselective (≥95%) reaction with a number of alkyl halides including methyl iodide, allyl bromide and isopropylbromide to give intermediate lactols, which were converted by Jones oxidation into the corresponding lactones **5a–c** to facilitate isolation and characterization (Scheme 3). It was essential to conduct these alkylations under rigorously degassed conditions to avoid the formation of products resulting from oxidative coupling.

Scheme 3



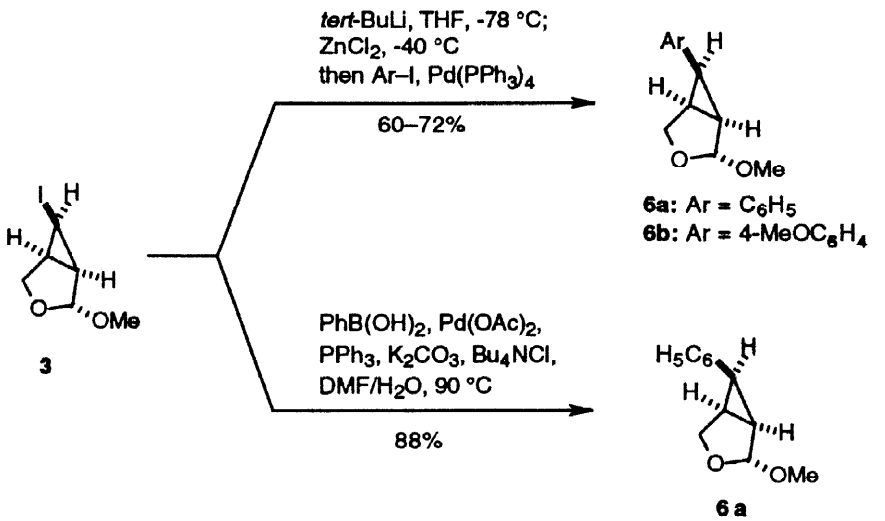
3

5a: R = Me
5b: R = $CH_2CH{=}CH_2$
5c: R = *i*-Pr

Aryl functionality could also be incorporated into **3** by utilizing a modified Negishi cross-coupling reaction.[13] Thus, the organozinc reagent derived from **3**, which was prepared by transmetallation of the organolithium reagent,[14] underwent palladium(0)-catalyzed arylation with several aryl iodides to give good yields of the arylated products **6a,b** with complete retention of configuration (Scheme 4). Inasmuch as aryl iodides are readily available, this method lends itself to the incorporation of a wide variety of aryl groups. Aryl groups may also be introduced onto the cyclopropane via modified Suzuki reactions according to the protocol recently reported

by Charette,[15] although this tactic for introducing aryl groups is more restricted owing to the limited availability of the requisite aryl boronic acids (Scheme 4).

Scheme 4



In summary, we have demonstrated that the iodocyclopropane **2** is a versatile intermediate for the synthesis of cyclopropanes bearing a wide variety of substituents including stannyl, acyl, aryl, and alkyl groups. Currently, this methodology is being extended to include other substituted iodocyclopropanes and to the construction of cyclopropane-containing dipeptide isosteres for incorporation into biologically active unnatural products. These results will be reported in due course.

Acknowledgments. We thank the National Institutes of Health and the Robert A. Welch Foundation for support of this research.

REFERENCES AND NOTES

1. (a) Martin, S. F.; Austin, R. E.; Oalmann, C. J. *Tetrahedron Lett.* **1990**, *31*, 4731. (b) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; DeLara, E., Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710. (c) Baker, W. R.; Jae, H.-S.; Martin, S. F.; Condon, S. L.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1045. (d) Martin, S. F.; Oalmann, C. J.; Liras, S.*Tetrahedron* **1993**, *49*, 3521.
2. Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.
3. Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493.
4. For other methods for preparing iodocyclopropanes, see: (a) Piers, E.; Coish, P. D. G. *Synthesis* **1995**, 47. (b) Piers, E.; Coish, P. D. G. *Synthesis* **1996**, 502.

5. The structure assigned to each compound was in accord with its spectral (^1H and ^{13}C NMR, IR and mass) characteristics. Yields cited are for compounds judged to be >95% pure by ^1H NMR. Analytical samples of all new compounds were obtained by distillation, recrystallization, preparative HPLC or flash chromatography and gave satisfactory identification by high resolution mass spectrometry.
6. Walborsky, H. M.; Impastato, F. J.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3283.
7. (a) Corey, E. J.; De, B. *J. Am. Chem. Soc.* **1984**, *106*, 2735. (b) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415. (c) Tanaka, K.; Minami, K.; Funaki, I.; Suzuki, H. *Tetrahedron Lett.* **1990**, *31*, 2727. (d) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213. (d) Isono, N.; Mori, M. *J. Org. Chem.* **1996**, *61*, 7867.
8. (a) Piers, E.; Nagakura, I.; Morton, H. E. *J. Org. Chem.* **1978**, *43*, 3630. (b) Piers, E.; Ruediger, E. H. *J. C. S. Chem Comm.* **1979**, 166. (c) Piers, E.; Reissig, H.-U. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 791. (d) Walborsky, H. M.; Banks, R. B.; Banks, M. L. A.; Duraisamy, M. *Organometallics* **1982**, *1*, 667. (e) Morgans, D. J., Jr.; Feigelson, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 5477. (f) Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J.-Y. *J. Am. Chem. Soc.* **1996**, *116*, 6096.
9. (a) Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1600. (b) Yamamoto, H.; Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1997**, *99*, 5816.
10. For examples of reactions of secondary alkyl iodides with cuprates with loss of stereochemistry, see: (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928. (b) Ashby, E. C.; Coleman, D. *J. Org. Chem.* **1987**, *52*, 4554.
11. For reviews of higher-order cuprates, see: (a) Lipshutz, B. H. *Synlett* **1990**, 119. (b) Lipshutz, B. H. *Synthesis* **1987**, 325-341. (c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowksi, J. A. *Tetrahedron* **1984**, *40*, 5005.
12. Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.
13. (a) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958.
14. Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *28*, 5075.
15. (a) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718. (b) Charette, A. B.; De Freitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809.