Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: C. Ferreri , M. Ambrosone & C. Chatgilialoglu (1995) A Facile Entry to Secondary Cyclopropylcarbinols Further Developments in the Stereospecific Synthesis of (E)-Homoallylic Bromides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:21, 3351-3356, DOI: 10.1080/00397919508013855

To link to this article: http://dx.doi.org/10.1080/00397919508013855

SYNTHETIC COMMUNICATIONS, 25(21), 3351-3356 (1995)

A FACILE ENTRY TO SECONDARY CYCLOPROPYLCARBINOLS: FURTHER DEVELOPMENTS IN THE STEREOSPECIFIC SYNTHESIS OF (*E*)-HOMOALLYLIC BROMIDES

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Abstract: *Cyclopropanecarboxaldehyde has been used in an improved synthesis of secondary cyclopropylcarbinols, thus allowing for further developments in the stereospecific ring opening leading to (E)-homoallylic bromides.*

The Julia synthesis of homoallylic compounds[1] and the modified versions introduced by others[2] brought to the attention of synthetic organic chemists the utility of cyclopropylcarbinols as intermediates. Both secondary and tertiary cyclopropylcarbinols are easily transformed by these methods into homoallylic bromides and iodides, which can be further used in natural products synthesis.[3]

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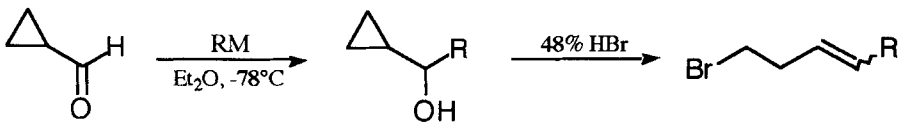
In all cases, stereoselective ring opening affording homoallylic compounds is observed. Secondary cyclopropylcarbinols afford mainly (*E*)-homoallylic products and they are found to be more stereoselective than tertiary.

Due to their utility, secondary cyclopropylcarbinols have been synthesized by several routes,[4] i.e., reduction of available cyclopropyl ketones, cyclopropanation of allylic alcohols, and coupling of organometallic reagents with cyclopropyl derivatives. During our study of 2,6-disubstituted-δ,ε-unsaturated carboxylic acid derivatives as starting materials for free-radical cyclizations,[5] we were interested in preparing compounds **3** for further transformations. In this paper we wish to report a very simple synthesis of secondary cyclopropylcarbinols **2**, starting from cyclopropanecarboxaldehyde (**1**), as well as their corresponding ring opening products **3**, as shown in the Scheme.[6] The role of the size of the R group in the stereoselectivity of the cyclopropyl ring opening has been also considered.

The reaction of commercially available aldehyde **1**[7] with an appropriate organometallic reagent is easy to perform (see Experimental Section). The yields of the secondary cyclopropylcarbinols **2** are reported in Table and were close to quantitative when the temperature was carefully mantained at -78 °C until workup. The ring opening of these cyclopropyl derivatives was performed following the Julia conditions, and the results, including the stereochemical outcomes, are also reported in Table. Most of the (*E*)-homoallylic bromides synthesized by this route are new compounds. For R being a methyl group, we observed an isomeric composition of *E*/*Z*=90/10, whereas with all other substituents the ring opening showed higher stereoselectivity, i.e. *E*/*Z*≥97/3. These results are in accord with the explanation advanced by Brady *et al.* based on nonbonded interactions operating in the ring opening transition state.[2a]

In conclusion, the route described herein represents a facile access to differently 1-substituted homoallylic bromides. Another synthetic use of cyclopropanecarboxaldehyde has been demonstrated, which allows for a systematic exploitation of the reactivity of cyclopropylcarbinols as well as for their extended use in synthesis.



1 **2** **3**

Scheme

Table. Reaction of aldehyde **1** with some organometallic reagents (RM) and HBr-mediated ring opening of the resulting cyclopropylcarbinols

R	RM	**2** (yield, %)	**3** (yield, %)	*E/Z*
Me	RLi	**2a** (94)	**3a** (90)	90/10
Et	RMgBr	**2b** (95)	**3b** (87)	97/3
$PhCH_2$	RMgCl	**2c** (95)	**3c** (92)	98/2
c-C_6H_{11}	RMgBr	**2d** (90)	**3d** (95)	98/2
Me_3SiCH_2	RMgCl	**2e** (92)	**3e** (94)	98/2

EXPERIMENTAL SECTION

Materials. Commercially available chemicals were obtained from Aldrich and used without further purification; the organometallic reagents were commercially available solutions in THF or diethyl ether. Dry diethyl ether was freshly distilled over $LiAlH_4$ under a nitrogen atmosphere. Compound **2a** was identical with a commercially available sample (Aldrich) and compounds **3a** showed identical physical and spectroscopical properties with those previously reported.[8]

General Methods. NMR spectra were recorded on a Varian VXR 200 spectrometer at 200 and 50.3 MHz for ^1H and ^{13}C, respectively. All chemical shifts were reported in ppm using tetramethylsilane as an internal standard and

deuterated chloroform as solvent. The *E/Z* ratio was determined for the crude reaction, after workup, by GC/MS and ^{13}C NMR spectroscopy.[9] TLC was carried out using Merck PF254 silica gel plates; flash-chromatography was carried out on 230-400 mesh silica gel 60 (Merck).

Coupling of Cyclopropane Carboxaldehyde with Organometallic Reagents. General Procedure. To the organometallic reagent (1.05 equiv.), kept at -78 °C (dry ice-acetone bath) under argon, was added the aldehyde (1 equiv.) dissolved in anhydrous ether (50 mL) and the mixture allowed to react for 2 hours. The reaction mixture was then hydrolyzed at that temperature by the addition of saturated NH_4Cl solution, and extracted with ether (2 x 30 mL). The ethereal layers were collected, dried over anhydrous sodium sulfate and evaporated under vacuum to give the corresponding alcohol. When possible, further distillation of the crude product afforded pure compounds. **2b**: B.p. 139-140 °C; ^1H NMR: 0.21 (m, 2H), 0.48 (m, 2H), 0.85 (m, 1H), 0.96 (t, 3H, J=7.4 Hz), 1.59 (q, 2H, J=7.4 Hz), 2.77 (q, 1H, J=6.5 Hz, CH-O); ^{13}C NMR: 2.2, 2.7, 10.0, 17.5, 30.0; GC/MS m/z: 99(M^+-H), 71, 57. **2c**: B.p. 90-2 °C/3 mmHg. ^1H NMR: 0.14 (m, 1H), 0.31 (m, 1H), 0.51 (m, 2H), 0.94 (m, 1H), 2.82 (m, 1H, benzyl CH), 2.95 (m, 1H, benzyl H), 3.09 (m, 1H, CH-OH). ^{13}C NMR: 2.7, 2.9, 17.3, 37.9, 43.6, 65.3, 126.3, 127.6, 129.4, 138.4; GC/MS m/z: 162(M^+), 144(M^+-H_2O), 129, 116, 91, 77. **2d**: oil. ^1H NMR: 0.19 (d, 2H, J=5 Hz), 0.46 (m, 2H), 0.87 (m, 1H), 1.13 (m, 6H), 1.44 (m, 1H), 1.76 (m, 4H), 2.52 (dd, 1H, J=5.9 Hz, CH-O); ^{13}C NMR: 1.8, 3.7, 15.6, 24.1, 21.2, 26.6, 28.8, 29.1, 35.5, 44.5, 81.2; GC/MS m/z: 154(M^+), 71, 55. **2e**: oil. ^1H NMR: 0.23 (m, 1H), 0.37 (m, 1H), 0.49 (m, 1H), 0.69 (m, 1H), 0.94 (m, 1H), 0.96 (m, 1H, CHSi), 1.41(m, 1H, CHSi), 3.05 (m, 1H, CH-O); ^{13}C NMR: 0.7, 1.3, 1.9, 3.4, 15.2, 41.3; GC/MS m/z: 158(M^+), 157(M^+-H), 87, 73, 59.

HBr Mediated Ring Opening. For the ring opening, the alcohols were used without further purification, by adding a 48% HBr solution to the crude product following the Julia methodology.[1] **3b**: ^1H NMR: 0.98 (t, 3H, J=7.2 Hz, C-1), 2.02 (quintet, 2H, J=7.1 Hz, C-2), 2.55 (quartet, 2H, J=6.8 Hz, C-5), 3.36 (t, 2H, J=7.3 Hz, C-6), 5.38 (dt, 1H, J_{trans}=15.6 Hz and J= 6.8 Hz, C-4), 5.56 (dt, 1H, J_{trans} = 15.6 Hz and J= 6.8 Hz, C-3). ^{13}C NMR: 13.6, 25.5, 31.6, 32.8, 36.0, 125.4, 135.4; GC/MS m/z (*E*-isomer): 164(M^++2), 162(M^+), 83,

67, 55; GC/MS m/z (*Z*-isomer): 164(M^++2), 162(M^+), 83, 67, 55; high-resolution MS, calcd for $C_6H_{11}Br$: m/z 162.0044, found 162.0048. **3c**: ^1H NMR: 2.52 (q, 2H, J=6.4 Hz, C4-H), 3.42 (m, 4H, C1-H + C5-H), 5.63 (dt, 2H, $J_{2,3}$=15 Hz and $J_{(1,2 \text{ and } 3,4)}$= 6.4 Hz, C2-H and C3-H), 7.30 (m, 5H, C_6H_5). ^{13}C NMR: 32.6, 35.9, 38.9, 125.9, 128.5, 129.0, 132.3; GC/MS m/z (*E*-isomer): 226(M^++2), 224(M^+), 145, 117, 91; GC/MS m/z (*Z*-isomer): 226(M^++2), 224(M^+), 145, 117, 91; high-resolution MS, calcd for $C_{11}H_{13}Br$: m/z 224.0201, found 224.0206; Anal. Calcd for $C_{11}H_{13}Br$: C, 58.69; H, 5.82. Found C, 58.87; H, 5.70. **3d**: ^1H NMR: 1.15 (m, 6H), 1.68 (m, 4H), 1.90 (m, 1H), 2.51 (q, 2H, J=7.2 Hz, C-3), 3.33 (t, 2H, J= 7.2 Hz, C-4), 5.32 (dt, 1H, $J_{1,2}$= 15.6 Hz and $J_{2,3}$= 5.76 Hz, C-2), 5.48 (dd, 1H, $J_{1,2}$= 15.6 Hz and J_{vic}=6.23 Hz, C-1); ^{13}C NMR: 26.0, 26.1, 32.9, 36.1, 40.6, 123.8, 139.8; GC/MS m/z (*E*-isomer): 218(M^++2), 216(M^+), 137, 109, 95, 81, 67; GC/MS m/z (*Z*-isomer): 218(M^++2), 216(M^+), 137, 109, 95, 81, 67; high-resolution MS, calcd for $C_{10}H_{17}Br$: m/z 216.0514, found 216.0510. **3e**: ^1H NMR: 1.66 (d, 2H, J=5.9 Hz, C-1), 2.53 (q, 2H, J=6.8 Hz, C-4), 3.35 (t, 2H, J= 6.5 Hz, C-5), 5.38 (dt, 1H, $J_{2,3}$=15.5 Hz and $J_{3,4}$=6.1 Hz, C-3), 5.55 (dd, 1H, $J_{2,3}$= 15.5 Hz and $J_{1,2}$=5.9 Hz, C-2); ^{13}C NMR: 1.9, 14.1, 17.9, 22.6, 31.6, 32.8, 36.0, 127.7, 128.3; GC/MS m/z (*E*-isomer): 150[(M^++2)-$SiMe_3$], 148(M^+-$SiMe_3$), 69, 55; GC/MS m/z (*Z*-isomer): 150[(M^++2)-$SiMe_3$], 148(M^+-$SiMe_3$), 69, 55; Anal. Calcd for $C_8H_{17}BrSi$: C, 43.44; H, 7.75. Found C, 43.66; H, 7.65.

Acknowledgements: Financial supports from Ministero della Ricerca Scientifica e Tecnologica (MURST 60%) to CF and from the Progetto Strategico del CNR "Tecnologie Chimiche Innovative" to CC are gratefully acknowledged.

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(Received in the UK 21 March 1995)