Organic Letters

Supporting Information

The First Cyclopropanation Reaction of Unmasked α,β -Unsaturated Carboxylic Acids: Direct and Complete Stereospecific Synthesis of Cyclopropanecarboxylic Acids Promoted by Sm/CHI₃

José M. Concellón,* Humberto Rodríguez-Solla and Carmen Simal

Departamento de Química Orgánica e Inorgánica. Facultad de Química, Universidad de Oviedo, C/ Julián Clavería, 8, 33006, Oviedo, Spain.

jmcg@uniovi.es

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GENERAL

Reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased in the higher quality available and were used without further purification. Flash column chromatography was carried out on silica gel 230-400 mesh. Compounds were visualized on analytical thin layer chromatograms (TLC) by UV light (254 nm). ^1H NMR spectra were recorded at 200, 300 or 400 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 50 or 75 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which is used as an internal standard, and coupling constants (J) are reported in Hz. The diastereoisomeric ratio were obtained using ^1H NMR analysis and GC-MS of crude products. GC-MS and HRMS were measured at 70 eV or using FAB conditions. When HRMS could not be measured on molecular ion the HRMS of a significant fragment is given. Only the most important IR absorptions (cm^{-1}) and the molecular ions and/or base peaks in MS are given.

General Procedure.

Synthesis of cyclopropanecarboxylic acids 2:

To a stirred suspension of Sm metal (2.4 mmol, 6 equiv.) and the corresponding carboxylic acid **1** (0.4 mmol, 1 equiv.) in THF (50 ml) was added CHI_3 (2 mmol, 5 equiv.). After sonication for one hour and before the reaction mixture was quenched with aqueous HCl 0.1 M, the excess of SmI_2 was oxidized by bubbling an stream of air through the solution. The organic layer was then extracted with diethyl ether and the combined extracts were washed with an aqueous sodium thiosulphate solution, dried over Na_2SO_4 and concentrated under vacuum to yield the crude cyclopropanecarboxylic acids **2** which were purified by flash chromatography on silica gel (Hexane/EtOAc 1/1) to afford pure products **2**.

In the case of compounds **2a-b**, and **2h-k** a few drops of bromine was added to the crude reaction product in CCl_4 prior to the flash column chromatography.

Although all compounds **2** (excepting **2e** and **2l**) were previously synthesized, no fully characterization was however given or no easily accessible journals were cited. For this reason, the fully characterization of these compounds is also given in this Supporting Information.: **2a**, **2g**, and **2k**: Vallgård, J.; Appelberg, U.; Csöreg, I.; Hacksell, U. *J. Chem. Soc., Perkin Trans 1* **1994**, 461-470. **2b**: O'Brien, E. M.; Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2003**, *125*, 10498-10499. **2c-d**: Tchilibon, S.; Kim, S. -K.; Gao, Z. -G.; Harris, B. A.; Blaustein, J. B.; Gross, A. S.; Duong, H. T.; Melman, N.; Jacobson, K. A. *Bioorg. Med. Chem.* **2004**, *12*, 2021-2034. **2f**, **2h-i**: Pryde, D. C.; Cook, A. S.; Burring, D. J.; Jones, L. H.; Foll, S.; Platts, M. Y.; Sanderson, V.; Corless, M.; Stobie, A.; Middleton, D. S.; Foster, L.; Barker, L.; Van Der Graaf, P.; Stacey, P.; Kohl, C.; Coggon, S.; Beaumont, K. *Bioorg. Med. Chem.* **2007**, *15*, 142-159. **2j**: Toy, P. H.; Dhanabalasingam, B.; Newcomb, M.; Hanna, I. H.; Hollenberg, P. F. *J. Org. Chem.* **1997**, *61*, 9114-9122. **2m**: Lishanskii, I. S.; Pomerantsev, V. I.; Illarionova, N. G.; Khachaturov, A. S.; Vakorina, T. I. *J. Org. Chem. USSR* **1971**, *7*, 1870-1875; *Zh. Org. Khim.* **1971**, *7*, 1803-1810.

***trans*-2-Phenylcyclopropanecarboxylic acid (2a)**

^1H NMR (300 MHz, CDCl_3): δ = 7.32-7.00 (m, 5 H), 2.61 (ddd, J = 9.48, 6.63, 4.65 Hz, 1 H), 1.91 (dt, J = 8.34, 4.65 Hz, 1 H), 1.67 (dt, J = 9.48, 4.65 Hz, 1 H), 1.42 (ddd, J = 8.34, 6.63, 4.65 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 179.6 (C), 139.4 (C), 128.5 (2xCH), 126.6 (CH), 126.2 (2xCH), 27.0 (CH), 23.9 (CH), 17.4 (CH_2); MS (70 eV): m/z (%): 162 [M^+] (46), 144 (20), 117 (100), 107 (19), 91 (39); HRMS calcd for $\text{C}_{10}\text{H}_{10}\text{O}_2$ 162.0681, found 162.0673; IR (neat): $\tilde{\nu}$ = 3442, 3055, 1698, 1266, 739 cm^{-1} ; R_f = 0.40 (hexane:ethyl acetate 1:1)

***cis*-2-Phenylcyclopropanecarboxylic acid (2b)**

^1H NMR (300 MHz, CDCl_3): δ = 7.35-7.17 (m, 5 H), 2.75-2.61 (m, 1 H), 2.06 (ddd, J = 9.84, 7.77, 5.13 Hz, 1 H), 1.68 (dt, J = 7.77, 5.13 Hz, 1 H), 1.39 (ddd, J = 8.64, 7.77, 5.13 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ = 176.8 (C), 135.8 (C), 129.2 (2xCH), 127.9 (2xCH), 126.7 (CH), 26.5 (CH), 21.3 (CH), 11.9 (CH_2); MS (70 eV): m/z (%): 162 [M^+] (39), 144 (19), 117 (100), 115 (84), 91 (36), 39 (20); HRMS calcd for $\text{C}_{10}\text{H}_{10}\text{O}_2$ 162.0681, found 162.0688; IR (neat): $\tilde{\nu}$ = 3410, 2349, 1689, 1456, 1022 cm^{-1} ; R_f = 0.50 (hexane:ethyl acetate 1:1)

***trans*-2-(4-Methylphenyl)cyclopropanecarboxylic acid (2c)**

^1H NMR (300 MHz, CDCl_3): δ = 7.10 (d, J = 8.04 Hz, 2 H), 7.00 (d, J = 8.04 Hz, 2 H), 2.58 (ddd, J = 9.54, 6.75, 4.56 Hz, 1 H), 2.32 (s, 3 H), 1.86 (dt, J = 8.57, 4.56 Hz, 1 H), 1.65 (dt, J = 9.54, 4.56 Hz, 1 H), 1.38 (ddd, J = 8.37, 6.75, 4.56 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 179.6 (C), 136.4 (C), 136.3 (C), 129.1 (2xCH), 126.1 (2xCH), 26.8 (CH), 23.8 (CH), 20.9 (CH₃), 17.3 (CH₂); MS (70 eV): m/z (%): 176 [M^+] (33), 158 (20), 131 (100), 115 (55), 91 (39), 77 (16); HRMS calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2$ 176.0837, found 176.0857; IR (neat): $\tilde{\nu}$ = 3440, 2925, 1692, 1454, 810 cm^{-1} ; R_f = 0.55 (hexane:ethyl acetate 1:1)

***trans*-2-(3-Methylphenyl)cyclopropanecarboxylic acid (2d)**

^1H NMR (300 MHz, CDCl_3): δ = 7.22-6.90 (m, 4 H), 2.57 (ddd, J = 9.60, 6.60, 4.56 Hz, 1 H), 2.33 (s, 3 H), 1.89 (dt, J = 8.19, 4.56 Hz, 1 H), 1.65 (dt, J = 9.60, 4.56 Hz, 1 H), 1.44-1.38 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 179.5 (C), 139.4 (C), 138.1 (C), 128.4 (CH), 127.4 (CH), 127.0 (CH), 123.2 (CH), 27.0 (CH), 23.8 (CH), 21.3 (CH_3), 17.4 (CH_2); MS (70 eV): m/z (%): 176 [M^+] (32), 158 (18), 131 (100), 115 (55), 91 (41), 77 (17); HRMS calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2$ 176.0837, found 176.0794; IR (neat): $\tilde{\nu}$ = 3420, 2924, 1692, 1231, 781 cm^{-1} ; R_f = 0.52 (hexane:ethyl acetate 1:2)

***trans*-2-(4-Bromo-3-methylphenyl)cyclopropanecarboxylic acid (2e)**

^1H NMR (300 MHz, CDCl_3): δ = 7.42 (d, J = 8.19 Hz, 1 H), 6.98 (d, J = 2.20 Hz, 1 H), 6.78 (dd, J = 8.19, 2.20 Hz, 1 H), 2.53 (ddd, J = 9.39, 6.75, 4.69 Hz, 1 H), 2.36 (s, 3 H), 1.85 (dt, J = 8.34, 4.69 Hz, 1 H), 1.65 (dt, J = 9.39, 4.69 Hz, 1 H), 1.36 (ddd, J = 8.34, 6.75, 4.69 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 179.4 (C), 138.7 (C), 137.9 (C), 132.3 (CH), 128.8 (CH), 125.1 (CH), 122.8 (C), 26.4 (CH), 23.8 (CH_3), 22.8 (CH), 17.3 (CH_2); MS (70 eV): m/z (%): 254 [M^+] (25), 209 (17), 157 (17), 147 (28), 130 (100), 115 (63); HRMS calcd for $\text{C}_{11}\text{H}_{11}\text{BrO}_2$ 253.9942, found 253.9878; IR (neat): $\tilde{\nu}$ = 3444, 3055, 1700, 1266, 739 cm^{-1} ; R_f = 0.35 (hexane:ethyl acetate 1:1)

***trans*-2-(4-Methoxyphenyl)cyclopropanecarboxylic acid (2f)**

^1H NMR (300MHz, CDCl_3): δ = 7.05 (d, J = 8.91 Hz, 2 H), 6.83 (d, J = 8.91 Hz, 2 H), 3.79 (s, 3 H), 2.57 (ddd, J = 9.45, 6.78, 4.80 Hz, 1 H), 1.86-1.80 (m, 1 H), 1.63 (dt, J = 9.45, 4.80 Hz, 1 H), 1.35 (ddd, J = 8.34, 6.78, 4.80 Hz, 1 H); ^{13}C NMR (75MHz, CDCl_3) δ = 179.8 (C), 158.4 (C), 131.4 (C), 127.4 (2xCH), 113.9 (2xCH), 55.2 (CH_3), 26.5 (CH), 23.6 (CH), 17.1 (CH_2); MS (70 eV): m/z (%): 192 [M^+] (46), 174 (9), 147 (100), 131 (21), 115 (26), 103 (23), 91 (30), 77 (22); HRMS calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$ 192.0786, found 192.0810; IR (neat): $\tilde{\nu}$ = 3456, 1691, 1515, 1266, 740 cm^{-1} ; R_f = 0.375 (hexane:ethyl acetate 1:1)

***trans*-2-(2-Methoxyphenyl)cyclopropanecarboxylic acid (2g)**

^1H NMR (300 MHz, CDCl_3): δ = 7.24-7.18 (m, 1 H), 6.94-6.86 (m, 3 H), 3.86 (s, 3 H), 2.81 (ddd, J = 9.18, 7.00, 4.38 Hz, 1 H), 1.84 (dt, J = 8.19, 4.38 Hz, 1 H), 1.61 (dt, J = 9.18, 4.38 Hz, 1 H), 1.41 (ddd, J = 8.19, 7.00, 4.38 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 180.0 (C), 158.3 (C), 127.7 (C), 127.7 (CH), 126.0 (CH), 120.3 (CH), 110.3 (CH), 55.4 (CH_3), 22.5 (CH), 22.1 (CH), 16.1 (CH_2); MS (70 eV): m/z (%): 192 [M^+] (68), 174 (23), 159 (35), 147 (100), 131 (65), 115 (52), 91 (66); HRMS calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$ 192.0786, found 192.0792; IR (neat): $\tilde{\nu}$ = 3434, 1693, 1495, 1250, 745 cm^{-1} R_f = 0.35 (hexane:ethyl acetate 1:1)

***trans*-2-(4-Fluorophenyl)cyclopropanecarboxylic acid (2h)**

^1H NMR (300MHz, CDCl_3): δ = 7.10-7.06 (m, 2 H), 7.00-6.95 (m, 2 H), 2.58 (ddd, J = 9.48, 6.78, 4.80 Hz, 1 H), 1.85 (dt, J = 8.46, 4.80 Hz, 1 H), 1.65 (dt, J = 9.48, 4.8 Hz, 1 H), 1.36 (ddd, J = 8.46, 6.78, 4.80 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 179.2 (C), 161.7 (d, $^1J_{\text{CF}}$ = 243.85 Hz, C), 135.0 (C), 127.9 (CH), 127.8 (CH), 115.5 (CH), 115.2 (CH), 26.3 (CH), 23.6 (CH), 17.3 (CH_2); MS (70 eV): m/z (%): 180 [M^+] (58), 162 (28), 135 (100), 125 (25), 115 (38), 109 (50); HRMS calcd for $\text{C}_{10}\text{H}_9\text{FO}_2$ 180.0587, found 180.0597; IR (neat): $\tilde{\nu}$ = 3444, 1698, 1517, 1266, 739 cm^{-1} ; R_f = 0.375 (hexane:ethyl acetate 1:1)

***trans*-2-(4-Chlorophenyl)cyclopropanecarboxylic acid (2i)**

^1H NMR (300 MHz, CDCl_3): δ = 7.25 (d, J = 8.37 Hz, 2 H), 7.04 (d, J = 8.37 Hz, 2 H), 2.56 (ddd, J = 9.39, 6.60, 4.68 Hz, 1 H), 1.90-1.84 (m, 1 H), 1.66 (dt, J = 9.39, 4.68 Hz, 1 H), 1.37 (ddd, J = 8.30, 6.60, 4.68 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 179.4 (C), 137.9 (C), 132.4 (C), 128.6 (2xCH), 127.6 (2xCH), 26.4 (CH), 23.9 (CH), 17.4 (CH_2); MS (70 eV): m/z (%): 196 [M^+] (31), 178 (13), 151 (100), 89 (17), 63 (15); HRMS calcd for $\text{C}_{10}\text{H}_9\text{ClO}_2$ 196.0291, found 196.0288; IR (neat): $\tilde{\nu}$ = 3424, 3055, 1698, 1266, 740 cm^{-1} ; R_f = 0.30 (hexane:ethyl acetate 1:1)

***trans*-2-(4-Trifluoromethylphenyl)cyclopropanecarboxylic acid (2j)**

^1H NMR (300 MHz, CDCl_3): δ = 7.55 (d, J = 8.27 Hz, 2 H), 7.21 (d, J = 8.27 Hz, 2 H), 2.65 (ddd, J = 9.75, 6.51, 4.80 Hz, 1 H), 1.96 (dt, J = 8.34, 4.80 Hz, 1 H), 1.73 (dt, J = 9.75, 4.80 Hz, 1 H), 1.44 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 179.0 (C), 143.6 (C), 128.9 (q, $^2J_{\text{CF}}$ = 31.64 Hz, C), 126.9 (q, $^1J_{\text{CF}}$ = 270.31 Hz, C), 126.5 (2xCH), 125.4 (q, $^3J_{\text{CF}}$ = 3.82 Hz, 2xCH), 26.5 (CH), 24.2 (CH), 17.7 (CH_2); MS (70 eV): m/z (%): 230 [M^+] (61), 212 (25), 185 (82), 175 (25), 165 (60), 115 (100); HRMS calcd for $\text{C}_{11}\text{H}_9\text{F}_3\text{O}_2$ 230.0555, found 230.0558; IR (neat): $\tilde{\nu}$ = 3443, 1689, 1326, 1264, 731 cm^{-1} ; R_f = 0.475 (hexane:ethyl acetate 1:2)

***trans*-2-(2-Trifluoromethylphenyl)cyclopropanecarboxylic acid (2k)**

^1H NMR (300 MHz, CDCl_3): δ = 7.66 (d, J = 7.77 Hz, 1 H), 7.48 (t, J = 7.77 Hz, 1 H), 7.34 (t, J = 7.77 Hz, 1 H), 7.15 (d, J = 7.77 Hz, 1 H), 2.95-2.83 (m, 1 H), 1.95-1.89 (m, 1 H), 1.71 (dt, J = 9.35, 4.65 Hz, 1 H), 1.48 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 179.2 (C), 137.4 (C), 131.9 (CH), 130.0 (q, $^2J_{\text{CF}}$ = 30.02 Hz, C), 127.1 (CH), 126.9 (CH), 126.1 (q, $^3J_{\text{CF}}$ = 4.91 Hz, C), 124.2 (q, $^1J_{\text{CF}}$ = 262.00 Hz, C), 23.8 (CH), 23.2 (CH), 16.1 (CH_2); MS (70 eV): m/z (%): 230 [M^+] (31), 190 (30), 185 (54), 165 (84), 146 (100), 115 (91); HRMS calcd for $\text{C}_{11}\text{H}_9\text{F}_3\text{O}_2$ 230.0555, found 230.0556; IR (neat): $\tilde{\nu}$ = 3441, 1702, 1315, 1266, 740 cm^{-1} ; R_f = 0.52 (hexane:ethyl acetate 1:2)

***trans*-2-(3-Hydroxyphenyl)cyclopropanecarboxylic acid (21)**

^1H NMR (300 MHz, CDCl_3): δ = 7.15 (t, J = 7.85 Hz, 1 H), 6.68 (dd, J = 7.85, 1.74 Hz, 2 H), 6.58 (s, 1 H), 2.54 (ddd, J = 9.61, 6.63, 4.11 Hz, 1 H), 1.89 (dt, J = 8.82, 4.11 Hz, 1 H), 1.64 (dt, J = 9.61, 4.11 Hz, 1 H), 1.41-1.35 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 178.7 (C), 155.7 (C), 141.5 (C), 129.7 (CH), 118.7 (CH), 113.6 (CH), 113.2 (CH), 26.8 (CH), 23.7 (CH), 17.4 (CH_2); MS (70 eV): m/z (%): 178 [M^+] (48), 160 (25), 133 (100), 105 (59), 77 (61), 51 (26), 39 (30); Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_3$ C, 67.41; H, 5.66. Found: C, 67.79; H, 5.54; IR (neat): $\tilde{\nu}$ = 3381, 2890, 1694, 1590, 1453 cm^{-1} ; R_f = 0.25 (hexane:ethyl acetate 1:1)

***trans*-(*E*)-2-(Propen-1-yl)cyclopropanecarboxylic acid (2m)**

^1H NMR (300 MHz, CDCl_3): δ = 5.62 (dq, J = 15.17, 6.45, 0.58 Hz, 1 H), 5.02 (ddq, J = 15.17, 8.22, 1.59 Hz, 1 H), 2.07-1.97 (m, 1 H), 1.65 (dd, J = 6.45, 1.59 Hz, 3 H), 1.56 (dt, J = 8.22, 4.26 Hz, 1 H), 1.37 (dt, J = 9.09, 4.26 Hz, 1 H), 0.98 (ddd, J = 8.22, 6.45, 4.26 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 180.2 (C), 130.2 (CH), 126.4 (CH), 25.8 (CH), 21.5 (CH), 17.3 (CH₃), 16.0 (CH₂); MS (70 eV): m/z (%): 126 [M^+] (20), 97 (46), 81 (100), 79 (67), 53 (45), 41 (55), 39 (60); HRMS calcd for $\text{C}_7\text{H}_{10}\text{O}_2$ 126.0681, found 126.0685; IR (neat): $\tilde{\nu}$ = 3457, 2978, 1696, 1456, 736 cm^{-1} ; R_f = 0.65 (hexane:ethyl acetate 1:2)