One-Pot Synthesis of 1-Substituted Cyclopropanols from Carboxylic Acid Chlorides

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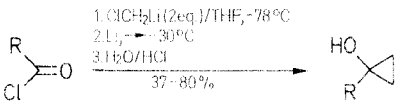
The *in situ* generated chloromethyl-lithium reacts at −78 °C to −30 °C with different acid chlorides (2:1 molar ratio) to afford, after lithiation with lithium powder, 1-substituted cyclopropanols.

Cyclopropanols[1] are interesting molecules in organic synthesis due mainly to their ability to be transformed into homoenolate derivatives.[2] Recently, we have reported a new method to prepare 1-substituted cyclopropanols starting from α,α′-dichloroacetone.[3] In the present communication we report a new route for these compounds using commercially available carboxylic acid chlorides.

When different carboxylic acid chlorides **1** were successively allowed to react with *in situ* generated chloromethyllithium (from chloroiodomethane and methyllithium;[4] 1:2 molar ratio) in the presence of lithium bromide at −78 °C, and an excess of lithium powder (1:5 molar ratio) at temperature ranging between −78 and −30 °C, the corresponding 1-substituted cyclopropanols **2** were isolated (Tables 1 and 2). It is necessary to keep the temperature below −30 °C in order to avoid the formation of ethylketones[3] as by-products.



1 **2a-h**

The mechanism of the reaction involves in the first step the lithium alcoholate **3**, which undergoes lithiation to give the monolithiated species **4**; the latter then suffers an spontaneous γ-elimination yielding after acid hydrolysis the cyclopropanols **2**.

Table 1. 1-Substituted Cyclopropanols **2** Prepared

Product	R	Yield (%)[a]	b.p. (°C)/mbar[b]	Molecular Formula[c] or Lit. b.p. (°C)/mbar
2a	*c*-C_3H_5	45[d]	56–59/20	$C_6H_{10}O$ (98.1)
2b	*n*-C_3H_7	37	42–44/20	42–43/20[3]
2c	*c*-C_4H_7	65	65–67/20	$C_7H_{12}O$ (112.2)
2d	*n*-C_4H_9	42	63–65/20	64–66/20[3]
2e	$C_2H_5OCH_2$	50	58–60/20	$C_6H_{12}O_2$ (116.2)
2f	C_6H_5	80[d]	103–105/20	102–104/20[3]
2g	*c*-C_6H_{11}	40	91–93/20	$C_9H_{16}O$ (140.2)
2h	4-$CH_3OC_6H_4$	63	90–100/0.13[e]	75–78/0.7[6]

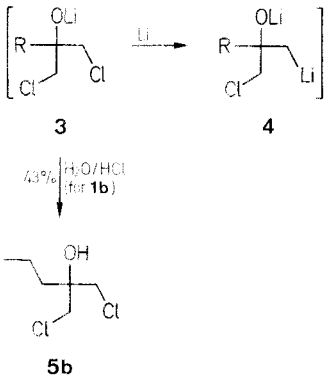
[a] Isolated yield based on the starting compound **1**.
[b] Distillation interval.
[c] Satisfactory microanalyses obtained: ±0.3, H ±0.2.
[d] Hexamethylphosphoric triamide (HMPT) was added to the reaction mixture (1/HMPT: 1/2 molar ratio).
[e] Bath temperature.

Table 2. Spectral Data of 1-Substituted Cyclopropanols **2**

Product	IR (Film)[a] ν (cm^{-1})	^{1}H-NMR (CCl_4, TMS + D_2O capillary)[b] δ (ppm)	^{13}C-NMR (CCl_4 + D_2O capillary)[b] δ (ppm)	MS[c] *m/e* (rel. int. %)
2a	3420 (OH); 3080, 3010 (CH ring)[d]	0.1–0.8 (m, 8H, ring CH_2); 0.9–1.1 (m, 1H, CH); 2.6 (s, 1H, OH)	2.4 (cyclopropyl CH_2); 11.1 (cyclopropanol CH_2); 16.2 (CH); 55.7 (C–O)	98 (M^+, 1), 69 (54); 56 (25); 55 (67); 43 (36); 42 (34); 41 (100); 39 (86)
2b	3350 (OH); 3080 (CH ring)	0.2–0.7 (2m, 4H, ring CH_2); 0.8–1.1 (m, 3H, CH_3); 1.3–1.6 (m, 4H, CH_2CH_2), 1.6–1.8 (m, 1H, OH)[e]	12.6 (ring CH_2); 13.9 (CH_3); 18.9 (CH_2–CH_3); 42.0 (CH_2–COH); 54.2 (C–O)	100 (M^+, 19); 83 (16); 72 (57); 71 (77); 70 (21); 57 (99); 55 (100); 53 (26); 43 (87); 42 (19); 41 (40); 39 (30)
2c	3350 (OH); 3080 (CH ring)	0.3–0.6 (2m, 4H, cyclopropyl CH_2; 1.5–2.2 (m, 8H, OH, cyclobutyl CH_2 and CH)	10.3 (cyclopropyl CH_2); 17.4, 24.1; (cyclobutyl CH_2); 41.4 (CH); 56.0 (C–O)	112 (M^+, 0.4); 84 (70); 83 (100); 55 (50)
2d	3350 (OH); 3080 (CH ring)	0.4–0.7 (2m, 4H, ring CH_2); 0.8–1.1 (m, 3H, CH_3); 1.2–1.8 [m, 7H, OH and $(CH_2)_3$]	12.5 (ring CH_2; 15.0 (CH_3); 22.5, 27.9, 37.8 [$(CH_2)_3$]; 54.3 (C–O)	114 (M^+, 12); 85 (46); 72 (52); 70 (46); 57 (100); 55 (95); 43 (30); 41 (30)
2e	3380 (OH); 3080 (CH ring)	0.3–0.8 (2m, 4H, ring CH_2); 1.2 (t, 3H, J = 9 Hz, CH_3); 2.9 (s, 1H, OH); 3.4 (s, 2H, O–CH_2); 3.5 (q, 2H, J = 9 Hz, CH_2–CH_3)	11.2 (ring CH_2); 14.9 (CH_3); 53.9 (C–O); 66.4, 76.8 (2xCH_2–O)	115 (M^+ – 1); 88 (70); 73 (23); 72 (44); 71 (16); 70 (37); 60 (100); 59 (18); 57 (22); 55 (19); 43 (41); 42 (53); 41 (20); 31 (24)
2f	3340 (OH); 3080 (CH ring); 3060, 3020, 1600, 1490, 750, 690 (HC=C)	0.8–1.2 (2m, 4H, ring CH_2); 1.5 (s, 1H, OH); 6.8–7.2 (m, 5H_{arom})	17.4 (ring CH_2); 55.5 (C–O); 124.1, 125.5, 127.7, 144.4 (C_{arom})	134 (M^+, 24); 133 (100); 115 (16); 105 (65); 77 (51); 51 (17)
2g	3340 (OH); 3070 (CH ring)	0.3–0.6 (2m, 4H, ring CH_2); 0.6–0.8 (m, 1H, OH); 0.8–1.7 (2m, 11H, cyclohexyl CH_2 and CH)	11.7 (cyclopropyl CH_2); 26.5, 26.7, 28.9 (cyclohexyl CH_2); 34.3 (CH); 58.2 (C–O)	140 (M^+, 17); 111 (32); 83 (100); 57 (18); 55 (62); 41 (22); 39 (18)
2h	3420 (OH); 3070 (CH ring); 3010, 1600 1510 (HC=C)[d]	0.7–1.2 (2m, 4H, ring CH_2); 2.0–2.2 (m, 1H, OH); 3.6 (s, 3H, O–CH_3); 6.6–7.2 (m, 4H_{arom})	16.9 (ring CH_2); 54.6 (CH_3–O); 55.4 (C–O); 113.4, 125.8, 136.8, 149.8 (C_{arom})	164 (M^+, 13); 135 (100); 92 (13); 77 (14)

[a] Recorded on a Perkin-Elmer 298 infrared spectrometer.
[b] Recorded on a Varian FT-80A spectrometer.
[c] Recorded on a HP-5987A spectrometer.
[d] In CCl_4.
[e] In CCl_4 + $TMS_{capillary}$; Recorded on a Varian EM-390 spectrometer.

Thus, in the case of R = n-C_3H_7, when the reaction mixture was hydrolyzed before the lithiation step, the expected dichloromethyl carbinol **5b** was isolated.



5b

1-Substituted Cyclopropanols 2; General Procedure:
To a stirred solution of chloroiodomethane (3.88 g, 22 mmol), the carboxylic acid chloride (10 mmol) and lithium bromide (1.91 g, 22 mmol) in tetrahydrofuran (40 ml),[5] is added an ether solution of methyllithium (22 mmol) in 20 min, at –78 °C (bath temperature) under argon. Stirring is continued for 2 h at the same temperature and then lithium powder (0.62 g, 90 mmol) is added to the mixture and it is stirred for 7 h, allowing to rise the temperature till –30 °C. The mixture is then successively hydrolyzed with water (15 ml) and aqueous hydrochloric acid (10 ml), extracted with ether (3 × 15 ml), the organic layer dried with sodium sulfate, and evaporated (20 mbar). The residue is distilled *in vacuo* to afford the cyclopropanol **2** (Tables 1 and 2).

1-Chloro-2-(chloromethyl)-2-pentanol (5b):
To a stirred solution of chloroiodomethane (3.88 g, 22 mmol), *n*-butyryl chloride (**1b**; 1.06 g, 10 mmol), and lithium bromide (1.91 g, 22 mmol) in tetrahydrofuran (40 ml), is added an ether solution of methyllithium (22 mmol) in 20 min, at –78 °C (bath temperature) under argon. Stirring is continued for 2 h at the same temperature and then the mixture is successively hydrolyzed with water (15 ml) and aqueous hydrochloric acid (10 ml), extracted with ether (3 × 15 ml), the organic layer is dried with sodium sulfate, and evaporated (20 mbar). The residue is distilled *in vacuo*; yield 0.74 g (43%); b.p. 79–83 °C/20 mbar (Lit.,[3] b.p. 80–84 °C/20 mbar)

IR (Film): ν = 3400 cm^{-1} (OH).

^{1}H-NMR (CCl_4 + D_2O capillary): δ = 0.8–1.1 (deformed t, 3H, CH_3); 1.3–1.6 (m, 4H, $CH_3\underline{CH_2}\underline{CH_2}$); 3.1 (br s, 1H, OH); 3.5 ppm (s, 4H, 2 × CH_2Cl).

^{13}C-NMR (Neat + D_2O capillary): δ = 15.3, 17.1, 38.5 ($CH_3CH_2CH_2$); 49.4 (CH_2Cl); 74.1 ppm (C–O).

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(1) For a review, see: Gibson, D.H., De Puy, C.H. *Chem. Rev.* **1974**, *74*, 605.
(2) For reviews, see:
Weystiuk, N.H. *Tetrahedron* **1983**, *39*, 205.
Hoppe, D. *Angew. Chem.* **1984**, *96*, 930; *Angew. Chem. Int. Ed. Eng.* **1984**, *23*, 932.
Stowell, J.C. *Chem. Rev.* **1984**, *84*, 409.
(3) Barluenga, J., Flórez, J., Yus, M. *Synthesis* **1983**, 647.
(4) Matteson, D.S., Sadhu, K.M. *Tetrahedron Lett.* **1986**, 795.
(5) In the case of comounds **2a** and **2f** hexamethylphosphoric triamide (3.94 g, 22 mmol) was added to the reaction mixture.
(6) Brown, H.C., Rao, C.G., Ravindranathan, M. *J. Am. Chem. Soc.* **1977**, *99*, 7663.