An Expedient Synthesis of Cyclopropanone Cyanohydrins

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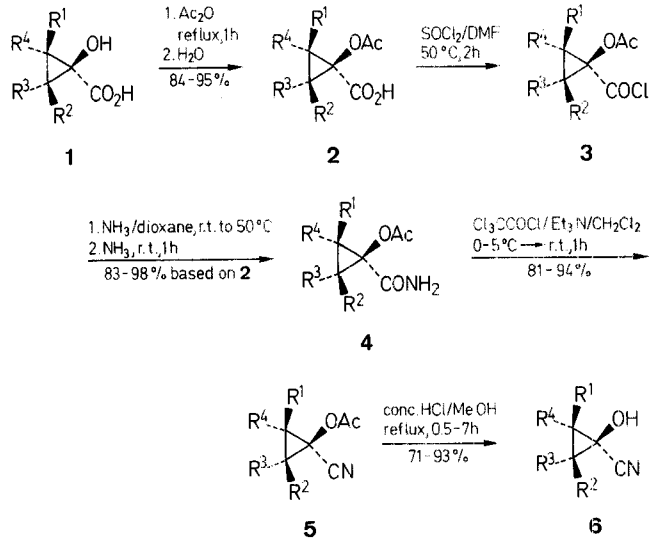
Dedicated to Professor Dr. H. Rudolph on the occasion of his 60th birthday.

A practical and general synthesis of cyclopropanone cyanohydrins starting from readily available 1-hydroxycyclopropanecarboxylic acids is described.

1-Hydroxycyclopropanecarbonitriles **6** represent an attractive class of geminal bifunctional cyclopropane derivatives. Reluctance to dissociate into strained cyclopropanones[1] and hydrocyanic acid imparts a remarkable stability to these cyanohydrins. Storable and easy to handle, compounds **6** can be used for various transformations, such as Tiffeneau–Demjanov ring expansions[2,3] or Strecker synthesis of the novel amino acid cleonine, i.e., (1-hydroxycyclopropyl)glycine.[4] Several methods of preparing **6** have emerged since the outset of intense work on cyclopropanone chemistry.[1] The parent compound **6a** has been obtained by addition of hydrocyanic acid to cyclopropanone,[5] from cyclopropanone precursors and alkali metal cyanides,[6,7] by cyclization of protected 3-chloro-2-hydroxybutanenitrile,[2]



1–6	R^1	R^2	R^3	R^4
a	H	H	H	H
b	CH_3	H	H	H
c	CH_3	H	H	CH_3
d	*t*-Bu	H	H	H
e	$(CH_2)_3$		H	H
f	$(CH_2)_4$		H	H
g	$CH_2CH=CHCH_2$		H	H

Table 1. 1-Acetoxycyclopropanecarboxylic Acids **2** Prepared

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)
2a	86	96.5–97[d] (Et_2O)	$C_6H_8O_4$ (144.1)	1.12–1.38 (m, 2H); 1.45–1.73 (m, 2H); 2.10 (s, 3H)
2b	84	84–86[d] (Et_2O)	$C_7H_{10}O_4$ (158.2)	0.87–0.92 (m, 1H); 1.15 (d, 3H); 1.67–1.73 (m, 1H); 1.83–1.88 (m, 1H); 2.13 (s, 3H)[e]
2c	93	66–67.5[d] (Et_2O/pentane)	$C_8H_{12}O_4$ (172.2)	0.99 (d, 1H, J = 6.3); 1.26 (s, 3H); 1.31 (s, 3H); 1.68 (d, 1H, J = 6.3); 2.10 (s, 3H)[e]
2d	90	120.5–121.5[d] (Et_2O)	$C_{10}H_{16}O_4$ (200.2)	1.08 (s, 9H); 1.30–1.93 (m, 2H); 2.15 (s, 3H)
2e	95	150–151.5[f] (toluene)	$C_9H_{12}O_4$ (184.2)	1.10–2.44 (m, 8H); 2.18 (s, 3H)
2f	87	159–159.5[f] (Et_2O)	$C_{10}H_{14}O_4$ (198.2)	1.10–2.10 (m, 10H); 2.23 (s, 3H)
2g	89	165–166[f] (toluene)	$C_{10}H_{12}O_4$ (196.2)	1.90–2.75 (m, 6H); 2.10 (s, 3H); 5.62 (br s, 2H)

[a] Uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.28, H ±0.23, N ±0.22.
[c] Recorded with a Bruker WP-80 spectrometer.
[d] Measured with a Reichert Thermovar apparatus.
[e] Obtained on a Bruker AC 250 spectrometer.
[f] Determined on a Büchi SMP 510 capillary apparatus.

and photolysis of diazomethane in the presence of 2-acetoxyacrylonitrile.[8] By analogy, cyanohydrins of substituted cyclopropanones are available from 2-acetoxy- or 2-trimethylsiloxyacrylonitrile and diazoalkanes, either by carbene addition or via 1,3-dipolar addition with subsequent elimination of nitrogen from the resulting pyrazolines.[8] Finally, fused-ring cyclopropanone cyanohydrins have been shown to form in the reaction of potassium cyanide with selected 2-methanesulfonyloxy- and 2-halocycloalkanones.[3] The aforementioned methods appear to suffer disadvantages, such as low yield, limited scope, difficulty in obtaining starting materials, or use of hazardous reagents. This manuscript describes a practical and more general synthesis of **6** proceeding from 1-hydroxycyclopropanecarboxylic acids **1**. These acids are readily available by benzilic acid-type rearrangement of 1,2-cyclobutanediones,[9-14] autoxidative ring contraction of 1,2-bis(trimethylsiloxy)cyclobutenes,[15] and hydrolysis of 1,5-dichloro-2,4-dioxabicyclo[3.2.0]heptan-3-ones.[16]

Conversion of carboxylic acids into the corresponding primary carboxamides and subsequent dehydration is one of the standard methods in nitrile synthesis. In the present case, the most direct approach to the required 1-hydroxycyclopropanecarboxamides[17] would involve ammonolysis of alkyl esters of **1**. However, several attempts to carry out this reaction were uniformly unsuccessful. Thus, treating methyl 1-hydroxycyclopropanecarboxylate[20] with concentrated aqueous ammonia under various conditions led either to the recovery of the starting material or the formation of products resulting from ring-opening. This indicated that a more reactive *N*-acylating derivative of **1**, that is to say an acid halide, was necessary. Transformation of hydroxy acids into their acid chlorides is known to generally proceed with concomitant attack at the hydroxy group leading to various products.[21-24] Protection of the hydroxy group, obviously indispensable,[25] was simply accomplished by acetylation. Treating **1** with excess acetic anhydride followed by aqueous work-up furnished the 1-acetoxycyclopropanecarboxylic acids **2** in 84 to 95% yield (Table 1). The subsequent reaction of the acids **2** with thionyl chloride in the presence of a catalytic amount of dimethylformamide gave the acid chlorides **3** almost quantitatively. Compounds **3** are sufficiently stable at room temperature, however, they variably tend to decompose[27] on attempted distillation. When the crude acid chlorides **3** were allowed to react with gaseous ammonia in anhydrous dioxane, 1-acetoxycyclopropanecarboxamides **4** were obtained in excellent yields (Table 2).

The preparation of nitriles by dehydration of primary carboxamides is well established and in particular a number of methods involving mild conditions have been developed.[28] It was found that the recently recommended system trichloroacetyl chloride/triethylamine[29] is a suitable agent for the efficient transformation of **4** into the 1-acetoxycyclopropanecarbonitriles **5** (Table 3).

Removal of the acetyl group as the final step was achieved by treating **5** in methanol solution with concentrated aqueous hydrochloric acid. Nitriles **5a–d** underwent deprotection to give **6a–d** almost quantitatively (Table 4). Hydrolysis of the fused-ring derivatives **5e–g**, however, proceeded less readily and in addition to **6e–g**, produced substantial quantities of the starting materials **1e–g** along with minor amounts of **2e–g**, **3e–g** as well as the corresponding hydroxy amides. The lower selectivity observed in these cases can most likely be attributed to steric shielding of the acetoxy group by the adjacent alicyclic ring, thereby retarding the deacetylation and permitting the hydrolysis of the cyano group to become competitive.

Hydroxy acids **1a, b, d, f,** and **g** were prepared according to Ref. 13. Acids **1c**[13] and **1e** were obtained by alkaline hydrolysis[30] of 1,5-dichloro-6,6-dimethyl-2,4-dioxabicyclo[3.2.0]heptan-3-one[31] and 2,6-dichloro-3,5-dioxatricyclo[5.3.0.$0^{2,6}$]decan-4-one,[32] respectively. Reagents were of commercial quality and were distilled prior to use. Solvents were dried according to standard procedures.

Table 2. 1-Acetoxycyclopropanecarboxamides **4** Prepared

Product	Yield (%)	mp (°C)[a] (EtOAc)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)
4a	92	113.5–114.5[d]	$C_6H_9NO_3$ (143.1)	0.88–1.13 (m, 2H); 1.20–1.53 (m, 2H); 2.08 (s, 3H)
4b	83	97–98[d]	$C_7H_{11}NO_3$ (157.2)	0.71–0.76 (m, 1H); 1.12 (d, 3H); 1.63–1.67 (m, 1H); 1.69–1.78 (m, 1H); 2.16 (s, 3H)[e]
4c	85	90–91[d]	$C_8H_{13}NO_3$ (171.2)	0.66 (d, 1H, J = 5.9); 1.13 (s, 3H); 1.21 (s, 3H); 1.58 (d, 1H, J = 5.9); 2.08 (s, 3H)[e]
4d	85	133–133.5[f]	$C_{10}H_{17}NO_3$ (199.2)	1.03 (s, 9H); 1.05–1.55 (m, 2H); 1.75–1.98 (m, 1H); 2.18 (s, 3H)
4e	88	178–179[d]	$C_9H_{13}NO_3$ (183.2)	1.02–2.35 (m, 8H); 2.20 (s, 3H)
4f	94	174–177[d]	$C_{10}H_{15}NO_3$ (197.2)	0.95–2.50 (m, 10H); 2.25 (s, 3H)
4g	98	215–216[d]	$C_{10}H_{13}NO_3$ (195.2)	1.75–2.40 (m, 6H); 2.06 (s, 3H); 5.60 (br s, 2H)

[a–f] See Table 1.

Table 3. 1-Acetoxycyclopropanecarbonitriles **5** Prepared

Product	Yield (%)	bp (°C)/mbar and/or mp (°C)[a] (solvent)	n_D^{20}	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)
5a	85	44/0.3 45/0.6[8] 24–25[d] (Et_2O)	1.4302	$C_6H_7NO_2$ (125.1)	1.25–1.40 (m, 2H); 1.45–1.58 (m, 2H); 2.15 (s, 3H)
5b	94	56–58/0.6	1.4348	$C_7H_9NO_2$ (139.2)	0.96–0.99 (m, 1H); 1.15 (d, 3H); 1.58–1.80 (m, 2H); 2.14 (s, 3H)[e]
5c	86	56–57/1.5	1.4430	$C_8H_{11}NO_2$ (153.2)	1.12 (d, 1H, J = 6.8); 1.15 (s, 3H); 1.33 (d, 1H, J = 6.8); 1.38 (s, 3H); 2.13 (s, 3H)[e]

Table 4. 1-Hydroxycyclopropanecarbonitriles **6** Prepared

Product	Reaction Time (h)	Yield (%)	bp (°C)/mbar and/or mp (°C)[a] (solvent)	Molecular Formula[b]	n_D^{20}	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J (Hz)
6a	0.5	93	55.5/0.5 48.0/0.4[2]	C_4H_5NO (83.1)	1.4363	1.28 (s, 4H)
6b	1.5	91	56–58/0.7	C_5H_7NO (97.1)	1.4446	0.80–0.85 (m, 1H); 1.21 (d, 3H); 1.37–1.52 (m, 2H)[e]
6c	2.5	93	64/1.0	C_6H_9NO (111.1)	1.4412	0.98 (d, 1H, J = 6.1); 1.12 (d, 1H, J = 6.1); 1.25 (s, 3H); 1.28 (s, 3H)[e]
6d	3.5	90	82–84/0.9 20–22[d] (pentane)	$C_8H_{13}NO$ (139.2)		1.08 (s, 9H); 1.18–1.45 (m, 3H)

[a–e] See Table 1.

1-Acetoxycyclopropanecarboxylic Acids 2; General Procedure:
A solution of the respective hydroxy acid **1** (0.5 mol) in Ac_2O (200 mL) is refluxed for 1 h. After cooling to 80°C H_2O (350 mL) is added. The mixture is evaporated under vacuum. The solid residue is dried at 20°C/0.5 mbar and recrystallized using the solvents given in Table 1.

1-Acetoxycyclopropanecarboxylic Acid Chlorides 3; General Procedure:
The respective acetoxy acid **2** (except **2c**) (0.4 mol), $SOCl_2$ (100 mL) and DMF (0.2 mL) are placed in a round-bottomed flask fitted with a stirrer and a reflux condenser. The mixture is stirred at 50°C for 2 h. Excess $SOCl_2$ is distilled off under vacuum. The residual yellow-brown oil is kept at 20°C/0.5 mbar for 2 h and used without purification.

1-Acetoxy-2,2-dimethylcyclopropanecarboxylic Acid Chloride (3c):
In order to avoid a considerable formation of the anhydride of acid **2c**, which is rather unreactive towards excess $SOCl_2$, the following slightly modified procedure is employed. To stirred $SOCl_2$ (250 mL) containing DMF (0.3 mL) in a suitable flask, a solution of **2c** (0.4 mol) in CH_2Cl_2 (350 mL) is added dropwise within 1 h. Stirring is maintained at 50°C for 2 h. Evaporation under vacuum yields a yellow oil which, treated as described above, is sufficiently pure for further transformation.

1-Acetoxycyclopropanecarboxamides 4; General Procedure:
A round-bottomed flask equipped with a reflux condenser, stirrer, dropping funnel, and a gas inlet tube is charged with dioxane (350 mL). The dioxane is saturated with gaseous NH_3 at r.t. within 0.5 h. A solution of the crude acid chloride **3** (from 0.4 mol of the acid **2**) in dioxane (250 mL) is added dropwise to the stirred solution at a rate so that the reaction temperature does not exceed 50°C. After cooling to r.t., a gentle stream of NH_3 is passed through the solution for 1 h. Following suction filtration the precipitate is extracted with hot dioxane (2 × 100 mL). The combined filtrates are evaporated under vacuum, and the solid residue is recrystallized from EtOAc.

1-Acetoxycyclopropanecarbonitriles 5; General Procedure:
To a stirred solution of the carboxamide **4** (0.35 mol) and NEt_3 (0.7 mol) in CH_2Cl_2 (300 mL) a solution of trichloroacetyl chloride (72.7 g, 0.4 mol) in CH_2Cl_2 (350 mL) is added dropwise at 0–5°C. Subsequently the mixture is stirred at r.t. for 1 h. The solution is washed with H_2O (3 × 300 mL), dried (Na_2SO_4), and concentrated at reduced pressure. Products **5** are isolated either by vacuum distillation (**5a–e**) or by recrystallization (**5f** and **5g**).

1-Hydroxycyclopropanecarbonitriles 6; General Procedure:
To a solution of the 1-acetoxycyclopropanecarbonitrile **5** (0.25 mol) in MeOH (70.0 mL) is added 35% HCl (6.0 mL). The mixture is refluxed for a period of time given in Table 4. Subsequently the solvent is removed at 25°C/50 mbar. The residue is taken up in Et_2O (100 mL). Insoluble material is separated by suction, and the filtrate is dried (Na_2SO_4). After evaporation the product is purified either by vacuum distillation (**6a–e**) or column chromatography (silica gel, toluene/EtOAc, 10:1) (**6f** and **6g**) and recrystallization.

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Errata:

Hartmann, W. *Synthesis* **1989**, 272. Tables 3 and 4 are incomplete. The corrected Tables below can be copied and pasted over the incomplete Tables appearing on pp. 273 and 274.

Table 3. 1-Acetoxycyclopropanecarbonitriles **5** Prepared

Product	Yield (%)	bp (°C)/mbar and/or mp (°C)[a] (solvent)	n_D^{20}	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)
5a	85	44/0.3; 45/0.6;[8] 24–25[d] (Et_2O)	1.4302	$C_6H_7NO_2$ (125.1)	1.25–1.40 (m, 2H); 1.45–1.58 (m, 2H); 2.15 (s, 3H)
5b	94	56–58/0.6	1.4348	$C_7H_9NO_2$ (139.2)	0.96–0.99 (m, 1H); 1.15 (d, 3H); 1.58–1.80 (m, 2H); 2.14 (s, 3H)[e]
5c	86	56–57/1.5	1.4430	$C_8H_{11}NO_2$ (153.2)	1.12 (d, 1H, J = 6.8); 1.15 (s, 3H); 1.33 (d, 1H, J = 6.8); 1.38 (s, 3H); 2.13 (s, 3H)[e]
5d	94	56–57/0.1; 39.5–40[d] (Et_2O)	1.4406	$C_{10}H_{15}NO_2$ (181.2)	1.05 (s, 9H); 1.18–1.78 (m, 3H); 2.13 (s, 3H)
5e	93	78–80/0.45; 58.5–60[f] (Et_2O)		$C_9H_{11}NO_2$ (165.2)	0.98–2.40 (m, 8H); 2.20 (s, 3H)
5f	81	42–43[f]		$C_{10}H_{13}NO_2$ (179.2)	1.00–2.50 (m, 10H); 2.20 (s, 3H)
5g	84	92.5–93[f]		$C_{10}H_{11}NO_2$ (177.2)	1.80–2.78 (m, 8H); 2.08 (s, 3H); 5.58 (br s, 2H)

[a–f] See Table 1.

Table 4. 1-Hydroxycyclopropanecarbonitriles **6** Prepared

Product	Reaction Time (h)	Yield (%)	bp (°C)/mbar and/or mp (°C)[a] (solvent)	Molecular Formula[b]	n_D^{20}	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)
6a	0.5	93	55.5/0.5; 48.0/0.4[2]	C_4H_5NO (83.1)	1.4363	1.28 (s, 4H)
6b	1.5	91	56–58/0.7	C_5H_7NO (97.1)	1.4446	0.80–0.85 (m, 1H); 1.21 (d, 3H); 1.37–1.52 (m, 2H)[e]
6c	2.5	93	64/1.0	C_6H_9NO (111.1)	1.4412	0.98 (d, 1H, J = 6.1); 1.12 (d, 1H, J = 6.1); 1.25 (s, 3H); 1.28 (s, 3H)[e]
6d	3.5	90	82–84/0.9; 20–22[d] (pentane)	$C_8H_{13}NO$ (139.2)		1.08 (s, 9H); 1.18–1.45 (m, 3H)
6e	5	82	86–88/0.25; 35.5–37[d] (Et_2O)	C_7H_9NO (123.2)		1.00–2.25 (m, 8H)
6f	7	75	49.5–50.5[f] (Et_2O/pentane)	$C_8H_{11}NO$ (137.2)		1.10–2.90 (m, 10H)
6g	7	71	61.0–61.5[f] (Et_2O)	C_8H_9NO (135.2)		1.50–2.98 (m, 6H); 5.63 (br s, 2H)

[a–f] See Table 1.