Nitration of the DBHA Cyclopropanecarboxylate Enolate – A New and Efficient Route to 1-Aminocyclopropane-1-carboxylic Acid**

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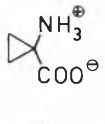
Abstract: 1-Aminocyclopropane-1-carboxylic acid (**1**) is synthesized from 2,6-di-*tert*-butyl-4-methoxy-phenyl cyclopropanecarboxylate (**4**) by an overall electrophilic amination. Key step is the nitration of the highly reactive enolate **5** generated by deprotonation of the ester **4** with *tert*-butyllithium.

1-Aminocyclopropane-1-carboxylic acid (ACPC, **1**) was first synthesized by *Ingold* et al.[1] in 1922, long before *Borroughs*[2] and *Vähätalo* and *Virtanen*[3] showed it to be a naturally occurring amino acid. ACPC was found to be an intermediate in the biosynthesis of ethylene, a natural plant growth hormone[4,5], from methionine. It also acts as the sole source of nitrogen for the bacterium *Pseudomonas* sp. ACP[6,7] as well as for the yeast *Hansenula saturnus*[6]. Introduction of ACPC into peptides[8] changes the N-C-CO angle relative to that of normal amino acid units in peptides. A search in the Cambridge Crystallographic Data File (version of 03.10.85) gave an angle $\alpha \approx 109°$ as mean value of 93 α-methylalanine derivatives (see **2a**) whereas for (−)-coronamic acid *N*-acetate (**2b**) a value of 116.31° is reported for β[9].



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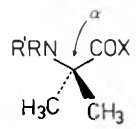

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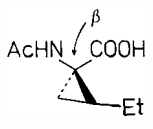
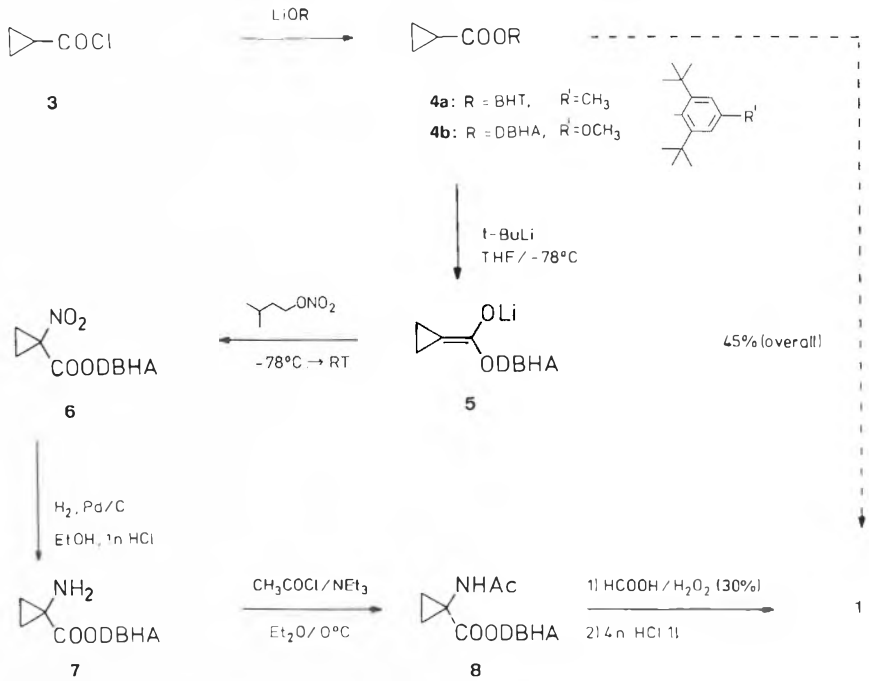


2b

Due to the importance of 1-aminocyclopropane-1-carboxylic acid, several groups have recently developed syntheses of it[1,10a–k]. While some methods involve carbene addition to an appropriate alkyl acrylate[10b,c,d,g,h], others use an ethylidation of a glycine derivative[10c,f] or a γ-elimination[7a,10e,i] for the formation of the three-membered ring. The amino acid **1** was also prepared from cyclopropane-1,1-dicarboxylic acid derivatives via Hofmann or Curtius degradation[1,10a,k]. Common to all of these routes is that they start from a geminally difunctionalized precursor.

We now report a totally different route to **1**: In our work with ketenes[11,12] generated in situ from ester enolates we found that esters such as **4** (prepared from cyclopropanecarbonyl chloride **3**) with sterically protected carbonyl groups could easily be deprotonated with *t*BuLi[13] in tetrahydrofuran (THF) at −78 °C[14]. Treatment of the enolate **5** from the «DBHA» ester **4b** with isoamyl nitrate gave DBHA 1-nitrocyclopropanecarboxylate **6** in 71% yield[15].

The α-nitro-acid was catalytically hydrogenated over Pd/C to the amino-acid derivative **7** (86%). Acetylation of **7** (→**8**) and oxidative removal[17] of the protecting group followed by hydrolysis with 4N hydrochloric acid gave **1** in 73%. In the approach to aminocyclopropane carboxylic acid (**1**) described here, the amino functional group is introduced by overall electrophilic amination. Thus, it should be applicable to many substituted cyclopropane carboxylic acids, and to the α-bromo derivatives **9** (from CBr_2 adducts) as well.



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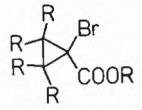

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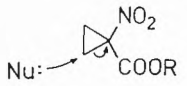

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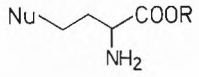

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Finally, the intermediates **10** are amenable to nucleophilic cyclopropane ring opening[18] (see **10**)[19], thus being equivalent to 2-aminobutanoic acid a⁴-synthons (see **11**).

Experimental Section

General remarks: Tetrahydrofuran (THF) was freshly distilled over potassium before use. Commercially available solutions of *n*-butyllithium (BuLi, *ca.* 1.6 M in hexane) and *tert*-butyllithium (*t*BuLi, *ca.* 1.6 M in pentane) were standardized by the diphenylacetic acid method[20]. For flash chromatography[21] silica gel 60 (Fluka AG, Buchs, particle size 0.040–0.063 mm, 230–400 mesh, ASTM), for ion exchange chromatography Dowex® 50W × 8 (strongly acidic cation exchange resin) were used. Hydrogenation was carried out by using a Niederdruck-Hydrierapparat (System Roche) of Adolf Kühner AG, Basel. – The elemental analyses of **4b**, **6**, **7**, and **8** were found to be correct within ± 0.2%.

2,6-Bis(1,1-dimethylethyl)-4-methoxyphenyl cyclopropanecarboxylate (DBHA cyclopropanecarboxylate **4b**): To an ice-cooled solution of 2,6-bis (1,1-dimethylethyl)-4-methoxyphenol (DBHA, 11.8 g, 50 mmol) in 100 mL of THF stirred under an argon atmosphere was added 50 mmol of BuLi. After 10 min cyclopropanecarbonyl chloride (**3**, 5.75 g, 55 mmol) was added and stirring was continued at room temperature for 24 h. The mixture was poured onto 20 mL of saturated aq. NH_4Cl. After separation of the two layers, the water phase was extracted once with 50 mL of ether. The organic phases were combined, washed twice each with sat. aq. $NaHCO_3$ and sat. aq. NaCl, and dried over Na_2SO_4. Evaporation of the solvent and bulb-to-bulb distillation gave 14.1 g (93%) of **4b** as a colorless liquid which turned slightly yellow upon storage, *b.p.* 125°C/0.05 Torr. – IR ($CHCl_3$): 3000, 2970s, 2920, 2880, 2840, 1750s, 1590s, 1485, 1450, 1425, 1400, 1385s, 1370, 1305, 1255, 1180s, 1150s, 1100s, 1065s, 1035, 1025, 945, 890, 870, 850 cm^{-1}. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.99–1.04 (m, 2 H, CH_2), 1.12–1.17 (m, 2 H, CH_2), 1.34 (s, 18 H, *t*Bu), 1.88–1.94 (m, 1 H, CH), 3.78 (s, 3 H, OCH_3), 6.84 (s, 2 H, ArH). – ^{13}C-NMR (25 MHz, $CDCl_3$): δ = 8.88(t), 14.04(d), 31.35(q), 35.62(s), 55.15(q), 111.48(d), 141.8(s), 143.48(s), 156.18(s), 175.14(s). – MS: *m/z* 304 (M^+, 9%), 236 (100).

[2,6-Bis(1,1-dimethylethyl)-4-methoxyphenyl] 1-nitro-1-cyclopropanecarboxylate (**6**): To a solution of DBHA-ester **4b** (4.56 g, 15 mmol) in 30 mL of THF stirred at –75°C was added dropwise under argon *t*BuLi (15 mmol). After 30 min a THF solution of isopentyl nitrate (2.20 g, 16.5 mmol) was added. The mixture was allowed to warm up to room temperature within 2 h and poured onto 20 mL of sat. aq. NH_4Cl. After separation of the two layers, the water phase was twice extracted with 20 mL of ether. The organic phases were combined, washed twice with sat. aq. NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (pentane:acetone = 95:5) to give 3.70 g (71%) of **6** as a colorless solid. Alternatively the crude product can be purified by recrystallization from ether/pentane to yield **6** in about 60%, *m.p.* (ether/pentane) 133.2–133.8°C. – IR ($CHCl_3$): 2980, 2920, 2880, 2840, 1760s, 1590, 1550s, 1485, 1465, 1450, 1420, 1400, 1370, 1340, 1325, 1305, 1170s, 1150s, 1100, 1065, 910, 890, 870 cm^{-1}. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 18 H, *t*Bu), 1.88–1.94 (m, 2 H, CH_2), 1.97–2.03 (m, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 6.85 (s, 2 H, ArH). – ^{13}C-NMR (25 MHz, $CDCl_3$): δ = 18.34(t), 31.24(q), 35.62(s), 55.19(q), 67.27(s), 111.67(d), 141.27(s), 143.51(s), 156.80(s), 166.76(s). MS: *m/z* 349 (M^+, 39%), 235 (100).

[2,6-Bis(1,1-dimethylethyl)-4-methoxyphenyl 1-amino-1-cyclopropanecarboxylate (**7**): To a solution of the nitro ester **6** (3.49 g, 10 mmol) in a mixture of 100 mL ethanol and 20 mL 1N HCl was added palladium on charcoal (5% w/w, 0.70 g). The mixture was stirred under a hydrogen atmosphere for 48 h, filtered through celite, and concentrated. The residue was dissolved in ether, washed twice each with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over Na_2SO_4, concentrated, and purified by flash chromatography (pentane: ether = 4:1 to 0:1) to give 2.73 g (86%) of **7** as colorless crystals, *m.p.* (pentane) 71.2–72.6°C. – IR ($CHCl_3$): 2970s, 2920, 2880, 2840, 1740s, 1595s, 1485, 1450, 1420, 1400, 1365, 1305s, 1270, 1255, 1180s, 1125s, 1065s, 1025, 890, 870, 850, 825 cm^{-1}. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.16–1.19 (m, 2 H, CH_2), 1.39 (s, 18 H, *t*Bu), 1.51–1.55 (m, 2 H, CH_2), 2.12 (s, br, 2 H, NH_2), 3.79 (s, 3 H, OCH_3), 6.85 (s, 2 H, ArH). – ^{13}C-NMR (25 MHz, $CDCl_3$): δ = 19.12(t), 31.39(q), 35.64(s), 37.01(s), 55.18(q), 111.64(d), 142.00(s), 143.28(s), 156.26(s), 176.40(s). – MS: *m/z* 319 (M^+, 4%), 236 (100).

1-Aminocyclopropane-1-carboxylic acid (ACPC, **1**): To an ice-cooled solution of the amino ester **7** (2.70 g, 8.5 mmol) and triethylamine (1.11 g, 10 mmol) in 50 mL of ether was added dropwise acetyl chloride (0.71 g, 9 mmol). The resulting slurry was stirred for 10 min, poured onto 20 mL of water and extracted 3 times with 30 mL each of ethyl acetate. The organic phases were combined and washed twice with sat. aq. NaCl, and dried over Na_2SO_4. Removal of the solvent gave 2.87 g (94%) of **8** as colorless crystals, *m.p.* (ethylacetate) 196.0–197.6°C. – ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.33 (s, 18 H, *t*Bu), 1.20–1.50 (m, 2 H, CH_2), 1.70–1.90 (m, 2 H, CH_2), 2.00 (s, 3 H, $NCOCH_3$), 3.80 (s, 3 H, OCH_3), 6.15 (s, br, 1 H, NH), 6.83 (s, 2 H, ArH). – The ester **8** (1.74 g, 4.82 mmol) was cleaved without further purification. It was dissolved in a mixture of 10 mL of formic acid and 3 mL of 30% aq. hydrogen peroxide, slowly warmed up to 60°C, and stirred for 30 min. After cooling to room temperature the solution was diluted with 20 mL of ether and extracted 3 times with 30 mL each of water. The water phase was concentrated to give 0.70 g of a solid residue which was dissolved in 9 mL 4N HCl. Refluxing for 4 h and concentrating gave 0.61 g of crude product which was passed through an ion exchange resin. Evaporation of the eluent gave 0.38 g (78%) of ACPC (**1**) which melted at 237–238°C with decomposition both before and after recrystallization from water/ethanol. ^{1}H-NMR (90 MHz, D_2O): δ = 1.15 (m, 2 H, CH_2), 1.30 (m, 2 H, CH_2).

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