Synthesis of γ-Amino Acids by Rearrangement of α-Cyanocyclopropanone Hydrates: Application to the Regioselective Labeling of Amino Acids

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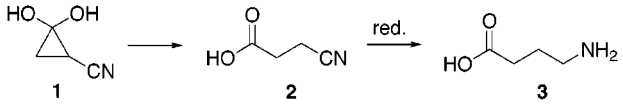
Introduction

γ-Aminobutyric acid (GABA) is one of the most ubiquitous inhibitory neurotransmitters. This compound and its derivatives have been the subject of extensive investigations because of their potential biological activity.[1] Several approaches are available for the synthesis of GABA and its analogues.[2] Herein, we report a novel route toward this class of compounds. Our strategy derives from a 1932 observation by Lipp et al., who reported the expeditious fragmentation of cyclopropanone hydrate into propanoic acid.[3] Also, we recently reported the synthesis of α- and β-amino acids by rearrangement of α-aminocyclopropanone hydrates.[4,5] In principle, an α-cyanocyclopropanone hydrate such as **1** should display the same reactivity and, hence, rearrange to the corresponding β-cyanoacid **2**. The latter, upon further reduction of the nitrile moiety, should afford 4-aminobutyric acid (**3**) (Scheme 1).

Results and Discussion

To corroborate this hypothesis, the preparation of five different potential precursors (**5a**−**e**) of γ-amino acids was undertaken (Scheme 2). Our syntheses started from the appropriate ketene acetal **4** that was cyclopropanized with diazoacetonitrile in the presence of $Rh_2(OAc)_4$.[6] This led to cyclopropylnitriles **5a**−**c,e** in satisfactory yields ranging from 55 to 78%.[5] Cyclopropane **5d** was prepared by LDA-induced metalation of **5a** followed by alkylation of the resulting anion with excess iodomethane. The choice of 1,2-benzenedimethyloxy acetal as hydrate protecting group was governed by its facile removal through catalytic reduction, thus providing swift access to the required cyclopropanone hydrate analogous to **1**.

Scheme 1



Scheme 2

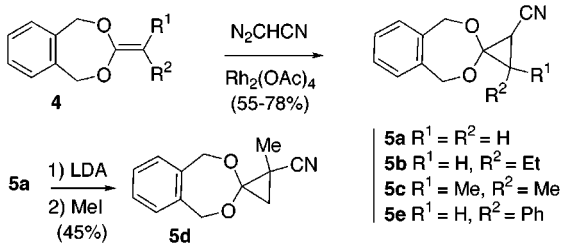
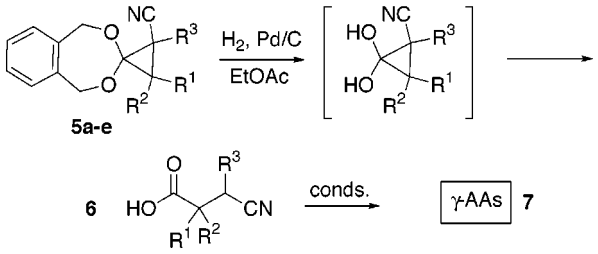


Table 1. Hydrogenolysis of Amino Acid Precursors



subst.	R^1	R^2	R^3	conds.	product	yield (%)
5a	H	H	H	—	**7a**	91
5b	H	Et	H	H_2, Pd/C AcOH, 72 hrs 1 Bar	**7b**	93
5c	Me	Me	H	H_2, PdO AcOH, 72 hrs 3 Bars	**7c**	91
5d	H	H	Me	H_2, PdO AcOH, 72 hrs 3 Bars	**7d**	95
5e	H	Ph	H	—	**7e**	96

Each of the five precursors was subjected, in the first step, to hydrogenolysis in EtOAc in the presence of Pd/C for 24 h, followed by hydrogenation of the cyano group under various conditions. The results are summarized in Table 1.

Except for substrate **5e**, the rearrangement was completely regioselective and afforded, after hydrogenation of the nitrile group of **6**, the expected γ-amino acid **7** as the only product and in nearly quantitative yield. For substrate **5a**, we were not able to observe the cyanoacid intermediate **6a** (the reduction of the nitrile occurred in

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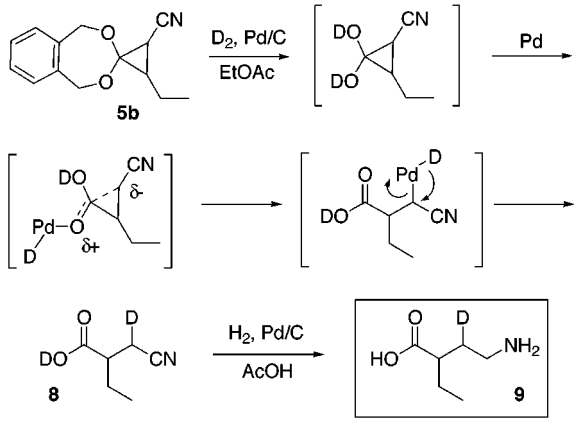
Scheme 3



situ within 24 h); for substrates **5b**−**d**, more drastic conditions (solvent, catalyst, and/or pressure) were necessary to reduce the nitrile to the corresponding amine. The two-step process, comprising ring opening and nitrile reduction, thus provides rapid, high-yielding access to γ-amino acid systems. The final example in Table 1 is the aryl-substituted substrate **5e**. Unfortunately, under the aforementioned conditions (H_2, Pd/C, EtOAc), **5e** spawned only the reduced cyclopropane **7e**.

As the rearrangement of the cyclopropane ring presumably occurs with internal proton transfer, the incorporation of a deuterium label on the hydrate moiety should afford selective β-labeling of the amino acid. The method was therefore applied to cyclopropane **5b**, which was treated with D_2 instead of H_2 in anhydrous EtOAc (Scheme 3). This afforded labeled **8** that was further reduced (Pd/C, AcOH) to give 3-[^{2}H]-4-amino-2-ethylbutyric acid (**9**) in 93% yield and 79% isotopic enrichment.

A postulated reaction mechanism involves palladium and its role in the key rearrangement step. Indeed, it has recently been reported that Pd/C catalyzes the ring opening of cyclopropanols.[7] On the basis of this report, we suggest that a palladium alkoxide is formed by oxidative addition of Pd(0) to the hydrate group. The hydrate oxygen atoms then act as electron donors, and the cyclopropane carbon atoms, as electron acceptors. The relative stability of the indicated partial negative charge directs the cyclopropane rearrangement. For example, the regioselectivity of the rearrangement is governed by the nitrile group that promotes stabilization of the partial negative charge at the α-carbon atom. Subsequent ring opening generates a σ-Pd complex[7] that undergoes exclusive reductive elimination. Indeed, **9** (derived from **8**) was labeled only on the β-carbon atom.

In conclusion, we have shown that the rearrangement of α-cyanocyclopropanone hydrates provides an easy route to γ-amino acids. The approach developed here permits the regioselective incorporation of isotopic labeling and is particularly well suited for the preparation of radioactively labeled amino acids using, for example, tritium gas.

Experimental Section

General Methods. ^{1}H NMR, ^{13}C NMR, and ^{2}H NMR spectra were recorded at 300, 75, and 46 MHz, respectively. Chemical shifts are reported in ppm from TMS (0 ppm). Flash column chromatography was performed on Merck silica gel (60 Å, 230−400 mesh). HRMS were recorded at the "Centre Régional de Mesures Physiques de l'Ouest". Reagents were purchased from Aldrich Chemical Co.

Synthesis of Cyclopropanecarbonitriles 5a−e. Cyclopropanecarbonitriles **5a**−**c,e** were prepared as previously described.[5] A procedure is given for the synthesis of cyclopropanecarbonitrile **5d**. At −10 °C (ice/salt bath) and under Ar, to a solution of cyclopropanecarbonitrile **5a** (0.098 g, 0.49 mmol, 1 equiv) in 10 mL of THF was added dropwise LDA (0.5 mL of a 2 M solution in THF/heptane/ethylbenzene, 2 equiv). The mixture was stirred 30 min at −10 °C, and iodomethane (0.3 mL, 10 equiv) was then added. The mixture was allowed to warm to room temperature. After 2 h, the reaction was quenched with 10% NH_4Cl and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude was purified on silica (hexane:EtOAc, 7:3) to afford cyclopropanecarbonitrile **5d** (white powder, 0.048 g, 45%). ^{1}H NMR ($CDCl_3$): δ 1.21 (d, J = 6.7 Hz, 1H), 1.51 (s, 3H), 1.75 (d, J = 6.7 Hz, 1H), 4.95 (s, 2H), 5.07 (m, 2H), 7.18−7.28 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 15.9, 17.4, 71.0, 71.1, 94.8, 120.8, 127.1, 127.2, 127.6, 127.8, 137.0, 137.5. MS (CI/NH_3): 216 (M + 1, 100). IR (KBr): 2239 cm^{-1} (CN). HRMS: calcd for $C_{13}H_{13}NO_2$ $(M)^+$, 215.0946; found, 215.0946.

Synthesis of γ-Amino Acids 7a−d and 9 and Hydrogenolysis of 5e. A typical experimental procedure is given for the synthesis of 4-aminobutyric acid (**7a**). To a solution of cyclopropanecarbonitrile **5a** (0.030 g, 0.15 mmol, 1 equiv) in 3 mL of EtOAc was added 10 wt % Pd on C (0.031 g, 20 mol %). The mixture was air evacuated and vigorously stirred under 1 bar of H_2 for 24 h. The catalyst was filtered out and rinsed with MeOH, and the solvents were removed under reduced pressure to afford GABA **7a**[8] as a white powder (0.014 g, 91%). ^{1}H NMR (D_2O): δ 1.84 (m, 2H), 2.23 (t, J = 7.3 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H). ^{13}C NMR (D_2O): δ 23.9, 34.7, 39.6, 181.8. MS (CI/NH_3): 104 (M + 1, 100).

4-Amino-2-ethylbutyric acid (7b).[9] **7b** was prepared as described for **7a** by starting from cyclopropanecarbonitrile **5b** (0.030 g, 0.13 mmol). After 24 h, the reaction was worked up as described above. The crude was taken into 2 mL of AcOH, and Pd/C (0.027 g, 20 mol %) was added. The mixture was air evacuated and vigorously stirred under 1 bar of H_2 for 72 h. The catalyst was filtered out and rinsed with MeOH, and the solvents were removed under reduced pressure to afford **7b** as a white powder (0.016 g, 93%). ^{1}H NMR (D_2O): δ 0.84 (t, J = 7.4 Hz, 3H), 1.49 (m, 2H), 1.77 (m, 2H), 2.21 (m, 1H), 2.93 (m, 2H). ^{13}C NMR (D_2O): δ 13.2, 27.5, 31.7, 40.1, 48.6, 184.5. MS (CI/NH_3): 132 (M + 1, 100).

4-Amino-2,2-dimethylbutyric acid (7c).[10] **7c** was prepared as decribed for **7b** by starting from cyclopropanecarbonitrile **5c** (0.025 g, 0.11 mmol). The nitrile reduction step was performed using a mixture of Pd/C (0.023 g, 20 mol %) and PdO (0.003 g, 20 mol %) under a pressure of 3 bar of H_2 for 72 h. **7c** was obtained as a white powder (0.013 g, 91%). ^{1}H NMR (D_2O): δ 1.14 (s, 6H), 1.82 (m, 2H), 2.98 (m, 2H). ^{13}C NMR (D_2O): δ 25.6, 37.0, 37.9, 42.4, 185.5. MS (CI/NH_3): 132 (M + 1, 100).

4-Amino-3-methylbutyric acid (7d).[11] **7d** was prepared as decribed for **7c** by starting from cyclopropanecarbonitrile **5d** (0.024 g, 0.11 mmol). **7d** was obtained as a white powder (0.012 g, 95%). ^{1}H NMR (D_2O): δ 1.02 (d, J = 5.3 Hz, 3 H), 2.21−2.42 (m, 3H), 2.87 (dd, J = 6.4 and 12.5 Hz, 1H), 3.01 (dd, J = 2.5 and 12.5 Hz, 1H).^{13}C NMR (D_2O): δ 17.0, 29.3, 41.1, 45.1, 179.4. MS (CI/NH_3): 118 (M + 1, 100).

(7-Benzyl-5,9-dihydro-6,8-dioxabenzocyclohepten-7-yl)-acetonitrile (7e). 7e was prepared as described for **7a** by starting from cyclopropanecarbonitrile **5e** (0.030 g, 0.11 mmol). **7e** was obtained as a thick oil (0.029 g, 96%). ^{1}H NMR ($CDCl_3$):

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δ 2.65 (s, 2H), 3.30 (s, 2H), 4.93 (d, J = 14.8 Hz, 2H), 5.11 (d, J = 14.8 Hz, 2H), 7.10−7.36 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 23.3, 39.4, 65.5, 103.1, 116.4, 126.2, 127.1, 127.3, 128.6, 130.2, 135.0, 136.8. MS (CI/NH_3): 297 (M + 18, 100). HRMS: calcd for $C_{18}H_{17}NO_2$ $(M)^+$, 279.1259; found, 279.1284.

3-[^{2}H]-4-Amino-2-ethylbutyric acid (9). A 10 mL flame-dried reaction vessel containing 10 wt % Pd on C (0.027 g, 20 mol %) was air evacuated. A pressure of 0.3 bar of deuterium gas was introduced at room temperature, and the catalyst was vigorously stirred for 30 min.[12] The gas was evacuated and replaced by a fresh aliquot of D_2. This operation was repeated 3 times. Cyclopropanecarbonitrile **5b** (0.030 g, 0.13 mmol, 1 equiv) in 2 mL of anhydrous EtOAc was then added. The solution was stirred at room temperature, under 1 bar of D_2, for 18 h. The catalyst was filtered and rinsed with MeOH, and the solvents were removed under reduced pressure. The crude material was taken into 2 mL of AcOH, and Pd/C (0.027 g, 20 mol %) was added. The mixture was air evacuated and stirred under 1 bar of H_2 for 72 h. The catalyst was filtered and rinsed with MeOH, and the solvents were removed under reduced pressure to afford **9** as a white powder (0.016 g, 93%). ^{1}H NMR (D_2O): δ 0.86 (t, J = 7.5 Hz, 3H), 1.46−1.56 (m, 2H), 1.77 (m, 1.2H), 2.28 (m, 1H), 2.93 (m, 2H). ^{13}C NMR (D_2O): δ 13.2, 27.4, 31.1 (t), 40.1, 48.5, 184.3. ^{2}H NMR (H_2O): δ 1.8. MS (CI/NH_3): 133 (M + 1, 100). HRMS: calcd for $C_6H_{12}DNO_2$ $(M)^+$, 132.1008; found, 132.1002.

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Supporting Information Available: Reproductions of ^{1}H and ^{13}C NMR spectra of compounds **5d**, **7a**−**e**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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