

Ultrasound-Assisted Reduction of Cyanides to Deuteriated Aliphatic Amines

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Summary

In the presence of ultrasound various mono-, di-, and α,β -unsaturated cyanides were reduced with Cu-Al alloy in NaOD-D₂O and THF to the corresponding deuteriated aliphatic amines, such as nonylamines, *Putrescine*, and 1,6-hexanediamine, in high deuterium content.

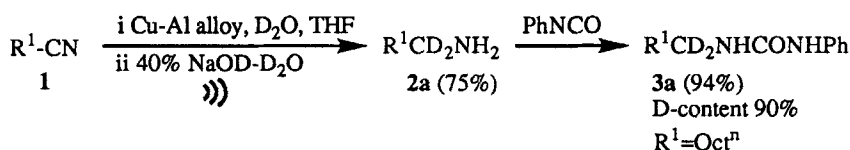
Key words: Deuteriation, Reduction, α,β -Unsaturated cyanides, Deuteriated amine
Raney copper-aluminium alloy, Ultrasound

Customarily, most amines have been prepared directly from nitrile compounds by converting the nitrile group into an aminomethyl group under either heterogeneous or homogeneous reaction conditions[1]. Deuterium labelled amines have played a significant role as tracers or internal references in the elucidation of biosynthetic pathways, e.g. amino acids, choline, and alkaloids have been used for investigating metabolic processes. It is also known that the activity of Na⁺-K⁺ATPase in a dog cerebrum is inhibited by long-chained alkyl amines[2]. It has been previously reported that deuteriated aliphatic carboxylic acids can be prepared utilizing the reducing system, Raney alloy and alkaline deuterium oxide[3]. We were therefore interested in the synthesis of deuteriated amines by the reduction of α,β -unsaturated nitriles. In the present study, we have deployed the above methodology towards the synthesis of the title compounds.

The effects of sonication on chemical reactions have been attracting great interest in organic synthesis. There are, however, relatively few examples concerning the benefit of sonication on the heterogeneous catalytic reduction, although a number of synthetically useful applications have been devised[4]. In the course of preliminary study using aqueous NaOH as base, we have found that the use of ultrasound provided a significant improvement; when the reduction of octyl cyanide (1) with copper-aluminium (Cu-Al) alloy in a mixture of an aqueous NaOH and tetrahydrofuran (THF) was

subjected to ultrasonic irradiation in addition to stirring, the reduction time could be reduced approximately two and half-fold compared to mere stirring and the expected nonylamine was obtained exclusively[5]. Therefore, we have adopted sonication as the technical aid in the following deuteration.

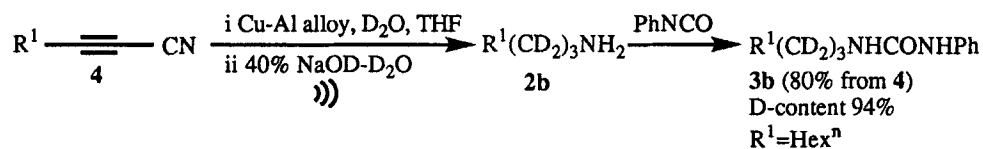
Under sonication a NaOD (40%) solution was added dropwise to a mixture of the cyanide (1) and Cu-Al alloy in D₂O and dry THF over a period of 1 h at ambient temperature with continuous stirring. At the end of the addition the alkaline concentration of the reaction mixture was approximately 5%. After removal of the inorganics and extraction with solvent, the desired [²H₂]nonylamine (2a) was isolated (90% deuterium content) (Scheme 1).



Scheme 1

The deuterium content of the deuteriated amines was determined on the basis of the ¹H n.m.r. spectroscopic analysis of the corresponding phenyl ureas. In our earlier study on the deuteration of phenylacetonitrile, hydrogen-deuterium (H-D) exchange occurred concurrently at the benzylic position during the reduction[6]. However, H-D exchange on the C-2 position in the cyanide (1) did not occur; on treatment of 1 with NaOD (20%) at 80 °C during 20 h only 9% of deuterium atoms were incorporated into the C-2 position.

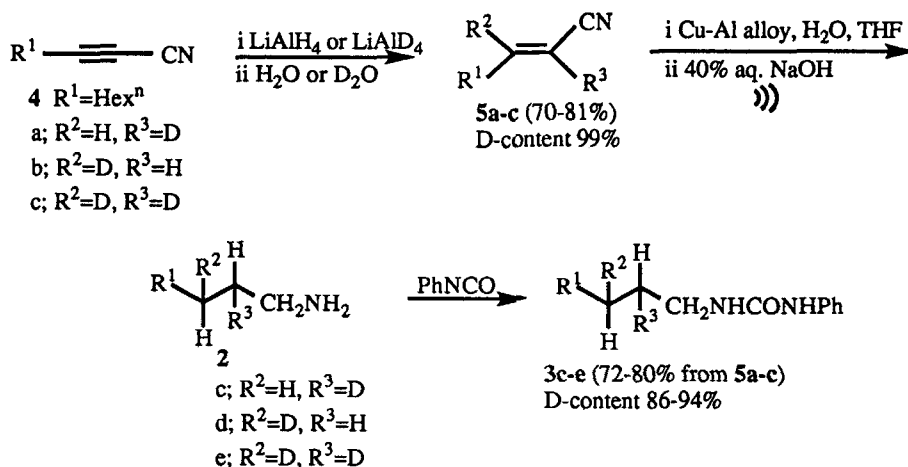
The successful transformation of saturated cyanide to the amines prompted us to further explore the synthesis of deuteriated amines from other cyanides. In the reduction of 1-octynecyanide (4) the triple bond was fully hydrogenated with the concomitant reduction of the nitrile group; the cyanide (4) was transformed into the [²H₆]nonylamine (2b) in one-step (Scheme 2).



Scheme 2

In the reduction of the cyanide (4) with a smaller quantity of Cu-Al alloy in an aqueous NaOH, a trace amount of 2-noninamine (CH₃(CH₂)₅C≡CCH₂NH₂) was obtained as a by-product. This demonstrates that the reduction of the nitrile group precedes that of the triple bond, and the adsorption of the nitrile group on the catalyst surface (anchor effect) might be a significant factor.

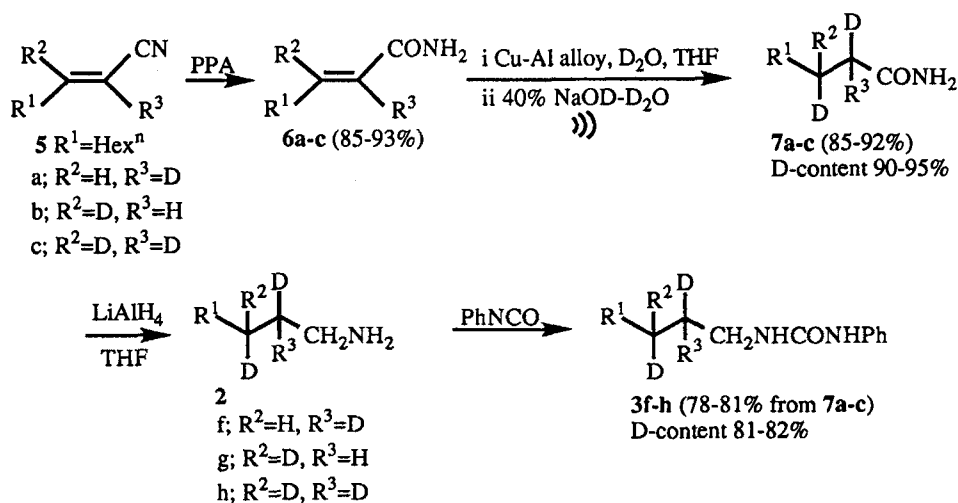
More remarkable is the two-step conversion of 1-octynecyanide (4) to yield the nonylamines (2c-e) labelled on the C-2 and/or C-3 position(s) by the combination of LiAlH₄ or LiAlD₄ and the following Cu-Al alloy reduction via the bis-alkenyl lithium-aluminium complexes[7] (Scheme 3). The cyanides (5a-c) were reduced with Cu-Al alloy in aqueous NaOH to the nonylamines (2c-e) with high deuterium content. However, it should be noted that attempts at converting 5a-c with Cu-Al alloy in NaOD-D₂O to the corresponding deuteriated amines (2) were unsuccessful; all the amines



Scheme 3

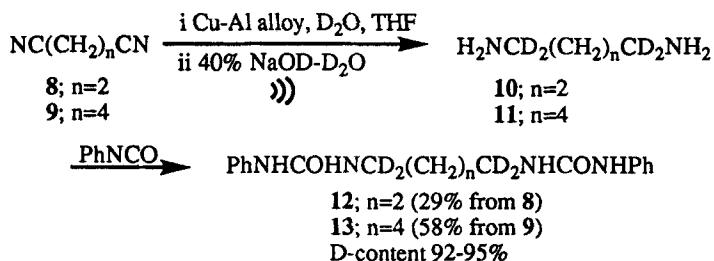
(2) were formed as a mixture of deuterio isotopomers due to the H-D exchange reaction. Although the detailed reason as for the above result is not clear at the present stage, it is suggested that the 1,5-hydrogen migration in the cyanides (5a-c) might partially occur to produce the corresponding ketene-imine forms, which are much more rapidly reduced than 5a-c.

Taking account of the curious reduction process mentioned above, our experiments were conducted with the corresponding amides (6a-c), since it is expected that these do not involve a hydrogen shift, as described earlier, during the reduction. Indeed, the reduction of 6a-c with Cu-Al alloy in NaOD-D₂O provided the saturated nonanamides (7a-c), followed by reduction with LiAlH₄ in THF, to be converted into the nonylamines (2f-h) (Scheme 4).



Scheme 4

Furthermore, this reducing system was effective for reducing the aliphatic dinitriles, such as 1,2-dicyanoethane (**8**) and 1,4-dicyanobutane (**9**), to 1,4-[²H₄]diaminobutane (*Putrescine*) (**10**) and 1,6-[²H₄]diaminohexane (**11**), respectively, although in both cases the yields were low (Scheme 5).



Scheme 5

In conclusion, the sequence described above represents efficient and systematic routes towards the synthesis of deuteriated nonylamines from α,β -unsaturated nitriles and amides in the presence of sonic waves. Additionally, this reducing system has been applied to the reduction of aliphatic terminal dicyanides. Secondary amines, occasionally formed in the catalytic hydrogenation, were not generated. Further study concerning the extension of this system to aromatic cyanides is currently in progress.

Experimental

General. —All of the melting points were determined in a Yanagimoto micro-apparatus and are uncorrected. M.s. spectra were recorded on a Nippon Denshi JMS-OISG-2 mass spectrometer at 75 eV by using a direct inlet system. ¹H and ¹³C{¹H} n.m.r. spectra were measured on a JEOL GSX-270 n.m.r. spectrometer at 270 MHz and at 67.94 MHz in CDCl₃ or DMSO-d₆ with Me₄Si as an internal reference, and chemical shifts are in ppm relative to Me₄Si. I.r. spectra were recorded on a Jasco IR-700 infrared spectrometer on KBr pellets or NaCl films. Elemental analyses were performed with a YANAKO MT-5 CHN-corder. Column chromatography was carried out on silica gel (Wako gel, C-300). All ultrasonic reductions were carried out using a Model B2200 ultrasonic laboratory cleaner (40 kHz, 100 W, BRANSON, Inc.).

Materials. —D₂O (99.9 atom %D) was purchased from Frosst Canada Inc., Division of Merk, and 40% NaOD-D₂O (99.5 atom %D) from Merk & Co. Inc. LiAlD₄ (99 atom %D) was provided from ISOTEC Inc. Cu-Al alloy (50:50 wt%) was available from Kishida Chemical Co., Ltd. Perprolio forms of the phenylureas (**3a-h**), (**12**), and (**13**) are new compounds. These structural assignments were based upon ¹H and ¹³C{¹H} n.m.r., i.r., and mass spectral data as well as elemental analyses.

[1,1-²H₂]Nonylamine (2a**).** —In a glove box under a nitrogen stream, octylcyanide (**1**) (1.10 g, 7.9 mmol), Cu-Al alloy (1.88 g), dry THF (2.3 ml), and D₂O (18.0 ml) were placed in a 100 ml round-bottom 3-necked flask. The reaction vessel was then removed from the box and the flask was partially submerged in the sonicator in a place that produced the greatest agitation of the contents. Under sonication to this stirred mixture was added dropwise NaOD-D₂O (40%; 2.6 ml) with mechanical stirring over a period of 1 h and the mixture was stirred for a further 1 h. The insoluble

materials were filtered off using celite and washed with CH_2Cl_2 . The filtrate was extracted with ether. The CH_2Cl_2 washing and the extracts were combined and dried (MgSO_4). The solvents were removed in vacuo to afford **2a** (860 mg, 75%) as a colourless liquid, b.p. $100^\circ\text{C} / 6$ Torr (lit.,[8] 195°C as for $^2\text{H}_0$ form). Then, to the stirred **2a** (350 mg, 2.4 mmol) was added dropwise phenyl isocyanate (280 mg, 2.4 mmol) at ambient temperature. The crystalline precipitate was dissolved in hot benzene and the insoluble material removed by filtration. The filtrate was concentrated in vacuo to afford 1-[1,1- $^2\text{H}_2$]nonyl-3-phenylurea (**3a**) (600 mg, 94%) as colourless prisms (benzene): m.p. $77-78^\circ\text{C}$ ($77-78.5^\circ\text{C}$ as for $^2\text{H}_0$ form); ν (KBr) 3334, 2954, 2924, 2850, 2188, 2108, 1628, 1597, 1562, 1498, 1469, 1444, 1396, 1317, 1298, 1250, 1157, 730, and 694 cm^{-1} ; δ (CDCl_3) 0.87 (3H, t, J 7.0 Hz), 1.23 (12H, brs), 1.41 (2H, m), 5.57 (1H, brs), 6.97-7.29 (5H, m), and 7.41 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.7, 27.0, 29.3, 29.4, 29.6, 30.0, 31.9, 39.6 (quint, J 21.0 Hz), 120.3, 123.0, 129.0, 139.1, and 156.7.

[1,1,2,2,3,3- $^2\text{H}_6$]Nonylamine (**2b**). —To a mixture of 1-octynecyanide (**4**) (540 mg, 4.0 mmol), Cu-Al alloy (2.5 g), dry THF (0.6 ml), and D_2O (9.5 ml), placed in a 50 ml round-bottom 3-necked flask, was added NaOD- D_2O (40%; 1.4 ml) as described above to afford **2b** (530 mg) as a colourless liquid. Then, **2b** (530 mg, 4.0 mmol) was treated with phenyl isocyanate (480 mg, 4.0 mmol) to afford 1-[1,1,2,2,3,3- $^2\text{H}_6$]nonyl-3-phenylurea (**3b**) (860 mg, 80% from **4**) as colourless prisms (benzene): m.p. $75-78^\circ\text{C}$ ($77-78.5^\circ\text{C}$ as for $^2\text{H}_0$ form); ν (KBr) 3330, 2952, 2922, 2848, 2202, 2094, 1630, 1597, 1562, 1498, 1467, 1443, 1375, 1315, 1298, 1254, 1234, 1222, 728, and 693 cm^{-1} ; δ (CDCl_3) 0.87 (3H, t, J 7.0 Hz), 1.22 (10H, brs), 5.38 (1H, brs), 6.97-7.36 (5H, m), and 7.95 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.7, 25.9, (quint, J 19.0 Hz), 29.1, 29.3, 29.5, 31.9, 39.6 (quint, J 22.0 Hz), 120.7, 123.4, 129.1, 138.8, and 156.5.

Preparation of deuteriated 2-nonenecyanides (5a-c). Typical procedure. —Under a nitrogen stream, to a stirred mixture of LiAlH_4 (470 mg) and dry THF (22.0 ml) was added dropwise 1-octynecyanide (**4**) (3.0 g, 22.2 mmol) at -60°C and the content stirred at 0°C for 1 h. To the mixture was then added D_2O and aqueous HCl (3N), and the whole mixture was extracted with CH_2Cl_2 . The extracts were dried (MgSO_4) and removal of the solvents in vacuo yielded 2-[2- $^2\text{H}_1$]nonenecyanide (**5a**) (2.2 g, 72%) as a colourless liquid: b.p. $58^\circ\text{C} / 1.8$ Torr (lit.,[9] $68-70^\circ\text{C} / 2$ Torr as for $^2\text{H}_0$ form); ν (NaCl) 2956, 2930, 2856, 2220, 1620, 1465, 1379, 965, and 725 cm^{-1} ; δ (CDCl_3) 0.89 (3H, t, J 7.0 Hz), 1.21-1.36 (6H, m), 1.44 (2H, m), 2.22 (2H, t, J 7.0 Hz), and 6.72 (1H, m); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.0, 22.5, 27.6, 28.6, 31.5, 33.3, 99.4 (t, J 26.0 Hz), 117.6, and 156.2.

2-[3- $^2\text{H}_1$]Nonenecyanide (**5b**): Y. 70%; b.p. $60^\circ\text{C} / 2.0$ Torr (lit.,[9] $68-70^\circ\text{C} / 2$ Torr as for $^2\text{H}_0$ form); ν (NaCl) 2956, 2930, 2856, 2222, 1617, 1465, 1379, 965, and 724 cm^{-1} ; δ (CDCl_3) 0.89 (3H, t, J 7.0 Hz), 1.21-1.36 (6H, m), 1.44 (2H, m), 2.22 (2H, t, J 7.0 Hz), and 5.32 (1H, m); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.0, 22.5, 27.6, 28.7, 31.5, 33.2, 99.5, 117.6, and 155.9 (t, J 24.0 Hz).

2-[2,3- $^2\text{H}_2$]Nonenecyanide (**5c**): Y. 81%; b.p. $60^\circ\text{C} / 1.8$ Torr (lit.,[9] $68-70^\circ\text{C} / 2$ Torr as for $^2\text{H}_0$ form); ν (NaCl) 2956, 2930, 2856, 2260, 2220, 1602, 1466, 1379, 723, and 689 cm^{-1} ; δ (CDCl_3) 0.89 (3H, t, J 7.0 Hz), 1.25-1.36 (6H, m), 1.44 (2H, m), and 2.22 (2H, t, J 7.0 Hz); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.0, 22.5, 27.6, 28.7, 31.5, 33.2, 99.3 (t, J 26.0 Hz), 117.6, and 155.8 (t, J 24.0 Hz).

Reduction of deuteriated 2-nonenecyanides (5a-c). Typical procedure. —2-[2-²H₁]Nonenecyanide (5a) (350 mg, 2.6 mmol), Cu-Al alloy (1.56 g), THF (0.4 ml), and H₂O (5.8 ml) were placed in a 30 ml round-bottom 3-necked flask. Under sonication to this mixture was added dropwise aqueous NaOH (40%; 0.8 ml) with mechanical stirring over a period of 1 h and the whole mixture was stirred for an additional 1 h. The reaction mixture was treated in a similar manner with 1 to afford 1-[2-²H₁]nonylamine (2c) and the corresponding phenylurea (3c).

1-[2-²H₁]Nonyl-3-phenylurea (3c): Y. 72% (from 5a); colourless prisms (benzene); m.p. 78–80 °C (77–78.5 °C as for ²H₀ form); ν (KBr) 3324, 2954, 2918, 2850, 2142, 1639, 1600, 1570, 1499, 1480, 1465, 1442, 1313, 1297, 1240, 730, and 694 cm⁻¹; δ (CDCl₃) 0.84 (3H, t, *J* 7.0 Hz), 1.22 (12H, brs), 1.39 (1H, m), 3.13 (2H, d, *J* 7.0 Hz), 5.55 (1H, brs), 6.96–7.31 (5H, m), and 7.35 (1H, brs); ¹³C{¹H} δ (CDCl₃) 14.1, 22.7, 26.8, 29.3, 29.5, 29.8 (t, *J* 20.0 Hz), 31.9, 40.3, 120.6, 123.3, 129.1, 138.9, and 156.7.

1-[3-²H₁]Nonyl-3-phenylurea (3d): Y. 78% (from 5b); colourless prisms (benzene); m.p. 77–79 °C (77–78.5 °C as for ²H₀ form); ν (KBr) 3332, 2952, 2922, 2850, 2138, 1629, 1600, 1567, 1498, 1469, 1444, 1315, 1298, 1235, 733, and 694 cm⁻¹; δ (CDCl₃) 0.87 (3H, t, *J* 7.0 Hz), 1.21 (11H, brs), 1.38 (2H, m), 3.14 (2H, t, *J* 7.0 Hz), 5.59 (1H, brs), 6.96–7.31 (5H, m), and 7.40 (1H, brs); ¹³C{¹H} δ (CDCl₃) 14.1, 22.7, 26.5 (t, *J* 20.0 Hz), 29.3, 29.5, 30.1, 31.9, 40.3, 120.5, 123.2, 129.1, 138.9, and 156.7.

1-[2,3-²H₁]Nonyl-3-phenylurea (3e): Y. 80% (from 5c); colourless prisms (benzene); m.p. 78–80 °C (77–78.5 °C as for ²H₀ form); ν (KBr) 3330, 2954, 2922, 2850, 2138, 1632, 1597, 1564, 1499, 1467, 1444, 1317, 1297, 1240, 732, and 694 cm⁻¹; δ (CDCl₃) 0.87 (3H, t, *J* 7.0 Hz), 1.22 (11H, brs), 1.39 (1H, brs), 3.15 (2H, d, *J* 7.0 Hz), 5.52 (1H, brs), 6.99–7.28 (5H, m), and 7.32 (1H, brs); ¹³C{¹H} δ (CDCl₃) 14.1, 22.7, 26.4 (t, *J* 19.0 Hz), 29.3, 29.5, 29.7 (t, *J* 20.0 Hz), 31.9, 40.2, 120.5, 123.1, 129.1, 138.9, and 156.6.

Preparation of deuteriated 2-nonenamides (6a-c). Typical procedure. —In a 100 ml round-bottom 3-necked flask were placed deuteriated 2-[2-²H₁]nonenenitrile (5a) (1.50 g, 10.9 mmol) and polyphosphoric acid (PPA) (18.0 g), and the mixture heated with stirring at 110 °C for 1.5 h. After cooling to room temperature, to the reaction mixture was added H₂O under ice-cooling and the crystalline precipitate, which was collected by filtration, was washed with aqueous NaHCO₃ (5%) and H₂O to afford 2-[2-²H₁]noneneamide (6a) (1.48 g, 87%) as colourless needles (EtOH); m.p. 130.5–133 °C (lit.,[10] 131.4–131.7 °C as for ²H₀ form); ν (KBr) 3334, 3154, 2956, 2924, 2854, 2296, 1670, 1626, 1465, 1396, 1147, 1064, 923, 725, and 670 cm⁻¹; δ (CDCl₃) 0.88 (3H, t, *J* 7.0 Hz), 1.28–1.47 (8H, m), 2.19 (2H, q, *J* 8.0 Hz), 5.74 (1H, brs), 6.16 (1H, brs), and 6.84 (1H, t, *J* 7.0 Hz); ¹³C{¹H} δ (CDCl₃) 14.1, 22.6, 28.2, 28.9, 31.6, 32.1, 122.5 (t, *J* 23.0 Hz), 146.3, and 168.5.

2-[3-²H₁]Noneneamide (6b): Y. 93%; colourless needles (EtOH); m.p. 128–131 °C (lit.,[10] 131.4–131.7 °C as for ²H₀ form); ν (KBr) 3324, 3154, 2956, 2926, 2854, 2236, 1671, 1617, 1465, 1406, 1149, 894, 725, and 657 cm⁻¹; δ (CDCl₃) 0.88 (3H, t, *J* 7.0 Hz), 1.28–1.47 (8H, m), 2.18 (2H, t, *J* 8.0 Hz), 5.70 (1H, brs), 5.83 (1H, s), and 6.12 (1H, brs); ¹³C{¹H} δ (CDCl₃) 14.1, 22.6, 28.1, 28.9, 31.6, 32.0, 122.7, 146.2 (t, *J* 23.0 Hz), and 168.5.

2-[2,3-²H₂]Noneneamide (6c): Y. 85%; colourless prisms (EtOH); m.p. 127–130 °C (lit.,[10] 131.4–131.7 °C as for ²H₀ form); ν (KBr) 3324, 3154, 2956, 2926, 2854, 2234, 1671, 1617, 1465,

1394, 1149, 1092, 844, 722, and 669 cm^{-1} ; δ (CDCl_3) 0.88 (3H, t, J 7.0 Hz), 1.28-1.47 (8H, m), 2.18 (2H, t, J 8.0 Hz), 5.76 (1H, brs), and 6.19 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.6, 28.1, 28.9, 31.6, 31.9, 122.4 (t, J 23.0 Hz), 146.0 (t, J 23.0 Hz), and 168.6.

Reduction of deuteriated 2-noneneamides (6a-c). Typical procedure. —In a glove box under a nitrogen stream [2- $^2\text{H}_1$]noneneamide (6a) (500 mg, 3.2 mmol), Cu-Al alloy (1.00 g), THF (4.0 ml), and H_2O (18.0 ml) were placed in a 50 ml round-bottom 3-necked flask. The reaction vessel was then removed from the box, and under sonication to this mixture was added dropwise aqueous NaOH (40%; 2.5 ml) with mechanical stirring over a period of 1 h, and the whole mixture was stirred for an additional 1 h. The reaction mixture was treated in a similar manner to the case of **1** to afford [2,2,3- $^2\text{H}_3$]nonaneamide (7a) (472 mg, 92%) as colourless prisms (EtOH); m.p. 97-99 °C (lit.,[8] 99 °C as for $^2\text{H}_0$ form); ν (KBr) 3358, 3328, 3245, 3184, 2954, 2922, 2852, 2522, 2464, 2396, 1638, 1526, 1469, and 1404 cm^{-1} ; δ (CDCl_3) 0.88 (3H, t, J 7.0 Hz), 1.27-1.30 (10H, m), 1.60 (1H, brs), 5.62 (1H, brs), and 5.89 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.6, 25.1 (t, J 20.0 Hz), 29.1, 29.2, 29.3, 31.8, 35.3 (quint, J 21.0 Hz), and 176.1.

[2,3,3- $^2\text{H}_3$]Nonaneamide (7b): Y. 85%; colourless prisms (EtOH); m.p. 98-100.5 °C (lit.,[8] 99 °C as for $^2\text{H}_0$ form); ν (KBr) 3362, 3326, 3246, 3182, 2956, 2920, 2852, 2522, 2464, 2396, 2194, 2108, 1636, 1527, 1469, 1413, and 1258 cm^{-1} ; δ (CDCl_3) 0.88 (3H, t, J 7.0 Hz), 1.27-1.30 (10H, m), 2.18 (1H, s), 5.63 (1H, brs), and 6.04 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.7, 24.8 (quint, J 20.0 Hz), 29.0, 29.2, 29.3, 31.8, 35.5 (t, J 21.0 Hz), and 176.2.

[2,2,3,3- $^2\text{H}_4$]Nonaneamide (7c): Y. 90%; colourless prisms (EtOH); m.p. 97-100 °C (lit.,[8] 99 °C as for $^2\text{H}_0$ form); ν (KBr) 3358, 3328, 3245, 3184, 2954, 2920, 2852, 2522, 2462, 2398, 2200, 2094, 1637, 1524, 1469, 1404, and 1345 cm^{-1} ; δ (CDCl_3) 0.88 (3H, t, J 7.0 Hz), 1.28-1.30 (10H, m), 5.63 (1H, brs), and 6.01 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.6, 25.0 (quint, J 21.0 Hz), 29.0, 29.2, 29.3, 31.8, 35.2 (quint, J 20.0 Hz), and 176.2.

LiAlH_4 reduction of deuteriated nonaneamides (7a-c). Typical procedure. —Under a nitrogen stream, LiAlH_4 (30 mg) and dry THF (4.0 ml) were placed in a 30 ml round-bottom 3-necked flask. To this stirred mixture was added dropwise a THF solution (2.0 ml) of [2,2,3- $^2\text{H}_3$]nonaneamide (7a) (150 mg, 0.95 mmol) and the mixture was refluxed for 2 h. After cooling to room temperature, to the reaction mixture was added H_2O and then 10% aqueous KOH under ice-cooling. The precipitate which formed was filtered off and the filtrate extracted with CH_2Cl_2 . The extracts were dried (MgSO_4) and removal of the solvents afforded [2,2,3- $^2\text{H}_3$]nonylamine (2f). Then, 2f was treated with phenylisocyanate in a similar manner to the case of **1** to afford 1-[2,2,3- $^2\text{H}_3$]nonyl-3-phenylurea (3f) (113 mg, 81% from 7a) as colourless prisms (benzene); m.p. 77.5-79.5 °C (77-78.5 °C as for $^2\text{H}_0$ form); ν (KBr) 3330, 2954, 2922, 2850, 2186, 2134, 2098, 1636, 1597, 1563, 1498, 1468, 1443, 1314, 1297, 1240, 907, 730, and 694 cm^{-1} ; δ (CDCl_3) 0.87 (3H, t, J 7.0 Hz), 1.22 (11H, brs), 3.14 (2H, s), 5.63 (1H, brs), 6.97-7.29 (5H, m), and 7.41 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.7, 26.3 (t, J 19.0 Hz), 29.2, 29.3, 29.5, 31.9, 40.2, 120.4, 123.1, 129.0, 139.0, and 156.7.

1-[2,3,3- $^2\text{H}_3$]Nonyl-3-phenylurea (3g): Y. 78% (from 7b); colourless prisms (benzene); m.p. 76-78 °C (77-78.5 °C as for $^2\text{H}_0$ form); ν (KBr) 3328, 2954, 2920, 2850, 2174, 2100, 1632, 1597, 1563, 1498, 1467, 1443, 1316, 1298, 1235, 730, and 693 cm^{-1} ; δ (CDCl_3) 0.87 (3H, t, J 7.0

Hz), 1.20 (10H, brs), 1.36 (1H, t, J 7.0 Hz), 3.12 (2H, d, J 7.0 Hz), 5.68 (1H, brs), 6.96-7.30 (5H, m), and 7.51 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.7, 26.0 (quint, J 19.0 Hz), 29.2, 29.3, 29.5, 29.9 (t, J 19.0 Hz), 31.9, 40.2, 120.4, 123.1, 129.0, 138.9, and 156.8.

1-[2,2,3,3- $^2\text{H}_4$]Nonyl-3-phenylurea (3h): Y. 80% (from **7c**); colourless prisms (benzene); m.p. 77-78.5 °C (77-78.5 °C as for $^2\text{H}_0$ form); ν (KBr) 3328, 2954, 2922, 2850, 2184, 2084, 1634, 1598, 1564, 1498, 1467, 1443, 1315, 1297, 1240, 730, and 693 cm^{-1} ; δ (CDCl_3) 0.87 (3H, t, J 7.0 Hz), 1.20 (10H, brs), 3.13 (2H, brs), 5.59 (1H, brs), 6.96-7.31 (5H, m), and 7.41 (1H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (CDCl_3) 14.1, 22.7, 25.9 (quint, J 19.0 Hz), 29.1, 29.3, 29.5, 31.9, 40.2, 120.5, 123.2, 129.0, 138.9, and 156.7.

Reduction of 1,2-dicyanoethane (8). —A mixture of 1,2-dicyanoethane (**8**) (400 mg, 5.0 mmol), Cu-Al alloy (2.50 g), dry THF (0.8 ml), and D_2O (23.8 ml), placed in a 100 ml round-bottom 3-necked flask, was treated with NaOD- D_2O (40%; 3.4 ml) as described above to afford 1,4-[1,1,4,4- $^2\text{H}_4$]diaminobutane (*Putrescine*) (**10**) (190 mg) as a colourless liquid. Then, **10** (190 mg, 4.1 mmol) was reacted with phenyl isocyanate (490 mg, 4.1 mmol) to afford 1,4-[1,1,4,4- $^2\text{H}_4$]-bis-[N-phenylureid]butane (**12**) (480 mg, 29% from **8**) as colourless prisms (DMF): m.p. 234-237 °C (233-235 °C as for $^2\text{H}_0$ form); ν (KBr) 3324, 2938, 2860, 2182, 2112, 1636, 1598, 1558, 1499, 1476, 1444, 1311, 1257, 1229, and 735 cm^{-1} ; δ (DMSO- d_6) 1.45 (4H, brs), 6.16 (2H, brs), 6.87 (2H, m), 7.17-7.39 (8H, m), and 8.37 (2H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (DMSO- d_6) 27.1, 30.2 (quint, J 20.0 Hz), 117.6, 120.9, 128.6, 140.6, and 155.2.

Reduction of 1,4-dicyanobutane (9). —A mixture of 1,4-dicyanobutane (**9**) (540 mg, 5.0 mmol), Cu-Al alloy (2.50 g), dry THF (0.8 ml), and D_2O (23.8 ml), placed in a 100 ml round-bottom 3-necked flask, was treated with NaOD- D_2O (40%; 3.4 ml) as described above to afford 1,6-[1,1,6,6- $^2\text{H}_4$]diaminohexane (**11**) (350 mg) as a colourless liquid. Then, **11** (350 mg, 5.9 mmol) was reacted with phenyl isocyanate (700 mg, 5.9 mmol) to afford 1,6-[1,1,6,6- $^2\text{H}_4$]-bis-[N-phenylureid]hexane (**13**) (1.04 g, 58% from **9**) as colourless prisms (DMF): m.p. 213-215 °C (213-215 °C as for $^2\text{H}_0$ form); ν (KBr) 3324, 2928, 2856, 2186, 2112, 1632, 1597, 1558, 1465, 1444, 1315, 1240, 1156, 763, and 730 cm^{-1} ; δ (DMSO- d_6) 1.30-1.42 (8H, m), 6.09 (2H, brs), 6.87 (2H, m), 7.17-7.39 (8H, m), and 8.37 (2H, brs); $^{13}\text{C}\{^1\text{H}\}$ δ (DMSO- d_6) 26.0, 29.5, 30.2 (quint, J 20.0 Hz), 117.4, 120.8, 128.5, 140.5, and 155.1.

Acknowledgement

Partial financial support of this research from Tohwa University, Fukuoka, Japan, is gratefully acknowledged.

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