Supporting Information

A Solvent having Switchable Hydrophilicity

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1. Synthesis of Amidines.

Syntheses of N,N-dimethyl-N'-hexyl ethanimidamide (2).

This compound was prepared by a modification of Scoggin's method for acetamidines, as described for longer-chain analogues in a recent paper.¹ It was purified by distillation under vacuum. The ¹H NMR spectrum matched that reported in the literature.²

Synthesis of N,N-dibutylpentanamide

A round-bottom flask containing a magnetic stirring bar, diethyl ether (400 mL) and N,Ndibutylamine (37 mL, 0.22 mol, 2.2 eq.) was cooled in ice for 30 min. Valeroyl chloride (12.0 mL, 0.099 mol, 1.0 eq) was combined with diethyl ether (75 mL) and added dropwise over 30 min to the stirring dibutylamine solution. A white precipitate was observed. The flask was removed from ice and stirred at room temperature for 3 h. Two 500 mL extractions were performed with dilute HCl (0.24 M) to remove the excess amine and ammonium chloride byproduct. The ether layer was retained and dried over MgSO₄. The solution was concentrated in vacuo, yielding N,N-dibutylpentanamide in 97% yield. TLC with hexane:ethyl acetate (80:20 v/v) as eluent and KMnO₄ for visualization of the amine was used to determine if dibutylamine remained. If trace amine was evident in the product, the product was exposed to high vacuum, with stirring at 45 °C, until amine was no longer detectable by TLC.

¹H NMR (CDCl₃, 400 MHz): ∂ 3.23 (t, ³J_{HH} = 7.6 Hz, N(CH₂CH₂CH₂CH₂CH₃), 2H), 3.14 (t, ${}^{3}J_{HH} = 7.8 \text{ Hz}, \text{ N}(CH_{2}CH_{2}CH_{2}CH_{3})', 2H), 2.21 \text{ (t, } {}^{3}J_{HH} = 7.6 \text{ Hz}, C(O)CH_{2}CH_{2}CH_{2}CH_{3}, 2H),$ 1.55 (quintet, ${}^{3}J_{HH} = 7.6 \text{ Hz}, C(O)CH_{2}CH_{2}CH_{2}CH_{3}, 2H), 1.46 (m, N(CH_{2}CH_{2}CH_{2}CH_{3})', 2H),$ $N(CH_2CH_2CH_2CH_3),$ 2H), 1.20-1.32 $C(O)CH_2CH_2CH_2CH_3$, 1.43 (m, (m, N(CH₂CH₂CH₂CH₃)', N(CH₂CH₂CH₂CH₃), 6H), 0.93 (m, CH₃, 9H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): ∂ 172.6 (C=O), 49.6 (N(CH₂CH₂CH₂CH₂)'), 47.7 (N(CH₂CH₂CH₂CH₂)), 32.8 $(C(O)CH_2CH_2CH_2CH_3), 31.3 (N(CH_2CH_2CH_2CH_3)'), 29.9 (N(CH_2CH_2CH_2CH_3)), 27.6$ (C(O)CH₂CH₂CH₂CH₂CH₃), 22.5 (C(O)CH₂CH₂CH₂CH₃), 20.1 $(N(CH_2CH_2CH_2CH_3))'$ and N(CH₂CH₂CH₂CH₃)), 13.9 (CH₃).

Synthesis of N,N-dipropylbutyramide

A similar procedure implemented with N,N-dipropylamine (2.2 eq) and butyryl chloride (1.0 eq) gives N,N-dipropylbutyramide in 95% yield. The ¹H NMR spectrum (CDCl₃) matched that reported in the literature.³

Synthesis of N,N,N'-tripropylbutanamidine (3)

N,N,N'-tripropylbutanamidine was prepared in 32% yield from N,N-dipropylbutyramide and 1-propylamine using the method described below for the preparation of N,N,N'tributylpentanamidine (7).

¹H NMR (CDCl₃, 400 MHz): ∂ 3.10 (m, N(*CH*₂CH₂CH₃)₂ and C=N*CH*₂CH₂CH₂CH₃, 6H), 2.18 (m, C(=NPr)*CH*₂CH₂CH₃, 2H), 1.1-1.5 (m, *CH*₂CH₃, 8H), 0.85 (m, *CH*₃, 12H). ¹³C{¹H} NMR (CDCl₃): 160.1 (N=C-N), 51.1, 49.2, 27.8, 25.9, 21.7, 20.8, 14.3, 12.1, 11.5. IR (neat, cm⁻¹): 2961 (s), 2931 (m), 2873 (m), 1616 (s) (v(C=N)), 1464 (m), 1079 (m). ESI-MS (+ve ion mode): obs. 212.2248, calculated for C₁₃H₂₈N₂: 212.2252.

Synthesis of N,N,N'-tributylpentanamidine (4)

In the first step of this synthesis, N,N-dibutylpentanamide was O-methylated by dimethylsulfate. Similar methylations have been reported previously.^{4,5} The crude product, 1-methoxy-N,N-dibutyl-1-pentanaminium methylsulfate, was then reacted with butylamine to generate the desired amidine (equation S1).

$$\underset{Bu_2N}{\overset{O}{\longrightarrow}} \underset{Bu}{\overset{WeOS(O)_2OMe}{\longrightarrow}} \underset{Bu_2N}{\overset{O}{\longrightarrow}} \underset{Bu}{\overset{O}{\longrightarrow}} \underset{Bu_2}{\overset{O}{\longrightarrow}} \underset{Bu}{\overset{O}{\longrightarrow}} \underset{Bu}{\overset{O}{\longrightarrow}} \underset{Bu_2N}{\overset{WBu}{\longrightarrow}} \underset{WBu_2N}{\overset{WBu}{\longrightarrow}} \underset{WBu}{\overset{WBu}{\longrightarrow}} \underset{WBu}{\overset{WBu}{\overset{WBu}{\longrightarrow}} \underset{WBu}{\overset{WBu}{\longrightarrow}} \underset{WBu}{\overset{WBu}{\longrightarrow}} \underset{WBu}{\overset{WBu}{\overset{WBu}{\longrightarrow}} \underset{WBu}{\overset{WBu}{\overset{WBu}{\longrightarrow}} \underset{WBu}{\overset{WBu}{\overset{WBu}{\overset{WBu}{\longrightarrow}} \underset{WBu}{\overset{WBu}{\overset{WBu}{\overset{WBu}{\overset{WBu}{\overset{WBu}{\overset{WBu}{\overset{WBu}{\overset{$$

N,N-dibutylpentanamide (5.0 g, 0.023 mol, 1.0 eq) and a magnetic stirrer were added to a round bottom flask. The flask was fitted with a condenser, flushed with argon and heated to 95 °C. Dimethyl sulfate (4.5 mL, 0.046 mol, 2.0 eq.) was added by syringe. After 3 h, the reaction mixture was cooled to ambient temperature and washed with ether (2x50 mL). The ether layer took over 30 min to become transparent each time and was allowed to clear before the ether was decanted. Residual ether was removed in vacuo.

Butylamine (7.0 mL, 0.070 mol, 3.0 eq), methanol (40 mL), and a stir bar were added to a round-bottom flask containing the solid residue (crude 1-methoxy-N,N-dibutyl-1-pentanaminium methylsulfate), and a condenser was affixed. The flask was heated in a 95 °C oil bath for 3 h. After cooling, methanol and excess butylamine were removed in vacuo. The residue was dissolved in 115 mL of 1.8 M HCl. The aqueous phase was washed with ether (100 mL) to remove residual amide and then gradually basified gwith KOH, until pH paper indicated a pH >11. A thin organic layer formed on top of the aqueous layer as base was added, presumed to contain the desired amidine. The product was extracted with ether (100 mL), dried with MgSO₄, and concentrated in vacuo, yielding N,N,N'-tributylpentanamidine. The overall isolated yield was 23%.

¹H NMR (CDCl₃, 400 MHz): ∂ 3.12 (t, N(*CH*₂CH₂CH₂CH₃)₂, 4H), 3.10 (t, C=N*CH*₂CH₂CH₂CH₃, 2H), 2.17 (m, C(=NBu)*CH*₂CH₂CH₂CH₃, 2H), 1.15-1.45 (m, C(=NBu)CH₂*CH*₂*CH*₂CH₂CH₃, C=NCH₂*CH*₂*CH*₂CH₂CH₃, and N(CH₂*CH*₂*CH*₂CH₃)₂, 16H), 0.86 (m, CH₃, 12H). ¹³C{¹H} NMR (CDCl₃, 100 MHz): ∂ 160.1 (*C*=N), 48.8 (C=N*CH*₂CH₂CH₂CH₂CH₃), 47.0 (N(*CH*₂CH₂CH₂CH₃)₂), 35.0, 30.8, 29.4, 25.6 (C(=NBu)*CH*₂CH₂CH₂CH₃), 23.0, 20.7, 20.3, 14.1, 14.0. IR (neat, cm⁻¹): 2957 (s), 2928 (s), 2872 (m), 1616 (s) (v(C=N)), 1465 (m), 1089 (m). ESI-MS (+ve ion mode): obs. 269.2876, calculated for C₁₇H₃₆N₂: 268.2878.

2. Synthesis of Guanidines.

General procedure for the synthesis of guanidines.

All syntheses were carried out under argon of 99.998% purity using standard Schlenk line techniques or in a glovebox under nitrogen. Glassware was dried in an oven at 100 °C overnight or flame dried under high vacuum. Solvents and reactants were dried, distilled under argon, degassed and stored over activated 4 Å molecular sieves prior use. Acetonitrile was dried over potassium carbonate for 48 hours, methylene chloride and deuterated chloroform was dried over calcium hydride for 7 days. Hexylamine and octylamine were dried over potassium carbonate, butylamine was dried over calcium hydride for 24 hours. Tetraalkylureas were dried over activated molecular sieves (4 Å) for 48 hours and used without any further purification.

The two-part synthesis (equation S2) involves the reaction of a urea with oxalyl chloride using the method of Fujisawa,⁶ followed by the reaction of the resulting chloro-1,1,3,3-tetraalkylformamidinium chloride with amine using the method of Wieland and Simchen.⁷

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Oxalyl dichloride (1.7 equivalents) was added dropwise to a stirred solution of the 1,1,3,3tetraalkylurea in dry methylene chloride (1.00 mL per mmol of 1,1,3,3- tetraalkylurea). The colourless solution turned yellow and the mixture was stirred for 18 h at 60 °C. After cooling to room temperature, the solvent was removed in vacuo. The ¹H and ¹³C{¹H} NMR spectra of the crude chloro-1,1,3,3-tetraalkylformamidinium chloride were obtained but the material was not further characterized. The material was dissolved in dry acetonitrile (0.50 ml per mmol of 1,1,3,3-tetraalkylurea) and a solution of 3 equivalents of the appropriate dry amine in dry acetonitrile (0.50 ml per mmol of 1,1,3,3-tetraalkylurea) was added slowly at room temperature. During the exothermic reaction, gas development was observed. The resulting dark brown but clear solution was heated to 60 °C for 4 h, following which the solvent was removed in vacuo. Wet diethyl ether (3.50 mL per mmol of 1,1,3,3-tetraalkylurea) was added to the brown oily residue. Under vigorous stirring, a solution of sodium hydroxide (0.20 g per mmol 1,1,3,3-tetraalkylurea) in water (1.33 mL per mmol of 1,1,3,3-tetraalkylurea) saturated with potassium carbonate was added at 0 °C. The resulting two phases were separated and the aqueous phase was extracted twice with diethyl ether (0.70 mL per mmol of 1,1,3,3)tetraalkylurea). The combined organic layers were dried over potassium carbonate and concentrated in vacuo to yield a brown oily residue. The crude product was distilled under reduced pressure to give the guanidine in high yields.

Chloro-1,1,3,3-tetramethylformamidinium chloride.

Slightly green solid. ¹H NMR (400 MHz, CDCl₃, 25 °C) δ 3.50. ¹³C{¹H} NMR (101 MHz, CDCl₃, 25 °C) δ 159.1 (*C*=N), 45.2 (*C*H₃).

Chloro-1,1,3,3-tetraethylformamidinium chloride.

Brown oil. ¹H NMR (400 MHz, CDCl₃) δ 3.69 (q, ³J_{HH} = 7.2, 8H, CH₂CH₃), 1.19 (t, ³J_{HH} = 7.2, 12H, CH₂CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 158.4 (C=N), 50.1 (CH₂CH₃), 13.0 (CH₂CH₃).

Chloro-1,1,3,3-tetra(n-butyl)formamidinium chloride.

Dark green oil. ¹H NMR (400 MHz, CDCl₃, 25 °C) δ 3.78 (t, ³J_{HH} = 7.8, 4H, CH₂CH₂CH₂CH₃), 3.09 (t, ³J_{HH} = 7.7, 4H, CH₂CH₂CH₂CH₂CH₃)'), 1.66 (m, 4H, CH₂CH₂CH₂CH₂CH₃), 1.43 (m, 4H, (CH₂CH₂CH₂CH₂CH₃)'), 1.32 (m, 4H, CH₂CH₂CH₂CH₃), 1.23 (m, 4H, (CH₂CH₂CH₂CH₃)'), 0.89 (t, ³J_{HH} = 7.3, 6H, CH₂CH₂CH₂CH₂CH₃), 0.83 (t, ³J_{HH} = 7.4, 6H, (CH₂CH₂CH₂CH₃)'). ¹³C{¹H} NMR (101 MHz, CDCl₃, 25 °C) δ 159.2 (C=N), 55.7, 30.1, 29.8, 20.2, 20.0, 13.9, 13.7.

2-Hexyl-1,1,3,3-tetramethylguanidine (6).

 C₁₁H₂₅N₃: 199.2048.

2-Butyl-1,1,3,3-tetraethylguanidine (7).

Clear colourless liquid, yield: 89 %. ¹H NMR (400 MHz, CDCl₃) δ 3.07 (q, ³*J*_{HH} = 7.1, 4H, N(C*H*₂CH₃)(CH₂CH₃)'), 3.03 (t, ³*J*_{HH} = 6.9, 2H, C*H*₂CH₂CH₂CH₃), 2.97 (q, ³*J*_{HH} = 7.1, 4H, N(CH₂CH₃)(C*H*₂CH₃)'), 1.46 (m, 2H, CH₂CH₂CH₂CH₃), 1.28 (m, 2H, CH₂CH₂CH₂CH₃), 0.96 (t, ³*J*_{HH} = 7.1, 6H, N(CH₂CH₃)(CH₂CH₃)(CH₂CH₃)'), 0.96 (t, ³*J*_{HH} = 7.1, 6H, N(CH₂CH₃)(CH₂CH₃)'), 0.84 (t, ³*J*_{HH} = 7.3, 3H, CH₂CH₂CH₂CH₂CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 158.2 (*C*=N), 49.8 (*C*H₂CH₂CH₂CH₃), 42.8 (N(CH₂CH₃)(*C*H₂CH₃)'), 41.6 (N(CH₂CH₃)(*C*H₂CH₃)'), 35.2 (CH₂CH₂CH₂CH₃), 20.9 (CH₂CH₂CH₂CH₃), 14.3 (CH₂CH₂CH₂CH₃), 13.9 (N(CH₂CH₃)'), 13.1 (N(CH₂CH₃)(CH₂CH₃)'). MS (TOF EI+): observed: 227.2374. Calculated for C₁₃H₂₉N₃: 227.2361.

2-Hexyl-1,1,3,3-tetraethylguanidine (8).

Clear colourless liquid, quantitative yield. ¹H NMR (400 MHz, CDCl₃) δ 3.07 (q, ³J_{HH} = 7.1, 4H, N(CH₂CH₃)(CH₂CH₃)'), 3.02 (t, ³J_{HH} = 7.0, 2H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 2.96 (q, ³J_{HH} = 7.1, 4H, N(CH₂CH₃)(CH₂CH₃)'), 1.46 (m, 2H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.23 (m, 6H, CH₂CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 0.96 (t, ³J_{HH} = 7.0, 6H, N(CH₂CH₃)(CH₂CH₃)'), 0.96 (t, ³J_{HH} = 7.0, 6H, N(CH₂CH₃)(CH₂CH₃)'), 0.96 (t, ³J_{HH} = 7.0, 6H, N(CH₂CH₃)(CH₂CH₃)'), 0.82 (t, ³J_{HH} = 6.6, 3H, CH₂CH₂CH₂CH₂CH₂CH₂CH₂CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 158.2 (C=N), 50.1 (CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 42.8 (N(CH₂CH₃)(CH₂CH₃)'), 41.6 (N(CH₂CH₃)(CH₂CH₃)'), 32.9, 32.0, 27.5, 22.9, 14.2 (CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 13.8 (N(CH₂CH₃)(CH₂CH₃)'), 13.1 (N(CH₂CH₃)(CH₂CH₃)'). MS (TOF EI+): observed: 255.2678. Calculated for C₁₅H₃₃N₃: 255.2674.

2-Hexyl-1,1,3,3-tetra(n-butyl)-guanidine (9).

Only a crude product was obtained, as a brown oil.

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