An Efficient Methodology for the Synthesis of 1-(Trimethylammoniummethyl)cyclohexaneacetic Acid Iodide: A Trimethylammonium Iodide Salt of Gabapentin

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The gabapentinoids pregabalin and gabapentin are structurally related to the inhibitory neurotransmitter γ-aminobutryic acid (GABA). These two agents, originally introduced as anticonvulsant (antepileptic) drugs, are now approved and commonly used in the treatment of neuropathic pain. Neuropathic pain is characteristically resistant to the analgesic actions of opioids and non-steroidal anti-inflammatory drugs. The accepted mechanism of action of gabapentinoids is based on their transport into neurons *via* a non-specific amino acid transporter where they bind with the alpha 2 delta subunit of voltage gated Ca^{2+} channels.[1,2] It has also been shown that TRPV1 channels, which are present on nociceptive neurons and are opened by agonists such as capsaicin,[3–5] allow the permeation of small organic molecules such as local anesthetics.[6] Accordingly, it is possible that opening of TRPV1 channels may provide a means to deliver gabapentinoids to their intracellular site of action. This concept may constitute a more effective alternative than reliance on the amino acid transporter and it may selectively target the gabapentinoids to nociceptive neurons. To test whether gabapentinoids pass through TRPV1 channels, a charged analog of gabapentin could be used to replace all Na^+ and Ca^{2+} ions in the extracellular fluid. For this reason, it was necessary to synthesize a quaternary salt of gabapentin **1**. We now describe an efficient methodology for the synthesis of 1-(trimethylammoniummethyl)cyclohexaneacetic acid iodide (**2**) using a four-step reaction sequence free of time consuming chromatography in 81% overall isolated yield starting from gabapentin (see structures in *Scheme 1*).
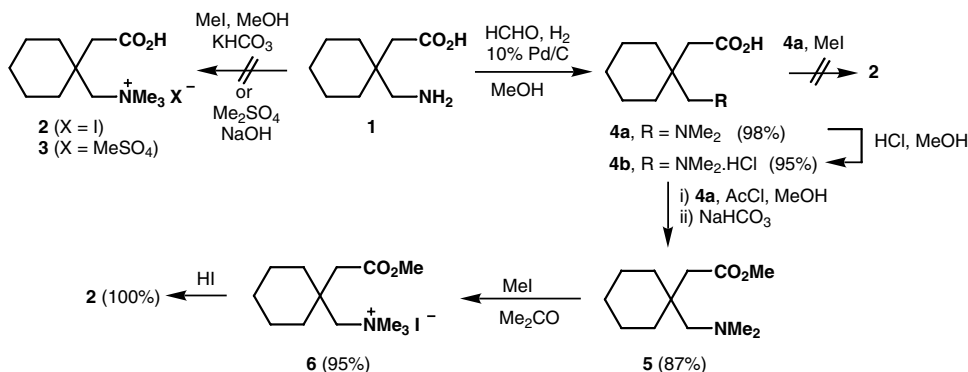
Scheme 1

The synthetic strategy used for the synthesis of (1-(trimethylammoniummethyl)-cyclohexaneacetic acid iodide (**2**) is illustrated in *Scheme 1*. *N*-quaternization of the amino group present in gabapentin **1** was initially investigated using methods reported to be successful for the *N*-methylation of GABA. For instance, treatment of gabapentin **1** with either methyl iodide and potassium bicarbonate,[7] or dimethyl sulphate and sodium hydroxide,[8] did not furnish the respective trimethylammonium salt **2** or **3**, presumably due to the low basicity of the amino group. 1-(Dimethylaminomethyl)cyclohexaneacetic acid (**4a**) was subsequently prepared *via* reductive alkylation of **1** with aqueous formaldehyde in the presence of 10% Pd/C and H_2 gas at 15 psi to increase the basicity of the amino group.[8] However, reaction of **4a** with methyl iodide[5] to produce the trimethylammonium salt **2** did not proceed. The failure of this reaction is attributed to the likelihood that the aminoacid **4a** exists as a non-reactive zwitterionic species. The amino acid **4a** was converted to its hydrochloride salt **4b**, that was used for analytical characterization, upon treatment with HCl.[9] To circumvent the non-reactivity of **4a**, the carboxylic group was esterified by treatment with acetyl chloride in MeOH[10] to afford methyl 1-(dimethylaminomethyl)-cyclohexaneacetate hydrochloride which on treatment with $NaHCO_3$ furnished the free base methyl 1-(dimethylaminomethyl)cyclohexaneacetate (**5**). The subsequent *N*-methylation of **5** with methyl iodide using acetone as solvent, rather than MeOH,[8] proceeded efficiently to give methyl 1-(trimethylammoniummethyl)cyclohexaneacetate iodide (**6**). Subsequent deprotection of the methyl ester group in **6** using aqueous hydriodic acid furnished the target product 1-(trimethylammoniummethyl)cyclohexaneacetic acid iodide (**2**).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer. Microanalyses (MicroAnalytical Service Laboratory, Department of Chemistry, University of Alberta) were performed for C, H and N and were within ±0.3% of theoretical values for all elements listed. 1-(Aminomethyl)cyclohexaneacetic acid (**1**, gabapentin) was purchased from TCI America. All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification.

1-(Dimethylaminomethyl)cyclohexaneacetic Acid (4a) and 1-(Dimethylaminomethyl)-cyclohexaneacetic Acid Hydrochloride (4b)

To a solution of 1-(aminomethyl)-cyclohexaneacetic acid (**1**, 15.0 g, 87.7 mmol) in methanol (900 mL) was added 37% aqueous formaldehyde (15 mL, 185.0 mmol) and 10% Pd/C (1.73 g). The reaction mixture was stirred at 25°C under H_2 gas (15 psi) for 5 h, the catalyst was removed by filtration through celite, and the filtrate was concentrated *in vacuo* to dryness. The residue was recrystallized from a mixture of acetone-hexanes to furnish **4a** (17.11 g, 98%) as colorless needle shaped crystals, mp 88–90°C; ^{1}H NMR (D_2O): δ 1.20–1.55 (m, 10H, cyclohexyl H-2, H-3, H-4, H-5, H-6), 2.52 (s, 2H, CH_2CO$_2$H), 2.82 (s, 6H, N*Me*$_2$), 3.05 (s, 2H, CH_2NMe$_2$).

For compound characterization, a solution of concentrated HCl was added dropwise to a solution of **4a** (200 mg, 1 mmol) in methanol (5 mL) with stirring at 25°C until the pH was about 2. The resulting mixture was concentrated *in vacuo* to dryness and the residue was recrystallized from a mixture of acetone-hexanes to afford **4b** (225 mg, 95%) as a white solid, mp 139–141° (*lit.*[9] 140–142°C); ^{1}H NMR (CD$_3$OD): δ 1.35–1.55 (m, 10H, cyclohexyl H-2, H-3, H-4, H-5, H-6), 2.68 (s, 2H, CH_2CO$_2$H), 2.99 (s, 6H, N*Me*$_2$), 3.26–3.35 (m, 2H, CH_2NMe$_2$). This ^{1}H NMR spectral data is in agreement with literature data.[9]

Methyl 1-(Dimethylaminomethyl)cyclohexaneacetate (5)

Acetyl chloride (8.8 mL, 123.9 mmol) was added to a solution of **4a** (18.0 g, 90.45 mmol) in methanol (200 mL) at 0°C and the reaction mixture was stirred at 60°C for 16 h. The mixture was then concentrated *in vacuo* to dryness to yield the hydrochloride salt of **5** to which a solution of saturated aqueous NaHCO$_3$ (200 mL) was added. The solution was extracted with EtOAc (3 × 300 mL), the combined EtOAc extracts were successively washed with water and brine, and the organic fraction was dried (MgSO$_4$). Filtration and then removal of the solvent *in vacuo* from the organic fraction afforded **5** as a colorless liquid (16.34 g, 87%), bp 130°C (1.5 mm Hg); ^{1}H NMR (D_2O): δ 1.20–1.55 (m, 10H, cyclohexyl H-2, H-3, H-4, H-5, H-6), 2.64 (s, 2H, CH_2CO$_2$Me), 2.95 (s, 6H, N*Me*$_2$), 3.28 (s, 2H, CH_2NMe$_2$), 3.69 (s, 3H, CO$_2$*Me*).

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found C, 67.75; H, 10.70; N, 6.61.

Methyl 1-(Trimethylammoniummethyl)cyclohexaneacetate Iodide (6)

Methyl iodide (23.50 mL, 375.6 mmol) was added to a solution of **5** (16.0 g, 75.1 mmol) in acetone (25 mL) and the reaction mixture was stirred at 25°C for 16 h. During this time a white solid formed which was filtered off, the white solid was washed several times with diethyl ether, and the solid was dried *in vacuo* to yield **6** as a white solid (25.46 g, 95%), mp 105–107°C; ^{1}H NMR (D_2O): δ 1.20–1.70 (m, 10H, cyclohexyl H-2, H-3, H-4, H-5, H-6), 2.82 (s, 2H, CH_2CO$_2$Me), 3.22 (s, 9H, N$^+$*Me*$_3$I$^-$), 3.50 (s, 2H, CH_2N$^+$Me$_3$I$^-$), 3.69 (s, 3H, CO$_2$*Me*).

Anal. Calcd for $C_{13}H_{26}INO_2$: C, 43.95; H, 7.38; N, 3.94. Found C, 43.77; H, 7.55; N, 3.90.

1-(Trimethylammoniummethyl)cyclohexaneacetic Acid Iodide (2)

Aqueous hydriodic acid (30 mL of 37% w/v) was added to **6** (15.0 g, 42.2 mmol) and the reaction mixture was refluxed for 2 h. The mixture was then concentrated *in vacuo* to dryness to furnish a reddish solid which upon recrystallion from acetone-hexanes afforded **2** as white crystals, (14.41 g, 100%), mp 160–162°C; ^{1}H NMR (DMSO-d$_6$): δ 1.15–1.75 (m, 10H, cyclohexyl H-2, H-3, H-4, H-5, H-6), 2.68 (s, 2H, C*H*$_2$CO$_2$H), 3.18 (s, 9H, N$^+$*Me*$_3$I$^-$), 3.49 (s, 2H, C*H*$_2$N$^+$Me$_3$I$^-$), 12.48 (s, 1H, CO$_2$*H* that exchanges with D$_2$O).

   Anal. Calcd for C$_{12}$H$_{24}$INO$_2$: C, 42.24; H, 7.09; N, 4.10. Found: C, 42.39; H, 7.31; N, 4.10.

Acknowledgements

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