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A novel and selective synthesis of di- and trimethylpiperazinium acetic acid iodide salts

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Abstract—A novel synthetic route has been developed for the preparation of 1-carboxymethyl-1,4,4-trimethylpiperazinium diiodide and 4-carboxymethyl-1,1-dimethylpiperazinium iodide salts. These quaternary piperazinium acids have potential, for example, in the development of novel water-soluble prodrugs or polymer derivatives.

Quaternization reactions of piperazine by N-alkylation have long been studied and reported methods typically yield symmetrical and asymmetrical, mono- and diquaternary products.[1–5] Quaternary piperazinium moieties are also known as part of larger molecules, for example, drug molecules.[6–10] The reported quaternary piperazinium derivatives have been synthesized by first attaching the secondary or tertiary piperazine moiety to a target compound followed by quaternization with alkyl halides. Unfortunately, this strategy often leads to mixtures of products, especially when the parent molecule has numerous functional groups, leading to the need for laborious separation of mono- and diquaternary piperazinium salts and side products. Here, we report a novel simple and selective method to synthesize di- and trimethylpiperazinium salts containing a free acid group. These molecules are potentially useful building blocks for pharmaceuticals, for example, in prodrug technology, and also in the synthetic modification of polymers with poor aqueous solubility.

Some quaternary piperazinium acids have been previously prepared.[4,11] Dega-Szafran et al. alkylated 1,4-dimethylpiperazine with ethyl chloroacetate, yielding 1-carboxymethyl-1,4-dimethylpiperazinium and 1,4-di(carboxymethyl)-1,4-dimethylpiperazinium salts, after conversion of the esters into acid groups.[11] Our aim was to prepare a full range of piperazinium acids with the quaternary nitrogen in alternative positions. Our procedure produces both a monoquaternary derivative **3b** with the carboxymethyl at position N-1 and also a diquaternary derivative **3a** with both possessing only one carboxymethyl moiety after conversion of the ester into acid (Scheme 1).

The synthesis was started from 1-(2-ethoxy-2-oxoethyl)-4-methylpiperazine **1**, prepared from 1-methylpiperazine and ethyl bromoacetate,[12] which was then treated with MeI in dry acetonitrile.[13] Diquaternary salt **2a** was obtained as a precipitate and monoquaternary salt **2b** remained in solution, both with 99% purity. When 4 equiv of MeI was used and the reaction carried out for 48 h, the yields of **2a** and **2b** were 13% and 82%, respectively, and with 10 equiv of MeI for 240 h, the yields were 57% and 42%, respectively. Ethyl esters were converted to acids by refluxing **2a** and **2b** in water.[14,15] Relatively long reaction times were needed to hydrolyze the ester under neutral conditions, which were necessary since addition of acids or bases tended to cleave the methyl group attached to N-1 from **2a**. Two 96 h periods of reflux in water removed approximately only 5% of this methyl. The end products were obtained as pure white crystals. The compounds were characterized with ^{1}H, ^{13}C and HSQC NMR spectra measured at 343 K, since at room temperature the methyl signals were broad due to dynamic equilibrium on the NMR time scale.[16] Long-range ^{1}H–^{13}C HMBC NMR spectra

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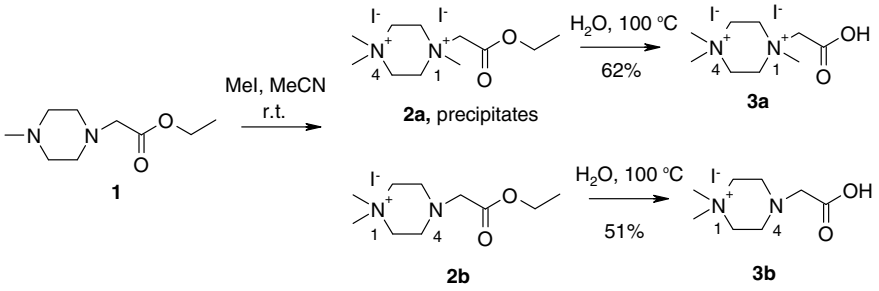

Scheme 1.

were measured to confirm the assignment of the methyl signals in **3a** and also to confirm that both methyl groups of **3b** were on the same nitrogen.

In conclusion, we have developed a novel and simple method for the preparation of 1-carboxymethyl-1,4,4-trimethylpiperazinium diiodide and 4-carboxymethyl-1,1-dimethylpiperazinium iodide salts. Both mono- and diquaternary products separated as pure compounds during the synthetic procedure, requiring no subsequent laborious purification. Yields from the quaternization steps were almost quantitative, and the ratio **2a**:**2b** can be altered by changing the amount of MeI and the reaction time.

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13. Compound **1** (6.96 g, 37.37 mmol) and MeI (9.3 ml, 149 mmol, 4 equiv) were dissolved in CH_3CN (270 ml) and the solution was stirred for 48 h under argon at room temperature. The resulting precipitate was filtered and washed with acetonitrile to yield **2a** (2.35 g, 13%) and the filtrate was evaporated to dryness to give **2b** (9.99 g, 82%). When repeated with 7.8 g (41.9 mmol) of **1** and 26.1 mL (420 mmol, 10 equiv) of MeI in 300 ml acetonitrile for 240 h, the reaction yielded 11.12 g (57%) of **2a** and 5.82 g (42%) of **2b**. Compound **2a**: ^{1}H NMR (500 MHz, 300 K, D_2O) δ 4.67 (2H, s, N^1–CH_2–CO), 4.37 (2H, q, $J = 7.2$ Hz, O–CH_2–CH_3), 3.9–4.3 (8H, br m, piperazinium), 3.59 (3H, s, N^1–*Me*), 3.47 (3H, s, *Me*–N^4), 3.44 (3H, s, *Me*–N^4), 1.33 ppm (3H, t, $J = 7.2$ Hz, O–CH_2–CH_3); ^{13}C NMR (125 MHz, 343 K) δ 167.03 (C=O), 67.08 (N^1–CH_2–CO), 58.49 (O–CH_2–CH_3), 58.27 (2C, Me_2–N^4–$(CH_2)_2$), 57.75 (2C, $(CH_2)_2$–N^1), 57.01 (N^1–*Me*), 53.60 (*Me*–N^4), 51.89 (*Me*–N^4), 16.03 (O–CH_2–CH_3) ppm. Compound **2b**: ^{1}H NMR (500 MHz, 300 K, D_2O) δ 4.24 (2H, q, $J = 7.2$ Hz, O–CH_2–CH_3), 3.51 (2H, s, N^4–CH_2–CO), 3.49 (4H, s, N^1–$(CH_2)_2$), 3.21 (6H, s, Me_2–N^1), 3.01 (4H, s, $(CH_2)_2$–N^4), 1.28 ppm (3H, t, $J = 7.2$ Hz, O–CH_2–CH_3); ^{13}C NMR (125 MHz, 343 K) δ 174.44 (C=O), 64.98 (O–CH_2–CH_3), 64.25 (N^4–CH_2–CO), 60.04 (2C, N^1–$(CH_2)_2$), 54.50 (2C, Me_2–N^1), 48.58 (2C, $(CH_2)_2$–N^4), 16.18 (O–CH_2–CH_3) ppm.
14. Compound **2a** (8.5 g) was dissolved into 700 ml of water and the solution was refluxed for 96 h. The reaction mixture was evaporated to dryness and refluxing in water was repeated for 96 h after which the water was evaporated. The residue was washed with acetonitrile and crystallized from water with ethanol yielding **3a** (4.98 g, 62%) as a white powder. Mp >250 °C. ^{1}H NMR (500 MHz, 343 K, D_2O) δ 4.45–4.35 (2H, m, CH_2–N^1), 4.34 (2H, s, N^1–CH_2–CO), 4.07–3.90 (6H, m, Me_2–N^4–$(CH_2)_2$; CH_2–N^1), 3.51 (3H, s, N^1–*Me*), 3.44 (3H, s, *Me*–N^4), 3.41 ppm (3H, s, *Me*–N^4); ^{13}C NMR (125 MHz, 343 K) δ 169.25 (C=O), 66.50 (N^1–CH_2–CO), 58.45 (2C, Me_2–N^4–$(CH_2)_2$), 57.05 (*Me*–N^4), 56.95 (2C, $(CH_2)_2$–N^1), 53.58 (*Me*–N^4), 51.89 ppm (N^1–*Me*). IR (KBr) ν_{max} 3003, 2956, 1737, 1631, 1469, 1395, 1306, 1265, 1237, 1106, 1075, 1014, 912, 860, 704 cm^{-1}. Anal. ($C_9H_{20}N_2O_2I_2$) C, H, N: calcd 24.45, 4.56, 6.34% and found 24.69, 4.66, 6.45%.
15. Compound **2b** (11.77 g) was dissolved into 600 ml of water and refluxed for 48 h. The reaction mixture was evaporated to dryness and the product was crystallized from ethanol with diethyl ether to give **3b** (5.48 g, 51%) as a white powder. Mp 212–215 °C. ^{1}H NMR (500 MHz,

343 K, D_2O) δ 3.73 (4H, m, N^1–(CH_2)$_2$), 3.69 (2H, s, N^4–CH_2–CO), 3.51 (4H, s, (CH_2)$_2$–N^4), 3.30 ppm (6H, s, Me_2–N^1); ^{13}C NMR (125 MHz, 343 K) δ 173.72 (C=O), 62.74 (2C, N^1–(CH_2)$_2$), 60.47 (N^4–CH_2–CO), 54.84 (2C, Me_2–N^1), 48.86 ppm (2C, (CH_2)$_2$–N^4). IR (KBr) ν_{max} 3413, 3005, 1958, 1711, 1598, 1409, 1222, 1159, 1137, 917, 894, 815, 699 cm^{-1}. Anal. ($C_8H_{17}N_2O_2I$) C, H, N: calcd 32.01, 5.71, 9.33% and found 32.12, 5.67, 8.86%.

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