Facile synthesis of amide and amine derivatives of 2,2,3,3-tetramethylcyclopropanecarboxylic acid

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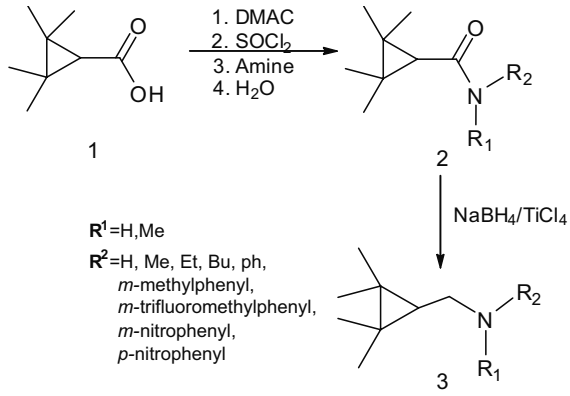
An efficient one-pot procedure for the synthesis of amide derivatives of 2,2,3,3-tetramethylpropanecarboxylic acid (TMCA) that involves the treating of TMCA in *N*,*N*-dimethylacetamide (DMAC) with thionyl chloride and stoichiometric amounts of reactant amines has been developed. The combined reagent $TiCl_4/NaBH_4$ was found to be effective for the reduction of the amide derivatives of TMCA to the corresponding amines.

Keywords: 2,2,3,3-tetramethylpropanecarboxylic acid, *N*,*N*-dimethylacetamide, reduction reaction, $TiCl_4/NaBH_4$

Amide and amine derivatives of 2,2,3,3-tetramethylpropanecarboxylic acid (TMCA) are versatile intermediates for the synthesis of a wide variety of pharmaceutically important compounds.[1-7] Amide derivatives of TMCA can be prepared[8-12] by the coupling reaction of TMCA chloride with suitable reactant amines in an inert organic solvent such as tetrahydrofuran (THF) and CH_2Cl_2, using TMCA and thionyl chloride as raw materials. Amines derived from TMCA were prepared by the reduction of the corresponding amides. The general methods reported for the preparation of amide derivatives of TMCA so far usually require bases such as triethylamine and pyridine and employ volatile organic solvents (VOCs) in cumbersome extraction procedures. The reduction of amide derivatives of TMCA to the corresponding amines using lithium aluminum hydride suffers from harsh reaction conditions and high operating cost. In view of the wide use of amide and amine derivatives of TMCA, it was of interest to develop milder, economically more attractive alternatives to these processes.

Since the solubility of reactant amine HCl salt that is formed in the chemical process for preparing amide derivatives of TMCA might affect the yield of product, we report here a mild and efficient one-pot procedure that directly converts TMCA to the corresponding amides in *N*,*N*-dimethylacetamide (DMAC) using thionyl chloride and reactant amine compounds (Scheme 1). We also describe a series of amine derivatives of TMCA which have been prepared from the now conveniently accessible TMCA amides by reduction with the combined reagent $TiCl_4/NaBH_4$.



Scheme 1 Synthesis of amide and amine derivatives of TMCA.

Results and discussion

The purpose of this study was to develop mild, simple and efficient procedures for the preparation of amide and amine derivatives of TMCA. In order to optimise the reaction conditions for the preparation of amide derivatives of TMCA, we examined the synthesis of *N*-phenyl-2,2,3,3-tetramethylcyclopropanecarboxamide (**2e**) as a model reaction. It was observed that when TMCA was dissolved in DMAC at low temperature (–5 °C) and treated sequentially with thionyl chloride and stoichiometric amounts of reactant amine in the absence of a base, a slow reaction occurred, which when warmed to room temperature (20 °C) resulted in the complete formation of amide derivatives of TMCA. The effect of molar ratios of TMCA, thionyl chloride and aniline on the yields at 20 °C for 60 min was investigated. It was found the best yields could be obtained under the reaction conditions of n(TMCA): $n(SOCl_2)$:n(aniline) = 1 : 1.2 : 1. The product was isolated in high yield by crystallisation with the simple addition of water to the reaction. The results are shown in Table 1.

The effect of reaction time on the yields with the best molar ratio of reaction reagents was also surveyed and it was found that the best yields could be obtained at 20 °C for 60 min. A further increase in reaction time had no significant effect on the yields. The results are given in Table 2.

A comparison between DMAC and *N*,*N*-dimethylformamide (DMF) as solvents was conducted under the same reaction conditions. The use of DMF in place of DMAC gave only a 40% yield of the compound (**2e**). After warming to 60 °C, the amide could be obtained in an 80% yield, which was lower than that obtained in DMAC (95%). It can be seen that the use of DMAC as solvent gave a higher conversion along

Table 1 Effect of molar ratios of reaction reagents on the yields

n(TMCA):*n*($SOCl_2$):n(aniline)	1 : 0.8 : 1	1 : 1.0 : 1	1 : 1.2 : 0.8	1 : 1.2 : 1	1 : 1.2 : 1.2
Yield/%	61	86	78	95	95

Table 2 Effect of reaction time on the yields

Time/min	10	20	30	40	50	60	70	80
Yield/%	36	62	81	88	93	95	95	96

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with a better yield of amide compared to the use of DMF. The experimental results presented coincide with those obtained by Cvetovich and DiMichele.[13]

The generality of amide derivatives of TMCA formation in DMAC with this simple and efficient procedure using various reactant amines was tested and the results are summarised in the experimental section. In each case, the amines were successfully converted to amide derivatives of TMCA and reactions were completed rapidly and gave good isolated yields of the corresponding amides as crystalline solids.

Although excellent yields (> 90%) of amide derivatives of TMCA were obtained using aromatic amines as reactants in DMAC in the absence of bases alkylamines gave poorer yields. When TMCA was treated with thionyl chloride and butylamine, the product *N*-butyl-2,2,3,3-tetramethylcyclopropanecarboxamide (**2d**) was obtained in an 74% yield, even in the presence of excess butylamine. The influence of reactant amine types on the yields is mainly due to the poor solubility of the alkylamine HCl salt in DMAC and is independent of the basicity of reactant amine. This conclusion was confirmed by using aromatic amines which contain various substituent groups as reactants and the similar isolated yields of amide derivatives of TMCA could be observed.

Amine derivatives of TMCA can be obtained by reducing the corresponding amide with a Lewis acid/$NaBH_4$ reduction system, the reducing properties of which are milder than that of $LiAlH_4$.[14-16] We found that the combined reagent $TiCl_4$/$NaBH_4$ can be used to advantage for the reduction of amide derivatives of TMCA. Thus, a series of amide derivatives of TMCA were subjected to reduction in the presence of $NaBH_4$ and $TiCl_4$ to furnish the corresponding amine compounds. The results are summarised in the corresponding experimental section.

In conclusion, we have developed a mild and efficient method to convert TMCA to amide derivatives directly in a one-pot reaction by the action of TMCA, thionyl chloride and reactant amines in *N*,*N*-dimethylacetamide. The amide derivatives of TMCA can be smoothly reduced to corresponding amines by using the combined reagent $TiCl_4$/$NaBH_4$.

Experimental

Chemicals, materials, and methods

All the reagents used in the experiment were AR grade and purchased from Sigma-Aldrich. All melting points (°C) were determined on an X-4 microscopic digital melting-point apparatus. ^{1}H NMR spectra were recorded on a Varian INOVA 400 spectrometer at ambient temperature in $CDCl_3$ using TMS as internal standard, and NMR chemical shifts (δ) were quoted in ppm. Coupling constants (*J* values) were given in Hz. High-resolution mass spectra were measured using a JEOL JMS-DX300 mass spectrometer. IR spectra of the compounds were measured on a Nicolet Avatar 360 FT-IR instrument using KBr discs in the 4000–400 cm^{-1} regions. Elemental analyses were obtained in an EA 1112 elemental analyser. C, H, N analyses of all newly synthesised compounds had satisfactory results (within ±0.4 of theoretical values).

General procedure for the synthesis of **2a-j**

In a standard reaction procedure, a solution mixture of dimethylacetamide (20 mL) and 2,2,3,3-tetramethylpropanecarboxylic acid (0.06 mol) was cooled to –5 °C in a mechanically stirred three-necked flask equipped with a an exit gas absorber. Then, thionyl chloride (0.072 mol) and stoichiometric amounts of the reactant amine (0.06 mol) were added slowly from a dropping funnel with sufficient stirring. When the addition was complete, the reaction mixture was warmed to room temperature (20 °C) and stirred for 60 min. With the reaction mixture at 20 °C, water (300 mL) was added dropwise over 30 min and stirred for a further 60 min. The product was then filtered and washed with water. Recrystallisation from EtOH/H_2O gave the pure target compounds (**2a–j**).

2,2,3,3-tetramethylcyclopropanecarboxamide (**2a**): White crystalline solid, 89% yield, m.p. 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 7.16 (s, 1H, N*H*), 1.48 (s, 1H, C*H*), 1.25–1.15 (12H, CH_3). HRMS (*m*/*z*): 141.1162 (Calcd for $C_8H_{15}NO$, 141.1153). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.74; H, 11.01; N, 9.24%.

N-Methyl-2,2,3,3-tetramethylcyclopropanecarboxamide (**2b**): White crystalline solid (88% yield) m.p. 97–99 °C (lit.[10] 98 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 5.672 (s, 1H, N*H*), 2.761–2.782 (d, *J* = 8.4, 3H, NHCH_3), 1.146–1.254 (12H, CH_3), 0.836 (s, 1H, C*H*). HRMS (*m*/*z*): 155.1332 (Calcd for $C_9H_{17}NO$,155.1310). Anal. Calcd for $C_9H_{17}NO$: C, 69.62; H, 11.04; N, 9.03. Found: C, 68.91; H, 10.86; N, 9.74%.

N-Ethyl-2,2,3,3-tetramethylcyclopropanecarboxamide (**2c**): White needle-like solid (80% yield) m.p. 80–82 °C (lit.[9] 81–82 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 5.782–5.816 (t, *J* = 6.8, 1H, N*H*), 3.131–3.223 (m, 2H, NHC$_2H_5$), 1.082–1.123 (t, *J* = 8.2, 3H, CH_3), 1.148–1.253 (12H, CH_3), 0.821 (s, 1H, C*H*). HRMS (*m*/*z*): 169.1432 (Calcd for $C_{10}H_{19}NO$, 169.1466). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C,70.91; H, 11.39; N, 8.31%.

N-(n-Butyl)-2,2,3,3-tetramethylcyclopropanecarboxamide (**2d**): White crystalline solid (74% yield) m.p. 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 5.450 (s, 1H, N*H*), 3.217–3.249 (t, *J* = 6.4, 2H, NHC$_4H_9$), 1.454–1.506 (m, 2H, NHC$_4H_9$), 1.319–1.372 (m, 2H, NHC$_4H_9$), 1.149–1.258 (12H, CH_3), 0.905–0.940 (t, *J* = 7.0, 3H, NHC$_4H_9$), 0.825 (s, 1H, C*H*). HRMS (*m*/*z*): 197.1790 (Calcd for $C_{14}H_{19}NO$, 197.1778). Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.92; H, 11.96; N, 7.09%.

N-Phenyl-2,2,3,3-tetramethylcyclopropanecarboxamide (**2e**): White crystalline solid (95% yield) m.p. 152–154 °C (lit.[10] 149 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 7.472 (s, 1H, N*H*), 7.330–7.047 (m, 5H, Ar*H*), 1.195–1.319 (d, *J* = 27.8, 12H, CH_3), 0.999 (s, 1H, C*H*). HRMS (*m*/*z*): 217.1474 (Calcd for $C_{14}H_{19}NO$, 217.1466). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.37; H, 8.82; N, 6.45. Found: C, 77.62; H, 8.55; N, 6.53%.

N-(3-Methylphenyl)-2,2,3,3-tetramethylcyclopropanecarboxamide (**2f**): White crystalline solid (92% yield) m.p. 146–147°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 7.417 (s, 1H, N*H*), 6.883–7.259 (m, 4H, Ar*H*), 2.321 (s, 3H, ArCH_3), 1.206–1.321 (12H, CH_3), 0.980 (s, 1H, C*H*). HRMS *m*/*z*: 231.1598 (Calcd for $C_{15}H_{21}NO$, 231.1623). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.90; H, 9.09; N, 6.02%.

N-(3-Trifluoromethylphenyl)-2,2,3,3-tetramethylcyclopropanecarboxamide (**2g**): White crystalline solid (94% yield) m.p. 136–138 °C. ^{1}H NMR ($CDCl_3$): 7.793 (s, 1H, N*H*), 7.262–7.677 (m, 4H, Ar*H*), 1.223–1.329 (12H, CH_3), 0.995 (1H, s). HRMS *m*/*z*: 285.1362 (Calcd for $C_{15}H_{18}F_3NO$, 285.1340). Anal. Calcd for $C_{15}H_{18}F_3NO$: C, 63.15; H, 6.36; N, 4.91. Found: C, 63.12; H, 6.42; N, 4.95%.

N-(3-Nitrophenyl)-2,2,3,3-tetramethylcyclopropanecarboxamide (**2h**): White crystalline solid (90% yield) m.p. 146–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 8.360 (s, 1H, N*H*), 7.264–7.911 (m, 4H, Ar*H*), 1.239–1.336 (12H, CH_3), 1.022 (s, 1H, C*H*). HRMS (*m*/*z*): 262.1326 (Calcd for $C_{14}H_{18}N_2O_3$, 262.1317). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.30; H, 6.63; N, 10.74%.

N-(4-Nitrophenyl)-2,2,3,3-tetramethylcyclopropanecarboxamide (**2i**): White crystalline solid (92% yield) m.p. 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 8.187 (s, 1H, N*H*), 7.629–8.164 (m, 4H, Ar*H*), 1.233–1.329 (12H, CH_3), 1.045(s, 1H, C*H*). HRMS (*m*/*z*): 262.1326 (Calcd for $C_{14}H_{18}N_2O_3$, 262.1317). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.32; H, 6.65; N, 10.76%.

N,N-Dimethyl-2,2,3,3-tetramethylcyclopropanecarboxamide (**2j**): Oil (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 3.061 (s, 1H, NCH_3), 1.153–1.262 (12H, CH_3), 1.042 (s, 1H, C*H*). HRMS (*m*/*z*): 169.1482 (Calcd for $C_{10}H_{19}NO$, 169.1466). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.86; H, 11.46; N, 8.26%.

General procedure for the synthesis of compounds **3a–e**

In a standard reaction procedure, a solution mixture of 2,2,3,3-tetramethylcyclopropanecarboxamide (10 mmol) in anhydrous 1,2-dimethoxyethane (DME) was added dropwise to an ice-cooled, stirred mixture of $TiCl_4$ (20 mmol) and sodium borohydride (20 mmol) of anhydrous DME (30 mL) in 0.5 h. After the addition was complete, the reaction mixture was warmed to 60 °C, and stirred for 14 h. It was then quenched by the addition of water (50 mL) with ice cooling. The mixture was basified with concentrated aqueous ammonia (28%) and then extracted with ethyl acetate (2×70 mL). The extract was washed with saturated sodium chloride solution (100 mL) and dried over Na_2SO_4. The target product (**3a–e**) was then further purified by distillation under reduced pressure.

2,2,3,3-tetramethylcyclopropanemethylamine (**3a**): Colourless liquid (69% yield) b.p. 116–118 °C. FT-IR (ν, cm^{-1}): 3355, 3283, 2980, 2900, 2725, 1593, 1465, 1373, 932. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 2.683–2.665 (2H, CH_2), 1.246 (s, 2H, NH_2), 1.080–0.978 (12H, CH_3), 0.358–0.321 (t, *J* = 7.4, 1H, C*H*). HRMS (*m*/*z*): 127.1384 (Calcd for $C_8H_{17}N$, 127.1361). Anal. Calcd for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.46; H, 11.54; N, 11.06%.

N-Methyl-2,2,3,3-tetramethylcyclopropanemethylamine (**3b**): Colourless liquid (75% yield) b.p. 162–164 °C. FT-IR (ν, cm^{-1}): 2996, 2934, 2873, 2811, 2755, 1465, 1388, 1024, 850. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 2.533–2.570 (d, *J* = 14.8, 2H, CH_2), 2.435 (s, 3H, CH_3), 1.544 (s, 1H, N*H*), 0.964–1.076 (12H, CH_3), 0.333–0.368 (t, *J* = 7.0, 1H, C*H*). HRMS (*m*/*z*): 141.1526 (Calcd for $C_9H_{19}N$, 141.1517). Anal. Calcd for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 75.49; H, 13.61; N, 9.98%.

N-(n-Butyl)-2,2,3,3-tetramethylcyclopropanemethylamine (**3c**): Colourless liquid (70% yield) b.p. 185–187 °C. FT-IR (ν, cm^{-1}): 3298, 2996, 2975, 2817, 2730, 1460, 1378, 1122. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 3.644–3.663 (t, *J* = 7.6, 2H, CH_2), 2.578–2.595 (d, *J* = 6.8, 2H, CH_2), 1.683 (s, 1H, N*H*), 1.443–1.520 (m, 2H, CH_2), 1.296–1.391 (m, 2H, CH_2), 1.001–1.147 (12H, CH_3), 0.903–0.958 (t, *J* = 14.8, 3H, CH_3), 0.536–0.596 (t, *J* = 12.0, 1H, C*H*). HRMS (*m*/*z*): 183.1962 (Calcd for $C_{12}H_{25}N$, 183.1986). Anal. Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.74; N, 7.64. Found: C, 78.56; H, 13.82; N, 7.68%.

N-Phenyl-2,2,3,3-tetramethylcyclopropanemethylamine (**3d**): Colourless liquid (68% yield) b.p. 164–166 °C /30 mmHg. FT-IR (ν, cm^{-1}): 3416, 3052, 2986, 3863, 1603, 1500, 748, 686, 497. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 6.603–7.243 (m, 5H, Ar*H*), 3.502 (s, 1H, N*H*), 3.045–3.064 (d, *J* = 7.6, 2H, CH_2), 1.016–1.114 (12H, CH_3), 0.491–0.527 (t, *J* = 7.2, 1H, C*H*). HRMS (*m*/*z*): 203.1622 (Calcd for $C_{14}H_{21}N$, 203.1674). Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.64; H, 10.49; N, 6.92%.

N,N-Dimethyl-2,2,3,3-tetramethylcyclopropanemethylamine (**3e**): Colourless liquid (78% yield) b.p. 145–147 °C. FT-IR (ν, cm^{-1}): 3283, 2986, 2904, 2780, 1465, 1378, 1142, 727. ^{1}H NMR (400 MHz, $CDCl_3$, δ TMS): 2.413–2.454 (d, *J* = 16.4, 2H, CH_2), 2.357 (s, 6H, CH_3), 1.016–1.076 (12H, CH_3), 0.412–0.435 (t, *J* = 4.6, 1H, C*H*). HRMS (*m*/*z*): 155.1698 (Calcd for $C_{10}H_{21}N$, 155.1674). Anal. Calcd for $C_{10}H_{21}N$: C, 77.35; H, 13.63; N, 9.02. Found: C,77.37; H, 13.57; N, 8.98%.

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