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SHORT COMMUNICATION

SYNTHESIS OF CYCLOBUTANE ANALOGUES

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ABSTRACT. 2-(3-Acetyl-2,2-dimethylcyclobutyl)acetic acid (pinonic acid) was synthesized using *α*-pinene as raw material and potassium permanganate as oxidant. This compound reacted with substituted aniline to produce eight kinds of derivatives with cyclobutane moiety. The yields of the cyclobutane analogues ranged from 24.9 to 78.2 %.

KEY WORDS: Cyclobutane analogues, Pinonic acid, Oxidation

INTRODUCTION

Terpenes are convenient chiral precursors due to their availability and low cost, and among them, *a*-pinene (both enantiomers) and verbenone are prominent. For instance, *a*-pinene has been used as starting material for the production of some compounds of industrial interest and as chiral solvent in the resolution of enantiomers by direct crystallization [1]. For a long time *a*-pinene has been used in industrial applications. The products of *a*-pinene can be used as perfume in cosmetic industry [2], as antifeedant [3], juvenile hormone [4] or repellent [5] of insects in the agriculture, as antifungal [6] and disinfectant [7] in the pharmaceutical industry, as odorant and disinfectant in the cleaning industry and as metal flotation agent in mineral industry.

Oxidation of *a*-pinene (**1**) gave 2-(3-acetyl-2,2-dimethylcyclobutyl)acetic acid (pinonic acid **2**). This acid has a cyclobuane ring. The cyclobutane moiety is a structural feature present in several natural or designed products with interesting biological properties [1]. Many cyclobutane analogues have been proved to be bioacitive. In order to find new kinds of bioacitive products we synthesized eight kinds of acetamide derivatives of pinonic acid.

RESULTS AND DISCUSSION

The synthetic routes involve the oxidation of *a*-pinene to afford pinonic acid, the activation of pinonic acid with $SOCl_2$ to afford acetyl chloride of pinonic acid, the condensation of acetyl chloride with substituted aniline to afford the goal products. The synthetic routes are shown in Scheme 1.

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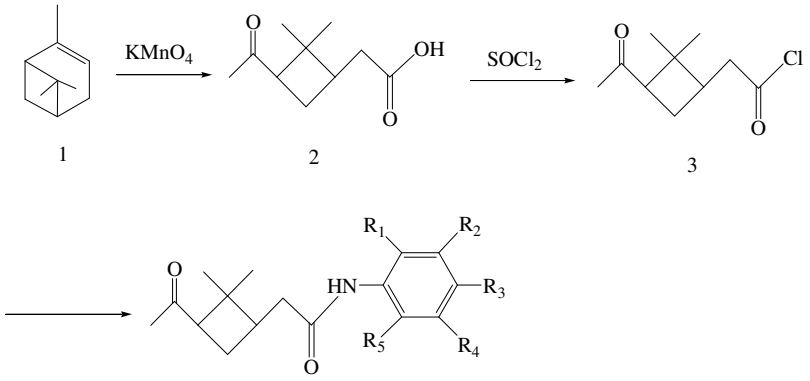

1 2 3

4

4a	$R_1 = H$	$R_2 = H$	$R_3 = H$	$R_4 = H$	$R_5 = H$
4b	$R_1 = CH_3$	$R_2 = H$	$R_3 = H$	$R_4 = H$	$R_5 = H$
4c	$R_1 = H$	$R_2 = H$	$R_3 = CH_3$	$R_4 = H$	$R_5 = H$
4d	$R_1 = CH_3$	$R_2 = H$	$R_3 = CH_3$	$R_4 = H$	$R_5 = H$
4e	$R_1 = H$	$R_2 = H$	$R_3 = F$	$R_4 = H$	$R_5 = H$
4f	$R_1 = F$	$R_2 = H$	$R_3 = H$	$R_4 = H$	$R_5 = F$
4g	$R_1 = H$	$R_2 = F$	$R_3 = H$	$R_4 = F$	$R_5 = H$
4h	$R_1 = H$	$R_2 = H$	$R_3 = CF_3$	$R_4 = H$	$R_5 = H$

Scheme 1. The synthetic routes of the goal products.

Pinonic acid can be synthesized through the ozonolysis or the oxidation of *a*-pinene using oxidants such as potassium permanganate. The ozone oxidation is environment friendly. But the oxidation products are complex and the yield of pinonic acid is low. So we use potassium permanganate as oxidation reagent. Since *a*-pinene is oil-soluble and the reaction medium is water, the usage of phase-transfer catalysts may be useful to the reaction. So we chose tetrabutyl ammonium bromide as phase-transfer catalyst. After the reaction was complete manganese dioxide formed in the reaction was removed through filtration. But the precipitate was sticky and the filtration process required a lot of time. The yield of pinonic acid was less than 25 %. So the oxidation process was not complete. The usage of tetrabutyl ammonium bromide was not useful to the reaction.

In the process of oxidation KOH was produced as the by-product and the reaction solution was alkaline. So the application of pH regulators was advantageous to the oxidation. But in our research we found that the usage of high acidity compounds, such as sulfuric acid and hydrochloric acid, would reduce the yield of pinonic acid greatly. Ammonium sulfate was a low acidity compound and could be used as buffering agent in the reaction [8]. So we chose ammonium sulfate as the pH regulator in the oxidation. The filtration process was easily operated and the yield of pinonic acid was as high as 60 %.

The products were generally identified by ^{1}H NMR and FT-IR spectroscopy. In our previous work we have reported the crystal structure of 2-[(1S,3S)-3-acetyl-2,2-dimethylcyclobutyl]-N-(2, 6-difluorophenyl)acetamide [9]. The crystal belongs to monoclinic system; parameters of the unit cell are: a = 8.7840(18) Å, b = 12.914(3) Å, c = 13.747(3) Å, α = 90.00°, β = 99.20(3) °, γ = 90.00 °; space group P 2_1/n, Z = 4, composition $C_{16}H_{19}F_2NO_2$. The crystal structure confirms that the conformation of 2,2-dimethylcyclobutane fragment is not flat but flexed as though

folded from C3 to C5. The two chiral centers lie on the C3 and C5 and the dihedral angle between C3—C6—C5 and C3—C4—C5 was 29.5°. The structure of cyclobutane moiety represents semi-chair. The configuration of 2-[(1S,3S)-3-acetyl-2,2-dimethylcyclobutyl]-N-(2,6-difluorophenyl)acetamide is shown in Figure 1.

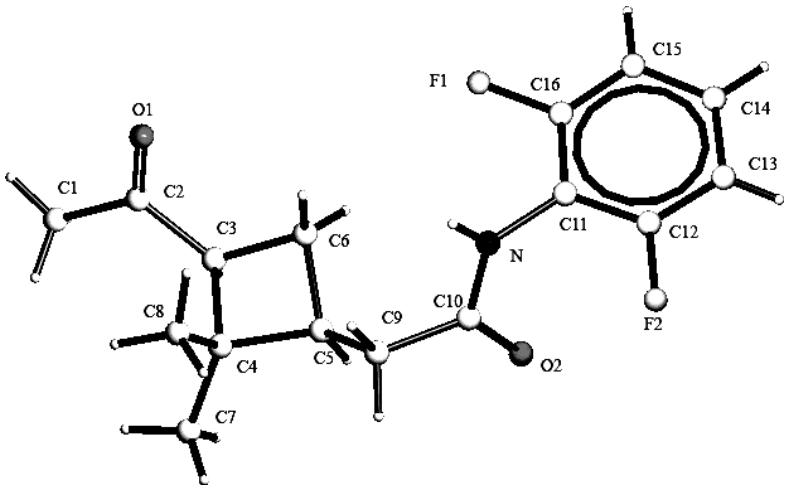

Figure 1. The crystal structure of 2-[(1S,3S)-3-acetyl-2,2-dimethylcyclobutyl]-N-(2,6-difluorophenyl)acetamide.

EXPERIMENTAL

General

The materials used were of technical grade. All the melting points were determined using a XT4A melting point apparatus and were uncorrected. IR (KBr) spectra (ν_{max} in cm^{-1}) were obtained on a Bruker spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ on Bruker AV-500 spectrometer operating at 500 MHz.

The synthesis procedures of ***2***. *a*-Pinene (60 g, 0.44 mol) was mixed with water (600 mL) and ammonium sulfate (31 g, 0.23 mol). The temperature was kept below 10 °C. Potassium permanganate (160 g, 1.01 mol) was added into the mixture in batch with efficient stirring. After the addition of potassium permanganate was complete the mixture was stirred until the color of potassium permanganate had disappeared. The manganese dioxide formed in the reaction was removed by filtration. The precipitate was washed with water (50 mL × 3). The filtrate was acidified with dilute sulfuric acid and colorless solid pinonic acid was obtained by filtration. The yield was 60 % and the product was used in the following reaction without purification.

General process for the preparation of acetamide ***4a-4h***. Pinonic acid (10 g, 0.054 mol) and thionyl chloride (8.4 mL, 0.117 mol) were dissolved in dichloromethane (50 mL). The resulting mixture was refluxed for 8 h. After refluxing the solvent was distilled away under vacuum and the remainder was 2-(3-acetyl-2,2-dimethylcyclobutyl)acetyl chloride. The acetyl chloride was used in the following reaction without purification. The substituted aniline (0.054 mol) and triethylamine (15 mL) were dissolved in dichloromethane (50 mL). 2-(3-Acetyl-2,2-

dimethylcyclobutyl)acetyl chloride was added dropwise to the mixture under room temperature. After stirring overnight the solvent was distilled away under vacuum. The remainder was recrystallized from a mixture of ethanol (40 mL) and water (40 mL) and the pure product was obtained by recrystallization for three times.

2-(3-Acetyl-2,2-dimethylcyclobutyl)-N-phenylacetamide ***4a***. Yield 70.6 %; pale yellow powder; m.p. 113.9-115.2 ^{o}C; IR (KBr) *v*: 3346, 3058, 2960, 2919, 2868, 1705, 1680, 1600, 1546, 759, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.49 (s, 1H, NH), 7.48 (s, 2H, C=CH), 7.29 (q, 2H, C=CH), 7.09 (t, 1H, C=CH), 2.92 (t, 1H, CH), 2.51,2.05 (m, 2H, CH_2), 2.38,1.99 (m, 2H, CH_2), 2.29 (q, 1H, CH), 2.02 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

2-(3-Acetyl-2,2-dimethylcyclobutyl)-N-(o-methylphenyl)acetamide ***4b***. Yield 69.8 %; pale yellow powder; m.p. 104.1-105.6 ^{o}C; IR (KBr) *v*: 3442, 3309, 2950, 2924, 2867, 1701, 1652, 1536, 1457, 1372, 1182, 752, 718, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.72 (d, 1H, NH), 7.20 (s, 1H, C=CH), 7.18 (d, 1H, C=CH), 7.07 (t, 1H, C=CH), 7.00 (s, 1H, C=CH), 2.93 (t, 1H, CH), 2.50, 2.02 (m, 2H, CH_2), 2.41 (q, 1H, CH), 2.31, 1.99 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 0.92 (s, 3H, CH_3).

2-(3-Acetyl-2,2-dimethylcyclobutyl)-N-(p-methylphenyl)acetamide ***4c***. Yield 36.4 %; pale yellow needle; m.p. 120.9-121.9 ^{o}C; IR (KBr) *v*: 3367, 3197, 2955, 2914, 2868, 1690, 1603, 1531, 1453, 1366, 1186, 821, 687, 512 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.65 (s, 1H, NH), 7.35 (d, 2H, C=CH), 7.08 (d, 2H, C=CH), 2.91 (t, 1H, CH), 2.50, 2.04 (m, 2H, CH_2), 2.36, 1.95 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.26 (t, 1H, CH), 2.04 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 0.89 (s, 3H, CH_3).

2-(3-Acetyl-2,2-dimethylcyclobutyl)-N-(2,4-dimethylphenyl)acetamide ***4d***. Yield 78.2 %; pale yellow powder; m.p. 123.6-124.4 ^{o}C; IR (KBr) *v*: 3305, 3022, 2950, 2863, 1711, 1654, 1582, 1459, 1376, 1181, 800, 728, 579 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.58 (s, 1H, NH), 7.05 (d, 1H, C=CH), 6.88 (t, 2H, C=CH), 2.93 (t, 1H, CH), 2.50, 2.08 (m, 2H, CH_2), 2.42, 2.00 (m, 2H, CH_2), 2.32 (t, 1H, CH), 2.30 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

2-(3-Acetyl-2,2-dimethylcyclobutyl)-N-(4-fluorophenyl)acetamide ***4e***. Yield 52.8 %; pale yellow powder; m.p. 114.6-116.5 ^{o}C; IR (KBr) *v*: 3249, 3151, 3068, 2960, 2914, 2873, 1700, 1654, 1618, 1546, 850, 790, 517 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.51 (s, 1H, NH), 7.44 (t, 2H, C=CH), 6.98 (t, 2H, C=CH), 2.94 (t, 1H, CH), 2.50, 2.01 (m, 2H, CH_2), 2.38, 1.96 (m, 2H, CH_2), 2.28 (q, 1H, CH), 2.06 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

2-(3-Acetyl-2,2-dimethylcyclobutyl)-N-(2,6-difluorophenyl)acetamide ***4f***. Yield 24.9 %; pale yellow needle; m.p. 118.9-119.6 ^{o}C; IR (KBr) *v*: 3269, 3202, 2955, 2878, 1680, 1618, 1608, 1478, 1387, 1021, 800, 708, 507 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.24 (s, 1H, NH), 7.16 (t, 1H, C=CH), 6.89 (t, 2H, C=CH), 2.89 (t, 1H, CH), 2.49, 2.10 (m, 2H, CH_2), 2.42, 1.95 (m, 2H, CH_2), 2.37 (q, 1H, CH), 2.02 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 0.89 (s, 3H, CH_3).

2-(3-Acetyl-2,2-dimethylcyclobutyl)-N-(3,5-difluorophenyl)acetamide ***4g***. Yield 34.9 %; pale yellow powder; m.p. 121.9-123.9 ^{o}C; IR (KBr) *v*: 3295, 2950, 2924, 2868, 1705, 1664, 1608, 1597, 1453, 1376, 1186, 800, 728, 564 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.72 (d, 1H, NH), 7.09 (t, 1H, C=CH), 7.03 (s, 1H, C=CH), 6.75 (t, 1H, C=CH), 2.94 (t, 1H, CH), 2.50, 2.01 (m, 2H, CH_2), 2.41,1.97 (m, 2H, CH_2), 2.32 (q, 1H, CH), 2.06 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 0.91 (s, 3H, CH_3).

2-(3-Acetyl-2,2-dimethylcyclobutyl)-N-(4-trifluoromethyl-phenyl)acetamide ***4h***. Yield 69.8 %; pale yellow powder; m.p. 129.8-131.5 ^{o}C; IR (KBr) *v*: 3357, 2960, 2868, 1690, 1618, 1536, 1464, 1407, 1330, 1109, 846, 702, 605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.00 (s, 1H, NH), 7.64 (d, 2H, C=CH), 7.54 (d, 2H, C=CH), 2.96 (t, 1H, CH), 2.53,2.04 (m, 2H, CH_2), 2.44,1.96 (m, 2H, CH_2), 2.34 (q, 1H, CH), 2.08 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

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