Synthesis, Reactions, and Antimicrobial Activity of N-Hydroxy-triacetonamine Derivatives

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Introduction

Preparation of 2,2,6,6-tetramethyl-piperidin-4-one (triacetonamine) still attract researchers all over the world because of its importance and various applications[1-3]. 2,2,6,6-Tetramethyl-piperidine derivatives have different biological effects. 2,2,6,6- Tetramethyl- piperidine derivatives have anticancer, analgesic, antipyretic and anticholinergic effects[4,5]. Also, 2,2,6,6-tetramethyl-piperidin-4-one have hypotensive and vasodilating activity as demonstrated by intravital microcirculation method[6].

Preperation of 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one (N-hydroxy-triacetonamine) starting from 2,2,6,6- tetramethylpiperidin-4-one was done through two steps (Scheme 1)[21]. The methods of preparation of 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one which is mentioned in the literature are difficult and expensive, so we will report simple and one step method for its preparation.

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preparation (Scheme 1)\[21\].

Also, reactions of \(N\)-hydroxytriacetonamine with various organic reagents will be reported.

**Results and Discussion**

\(2,2,6,6\)-Tetramethyl-4-piperidone contains different functions groups which could be used to react with various organic reagents. Active methylene adjacent to carbonyl group was used to prepare different chalcones which further react with different organic reagents\[22\]. In this article, we will prepare \(N\)-hydroxy derivative of triactonamine which will be the starting material. Although the oxygen of hydroxyl group linked to nitrogen in \(N\)-hydroxy-\(2,2,6,6\)-tetramethyl-4-piperidone (2) which is good electronegative atom, the oxygen atom of hydroxyl group is still a nucleophile which can react with different electrophiles.

\(2,2,6,6\)-Tetramethyl-4-piperidone (I) reacts with hydrogen peroxide in potassium hydroxide to afford \(N\)-hydroxy-\(2,2,6,6\)-tetramethyl-4-piperidone (2) (Scheme 1). \(N\)-Hydroxy-\(2,2,6,6\)-tetramethyl-4-piperidone (2) reacts with formaldehyde to give compound (3) which reacts with piperidine to affords compound (4) (Scheme 2). Compound (4) can be prepared directly by reacting \(N\)-hydroxy-\(2,2,6,6\)-tetramethyl-4-piperidone (2) with formaldehyde and piperidine (Scheme 2). Spectral data (IR, MS, \({}^1\)H NMR) are in agreement with the assigned structure of compounds (2), (3) and (4). The mass spectrum of compound (2) shows molecular ion peak at m/z 171. The \({}^1\)H NMR spectrum of compound (3) show characteristic signal at δ4.8 corresponding to OCH\(_2\). The IR spectrum of compound (4)
N-Hydroxy-2,2,6,6-tetramethyl-4-piperidone (2) reacts with sodium azide to afford 1-azido-2,2,6,6-tetramethylpiperidin-4-one (5) and 1-azido-2,2,7-trimethyl-1,4-diazepan-5-one (6). Although separation of compound (6) was done accidently, but it is expected. Ring expansion of piperidine derivative while reaction with sodium azide is reported[23]. The Infrared spectrum of compounds (5) and (6) show characteristic absorption band for azide group. Also, the IR spectrum of compound (6) show absorption band for carbonyl group of amide. The 1H NMR of compound (6) shows signal for CH$_2$N at δ 4.00.

N-Hydroxy-2,2,6,6-tetramethyl-4-piperidone (2) reacts with α-bromoacetoglucose and α-bromoacetoxylose to afford 2-(acetoxymethyl)-6-((2,2,6,6-tetramethyl-4-oxopiperidin-1-yl)oxy) tetrahydro-2H-pyran-3,4,5-triyl triacetate (7a) and 2-((2,2,6,6-tetramethyl-4-oxopiperidin-1-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (7b) respectively. Deacetylation of compounds (7a,b) were accomplished by ammonia solution to afford 2,2,6,6-tetramethyl-1-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (7a,b) respectively.
piperidin-4-one (8a) and 2,2,6,6-tetramethyl-1-(3,4,5-trihydroxytetrahydro-2H-pyran-2-yl) oxy) piperidin-4-one (8b). The structures of compounds (7a,b) and (8a,b) were elucidated from $^1$H NMR, IR, and mass spectral data. The IR of compounds (7a,b) show disappearance of absorption band for hydroxyl group and appearance of absorption band for carbonyl group of an ester. The $^1$H NMR of compound (7a) shows signal at $\delta$2.30 corresponding to CH$_3$CO. The IR spectra of compounds (8a,b) show appearance of absorption band for hydroxyl group which indicate deacetylation of compounds (7a,b). N-Hydroxy-2,2,6,6-tetramethyl-4-piperidone (2) reacts with 2-amino-4-(4-chlorophenyl)-3-cyano-5,5,7,7-tetramethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl acetate (9). Also, N-hydroxy-2,2,6,6-tetramethyl-4-piperidone (2) reacts with p-chlorobenzaldehyde and cyanoacetamide to afford 2-amino-3-carbamoyl-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,5,7,7-tetramethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl acetate (10a). In addition, N-hydroxy-2,2,6,6-tetramethyl-4-piperidone (2) reacts with p-chlorobenzaldehyde and ethylcyanoacetate to produce ethyl-6-acetoxy-2-amino-8-(4-chlorobenzylidene)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate (10b). The spectral data of compounds (9), and (10a,b) are compatible with the proposed structure. The IR spectrum of compound (9) shows absorption band for cyano group at 2201 cm$^{-1}$. The $^1$H NMR spectrum of compound (9) shows signal for aromatic protons at 7.25 and 7.68. The $^{13}$C NMR of compound (9) shows signals for SP$^2$ carbon. The IR spectrum of compound (10a) show absorption band for carbonyl group of amide at 1644 cm$^{-1}$. The $^1$H NMR of compounds (10a,b) show signals at $\delta$ 4.73 and 5.99 corresponding to hydrogen linked to SP$^2$ carbon.

**Antimicrobial activity**

The antimicrobial activity of new compounds was done according to reported procedure [24]. Antimicrobial screening of some of the synthesized compounds is summarized in the following table (Table 1). Most of tested compounds show moderate activity against reference drug. Compound (5) shows highest antibacterial activity against reference drug cefotaxime. Also, compound (10a) shows highest antifungal activity against reference drug nystatin.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Gram positive bacteria</th>
<th>Gram negative bacteria</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B. subtilis</td>
<td>B. cereus</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>20</td>
<td>20</td>
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</tr>
<tr>
<td>9</td>
<td>10</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>10a</td>
<td>16</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>26</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Nystatin</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

**Experimental**

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus (Shimadzu, Tokyo, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). $^1$H NMR was determined on a JEOL-Ex-400 NMR spectrometer (JEOL, Tokyo, Japan) and chemical shifts were expressed as part per million; ppm ($\delta$ values) against TMS as internal standard. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo electron corporation, USA). Microanalyses were operated using Mario El Mentar apparatus and satisfactory results were within the accepted range ($\pm 0.30$) of the calculated values. Follow up the reactions and checking the purity of the compounds was made by TLC on silica gel-protected aluminium sheets (Type 60 F254, Merck). Mass spectra, and elemental analysis were done in Microanalytical Centre in Faculty of Science, Cairo University. $^1$H &$^{13}$C NMR, IR spectra, and antimicrobial activity were done in National Research Centre, Cairo, Egypt. All used chemicals were of reagent grade and were used as supplied directly unless otherwise stated.

1-Hydroxy-2,2,6,6-tetramethylpiperidin-4-one (2)

Triacetonamine 1 (1.55 g, 0.01 mol) was dissolved in 20 ml methanol. This solution was added to 20 ml acetone containing KOH solution (1g. KOH in 5 ml H2O). Then, we add 5 ml H2O2 (36 %) dropwise with stirring at room temperature. The reaction mixture is heated at 70 °C with stirring for 2 hours. The reaction mixture is evaporated under reduced pressure. The solid residue crystallized from water to give compound 2 in 71 % yield (m.p. 98-99 °C). IR (KBr, cm−1): 3490 (OH), 1719 (C=O). MS, m/z (%) 201 (M+, 90%), 184 (M+-OH, 34%). 1HNMR (CDCl3) δ ppm: 1.15 (s, 6H, 2 CH3), 1.17 (s, 6H, 2 CH), 2.17 (s, 4H, 2 CH2), 7.25 (brs, 1H, OH). Anal. calcd. For C8H15NO (171.24): C, 51.17; H, 8.11; N, 33.15. Found: C, 51.20; H, 8.18; N, 33.20.

Preparation of compounds (5) and (6)

Compound 2 (0.01 mole) is refluxed with sodium azide (0.01 mole) in 5 mL acetic acid and 4 drops of water for 15 minutes. The precipitate is filtered, dried and crystallized from benzene to afford compound 5. The filtrate is evaporated under reduced pressure to produce compound 6.

1-Azido-2,2,7-trimethyl-1,4-diazepan-5-one (6)

Yield 73%, m.p. 220-222 °C, brown powder. IR (KBr, cm−1): 3225 (N=O), 1737 (C=O). MS, m/z (%) 211 (M+, 70%). 1HNMR (CDCl3) δ ppm: 2.12 (s, 6H, 2 CH3), 1.57 (s, 6H, 2 CH), 1.92 (s, 4H, 2 CH2), 5.01 (brs, 1H, NH). Anal. calcd. For C12H15N2O (196.25): C, 55.12; H, 8.28; N, 28.60. Found: C, 55.12; H, 8.28; N, 28.60.

General method for preparation of compounds (7a,b)

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide or 2-hydroxytetrahydro-2H-pyran-3,4,5-triyli triacetate (0.005 mole) dissolved in aceton (15 ml) was added portion-wise to a clear solution of compound 2 (0.005 mole) and potassium hydroxide (0.28g, 0.005 mole) in distilled water (2 ml). The reaction mixture was stirred at room temperature until reaction was judged complete by TLC(pet. ether/ethyl acetate, 4:1 v/v). Evaporation of the solvent afforded a residue which was washed with distilled water (10 mL) followed by extraction with chloroform. The obtained residue after removal of chloroform was triturated with petroleum ether (b.p. 40-60 °C) (45 mL) with stirring. The solid product was filtered, dried and recrystallized from ethanol to produce compound 7a,b.
2-(Acetoxymethyl)-6-((2,2,6,6-tetramethyl-4-oxopiperidin-1-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyi triacetate(7a)

IR (KBr, cm⁻¹): ν: 1721 (C=O), 1737 (C=O). CH₃NMR (CDCl₃) δ ppm: 1.35 (s, 6H, 2 CH₃), 1.52 (s, 6H, 2 CH₂), 2.25 (s, 4H, 2 CH₂), 3.70 (t, 2H, J=7 Hz, CH₂), 3.91 (d, 2H, J=7 Hz, CH), 3.98 (d, 2H, J=7 Hz, OCHO), 7.10 (brs, 3H, NH). Anal.calcd. For C₁₅H₂₅NO₉ (398.89): C, 63.23; H, 5.88; N, 14.09.

2-Amino-4-(4-chlorophenyl)-3-cyano-5,5,7,7-tetramethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl acetate(9)

Compound 2 (0.01 mole) is heated under reflux for 4 hours with 2-(4-chlorobenzylidene) malononitrile (0.01 mole) and acetic acid (10 mL). The reaction mixture is poured into water. The solid precipitate is filtered, dried, crystalized from ethanol/ water mixture (5:1). Yield 71 %, m.p. 180-182°C, brown powder. IR (KBr, cm⁻¹): ν: 3364 (NH), 2201 (CN), 1759 (C=O). MS, m/z (%) 398 (M⁺), 23%.¹H NMR (CDCl₃) δ ppm: 1.24 (s, 6H, 2 CH₂), 1.35 (s, 6H, 2 CH₂), 2.03 (s, 2H, CH₂), 2.44 (s, 3H, CH₃), 5.41 (brs, 2H, NH₂), 7.25 (d, 2H, J=7 Hz, Ar), 7.68 (d, 2H, J=7 Hz, Ar). ¹³C NMR (CDCl₃) δ ppm: 1.0, 1.7, 24.8, 29.7, 30.9, 113.7 (CN), 128.6, 128.9, 129.0, 129.1, 129.2, 129.4, 135.0, 136.0 (Ar=C), 153.8 (C=O). Anal.calcd. For C₁₅H₂₅ClNO₅ (539.46): C, 62.33; H, 5.81; N, 14.05. Found: C, 63.30; H, 5.88; N, 14.09.

3,4,5-Trihydroxytetrahydro-2H-pyran-3,4,5-triyi triacetate(7b)

IR (KBr, cm⁻¹): ν: 1709 (C=O), 1742 (C=O). CH₃NMR (CDCl₃) δ ppm: 1.0, 1.7, 24.8, 29.7, 30.9, 40.2, 45.5 (C), 116.4 (CH=), 116.4, 120.6, 128.3, 128.7, 128.9, 129.1, 129.2, 129.4, 135.0, 136.0 (Ar-C), 153.8 (C=O). Anal.calcd. For C₁₅H₂₅ClNO₅ (539.46): C, 62.33; H, 5.81; N, 10.39. Found: C, 62.39; H, 5.28, N, 10.42.

General method for preparation of compounds (8a,b)

The acetylated glycosides 7a,b (5 mmol) was dissolved in dry saturated methanolic ammonia solution (20 mL) and stirred at 0 °C for 1 h, then stirring was persisted at r.t. for 5 h. Removal of the solvent under vacuum at 40 °C gave a solid residue, which was recrystallized from ethanol to give the corresponding free glycoside 8a,b.

2,2,6,6-Tetramethyl-1-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)piperidin-4-one(8a)

IR (KBr, cm⁻¹): ν: 1709 (C=O), 1742 (C=O). CH₃NMR (CDCl₃) δ ppm: 1.18 (s, 6H, 2 CH₃), 8.16; N, 4.20. Found: C, 54.10; H, 8.19; N, 4.29.

2,2,6,6-Tetramethyl-1-((3,4,5-triroyl tetrahydro-2H-pyran-2-yl)oxy)piperidin-4-one(8b)

IR (KBr, cm⁻¹): ν: 1721 (C=O), 1737 (C=O). CH₃NMR (CDCl₃) δ ppm: 1.0, 1.7, 24.8, 29.7, 30.9, 40.2, 45.5 (C), 116.4 (CH=), 116.4, 120.6, 128.3, 128.7, 128.9, 129.1, 129.2, 129.4, 135.0, 136.0 (Ar-C), 153.8 (C=O). Anal.calcd. For C₁₅H₂₅ClNO₅ (539.46): C, 62.33; H, 5.81; N, 10.39. Found: C, 62.39; H, 5.28, N, 10.42.
precipitate formed is filtered, dried, crystalized from ethanol/water (5:1). Yield 51 %, m.p. 210-212°C, pale yellow powder. IR (KBr, cm−1): ν: 3452 (NH), 1737 (C=O), MS, m/z (%) 568 (M+, 7%). 1H NMR (CDCl3) δ ppm: 1.20 (s, 6H, 2 CH3), 1.69 (s, 6H, 2 CH3), 1.75 (t, 3H, J=8 Hz, CH3), 2.04 (s, 3H, CH3), 3.78 (q, 2H, J=8 Hz, OCH3), 2.99 (s, 1H, =CH), 7.25 (d, 4H, J=7.5 Hz, Ar), 7.37 (d, 4H, J=7.5 Hz, Ar), 7.48 (brs, 2H, NH). 13C NMR (CDCl3) δ ppm: 13.4, 13.5, 45.3, 50.2, 50.8, 57.8, 58.7, 61.5, 62.6, 99.8, 128.1, 128.9, 129.0, 129.4, 129.1, 129.2, 129.6, 129.7 (Ar-C), 166.0, 166.3 (2C=O). Anal.calcd. For C21H26ClN4O3 (568.50): C, 63.38; H, 5.50; N, 7.39. Found: C, 63.42; H, 5.56; N, 7.42.

References


تحضير، التفاعلات، و الفاعليه ضد الميكروبات لمشتقات ان-هيدروكسي-تراياسيتونامين

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تم تحضير ان-هيدروكسي-تراياسيتونامين 1 في خطوة واحدة و بسيطة. ان-هيدروكسي-تراياسيتونامين 1 يتفاعل مع العديد من الكواشف العضويه. ان-هيدروكسي-تراياسيتونامين 1 يتفاعل مع الفورمالدهايد و الفورمالدهايد و البيبريدين لتحضير مركبات 2 و 4. ان-هيدروكسي-تراياسيتونامين 1 يتفاعل مع ازيد الصوديوم و الفا بروموشوجر لكي يكون المركبات المقابله. ان-هيدروكسي-تراياسيتونامين 1 يتفاعل مع مركبات من المالونونيتريل لكي يكون المركبات المقابله. ان-هيدروكسي-تراياسيتونامين 1 يتفاعل مع بارا كلوروبنزالدهايد و سيانواسيتاميد لكي يكون مركبات من 9-نفثريدين 1. ان-هيدروكسي-تراياسيتونامين 1 يتفاعل أيضا مع بارا كلوروبنزالدهايد و سيانواسيتاميد لكي يكون مشتق من 8-نفثريدين 1. ان-هيدروكسي-تراياسيتونامين 1 يتفاعل أيضا مع بارا كلوروبنزالدهايد و اليمين سيلانو اسيتات لكي يكون مشتق من 10-نفثريدين 1. الفاعليه ضد الميكروبات المحضره تم قياسها.