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Research Paper

Tungstate catalyzed oxidation of Pyrimidines with hydrogen peroxide: A novel and industrial scale synthesis of Minoxidil, Kopyrrol and Kopexil

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ABSTRACT: *The sodium tungstate catalyzed oxidation of pyrimidine's with hydrogen peroxide give the corresponding pyrimidine N-oxides, which are versatile synthetic intermediates for the synthesis of therapeutically active derivatives like Minoxidil, Kopyrrol and Kopexil. The present invention aims to provide an industrially scalable process for the 2,4-Diamino-6-chloropyrimidine-3-oxide which shall be easily converted to many therapeutically active derivatives.*

KEYWORDS: *Pyrimidine N-oxides, Tungstate catalyzed oxidation, Minoxidil, Kopyrrol and Kopexil.*

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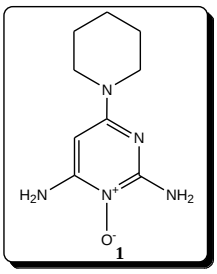
I. INTRODUCTION

Minoxidil (**1**), Kopyrrol (**2**) and Kopexil (**3**), are therapeutically active Pyrimidine N-oxide derivatives possess variety of therapeutic activities like antihypertensive and are widely used as in cosmetics since these derivatives effectively stimulates hair growth. Overall, minoxidil[1] is a valuable antihypertensive agent and also the widely used hair growth product worldwide and used in the treatment of alopecia. Different literatures disclosed different processes for the preparation of 2,4-Diamino-6-chloropyrimidine-3-oxide, from 2,4-Diamino-6- chloropyrimidine using various oxidizing agents. In this work, a simple, efficient and robust process has been developed to synthesize Minoxidil (**1**), Kopyrrol (**2**) and Kopexil (**3**) with high overall yields with purity of > 99.5% in a large-scale production. And also, the synthetic process avoided the use of conventional oxidising agents and tedious isolation process which are not desirable for industrial production.



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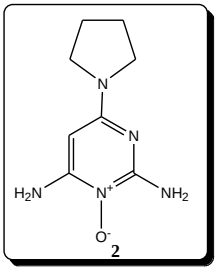

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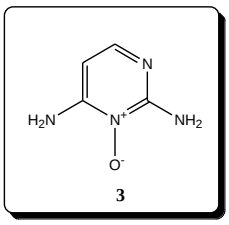

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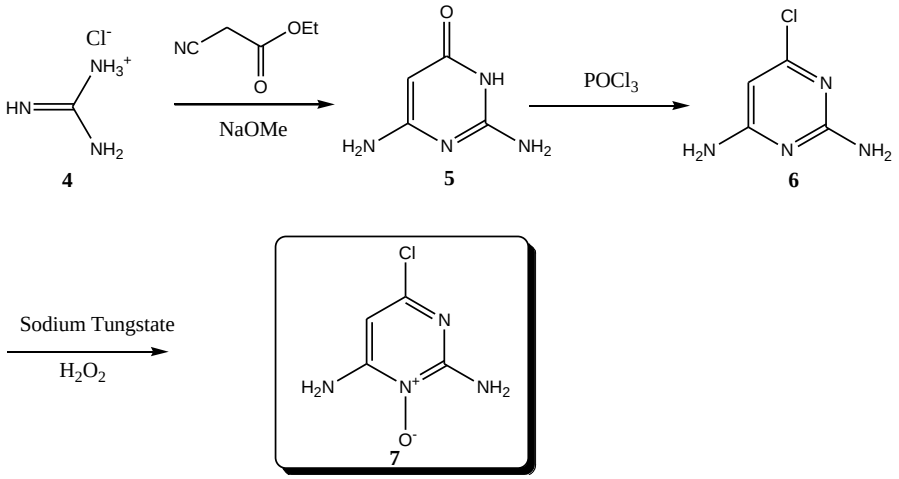
N-Oxidations of nitrogen containing heterocyclic compounds have received much attention due to the usefulness of the N-oxides as synthetic intermediates and their biological importances.[1] N-oxidation of 2,4-Diamino-6- chloropyrimidine has been achieved by various oxidizing agents including peracetic acid,[2] m-chloroperbenzoic acid (m-CPBA),[3] magnesium monoperphthalate (MMPP),[4] hydrogen peroxide-phthalicanhydride,[5] hydrogen peroxide-trifluoroacetic acid,[6] cobalt ferrite-hydrogen peroxide,[7] and dioxiranes.[8] All these processes suffer from various drawbacks such as use of expensive oxidizing agents, longer reaction time with more no. of reaction steps, high reaction temperatures, the conventional reagents used for oxidation

being potentially more hazardous, overall yields being lower because of no. of reaction steps and purification required in each step. The present invention aims to provide an economically practicable process of 2,4-Diamino-6- chloropyrimidine-3-oxide which renders possible to easily produce this compound in a good yield and in a purity at an industrial scale overcoming most of the above drawbacks. The present methodology, Sodium tungstate catalyzed oxidation of pyrimidine's with hydrogen peroxide gave the corresponding pyrimidine N-oxides in high yields.

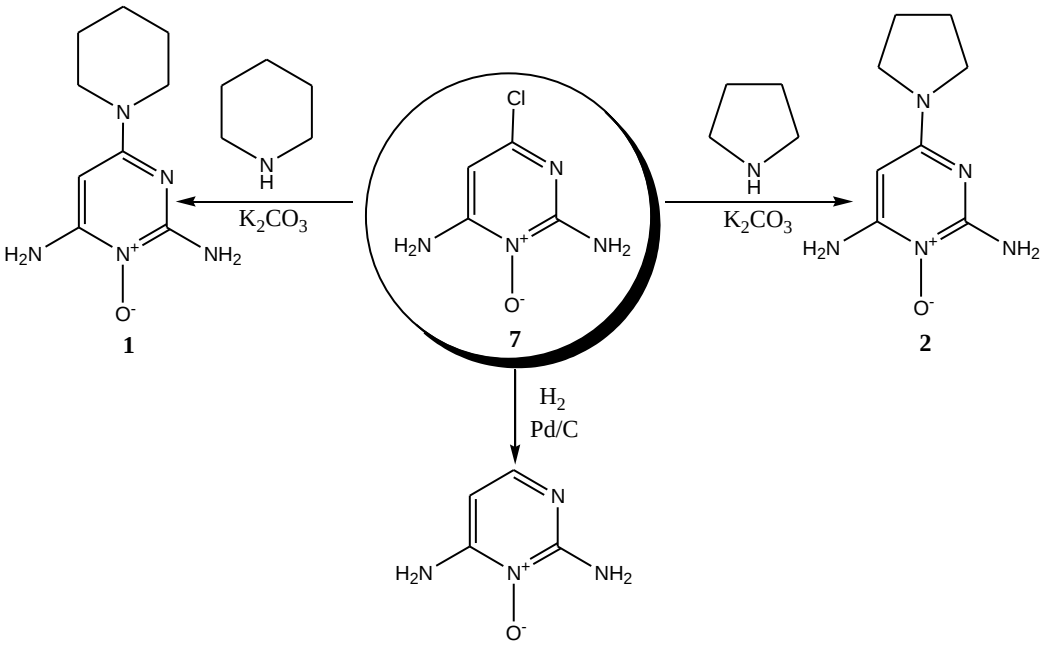
II. RESULTS AND DISCUSSION

Treatment of Guanidinium chloride (**4**) with methyl cyanoacetate in presence of sodium methoxide in methanol delivered 2,6-diaminopyrimidin-4(3H)-one (**5**) with 94 % yield. The resultant product was subjected to $POCl_3$ reaction to yield the 6-chloropyrimidine-2,4-diamine (**6**) in 80 % yield. Now the crucial step of our synthesis is the sodium tungstate catalyzed oxidation of 6-chloropyrimidine-2,4-diamine (**6**) with hydrogen peroxide delivered the 2,4-Diamino-6-chloropyrimidine-3-oxide (**7**) in 92 % yield. This process provides an industrial scale application for the synthesis of 2,4-Diamino-6-chloropyrimidine-3-oxide (**7**).



Scheme 1

It is evident from the literature that, the N-Oxidation chloropyridines shall be activated toward chlorine replacement, as a consequence of the electron-withdrawing effect of the N-oxygen atom.[9] The intermediate, 2,4-Diamino-6-chloropyrimidine-3-oxide shall be converted in to Minoxidil (**1**) by the condensation of piperidine with compound **7** in acetone and in presence of Potassium carbonate base. The crude product was recrystallized in isopropanol solvent to deliver the pure Minoxidil (**1**). In a similar manner, compound **7** on condensation with condensation of pyrrolidine followed by recrystallization in isopropanol delivered the pure Kopyrrol (**2**). The Kopexil (**3**), was obtained in good purity by subjecting the compound **7** for hydrogenation followed by recrystallization in isopropanol.



1 **7** **2**

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Scheme 2

III. EXPERIMENTAL DETAILS

Preparation of 2,6-Diamino-4-pyrimidinol (5). To a stirred solution of sodium methoxide **(**565.0 g, 10.46 mol) in 2 L of methanol at below 20 ^{o}C was added guanidinium chloride (500.0 g, 5.23 mol) and methyl cyanoacetate (544.3 g, 5.49 mol) and stirred the reaction mass for 15 min at 10 - 20 ^{o}C followed by maintaining the reaction mass for 8 hours at reflux temperature. The solvent was distilled under vacuum at below 60 ^{o}C and water (2 L) was added to the resultant reaction mass and adjusted the reaction mass pH to 7 - 8 by using Concentrated HCl (550 mL). The resultant heterogeneous reaction mass was cooled to 5-10 ^{o}C and maintained at 5-10 ^{o}C for 1-2 hours and the precipitate was filtered off, washed with chilled water (500 mL) and dried the solid at 60-65 ^{o}C to delivered the 2,6-Diamino-4-pyrimidinol (627.0 g. 95.0%); mp 286"C-287 ^{o}C (decomp.) (lit.[10] 286 ^{o}C (decomp.). ^{1}H-NMR. (400 MHz, (DMSO-d_6): 5.69 *(s,* 1 H); 6.31 *(s,* 2 H); 6.57 *(s,* 2 H).

Preparation of 2,4-Diamino-6-chloropyrimidine (6). To a stirred solution of $POCl_3$ (2.94 kg, 19.17 mol) was added 2,6-Diamino-4-pyrimidinol (500.0 g, 3.96 mol) at room temperature and stirred the reaction mass for 15 min at room temperature. The reaction mass temperature was raised to 100-105 ^{o}C and maintained for 8 hours at 100-105 ^{o}C. After the reaction completion excess $POCl_3$ was distilled off and cooled the reaction mass to below 20 ^{o}C. The reaction mass was quenched with the crushed ice (15.0 kg) at below 50 ^{o}C and then the reaction mass PH was adjusted to 6-7 by using 50 % NaOH solution (2.5 L). The resultant heterogeneous reaction mass was cooled to 20-30 ^{o}C and maintained for 1-2 hours at 20-30 ^{o}C. The precipitate was filtered off, washed with chilled water (750 mL) and dried the solid at 65-70 ^{o}C to deliver 2,4-Diamino-6-chloropyrimidine (490.0 g. 85.2%); mp 200 ^{o}C-201^{o}C (decomp) (lit.[11] 200 ^{o}C-201^{o}C (decomp). ^{1}H-NMR. (400 MHz, (DMSO-d_6): 5.69 *(s,* 1 H); 6.31 *(s* , 2 H); 6.57 *(s,* 2 H).

Preparation of 2,4-Diamino-6-chloropyrimidine-3-oxide (7). To a stirred solution of 2,4-Diamino-6-chloropyrimidine (500.0 g, 3.46 mol) in 2 L methanol was added sodium tungstate dihydrate (11.4 g, 0.034 mol) at room temperature followed by drop wise addition of 50 % hydrogen peroxide (353 mL, 5.19 mol) and stirred the reaction mass for 10 min at room temperature. The reaction mass temperature was raised to 70-75 ^{o}C and maintained for 4-5 hours at 70-75 ^{o}C. After the reaction completion, the reaction mass temperature was cooled to to below 20 ^{o}C and 2.5 L water was added to the reaction mass and stirred for 20-30 minutes. The resultant heterogeneous reaction mass was further cooled to 10-20 ^{o}C and maintained for 2-3 hours at 10-20 ^{o}C. The precipitate was filtered off, washed with chilled water (500 mL) and dried the solid at 60-65 ^{o}C to deliver 2,4-Diamino-6-chloropyrimidine-3-oxide (455.0 g. 82.0%); mp 210 ^{o}C -211 ^{o}C (decomp.) (lit.,[12] 210 ^{o}C -211 ^{o}C (decomp.). ^{1}H-NMR. (400 MHz, (DMSO-d_6): 6.09 *(s,* 1 H); 37.57 *(br, 4* H). MS.: 160.56 *(Mt).* C4H5ClN4O (160.56). FT-IR (Vmax, cm^{-1}, neat); 3473, 3415, 3339, 3284, 1618, 1567, 1483, 1372.

Preparation of 2,4-Diamino-6-piperidino pyrimidine-3-oxide, Minoxidil. (1). To a stirred solution of 2,4-Diamino-6-chloropyrimidine-3-oxide (100.0 g, 0.63 mol) in 400 mL acetone was added potassium carbonate (173.2 g, 1.25 mol) and piperidine (58.7 g, 0.69 mol) at room temperature and stirred the reaction mass for 10 min. The reaction mass temperature was raised to 55-60 ^{o}C and maintained for 11-12 hours at 55-60 ^{o}C. After the reaction completion, the reaction mass temperature was cooled to room temperature and adjusted the pH to 6.0-6.5 with aqueous citric acid solution followed by workup with ethyl acetate (600 mL). The ethyl acetate layer was separated and the solvent was distilled to get the crude Minoxidil crude product. To the above solid isopropanol (400 mL) was added and heated the reaction mass to 55-60 ^{o}C and stirred for 60-90 minutes. After the maintenance at 55-60 ^{o}C, the reaction mass was cooled to 5-10 ^{o}C and maintained for 10-12 hours at 5-10 ^{o}C. The precipitate was filtered off, washed with chilled isopropanol (50 mL) and dried the solid at 55-60 ^{o}C to deliver pure Minoxidil. (105.7 g. 81.0%). m.p. 261-262 ^{o}C (decomp.) (lit.,[13] 260 ^{o}C -262 ^{o}C (decomp.).. ^{1}H-NMR. (400 MHz, (DMSO-$d_{6,}$): 1.44-1.62 *(in, 6* H); 3.36 *(t, J=5.32 Hz, 4* H); 5.35 **(s,** 1 H); 6.83 (br, *4* H). ^{13}C-NMR. (125 MHz, (DMSO-$d_{6,}$): 24.58, 25.36, 45.39, 73.52, 152.27, 153.47, 155.52. MS.: 209.2 *(Mt).* $C_9H_{15}N_9O$. FT-IR (Vmax, cm^{-1}, neat); 3307, 2932, 2853, 2261, 1651, 1611, 1475, 1374.

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Preparation of 2,4-Diamino-6-pyrrolidino pyrimidine-3-oxide, Kopyrrol, (2). To a stirred solution of 2,4-Diamino-6-chloropyrimidine-3-oxide (50.0 g, 0.31 mol) in 200 mL acetone was added potassium carbonate (86.6 g, 0.63 mol) and pyrrolidine (25.0 g, 0.35 mol) at room temperature and stirred the reaction mass for 10 min. The reaction mass temperature was raised to 55-60 ^{o}C and maintained for 11-12 hours at 55-60 ^{o}C. After the reaction completion, the reaction mass temperature was cooled to room temperature and adjusted the pH to 6.0-6.5 with aqueous citric acid solution followed by workup with ethyl acetate (350 mL). The ethyl acetate layer was separated and the solvent was distilled to get the crude Kopyrrol. To the above crude product, isopropanol (220 mL) was added and heated the reaction mass to 55-60 ^{o}C and stirred for 60-90 minutes. After the maintenance at 55-60 ^{o}C, the reaction mass was cooled to 5-10 ^{o}C and maintained for 10-12 hours at 5-10 ^{o}C. The precipitate was filtered off, washed with chilled isopropanol (50 mL) and dried the solid at 55-60 ^{o}C to deliver pure Kopyrrol. (46.2 g. 76.0%). m.p. 276-278 ^{o}C (decomp.) (lit.,[13] 278 ^{o}C (decomp.).. ^{1}H-NMR. (400 MHz, (DMSO-$d_{6,}$): 1.80-1.94 *(in, 4* H); 3.22-3.35 *(m, 4* H); 5.09 **(s,** 1 H); 6.82 (br, *4* H). ^{13}C-NMR. (100 MHz, (DMSO-$d_{6,}$): 28.28, 51.21, 84.27, 148.45, 157.48. MS.: 195.27 *(Mt).* $C_8H_{13}N_9O$. FT-IR (Vmax, cm^{-1}, neat); 3302, 2924, 2848, 2258, 1652, 1608, 1472, 1372.

Preparation of 2,4-Diamino pyrimidine-3-oxide, Kopexil (3). To a stirred solution of 2,4-Diamino-6-chloropyrimidine-3-oxide (50.0 g, 0.31 mol) in 300 mL methanol was added catalytic 10% Pd/C and stirred the reaction mass under hydrogen atmosphere for 8-10 hours. After the reaction completion, the reaction mass was filtered through celite bed and washed with 50 mL of methanol. The solvent was distilled and the crude product was dissolved in isopropanol (220 mL) and heated the reaction mass to 55-60 ^{o}C and stirred for 60-90 minutes. After the maintenance at 55-60 ^{o}C, the reaction mass temperature was cooled to 5-10 ^{o}C and maintained for 10-12 hours at 5-10 ^{o}C. The precipitated solid was filtered off, washed with chilled isopropanol (50 mL) and dried the solid at 55-60 ^{o}C to deliver pure kopexil. (28.2 g. 72.0%). ^{1}H-NMR. (400 MHz, (DMSO-d_6): 5.37 (s, I H); 7.08 (br. 4 H). MS.: 126.06 *(Mt).* $C_4H_6N_4O$ (126.12).

IV. CONCLUSION

In this study, we have developed a novel methodology for the *N* -oxidation of 6-chloro-2,4-diaminopyrimidine using H_2O_2 in the presence of Sodium Tungstate catalyst in methanol under reflux conditions. The resultant 2,6-diamino-4-chloro-pyrimidine *N* -oxide is converted in to therapeutically active compounds Minoxidil (**1**), Kopyrrol (**2**) and Kopexil (**3**). Based on the obtained results, the current methodology has prominent advantages in plant scale production of 2,6-diamino-4-chloro-pyrimidine *N* –oxide.

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