Asian Journal of Chemistry; Vol. 23, No. 8 (2011), 3546-3548

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis and Characterization of Pyridyl Propargyloximes

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(*Received*: 13 October 2010; *Accepted*: 25 April 2011) AJC-9843

4-Pyridiniumaldoxime and 3-pyridiniumaldoxime are synthesized by the treatment of 4- and 3-pyridinecarboxaldehydes with hydroxylamine hydrochloride, respectively. Methyl triflate salts were obtained by the treatment of methyl triflate with corresponding 4-pyridiniumaldoxime and 4-pyridinecarboxaldehyde O-propragyloxime. The reactions of 4-pyridiniumaldoxime and 3-pyridiniumaldoxime with 3-bromo-1-trimethylsilyl-1-propyne yielded the corresponding pyridinecarboxaldehyde O-propragyloximes. The structures of these products were determined by ^{1}H, ^{13}C NMR data and X-ray structural analysis.

Key Words: Aldoxime, Pyridyl propargyloximes.

INTRODUCTION

Pyridinium aldoximes are versatile building blocks for organic synthesis, since they constitute an important class of natural products and the key intermediates thereof[1-4]. Hydroxylamine reactivated organophosphoryl-inhibited cholinesterases faster than water did[5] and later it was reported that 2-pyridinium aldoxime-2-methyl salt was far more effective than hydroxylamine in reactivating the enzyme[6]. After thorough study of many of these compounds, *bis*-pyridinium oximes have been developed and are used currently in many countries[7].

In this study a new, simple and selective method is developed for pyridinecarboxaldehyde O-propargyloximes which are rather valuable for medicinal chemistry such as antiulcer agents[8-10] and these compounds could be starting materials of more effective oxime reactivators. Due to the effectiveness of methyl salts of these compounds, it was converted the corresponding compounds to the methyl salts *via* methyl triflate.

EXPERIMENTAL

Commercial reagents were purchased from standard chemical suppliers. Solvents were purified and dried by passing through activated aluminum oxide under argon pressure. Flash column chromatography was carried out on silica gel 60 (230-400 mesh, E. Merck). TLC was performed on pre-coated glass plates of silica gel 60 F_{254} (0.25 mm, E. Merck); detection was done by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$ and H_2SO_4 in water or ninhydrin and acetic acid solution in *n*-butanol and subsequent heating on a hot plate. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AMX 400 and 500 MHz instruments. Chemical shifts are in ppm from Me_4Si, generated from the $CDCl_3$. IR spectra were taken with a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Elemental analyses were measured with a Perkin-Elmer 2400CHN instrument. Mass spectra were obtained with a FAB JMS-700 double focusing mass spectrometer (Jeol, Tokyo, Japan).

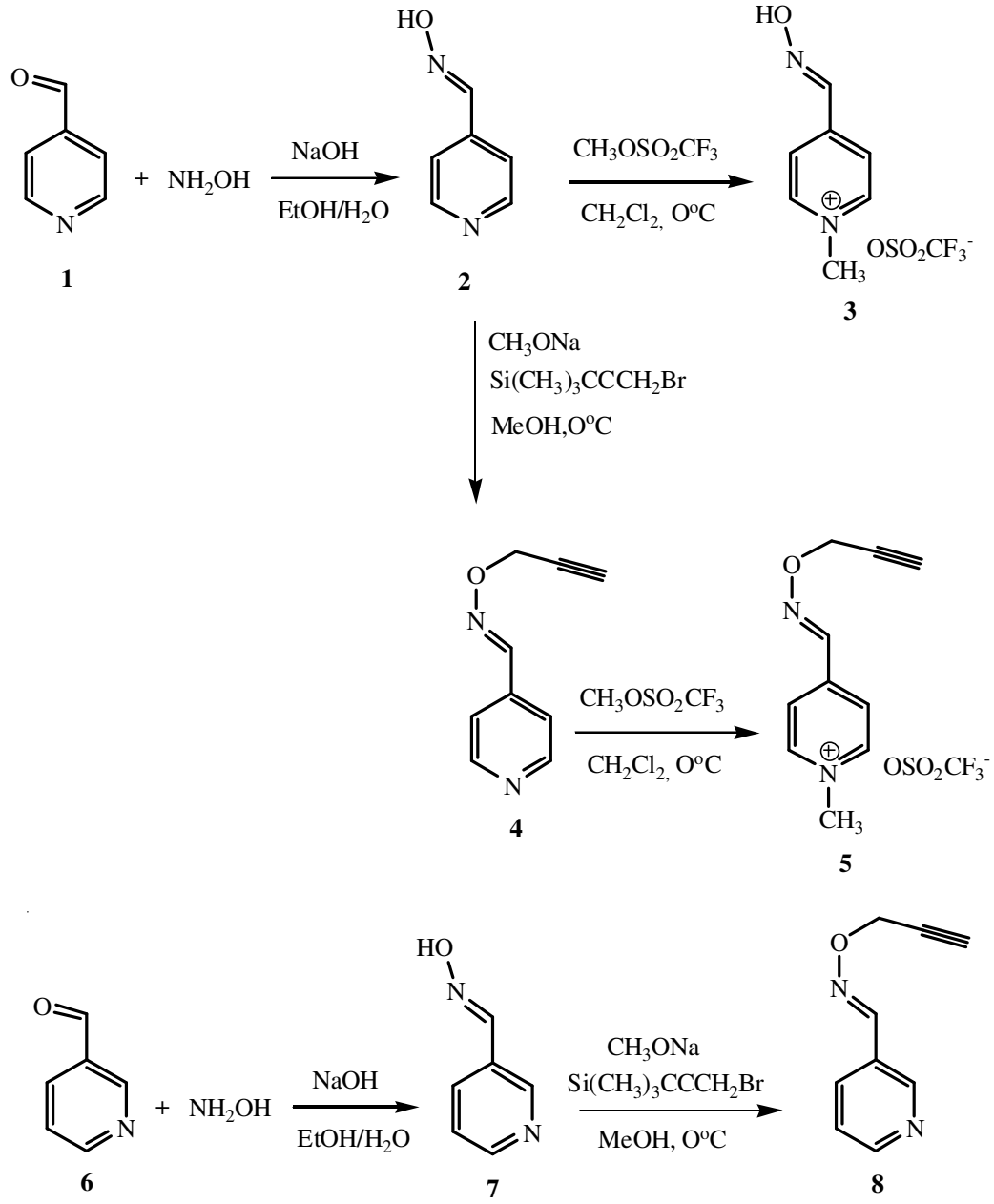
4-Pyridiniumaldoxime (2): To a solution of 4-pyridinecarboxaldehyde (1.0 g, 0.89 mL) in ethanol (5.0 mL) was added hydroxylamine hydrochloride (0.71 g, 10.2 mmol) and sodium hydroxide (0.19 g, 4.7 mmol) in water (3.0 mL). After the completion of the reaction for 0.5 h at room temperature, the crude material was extracted with ether, dried over $MgSO_4$, concentrated under *vacuo* to yield the product[11,12] (0.54 g, 47 %). 1H NMR (400 MHz, $CDCl_3$), δ = 7.54 (d, J = 6.1 Hz, 2H), 8.14 (s, 1H), 8.65 (d, J = 6.1 Hz, 2H), 10.45 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ = 121.3, 140.9, 147.4, 149.8; Ms (FAB), m/z (%) = 123 $[M + H]^+$; elemental analysis calcd. (%) for $C_6H_6N_2O$, C 59.01, H 4.95, N 22.94, found (%) C 59.05, H 4.97, N 22.91.

1-Metyl-4-aldoximepyridinium triflate (3): To a solution of aldoxime (0.20 g, 1.64 mmol) in CH_2Cl_2 (5.0 mL) was added methyl triflate (0.32 g, 0.22 mL, 1.97 mmol) at 0 ºC. Reaction was completed for 0.5 h and the product precipitated from solution as a fine white crystalline powder (0.45 g, 96 %), m.p. 96-97 ºC; ^{1}H NMR (400 MHz, DMSO-*d*), δ = 4.14 (s, 3H), 8.11 (d, J = 6.0 Hz, 2H), 8.35 (s, 1H), 8.79 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d*), d = 47.9, 124.1, 145.5, 145.9, 148.3; IR (MeOH), ν = 1034, 1166, 1262, 1612, 1649;

UV/VIS (CH_2Cl_2), λ_{max} (ε) = 205 (1580), 222 (1650), 285 (2860); Ms (FAB), m/z (%) = 137 [M-OSO_2CF_3] + (100), elemental analysis calcd. (%) for; $C_8H_9N_2O_4SF_3$ (286.2), C 33.57, H 3.17, N 9.79, found (%) C 33.55, H, 3.15, N 9.81.

4-Pyridinecarboxaldehyde O-propragyloxime (4): To a solution of aldoxime **2** (0.29 g, 2.38 mmol) in MeOH (5.0 mL) was added sodium methoxide (0.129 g, 2.38 mmol) and 3-bromo-1-trimethylsilyl-1-propyne (0.45 g, 0.40 mL, 2.38 mmol) at 0 ºC. After the completion of the reaction for 10 h at room temperature, water was added. The mixture was extracted with diethyl ether (3 × 10 mL), dried over $MgSO_4$, concentrated under *vacuo*, purified by column chromatography (silica, hexane/EtOAc, 4/1) to yield the product[10] (0.14 g, 37 %). ^{1}H NMR (500 MHz, $CDCl_3$), δ = 2.50 (t, *J* = 2.1 Hz, *J* = 4.1 Hz, 1H), 4.78 (d, *J* = 2.1 Hz, 2 H), 7.44 (d, *J* = 5.7 Hz, 2H), 8.04 (s, 1H), 8.61 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ = 62.3, 75.1, 78.9, 121.1, 139.0, 147.8, 150.3; Ms (FAB), m/z (%) = 161 $[M + H]^+$ (100); IR (CH_2Cl_2, ν_{max}, cm^{-1}) 1008, 1045, 1417, 1550, 1598, 2051, 2125, 2302, 2405, 2516, 2676, 3306, 3690, 3756, 3940; HRMS (FAB^+) calcd. (%) for $C_9H_8N_2O$: m/z 160.0637, found (%) m/z 160.0635.

1-Methyl-4-pyridinecarboxaldehyde O-propragyloxime triflate (5): To a solution of propragyloxime **4** (78 mg, 0.49 mmol) in CH_2Cl_2 (4.0 mL) was added methyl triflate (96 mg, 64 µL, 0.59 mmol) at 0 ºC. Reaction was completed for 4 h and the product precipitated from solution as a fine white crystalline powder (0.13 g, 82 %); ^{1}H NMR (400 MHz, d-acetone), δ = 3.15 (t, *J* = 2.4 Hz, *J* = 4.8 Hz, 1H), 4.57 (s, 3H), 4.95 (d, *J* = 2.4 Hz, 2H), 8.35 (d, *J* = 6.0 Hz, 2H), 8.55 (s, 1H), 9.1 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, d-acetone), δ = 47.9, 63.1, 76.7, 78.5, 124.7, 145.9, 146.3, 147.4; UV/VIS (MeOH), λ_{max} (ε) = 287 (13900); HRMS (FAB^+) calcd. (%) for $C_{11}H_{11}N_2O_4SF_3$: m/z 324.0397, found (%) m/z 324.0394.



Scheme-I

3-Pyridiniumaldoxime (7): To a solution of 3-pyridinecarboxaldehyde (1.0 g, 0.89 mL) in ethanol (5.0 mL) was added hydroxylamine hydrochloride (0.71 g, 10.2 mmol) and sodium hydroxide (0.19 g, 4.7 mmol) in water (3.0 mL). After the completion of the reaction for 0.5 h at room temperature, the crude material was extracted with ether, dried over $MgSO_4$, concentrated under *vacuo* to yield the product[13] (0.54 g, 47 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.33 (dd, *J* = 4.9 Hz, 7.9 Hz, 1H), 7.95 (dt, *J* = 1.9 Hz, *J* = 7.9 Hz, 1H), 8.16 (s, 1H), 8.62 (dd, *J* = 1.6 Hz, *J* = 4.9 Hz, 1H), 8.80 (d, *J* = 1.7 Hz, 1H), 8.84 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ = 123.7, 128.5, 138.7, 147.0, 148.4, 150.4; UV/VIS (CH_2Cl_2), λ_{max} (ε) = 201 (5060), 245 (5920). HRMS (FAB$^+$) calcd. (%) for $C_6H_6N_2O$: m/z 122.0480, found (%) m/z 122.0483.

3-Pyridinecarboxaldehyde O-propragyloxime (8): To a solution of aldoxime **7** (0.28 g, 2.29 mmol) in MeOH (5.0 mL) was added sodium methoxide (0.136 g, 2.52 mmol) and 3-bromo-1-trimethylsilyl-1-propyne (0.48 g, 0.39 mL, 2.52 mmol) at 0 ºC under nitrogen. After the completion of the reaction for 10 h at room temperature, water was added. The mixture was extracted with diethyl ether (3 × 10 mL), dried over $MgSO_4$, concentrated under *vacuo*, purified by column chromatography (silica, hexane/EtOAc, 4/1) to yield the product[8] (0.1 g, 28 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ = 2.52 (t, *J* = 2.4 Hz, *J* = 4.8 Hz, 1H), 4.79 (d, *J* = 2.3 Hz, 2H), 7.31 (dd, *J* = 4.8 Hz, *J* = 7.9 Hz, 1H), 7.98 (dt, *J* = 1.8 Hz, *J* = 3.6 Hz, *J* = 7.9 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ = 61.9, 74.9, 79.2, 123.6, 127.7, 133.5, 146.9, 148.9, 150.9; IR (CH_2Cl_2, ν_{max}, cm^{-1}): 1045, 1417, 1590, 2051, 2132, 2309, 2413, 2523, 2686, 3306, 3697, 3763, 3940; UV/VIS (CH_2Cl_2), λ_{max} (ε) = 253 (10000); HRMS (FAB$^+$) calcd. (%) for $C_9H_8N_2O$: m/z 160.0637, found (%) m/z 160.0639.

RESULTS AND DISCUSSION

First, starting compound was synthesized, (E)-4-pyridinium aldoxime **2** by treating the 4-pyridinecarboxaldehyde with hydroxylamine hydrochloride and sodium hydroxide. (E)-3-pyridinium aldoxime **7** was generated in the same manner. This aldoxime **2** was converted to the salt by using methyl triflate at 0 ºC in CH_2Cl_2 in high yields (96 %). Aldoxime 2 was treated with 3-bromo-1-trimethylsilyl-1-propyne in the presence of sodium methoxide in MeOH at 0 ºC to form the propargyloxime **4** purified by column chromatography (**Scheme-I**). The characteristic signals observed in ^{1}H NMR spectra for propargyl oxime **4** are 2.50 ppm as triplet (acetylenic proton) and 4.78 as doublet (methylenic proton) and seven lines in the ^{13}C NMR (Dept) spectra are also in agreement with the proposed structure **4**. Propargloxime was treated with methyl triflate at 0 ºC to form the methyl triflate salt **5**. Although there are literatures about 4-pyridinepropargyloxime **4** and 3-pyridinepropargyloxime **8**, There aren't experimental details and full spectral data such as ^{1}H NMR, ^{13}C NMR, IR of these compounds.

The molecular structure with atom-numbering scheme for compound **2** is shown in Fig. 1. The crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Center (CCDC-604549).

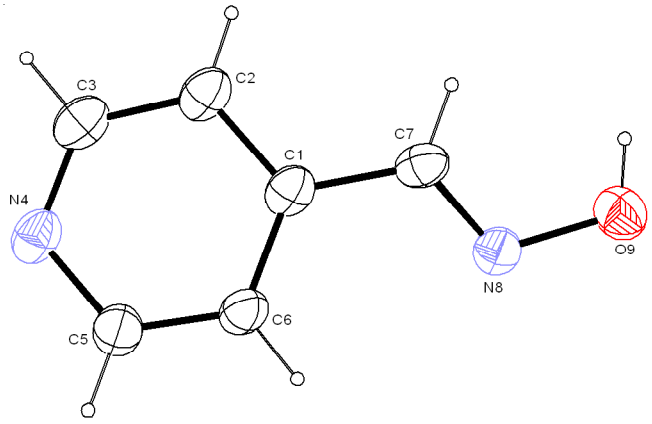


Fig. 1. Crystal structure of compound 4-pyridiniumaldoxime (**2**) with atomic numbering scheme

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