Synthesis of Some Benzyl Oxime Ethers

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Submission data: 25/1/2025 Electronic publishing data: 28/2/2025

Abstract: A reaction between hydroxylamine hydrochloride with five aldehydes and ketones under basic conditions produced oximes 1 – 5 in moderate to excellent yields. These five resulting oximes were characterized using spectroscopic techniques, including IR, ^{1}HNMR and mass spectrometry. The obtained analytical data confirmed the structures of all five oximes. The ^{1}HNMR of the acetaldehyde oxime 1 showed the formation of two geometrical isomers in a ratio of (1:1) These oximes were then subjected into a reaction with the benzyl chloride mild basic conditions by which the corresponding benzyl oxime ethers 6 – 10 were obtained in moderate to excellent yields ranging from 37% to 95%.

Keywords: Oximes, spectroscopic, geometrical isomers, oxime ether

1. Introduction:

Oximes are present in a versatile categories of compounds that hold significant potentials in numerous fields of research and applications [1], such as bio-conjugation, cycloaddition, and materials science [2]. They serve as therapeutic agents in the treatment of organophosphate poisoning[3,4]. Another convenient method for the synthesis of oxime ethers using one-pot electrochemical system based on MgO in a self-supporting carbon nanofiber membrane catalyst (MgO-SCM). In this method, the hydroxyl amine was generated *in situ* from nitrogen oxide coupled with aldehydes *via* electrocatalytic reduction to produce 4-cyanobenzaldehyde oxime. Subsequent reaction with benzyl bromide afforded the corresponding oxime ether in an excellent yield [5]. Oxime ethers are a group of compounds that contain in their structures the (C=NOR). These compounds have demonstrated a wide range of biological importance like bactericidal, fungicidal, *anti*-depressant, *anti*-cancer and herbicidal activities [6]. The characteristics of oxime ethers have also been assessed through the utilization of density functional theory techniques, including geometrical properties, uv analysis and molecular electrostatic potential [7].

2. Experimental:

2.1. Materials:

Acetaldehyde, acetone, benzaldehyde,acetophenone, benzophenone, hydroxyl- amine hydrochloride, benzyl bromide or benzyl chloride, potassium hydroxide, potassium iodide, chloroform, DMSO and ethanol. These chemicals were used without further purification

2.2. Instrumentation:

Melting point apparatus was measured on a Bio Cote. thin-layer chromatography (TLC). The Ph was measured using JENWAY pH meter 3505. Infrared spectrum was recorded on Perkin Elmer FT-IR spectrometer Frontier. Nuclear magnetic resonance ^{1}HNMR was recorded on a JEOL 500 spectrometer. Residual proton signal from the deuterated solvents were used as references ($CDCl_3$ 1H, 7.27 ppm). Coupling constants were measured in Hz. Mass spectrometer was recorded on a Shimadzu Qp - 2010 Plus spectrometer.

2.2.1. General procedure for the synthesis of oximes:

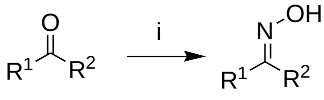
A literature procedure [8] was adapted towards the synthesis of the desired oxime. Solution of hydroxylamine hydrochloride (71.94 mmol in 10 cm^3 of distilled water) and a solution of potassium hydroxide (53.48 mmol in 5 cm^3 of distilled water) were placed in a round-bottomed flask and stirred at room temperature. Acetaldehyde (65.71 mmol) was then added while stirring and the reaction mixture was refluxed. At the start of the boiling, small amounts of ethanol (5 cm^3) were added from time to time to the reaction mixture through the condenser until the boiling solution became clear. The reaction was left under reflux for further an hour after which the reaction vessel was allowed to cool gradually to the room temperature. The pH of the reaction mixture was measured and found, as expected, to be acidic. A solution of 1N KOH was added to the reaction mixture until the solution became neutral. The reaction mixture was then refluxed for further 30 min, cooled to room temperature and the pH was measured and found to be still acidic. Addition of 1N KOH solution was required and the reaction mixture was refluxed for further 10 min, cooled to room temperature and the pH was measured and found to be neutral. The reaction mixture was transferred into a beaker containing ice-water (100 cm^3). The acetaldehyde oxime was extracted from chloroform, dried over anhydrous Na_2SO_4, filtered and evaporated to give the desired compound. **Compound 1:** brown oil (3.28 gm, 55.56 mmol, 85% yield); IR ν_{max} (cm^{-1}) 3261 (OH), 1715 (C=N). ^{1}HNMR (500 MHz, $CDCl_3$) **Major isomer** (formation ratio of **53%**): δ 7.09 (1H, s, O*H*), 6.80 (1H, q, J = 10 Hz, CHO), 1.31 (3H, d, J = 10 Hz, CH_3); **Minor isomer** (formation ratio of **47%**) δ 7.43 (1H, q, J = 10 Hz, CHO), 7.09 (1H, s, OH), 1.31 (3H, d, J = 10 Hz, C*H*$_3$). **Compound 2:** white semisolid (2.88 gm, 39.45 mmol, 60% yield); IR ν_{max} (cm^{-1}) 3337 (OH), 1677 (C=N). ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.62 (1H, br s, OH), 1.91 (6H, s, 2 × CH_3). **Compound 3:** oil (5.44 gm, 44,93 mmol, 68% yield); IR v_{max} (cm^{-1}) 3337 (OH), 1677 (C=N). ^{1}HNMR (500 MHz, $CDCl_3$) δ 9.50 (1H, br s, OH), 8.30 (1H, s, CHO), 7.69 – 7.66 (2H, m, Ar-CH), 7.45 – 7.43 (3H, m, Ar-CH). **Compound 4:** white solid (7.37 gm, 54.59 mmol, 82% yield); IR v_{max} (cm^{-1}) 3209 (OH), 1979, 1496 (C=N). ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.86 (1H, br s, OH), 7.68 – 7.65 (2H, m, Ar-CH), 7.43 – 7.41 (3H, m, Ar-CH), 2.36 (3H, s, CH_3). **Compound 5:** a white powder (11.90 gm, 64.32 mmol, 98.70% yield); IR v_{max} (cm^{-1}) 3298 (OH), 1649 (C=N). ^{1}HNMR (500 MHz, $CDCl_3$), δ 7.84 – 7.82 (3H, m, Ar-CH), 7.63 – 7.47 (7H, m, Ar-CH), 6.27 (1H, br s. OH).

2.4 – General procedure for the synthesis of oxime ethers:

An adapted literature procedure [9] was followed to synthesize this oxime ether. The acetaldehyde oxime (5.0 mmol) was placed into a round-bottomed flask (50 cm^3) and dissolved in DMSO (5 cm^3). Benzyl chloride (10.0 mmol), KI and KOH (10.0 mmol) were then added. The reaction mixture was intensively stirred for 4 h at the room temperature (monitored by TLC). Water (30 cm^3) and chloroform (30 cm^3) were added to the reaction mixture after which the organic layer was extracted, washed with water (4 × 25 cm^3), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated to obtain the desired the oxime ether. **Compound 6:** dark oil (0.445 gm, 3.053 mmol, 37%); IR v_{max} (cm^{-1}) 1602 (C=N), 1026 (C-O). ^{1}HNMR (500 MHz, $CDCl_3$), δ 8.15 (1H, q, J = 15 Hz, CHO), 7.49 – 7.39 (10H, m, Ar-CH), 4.61 (2H, s, $PhCH_2$), 1.93 (3H, d, J = 10 Hz, CH_3). Mass spec (EI) m/z ($C_9H_{11}NO$, calculated MWt 149.08) Found: 149 (0.08), 134 (0.1), 91 (100). **Compound 7:** oil (1.22 gm, 7.53 mmol, 95% yield); IR v_{max} (cm^{-1}) 1602 (C=N), 1016 (C-O). ^{1}HNMR (500 MHz, $CDCl_3$), δ 6.71 – 6.68 (H, m, Ar-CH), 6.56 – 6.54, (H, m, Ar-CH), 4.34 (2H, s, $PhCH_2$), 3.68 (3H, s, 2 × CH_3). Mass spec (EI) m/z ($C_{10}H_{13}NO$, calculated MWt 163.10) Found: 163 (0.02), 91 (100), 72 (0.24). **Compound 8:** dark oil (1.83 gm, 8.65 mmol, 83% yield); IR v $_{max}$ (cm^{-1}) 1603 (C-O), 1025 (C=N). **^{1}**HNMR (500 MHz, $CDCl_3$), δ 8.16 **(**1H, s, CHO**)**, 7.42 – 7.38 (10H, m, 2 × Ar-CH), 4.62 (2H, s, $PhCH_2$). Mass spec (EI) m/z ($C_{10}H_{13}NO$, calculated MWt 211.10) Found: 211 (0.07), 196 (0.11), 120 (0.53), 91 (100). **Compound 9:** brown oil (1.78 gm, 7.93 mmol, 88%yield); IR v_{max} (cm^{-1}) 1602 (C=N), 1024 (C-O). ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.79 – 7.76 (H, m, Ar-CH), 7.50 – 7.40, (H, m, Ar-CH), 4.67 (2H, s, $PhCH_2$), 2.38 (3H, s, CH_3). Mass spec (EI) m/z ($C_{14}H_{13}NO$, calculated MWt 225.12) Found: 225 (0.08), 211 (3.0), 134 (0.26), 91 (100). **Compound 10:** yellow oil (1.34 gm, 4.67 mmol, 73% yield); IR v_{max} (cm^{-1}) 1658 (C=N), 1027 (C-O).**^{1}**HNMR (500 MHz, $CDCl_3$), δ 7.87 – 7.79 (14H, m, Ar-CH), 7.62 – 7.34 (H, m, Ar-CH), 4.62 (2H, s, $PhCH_2$). Mass spec (EI) m/z ($C_{20}H_{17}NO$, calculated MWt 287.13) Found: 287 (4.05), 210 (0.04), 196 (0.37), 91 (100).

3.Results and discussion

A direct method is adopted for the synthesis [8]. First, the oxime was synthesized from an aldehyde or ketone through a reaction with hydroxylamine hydrochloride in the presence of potassium hydroxide under reflux for about 3 h. The desired compounds, an aldoxime or a ketoxime, were formed in good to excellent yields. **(Scheme1)**



1 **2**

R^1 may be Me or Ph
R^2 may be H, Me or Ph

Reagents & reaction conditions: (i) $NH_2OH.HCl$, KOH, Na_2SO_4, 0-5^{o}C reflux, 3 h

Scheme 1: General reaction for the synthesis of oximes under study 1 – 5

The five obtained oximes were characterized, using IR and ^{1}HNMR spectroscopy. The spectroscopic data showed that all targeted five **1 – 5** were successfully formed. The IR spectroscopy showed absorption bands of the hydroxyl group and the imine group (OH/C=N) for the oximes **1 – 5** at 3261 cm^{-1}/1715 cm^{-1}, 3337cm^{-1}/1677 cm^{-1}, 3337cm^{-1}/1677 cm^{-1}, 3209 cm^{-1}/1496 cm^{-1} and 3298 cm^{-1}/ 1649 cm^{-1} respectively. The formation of these oximes was further confirmed by the ^{1}HNMR, as the hydroxyl proton of the oximes **1 – 5** appeared along with all the other expected chemical shifts for all protons. However, in the case of the oxime **1**, two geometrical isomers were formed in the ratio of about (1:1). The ^{1}HNMR spectrum of this oxime, two quartet signals for the aldehyde hydrogen were seen equivalent to 53% and 47% along with two overlapped doublets for the three hydrogens of the methyl groups of each isomer. Two overlapped singlet signals for the hydroxyl hydrogens of each isomer were also noticed **(Fig. 1)**.

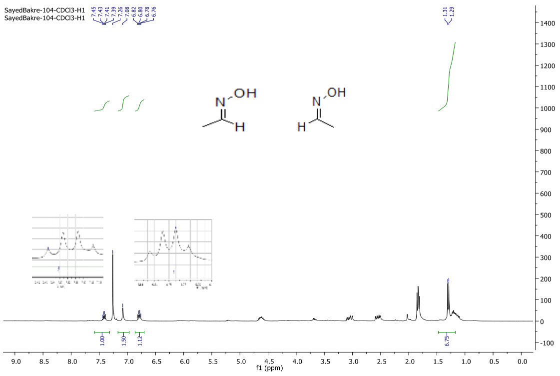
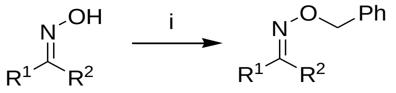


Figure 1: ^{1}HNMR of the acetaldehyde oxime 1 showing two geometrical isomers in a ratio of ~ (1:1)

3.2. **Synthesis of oxime ether 6 – 10**

The oxime ethers were synthesized from the obtained oximes throughout a reaction with the benzyl chloride individually in the presence of potassium iodide under basic conditions to form the corresponding benzyl oxime ethers in good yields (**Scheme 2**).



2 **3**

R^1 may be Me or Ph
R^2 may be H, Me or Ph

Reagents & reaction conditions:(i) BnCl, KOH,KI, DMSO, $CHCl_3$, stirring in the temperture room, 4 h

Scheme 2: General reaction for the synthesis of the benzyl oxime ethers 6 – 10

The five benzyl oxime ethers **6 - 10** were characterized using the IR, ^{1}HNMR and mass spectrometry. The spectroscopic data showed that all five benzyl oxime ethers were successfully formed. A detailed description of the synthetic route and spectral analysis of all five benzyl oxime ethers are explained below. The IR showed the disappearance of the hydroxyl group**,** whereas the absorption band of the etheric bond and the imine group (C–O/C=N) appeared for the oxime ethers **6** – **10** at 1026 cm^{-1}/1602 cm^{-1}, 1016 cm^{-1}/1602 cm^{-1}, 1025 cm^{-1}/1603 cm^{-1}, 1024 cm^{-1}/1602 cm^{-1}, 1027 cm^{-1}/1658 cm^{-1} respectively. The formation of these ethers was also confirmed by the ^{1}HNMR. The oxime hydroxyl proton in each oxime ether **6–10** along with the other chemical shifts for all different protons were in the spectra. The mass spectrometry gave the molecular weights for all oxime ethers **6 –10**.

4. Conclusion

Five oximes **1 – 5** derived from selected ketones and aldehydes were synthesized under basic reaction conditions. The oximes were produced in moderate to excellent yields ranging from 60% to 98%. The spectroscopic data confirmed the formation of these oximes. These resultant oximes then underwent mild basic reactions with the benzyl chloride in a ratio of (1:2 mmol/mmol). The corresponding benzyl oxime ethers were obtained in moderate to excellent yields ranging from 37% to 95%.

Acknowledgements

Authors would like to thank the department of chemistry and the bioresearch center for providing all possible facilities that were required for this work.

References

[1] Eddleston, M.; Szinicz, L.; Eyer, P.; Buckley, N.; "Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials"; *Qjm*, 2002, **95**, 275.

[2] Wang, L.; Wang, S.; Tang, J.; Espinoza, V.B.; Loredo, A.; Tian, Z.; Weisman, R.B.; Xiao, H.; "Oxime as a general photocage for the design of visible light photo-activatable fluorophores"; *Chemical Science*, 2021, 15572.

[3] López-Gómez, P.; Buezo, J.; Urra, M.; Cornejo, A.; Esteban, R.; de Los Reyes, J.F.; Urarte, E.; Rodríguez-Dobreva, E.; Chamizo-Ampudia, A.; Eguaras, A.; "A new oxidative pathway of nitric oxide production from oximes in plants"; *Molecular Plant*, 2024, **17**, 178

[4] Rykaczewski, K.; Wearing, E.; Blackmun, D.; Schindler, C.; "Reactivity of oximes for diverse methodologies and synthetic applications"; *Nature Synthesis*, 2022, **1**, 24.

[5] Surowiak, A.K.; Lochyński, S.; Strub, D.J.; "Unsubstituted oximes as potential therapeuticagents"; *Symmetry*, 2020, **12**, 575.

[6] Damljanović, I.; Vukićević, M.; Vukićević, R.D.; "A simple synthesis of oximes"; *MonatsheftrfürChemie/ChemicalMonthly,* 2006, **137**, 301.

[7] Kosmalski, T.; Kupczyk, D.; Baumgart, S.; Paprocka, R.; Studzińska, R.; "A Review of Biologically Active Oxime Ethers"; *Molecules*, 2023, **28**, 5041

[8] Bawa, R.A.; Swairi, A.R.; "Synthesis of Some Alicyclic Oximes and Study of the Expected Conformational Isomerism"; *Academic Journal of Life Sciences*, 2019, **5,** 116.

[9] Shahab, S.; Sheikhi, M.; Shekoohi, K.; Kaviani, S.; Shiroudi, A.; Zarenezhad, E.; "Theoretical Approach Using DFT Calculations of Novel Oxime Derivative"; *Biointerface Research in Applied Chemistry,* 2023, **13**, 170.

[10] Kosmalski, T.; Studzińska, R.; Daniszewska, N.; Ullrich, M.; Sikora, A.; Marszałł, M.; Modzelewska- Banachiewicz, B.; "Study of the Room-Temperature Synthesis of Oxime Ethers by using a Super Base"; *Chemistry Open*, 2018, **7**, 551.