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Synthesis of Some Alicyclic Oximes and Study of the Expected Conformational Isomerism

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Abstract

Five alicyclic oximes 1 – 5 have been readily synthesized in moderate to good yields. These oximes were obtained through a reaction between the hydroxylamine hydrochloride and a number of alicyclic ketones (cylobutanone, cyclopentanone, cyclohexanone, cycloheptanone and cyclooctanone) under mild reaction conditions. The spectroscopic data confirmed the formation of the first four oximes 1 – 4 as single conformational isomers. However, the cyclooctanone oxime 5 was obtained as a mixture of two conformational isomers with 81% for the major and only 19% for the minor isomer. Such finding could be an indication for the relationship between the increase of the ring size of the oxime and the raising possibility of the formation of conformational isomers as the flexibility of the ring increases.

Keywords: Alicyclic; Oximes; Synthesized; Spectroscopic; Conformational isomers; Ring size.

1. Introduction

Oximes could be found in a number of bioactive compounds. Such oxime derivatives have a wide range of activities, including antibacterial, antifungal, anti-inflammatory, antioxidant, anti-diabetes and cytotoxic activities [1]. They have also shown some insecticidal activities [2]. Additionally, oximes have been employed as key precursors in the synthesis of the photosensitive materials [3]. Oximes are characterized by various derivatives including oxime ethers, oxime esters, dioxime oxalates, oxime glyoxylates, oxime oxalate, amides, oxime carbonates and oxime carbamates. Oximes could also be used as building blocks in the synthesis of agrochemicals [4]. Classically, oximes are synthesized by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride in the presence of base [4, 5]. The reaction of aldehydes or ketones with hydroxylamine or its hydrochloride salt in polar solvent like ethanol could be a convenient method to obtain oximes. The reaction rate is a pH-dependent and the base could be added at the beginning or continuously during the reaction. Basic solvents like pyridine could also be employed as base and/or solvent. The reaction temperature is generally ranging from 60 to 120° C [2, 6-9]. Herein, some alicyclic oximes and their terphthaloyl esters have been synthesized and characterized using a number of spectroscopic techniques.

2. Experimental

2.1. Materials

Cyclobutanone, cyclopentanone, cyclohexanone,cycloheptanone, cyclooctanone, hydroxylamine hydrochloride, terphthaloyl chloride, potassium hydroxide, anhydrous sodium sulphate, triethyl amine and chloroform. These chemicals were used without further purification.

2.2. Instrumentation

Melting points were measured on a Barnstead electrothermal IA 9100. ^{1}HNMR spectrum was recorded on a JEOL ECA-500 II spectrometer. Residual proton signal from the deuteriated solvent was used as reference [DMSO (^{1}H, 2.50 ppm), whereas coupling constants were measured in hertz (Hz)]. Infrared spectrum was recorded on Jasco FT/IR-4100 Fourier transform infrared spectrometer. Mass spectrum was recorded on a Micromass Autospec M spectrometer.

2.2.1. Synthesis of Cyclobutanone Oxime

A literature procedure [2] was adapted towards the synthesis of the desired oxime. Solution of hydroxylamine hydrochloride (5.0 gm, 71.94 mmol in 10 cm^3 of distilled water) and a solution of potassium hydroxide (3.0 gm, 53.48 mmol in 5 cm^3 of distilled water) were placed in a round-bottomed flask and stirred at room temperature. Cyclobutanone (4.60 gm, 65.71 mmol) was then added while stirring and the reaction mixture was refluxed. At the start of boiling, small amounts of ethanol (5 cm^3) were added from time to time to reaction mixture through the condenser until the boiling solution becomes clear. The reaction was left under reflux for further an hour after which the reaction vessel was allowed to cool gradually to room temperature. The pH of the reaction mixture was measured

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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. The pH was measured and found to be still acidic. Addition of 1N KOH solution was required and the reaction mixture was refluxed for another 10 min, cooled, pH was measured and found to be neutral. The reaction mixture was transferred into a beaker containing ice – water (100 cm^3), the cyclobutanone oxime was precipitated rapidly, filtered, washed with cold water (3 × 10 cm^3) and air dried to give a white powder of the desired compound (2.70 gm, 31.77 mmol, 48% yield). The product was found clean enough for the next chemical processes; IR ν_{max} (cm^{-1}) 3392 (OH), 1630 (C=N).

2.2.2. Synthesis Cyclopentanone Oxime

A literature procedure [10] was adapted towards the synthesis of the desired oxime. Solution of hydroxylamine hydrochloride (5.0 gm, 71.94 mmol in 10 cm^3 of distilled water) and a solution of potassium hydroxide (3.0 gm, 53.48 mmol in 5 cm^3 of distilled water) were placed in a round-bottomed flask and stirred at room temperature. Cyclopentanone (5.60 gm, 66.67 mmol) was then added while stirring and the reaction mixture was refluxed. At the start of boiling, small amounts of ethanol (5 cm^3) were added from time to time to reaction mixture through the condenser until the boiling solution becomes clear. The reaction was left under reflux for further an hour after which the reaction vessel was allowed to cool gradually to 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. The pH was measured and found to be still acidic. Addition of 1N KOH solution was required and the reaction mixture was refluxed for another 10 min, cooled, pH was measured and found to be neutral. The reaction mixture was transferred into a beaker containing ice-water (100 cm^3), the cyclopentanone oxime was precipitated rapidly, filtered, washed with cold water (3 × 10 cm^3) and air dried to give a white powder of the desired compound (3.39 gm, 34.24 mmol, 51% yield). The product was recrystallized from diethyl ether; IR ν_{max} (cm^{-1}) 3229 (OH), 1687(C=N). ^{1}HNMR (DMSO-d6, 500 MHz) δ 10.14 (1 H, s, O*H*), 2.24 (4 H, m, 2 × CH_2), (4 H, m, 2 × CH_2). ^{13}CNMR (DMSO-d6, 500 MHz) δ 164.14 (*C*=N), 30.54 (*C*H_2), 27.10 (*C*H_2), 25.22 (*C*H_2), 24.57 (*C*H_2).

2.2.3. Synthesis Cyclohexanone Oxime

A literature procedure [2] was adapted towards the synthesis of the desired oxime. Solution of hydroxylamine hydrochloride (5.0 gm, 71.94 mmol in 10 cm^3 of distilled water) and a solution of potassium hydroxide (3.0 gm, 53.48 mmol in 5 cm^3 of distilled water) were placed in a round-bottomed flask and stirred at room temperature. Cyclohexanone (6.53 gm, 66.63 mmol) was then added while stirring and the reaction mixture was refluxed. At the start of boiling, small amounts of ethanol (5 cm^3) were added from time to time to reaction mixture through the condenser until the boiling solution becomes clear. The reaction was left under reflux for further an hour after which the reaction vessel was allowed to cool gradually to 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. The pH was measured and found to be still acidic. Addition of 1N KOH solution was required and the reaction mixture was refluxed for another 10 min, cooled, pH was measured and found to be neutral. The reaction mixture was transferred into a beaker containing ice-water (100 cm^3), the cyclohexanone oxime was precipitated rapidly, filtered, washed with cold water (3 × 10 cm^3) and air dried to give a white powder of the desired compound (4.50 gm, 44.56 mmol, 67% yield). The product was recrystallized from diethyl ether; IR ν_{max} (cm^{-1}) 3440 (OH), 1659 (C=N). ^{1}HNMR (DMSO-d6, 500 MHz) δ 10.06 (1 H, s, O*H*), 2.37 (2 H, m, CH_2), 2.10 (2 H, m, CH_2), 1.55 (6 H, m, 3 × CH_2). ^{13}CNMR (DMSO-d6, 500 MHz) δ 157.61 (*C*=N), 32.07 (*C*H_2), 27.15 (*C*H_2), 25.91 (*C*H_2), 25.73 (*C*H_2), 24.32 (*C*H_2)

2.2.4. Synthesis of Cycloheptanone Oxime

A literature procedure [2] was adapted towards the synthesis of the desired oxime. Solution of hydroxylamine hydrochloride (5.0 gm, 71.94 mmol in 10 cm^3 of distilled water) and a solution of potassium hydroxide (3.0 gm, 53.48 mmol in 5 cm^3 of distilled water) were placed in a round-bottomed flask and stirred at room temperature. Cycloheptanone (7.46 gm, 66.61 mmol) was then added while stirring and the reaction mixture was refluxed. At the start of boiling, small amounts of ethanol (5 cm^3) were added from time to time to reaction mixture through the condenser until the boiling solution becomes clear. The reaction was left under reflux for further an hour after which the reaction vessel was allowed to cool gradually to 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. The pH was measured and found to be still acidic. Addition of 1N KOH solution was required and the reaction mixture was refluxed for another 10 min, cooled, pH was measured and found to be neutral. The reaction mixture was transferred into a beaker containing ice-water (100 cm^3), the cycloheptanone oxime was extracted with cholroform, washed with distilled water (3 × 10 cm^3), dried over Na_2SO_4, filtered and evaporated to give the desired compound as an oil (4.76 gm, 37.48 mmol, 56% yield). IR ν_{max} (cm^{-1}) 3219 (OH), 1649 (C=N). ^{1}HNMR (DMSO-d6, 500 MHz) δ 10.11 (1 H, s, O*H*), 2.42 – 2.39 (2 H, m, CH_2), 2.29 – 2.27 (2 H, m, CH_2), 1.62 – 1.59 (2 H, m, CH_2), 1.58 – 1.50 (6 H, m, 3 × CH_2). ^{13}CNMR (DMSO-d6, 500 MHz) δ 160.24 (*C*=N), 33.60 (*C*H_2), 30.45 (*C*H_2), 30.31 (*C*H_2), 28.47 (*C*H_2), 27.88 (*C*H_2), 24.59 (*C*H_2).

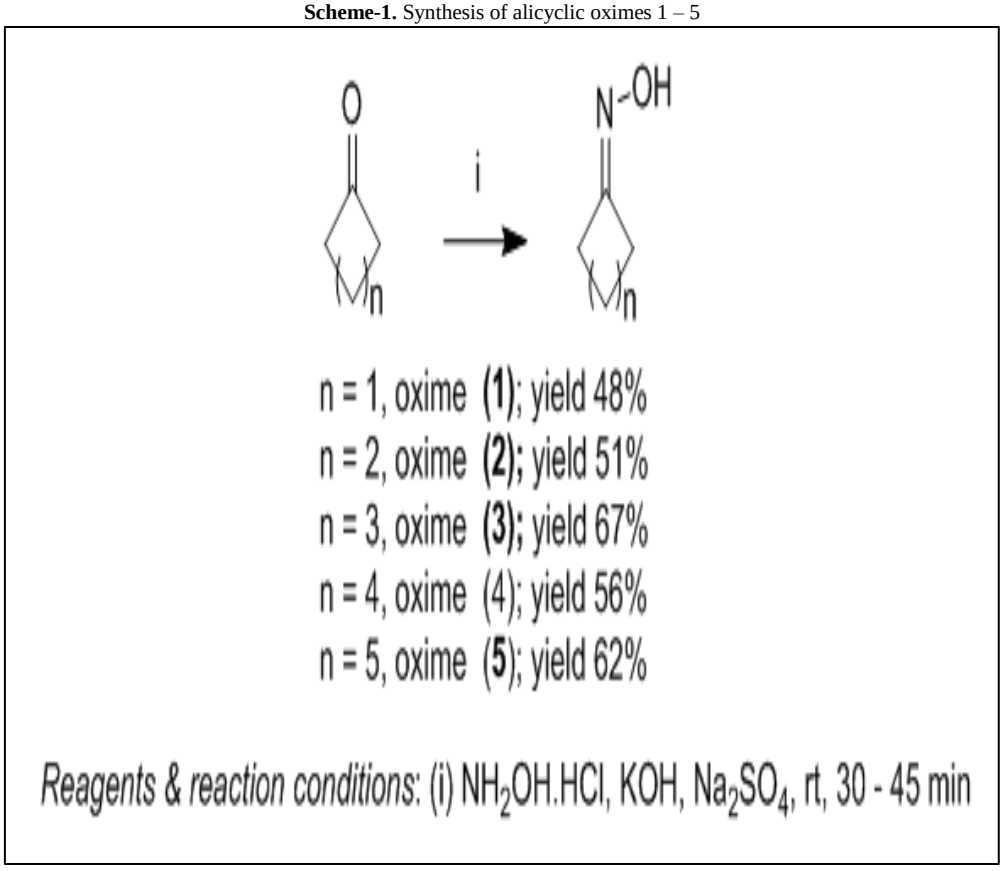
2.2.5. Synthesis of Cyclooctanone Oxime

A literature procedure [2] was adapted towards the synthesis of the desired oxime. Solution of hydroxylamine hydrochloride (5.0 gm, 71.94 mmol in 10 cm^3 of distilled water) and a solution of potassium hydroxide (3.0 gm, 53.48 mmol in 5 cm^3 of distilled water) were placed in a round-bottomed flask and stirred at room temperature. Cyclooctanone (8.4 gm, 66.67 mmol) was then added while stirring and the reaction mixture was refluxed. At the start of boiling, small amounts of ethanol (5 cm^3) were added from time to time to reaction mixture through the condenser until the boiling solution becomes clear. The reaction was left under reflux for further an hour after which the reaction vessel was allowed to cool gradually to 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. The pH was measured and found to be still acidic. Addition of 1N KOH solution was required and the reaction mixture was refluxed for another 10 min, cooled, pH was measured and found to be neutral. The reaction mixture was transferred into a beaker containing ice-water (100 cm^3), the cyclooctanone oxime was extracted with chloroform, washed with distilled water (3 × 10 cm^3), dried over Na_2SO_4, filtered and evaporated to give the desired compound as an oil (5.78 gm, 40.99 mmol, 62% yield). IR ν_{max} (cm^{-1}) 3205 (OH), 1694 (C=N). **Major isomer (81%):** ^{1}HNMR (DMSO-d6, 500 MHz) δ 10.11 (1 H, s, O*H*), 2.35 – 2.21 (2 H, m, CH_2), 2.20 – 2.18 (2 H, m, CH_2), 1.70 – 1.67 (4 H, m, 2× CH_2), 1.66 – 1.41 (6 H, m, 3 × CH_2). **Minor isomer (19%):** ^{1}HNMR (DMSO-d6, 500 MHz) δ 8.30 (1 H, s, O*H*), 3.18 (2 H, s, CH_2), 2.55 (2 H, s, CH_2), 1.80 – 1.76 (6 H, m, 3 × CH_2), 1.31 – 1.25 (4 H, m, 2× CH_2). ^{13}CNMR (DMSO-d6, 500 MHz) δ 160.88 (*C*=N), 33.23 (*C*H_2), 27.32 (*C*H_2), 26.69 (*C*H_2), 26.54 (*C*H_2), 25.57 (*C*H_2), 24.79 (*C*H_2), 24.43 (*C*H_2).

3. Results and Discussion

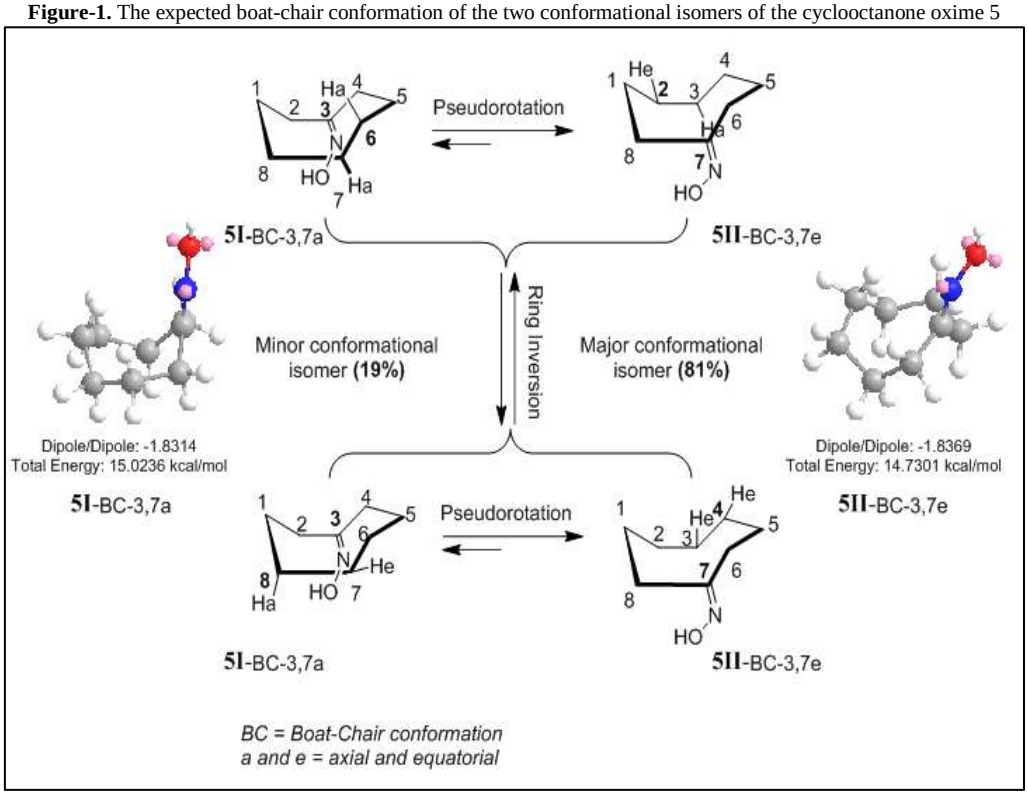
Five alicyclic oximes have been synthesized starting from cyclobutanone, cyclopentanone and cyclohexanone, cycloheptanone and cyclooctanone through a reaction between these alicyclic ketones and the hydroxyl amine hydrochloride in the presence of potassium hydroxide to form the desired alicyclic oximes **1 – 5** respectively in moderate to good yields (Scheme 1).

Scheme-1. Synthesis of alicyclic oximes 1 – 5



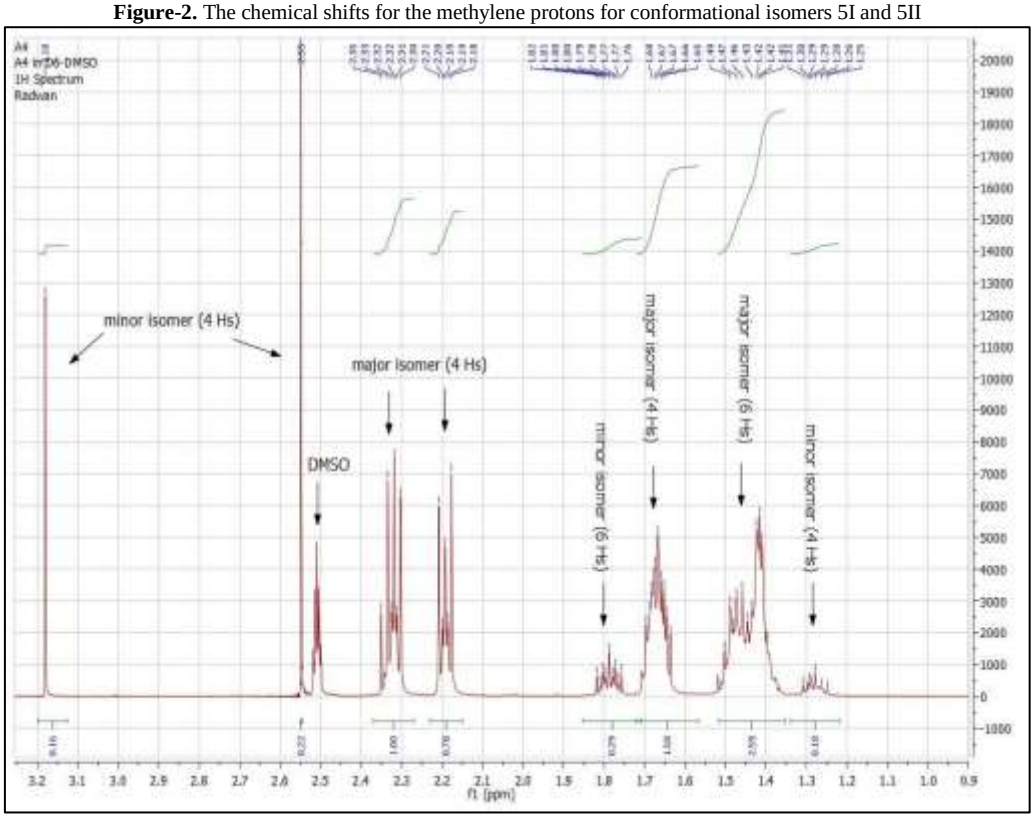
The resulting five oximes were characterized in which the IR, ^{1}HNMR and the ^{13}CNMR spectroscopic data revealed that the all oximes **1** – **5** were formed successfully as. The IR spectroscopy showed the absorption bands of the induced hydroxyl group and the imine group (OH/C=N) for the oximes **1** – **5** at 3392 cm^{-1}/1630 cm^{-1}, 3229 cm^{-1}/1687 cm^{-1}, 3440 cm^{-1}/1659 cm^{-1}, 3219 cm^{-1}/1649 cm^{-1} and 3205 cm^{-1}/1694 cm^{-1} respectively. The NMR data confirmed the structures of the resulting alicyclic oximes **2 – 5** by showing the expected chemical shifts for all protons and carbon atoms. The oximes of ring size less than eight, were formed as single isomers, whereas the cyclooctanone oxime **5** was obtained as a mixture of two conformational isomers (major isomer 81% and minor isomer 19%) (Fig. 1).

Figure-1. The expected boat-chair conformation of the two conformational isomers of the cyclooctanone oxime 5



The upfield chemical shifts observed in the ^{1}HNMR spectrum of the mixture of the two conformational isomers of the cyclooctanone oxime **5I** and **5II** (Fig 2) could be well explained by the boat-chair conformation, since the chemical shift for a proton in the axial position is directly above the π bond of the oxime group and should thus be strongly shielded [11].

Figure-2. The chemical shifts for the methylene protons for conformational isomers 5I and 5II



According to the MM2 method used for minimizing the total energy, the major conformational isomer is thought to be **5II** (81%), which has theoretically been found to be more stable than the other conformational isomer **5I** (19%) with total energies of 14.7301 kcal/mol and 15.0236 kcal/mol respectively (Fig 1). Although the formation percentage of the minor conformational isomer of the cyclooctanone oxime **5** was rather low (only 19%), it could be an indication of the fact that the possibility for observing isomerism increases as the ring size reaches eight carbons

or above. This might be rationalized to raising the flexibility of the ring as the number of carbons of the cyclic skeleton increases. This requires further studies to be confirmed.

4. Conclusion

Five alicyclic oximes **1 – 5** have been readily synthesized in moderate to good yields. These oximes were obtained through an oximation reaction of cylobutanone, cyclopentanone, cyclohexanone, cycloheptanone and cyclooctanone under mild reaction conditions. The spectroscopic data confirmed the formation of these oximes as single isomers except the cyclooctanone oxime **5** which was formed as a mixture of two isomers giving the major a formation percentage marking 81%. Such observation could be an indication for the relationship between the increase of the ring size of the oxime and the raising possibility of the formation of two or more isomers as the flexibility of the ring increases.

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References

[1] Swairi, A. and Bawa, R., 2019. *Synthesis of some alicyclic oximes*. The 3rd conference on theories and applications of basic and biosciences, Faculty of Science, Misurata University, Misurata, Libya, September 7th.

[2] Bawa, R. and Sawalem, M., 2018. "Synthesis and spectroscopic study of acetyl acetone mono oxime and its corresponding benzoyl ester." *Int. Journal of Academic Research*, vol. 12, pp. 346-355.

[3] Vessally, E., Saeidian, H., Hosseinian, A., Edjlali, L., and Bekhradnia, A., 2017. "A review on synthetic applications of oxime esters." *Current Organic Chemistry*, vol. 21, pp. 249–271.

[4] Harikrishna, A., Krishna, K., and Elias, G., 2017. "Oxime esters as potential pharmacological agents – a review." *I. J. P. C. B. S.*, vol. 7, pp. 128–137.

[5] Jadhav, D., Gade, E., Angarkhe, B., and Durrani, A., 2018. "An efficient one pot synthesis of oxime by classical method." *International Journal of Chemical and Physical Sciences*, vol. 7, pp. 12–16.

[6] Kunimoto, K., Oka, H., Ohwa, M., Tanabe, J., Kura, H., and Birbaum, J., 2005. *Oxime ester photoinitiators*. U.S. Patent, No. 6,949,678, Washington, DC: U.S.

[7] Liu, X., Zhi, L., Song, B., and Xu, H., 2008. "Synthesis, characterization and antibacterial activity of new 5-aryl pyrazole oxime ester derivatives." *Chemical Research in Chinese Universities*, vol. 24, pp. 454–458.

[8] Song, B., Liu, X., Yang, S., Hu, D., Jin, L., and Zhang, Y., 2005. "Recent advance in synthesis and biological activity of oxime derivatives." *Chinese Journal of Organic Chemistry*, vol. 25, pp. 507–525.

[9] Tanabe, J., Kunimoto, K., Kura, H., Oka, H., and Ohwa, M., 2010. *Oxime ester photoinitiators, U.S. Patent, No. 7,759,043*. Washington, DC: U.S.

[10] Bawa, R. and Swaleam, M., 2018. "Synthesis of some unsymmetrical dioxime esters using the acetylacetone as a precursor." *Scientific Review*, vol. 5, pp. 19–23.

[11] Anet, F., 1974. "Dynamics of eight-membered rings in the cylooctane class" dynamic chemistry, part of the topics in current chemistry fortschritte der chemischen forschung book series." *Topcurrchem*, vol. 45, pp. 169 – 220.