Synthesis of 2-Isoxazoline Derivatives through Oximes of 1,3-Dicarbonyl Arylidenes

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Abstract:

Novel derivatives of 2-isoxazoline oxime and 5-hydroxy-2-isoxazoline derivatives were synthesized by the oximation reaction of benzylidenacetylacetone and its derivatives with hydroxylamine hydrochloride using two methods. Benzylidenacetyl-acetone was introduced to oximation reaction under strong basic conditions to produce a *trans*-isomer of 2-isoxazoline oxime with 64% yield. In contrast, the oximation reactions of 2-nitro, 4-methoxybenzylideneacetylacetone derivatives under milder conditions gave various heterocyclic compounds depending on the nature and position of the substituent. The reaction of 2-nitrobenzylidenacetylacetone led to the synthesis of *Z* and *E*-isomers of 5-hydroxy-2-isoxazoline derivative with *Z*/*E* ratio equal 1:1, and the reaction of 4-methoxybenzylidenacetylacetone gave also *Z*- and *E*-5-hydroxy-2-isoxazoline derivative but the ratio was 1:2 of *Z*/*E* isomers.

Keywords*: Oxime, 1,3-Dicarbonyls, Knoevenagel condensation, Isoxazoline.*

Introduction

Oximes are chemical compounds belonging to imines, generally oximes are usually generated by the reaction of hydroxylamine and aldehydes or ketones. The common method of obtaining oxime is by the reaction of corresponding carbonyl compounds with hydroxylamine salt in the presence of alcoholic base.[1] The condensation gives oximes along with water as a by-product.[2] The first condensation was reported by Schiff in 1864 and since then a great number of these reactions were actively investigated.[3] Oximes have a very interesting reactivity, and also, they are widely used for example, as anticancer agents,[4] and bacteriostatic agents.[5,6]

They can also serve as precursors in the synthesis of a number of heterocycles such as aziridines, furazans, isoxazoles, isoxazolines pyrazole and pyrazoline. Oximation of 1,3-dicarbonyl compounds are one of the popular isoxazole synthesis. Claisen described the first synthesis of isoxazoles.[7] The process involved the reaction of 1,3-dicarbonyl compound with hydroxylamine followed by cyclization of the intermediate oxime. This became an important route to 3,5-disubstituted isoxazoles. Passacantilli *et al*. reported the enone which treated with two equivalents of hydroxylamine was able to undergo conjugate addition, and reaction directly afforded the isoxazoline derivative.[8,9] Zheng *et al*. reported synthesis of bridged bicyclic isoxazolidines via a double hetero-Michael addition of *N*-benzylhydroxylamine to quinone monoketal in acetonitrile in the presence of DBU.[10] The reaction of an equivalent of benzyliden-acetylacetone with two equivalents of *p*-substituted aniline to from diimine as one of its synthetic applications.[11,12] Sargsyan *et al*. reported the interaction of benzylidenacetylacetone with ethoxycarbonylacetamides in the presence of triethylamine. A convenient method has been developed for the synthesis of heterocyclization piperidine products of the starting materials.[13] Boullet *et al*. reported the reaction of various enamino ketones with benzylidenacetylacetone without solvent at room temperature or under

microwaves irradiation to give highly functionalized cyclohexenes in good yields.[14] Herein, we wish to report the oximation reaction of benzylidenacetylacetone and its derivatives with hydroxylamine hydrochloride using two methods.

Material and Methods

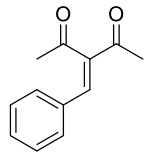
General

Starting materials and solvents were purchased from common commercial sources. All melting points were uncorrected. All R_f values were obtained by using GF_{254} TLC, on pre-coated silica plates. The IR spectra were recorded using Perkin-Elmer FT-IR spectrophotometer accessorized with ATR. ^{1}HNMR and ^{13}CNMR spectral data were registered on Mercury-300BB (300 MHz) NMR spectrometer and ECA-500 JEOL (500 MHz) NMR spectrometer, making a solution of samples in $CDCl_3$, DMSO-d_6, and D_2O solvents and using the chemical shift of the solvents as reference. MS spectral data was obtained using a Shimadzu Qp-2010 plus GC/mass spectrometer and MS spectra were recorded using EI at 70 eV.

General procedure A: preparation of benzylidenacetylacetone and their derivatives

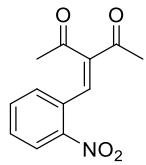
Anhydrous aluminum chloride (6.6 mmol, 0.33 equiv.) was added to a solution of the acetylacetone (40.0 mmol, 2.00 equiv.) in DCM (20 mL), stirring at room temperature for 15 min, and then the aldehyde (20.0 mmol, 1.00 equiv.) was added. The reaction was stirred at room temperature until the reaction was completed (TLC detection), then quenched with saturated $NaHCO_3$ solution and extracted. The DCM extract was dried over Na_2SO_4, evaporated under reduced pressure, and the crude mixture was purified by recrystallization (EtOAc/petroleum ether).[15]

Benzylidenacetylacetone (1)



Compound **1** was prepared according to the general procedure **A**, using benzaldehyde **8** and acetylacetone **7** as starting materials. Yield: 62% (HPLC); yellow oil; IR cm^{-1}: 1701, 1656, 1615, 1593. which was used in the next step without further purification.

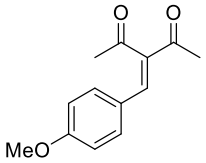
2-Nitrobenzylidenacetylacetone (2)



Compound **2** was prepared according to the general procedure **A** using 2-nitrobenzaldehyde **9** and acetylacetone **7** as starting materials. Yield: 50%; brown solid; m.p 76−80 °C [lit.[16] 75.5-76.5°C]; (R_f = 0.40, EtOAc: petroleum ether 3:7); IR (neat) cm^{-1}: 1694, 1662, 1628, 1605, 1520, 1351, 754; ^{1}HNMR (300 MHz, $CDCl_3$) δ_H

2.09 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 7.90 (s, 1 H, C=C*H*), 7.37 (d, *J* = 7.2 Hz, 1 H, Ar*H*), 7.60 (m, 2 H, Ar*H*), 8.20 (dd, *J* = 9, 1 Hz, 1 H, Ar*H*).

4-Methoxy benzylidenacetylacetone (3)

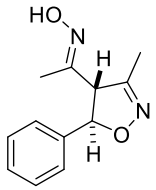


Compound **3** was prepared according to the general procedure **A** using 4-methoxy-benzaldehyde **10** and acetylacetone **7** as starting materials. Yield: 52%; white solid; m.p 66 - 67 °C [lit.[17] 62-64°C] (R_f =0.70, EtOAc: petroleum ether 3:7); IR (neat) cm^{-1}: 1695, 1643, 1592, 1514, 812, 831; ^{1}HNMR (300 MHz, $CDCl_3$) δ_H 2.29 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3) 7.26 (s, 1 H, C=C*H*), 6.60 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.31 (d, *J* = 8.0 Hz, 2 H, Ar*H*).

Oximation reaction of benzylidenacetylacetone and its derivatives

Oximation of benzylidenacetylacetone using NaOH

(*E*)-1-((4*R*,5*R*)-3-methyl-5-phenyl-4,5-dihydroisoxazol-4-yl)ethan-1-one oxime (4)

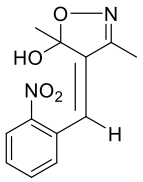


Benzylidenacetylacetone **1** (2.82 g,15.0 mmol) was added to a mixture of hydroxylamine hydrochloride (6.15 g, 88.5 mmol) and sodium hydroxide (9.60 g, 240.0 mmol) in water (4.5 mL) and ethanol (32 mL). The mixture obtained was stirred for 2 h at 60 °C. The mixture was concentrated by rotary evaporation. the residue was partitioned into water and EtOAc, the separated organic layer was then extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a pale-yellow oil. This oil was dissolved in dichloromethane (10 mL) at 25 °C before hexane (20 mL) was added over two min. Upon clouding, the solution was cooled in an ice/water bath to 0–5 °C. Crystals were allowed to be kept in the fridge overnight before filtration, the white cotton-like solid was washed with ambient temperature hexane (3 mL). yielding solid that was purified via crystallization using ethanol. Yield: 64%; white solid; m.p 84−83 °C; (R_f = 0.40, EtOAc: petroleum ether 3:7); IR (neat) cm^{-1}: 3242, 2917, 1634, 1433, 960; ^{1}HNMR (300 MHz, DMSO-d_6) δ_H 1.83 (s, 3 H, CH_3), 1.89 (d, *J* = 1 Hz, 3 H, CH_3), 3.96 (dd, *J* = 7.8, 1 Hz, 1 H, C*H*), 5.45 (d, *J* = 7.5 Hz, 1 H, C*H*), 7.33 (m, 5 H, Ar*H*), 10.95 (s, 1 H, deuterium exchangeable, CNO*H*). MS (EI) calc. for $[M]^+$ ($C_{12}H_{14}N_2O_2$) *m/z* 218.2 found 218.2 and 55 base peaks.

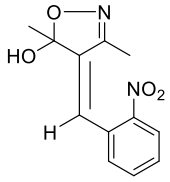
General procedure B for oximation of benzylidenacetylacetone derivatives under mild conditions.

Hydroxylamine hydrochloride (30 mmol, 2.08 g, 3 equiv.) and anhydrous sodium acetate (30 mmol, 2.46 g, 3 equiv.) in (25 mL) methanol was stirred for 15 min. the precipitated solid NaCl was filtered off. The filtrate of the mixture was transferred into a 50 mL one-necked round-bottomed flask and was charged with 2-nitro and 4-methoxy benzylideneacetylacetone derivatives **2** and **3** (10.0 mmol, 1.88 g, 1.00 equiv.). The reaction mixture was stirred for 15-20 min. at room temperature until TLC indicated a complete consumption of the starting material. The reaction was quenched with water and was concentrated by rotary evaporation. The aqueous solution was transferred to a 50 mL separatory funnel was extracted three times with ethyl acetate (3 x 10 mL). The combined organic layers were dried over with Na_2SO_4, filtered, and then evaporated under reduced pressure, and the solid yielding that was purified via crystallization using (EtOAc/petroleum ether).

(*Z*) and (*E*) 3,5-Dimethyl-4-(2-nitrobenzylidene)-4,5-dihydroisoxazol-5-ol (5)



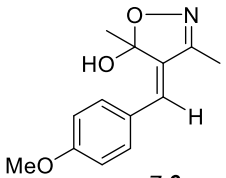
***Z*-5**



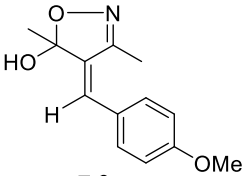
***E*-5**

A mixture of isomers *Z/E*-**5** was prepared according to the general procedure **B** using 2-nitrobenzylidenacetylacetone **2** (2.33 g, 10 mmol) and hydroxylamine hydrochloride (2.08 g, 30 mmol) as starting materials. Yield: 26%; yellow solid; m.p 104−105 °C; (R_f = 0.50, EtOAc: petroleum ether 3:7); IR cm^{-1}: 3204, 1608, 1524, 1344, 1427; ^{1}HNMR (300 MHz, DMSO-d_6) assigned to *Z*-isomer **Z-5**: δ_H 1.16 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 7.20 (s, 1 H, C=C*H*), 7.39 (s, 1 H, deuterium exchangeable, O*H*), 7.64 (t, *J* = 8.1 Hz, 1 H, Ar*H*), 7.76 (dd, *J* = 15.3, 8.1 Hz, 1 H, Ar*H*), 7.92 (d, *J* = 8.1 Hz, 1 H, Ar*H*), 8.12 (d, *J* = 15.3 Hz, 1 H, Ar*H*). The same sample was reanalyzed ^{1}HNMR (500 MHz, DMSO-d_6) after 1.5 months. Assigned to *Z*-isomer **Z-5**: δ_H 1.16 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 7.21 (s, 1 H C=C*H*), 7.44 (s, 1 H, deuterium exchangeable, O*H*), 7.92 (dd, *J* = 8.1, 1 Hz, 1 H, Ar*H*), 7.64 (t, *J* = 8.1 Hz, 1 H Ar*H*), 7.98 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.82 – 7.76 (m, 1 H, Ar*H*). Assigned to *E*-isomer ***E*-5**: ^{1}HNMR (500 MHz, DMSO-d_6) δ_H 1.92 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 6.15 (d, *J* = 4.8 Hz, 1 H, deuterium exchangeable O*H*) 6.22 (d, *J* = 4.9 Hz, 1 H, collapse to singlet on addition D_2O C=C*H*), 7.98 (d, *J* = 7.7 Hz, 1 H, Ar*H*), 7.92 (dd, *J* = 8.1, 1.0 Hz, 1 H, Ar*H*), 7.82 – 7.76 (m, 2 H, Ar*H*), ^{13}CNMR for *Z/E*-isomers (125 MHz, DMSO-d_6) δ_C 165.9, 158.7, 154.0, 148.0, 147.6, 143.0, 136.8, 133.3, 133.0, 132.3, 129.7, 129.3, 128.7, 128.2, 125.5, 124.6, 124.5, 115.3, 103.9, 103.4, 61.1, 23.2, 10.7, 10.1. MS (EI) calc. for $[M]^+$ ($C_{12}H_{12}N_2O_4$) *m/z* 248 found 247 and 124 was the base peak.

(*Z*) and (*E*)-4-(4-Methoxybenzylidene)-3,5-dimethyl-4,5-dihydroisoxazol-5-ol (6)



Z-**6**



E-**6**

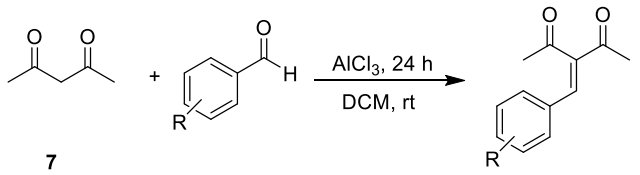
A mixture of isomers *Z*/*E*-**6**was prepared according to the general procedure **B** using 4-methoxybenzylidenacetylacetone **3** (2.18 g, 10 mmol) and hydroxylamine hydrochloride (2.08 g, 30 mmol) as starting materials. Yield: 80%; white solid; IR cm^{-1}: 3258, 1605, 1575, 1514, 725; ^{1}HNMR (300 MHz, DMSO-d_6) Assigned to *Z*-isomer ***Z*-6**: δ_H 1.72 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 6.70 (s, 1 H, C=C*H*), 6.89 (s, 1 H, deuterium exchangeable O*H*), 7.78 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.52 (d, *J* = 9 Hz, 2 H, Ar*H*).

The same sample was reanalyzed ^{1}HNMR (500 MHz, DMSO-d_6) after 1.5 months. Assigned to *E*-isomer: δ_H 1.97 (s, 3 H, CH_3). 2.30 (s, 3 H, CH_3), 3.73 (s, 3 H, OCH_3), 5.75 (d, *J*= 3.9 Hz, 1 H, deuterium exchangeable O*H*), 5.64 (d, *J* = 3.8 Hz, 1 H, collapse to singlet on addition D_2O), 7.23 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.89 (d, *J* = 8.7 Hz, 2 H, Ar*H*). ^{13}CNMR (125 MHz, DMSO-d_6): δ_C 164.8, 158.6, 158.2, 135.5, 127.0, 117.5, 113.5, 64.8, 55.0, 11.0, 10.4.

Results and Discussion

The literatures survey showed the synthetic importance of the oximes in the synthesis of heterocyclic systems. This project explores the synthesis of five membered ring heterocyclic compounds derived from *α*,*β*-unsaturated oximes of acetylacetone.

Preparation of benzylidenacetylacetone and their derivatives



7

8, R = H
9, R = 2-NO_2
10, R = 4-OMe

1, R = H **(62%)**
2, R = 2-NO_2 **(50%)**
3, R = 4-OMe **(52%)**

Scheme 1

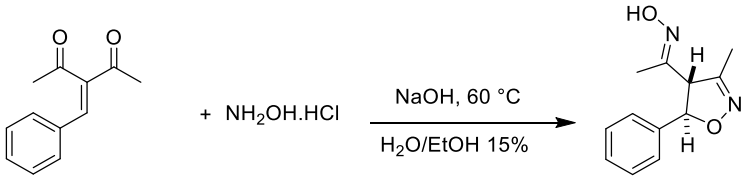
According to Raman and co-workers,[18] the Knoevenagel condensation reaction between acetylacetone and benzaldehyde in the presence of 20 mol% of $AlCl_3$. Another two benzaldehyde derivatives carrying NO_2 as electron withdrawing group (EWG) and OMe as electron releasing group (ERG) were reacted under the same reaction condition (Scheme 1). EWG at position 2 was assumed to increase the electrophilicity of the carbonyl group carbon atom, however, the yield of benzaldehyde was (62%) while -NO_2 and 4-OMe derivatives gave similar yields (50 and 52%).

Oximation of benzylidenacetylacetone and their derivatives

Oximation of benzylidenacetylacetone using NaOH

The produced arylideneacetylacetones were subjected to the standard oximation conditions to form unsaturated oximes. An initial attempt was carried out to reach the optimum conditions by utilizing benzylidenacetylacetone **1** as a model substrate. According to a published procedure, benzylidenacetylacetone was reacted with hydroxylamine hydrochloride and NaOH in water/ethanol as a mixed solvent at 60 °C. The completion of the reaction was monitored by TLC, which showed forming a single pure product in 2 hours.[19]

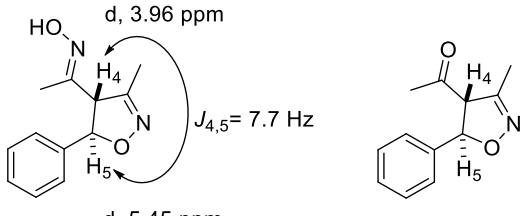
The data of compound **4** was consistent with the absorptions of a similar compound **12**. The IR spectrum showed a broad absorption band at 3242 cm^{-1} for the hydroxyl group, as well as a characterized absorption band at 1634 cm^{-1} for the azomethine group C=N. ^{1}HNMR data showed a singlet peak for the hydroxylic proton seen at 10.95 ppm (exchanged by D_2O) and two peaks of both methine protons were observed as a doublet of doublet signal at 3.96 ppm and a doublet peak at 5.45 ppm. Additionally, the rest of NMR signals, the *J* values and the proposed molecular formula (from the mass spectrum data) suggested that a further unexpected intramolecular oxa-Michael addition reaction was occurred to produce isoxazoline system **4** (Scheme 2).



1 **11** **4, 64%**

Scheme 2

Moreover, the relative stereochemistry of C-4 and C-5 has been established using the coupling constant values of the methine protons in the isoxazoline ring which has a feature $J_{cis} > J_{trans}$. Thus, the suggested configuration of the isolated compound was *trans*-isomer **4**, the $J_{4,5}$ value was 7.7 Hz which was consistent with *J* constant of H_4 and H_5 of compound **12** (Figure 1).[20,21]



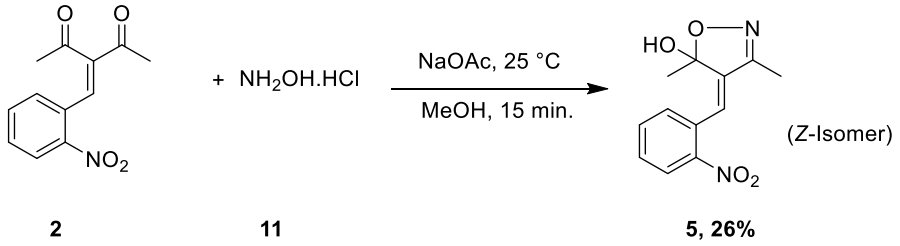
4 **12**

Figure 1

Oximation of benzylidene derivatives under milder conditions

Oximation of 2-nitrobenzylidenacetylacetone

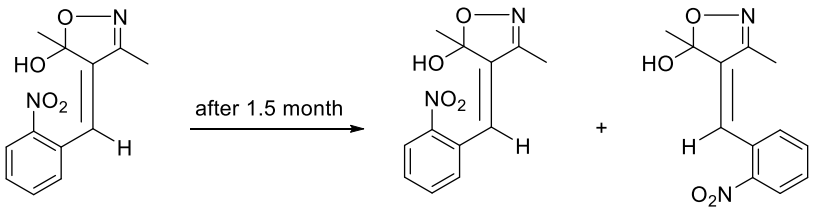
Alternatively, milder conditions were suggested to avoid the intramolecular oxa-Michael addition reaction by using a weaker base (NaOAc) at room temperature and 2-nitrobenzylidenacetylacetone. 2-Nitrobenzylidenacetylacetone was reacted with hydroxylamine hydrochloride in the above conditions,[22] to produce almost a single product in 15 minutes. The structural formula of the resultant compound **5** was confirmed by various spectroscopic analysis. The IR spectrum showed absorption band at 3204 cm^{-1} for the hydroxyl group, along with the distinctive absorption band for azomethine group at 1608 cm^{-1} and two strong absorption bands at 1524 and 1344 cm^{-1} which indicate the presence of nitro group. ^{1}HNMR spectrum of the product exhibited a singlet peak at 7.39 ppm that attributed to the proton of the hydroxyl group, which was chemically exchanged with deuterium oxide. ^{1}HNMR spectra also showed a singlet peak at 7.20 ppm for vinylic proton and two singlet peaks at 1.16 ppm of ($CH_3C(OH)$) and 2.07 ppm of (CH_3 C=N) (Scheme 3).



2 **11** **5, 26%**

Scheme 3

The ^{13}CNMR spectroscopy of the same sample of compound **5** was measured at later time (1.5 months), the spectrum showed extra signals more than expected. Consequently, ^{1}HNMR was re-measured, the spectrum showed the presence of all protons of the previously established compound (5-hydroxy-2-isoxazoline derivative **5)** accompanied with a several peaks of another compound which has an equal number of protons to the compound **5** with different chemical shifts. The acceptable explanation for this behavior was suggested to be that the product **5** over the time underwent isomerization around the olefinic double bond forming *Z*- and *E*-isomers mixture in 1:1 relative ratio. It seems that *E*-isomer is more stable than *Z*-isomer due to steric hindrance, which means that the *Z*-isomer was formed first (Scheme 4).[23,24]



Z-Isomer *Z*-Isomer (1:1) *E*-Isomer

***Z*-5** ***Z*- 5** ***E*- 5**

Scheme 4

Several evidences support the occurrence of this isomerization. Firstly, and interestingly, the appearance of hydroxylic proton in *E*-isomer as a doublet signal at 6.22 ppm (J = 4.8 Hz) due to the presence of a spin-spin long range coupling with the olefinic proton at 6.15 ppm that appeared as a doublet (J = 4.8 Hz). This coupling was established by the addition of D_2O which led to the totally disappearing of the doublet signal of hydroxylic group and the doublet peak of the olefinic proton was collapsed to a singlet. The literatures have many examples that show the presence of a coupling between a hydroxyl proton and a neighboring proton.[25] In contrast, the ^{1}HNMR data of the *Z*-isomer did not show the described spin-spin coupling. Secondly, the hydroxylic proton of the *Z*-isoxazoline derivative was highly deshielded (7.39 ppm) which could be attributed to two reasons, the inductive effect of the nitro group (EWG) and the possibility of forming an intramolecular hydrogen bond (Figure 2).

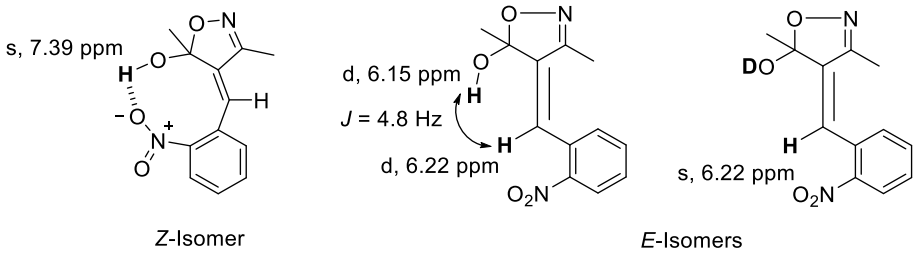
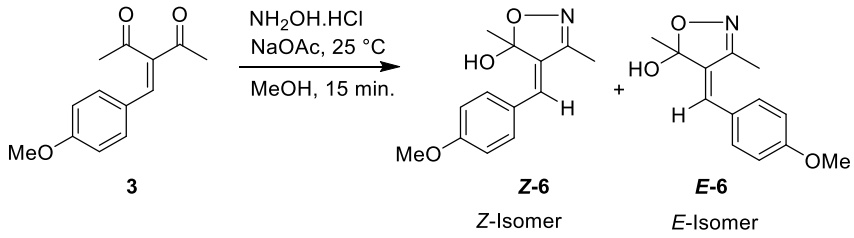


Figure 2

The ^{13}CNMR spectral data showed signals represent the mixture of *E*/*Z* isomers ***E*-5** and ***Z*-5** in 1:1 ratio, which support the suggested structures using the ^{1}HNMR data.

Oximation of 4-methoxybenzylidenacetylacetone

3,5-dimethyl-4-(4′-Methoxybenzylidene)-5-hydroxy-2-isoxazoline isomers **Z-6** and ***E*-6** were obtained in 80% yield by treating 4-methoxy benzylidenacetylacetone **3** with hydroxylamine hydrochloride (Scheme 5).



Scheme 5

The spectroscopic measurements were carried out to confirm the structure of the products, IR spectrum showed a broad absorption band at 3258 cm^{-1} for the hydroxyl group and a characterized absorption band at 1605 cm^{-1} for the azomethine group

C=N. ^{1}HNMR showed the presence of a mixture of two compounds *Z* and *E*-isomers in 2:1 ratio respectively, similar behaviour to the oximation reaction of 2-nitrobenzyliden-acetylacetone **5**.

^{1}HNMR spectrum of *Z*-isomer exhibited a singlet peak at 6.89 ppm for the proton of the hydroxyl group, which disappeared by adding D_2O. The singlet peak at 6.70 ppm was attributed to the vinylic proton. In contrast, the ^{1}HNMR of *E*-isomer showed a doublet peak at 5.75 ppm, which completely disappeared when the sample was treated with D_2O, this peak could be assigned to the OH proton. In addition, the doublet peak of the vinylic proton at 5.64 ppm turned to a singlet signal. ^{1}HNMR data also showed the expected chemical shifts for all other protons which were in accordance with the structures of *E*- and *Z*-isomers.

Conclusion

The achievements from this study involve the preparation of benzylidenacetylacetone and its 2-nitro, 4-methoxy-derivatives using the Knoevenagel reaction conditions with (50-62%) yields. Exploring the behavior of the prepared benzylidenes (with different electron density of the aromatic ring) toward oximation reaction. The reaction of benzylidenacetylacetone with hydroxylamine hydrochloride in a strong basic condition and raised temperature gave *trans*-isoxazoline oxime via oximation reaction followed by oxa- Michael reaction. While in the second method, benzylidenacetyl-acetone derivatives (2-NO_2 and 4-OMe) were explored toward oximation reaction under milder conditions using sodium acetate at room temperature to produce a various products including *Z* and *E*-5-hydroxy-2-isoxazoline derivatives that produced through oximation reaction followed by hemi-ketal formation.

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الملخص

تم تحضير مشتقات جديدة من الايزوكسازولين أوكسيم بالإضافة إلى مشتق 5-هيدروكسي-2-ايزوكسازولين ذلك من خلال تفاعل البنزاليديين أسيتيل اسيتون ومشتقاته مع الهيدروكسيل أمين هيدروكلوريد باستخدام طريقتين. جميع المركبات المحضرة تم إثبات تركيبها الكيميائي بواسطة تقنية الاشعة تحت الحمراء FT-IR و طيف الرنين النووي المغناطيسي ^{1}HNMR,^{13}CNMR بالإضافة الي طيف الكتلة. تم اجراء تفاعل تكوين الأوكسيم باستخدام بنزاليديين أسيتيل اسيتون في وجود قاعدة قوية حرارة عالية نتج عنه تكوين الايزومر ترانس من ايزوكسازولين أوكسيم بنسبة ناتج 64%. كما أجري تفاعل تكوين الأوكسيم مع مشتق 2-نيترو و 4-ميثوكسي في وسط قاعدي ضعيف وعند درجة حرارة الغرفة، حيث كانت النواتج مختلفة التركيب تحتوي علي حلقات غير متجانسة. تم الحصول علي الايزومرين *Z*- و*E*- من مشتق 5-هيدروكسي-2- ايزوكسازولين بنسبة 1:1 للمشتق 2-نيترو بنزاليديين أسيتيل اسيتون و1:2 لمشتق 4-ميثوكسي بنزاليديين أسيتيل اسيتون.