Synthesis of Acetophenone Oxime And Determination of The Ration of Its Geometric Isomers

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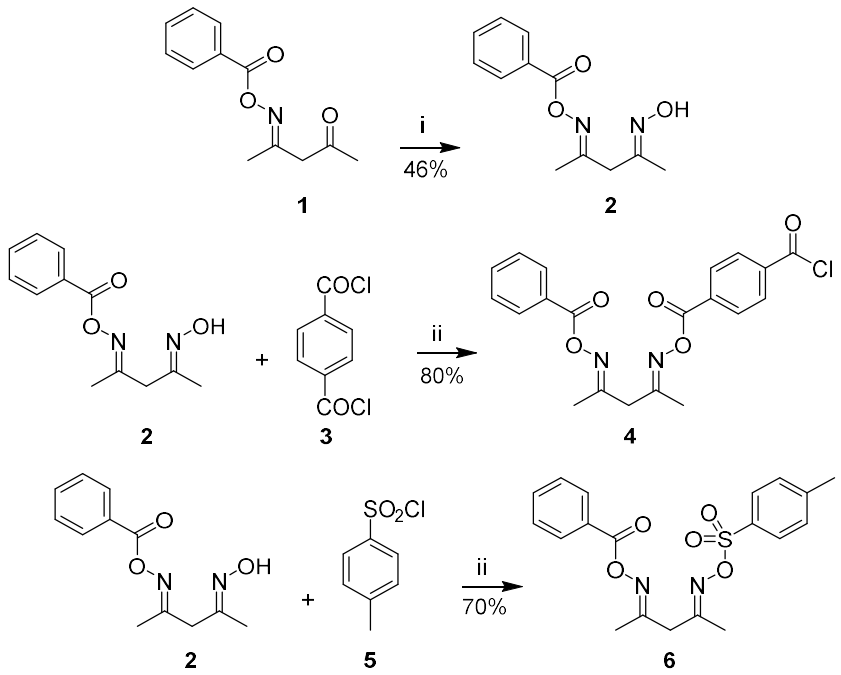
Abstract: The acetophenone oxime was obtained in moderate yield (31%) throughout a reaction between the acetophenone and the hydroxylamine hydrochloride under basic conditions. The structural formula of the obtained acetophenone oxime was confirmed by the IR, NMR and mass spectrometer. The ^{1}HNMR data also revealed that the acetophenone oxime was resulted in two geometrical isomeric forms, *E*- and *Z*- isomers, in the ratio of (8:1) respectively.

Keywords: Acetophenone oxime, geometrical, E- and Z-isomers.

INTRODUCTION

Oximes have been considered as useful compounds for protecting and purifying carbonyl compounds in the synthetic organic chemistry [1]. These compounds have also shown antimicrobial, antioxidant, antitumor, anti-depressive, antiviral agents and anticonvulsant behaviors [2 – 7]. Oximes have been used as starting materials for the synthesis of amines being used in paints, fibers, medical tools and in the synthesis of some lactams [8 – 11]. The (*2E,4E*)-pentane-2,4-dione O^4-benzoyl dioxime **2** was prepared first to be the precursor towards the synthesis of (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane **4**. It was synthesized through a reaction of (1:1 mole/mole) between the hydroxylamine hydrochloride and the (*E*)-4-(benzoyloxyimino)pentan-2-one **1** under basic conditions at ambient temperature. The (*2E,4E*)-pentane-2,4-dione O^4-benzoyl dioxime **2** was obtained. The latter was converted to the (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane **4 (Scheme 1)**. Similarly, the (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane **6** was also obtained by reacting one mole of the (*2E,4E*)-pentane-2,4-dione O^4-benzoyl dioxime **2** with one mole of tosyl chloride under similar basic conditions **(Scheme 1)** [12].



Reagents & reaction conditions: (i) $NH_2OH.HCl$, K_2CO_3, Na_2SO_4, rt, 45 min; (ii) Et_3N, $CHCl_3$, 0-7 °C, 30 min, then rt, 2 hrs

Scheme 1: Synthesis of (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane 4 and the (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane 6

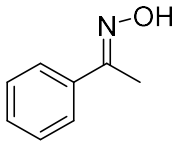
The pentane-2,4-dione dioxime was reported to be formed as a mixture of two geometric isomers in the ratio of (4.5:1). The major isomer was predicted by applying the MM2 calculations in which the (*Z,E*)-pentane-2,4-dione dioxime was proposed to be the major isomer (82.8%). However, the (*E,E*)-pentane-2,4-dione dioxime was suggested to be the minor isomer (18.2%). The Obtained pentane-2,4-dione dioxime was then subjected to three esterification reactions with benzoyl chloride, terphthaloyl chloride and tosyl chloride to produce three corresponding dioxime esters (2*E*,4*E*)-pentane-2,4-dione *O*,*O*-dibenzoyl dioxime, (2*E*,4*E*)-pentane-2,4-dione *O,O*-diterphetaloyl dioxime and (2*E*,4*E*)-pentane-2,4-dione *O*,*O*-ditosyl dioxime respectively [13]**.**

MATERIALS AND METHODS

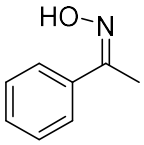
Acetophenone, hydroxylamine hydrochloride, potassium carbonate, anhydrous sodium sulphate, triethyl amine and chloroform. These chemicals were used without further purification.

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.

Synthesis of acetophenone oxime 1: [12]



major isomer (88.2%)

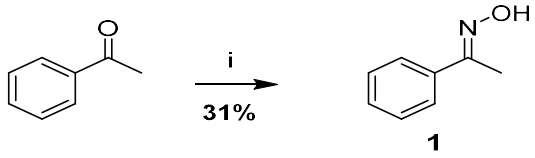


minor isomer (11.8%)

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. Acetophenone (8.0 gm, 66.58 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 of 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 further 10 min, cooled, pH was measured and found to be neutral. The reaction mixture was poured into a beaker containing ice–water (100 cm^3), by which the acetophenone oxime precipitated rapidly. The resulting oxime was filtered, washed with cold water (3 × 10 cm^3) and air dried to give a white powder of the desired compound (2.80 gm, 20.74 mmol, 31% yield). The product was recrystallized from diethyl ether; mp 67 ºC (lit. 55 – 60 ºC) [Aldrich]; IR ν_{max} (cm^{-1}) 3212 (OH), 1497 (C=N). **Major isomer (88.2 %):** ^{1}HNMR (DMSO-d6, 500 MHz) δ 11.24 (1 H, s, OH), 7.65 (2 H, d, *J* 7.7, 2 × Ar-CH), 7.38 – 7.32 (3 H, m, 3 × Ar-CH), 2.15 (3 H, s, CH_3); **Minor isomer (11.8%):** ^{1}HNMR (DMSO-d6, 500 MHz) δ 11.23 (1 H, s, OH), 7.94 (2 H, d, *J* 7.9, 2 × Ar-CH), 7.52 – 7.49 (3 H, m, 3 × Ar-CH), 2.56 (3 H, s, CH_3). Mass spec m/z (C_8H_9NO, MWt 135.15)

RESULTS AND DISCUSSION

The acetophenone was refluxed with a solution of hydroxylamine hydrochloride under basic conditions. The acetophenone oxime was obtained as a white solid in moderate yield **(Scheme 1)**.



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Reagents & reaction conditions: (i) $NH_2OH.HCl$, K_2CO_3, Na_2SO_4, rt then reflux, 30 - 45 min

Scheme 2: Synthesis of acetophenone oxime

The IR data revealed that the oxime **1** was formed as the hydroxyl group of the resulted oxime appeared at 3212 cm^{-1} in addition to the appearance of the imino group (C=N) at 1497 cm^{-1} at the expense of the carbonyl group (C=O). The ^{1}HNMR spectroscopy showed that the oxime **1** was formed in two isomeric forms in the ratio of about (8:1). The ^{1}HNMR spectrum clearly revealed all the expected chemical shifts for all existing protons for both major and minor isomers **(Fig. 1)**. In the case of the major isomer, the proton of the hydroxyl group of the oxi me is clearly seen at 11.24 ppm as a singlet peak along with the five aromatic protons appeared as one doublet peak for two aromatic protons at 7.65 ppm with coupling constant (*J* value) of 7.7 Hz and one multiplet peak for the other three aromatic protons at 7.38 to 7.32 ppm. The protons of the methyl group is seen at 2.15 ppm as a singlet peak. The chemical shifts of the oxime **1** indicated the existence of another singlet peak appeared as a small shoulder could barely be seen at 11.23 ppm belongs to the proton of the hydroxyl group of the minor isomer of the oxime **1 (Fig 1)**. Whereas, the five aromatic protons are observed at 7.94 ppm as a doublet peak for two protons and a multiplet peak at 7.52 to 7.49 ppm for the remaining three aromatic protons. Finally, the methyl protons appeared at 2.56 ppm as a singlet peak **(Fig 1)**.

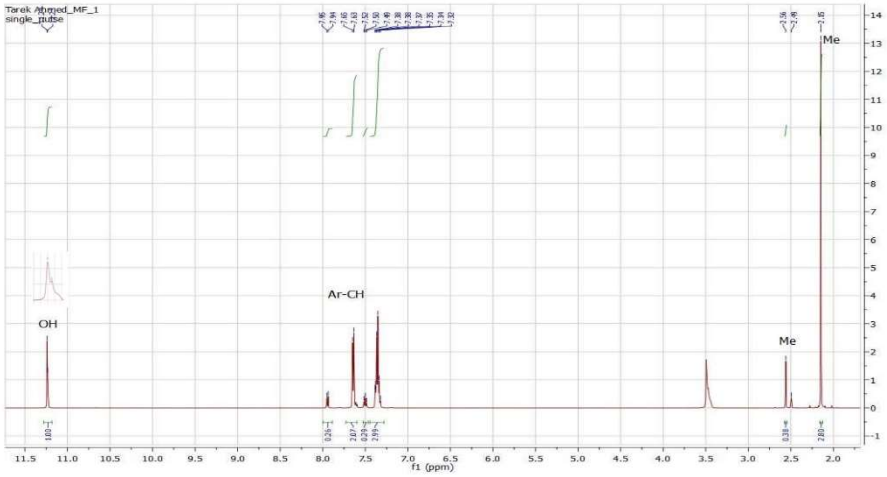

Figure 1: ^{1}HNMR spectrum showing the isomeric forms of oxime 1

The theoretical calculations were carried out using ChemBio3D Ultra 14.0 revealed that the major isomer of the oxime **1** was the *E*-isomer in which the hydroxyl group of the oxime was placed *opposite* to the phenyl group, however, they were placed *syn* in the minor counterpart **(Fig 2)**. The minimizing energies for these two isomers were calculated employing the mechanical mechanism method (MM2). The minimized energies were found to be 3.65 Kcal/mol for the major isomer (*E*-isomer) and 6.88 Kcal/mol for the minor isomer (*Z*-isomer). It means that the *E*-isomer is more stable than the *Z*-isomer that has just above two folded stabilizing energy higher than the major *E*-isomer **(Fig 2)**. This is in accordance with the formation percentages of these two isomers that were measured through the integrals of the ^{1}HNMR signals equaling 88.2 % and 11.8 % for the major and the minor respectively **(Fig 2)**.

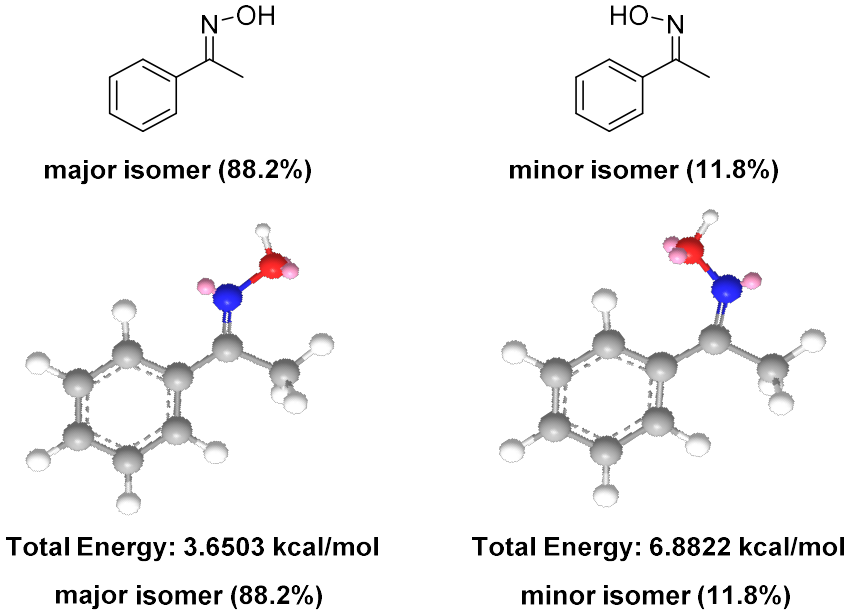

Figure 2: Total energies of the *E*- and *Z*-isomers of the oxime 1 calculated using ChemBio3D Ultra 14.0

Finally, the mass spectrometer provided a further evidence on the formation of the oxime **1** as the molecular ion peak was observed at 135 m/z along with some other fragments which were in the accordance with the expected fragmentation pattern.

CONCLUSION

The acetophenone oxime was synthesized in moderate yield (31%). The ^{1}HNMR data revealed that the acetophenone oxime was formed in two geometrical isomeric forms *E*- and *Z*-isomer in the ratio of (8:1) respectively.

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