Synthesis of heterocyclic compounds derived from oximation of benzylidene acetylacetone derivatives

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Abstract: New derivatives of heterocyclic compounds were synthesized by the oximation reaction of 1,3-dicarbonyl acetylacetone derivatives with hydroxylamine hydrochloride, gave various heterocyclic compounds depending on the nature of the substituent. The reaction of 4-(*N*,*N*-dimethylamino)benzylidene acetylacetone led to the synthesis of mixture of corresponding *Z*-5-hydroxy-2-isoxazoline and *cis*-2-isoxazoline oxime with a 31%, 33% yield respectively. The reaction was also carried out using 4-nitrobenzylidene acetylacetone, the result was formation of *trans*-isoxazolidine oxime derivative with a 38% yield.

Keywords*: Oxime, 1,3-dicarbonyl Compound, heterocyclic compounds, Isoxazoline.*

Introduction

Isoxazoline (dihydroisoxazol) and isoxazole are subclasses of five-membered nitrogen-oxygen containing heterocyclic compounds, isoxazoline and isoxazole have a remarkable number of applications and demonstrated to be very versatile building blocks in organic synthesis [1]. and important heterocycles having a wide role in medicinal chemistry. these compounds are widely used as an anti-inflammatory [2], anti-bacteria [3] anti-fungi [4], and HIV-inhibitory activity [5]. Some isoxazole derivatives display agrochemical properties namely herbicidal [6]. Oximes have very remark reactivity and are often used as intermediates for the preparation of a great variety of compounds, oximation of 1,3-dicarbonyl compounds are one of the popular isoxazole syntheses. Claisen described the first synthesis of isoxazoles [7]. Grünanger *et al*. have reported that the reaction of 1,3-diaryl diketones with hydroxylamine in the presence of methanol yielded a mixture of two isomeric isoxazole, while the reaction of 1,3-diaryl diketones with hydroxylamine in presence of sodium methoxide hydrochloride give two isomeric of 3,5-diaryl-2-isoxazoline-5-ol with very low yield [8]. Chauhan *et al*. reported that the reaction of diaryl-l,3-diketone with hydroxylamine hydrochloride on silica gel under microwave irradiation to generate isoxazole derivative [9]. The investigation of the mechanism involved in the reaction of 1,3-diketones with hydroxylamine has been a subject of great interest in several research studies. 1,3-Diketones provide different types of electrophilic centers due to tautomerism and thus owing to binucleophilic nature, may attack first on any one of the electrophilic centers of 1,3-diketones. A number of cyclic and acyclic intermediates can be formed which finally lead to the formation of two regioisomeric

compounds [10,11]. Herein, a continuation of our previous study which reported the oximation reaction of different benzylidenacetylacetone derivatives with hydroxylamine hydrochloride [12].

Material and Methods

General

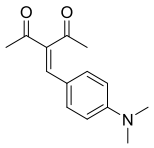
Starting materials and solvents were purchased from common commercial sources. All melting points were uncorrected. All R_f values were obtained by using GF_{254} TLC, on pre-coated silica plates. The IR spectra were recorded using on Perkin-Elmer FT-IR spectrophotometer accessorized with ATR. ^{1}HNMR 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, DMSO-d_6 and D_2O solvents and using the chemical shift of the solvents as standard. MS spectral data was obtained using a Shimadzu Qp-2010 ples GC/mass spectrometer and MS spectra were recorded using EI at 70 eV.

Preparation of benzylidene acetylacetone derivatives

General procedure A

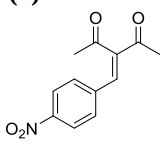
Anhydrous aluminum chloride (6.6 mmol, 0.33 equiv.) was added to a solution of the acetylacetone (40.0 mmol, 2.00 equiv.) in dichloromethane (2 mL), stirring at room temperature for 15 min, and then the aldehyde (20.0 mmol, 1.00 equiv.) was added. The reaction was stirred at room temperature until the reaction was complete (TLC detection), then quenched with saturated $NaHCO_3$ solution. The dichloromethane solution was then washed with the chloroform then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by recrystallization (EtOAc/petroleum ether) [13].

4-(*N*,*N*-dimethyl amino) benzylidene acetylacetone (1)



Compound **1** was prepared according to the general procedure **A** 4-(*N*,*N*-dimethyl amino) benzaldehyde **4** and acetylacetone **3** as starting materials. Yield: 56%; yellow-green solid; m.p 100 - 102 °C; (R_f = 0.70, EtOAc : petroleum ether 3:7); IR (neat) cm^{-1}: 1699, 1638, 1580, 1625; ^{1}HNMR (300 MHz, $CDCl_3$) δ_H 2.25(s, 3 H, C*H*$_3$), 2.27(s, 3 H, C*H*$_3$), 3.03 (s, 6 H, N(C*H*$_3$)$_2$) 7.26 (s, 1 H, C=C*H*), 6.67 (d, *J* = 9 Hz, 2 H, Ar*H*), 7.31 (d, *J* = 9 Hz, 2 H, Ar*H).*

4-Nitrobenzylidene acetylacetone (2)

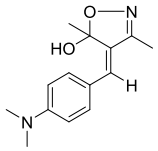


Compound **2** was prepared according to the general procedure **A** using 4-nitrobenzaldehyde **5** and acetylacetone **3** as starting materials. Yield: 68%; yellow solid; m.p 87−88 °C; (R_f = 0.25, EtOAc : petroleum ether 3:7); IR (neat) cm^{-1} : 1705, 1662, 1618, 1527, 1591; ^{1}HNMR (300 MHz, DMSO-d_6) δ_H 2.23 (s, 3 H, C*H*$_3$), 2.42 (s, 3 H, C*H*$_3$), 7.71 (s, 1 H, C=C*H*), 7.60 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 8.21 (d, *J* = 7.2 Hz, 2 H, Ar*H*).

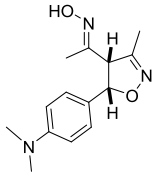
Oximation reaction of benzylidene acetylacetone derivatives
General procedure B

Hydroxylamine hydrochloride (30 mmol, 2.08 g, 3 equiv.) and anhydrous sodium acetate (30 mmol, 2.46 g, 3 equiv.) in (25 mL) methanol were 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 4-(*N*,*N*-dimethyl amino) and 4-nitro benzylidene acetylacetone 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*) 4-(4-(*N*,*N*-Dimethylamino) benzylidene)-3, 5-dimethyl-4,5-dihydroisoxazol-5-ol (3)

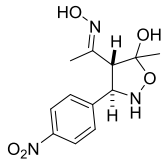


***Cis*-(5-(4-(*N*,*N*-dimethylamino)phenyl)-3-methyl-4,5-dihydro-isoxazol-4-yl) ethan-1-one oxime (4)**



Mixture of compounds **3**, **4** was prepared according to the general procedure **B** using 3-(4-(dimethyl amino) benzylidene) acetylacetone **1** (2.31 g, 10 mmol) and hydroxylamine hydrochloride (2.08 g, 30 mmol) as starting materials. Yields: **3**, 31% and **4**, 33%; yellow solid; IR cm^{-1}: 3278, 1607, 1520, 1446; ^{1}HNMR (500 MHz, DMSO-*d*6) assigned to product **3**: δ_H 1.38 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 2.77 (s, 6 H, N(CH_3)2), 5.16 (s, 1 H, C=C*H*), 6.23 (s, 1 H, deuterium exchangeable O*H*), 6.41 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 6.47 (d, *J* = 8.6 Hz, 2 H, Ar*H*). Assigned to product **4**: δ_H 1.80 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.79 (s, 6 H, N(CH_3)$_2$), 2.91 (d, *J* =10.0 Hz, 1 H, C*H*), 4.40 (d, *J* = 10.2, 1 H, C*H*), 6.80 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.94 (d, *J* = 8.6, 2 H, Ar*H*), 10.53 (s, 1 H, deuterium exchangeable CNO*H*). ^{13}CNMR (125 MHz, DMSO-*d*6) for two compounds **3** and **4**: δ_C11.1, 12.2, 13.4, 19.7, 25.3, 39.5, 39.6, 104.4, 112.3, 112.4, 116.1, 127.7, 129.1, 129.4, 130.5, 149.4, 149.9, 152.3, 159.2, 164.8, 164.8. For the two compounds **3** and **4**; MS (EI) calc. for $[M]^+$ ($C_{14}H_{19}N_3O_2$) m/z 261.15 found 261 and 229 (100), 55 (24.58),77 (21.39),121 (43.5),146 (44.39)

***Trans*-1-(5-hydroxy-5-methyl-3-(4-nitrophenyl) isoxazolidin-4-yl) ethan-1-one oxime (5)**

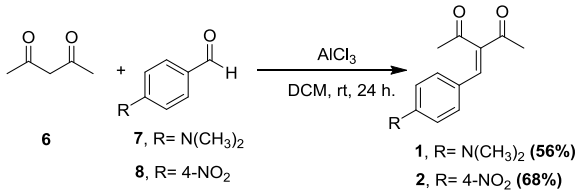


Isoxazolidine oxime **5** was prepared according to the general procedure **B** using 4-nitrobenzylidene acetylacetone **6** (2.33 g, 10 mmol) and hydroxylamine hydrochloride (2.08 g, 30 mmol) as starting materials. Yield: 32%; white powder; IR cm^{-1}: 3260, 3248, 3075, 1646 1600, 1525, 1349, 839 ; ^{1}HNMR (500 MHz, DMSO-d_6) δ_H 1.45 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 2.77 (d, J = 6.8 Hz, 1 H, C*H*), 5.00 (dd, J = 7.0, 6.8 Hz, 1 H, C*H*), 6.28 (s, 1 H, deuterium exchangeable N*H*), 7.58 (d, J = 8.7 Hz, 2 H, ArH), 7.25 (s, 1 H, deuterium exchangeable O*H*), 8.19 (d, J = 8.7 Hz, 2 H, Ar*H*), 10.70 (s, 1 H, deuterium exchangeable CNO*H*); ^{13}CNMR (125 MHz, DMSO-d_6) δ_C13.06, 13.9, 23.6, 61.5, 65.9, 106.1, 123.6, 127.2, 137.9, 146.3, 152.3, 167.6; MS (EI) calc. for $[M]^+$ ($C_{12}H_{15}N_3O_5$) m/z 281.2 found 252, and 57 (100), 23(100), 55 (90.20), 87 (60), 236 (75), 97 (72.5).

Results and Dicussion

The literature 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 based on the oximes benzylidene acetylacetone.

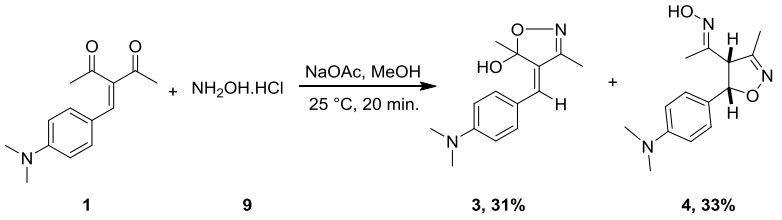
Preparation of benzylidene acetylacetone derivatives



Scheme 1

According to Li and co-workers [14], The condensation reaction between acetylacetone and 4-(*N*, *N*-dimethylamino),4-nitro benzaldehyde derivatives in the presence of 20 mol% of $AlCl_3$.The nitro group increases the electrophilicity of the carbonyl group carbon atom, thus 4-nitro benzaldehyde afforded slightly higher yields than 4-(*N*, *N*-dimethylamino) benzaldehyde.

Oximation of 4-(*N*,*N*-dimethylamino) benzylidene acetylacetone



Scheme 2

The reaction was carried out between 4-(*N*,*N*-dimethylamino) benzylidene acetylacetone **1** and $NH_2OH.HCl$ at room temperature to yield an inseparable mixture of two compounds **3**,**4**. The structures of products were confirmed using various spec-

troscopic techniques. The infrared spectra showed a broad absorption band at 3278 cm^{-1} for the hydroxyl group along with the characteristic azomethine group absorption at 1607 cm^{-1}. The ^{1}HNMR spectroscopy gave a clear indication to the presence of two compounds **3** and **4** (Scheme 2). *Z*-Isomer **3** exhibited a singlet at 6.23 ppm assigned for the hydroxylic proton, which confirmed by adding of D_2O. Furthermore, the spectrum showed the expected chemical shifts for all protons assuring the structure. The literatures have many examples that show the presence of a coupling between a hydroxyl proton and a neighboring proton. In contrast, the ^{1}HNMR data of the *Z*-isomer did not show the described spin-spin coupling[12,15].

In contrast, the ^{1}HNMR data of isoxazoline derivative **4** showed a singlet peak for the hydroxylic proton seen at 10.53 ppm, as an evidence of the presence of an oxime group, which was exchanged by D_2O. The two peaks of the protons H_5 and H_4 of the two methines in isoxazoline ring were observed as a doublet at 4.40 and 2.91 ppm, respectively. The stereochemistry has been established to be as a *cis*-isomer from the value of the *J* constant ($J_{4,5}$ = 10.1 Hz) (Figure 1), which was consistent with *J* values of H_4 and H_5 in similar systems as shown in the literatures [16,17]. The spectrum also showed the expected chemical shifts for the other protons.

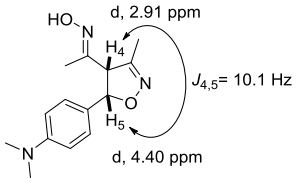
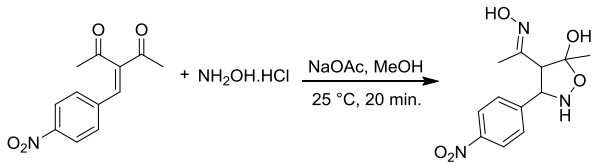


Figure 1

The ^{13}CNMR spectra showed two peaks at 164.9 and 164.8 ppm for azomethine carbons. Additionally, the remaining peaks of other carbons were consistent with the suggested structure **3**.

Oximation of 4-nitrobenzylidene acetylacetone



2 **9** **5, 32%**

Scheme 3

The oximation reaction of 4-nitrobenzylidene acetylacetone was carried out under the previously described conditions. By investigating the spectral data, different behavior was noticed in this reaction, which led to a new system. The IR showed absorption bands of the N-H and OH groups, along with the other characteristic groups (Scheme 3). By analyzing the ^{1}HNMR data it was clear that the reaction gave two compounds with 1:5 ratio. The major component showed a singlet peak seen at 10.70 ppm for the hydroxylic proton of oxime group. It also showed two singlet peaks for the OH at 7.25 and N-H at 6.28 ppm, these acidic protons were confirmed due to their disappearance when adding D_2O. Also gave two peaks (as a doublet at 2.77 and 5.00 ppm with *J* = 6.9 Hz) relating to the protons of the methine groups.

Additionally, ^{1}HNMR data showed the expected chemical shifts for all other protons, which were in accordance with the structure of isoxazolidine oxime **5**. As found in the literatures, the coupling constants of H_3 and H_4 of the vicinal protons in isoxazolidine ring gave an information about the stereochemistry of the ring. Generally, the coupling constant of H_3 and H_4 are in range 8.1-9.0 Hz for the *cis*-isomer and 6.0-8.1 Hz for the *trans*-isomer [18,19]. As a result, the geometry of the major product was suggested to be as *trans*-isomer.^{13}CNMR spectra showed the predominated compound, which displayed a peak at 167.6 ppm for the azomethine carbon. Furthermore, the number and position of the other signals were compatible with the suggested isoxazolidine oxim **5**.

الملخص: تم تحضير مشتقات حلقية غير متجانسة وذلك من خلال تفاعل مشتقات البنزايليدين أسيتيل اسيتون مع الهيدروكسيل أمين هيدروكلوريد، والذي أعطى مشتقات مختلفة من المركبات الحلقية غير متجانسة بناء علي طبيعة المستبدل. تم الحصول على خليط من مركبين الايزومر *سيس* ايزوكساولين أوكسيم بنسبة انتاجية 33% والايزومرZ-5-هيدروكسي- 2- ايزوكسازولين بنسبة انتاجية 31% الناتج من مفاعلة ثنائي ميثيل امينو بنزايليدين، وعند مفاعلة 4- نيترو بنزايليدين أسيتيل اسيتون تم الحصول على مركب الايزوكسازوليدين أوكسيم بنسبة إنتاجية 38%.

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