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Synthesis of a Series of *α, β*-Unsaturated Ketoximes and their Corresponding Acetate Esters

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Abstract

A series of 1,3-diarylprop-2-en-1-one oximes (7-12) were synthesized *via* reaction of 1,3-diarylprop-2-en-1-one (1-6) with NH_2OH. HCl in dry pyridine. In order to produce the required products (13-18) as anti-isomers, these products (7–12) were then treated with acetic anhydride in dry pyridine. Different substitutes are maintained, resulting in the separation of different products in different yields The recently produced esters are thought to be useful as building blocks for the synthesis of substituted pyridines and many other nitrogen-holding complexes, which are elaborate structures in medicinal chemistry and present in a variety of pharmaceutical medications. The synthesized products were characterized and their structural details were clarified using ^{1}H NMR spectroscopy of a representative one sample ester and oxime, (FT-IR, UV) investigations, and melting point analysis. Besides the elemental micro analysis (C, H, N) of the same samples, the suggested mechanisms for these reactions were investigated according to these calculations.

Keywords: Chalcone oxime, *α, β*-Unsaturated oxime, Oxime acetate, 1, 3-Diaryl-2-propen-1-one oxime, Oxime *O*-ester.

تحضير سلسلة من اوكزيمات الجالكون *α, β*-غير المشبعة واسترات الاستيتات المشتقة منها

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الخلاصة

سلسلة من 1,3-ثنائي اريل-2-بروبين-1-اون (7-12) الناتجة من تفاعل 1,3-ثنائي اريل-2-بروبين-1-اون (1-6) مع هيدروكسيل امين هيدروكلوريد في البريدين الجاف. هذه المركبات (7-12) تمت معاملتها مع انهيدريد الخليك في البريدين الجاف لتعطي المركبات المطلوبة (13-18) على شكل ترانس. حيث تم التعامل مع معوضات مختلفة التي ادت الى تكوين مركبات مختلفة وبنواتج متنوعة. الاسترات المحضرة الجديدة يعتقد ان تكون مهمة كمواد اولية في تحضير مركبات البريدين المعوضة والكثير من المعقدات الحاوية على نتروجين والتي تعتبر من المركبات المهمة في الكيمياء الطبية وتدخل في تحضير المركبات الصيدلانية. تم تفسير المركبات المحضرة بالاعتماد على درجة الانصهار, الطرق الطيفية الاشعة فوق البنفسجية والاشعة تحت الحمراء (FT-IR, UV) وايضا طيف الرنين النووي المغناطيسي ^{1}H NMR

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لعينة من الاستر والاكزيم بالاضافة الى تحليل العناصر الدقيق (C, H, N) لنفس النماذج. وتم التحقق من الميكانيكيات المقترحة لهذه التفاعلات استنادا الى تلك الحسابات .

1. Introduction

Oxime derivatives have drawn a lot of attention because they are used in a variety of commercial applications, such as blocking agents in the polymer and medicinal chemistry industries [3, 2], anti-skinning agents in paint [1, 2], and agrochemicals [3]. In addition, numerous oxime-containing compounds had strong bioactivities and moderate toxicity. In medicine and the manufacture of cephalosporin derivatives with antibacterial activity, several oximes have been used as ligands [4]. Oximes are frequently used as strong H-bond donors in supramolecular chemistry, which makes them potential participants in hydrogen bonding interactions with the protein's amino acid building blocks [5].

Chalcone oximes have been used as tyrosinase inhibitors [6, 7], potent immunosuppressive agents [6, 7], and adopted agonists of retinoid receptors RAR. They have also been used to synthesize isoxazolines and isoxazoles, which are crucial heterocyclic compounds in organic and pharmaceutical chemistry [8, 9]. Recent research suggests that chalcone oxime can prevent corrosion in carbon steel [10]. In the quantitative detection of metal ions, they were also utilized as chelating agents [11–13].

Due to their easily accessible and quickly activatable N-O linkages, oxime esters have become one of the most important synthons in heterocyclic chemistry [14, 15]. They are often utilized in the production and derivatization of pyridines as well as many other N-containing heterocyclic compounds.

Herein, we describe a convenient process towards the synthesis of new 1,3-diaryl oxime esters from chalcone oximes. Various substituted of chalcones have been employed to analyze the effect of the electron donating or electron withdrawing groups on the nature and yield of the products of reactions obtained under these conditions. Moreover, no examples are available for synthesizing such compounds except models reported by Too, Wang and Chiba [16] or Rong *et al*. [17] for acetylation of chalcone oxime.

2. EXPERIMENTAL SECTION

2.1. Materials and methods

Unless otherwise stated, all chemicals were supplied from Fluka, Sigma and Aldrich Company, and used without further purification. Melting points were determined by Electrothermal 1A 9000 Digital – series 1998 apparatus (uncorrected). UV-Visible spectra were recorded using Shimadzu UV-Visible spectrophotometer 160. Infrared spectra (IR) were recorded on Bruker Tensor spectrophotometer 2003 (Germany). Nuclear magnetic resonance ^{1}H NMR spectral data were recorded using a 300 MHz Bruker spectrometer, (Germany) by using tetramethylsilane (TMS) as an internal standard, and d_6-DMSO as solvent. ^{1}H NMR chemical shifts data are described in (ppm). CHN was measured by using Euro Vactor Model EA 3000 A (Italy).

2.2. General procedure for the preparation of α, β-unsaturated ketones (1-6)

The acetophenone derivative (5 mmol) was added dropwise to the reaction mixture after the ethanolic NaOH solution (5%, 5 mL) was added to a stirred solution of benzaldehyde derivative (5 mmol) in 20 ml of ethanol at 0 ^{0}C. After 4 hours of stirring at room temperature, the reaction mixture was diluted with water. The obtained precipitate was filtered, washed

with water several times, and recrystallized from ethanol to give the pure chalcone in a quantitative yield as shown in Table 1 [18-20].

2.3. General procedure for the preparation of chalcone oximes (7– 12)

A solution of hydroxylamine hydrochloride (15 mmol) in dry pyridine (20 mL) was added to chalcone derivative (10 mmol). The reaction mixture was then heated to reflux for 24 hours. After cooling to the room temperature, water was added to the mixture, and the solid formed was filtered off, washed with water, dried and recrystallized from ethanol as shown in Table 1 [21, 22].

2.4. General procedure for the preparation of O-acetyl oxime derivatives (13-18)

A mixture of oxime derivative (1 mmol), pyridine (20 mL), and acetic anhydride (10 mL) was refluxed for 24 hours. After cooling to the room temperature. Water was added to the reaction mixture, and the solid materials were then filtered off, washed with water, dried and recrystallized from ethanol as described in Table 2 [23].

Table 1: Some physical properties of compounds (1-12)

Cpd. No.	R^1	R^2	Colour	Isolated yield (%)	m.p. (^{0}C)	Oxime No.	Colour	Isolated yield (%)	m.p. (^{0}C)
1	4-Cl	4-NO_2	Yellow	84.5%	153-155	7	Light yellow	50.4	165-167
2	4-CH_3	4-OCH_3	Pale yellow	80.9%	88-90	8	Off white	50.9	131-135
3	4-NO_2	4-CH_3	Yellow	79.3%	160-161	9	Pale yellow	42.7	150-152
4	4-OCH_3	2-Cl	Off white	81.7%	80-82	10	Off white	25.1	132-134
5	4-OCH_3	4-OCH_3	Yellow	83.0%	96-98	11	Pale yellow	28.3	118-120
6	4-Cl	4-CH_3	White	80.1%	150-152	12	Off white	31.5	127-129

Table 2: Some physical properties of oxime *O*-acetates (13-18)

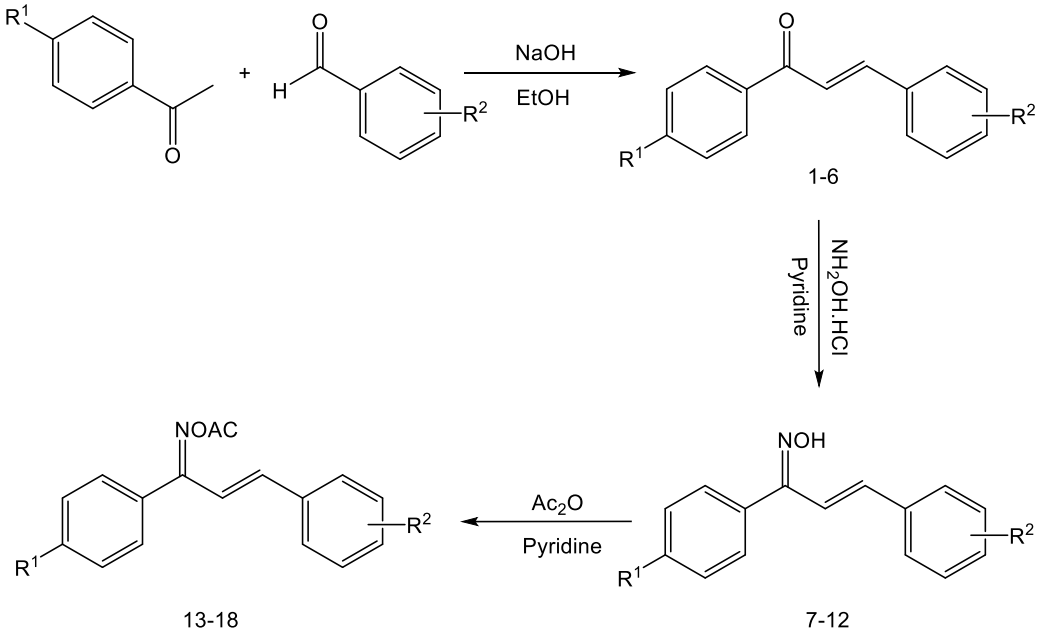
Cpd. No.	Oxime *O*-acetates	Colour	Isolated yield (%)	m.p. (^{0}C)
13	(2*E*)-1-(4-chlorophenyl)-3-(4-nitrophenyl) prop-2-en-1-one *O*-acetyl oxime	Light brown	23.3	124-126
14	(2*E*)-1-(4-methylphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one *O*-acetyl oxime	Pale yellow	68.5	121-123
15	(2*E*)-1-(4-nitrophenyl)-3-(4-methylphenyl) prop-2-en-1-one *O*-acetyl oxime	Light brown	50	114-116
16	(2*E*)-3-(4-methoxyphenyl)-1-(2-chlorophenyl) prop-2-en-1-one *O*-acetyl oxime	Off white	90.8	94-96
17	(2*E*)-1-(4-methoxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one *O*-acetyl oxime	Light brown	6.7	140-142
18	(2*E*)-1-(4-chlorophenyl)-3-(4-methylphenyl) prop-2-en-1-one *O*-acetyl oxime	Off white	36.4	166-168

3. Results and discussion

The synthesis of the parent α, β-unsaturated ketones 1-6 was outlined in Scheme 1. The chalcones were produced in yields ranging from 79% to 84% by the Claisen-Schmidt

condensation of aromatic aldehydes and acetophenone derivatives in the presence of sodium hydroxide in polar solvents like ethanol.

By treating the correspondingly synthesized chalcones 1-6 with hydroxylamine hydrochloride and pyridine as a base and catalyst, the desired chalcone oxime derivatives 7–12 were produced (Scheme 1).



R^1= 4-Cl, 4-CH_3, 4-NO_2, 4-OCH_3, R^2= 4-NO_2, 4-OCH_3, 4-CH_3, 2-Cl

Scheme 1: General synthetic route of oxime acetate derivatives (13-18)

The structures were confirmed by FT-IR, UV, and ^{1}H NMR spectra. The FT-IR spectra of the prepared oximes (7-12) (Table 3), showed broad bands at 3232-3452 cm^{-1} characteristic of the oxime hydroxyl group [24], a weak intensity bands at 1616-1658 cm^{-1} attributed to the inserted C=N group. In addition, the disappearance of the chalcone carbonyl group (Figure 1). The ^{1}H NMR spectrum of oxime 8 showed a singlet signal at 2.4 ppm is due to CH_3 group. A signal at 3.8 ppm is belong to the OCH_3 group. The signal of the OH group is appeared in 6.25-6.65 ppm. The *alpha* hydrogen of the carbonyl group is appeared at 6.9 ppm. While, the *beta* hydrogen of the carbonyl group is appeared at 7.35 ppm. Finally, the signals between 7.50-7.67 ppm are attributed to aromatic protons (Figure 2).

All compounds were generated from ethanol due to recrystallization, which suggests that this spectrum of oximes would show anti isomers in accordance with the reference data [7]. The elemental analysis of the oxime 8 Anal. Calcd. for $C_{17}H_{17}NO_2$: C 76.42, H 6.41, N 5.24, found: C 76.32, H 6.24, N 5.85.

However, the absence of peaks around 3.5–3.65 ppm [25] characteristic of oxazoline, indicates that the resulting *α*, *β*–unsaturated oxime did not suffer cyclisation under such conditions.

Table 3: Spectral data of chalcone oximes (7-12)

Cpd. No.	UV($CHCl_3$) λmax, nm, (ε $\times 10^{-3}$) $L.mole^{-1}.cm^{-1}$	IR(KBr) ν cm^{-1}							
		O-H	C-H	C=C	C=C arene	N=O	C-O	N-O	C-Cl
7	324 (2.737)	3255	2916	1593	1491	1344, 1512	….	955	750
8	338 (2.659)	3452	2833, 2918	1604	1514, 1576	….	1248	957	….
9	328 (2.817)	3255	2870, 2914	1601	1520	1334, 1527	….	955	….
10	324 (2.709)	3232	2898, 2968	1610	1518, 1560	….	1255	949	748
11	338 (2.786)	3249	2833, 2931	1606	1514, 1576	….	1250	949	….
12	316 (2.723)	3259	2908	1604	1495, 1566	….	….	939	793

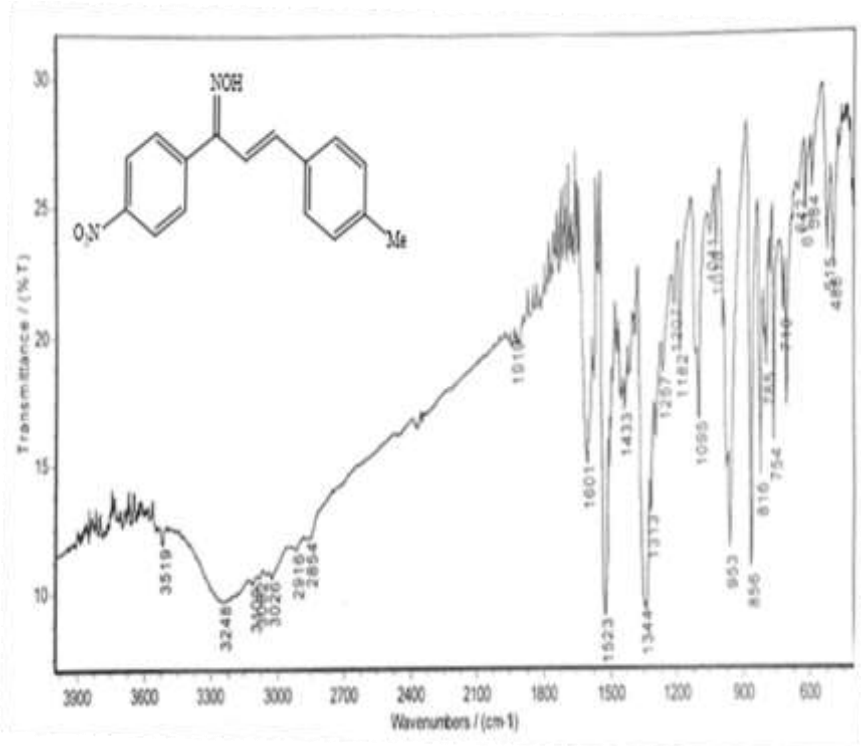


Figure 1: FT-IR spectrum of compound 9

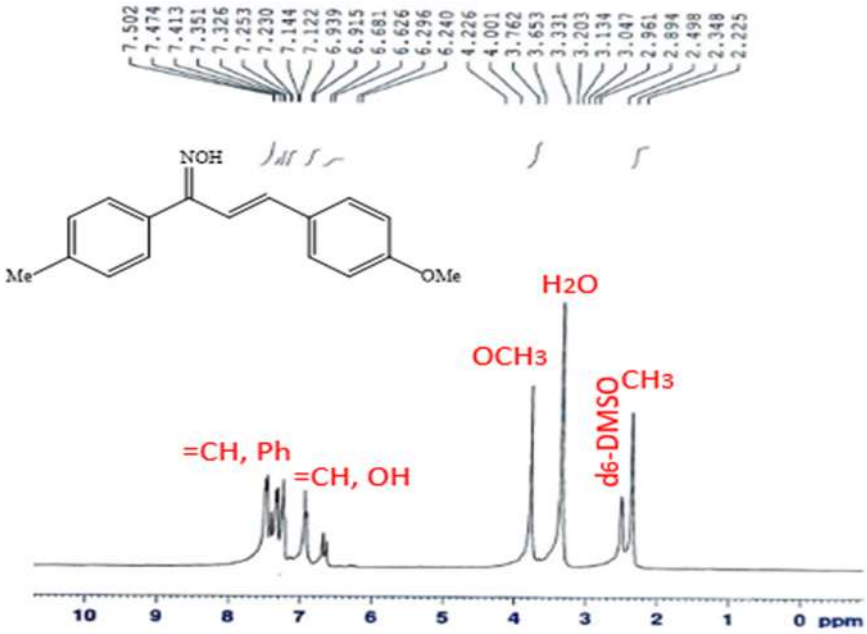


Figure 2: ^{1}H NMR spectrum of compound 8

By reacting the appropriate oximes 7–12 with acetic anhydride in pyridine, the acetate derivatives (13–18) were generated (Scheme 1). FT-IR spectroscopy verified the production of the acetate esters. Whereas the FT-IR spectra of the acetate esters (Table 4) demonstrated the absence of the oxime's OH band and the emergence of a new carbonyl band typical of an ester (Figure 3). The UV absorptions λ max around 300-340 nm are attributed to the forbidden n-π* absorption. The ^{1}H NMR spectrum of ester 14 showed a singlet signal at 2.25 ppm is due to $COCH_3$ group. A signal at 2.4 ppm is ascribed to CH_3 group. The signal of the OCH_3 group is appeared at 3.85 ppm. The *alpha* hydrogen of the carbonyl group is appeared at 6.98 ppm. While the *beta* hydrogen of the carbonyl group is appeared at 7.61 ppm. Finally, the aromatic proton signals are shown between 6.8-7.55 ppm in the spectrum (Figure 4). The spectrum revealed the absence of the hydroxyl peak and appearance of CH_3 peak corresponds to the acetate group. The elemental analysis of the ester 14 Anal. Calcd. For $C_{19}H_{19}NO_3$: C 73.77, H 6.19, N 4.53, found C 73.22, H 6.59, N 4.22.

Table 4: Spectral data of oxime *O*-acetates (13-18)

Cpd. No.	UV($CHCl_3$) λmax, nm, (ε × 10^{-3}) L.mole^{-1}.cm^{-1}	IR(KBr) ν cm^{-1}								
		C-H	C=O	C=N	C=C	C=C arene	N=O	C-O	N-O	C-Cl
13	340 (2.698)	2924	1770	1653	1599	1489	1346, 1516	….	930	750
14	334 (2.737)	2918, 2974	1766	1624	1599	1508, 1541	….	1261	928	….
15	334 (2.737)	2920, 2972	1782	….	1601	1518	1336	….	937	….
16	312 (2.647)	2937, 2981	1774	1637	1612	1514, 1549	….	1255	922	756
17	300 (2.613)	2939, 2962	1782	….	1614	1508	….	1252	949	….
18	310 (2.696)	2920	1680	1597	1566	1508	….	….	949	669

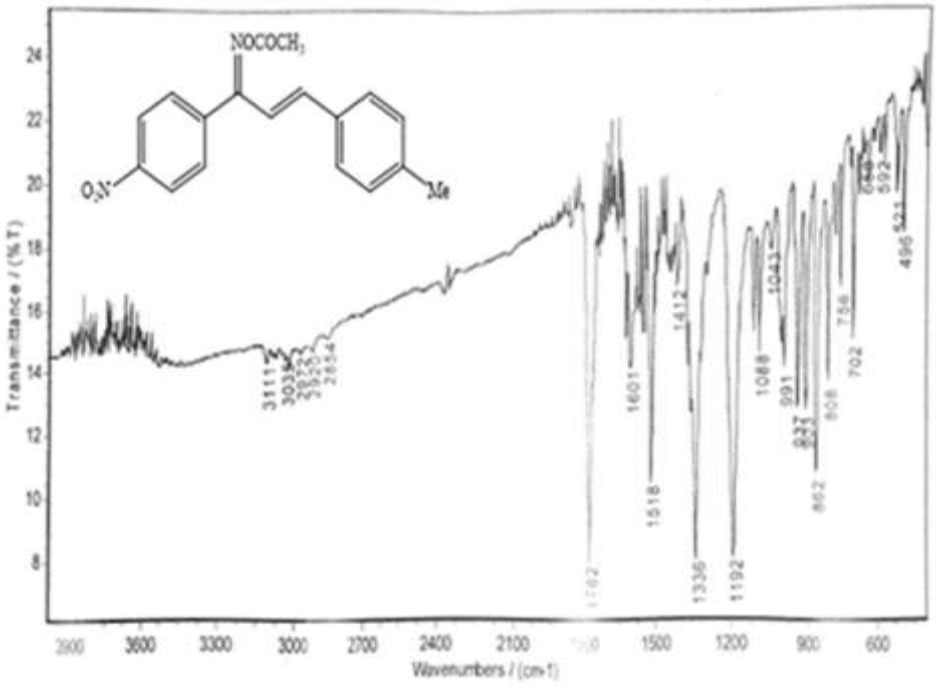


Figure 3: FT-IR spectrum of compound 15

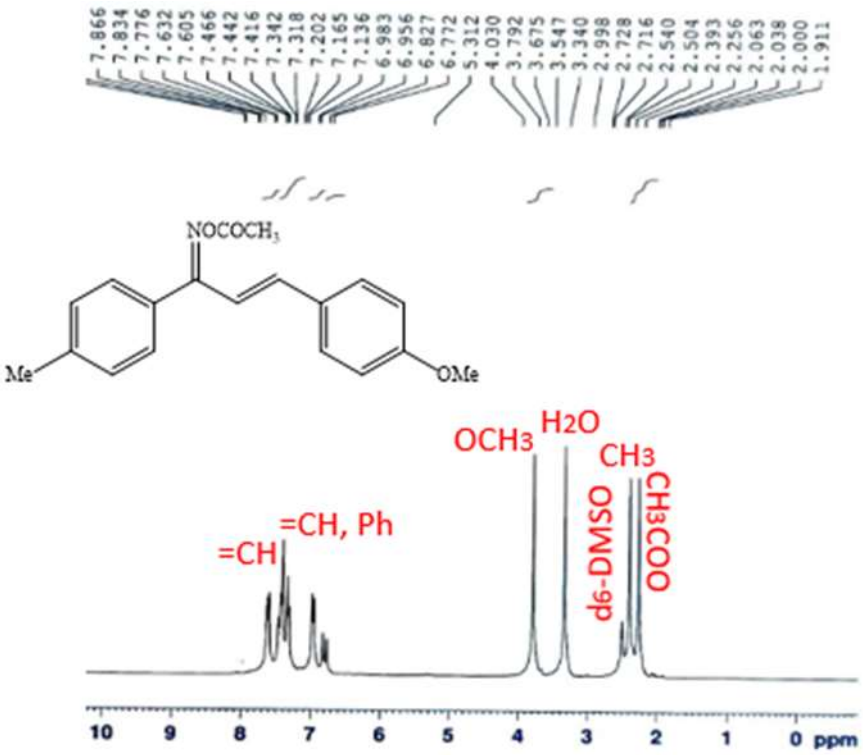
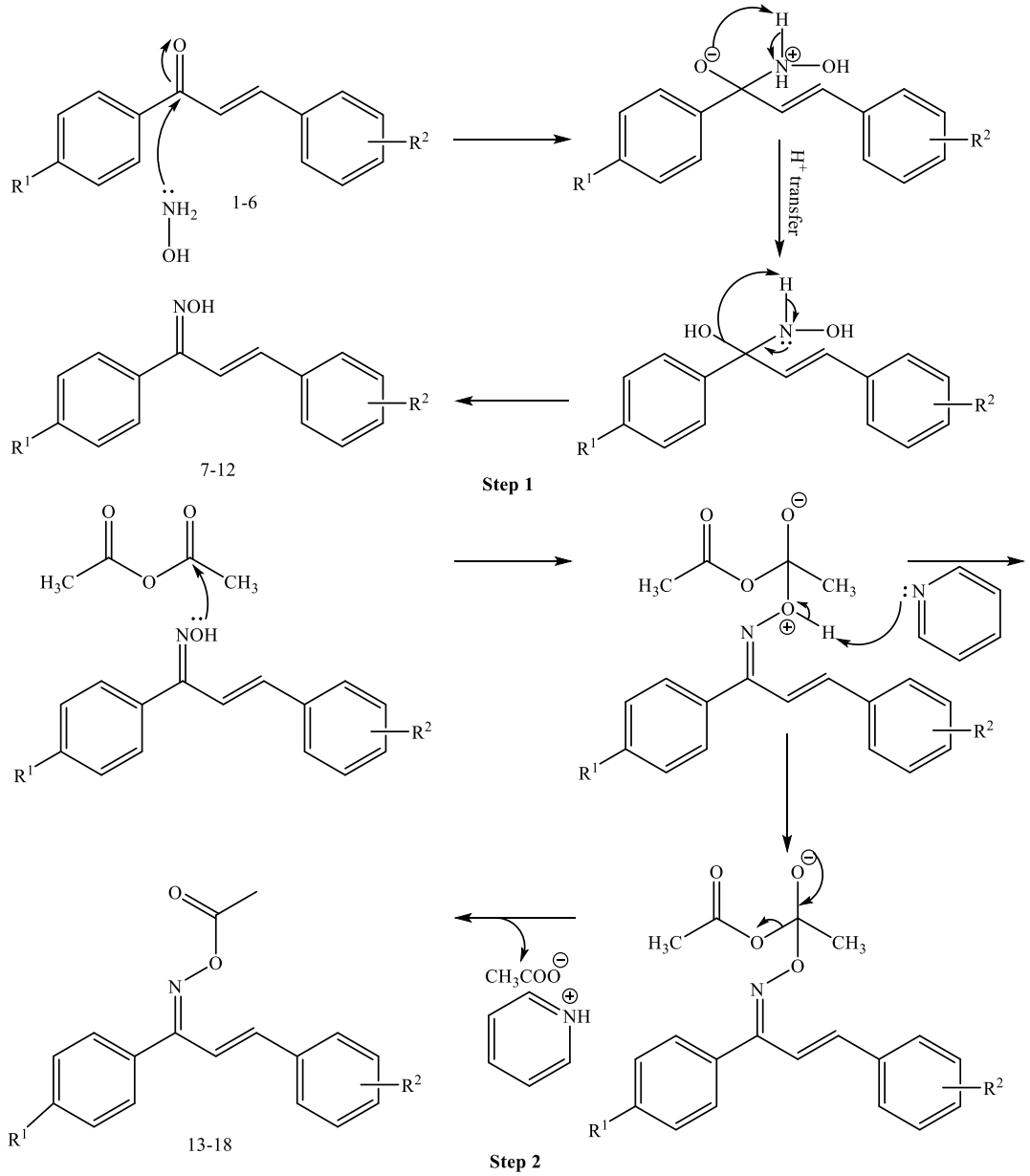


Figure 4: ^{1}H NMR spectrum of compound 14

4. Mechanism

A conceivable molecular pathway for the synthesis of *O*-acetyl oximes 13–18 is given based on our empirical results and other studies in the literature [7, 22, 26]. (Scheme 2). According to this mechanism, the reaction between chalcone and NH_2OH HCl results in the formation of an oxime. The hydroxyl group of acetic anhydrides then undergoes a nucleophilic attack to create the ester, which is followed by the removal of a carboxylate anion from the unstable intermediate.



Scheme 2: The proposed mechanism for the formation of oxime *O*-acetate. Step 1: synthesis of chalcone oxime; Step 2: synthesis of 1,3-diaryl oxime esters

5. Conclusion

This work describes an effective and practical technique for producing a number of novel *O*-acetyl oximes by reacting chalcone oximes with acetic anhydride while refluxing pyridine. The approach is effective for 1,3-diarylprop-2-en-1-one *O*-acetyl oximes using various substitutes. The formation is confirmed to be an anti-configuration by spectral analysis, according to our oxime ester synthesis.

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