Synthesis and Characterization of Novel Aromatic Substituted γ- and δ-Ketoxime Esters

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Abstract: By starting their corresponding keto esters **1a-j**, aryl-, substituted aryl- and heteroaryl-containing γ- and δ-oximes **2a-2j** (ten in total) were obtained. Proton nuclear magnetic resonance spectroscopy, carbon nuclear magnetic resonance spectroscopy, fourier transform infrared spectroscopy, mass spectrometry and elemental analyses were applied to the synthesized compounds for elucidating their structures and to find the (*E*)-isomers.

Keywords: Keto ester; γ-ketoxime ester; δ-ketoxime ester; hydroxylamine hydrochloride.

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INTRODUCTION

Oximes are very important building blocks in synthetic organic chemistry because they are capable of undergoing numerous transformations. Oximes are widely used to protect, purify and characterize aldehydes and ketones. In addition, oximes can successfully be converted into amides (1), nitriles (2,3), amines (4,5), hydroxyamines (6), hydroxyamine *O*-ethers (7), nitroalkanes (8), 1,3-oxazoles, thiazoles and diazoles (9), *etc.* The products, as starting compounds, are proven to be biologically active amino acids (10), alkoxyimino esters and alkoxyamino amides (11) and derivatives of pyrrole skeleton (12). Moreover, oxime groups could be transferred into water-soluble compounds. Through its oxime and oxime ether, limonin is rendered water soluble as being an anti-inflammatory and analgesic agent (13).

Recently, oxime esters and related compounds are shown to possess bioactivities, thus being attractive to researchers, especially working with agrochemicals and medicinal compounds. Fungicidal (14), insecticidal (15,16), antitumor (17,18), herbicidal (19,20), antineoplastic (21) and antiviral (22,23) activities were introduced for oxime esters. It has been about fifty years since the synthesis and biological activities of oxime esters were shown in a large number of researches. In a previous study, the synthesis of biologically active hydroxyimino-, methoxyimino- and benzyloxyiminotetradecanoic acid methyl esters were reported and their DNA-binding, antimicrobial and antifungal activities were investigated (24).

Being capable of coordinating to metal ions, oxime ligands have been interesting due to their variable geometries (25-28) and fine tuning of their substitutients (29,30). Oxime ligands are known to serve as analytical reagents (31,32) and also employed as models for Vitamin B_{12} and dioxygen carrier systems (33), as well as catalysts in chemical processes (34-37).

In this study, it was aimed to obtain pure γ- and δ- oxime esters numbered as **2a-2j** as compounds for reference purposes. In the previous paper, Imoto et al. reported the 4-hydroxyimino-4-phenyl-butyric acid methyl ester **2a** and 5-hydroxyimino-5-phenyl-pentanoic acid methyl ester **2f** and they used these compounds as intermadiates in the synthesis of oxyiminoalcanoic acids (38). Besides, **2a** was obtained as intermadiates compound for use in the Beckmann rearrengement (39). In the another study, **2e** was used as starting materials for synthesis of aliphatic amino acids (40). In this work, seven novel compounds containing aryl, substituted aryl and heteroaryl groups (**2b-2d, 2g-2j**) were synthesized. Their structures were elucidated with ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectrometry.

MATERIALS AND METHODS

Unless otherwise stated, all reagents were obtained from commercial suppliers. Hydroxylamine hydrochloride ($HONH_2.HCl$) was purchased from Sigma Aldrich. γ- and δ-keto esters as starting materials were synthesized by Friedel-Crafts acylation (41,42). The reactions of 2 were checked for completion on silica gel on aluminum plates. They were purified by flash column chromatography on silica gel (Merck; 230-400 mesh) and ethyl acetate and hexane (7:3, v:v) was used as eluent.

Proton nuclear magnetic resonance spectroscopy was obtained at 500 MHz and carbon nuclear magnetic resonance spectroscopy was recorded at 125 MHz. As an internal standard, tetramethylsilane in deuteriochloroform ($CDCl_3$) was employed. A Shimadzu QP2010 Plus was used as the GC/MS spectrometer. Fourier transform infrared spectra were recorded on a Mattson 1000 spectrometer. A Büchi melting point B-540 apparatus was used for melting point determinations. The chemical yields are expressed with the pure isolated substances.

General procedure : preparation of oxime esters (43,44)

As a general procedure, the keto ester (1.0 eq) 1a-j was dissolved in ethanol. Hydroxylamine hydrochloride (2.0 eq) was introduced into the reaction medium and the mixture was stirred overnight. Saturated ammonium chloride was used to dilute the mixture and it was extracted with ethyl acetate. Combined organic layers were washed with water and brine and dried over sodium sulfate. The solvent was evaporated and the crude product was subjected to column chromatography on silica gel and as eluent "(n-hexane:ethyl acetate 7:3)" to yield the oximes **2a-j**.

4-Hydroxyimino-4-phenyl-butyric acid methyl ester 2a

Yield: 90%; colorless oil. **Anal. calcd**. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76 Found: C, 63.50; H, 6.42; N, 6.66. **IR** (neat, cm^{-1}) *v* 3450 (OH stretching), 3030 (CH stretching of aromatic rings), 2953 (-CH_2- stretching), 1738 (C=O stretching of $COOCH_3$ group), 1680 (C=N stretching),1500, 1453 (C=C- stretching of aromatic rings), 1261(CH stretching in aliphatic plane), 1076 (C-O stretching), 769 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.28-7.27 (m, 3H), 3.55 (s, 3H, $COOCH_3$), 3.04 (t, *J* = 7.5 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 173.4 (C=O), 158.2 (C=N), 135.4 (C of aromatic ring), 129.6, 128.9, 126.5 (-

CH of aromatic ring), 52.0 ($COO\underline{C}H_3$), 30.6 ($\underline{C}H_2$), 22.3 ($\underline{C}H_2$). **MS** (m/z): 51, 77, 104, 117, 130, 158, 176, 206 (M^+ -1).

4-(4-Chloro-phenyl)-4-hydroxyimino-butyric acid methyl ester 2b

Yield: 88%; White crystal; mp:45-46°C. **Anal. Calcd**. for $C_{11}H_{12}ClNO_3$ C, 54.67; H, 5.00; Cl, 14.67; N, 5.80. Found: C, 54.73; H, 5.30; Cl, 14.55; N, 5,72. **IR** (neat, cm^{-1}) *v* 3447 (OH stretching), 3099 (CH stretching of aromatic rings), 2961 (-CH_2- stretching), 1734 (C=O stretching of $COOCH_3$ group), 1680 (C=N stretching),1503, 1456 (C=C- stretching of aromatic rings), 1263 (CH stretching in aliphatic plane), 1094 (C-O stretching), 939, 831 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 10.0 Hz, 2H), 7.24 (d, *J* = 10.0 Hz, 2H), 3.55 (s, 3H, $COOCH_3$), 3.04 (t, *J* = 7.5 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 172.9 (C=O), 157.3 (C=N), 135.6 (C of aromatic ring), 139.0, 129.7, 127.8 (-CH of aromatic ring), 51.9 ($COO\underline{C}H_3$), 30.8 ($\underline{C}H_2$), 22.1 ($\underline{C}H_2$). **MS** (m/z): 55, 75, 111, 138, 153, 164, 182, 206, 240(M^+ -1).

4-Hydroxyimino-4-(4-methoxy-phenyl)-butyric acid methyl ester 2c

Yield: 70%; colorless oil. **Anal. Calcd**. for $C_{12}H_{15}NO_4$ C, 60.75; H, 6.37; N, 5.90. Found: C, 60.90; H, 6.45; N, 5.80. **IR** (neat, cm^{-1}) *v* 3470 (OH stretching), 3022 (CH stretching of aromatic rings), 2953 (-CH_2- stretching), 1734 (C=O stretching of $COOCH_3$ group), 1685 (C=N stretching), 1526, 1456 (C=C- stretching of aromatic rings), 1263 (CH stretching in aliphatic plane), 1032 (C-O stretching), 939, 847 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 10.0 Hz, 2H), 6.83 (d, *J* = 10.0 Hz, 2H), 3.75 (s, 3H, Ar-OCH_3), 3.58 (s, 3H, $COOCH_3$), 3.02 (t, *J* = 7.5 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 173.3 (C=O), 160.9 (C=N), 157.7 (C of aromatic ring), 127.9, 127.6, 114.3 (-CH of aromatic ring), 55.5 (Ar-$O\underline{C}H_3$), 52.0 ($COO\underline{C}H_3$), 30.7 ($\underline{C}H_2$), 22.1 ($\underline{C}H_2$). **MS** (m/z): 55, 77, 91, 134, 149, 178, 207, 237(M^+).

4-Furan-2-yl-4-hydroxyimino-butyric acid methyl ester 2d

Yield: 60%; colorless oil. **Anal. Calcd**. for $C_9H_{11}NO_4$ C, 54.82; H, 5.62; N, 7.10. Found: C, 55.00; H, 5.40; N, 7.45. **IR** (neat, cm^{-1}) *v* 3462 (OH stretching), 3138 (CH stretching of aromatic rings), 2953 (-CH_2- stretching),1780 (C=O stretching of $COOCH_3$ group), 1680 (C=N stretching), 1510, 1456 (C=C- stretching of aromatic rings), 1248 (CH stretching in aliphatic plane), 1071 (C-O stretching), 824, 754 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.33 (m, 1H), 6.62 (d, *J* = 5.0 Hz, 1H), 6.36-6.35 (m, 1H), 3.61 (s, 3H, $COOCH_3$), 2.94 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 172.0 (C=O), 154.6 (C=N), 148.4 (C of aromatic ring), 141.5, 111.1, 109.6 (-CH of aromatic ring), 50.7 ($COO\underline{C}H_3$), 30.4 ($\underline{C}H_2$), 20.5 ($\underline{C}H_2$). **MS** (m/z): 55, 79, 93, 107, 120,138, 148,166,180,197 (M^+).

4-Hydroxyimino-4-thiophen-2-yl-butyric acid methyl ester 2e

Yield: 65%; White crystal; mp:59.5-60.5°C. **Anal. Calcd.** for $C_9H_{11}NO_3S$ C, 50.69; H, 5.20; N, 6.57; S, 15.04. Found: C, 50.96; H, 5.30; N, 6.15; S, 14.97. **IR (neat, cm^{-1})** *v* 3377 (OH stretching), 3115 (CH stretching of aromatic rings), 2953 (-CH_2- stretching), 1780 (C=O stretching of $COOCH_3$ group), 1675 (C=N stretching), 1549, 1456 (C=C- stretching of aromatic rings), 1186 (CH stretching in aliphatic plane), 1032 (C-O stretching), 855, 716 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47-7.46 (m, 2H), 6.93 (t, *J* = 5.0 Hz, 1H), 3.59 (s, 3H, $COOCH_3$), 3.02 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 172.1 (C=O), 152.7 (C=N), 137.8 (C of aromatic ring), 129.9, 126.3, 124.6 (-CH of aromatic ring), 50.8 ($COOCH_3$), 29.5 (CH_2), 21.6 (CH_2). **MS** (m/z): 55, 65, 84, 97, 110, 123, 136, 154,165, 196, 213(M^+).

5-Hydroxyimino-5-phenyl-pentanoic acid methyl ester 2f

Yield: 85%; White crystal; mp:55.5-56.5°C. **Anal. Calcd**. for $C_{12}H_{15}NO_3$ C, 65.14; H, 6.83; N, 6.33. Found: C, 65.10; H, 6.90; N, 6.20. **IR** (neat, cm^{-1}) *v* 3453 (OH stretching), 3023 (CH stretching of aromatic rings), 2946 (-CH_2- stretching), 1738 (C=O stretching of $COOCH_3$ group), 1682 (C=N stretching), 1500, 1453 (C=C- stretching of aromatic rings), 1246 (CH stretching in aliphatic plane), 1076 (C-O stretching), 769, 707 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.31-7.29 (m, 3H), 3.57 (s, 3H, $COOCH_3$), 2.79 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.84 (q, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 173.9 (C=O), 158.9 (C=N), 135.6 (C of aromatic ring), 129.5, 128.8, 126.5 (-CH of aromatic ring), 51.8 ($COOCH_3$), 33.8 (CH_2), 25.5 (CH_2), 21.8 (CH_2). **MS** (m/z): 51, 77, 104, 130, 144, 173, 204, 221(M^+ +1).

5-(4-Chlorophenyl)-5-hydroxyimino-pentanoic acid methyl ester 2g

Yield: 80%; White crystal; mp:51.5-52.5°C. **Anal. Calcd**. for $C_{12}H_{14}ClNO_3$ C, 56.37; H, 5.52; Cl, 13.87; N, 5.48. Found: **:** C, 56.20; H, 5.55; Cl, 13.80; N, 5,52. **IR** (neat, cm^{-1}) *v* 3454 (OH stretching), 3038 (CH stretching of aromatic rings), 2953 (-CH_2- stretching), 1734 (C=O stretching of $COOCH_3$ group), 1680 (C=N stretching), 1503, 1456 (C=C- stretching of aromatic rings), 1263 (CH stretching in aliphatic plane), 1094 (C-O stretching), 847, 762 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 5.0 Hz, 2H), 7.27 (d, *J* = 10.0 Hz, 2H), 3.59 (s, 3H, $COOCH_3$), 2.76 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.81 (q, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 173.9 (C=O), 158.1 (C=N), 135.5 (C of aromatic ring), 134.0, 129.0, 127.7 (-CH of aromatic ring), 51.8 ($COOCH_3$), 33.7 (CH_2), 25.4 (CH_2), 21.6 (CH_2). **MS** (m/z): 55, 75, 88, 102, 138, 164, 192, 224, 256(M^+).

5-Hydroxyimino-5-(4-methoxyphenyl)-pentanoic acid methyl ester 2h

Yield: 70%; White crystal; mp:102-103°C. **Anal. Calcd**. for $C_{13}H_{17}NO_4$ C, 62.14; H, 6.82; N, 5.57. Found: C, 62.04; H, 6.85; N, 5.50. **IR** (neat, cm^{-1}) *v* 3470 (OH stretching), 3015 (CH stretching of aromatic rings), 2961 (-CH_2- stretching), 1753 (C=O stretching of $COOCH_3$ group), 1685 (C=N stretching), 1526, 1456 (C=C- stretching of aromatic rings), 1256 (CH stretching in aliphatic plane), 1040 (C-O stretching), 847, 747 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 5.0 Hz, 2H), 6.82 (d, *J* = 10.0 Hz, 2H), 3.73 (s, 3H, Ar-OCH_3), 3.58 (s, 3H, $COOCH_3$), 2.77 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.83 (q, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 173.9 (C=O), 160.7 (C=N), 158.4 (C of aromatic ring), 128.0, 127.8, 114.2 (-CH of aromatic ring), 55.5 (Ar-OCH_3), 51.7 (COOCH_3), 33.8 (CH_2), 25.4 (CH_2), 21.8 (CH_2). **MS** (m/z) : 55, 77, 90, 103, 133, 160, 188, 205, 251(M^+).

5-Furan-2-yl-5-hydroxyimino-pentanoic acid methyl ester 2i

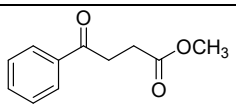
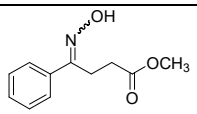
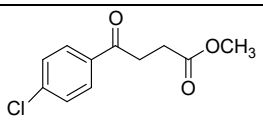
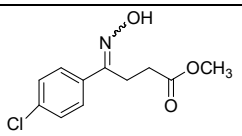
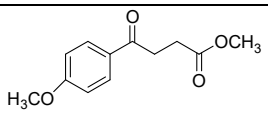
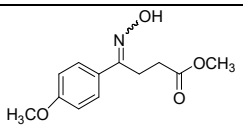
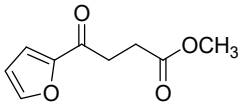
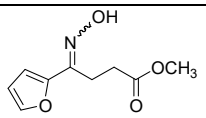
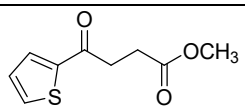
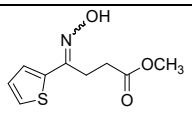
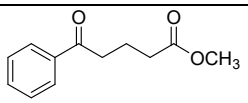
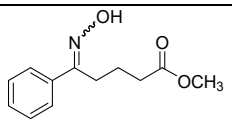
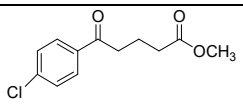
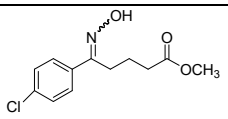
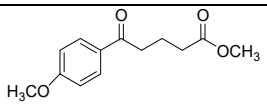
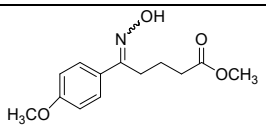
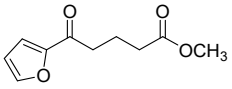
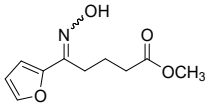
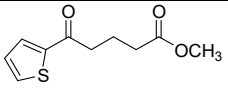
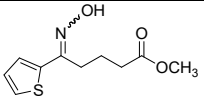
Yield: 65%; White crystal; mp:43.5-44.5°C. **Anal. Calcd**. for $C_{10}H_{13}NO_4$ C, 56.86; H, 6.20; N, 6.63. Found: C, 56.95; H, 6.10; N, 6.55. **IR** (neat, cm^{-1}) *v* 3462 (OH stretching), 3138 (CH stretching of aromatic rings), 2953 (-CH_2- stretching), 1742 (C=O stretching of $COOCH_3$ group), 1682 (C=N stretching), 1456, 1387 (C=C- stretching of aromatic rings), 1256 (CH stretching in aliphatic plane), 1078 (C-O stretching), 932, 754 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.37 (m, 1H), 6.60 (d, 1H), 6.36-6.35 (m, 1H), 3.60 (s, 3H, $COOCH_3$), 2.68 (t, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.91 (q, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 172.7 (C=O), 149.4 (C=N), 145.6 (C of aromatic ring), 142.6, 111.6, 109.2 (-CH of aromatic ring), 50.5 (COOCH_3), 32.4 (CH_2), 23.8 (CH_2), 20.8 (CH_2). **MS** (m/z) : 55, 85, 93, 107, 125, 138, 162, 160, 194, 205, 211(M^+).

5-Hydroxyimino-5-thiophen-2-yl-pentanoic acid methyl ester 2j

Yield: 65%; White crystal; mp:55-56°C. **Anal. Calcd**. for $C_{10}H_{13}NO_3S$ C, 52.85; H, 5.77; N, 6.16; S,14.11. Found: C, 52.95; H, 5.55; N, 6.20; S, 14.20. **IR** (neat, cm^{-1}) *v* 3462 (OH stretching), 3115 (CH stretching of aromatic rings), 2953 (-CH_2- stretching), 1742 (C=O stretching of $COOCH_3$ group), 1682 (C=N stretching), 1456, 1387 (C=C- stretching of aromatic rings), 1256 (CH stretching in aliphatic plane), 1078 (C-O stretching), 847, 716 (out-of-plane bending CH of aromatic ring). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50-7.47 (m, 2H), 7.03 (t, *J* = 5.0 Hz, 1H), 3.59 (s, 3H, $COOCH_3$), 2.72 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.97 (q, *J* = 7.5 Hz, 2H). **^{13}C NMR** (150MHz, $CDCl_3$) δ 172.1 (C=O), 152.7 (C=N), 137.8 (C of aromatic ring), 129.9, 126.3, 124.6 (-CH of aromatic ring), 50.8 (COOCH_3), 29.5 (CH_2), 21.6 (CH_2). **MS** (m/z) : 55, 84, 97, 110, 123, 136, 150, 178, 210, 227(M^+).

The isomeric ratios of the compounds are shown in Table 1.

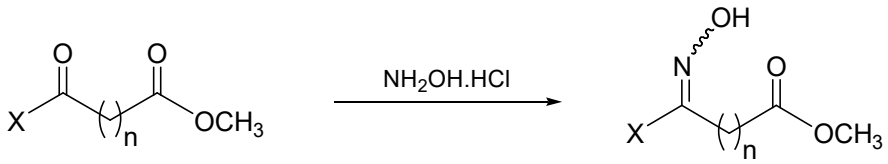
Table 1. Isomer ratios ((E)/(Z)) and yields of synthesized γ- and δ-ketoxime esters

Entry	Keto ester	Product	Yield[a]	(E)/(Z) Ratio[b]
1	 **1a**	 **2a**	90	*E*
2	 **1b**	 **2b**	88	*E*
3	 **1c**	 **2c**	70	*E*
4	 **1d**	 **2d**	60	*E*
5	 **1e**	 **2e**	65	*E*
6	 **1f**	 **2f**	85	*E*
7	 **1g**	 **2g**	80	*E*
8	 **1h**	 **2h**	70	*E*
9	 **1i**	 **2i**	65	*E*
10	 **1j**	 **2j**	65	*E*

[a] Isolated yield. [b] (E)/(Z) ratio was determined by ^{1}H NMR.

RESULTS AND DISCUSSION

We have obtained oxime esters **2a-2j** with high yields and the products were synthesized with the reaction between aryl, substituted aryl and heteroaryl γ- and δ-keto esters **1a-1j** and hydroxyamine hydrochloride (see Scheme 1).



2a-2j

1a (n=2, X=Ph) **1f** (n=3, X=Ph)
1b (n=2, X=*p*-Cl-C_6H_4) **1g** (n=3, X=*p*-Cl-C_6H_4)
1c (n=2, X= *p*-MeO-C_6H_4) **1h** (n=3, X= *p*-MeO-C_6H_4)
1d (n=2, X= 2-Furyl) **1i** (n=3, X= 2-Furyl)
1e (n=2, X= 2-Thienyl) **1j** (n=3, X= 2-Thienyl)

Scheme 1: Synthesis of γ- and δ-ketoxime esters

Hydroxyimino compounds are generally isolated as *E* isomer (45-47). In another work, hydroxyimino derivatives of keto esters were obtained also mainly as *E* isomer (24). According to these literatures (24, 45-48), the configuration of the synthesized compounds (**2a-2j**) in this work were determined by ^{1}H-NMR spectrum due to the splitting of the methoxy signal as studied in the previous study of our group (24). Two methoxy signals were seen for *E/Z* mixture. *E* signal resonated at lower field than *Z* signal (24, 48). ^{1}H-NMR spectras of the synthesized aryl-, substituted aryl- and heteroaryl containing γ- and δ-oxime esters **2a-2j** showed only one signal for methoxy peak as obtained in the previous study, therefore the configuration of these keto oxime esters were attributed to *E* structure. The position of phenyl grup let these keto oxime esters existing in *E* configuration because of the interaction between phenyl and hydroxy proton of the oxime groups and steric hinderance of the methylen protons.

As a conclusion, an extremely simple, suitable and efficient method was applied in this study for converting keto esters to their corresponding ketoxime esters of *E* configuration, which will be studied later for their biological activities.

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