

Synthesis of Arylfurfural Oximes and Their Biological Evaluation

SAMINA ASLAM^{1,2,*}, SAMIA KHAKWANI², AREESHA NAZEER³, MEHRZADI NOUREEN SHAHI¹, ASMA YAQOUB¹,
HAMNA SHAFIQ¹, RAFIA MANAZER¹, FAIZUL HASSAN NASIM¹ and MISBAHUL AIN KHAN¹

¹Department of Chemistry, The Islamia University of Bahawalpur, Bahawalpur, Pakistan

²Department of Chemistry, Women University Multan, Multan, Pakistan

³Institute of Chemistry, University of the Punjab, Quaid-e-Azam Campus, Lahore, Pakistan

*Corresponding author: E-mail: saminaaslam2009@gmail.com

Received: 18 September 2015;

Accepted: 14 January 2016;

Published online: 29 February 2016;

AJC-17776

Various oximes of arylfurfural were prepared and characterized through elemental analysis and spectroscopic techniques (FTIR, ¹H NMR, ¹³C NMR and Mass). Synthesized compounds were tested for their antioxidant, tyrosinase and chemotrypsin activities.

Keywords: Arylfurans, Oximes, Meerwein reaction, Antioxidant activity.

INTRODUCTION

Conversion of carbonyl functionalities into oximes is an important reaction in organic chemistry since oximes are highly crystalline compounds that find applications not only for protection of aldehyde function but also for the purification and characterization of carbonyl compounds [1,2]. Conversion into nitriles [3], nitro compounds [4,5], nitrones [6], amines [7] and synthesis of azaheterocycles [8] are some of the synthetic application of the oximes. They are also useful for selective α -activation [9] and are extensively used as intermediates for the preparation of amides by the Beckmann rearrangement [10,11]. In inorganic chemistry, oximes act as a versatile ligand [12]. These also have applications as fungicides and herbicides [13].

One such example is 1-phenyl-3-trifluoromethyl-5-phenoxy-pyrazole-4-carbaldehyde oxime (A) [12]. Another oxime (E)-tiglaloxime is found to be sweeter than sucrose [14]. There are some reports that some oxime esters of (A) or related structures show insecticidal activity and are good plant growth regulators [15], yet others have good antiviral activity [16]. Some flavanone oxime N,N-diethylaminoethyl ethers were found to have good antioxidant properties [17].

Our continuous interest in the chemistry of arylfurans [18-21] led us to the synthesis of 5-arylfuran-2-carbaldehydes oximes and their biological screening.

EXPERIMENTAL

All the reagents and solvents were used as obtained from the supplier. However when required these were purified by

recrystallization (for solids) or by redistillation (for liquids) as necessary. Thin layer chromatography was performed using aluminium sheets (Merck) coated with silica gel 60 F₂₅₄. IR spectra were recorded by using an IR Perkin-Elmer Spectrum 1 FTIR spectrophotometer and peaks are reported max (neat)/cm⁻¹ which refer to the min wave numbers. Proton magnetic resonance spectra were recorded in CDCl₃ with Bruker AM 300 spectrometers (Rheinstetten-Forchheim, Germany) operating at 300 MHz. ¹³C NMR spectra were recorded in CDCl₃ with Bruker AM 300 spectrometer operating at 75 MHz. Tetramethylsilane was used as an internal standard. Elemental analyses for C, H and N were recorded with Perkin-Elmer 2400 Series II CHN analyzer. Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

5-Arylfuran 2-carbaldehydes: These were prepared as described in an earlier publication [21].

General procedure for the preparation of oximes: Equimolar quantities (5 mmol) of 5-arylfuran-2-carbaldehyde and hydroxylamine hydrochloride were refluxed in ethanol for 30 min in the presence of 2, 3 drops of piperidine as a catalyst. On cooling precipitates were formed which were filtered, dried and recrystallized from ethanol.

5-(4'-Methyl benzoate)furan-2-carbaldehyde (1): Yield: 0.78 g (85 %) m.p.: 102-104 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1633.68 (C=N oxime), 2359.67 (aromatic ring), 1722 (C=O ester). ¹H NMR (CDCl₃, 300 MHz), δ ppm (J, Hz): 7.823-7.452 (4H, m, arom.), 7.283 (1H, d, J = 3.1, H-3), 6.940 (1H, d, J = 3.1, H-4), 2.524 (3H, s, CH₃). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 164.95 (C=O ester), 153.78, 151.90, 133.89, 131.45, 130.67, 130.13, 129.83, 127.65, 121.40, 118.79,

109.34 (Ar-C), 15.43 (CH₃); Anal. calcd. for C₁₃H₁₁NO₄: C 63.67; H 4.48; N 5.71 Found C 63.46; H 4.39; N 5.45 %.

5-(2'-Nitrophenyl)furan-2-carbaldehyde oxime (2): Yield: 0.8 g (75 %) m.p.: 194 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1639.02 (C=N oxime) 1532.80 and 1350.86 (Asym and sym-NO₂), ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 7.992-7.267 (4H, m, arom.), 7.096 (1H, d, *J* = 3.9, H-3), 6.910 (1H, d, *J* = 3.9, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 151.03, 150.28, 150.25, 147.17, 132.82, 130.27, 129.58, 124.25, 122.20, 119.50, 112.40 (Ar-C); Anal. calcd. for C₁₁H₈N₂O₄: C 56.89; H 3.44; N 12.06, Found C 56.75; H 3.40; N 11.86 %.

5-(3'-Nitrophenyl)furan-2-carbaldehyde oxime (3): Yield: 0.75 g (80 %) m.p.: 240 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1637.98 (C=N oxime) 1525.33 and 1351.43 (Asym and sym-NO₂), 2362.91 (aromatic ring). ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): : 8.560-7.518 (4H, m, arom.), 7.444 (1H, d, *J* = 3.1, H-3), 7.306 (1H, d, *J* = 3.1, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 154.56, 148.90, 147.34, 133.89, 131.45, 128.79, 127.90, 122.56, 121.34, 112.89, 110.98 (Ar-C); Anal. calcd. for C₁₁H₈N₂O₄: C 56.89; H 3.44; N 12.06, Found C 56.69; H 3.30; N 11.98 %.

5-(4'-Nitrophenyl)furan-2-carbaldehyde oxime (4): Yield: 0.8 g (85 %) m.p.: 152 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1636.99 (C=N oxime) 1536.54 and 1355.78 (Asym and sym-NO₂), 2363.65 (aromatic ring). ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 7.901-7.321 (4H, m, arom.), 7.650 (1H, d, *J* = 3.3, H-3), 6.890 (1H, d, *J* = 3.3, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 154.12, 150.91, 147.67, 129.53, 128.91, 125.17, 124.95, 124.52, 124.41, 111.20, 109.04 (Ar-C); Anal. calcd. for C₁₁H₈N₂O₄: C 56.89; H 3.44; N 12.06, Found C 56.74; H 3.29; N 11.84 %.

5-(2'-Chlorophenyl)furan-2-carbaldehyde oxime (5): Yield: 1 g (88 %) m.p.: 170 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 2363.07 (aromatic ring), 1612.88 (C=N oxime) 1088.40 (C-Cl), ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 7.938-7.353 (4H, m, arom.), 7.340 (1H, d, *J* = 2.9, H-3), 7.291 (1H, d, *J* = 2.9, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 152.22, 150.45, 148.86, 130.99, 130.85, 130.12, 129.78, 128.97, 127.86, 127.54, 119.60, 113.06 (Ar-C). Anal. calcd. for C₁₁H₈NO₂Cl: C 59.72; H 3.61; N 6.33, Found C 59.48; H 3.55; N 6.27 %.

5-(3'-Chlorophenyl)furan-2-carbaldehyde oxime (6): Yield: 0.8 g (75 %) m.p.: 96 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1559.37 (C=N oxime), 2360.51 (aromatic ring), 1091 (C-Cl). ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 7.745-7.231 (4H, m, arom.), 7.108 (1H, d, *J* = 2.1, H-3), 6.930 (1H, d, *J* = 2.1, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 155.67, 149.80, 134.56, 133.90, 131.20, 128.90, 127.89, 127.65, 122.34, 119.78, 110.67 (Ar-C). Anal. calcd. for C₁₁H₈NO₂Cl: C 59.72; H 3.61; N 6.33, Found C 59.64; H 3.48; N 6.15 %.

5-(4'-Chlorophenyl)furan-2-carbaldehyde oxime (7): Yield: 0.7 g (75 %) m.p.: 202 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1589.21 (C=N oxime), 2362.57 (aromatic ring), 1089.10 (C-Cl). ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 7.874-7.490 (4H, m, arom.), 7.410 (1H, d, *J* = 3.1, H-3), 6.843 (1H, d, *J* = 3.1, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 154.93, 150.17, 149.03, 133.16, 129.22, 128.09, 125.96, 120.08, 109.08 (Ar-C); Anal. calcd. for C₁₁H₈NO₂Cl: C 59.72; H 3.61; N 6.33, Found C 59.65; H 3.42; N 6.24 %.

5-(4'-Bromophenyl)furan-2-carbaldehyde oxime (8): Yield: 0.78 g (80 %) m.p.: 186 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1628.62 (C=N oxime), 2360.75 (aromatic ring), 1030.15 (C-Br). ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 7.890-7.425 (4H, m, arom.), 7.290 (1H, d, *J* = 2.1, H-3), 6.780 (1H, d, *J* = 2.1, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 154.97, 150.15, 149.06, 132.09, 128.40, 126.16, 121.82, 120.04, 109.54 (Ar-C); Anal. calcd. for C₁₁H₈NO₂Br: C 49.81; H 3.01; N 5.28, Found C 49.68; H 2.88; N 5.33 %.

5-(5'-Chloro-2'-nitrophenyl)furan-2-carbaldehyde oxime (9): Yield: 0.8 g (85 %) m.p.: 190 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1633.98 (C=N oxime), 1523.58 and 1345.71 (Asym and sym-NO₂), 2358.21 (aromatic ring), 1097.83 (C-Cl). ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 8.044-7.282 (3H, m, arom.), 7.234 (1H, d, *J* = 3.6, H-3), 7.222 (1H, d, *J* = 3.6, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 150.44, 150.37, 149.65, 145.53, 137.23, 129.88, 128.92, 126.10, 124.00, 119.44, 113.61 (Ar-C). Anal. calcd. for C₁₁H₇N₂O₄Cl: C 49.62; H 2.63; N 10.52, Found C 49.41; H 2.57; N 10.27 %.

5-(4'-Chloro-2'-nitrophenyl)furan-2-carbaldehyde oxime (10): Yield: 1.0 g (85 %) m.p.: 240 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 2363.16 (aromatic ring), 1633.29, (C=N oxime) 1108.62 (C-Cl), 1555.90 and 1342 (Asym and sym-NO₂), ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 8.121-7.336 (3H, m, arom.), 7.167 (1H, d, *J* = 3.1, H-3), 6.755 (1H, d, *J* = 3.1, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 153.42, 151.90, 148.79, 133.78, 132.67, 131.65, 130.56, 127.43, 126.30, 122.67, 119.70, 112.62 (Ar-C); Anal. calcd. for C₁₁H₇N₂O₄Cl: C 49.62; H 2.63; N 10.52, Found C 49.50; H 2.45; N 10.28 %.

5-(2'-Chloro-4'-nitrophenyl)furan-2-carbaldehyde oxime (11): Yield: 0.78 g (80 %) m.p.: 234 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1581.08 (C=N oxime), 2360.42 (aromatic ring), 1108.91 (C-Cl), 1506.66 and 1330.55 (Asym and sym-NO₂), ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 8.699-7.361 (3H, m, arom.), 7.349 (1H, d, *J* = 3.9, H-3), 7.175 (1H, d, *J* = 3.9, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 151.98, 150.12, 148.76, 133.90, 131.56, 130.63, 127.89, 122.54, 121.23, 119.87, 112.56 (Ar-C). Anal. calcd. for C₁₁H₇N₂O₄Cl: C 49.62; H 2.63; N 10.52, Found C 49.38; H 2.44; N 10.65 %.

5-(2',4'-Dinitrophenyl)furan-2-carbaldehyde oxime (12): Yield: 0.75 g (78 %) m.p.: 168 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1595.43 (C=N oxime), 2361.98 (aromatic ring), 1563.21 and 1350.56 (Asym and sym-NO₂), ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 7.945-7.455 (3H, m, arom.), 7.198 (1H, d, *J* = 3.1, H-3), 7.089 (1H, d, *J* = 3.1, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 155.10, 151.32, 148.90, 148.25, 133.78, 131.98, 130.79, 129.45, 127.34, 122.60, 121.62, 119.34, 110.61 (Ar-C). Anal. calcd. for C₁₁H₇N₃O₆: C 47.65; H 2.52; N 15.16, Found C 47.52; H 2.40; N 14.87 %.

5-(2',4'-Dichlorophenyl)furan-2-carbaldehyde oxime (13): Yield: 0.82 g (85 %) m.p.: 214 °C; FTIR (KBr, ν_{\max} , cm⁻¹): 1614.35 (C=N oxime), 1563.90 and 1354.67 (Asym and sym-NO₂), 2360.72 (aromatic ring). ¹H NMR (CDCl₃, 300 MHz), δ ppm (*J*, Hz): 8.699-7.361 (3H, m, arom.), 7.349 (1H, d, *J* = 3.1, H-3), 7.175 (1H, d, *J* = 3.1, H-4). ¹³C NMR (CDCl₃, 75 MHz) δ ppm: 151.92, 150.65, 133.43, 133.21, 131.87, 130.34, 129.56, 127.65, 123.60, 122.40, 121.72, 118.95, 110.43 (Ar-C). Anal. calcd. for C₁₁H₇NO₂Cl₂: C 51.76; H 2.74; N 5.49 Found C 51.63; H 2.58; N 5.24 %.

5-(2',5'-Dichlorophenyl)furan-2-carbaldehyde oxime (14): Yield: 0.76 g (80 %) m.p.: 252 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 1680.16 (C=N), 2359.30 (aromatic ring), 1041.23 cm^{-1} (C-Cl bond). ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 8.100-7.467 (3H, m, arom.), 7.108 (1H, d, $J = 2.9$, H-3), 6.923 (1H, d, $J = 2.9$, H-4). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 152.34, 151.39, 144.37, 133.87, 131.45, 130.89, 129.34, 127.49, 122.41, 121.65, 118.21, 109.82 (Ar-C). Anal. calcd. for $\text{C}_{11}\text{H}_7\text{NO}_2\text{Cl}_2$: C 51.76; H 2.74; N 5.49 Found C 51.48; H 2.55; N 5.29 %.

5-(3',4'-Dichlorophenyl)furan-2-carbaldehyde oxime (15): Yield: 0.80 g (85 %) m.p.: 182 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 2363.72 (aromatic ring), 1634.83 (C=N oxime) 1094.49 (C-Cl). ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 7.931-7.340 (3H, m, arom.), 7.182 (1H, d, $J = 3.1$, H-3), 7.021 (1H, d, $J = 3.1$, H-4). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 152.34, 151.39, 144.37, 133.87, 131.45, 130.89, 129.34, 127.49, 122.41, 121.65, 118.21, 109.82 (Ar-C). Anal. calcd. for $\text{C}_{11}\text{H}_7\text{NO}_2\text{Cl}_2$: C 51.76; H 2.74; N 5.49 Found C 51.68; H 2.54; N 5.20 %.

5-(2',3'-Dichlorophenyl)furan-2-carbaldehyde oxime (16): Yield: 0.75 g (82 %) m.p.: 210-212 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 2360.98 (aromatic ring), 1640.89 (C=N oxime), 1091.29 (C-Cl). ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 7.930-7.420 (3H, m, arom.), 7.378 (1H, d, $J = 2.9$, H-3), 6.993 (1H, d, $J = 2.9$, H-4). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 155.43, 151.89, 133.90, 132.73, 131.56, 130.90, 128.79, 127.65, 121.80, 119.60, 110.65 (Ar-C). Anal. calcd. for $\text{C}_{11}\text{H}_7\text{NO}_2\text{Cl}_2$: C 51.76; H 2.74; N 5.49 Found C 51.49; H 2.85; N 5.68 %.

5-(3',5'-Dichlorophenyl)furan-2-carbaldehyde oxime (17): Yield: 0.8 g (86 %) m.p.: 192 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 1558.70 (C=N oxime), 2361.94 (aromatic ring), 1091.25 (C-Cl). ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 8.023-7.531 (3H, m, arom.), 7.428 (1H, d, $J = 2.5$, H-3), 6.829 (1H, d, $J = 2.5$, H-4). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 153.65, 151.89, 133.72, 132.65, 131.34, 130.98, 130.12, 129.63, 127.33, 122.89, 118.93, 110.98 (Ar-C). Anal. calcd. for $\text{C}_{11}\text{H}_7\text{NO}_2\text{Cl}_2$: C 51.76; H 2.74; N 5.49 Found C 51.63; H 2.52; N 5.15 %.

5-(4'-Ethoxycarbonylphenyl)furan-2-carbaldehyde oxime (18): Yield: 0.76 g (83 %) m.p.: 114-116 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 2370.45 (aromatic ring), 1664.77 (C=N oxime), 1725.46 (C=O ester), ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 8.094-7.297 (4H, m, arom.), 7.285 (1H, d, $J = 3.3$, H-3), 7.117 (1H, d, $J = 3.3$, H-4), 2.524 (3H, t, $J = 4.5$, CH_3), 3.560 (2H, d, $J = 4.5$, CH_2). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 166.54 (C=O ester), 155.78, 151.75, 134.01, 133.45, 131.90, 130.98, 129.45, 127.56, 122.40, 121.67, 119.09, 110.11 (Ar-C), 64.32 (CH_2), 13.90 (CH_3); Anal. calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_4$: C 64.86; H 5.01; N 5.40 Found C 64.73; H 5.23; N 5.12 %.

5-(2'-Methyl-3'-nitrophenyl)furan-2-carbaldehyde oxime (19): Yield: 0.72 g (79 %) m.p.: 136 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 2363.63 (aromatic ring), 1640.75 (C=N oxime), 1518.40 and 1358.08 (Asym and sym $-\text{NO}_2$), ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 7.790-7.435 (3H, m, arom.), 7.109 (1H, d, $J = 2.3$, H-3), 6.845 (1H, d, $J = 2.3$, H-4), 2.539 (3H, s, CH_3). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 155.48, 151.23, 133.89, 132.13, 131.78, 127.90, 123.89, 122.45, 119.78, 109.65 (Ar-C), 13.90 (CH_3); Anal. calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_4$: C 58.53; H 4.06; N 11.38, Found C 58.44; H 3.76; N 11.09 %.

5-(2'-Methyl-5'-nitrophenyl)furan-2-carbaldehyde oxime (20): Yield: 0.75 g (80 %) m.p.: 178 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 2361.34 (aromatic ring), 1643.67 (C=N oxime), 1523.78 and 1360.65 (Asym and sym $-\text{NO}_2$), ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 8.7852-7.425 (3H, m, arom.), 7.235 (1H, d, $J = 2.3$, H-3), 6.980 (1H, d, $J = 2.3$, H-4), 2.428 (3H, s, CH_3). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 154.39, 151.23, 133.98, 132.65, 131.06, 130.98, 129.76, 127.54, 122.83, 118.96, 110.67 (Ar-C), 15.67 (CH_3); Anal. calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_4$: C 58.53; H 4.06; N 11.38, Found C 58.42; H 3.92; N 11.09 %.

3-(5'-Formylfuran-2-yl)benzoic acid oxime (21): Yield: 0.74 g (78 %) m.p.: Decompose < 200 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 1630.45 (C=N oxime), 1686.45 (C=O carboxylic acid), 2362.71 (aromatic ring). ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 10.783 (1H, s, -OH), 7.789-7.450 (4H, m, arom.), 7.327 (1H, d, $J = 2.9$, H-3), 6.980 (1H, d, $J = 2.9$, H-4). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 166.10 (C=O of COOH), 155.70, 151.34, 133.89, 132.90, 131.67, 130.67, 129.70, 127.43, 122.70, 118.97, 109.54 (Ar-C). Anal. calcd. for $\text{C}_{12}\text{H}_9\text{NO}_4$: C 62.33; H 3.89; N 6.06 Found C 62.19; H 3.72; N 6.25 %.

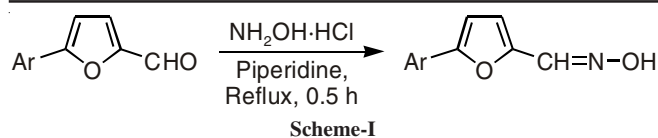
4-(5'-Formylfuran-2-yl)benzoic acid oxime (22): Yield: 0.72 g (75 %) m.p.: 120 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 2545.07 (aromatic ring), 1816.29 (C=O acid), 1568.03 (C=N oxime), 3250.83 (-OH acid). ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 10.980 (1H, s, -OH), 7.655-7.339 (4H, m, arom.), 7.290 (1H, d, $J = 3.1$, H-3), 6.845 (1H, d, $J = 3.1$, H-4). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 165.89 (C=O of COOH), 155.70, 151.34, 133.89, 132.90, 131.67, 130.67, 129.70, 127.43, 122.70, 118.97, 109.54 (Ar-C). Anal. calcd. for $\text{C}_{12}\text{H}_9\text{NO}_4$: C 62.33; H 3.89; N 6.06 Found C 62.22; H 3.75; N 5.83 %.

5-(2'-Methyl-4'-nitrophenyl)furan-2-carbaldehyde oxime (23): Yield: 0.75 g (81 %) m.p.: 184-86 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 2360.21 (aromatic ring), 1630.91 (C=N oxime), 1590.70 and 1365.71 (Asym and sym $-\text{NO}_2$), ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 7.765-7.378 (3H, m, arom.), 7.109 (1H, d, $J = 2.1$, H-3), 6.895 (1H, d, $J = 2.1$, H-4), 2.541 (3H, s, CH_3). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 155.45, 151.67, 133.98, 131.65, 130.90, 129.87, 127.83, 126.54, 123.67, 122.32, 118.93, 110.63 (Ar-C), 13.89 (CH_3); Anal. calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_4$: C 58.53; H 4.06; N 11.38, Found C 58.42; H 4.18; N 11.02 %.

5-(2'-Chloro-5'-nitrophenyl)furan-2-carbaldehyde oxime (24): Yield: 0.82 g (90 %) m.p.: 156 °C; FTIR (KBr, ν_{\max} , cm^{-1}): 2361.34 (aromatic ring), 1643.67 (C=N oxime), 1523.78 and 1360.65 (Asym and sym $-\text{NO}_2$), ^1H NMR (CDCl_3 , 300 MHz), δ ppm (J , Hz): 7.980-7.320 (3H, m, arom.), 7.201 (1H, d, $J = 3.3$, H-3), 6.852 (1H, d, $J = 3.3$, H-4). ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm: 155.80, 151.62, 133.90, 131.63, 130.98, 130.17, 129.65, 128.90, 127.65, 122.78, 121.87, 119.80, 109.97 (Ar-C), Anal. calcd. for $\text{C}_{11}\text{H}_7\text{N}_2\text{O}_4\text{Cl}$: C 49.62; H 2.63; N 10.52, Found C 49.29; H 3.76; N 11.29 %.

RESULTS AND DISCUSSION

5-Arylfuran-2-carbaldehyde oximes have been prepared in excellent yield by using a convenient one pot synthesis by the reaction of the aldehydes with hydroxylamine hydrochloride in the presence of piperidine as a catalyst (**Scheme-I**).



The prepared compounds were characterized, besides other analytical techniques, through their FTIR spectra when different compounds displayed absorption peaks in their respective regions as strong peak of a C=N moiety of oxime have been observed in the region of 1558.73 to 1643.67 cm^{-1} while NO_2 group showed symmetric and asymmetric peaks at 1532.80 and 1350.86 cm^{-1} , respectively. While in compound **17** and **18** peaks of C=O of ester group were observed in the region of 1710 and 1722 cm^{-1} , respectively. Compound **21** and **22** showed peaks in the region of 1686.45 and 1681.29 cm^{-1} for the carbonyl group of acid, these compounds also showed broad absorption band of -OH in the region of 3057.34 and 3250.83 cm^{-1} . Proton NMR and ^{13}C NMR results have been presented in the experimental section and these values are in accordance with their structure.

Antioxidant activity: Garret nitric oxide (NO) scavenging method was used for the determination of antioxidant activity [14]. The method is based on the principle that nitrate present in the sample must be reduced to nitrite. This method involves the determination of nitrite, instead of nitrate in the presence of Griss reagent. The results are presented in Table-1.

It is clear that most of the compounds show significant antioxidant activities. When the activities of the different 5-arylfuran-2-carbaldehydes oximes are compared, very

interesting results are obtained. The compound containing 4- NO_2 (**1**), 4-Cl substituent (**6**) at *para* position of the aryl group and **11** which has 2,4-dinitro substituent at aryl group show comparable IC_{50} value with standard ascorbic acid 50.43. While compound **4**, **8**, **9**, **13**, **16** and **22** show significant antioxidant activities in comparison with the standard.

It can be concluded that the 5-arylfuran-2-carbaldehydes oximes having the electron withdrawing group (- NO_2 , -Cl and -COOH) were the most active compounds.

Tyrosinase activity: Tyrosinase (EC 1.14.18.1) performs multiple functions in humans. It is glycosylated and copper containing oxidase which catalyzes the first two steps of melanogenesis in mammals. Tyrosinase overproduction causes hyperpigmentation, ocular retinitis pigmentosa; it also accelerates the induction of catecholamine quinone derivatives by its oxidase activity; over expression of tyrosinase results in increased intracellular dopamine contents in association with the formation of melanin pigments in neuronal stomata which causes apoptotic cell death.

Tyrosinase forms neuromelanin in human brain and causes dopamine neurotoxicity as well as contributes to neurodegeneration associated with Parkinson's disease. Tyrosinase also causes enzymatic browning reaction in damaged fruits during post-harvest handling and processing. Hyperpigmentation in human skin and enzymatic browning in fruits are not desirable. These phenomena have urged researchers to seek new potent tyrosinase inhibitors for use in food and cosmetics [15-18].

Enzyme assay: Total volume of reaction mixture contained 100 μL , 60 μL 100 mM phosphate buffer, pH 6.8, 10 μL

TABLE-1
BIOLOGICAL ACTIVITIES RESULTS OF 5-ARYLFURAN-2-CARBALDEHYDE OXIMES

Compound No.	Antityrosinase activity*		Chymotripson activity**		Antioxidant activity***		
	Percentage inhibition (0.5 mM)	IC_{50} (μM)	Percentage inhibition (0.5 mM)	IC_{50} (μM)	Percentage inhibition (0.5 mM)	Percentage inhibition (0.1 mM)	IC_{50} (μM)
1	26.27 \pm 0.35	–	38.13 \pm 0.12	–	–	–	–
2	-10.59 \pm 0.71	–	15.30 \pm 0.11	–	42.4 \pm 0.8	84.94 \pm 0.52	58.91
3	60.39 \pm 0.25	< 300	33.73 \pm 0.11	–	4.7 \pm 0.25	-37.9 \pm 0.7	NA
4	29.80 \pm 0.11	–	17.24 \pm 0.04	–	9.6 \pm 0.8	27.70 \pm 0.98	NA
5	30.59 \pm 0.25	–	17.42 \pm 0.01	–	21.9 \pm 0.7	51.85 \pm 0.59	96.9
6	90.69 \pm 0.14	52.00 \pm 0.12	30.36 \pm 0.11	–	–	–	–
7	-10.20 \pm 0.25	–	50.67 \pm 0.10	–	45.2 \pm 0.4	88.54 \pm 0.89	55.5
8	26.08 \pm 0.54	–	18.25 \pm 0.09	–	–	–	–
9	1.57 \pm 0.71	–	43.18 \pm 0.11	–	26.4 \pm 0.42	59.4 \pm 0.72	85.7
10	85.52 \pm 0.41	62.2 \pm 0.91	30.92 \pm 0.05	–	24.1 \pm 0.2	52.83 \pm 0.82	95
11	15.88 \pm 0.15	–	12.45 \pm 0.12	–	11.2 \pm 0.2	24.9 \pm 0.26	NA
12	7.45 \pm 0.11	–	15.23 \pm 0.11	–	45.6 \pm 0.41	72.9 \pm 0.18	58
13	49.80 \pm 0.31	–	12.26 \pm 0.13	–	–	–	–
14	21.18 \pm 0.31	–	42.36 \pm 0.07	–	32.1 \pm 0.94	58.35 \pm 0.13	84.01
15	5.88 \pm 0.88	–	34.54 \pm 0.11	–	–	–	–
16	0.39 \pm 0.35	–	43.18 \pm 0.08	–	–	–	–
17	35.88 \pm 0.26	–	45.60 \pm 0.12	–	25.3 \pm 0.35	51.08 \pm 0.9	97.9
18	15.49 \pm 0.33	–	13.45 \pm 0.04	–	4.3 \pm 0.23	-45.82 \pm 0.4	NA
19	14.90 \pm 0.82	–	18.08 \pm 0.10	–	20.2 \pm 0.76	41.1 \pm 0.47	NA
20	10.20 \pm 0.35	–	12.30 \pm 0.06	–	–	–	–
21	10.98 \pm 0.64	–	11.42 \pm 0.08	–	12.3 \pm 0.39	36.9 \pm 0.69	NA
22	–	–	–	–	25.8 \pm 0.30	54.95 \pm 0.56	91.25
23	11.18 \pm 0.64	–	22.28 \pm 0.04	–	-125 \pm 0.23	-44.42 \pm 0.72	NA
24	18.04 \pm 0.82	–	36.49 \pm 0.04	–	–	–	–
Standard	93.50 \pm 0.21	6.04 \pm 0.11	93.50 \pm 0.91	8.24 \pm 0.11	38.5 \pm 0.16	84.1 \pm 0.12	50.43

Standard *Kojic acid, Standard **Chemostatin, Standard ***Ascorbic acid

mushroom tyrosinase enzyme (5 units) and 10 μL 0.5 mM test compound mixed in 96-well plate [19]. Contents were preincubated for 5 min at 37 °C. After incubation, 20 μL of 10 mM L-dopamine was added as a substrate. Contents were mixed and incubated for further 0.5 h. Absorbance was taken at 490 nm using Synergy HT BioTek 96-well plate reader. The enzyme inhibition (%) was calculated by the bellow formula:

$$\text{Inhibition (\%)} = \left(100 - \frac{\text{Absorbance of test sample}}{\text{Absorbance of control}} \right) \times 100$$

IC₅₀ values (concentration at which there is 50 % in enzyme catalyzed reaction) compounds were calculated using EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA).

When tyrosinase activity of 5-arylfuran-2-carbaldehyde oximes were compared, most of the compounds showed less significant results (Table-1) while compounds **5** and **9** having (3-Cl and 4-Cl-2-NO₂, respectively) showed significant activity. So, it can be concluded from these results that 5-arylfuran-2-carbaldehydes oximes having electron withdrawing group (-NO₂ and -Cl) were the active compounds.

Chymotrypsin assay: The α -chymotrypsin inhibition activity is performed according to slightly modified method of Athar *et al.* [20]. A total volume of 100 μL assay mixture contained 60 μL Tris-HCl buffer (50 mM pH 7.7), 10 μL test compound and 20 μL (1.8 units) purified α -chymotrypsin enzyme (Sigma, USA). The contents were mixed and incubated for 20 min at 37 °C and pre-read at 410 nm. The reaction was initiated by the addition of 10 μL (1.3 mM) substrate (N-succinyl phenyl-alanine-*p*-nitroanilide). The change in absorbance was observed after 0.5 h at 410 nm. Synergy HT (BioTek, USA) 96-well plate reader was used in all experiments. All reactions were performed in triplicates. The positive and negative controls were included in the assay. Chymostatin (0.5 mM well⁻¹) was used as a positive control. The percentage inhibition was calculated by formula given below.

$$\text{Inhibition (\%)} = \left(100 - \frac{\text{Absorbance of test sample}}{\text{Absorbance of control}} \right) \times 100$$

IC₅₀ values of compounds were calculated using EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA).

5-Arylfuran-2-carbaldehyde oximes were tested for their chymotrypsin activity, but all synthesized compound showed less activity than the standard chemostatin (Table-1), so it can be concluded that these compounds were inactive against chymotrypsin activity.

Conclusion

A good and efficient method of 5-arylfuran-2-carbaldehydes oximes from the reaction of 5-arylfuran-2-carbaldehyde is presented. Although some of these oximes show reasonable antioxidant and tyrosinase activity however none of the oximes were active against chymotrypsin activity. These 5-arylfuran-2-carbaldehydes oximes can serve as starting materials for the synthesis of a variety of heterocyclic compounds.

ACKNOWLEDGEMENTS

The authors (SA and AN) would like to acknowledge the financial support by HEC Pakistan in the form of an indigenous PhD scholarships and IRSIP Fellowships. One of the authors, (MAK) thanks HEC for the Instrumental analysis support.

REFERENCES

1. S.R. Sandier and W. Karo, Organic Functional Group Preparations, Academic Press: San Diego, edn 2, pp 431-476 (1989).
2. T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, Wiley: Toronto, edn 3, pp 355-358 (1999).
3. S.K. Dewan, R. Singh and A. Kumar, *ARKIVOC*, 41 (2006).
4. P.R. Dave, F. Foroohar, T. Axenrod, K.K. Das, L. Qi, C. Watnick and H. Yazdekhashti, *J. Org. Chem.*, **61**, 8897 (1996).
5. F.P. Ballistreni, E. Barbuzzi, G.A. Tomaselli and R.M. Toscano, *Synlett.*, **11**, 1093 (1996).
6. P.A.S. Smith and S.E. Gloyer, *J. Org. Chem.*, **40**, 2508 (1975).
7. S. Negi, M. Matsukura, M. Mizuno, K. Miyake and N. Minami, *Synthesis*, 991 (1996).
8. K. Narasaka, *Pure Appl. Chem.*, **75**, 19 (2003).
9. J.K. Whitesell and M.A. Whitesell, *Synthesis*, 517 (1983).
10. C. Ramalingan and Y.-T. Park, *J. Org. Chem.*, **72**, 4536 (2007).
11. Y. Furuya, K. Ishihara and H. Yamamoto, *J. Am. Chem. Soc.*, **127**, 11240 (2005).
12. H. Hamaguchi, O. Kajihara and M. Katoh, *J. Pestic. Sci.*, **20**, 173 (1995).
13. B.A. Song, X.H. Liu, S. Yang, D.Y. Hu, L.H. Jin and Y.T. Zhang, *Chin. J. Org. Chem.*, **25**, 507 (2005).
14. T.J. Venanzi and C.A. Venanzi, *J. Comput. Chem.*, **9**, 67 (1998).
15. H. Dai, H.-B. Yu, J.-B. Liu, Y.-Q. Li, X. Qin, X. Zhang, Z.-F. Qin, T.-T. Wang and J.-X. Fang, *ARKIVOC*, 126 (2009).
16. G. Ouyang, Z. Chen, X.-J. Cai, B.-A. Song, P.S. Bhadury, S. Yang, L.-H. Jin, W. Xue, D.E.-Y. Hu and S. Zeng, *Bioorg. Med. Chem.*, **16**, 9699 (2008).
17. D. Metodiowa, A. Kochman and S. Karolczak, *Biochem. Mol. Biol. Int.*, **41**, 1067 (1997).
18. M.A. Khan and J.B. Polya, *Aust. J. Chem.*, **26**, 1147 (1973).
19. M.A. Khan and S.M.L. Uberti, *Rev. Latinoamer. Quim.*, **14**, 79 (1983).
20. M. Athar, M.A. Khan and S.M.L. Uberti, *J. Pure Appl. Sci.*, **22**, 129 (2003).
21. S. Aslam, N. Asif, M.N. Khan, M.A. Khan, M.A. Munawar and M. Nasrullah, *Asian J. Chem.*, **25**, 7738 (2013).