Synthetic Study of Ethyl (2*E*)-4-bromo-3-ethoxybut-2-enoate: Synthesis of New 1,4-Benzoxazines and Pyrrole-2-ones

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Abstract

Ethyl (2*E*)-4-bromo-3-ethoxybut-2-enoate **(2)** and ethyl (2*E*)-3-ethoxy-4-(2- and 4-nitrophenoxy)but-2-enoates **(4 and 5)** have been synthesized and used as synthones for the preparation of some new ethyl (2*Z*)-2*H*-1,4-benzoxazin-3(4*H*)-ylideneacetate **(6)**, 1-(substituted phenyl)-4-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones **(9)** and 4-ethoxy-1-(4-bromophenyl)-1,5-dihydro-2*H*-pyrrole-2-ones **(11)**. The structures of all synthesized compounds were confirmed by elemental analyses, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy and mass spectrometry.

Keywords: Ethyl (2*E*)-4-bromo-3-ethoxybut-2-enoate; 1,4-Benzoxazins; Pyrrol-2-ones; Mass spectrometry.

Introduction

The biological importance of 1,4-benzoxazins and pyrrol-2-one stimulated an intensive research work for the synthesis of many members of this class of compounds.[1,2] The pyrrolidine-2,4-dione ring system (tetramic acid) is present in various naturally occurring compounds exhibiting a wide range of biological and pharmaceutical activities.[3] In addition, tetramic acid derivatives are the key structural core found in a variety of natural products as a potent antiviral, antibiotic antifungal, and antitumor agents.[4-6] This acid could also be a novel structural framework of a potential inhibitor to photosynthesis.[7] On the other hand, the 1,4-benzoxazine scaffolds have been studied intensively as important heterocyclic systems for building natural and designed biologically active compounds, ranging from herbicides and fungicides to therapeutically usable drugs.[8]

As part of our ongoing research in the synthesis of new compounds of pharmacological and biological interest,[9-12] and as part of our research that is related to the chemistry of ethyl (2*E*)-4-bromo-3-ethoxybut-2-enoate **(2),**[13] we describe, herein, the synthesis and characterization of some new 1,4-benzoxazins **(6)** and pyrrol-2-ones **(11)**.

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Experimental

Reagents and instrumentation

Commercial reagents and solvents were used as received. Melting points were measured with an SMP2 Stuart melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR were recorded with the aid of Bruker-DPX 300 MHz spectrometers and are reported in ppm (δ) relative to TMS as an internal standard and with $CDCl_3$ or DMSO-d_6 as solvents. Infrared (IR) spectra were record as KBr discs on a Nicolet- MAGNA-IR-560 instrument. High resolution mass spectral data were acquired with a Brucker APEX (IV) mass spectrometer (Bremen, Germany). Elemental analyses were obtained using a Eurovector Euro EA3000, CHNS-O elemental analyzer. TLC was carried out using glass plates pre-coated with silica gel (E. Merck Kiesegel 60 F_{254} layer thickness 0.25 mm).

Ethyl (2E)-3-ethoxybut-2-enoate **(1)**

The title compound was synthesized according to published procedures[20] by reacting ethyl acetoacetate (13.0 g, 0.1 mol) with redistilled triethyl orthoformate (14.8 g, 0.1 mol) in absolute methanol (10 mL). Concentrated hydrochloric acid (0.05 mL) was added, and the mixture was immediately distilled to give ethyl (2*E*)-3-ethoxybut-2-enoate **(1)**, b.p 190-194 C° (14.2 g, 91% yield), [lit., 190-192 C° [14]].

Ethyl (2E)-4-bromo-3-ethoxybut-2-enoate **(2)**

This compound was synthesized according to the procedure outlined by Pelter and coworkers[13] which involved heating compound **1** (0.5 mol), with vigorous stirring, at 110-115 °C while N-bromosuccinimide (0.5 mol) was added in small portions. When addition was complete, the mixture was cooled to 70-80 °C and while vigorously stirring, water (125 mL) was added. The aqueous layer was separated and the organic layer was washed with water (3 x 35 mL), dried ($MgSO_4$), filtered, and distilled at once to give (91 g, 93%) b.p. 139-143 ^{o}C/29 mmHg [lit., 137-142 ^{o}C/28 mmHg[13]]. IR: 1709, 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.12 (s, 1H), 4.50 (s, 2H), 4.07 (q, *J* = 7.03 Hz, 2H), 3.87 (q, *J* = 7.03 Hz, 2H), 1.28 (t, *J* = 7.03 Hz, 3H), 1.20 (t, *J* = 7.03 Hz, 3H) ; ^{13}C NMR δ 168.32, 166.21, 93.55, 64.92, 59.79, 26.42, 14.85, 14.19.

Ethyl (2E)-3-ethoxy-4-(4-nitrophenoxy)but-2-enoate **(4)**

This compound was also prepared according to published procedures[14] where *p*-nitrophenol **(3b)** (1.38 g, 0.01 mol) in acetone (50 mL) was stirred at room temperature for 30 min. To this mixture, solid potassium carbonate (0.87 g, 6.30 mmol) was added and the mixture was stirred at room temperature for 15 min followed by the addition of ethyl (2*E*)-4-bromo-3-ethoxybut-2-enoate **(2)** (2.37 g, 0.01 mol) in of dry acetone (10 mL). The mixture was then refluxed for 24 h and the solid was filtered off. The solvent was either evaporated and the solid crude was recrystallized from ethanol, or was concentrated, extracted with dichlormethane/H_2O, then the filtrate was dried ($MgSO_4$) and the solvent evaporated on a rotary evaporator to afford the desired product **(4).** Yield 1.37 g (46.5 %), mp = 63-66 ^{o}C. IR (KBr): 1703, 1630 cm^{-1}. ^{1}H NMR

(DMSO): δ 8.16 (d, *J* = 9.20 Hz, 2H), 7.11 (d, *J* = 9.23 Hz, 2H); 5.25 (s, 1H), 5.21 (s, 2H), 4.03 (q, *J* = 7.09 Hz, 2H), 3.87 (q, *J* = 6.43 Hz, 2H), 1.17 (t, *J* = 6.43 Hz, 3H), 1.13 (t, *J* = 7.09 Hz, 3H); ^{13}C NMR: δ 167.32, 166.68, 164.05, 141.60, 126.30, 115.45, 94.67, 65.75, 65.11, 56.96, 14.58, 14.24. HRMS *m/z*: calcd for $C_{14}H_{17}NO_6Na$ $[M + Na]^+$ 318.0967, found 318.0960; calcd for $C_{14}H_{18}NO_6$ $[M + H]^+$ 296.1129, found 296.1148.

Ethyl (2E)-3-ethoxy-4-(2-nitrophenoxy)but-2-enoate **(5)**

Following the same procedure employed for the synthesis of **4**, compound **5** was synthesized: Yield 2.92 g (99 %), mp = 62-64 ^{o}C. IR (KBr): 1710, 1646 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.77 (d, *J* = 8.39 Hz, 1H), 7.46 (t, *J* = 8.39 Hz, 1H), 7.15 (d, *J* = 8.48 Hz, 1H), 6.99 (t, *J* = 8.39 Hz, 1H), 5.33 (s, 1H), 5.13 (s, 2H), 4.12 (q, *J* = 7.87 Hz, 2H), 3.82 (q, *J* = 6.89 Hz, 2H), 1.27 (t, *J* = 7.82 Hz, 3H), 1.23 (t, *J* = 7.87 Hz, 3H); ^{13}C NMR (DMSO): δ 167.96, 167.09, 151.98, 141.00, 125.48, 120.88, 133.94, 115.50, 93.92, 66.20, 64.75, 59.98, 14.31, 13.87. HRMS *m/z*: calcd for $C_{14}H_{17}NO_6Na$ $[M + Na]^+$ 318.0967, found 318.0984. Anal. Calcd for $C_{14}H_{17}N\ O_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 57.01; H, 5.84; N, 4.64.

Representative Procedure for Tandem Reduction: Ethyl (2Z)-2H-1,4-benzoxazin-3(4H)-ylideneacetate **(6)**

A mixture of 4.0 mL of glacial acetic acid with ethyl (2*E*)-3-ethoxy-4-(2-nitrophenoxy)but-2-enoate **(5)** (2.95 g, 0.01 mol) and iron powder (>10 mesh) (3.35 g ;0.06 mol) was heated with stirring at 115 °C (oil bath temperature 120 °C) for 30 min and then cooled. The crude reaction mixture was diluted with of ether (50 mL), transferred to a separatory funnel, and cautiously washed with $NaHCO_3$ (3×25 mL). The aqueous layer was back-extracted with ether (2×25 mL), and the combined ether layers were washed with brine; then the ether phase was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give the desired product as yellow oil. Yield 1.01 g (46 %); IR (KBr) 3413, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.11 (s,1H), 7.24-6.87 (m, 4H), 4.65 (s,2H), 4.54 (s,1H), 4.16 (q, *J* = 7.11 Hz, 2H), 1.27 (t, *J* = 7.11 Hz, 3H); ^{13}C NMR: δ 170.27, 149.09, 127.41, 123.04, 122.68, 117.93, 116.96, 115.65, 83.69, 66.41, 60.78, 14.24.

4-Hydroxy-1-(substitutedphenyl)-1,5-dihydro-2H-pyrrol-2-one **(9a-c)**

General procedure.

A mixture of substituted aniline **(8a-c)** (0.02 mol) and ethyl (2*E*)-4-bromo-3-ethoxybut-2-enoate **(2)** (2.37 g, 0.01 mol) was heated with stirring; the progress of reaction was monitored by TLC, and was completed within 1-3 h The reaction mixture was cooled, the solid dissolved in ethyl acetate and transferred to a separatory funnel. The organic layer was washed with $NaHCO_3$ (3×25 mL) and brine (25 mL). The organic layer was then portioned between brine and ethyl acetate (2x50 mL). The organic layer was dried over $MgSO_4$ anhydrous and the solvent was removed under reduced pressure to give the crude product. The residue was collected and further

purified by recrystallization from an appropriate solvent to afford the desired products **(9a-c)**.

4-Hydroxy-1-(2-nitrophenyl)-1,5-dihydro-2H-pyrrol-2-one **(9a)**

Yield = 1.63 g (74 %); mp 179-183^{o}C; IR 1745, 1628 cm^{-1}; ^{1}H NMR (DMSO): δ 9.73 (s, 1H), 8.06 (dd, *J* = 1.2, 8.43 Hz, 2H), 7.69 (m, 2H), 7.31 (m, 1H), 5.28 (s,1H), 4.89 (s, 2H); ^{13}C NMR (DMSO): δ 174.75, 163.94, 140.68, 135.82, 134.72, 126.39, 125.06, 123.84, 87.26, 68.91. HRMS *m/z*: calcd for $C_{10}H_8N_2O_4$ Na [M + Na]$^{+}$ 243.0382, found 243.0395. Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.39; H, 3.68; N, 12.52.

4-Hydroxy-1-(4-nitrophenyl)-1,5-dihydro-2H-pyrrol-2-one **(9b)**

Yield = 1.41 g (64 %); mp 252-254 ^{o}C; IR 1715, 1629 cm^{-1}; ^{1}H NMR (DMSO): δ 10.31 (s, 1H), 8.17 (d, *J* = 8.99 Hz, 2H), 7.90 (d, *J* = 9.04 Hz, 2H), 5.64 (s,1H), 4.90 (s, 2H); ^{13}C NMR: δ 175.04, 161.63, 146.80, 142.05, 126.88, 126.05, 118.23, 112.85, 88.50, 68.94. HRMS *m/z*: calcd for $C_{10}H_8N_2O_4$Na [M + Na]$^{+}$ 243.0382, found 243.0394; calcd for $C_{10}H_9N_2O_4$ [M + H]$^{+}$ 221.0562, found 221.0570. Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.59; H, 3.71; N, 13.01.

1-(2-Chloro-4-nitrophenyl)-4-hydroxy-1,5-dihydro-2H-pyrrol-2-one **(9c)**

Yield = 1.60 g (63 %), mp = 241-243 ^{o}C. IR (KBr): 1721, 1622 cm^{-}1; ^{1}H NMR (DMSO): δ 9.71 (s, 1H), 8.33 (s, *J* = 2.88 Hz, 1H), 8.12 (d, *J* = 9.11 Hz, 1H), 7.71 (d, *J* = 9.11 Hz, 1H), 5.56 (s, 1H), 4.93 (s, 2H); ^{13}C NMR: δ 174.65, 162.62, 143.285, 142.75, 124.47, 125.96, 123.84, 120.73, 86.46, 69,30.. HRMS *m/z*: calcd for $C_{10}H_7N_2O_4{}^{37}$ClNa [M + Na]$^{+}$ 278.9987, found 278.9975; calcd for $C_{10}H_7N_2O_4{}^{35}$ClNa [M + Na]$^{+}$ 276.9987, found 277.0006.

4-Ethoxy-1-(phenyl)-1,5-dihydro-2H-pyrrole-2-one **(11a-d)**

General procedure.

A mixture of substituted anilines **(10a-d)** (0.02 mole) and ethyl (2*E*)-4-bromo-3-ethoxybut-2-enoate **(2)** (2.37 g; 0.01 mole) in ethanol (50 mL) was allowed to stir at room temperature for 3-5 days. Completion of the reaction was checked by TLC. The solvent was removed and the residue was washed with water (50 mL) and then the product was extracted with ether (2x50 mL). The organic layer was dried over $MgSO_4$ anhydrous and the solvent was removed under reduced pressure to give the crude product. The residue was collected and further purified by recrystallization from an appropriate solvent to give the desired products **(11a-f).**

4-Ethoxy-1-(2-methylphenyl)-1,5-dihydro-2H-pyrrole-2-one **(11a)**

Yield 0.65 g (30 %); mp 161-163 ^{o}C; IR 1702, 1622 cm^{-1}; ^{1}H NMR (DMSO): δ 7.23-7.24 (m, 4H), 4.64 (s, 2H), 4.22 (q, *J* = 7.05 Hz, 2H), 2.11 (s, 3H), 1.31 (t, *J* = 7.05 Hz, 3H). ^{13}C NMR: δ 169.26, 165.86, 137.53, 136.80, 131.10, 128.12, 127.94, 127.04, 85.62, 67.02, 51.88, 18.39, 15.30. IR (KBr) 1702, 1622 cm^{-1}. HRMS *m/z*: calcd for $C_{13}H_{15}NO_2$Na [M + Na]$^{+}$ 240.00995, found 240.08342. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.15; H, 6.71; N, 6.73.

4-Ethoxy-1-(4-methylphenyl)-1,5-dihydro-2H-pyrrole-2-one **(11b)**

Yield 1.02 g (47 %); mp 131-132 ^{o}C; IR 1675, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.57 (d, *J* = 8.42 Hz, 2H), 7.26 (d, *J* = 8.42 Hz, 2H), 5.12 (s,1H), 4.23 (s,2H), 4.04 (q, *J* = 7.07 Hz, 2H), 2.29 (s, 3H), 1.41 (t, *J* = 7.07 Hz, 3H); ^{13}C NMR (DMSO): δ 171.54, 132.95, 129.61, 118.64, 95.74, 67.25, 51.05, 20.81, 14.18. IR (KBr) 1675, 1630 cm^{-1}. HRMS *m/z*: calcd for $C_{13}H_{15}NO_2Na$ [M + Na]$^{+}$ 240.00995, found 240.10223. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.27; H, 6.84; N, 6.27.

4-Ethoxy-1-(2-methoxylphenyl)-1,5-dihydro-2H-pyrrole-2-one **(11c)**

Yield 0.80 g (34 %); mp 158 - 163 ^{o}C; IR 1683, 1637 cm^{-1}; ^{1}H NMR (DMSO): δ 6.92-7.28 (m, 4H), 4.57 (s, *J* = 4.84 Hz, 2H), 4.23 (q, *J* = 7.03 Hz, 2H), 3.75 (s, 3H), 1.29 (t, *J* = 7.03 Hz, 3H). ^{13}C NMR: δ 169.04, 166.44, 155.40, 129.44, 129.09, 126.73, 120.88, 112.83, 85.88, 67.04, 56.12, 51.36, 15.31. IR (KBr) 1683, 1637 cm^{-1}. HRMS *m/z*: calcd for $C_{13}H_{15}NO_3Na$ [M + Na]$^{+}$ 256.0950, found 256.0348. Anal Calc for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.18; H, 6.52; N, 6.32.

4-Ethoxy-1-(4-methoxylphenyl)-1,5-dihydr-2H-pyrrole-2-one **(11d)**

Yield 0.86 g (37 %); mp 119-121^{o}C; IR 1687, 1628 cm^{-1}; ^{1}H NMR (DMSO): δ 7.53 (d, *J* = 9.13 Hz, 2H), 6.87 (d, *J* = 9.13 Hz, 2H), 5.22 (s,1H), 4.04 (q, *J* = 7.06 Hz, 2H), 4.38 (s, 2H), 3.69 (s, 3H), 1.30 (t, *J* = 7.06 Hz, 3H); ^{13}C NMR (DMSO): δ 172.71, 170.32, 155.42, 133.26, 120.25, 114.42, 95.49, 67.55, 55.69, 50.95, 14.51. HRMS *m/z*: calcd for $C_{13}H_{15}NO_3Na$ [M + Na]$^{+}$ 256.0950, found 256.0958. Anal Calc for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.76; H, 6.82; N, 6.18.

4-Ethoxy-1-(4-bromophenyl)-1,5-dihydro-2H-pyrrole-2-one **(11e)**

Yield 1.18 g (42 %), mp = 155-157 ^{o}C. IR (KBr): 1677, 1626 cm^{-1}. ^{1}H NMR (DMSO): δ 7.48 (d, *J* = 2.36 Hz, 2H), 7.44 (d, *J* = 2.36 Hz, 2H), 5.26 (s,1H), 4.07 (q, *J* = 7.05 Hz, 2H), 4.41(s,2H), 1.28 (t, *J* = 7.05 Hz, 3H); ^{13}C NMR: δ 173.30, 170.82, 131.93, 120.59, 120.13, 119.66, 93.34, 67.78, 50.38, 14.49. HRMS *m/z*: calcd for $C_{12}H_{12}NO_2{}^{79}BrNa$ [M + Na]$^{+}$ 303.9946, found 303.9966; calcd for $C_{12}H_{12}NO_2{}^{81}BrNa$ [M + Na]$^{+}$ 305.9946, found 305.9943.

4-Ethoxy-1-(4-chlorophenyl)-1,5-dihydro-2H-pyrrole-2-one **(11f)**

Yield 1.02 g (43 %), mp = 130-134 ^{o}C. ^{1}H NMR (DMSO): δ 7.72 (d, *J* = 8.96 Hz, 2H), 7.70 (d, *J* = 8.96 Hz, 2H), 5.29 (s,1H), 4.09 (q, *J* = 7.06 Hz, 2H), 4.45 (s,2H), 1.34 (t, *J* = 7.06 Hz, 3H); ^{13}C NMR (Acetic): δ 173.27, 170.79, 138.93, 129.28, 126.70, 119.87, 95.56, 67.76, 50.62, 14.47. IR (KBr): 1682, 1630 cm^{-1}. HRMS *m/z*: calcd for $C_{12}H_{12}NO_2{}^{35}ClNa$ [M + Na]$^{+}$ 260.04542, found 260.04797.

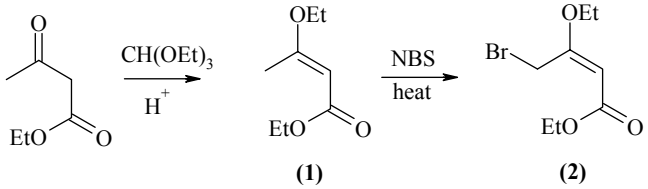
Ethyl (2E)-4-(4-aminophenoxy)-3-ethoxybut-2-enoate **(13)**

A mixture of 2-amino-1,3-thiazole **(12)** (2.00 g; 0.02 mole) and ethyl (2*E*)-4-bromo-3-ethoxybut-2-enoate **(2)** (2.37 g; 0.01 mole) in ethanol (50 ml) was heated with stirring at 200 ^{o}C for 10 h; the progress of reaction was monitored by TLC. After the completion of the reaction, the mixture was concentrated under vacuum and the residue was poured into water and extracted with ethyl acetate. The combined organic

extracts were dried over $MgSO_4$, concentrated under vacuum; addition of few drops of petroleum ether precipitated the product **(13)**. Yield 0.56 g (25 %), mp = 114-120 ^oC. ^1H NMR (DMSO): δ 9.50 (s, 1H), 7.30 (d, *J* = 4.02 Hz, 1H), 6.97 (d, *J* = 4.02 Hz, 1H), 5.30 (s, 1H), 4.08 (q, *J* = 6.80 Hz, 2H), 3.85 (q, *J* = 6.81 Hz, 2H), 3.32 (s, 2H), 1.18 (t, *J* = 6.81 Hz, 3H), 1.09 (t, *J* = 6.80 Hz, 3H),; ^{13}C NMR (Acetic): δ 169.68, 167.17, 164.96, 130.83, 107.77, 93.61, 65.77, 60.12, 14.71, 14.18. IR (KBr): 1695, 1618 cm^{-1}. HRMS *m/z*: calc for $C_{11}H_{16}N_2O_3SNa$ $[M + Na]^+$ 279.0779, found 279.0811.

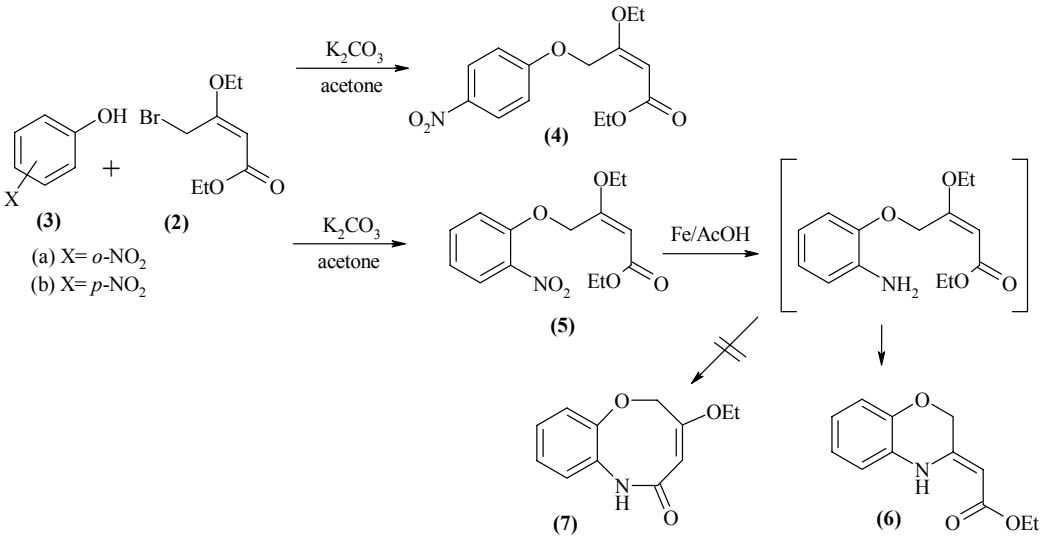
Results and Discussion

In an ongoing programme towards the synthesis of new compounds of pharmacological interest, we have recently reported the synthesis of new 4-substituted-3-alkoxy-2-butenoic acid esters through the O-alkylation of phenols with ethyl (2*E*)-4-bromo-3-alkoxybut-2-enoate **(2)** in the presence of potassium carbonate and acetone.[14] Compound **(2),** on the other hand, was prepared by allylic bromination of ethyl (2*E*)-3-ethoxy-2-butenoate **(1)**, using *N*-bromosuccinimide, (Scheme 1).[14]



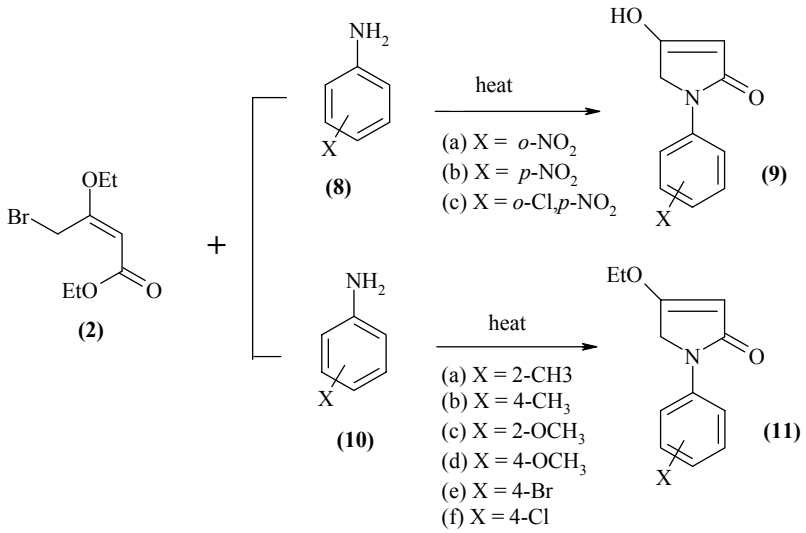
Scheme 1

It has been reported that the aromatic nitro group is selectively reduced in the presence of an α,β-unsaturated ester, and the resulting amine reacts with the carbonyl group in a subsequent step by a tandem reduction-Michael addition reaction.[15] In this respect, ethyl (2*E*)-3-ethoxy-4-(2- and 4-nitrophenoxy)but-2-enoates **(4 and 5**), prepared from ethyl (2*E*)-4-bromo-3-alkoxybut-2-enoate **(2)** and 2-and 4-nitrophenols [14] were used as synthone for synthesis of ethyl (2*Z*)-2*H*-1,4-benzoxazin-3(4*H*)-ylideneacetate **(6)** (Scheme 2).



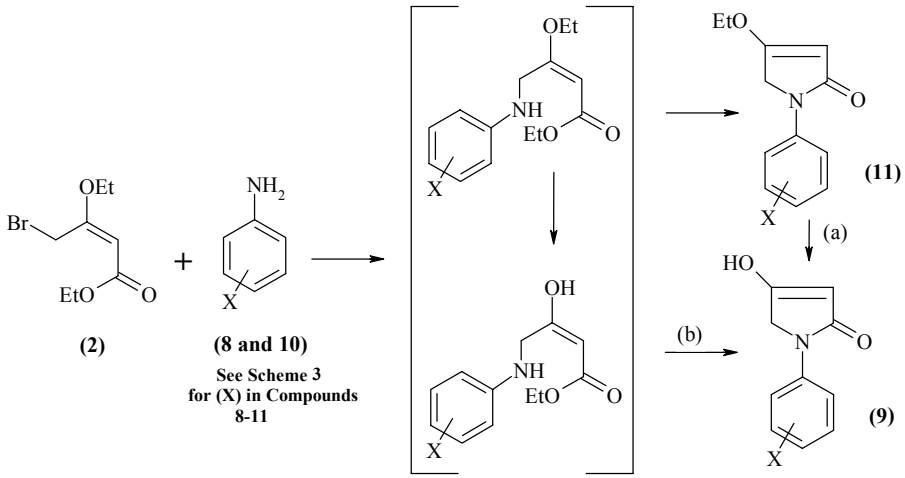
Scheme 2

Scheme **2** summarizes the synthesis of **6** from the reduction of nitro group in ethyl (2*E*)-3-ethoxy-4-(2-nitrophenoxy)but-2-enoate **(5)** by iron powder in glacial acetic acid to an amine which undergoes Michael addition reaction to give the expected *six-exo-rig* product **(6)**[16, 17] and not the Claisen addition product 3-ethoxy-2*H*-1,6-benzoxazocin-5(6*H*)-one **(7).** Other reducing agents were also investigated but yields were very low and some side-chain cleavage was observed in the ether-containing substrates as shown by TLC. In addition, N-alkylation of **2** with different aromatic amines **(8 and 10)** forms the traditional N-alkylated products, as intermediate which give tetramic acid derivatives (**9 and 11**) by C-amination/cyclization reactions (Scheme 3). Synthesis of tetramic acid derivatives through the reaction of ethyl (2*E*)-4-chloro-3-alkoxybut-2-enoate with aliphatic amines was described by other research groups.[18, 19]



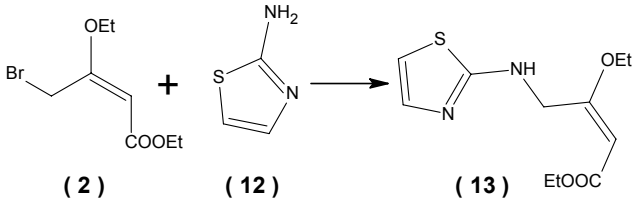
Scheme 3

It was observed that the reaction of **2** with aniline bearing strong electron-withdrawing groups such as NO_2 led to the formation of tetramic acids (**9)** while the reaction with aniline bearing electron-releasing groups, methyl tetramates **(11**) were obtained as shown in Scheme 3. Furthermore, the formation of compounds (**11**) can be explained on the basis of intramolecular nucleophilic attack of the secondary amino group of the N-alkylated intermediate upon the ester carbonyl group followed by elimination of ethanol, while the tetramic acid moiety in compounds (**9)** can be obtained either from cleavage of the ether group in the N-alkylated intermediate followed by cyclization (route b) or cyclization to form compounds **(11)** followed by ether cleavage (route a) Scheme 4.



Scheme 4

Interestingly however, the reaction between 2-amino-1,3-thiazole **(12)** with ethyl (2*E*)-4-bromo-3-alkoxybut-2-enoate **(2)** afforded the intermediate ethyl (2*E*)-4-(4-aminophenoxy)-3-ethoxybut-2-enoate **(13)** (Scheme 5). The formation of this product indicates that the cyclization step did not occur to give any of the pyrrolidinone ring systems **(9 or 11);** this may be due to the basic properties of 2-amino-1,3-thiazole **(12)**.



Scheme 5

^{1}H-NMR and ^{13}C-NMR spectra of the all prepared compounds are in total agreement with the suggested structures; the ^{1}H NMR spectra of compounds **9** and **11** showed signals corresponding to methylene, olefinic, aromatic and OH protons. DEPT experiments were employed to differentiate between secondary and quaternary carbons from primary and tertiary carbons. Moreover, the infrared spectra of the prepared compounds showed absorption bands characteristic for N-C=O groups in addition to other absorptions correlated to the assigned structures. Mass spectral data of the synthesized compounds are also in total agreement with the assigned structures and show the expected molecular ions, M^{+} as suggested by their molecular formulas.

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