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REGULAR ARTICLE

Intramolecular cyclization of *N*-hydroxy-2-phenoxyacetamides and 3-phenoxypropanamides

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Abstract. A novel route for the preparation of 2H-1,4- benzoxazin-3(4H)one and 1,5 benzoxazepinones by intramolecular cyclization of *N*-hydroxy 2-phenoxyacetamide and *N*-hydroxy -3 phenoxypropanamide using PPA and Lewis acid has been discussed.

Keywords. Intramocular cyclization; Benzoxazins; Benzoxazepins; PPA; Lewis acids.

1. Introduction

Direct amidation of aromatic substrates through electrophilic substitution reaction is not a common process. Wassmundt and Padegimas[1] showed that intermolecular direct amidation of anisole with acetohydroxamic acid gave 4-methoxyacetanilide and intramolecular cyclization of *N*-hydroxy3- phenyl propanamide furnished 3,4-dihydro-2-quinolone in hot polyphosphoric acid (PPA) as the medium. In 1981, March and Engenito[2] examine this reaction in greater detail. They showed that this reaction was successful primarily with electron-rich aromatic substrates and that an excess of hydroxamic acid was not required. Other reagents such as phosphorus pentoxide, methanesulfonic acid or polyphosphate esters were unsuccessful in this reaction. The intramolecular version of this reaction leading to benzofused 6 and 7 membered lactams was reported by Sliwinski.[3]

Our interest in this reaction was stimulated by the presence of 2H-benzo-1,4-oxazin-3- [4H]-one moiety in many compounds of the pharmaceutical industry. Some examples of Figure 1.[4–7] We conceived this heterocyclic unit could be readily derived by intramolecular amidation of *N*-hydroxy-2- phenoxyacetamides. The 2,3-Dihyrdo-1,5-benzoxazep in-4(5H)-one unit present in RIP-1.[8]

Several approaches for the synthesis of 2H-benzo-1-oxazin-3-[4H]one have been reported in the literature. Zhou Xu[9] and coworkers have used the Buchwald-Hartwig reaction for this purpose. Other methods include reductive cyclization[10–12] of 2-nitrophenoxy ethyl acetate, coupling reaction[13–16] between 2-halophenol and 2-haloacetamide. Synthesis of 2,3-Dihyrdo-1,5-benzoxazepin-4(5H)-one have been reported by Schmidt reaction[17] of 4-cromanone and Beckmann reaction[18] of 4-chromanone oxime. However, preparation of 2H-benzo-1-oxazin-3-[4H]one by aromatic electrophilic substitution was not found in the literature. These factors prompted us to examine in detail the intramolecular cyclization of appropriate hydroxamic acids leading to bezoxazins and benzoxazepinones.

2. Experimental

2.1 *General*

All reagents were purchased from commercial suppliers without further purification. Experiments were monitored by thin-layer chromatography (TLC) and the TLC was performed on precoated silica gel plates. The ^{1}H and ^{13}C NMR

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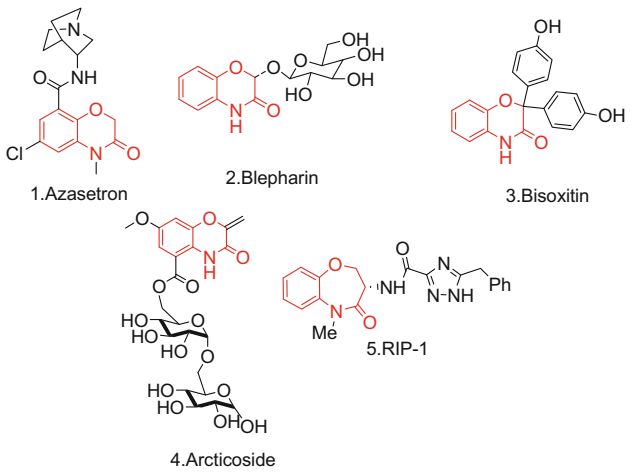
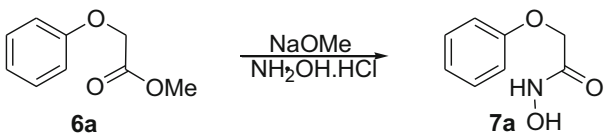


Figure 1. Pharmaceutically important compounds containing 2H-Benzo,1,4- oxazin and 1,5-benzoxazepinones.

spectra were recorded on a Bruker AC 250 (300 MHz) spectrometer with $CDCl_3$ and DMSO-d_6 as solvents and tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J values are given in Hertz (Hz). Column chromatography was carried out over 60-120 mesh silica gel. Melting points were determined with an Electrothermal IA 9300. IR spectra (KBr) were recorded on SHIMADZU FT-IR 800S. MASS spectral data were recorded with SHIMADZU GC-17A/QP5050A/AOC5000.

2.2 *General procedure A for the preparation of hydroxamic acids*

The following preparation of ***N*-hydroxy-2-phenoxyacetamide (7a)** is representative.



2.2a *N-hydroxy-2-phenoxyacetamide* ***(7a)***: To a solution of NaOMe (1.95 g, 36.11 mmol) in methanol (10 mL) was added hydroxylamine hydrochloride (1.67 g, 24.0 mmol) dissolved in methanol (20 mL). The reaction mixture was stirred for 10 min at room temperature and to it was added methylphenoxyacetate (1.0 g, 6.0 mmol) and refluxed for 8 h. After completion of the reaction (by TLC), the mixture was cooled to room temperature and acidified with 10% HCl to pH 4.5 to 5.0. The acidified reaction mixture was filtered to remove the salts. Methanol was evaporated and the residue diluted with water and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The resultant crude product was purified by column chromatography to furnish the required product **7a** (0.62g, 62%) as a white solid. M.p.: 114-115 °C (lit.114 °C).[19] IR (KBr) 694, 750, 1066, 1236, 1639, 1680, 2848, 3298 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.99 (s, 1H), 7.30 (t, *J* = 7.2 Hz, 2H), 6.95 (d, *J* = 7.5 Hz, 3H), 4.45(s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.28, 157.73, 129.41, 121.09, 114.57, 65.71; MS(70eV): m/z 167.2 (M^+).

2.2b *N-hydroxy-2-(4-methylphenoxy)acetamide* ***(7b)***: Compound **7b** was prepared in 52% yield from methyl(4-methylphenoxy)acetate using general procedure **A**. White solid. M.p. 135.5-136 °C; IR (KBr): 810, 837, 1070, 1240, 1512, 1639, 1678, 2856, 3300 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.82 (s, 1H), 9.01 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.41 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.34, 155.68, 129.80, 129.72, 114.44, 65.90, 20.04; MS(70eV): m/z 181(M^+); HRMS calcd. for (M+Na)204.0637; Found: 204.0639.

2.2c *N-hydroxy-2-(4chlorophenoxy)acetamide* ***(7c)***: Compound **7c** was prepared in 58% yield from methyl(4-chlorophenoxy)acetate using general procedure **A**. White solid. M.p. 144-145 °C; IR (KBr): 831, 1068, 1240, 1491, 1643, 1683, 2843, 3296 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.86 (s, 1H), 9.01 (s, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.08, 156.61, 129.15, 124.93, 116.41, 66.01; MS(70eV): m/z 201(M^+); HRMS calcd. for (M+)201.0193; Found for (M+Na) 224.0195.

2.2d *N-hydroxy-2-(4-bromophenoxy)acetamide* ***(7d)***: Compound **7d** was prepared in 42% yield from methyl(4-bromophenoxy)acetate using general procedure **A**. White solid. M.p. 148-149 °C; IR (KBr): 808, 831, 1066, 1236, 1489, 1639, 1681, 3296 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.40 (s, 1H), 9.02 (bs, 1H), 7.38 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.51 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6): δ 164.08, 156.24, 131.76, 116.10, 113.31, 66.13; MS(70eV): m/z 245, 247(1:1)(M^+); HRMS calcd. for (M+Na) 267.9585; Found: 267.9583.

2.2e *N-hydroxy-3-phenoxypropanamide* ***(7e)***: Compound **7e** was prepared in 60% yield from methyl-3-phenoxypropanoate using general procedure **A**. White solid. M.p. 142-143 °C; IR (KBr): 686, 752, 1242, 1471, 1494, 1629, 3161 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.89 (s, 1H), 7.27 (quint, *J* = 2.1 Hz, 2H), 6.90 (qurt, *J* = 8.4 Hz, 3H), 4.16 (t, *J* = 6 Hz, 2H), 2.43 (t, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.60, 158.24, 129.46, 120.55, 114.31, 63.47, 32.56; MS(70eV): m/z 181(M^+); HRMS calcd. for (M+Na) 204.0637; Found: 204.0639.

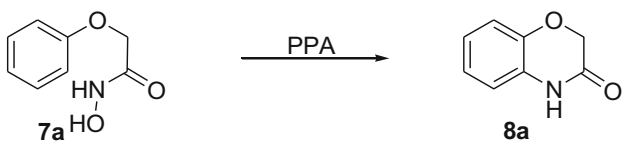
2.2f *N-hydroxy-3-(4-methylphenoxy)propanamide (7f)*: Compound **7f** was prepared in 56% yield from methyl-3-(4-methylphenoxy)propanoate using general procedure **A**. White solid. M.p.: 136-138 °C. IR (KBr): 503, 821, 1240, 1510, 1635, 3174 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.55 (s, 1H), 8.88 (s, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 9.6, 2.7 Hz, 2H), 4.11 (t, J = 6 Hz, 2H), 2.40 (t, J = 6 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.66, 156.24, 129.78, 129.22, 114.18, 63.63, 32.55, 20.02; MS(70eV): m/z 195(M^+); HRMS calcd. for (M+Na)218.0793; Found: 218.0794.

2.2g *N-hydroxy-3-(4chlorophenoxy)propanamide (7g)*: Compound **7g** was prepared in 52% yield from methyl-3-(4-chlorophenoxy)propanoate using general procedure **A**. White solid. M.p.:125-126 °C; IR (KBr): 657, 819, 1236, 1492, 1631, 3163 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.55 (s, 1H), 8.88 (s, 1H), 7.32 (dd, J = 6.6, 2.1 Hz, 2H), 6.94 (dd, J = 6.6, 2.1 Hz, 2H), 4.16 (t, J = 6 Hz, 2H), 2.41 (t, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.46, 157.21, 129.25, 124.36, 116.17, 64.09, 32.53; MS(70eV): m/z 215(M^+); HRMS calcd. for (M+Na) 238.0247; Found: 238.0247.

2.2h *N-hydroxy-3-(4-bromophenoxy)propanamide (7h)*: Compound **7h** was prepared in 48% yield from methyl-3-(4-bromophenoxy)propanoate using general procedure **A**. White solid. M.p. 135-136 °C: IR (KBr): 813, 1051, 1236, 1483, 1629, 3159 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.56 (s, 1H) 8.89 (s, 1H), 7.42 (t, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.16 (t, J = 6 Hz, 2H), 2.42 (t, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.45, 157.55, 132.09, 116.67, 111.94, 63.93, 32.30; MS(70eV): m/z 259, 261(1:1) (M^+); HRMS calcd. for (M+Na)281.9742; Found: 281.9751.

2.3 *General procedure B for the cyclisation of hydroxamic acids using PPA*

The following preparation of **8a** is representative.



2.3a *2H-1,4-benzoxazin-3(4H)one (8a)*: A mixture of the *N*-hydroxy-2- phenoxy acetamide (1.0 g, 6.0 mmol) and polyphosphoric acid (PPA) (5.0 g) was stirred vigorously at 100 °C for 5 h. After completion of the reaction (by TLC) the reaction mixture was cooled to 70 °C, diluted with water (100 mL) and cooled to room temperature. The diluted reaction mixture was extracted with dichloromethane and the combined organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the resultant crude product was purified by column chromatography to furnish the required product **8a** (0.21 g, 24%) as a white solid. M.p: 166-168 °C (lit 168-172 °C)[15]; IR (KBr): 748, 1047, 1402, 1500, 1705, 2982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.10 (s, 1H), 7.06-6.91 (m, 3H), 6.93-6.80 (m, 1H), 4.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.32, 143.64, 126.03, 124.25, 122.73, 116.77, 116.09, 67.15; MS (70eV): m/z 149 (M^+).

2.3b *6-methyl-2H-1,4-benzoxazin-3(4H)-one (8b)*: Compound **8b** was prepared in 24% yield from *N*-hydroxy-2-(4-methylphenoxy) acetamide using general procedure **B**. White solid. M.p.: 207-209 °C; IR (KBr): 800, 1045, 1219, 1400,1492, 1519, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.26 (s, 1H), 6.94-6.63 (m, 3H), 4.62 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.55, 141.46, 132.55, 125.74, 124.68, 116.43, 67.25, 20.64; MS (70eV): m/z 163 (M^+).

2.3c *6-chloro-2H-1,4-benzoxazin-3(4H)-one (8c)*: Compound **8c** was prepared in 31% yield from *N*-hydroxy-2-(4-chlorophenoxy) acetamide using general procedure **B**. White solid. M.p.: 217-218 °C. IR (KBr): 729, 860, 1041, 1211, 1398, 1492, 1701, 2958 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.81 (s, 1H), 7.00-6.84 (m, 3H), 4.59 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.65, 142.13, 128.68, 125.67, 122.36, 117.58, 115.15, 66.64; MS (70eV): m/z 183 (M^+).

2.3d *6-bromo-2H-1,4-benzoxazin-3(4H)-one (8d)*: Compound **8d** was prepared in 48% yield from *N*-hydroxy-2-(4-bromophenoxy) acetamide using general procedure **B**. White solid. M.p.: 222-224 °C; IR (KBr): 802, 1217, 1492, 1681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.09 (dd, J = 8.7, 2.1 Hz, 1H), 6.97 (d, J = 1.8 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6): δ 164.91, 142.47, 128.23, 125.77, 118.69, 117.63, 114.14, 66.92; MS (70eV): m/z 230, 232 (1:1) (M^+).

2.3e *2,3-dihydro-1,5-benzoxazepin-4(5H)-one (8e)*: Compound **8e** was prepared in 48% yield from *N*-hydroxy-3-phenoxypropanamide using general procedure **B**. White solid. M.p. 130.5-131.5 °C; IR (KBr): 526, 752, 788, 1219, 1394, 1498, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.90 (s,1H), 7.11-6.97 (m, 4H), 4.47 (t, J = 5.7 Hz, 2H), 2.88 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.27, 148.65, 128.92, 125.35, 123.76, 122.08, 121.77, 68.74, 37.06; MS (70eV): m/z 163 (M^+).

2.3f *7-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (8f)*: Compound **8f** was prepared in 45% yield from *N*-hydroxy-3-(4-methylphenoxy) propanamide using general procedure **B**. White solid. M.p. 130.5-131.6 °C;

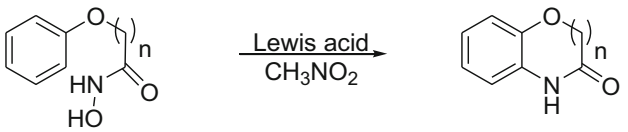
IR (KBr): 534, 835, 1217, 1392, 1512, 1672, 3188 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.56 (s, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.86 (dd, J = 8.1, 1.5, Hz, 1H), 6.79 (s, 1H), 4.45 (t, J = 6 Hz, 2H), 2.84 (t, J = 5.7 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.16, 146.50, 133.48, 128.95, 126.25, 122.09, 121.91, 69.34, 36.78, 20.54; MS (70eV): m/z 177 (M^+).

2.3g *7-chloro-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (**8g**)*: Compound **8g** was prepared in 24% yield from *N*-hydroxy-3-(4-chlorophenoxy) propanamide using general procedure **B**. White solid. M.p.:169.5-170.5 °C; IR (KBr): 538, 813, 871, 1041, 1217, 1423, 1492, 1678,3209 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.09-6.92 (m, 3H), 4.46 (t, J = 5.4 Hz, 2H), 2.88 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.88, 147.34, 129.97, 128.58, 125.28, 123.34, 121.41, 68.93, 36.89; MS (70eV): m/z 197 (M^+).

2.3h *7-bromo-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (**8h**)*: Compound **8h** was prepared in 31% yield from *N*-hydroxy-3-(4-bromolphenoxy) propanamide using general procedure **B**. White solid. M.p.: 171.5-172.5 °C. IR (KBr): 802, 1215, 1419, 1492, 1674, 2993, 3209 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.43 (s,1H), 7.15 (sexet, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 4.46 (t, J = 5.7 Hz, 2H), 2.88 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.75, 147.83, 130.26, 128.25, 124.27, 123.74, 115.78, 68.89, 36.86; MS (70eV): m/z 241, 243 (1:1) (M^+).

2.4 *General procedure C for the cyclisation of hydroxamic acids using Lewis acids*

The following preparation of **8a** is representative.



7a,7e **8a,8e**

2.4a *2H-1,4-benzoxazin-3(4H)-one (**8a**)*: To a stirred solution of *N*-hydroxy-2- phenoxyacetamide (1.67 g, 10 mmol) in nitromethane (15 mL) was added anhydrous ferric chloride (2 g, 12 mmol). The reaction mixture was warmed to 60 °C for 2 h with vigorous stirring. After completion of the reaction (by TLC) nitromethane was removed under vacuum. The crude reaction mixture was diluted with water (70 mL) and CH_2Cl_2 (10 mL) and was stirred for 5 min. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2) and the combined organic layer was washed with water (50 mL × 2) and dried over Na_2SO_4. The solvent was evaporated and the resultant crude product was purified by column chromatography to furnish the required product **8a** (0.45 g, 30%) as a white solid.

2.5 *General procedure D for the acetylation of hydroxamic acids*

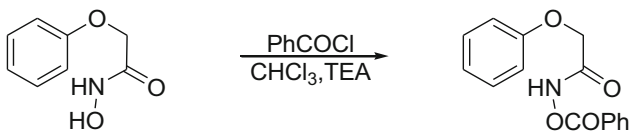
The following preparation of **9a** is representative.

2.5a *N-(acetoxy)-2-phenoxyacetamide (**9a**)*: A mixture of *N*-hydroxy-2-phenoxy aceta mide (1 g, 6.0 mmol), acetic anhydride (5 mL) and dimethylaminopyridine (0.02 g, 0.16 mmol) was stirred for 3 h at room temperature. After completion of reaction (by TLC) it was diluted with water (70 mL) and stirred for additional 1 h. The diluted reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The total organic layer was washed with 5% $NaHCO_3$ solution (75 mL) and with water (50 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated and the resultant crude product was purified by column chromatography to furnish the product **9a** (1.12 g, 90%) as a white solid. M.p. 102-103 °C. IR (KBr): 688, 748, 1193, 1493, 1662, 1799, 2960, 3148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.41-7.25 (m, 2H), 7.13-6.52 (m, 1H), 7.00-6.87 (m, 2H), 4.66 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.13, 165.14, 156.89, 129.81, 122.48, 114.66, 67.08, 18.15; HRMS calcd. for (M+Na) 232.0586; Found: 232.0588.

2.5b *N-(acetyloxy)-3-phenoxypropanamide (**9b**)*: Compound **9b** was prepared in 86% yield from *N*-hydroxy-3-phenoxypropanamide using general procedure **D**. White solid. M.p.: 111-113 °C; IR (KBr): 684, 746, 1045, 1201, 1253, 1494, 1656, 1795, 3155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.38-7.22 (m, 2H), 7.07-6.87 (m, 3H), 4.27 (t, J = 6 Hz, 2H), 2.77 (t, J = 6 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.50, 157.87, 129.58, 121.59, 114.68, 63.22, 34.02, 18.26; HRMS calcd. for (M+Na) 246.0742; Found: 246.0737.

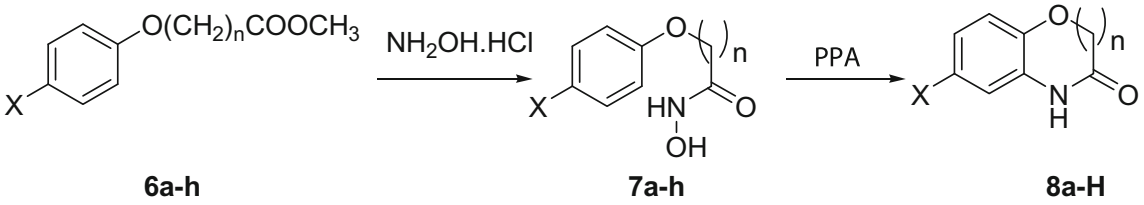
2.6 *General procedure E for the benzoylation of hydroxamic acids*

The following preparation of **9c** is representative.



8a **9c**

2.6a *N-(benzoyloxy)-2-phenoxyacetamide (**9c**)*: To a stirred solution of *N*-hydroxy-2- phenoxyacetamide (1.0 g, 6.0 mmol) in $CHCl_3$ (10 mL) at 0 °C was added Et_3N (0.64 g, 6.3 mmol), followed by dropwise addition of benzoyl chloride (0.84 g, 6.0 mmol). The reaction was stirred for 2 h at room temperature. After completion of reaction (by



Scheme 1. Amidocyclisation with PPA.

Table 1. Cyclization of hydroxamic acids with PPA.

X	n	Time (h)	Temp. (°C)	Yield (%)
7a (H)	1	5	100	24 (8a)
7b (Me)	1	5	85	24 (8b)
7c (Cl)	1	6	97	31 (8c)
7d (Br)	1	24	90	48 (8d)
7e (H)	2	21	75	48 (8e)
7f (Me)	2	18	97	45 (8f)
7g (Cl)	2	5	104	24 (8g)
7h (Br)	2	6	97	31 (8h)

TLC) it was diluted with water (70 mL) and extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated and the resultant crude product was purified by column chromatography to furnish the product **9c**. Yield (1.36 g, 86%) white material with M.p.: 125-126 °C; IR (KBr): 710, 1001, 1084, 1237, 1492, 1688, 1767, 3219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.96 (s,1H), 8.13 (dt, J = 0.6, 5.1 Hz, 2H), 7.63 (t, J = 9.0 Hz, 1H), 7.50 (quint, J = 6.0 Hz, 2H), 7.36 (sext, J = 3, 2H), 7.09-6.97 (m, 3H), 4.74 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.22, 164.32, 156.97, 134.39, 130.08, 129.86, 128.76, 126.29, 122.52, 114.72, 67.27; HRMS calcd. for (M+Na) 294.0742; Found: 294.0758

2.6b *N-(benzoyloxy)-3-phenoxypropanamide (**9d**)*: Compound **9d** was prepared in 82% yield from *N*-hydroxy-3-phenoxypropanamide using general procedure **E**. White solid. M.p.: 117-119 °C; IR (KBr): 704, 1058, 1236, 1599, 1691, 1772, 3178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.84 (s, 1H), 8.10 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.29 (qurt, J = 7.8 Hz, 2H), 6.98 (qurt, J = 7.5 Hz, 3H), 4.31 (t, J = 6 Hz, 2H), 2.85 (t, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.61, 157.94, 134.23, 129.98, 129.58, 128.69, 126.49, 121.55, 114.73, 63.27, 34.14; HRMS calcd. for (M+Na) 308.0899; Found: 308.0893.

3. Results and Discussion

The required starting materials, hydroxamic acid derivatives, were prepared from the reaction of esters (6a-6h) of aryloxy substituted carboxylic acids and hydroxylamine hydrochloride. All new compounds were characterized by IR, ^1H and ^{13}C-NMR and HRMS. Initially, all hydroxamic acids 7a-h were cyclized in hot PPA (Scheme 1). The products were obtained in moderate yields (Table 1).

Table 2. Amidocyclization of acylated hydroxamic acids with PPA.

R	N	Time (h)	Temp.(^{0}C)	Yield (%)
R^1	1(9a)	2	65	56 (8a)
R^2	1(9c)	2	60	52 (8a)
R^1	2(9b)	3	65	62 (8e)
R^2	2(9d)	14	80	61 (8e)

Other cyclizing agents such as H_2SO_4, triflic acid and oleum(60%) did not furnish the required product.

To improve the yields of this reaction, the hydroxyl group was acylated with acetic anhydride or benzoyl chloride and the resulting derivatives cyclized with PPA as shown in Scheme 2 and Table 2. This modification gave improved yields of the cyclized products under milder conditions.

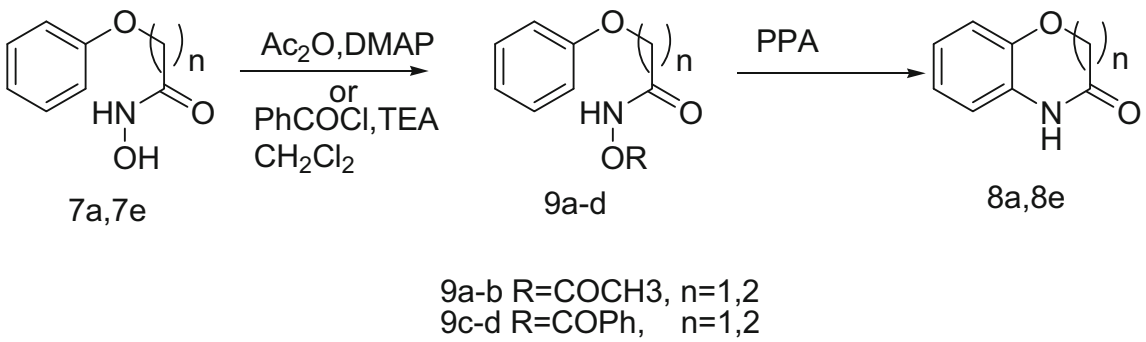
As lewis acids are also known to bring about electrophilic substitution reactions, the use of such reagents was re-examined in this reaction. Anhydride $FeCl_3$, BF_3-Et_2O gave moderate yields of the desired product. The reaction was unsuccessful with $AlCl_3$, $ZnCl_2$, $TiCl_4$ and $SnCl_4$. As listed in Scheme 3 and Table 3 this reaction applied only to *N*-hydroxy-2-phenoxyacetamide and its derivatives. No cyclized product was formed from *N*-hydroxy-3-phenoxypropanamide. The reason for this result is not clear. When started the reaction with acetyl and benzoyl derivatives of hydroxamic acids, $ZnCl_2$ and $SnCl_4$ also gave the cyclized product.

4. Conclusions

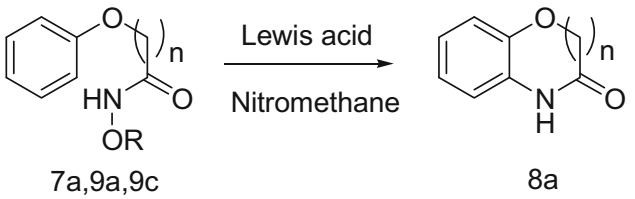
We have established a convenient method for intramolecular aromatic amidation of *N*-hydroxy-2-phenoxy acetamides and *N*-hydroxy-3-phenoxy

Table 3. Cyclization using lewis acids.

Substrate	Lewis acid	Time (h)	Temp. (°C)	Yield (%) (8a)
7a	$FeCl_3$	5	65	30
7a	BF_3-Et_2O	8	90	22
9a	$FeCl_3$	2	50	55
9a	BF_3-Et_2O	4	90	38
9a	$ZnCl_2$	6	100	22
9a	$SnCl_4$	4	50	20
9c	$FeCl_3$	2	50	59
9c	BF_3-Et_2O	4	70	45
9c	$ZnCl_2$	8	100	28
9c	$SnCl_4$	6	50	25



Scheme 2. Amidocyclization of acylated hydroxamic acids.



Scheme 3. Amidocyclization with Lewis acids.

propanamides leading to 2H-benzo-1,4-oxazin-3-[4H]ones, 2,3-Dihydro-1,5-benzoxazepin-4(5*H*)-one. This method also results in activated hydroxamic acids with better yields under milder conditions. Although yields in our method are only moderate, the easy availability of starting materials makes this an attractive proposition when compared to the other routes reported in the literature.

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