First Synthetic Method for the Preparation of 6-Unsubstituted-2,3-dihydro-1,3-oxazin-4-ones

Giorgio Bertolini,* Mario Aquino, Francesco Ferrario, Gianfranco Pavich, Andrea Zaliani, and Alberto Sala

Italfarmaco Research Centre, via dei Lavoratori 54, 20092 Cinisello Balsamo, Milan, Italy

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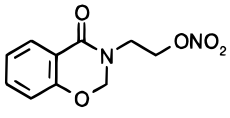
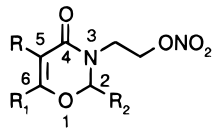
The first synthetic pathway to synthesize 6-unsubstituted-2,3-dihydro-1,3-oxazin-4-ones is described. The α-formylation of the starting amide and the cyclization of the α-formylamide with a desired aldehyde under acidic conditions gave compounds **5a**−**h** (R = nPr, iPr, cPr, cHex, Ph, CH_2Ph, nHex, and R_1 = H, Me). This strategy was used with little modification for the preparation of new monocyclic organic nitrates such as **2a**−**c** (**2a** (R = Ph, R_1 = H, and R_2 = H), **2b** (R = Ph, R_1 = H, and R_2 = Me), and **2c** (R = H, R_1 = Ph, and R_2 = H).

Introduction

Since the discovery of glyceryl trinitrate (GTN), organic nitrates have been in therapeutic use for over a century. Consequently, during the past decade, the search for new organic nitrates with reduced side effects and improved oral bioavailability has greatly intensified.[1] During our study of new organic nitrates with pharmacological profiles different from GTN, we identified ITF 296 (**1**), which is characterized by preferential action on large coronary vessels and good oral bioavailability.[2]



1 ITF 296



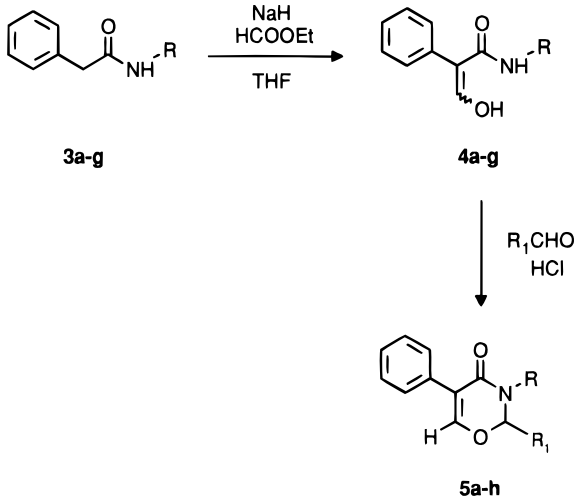
	R	R_1	R_2
2a:	Ph	H	H
2b:	Ph	H	Me
2c:	H	Ph	H

In order to assess the role of this fused bicyclic system in the observed pharmacological profile, we decided to synthesize new monocyclic nitroesters **2a**−**c**. However, the synthesis of 6-unsubstituted-2,3-dihydro-1,3-oxazin-4-ones, such as compounds **2a** and **2b** (R_1 = H), has not been described in the literature, and the methods reported for the synthesis of 6-substituted-2,3-dihydro-1,3-oxazin-4-ones,[3−5] such as the reaction between acyl Meldrums acids and Schiff bases, were not suitable for the synthesis of the 6-unsubstituted species. We therefore developed a new general synthetic pathway for the preparation of these compounds, and the results are reported in this paper.

Results and Discussion

The general strategy we developed for the synthesis of 6-unsubstituted-2,3-dihydro-1,3-oxazin-4-ones involved an α-formylation of the starting amide **3a**−**g** and a cyclization of the α-formyl amide **4a**−**g** with a desired aldehyde giving compounds **5a**−**h** (Scheme 1). The treatment of amide **3a**−**g** with 2 equiv of NaH gave the dianion which was treated with ethyl formate. In all cases studied, no N-formylation products were isolated or detected. α-Formyl amides **4a**−**g** were characterized by a complex ^{1}H NMR spectrum due to the presence in solution of both possible enols and a small amount of the corresponding aldehyde. Cyclization of **4a**−**g** with a desired aldehyde under acidic conditions gave 6-unsubstituted-2,3-dihydro-1,3-oxazin-4-ones **5a**−**h** in good yield (Table 1). This approach represents the first general method for the preparation of this class of compounds.

Scheme 1



When we tried to apply this method to the synthesis of nitro ester **2a**, however, we found that *N*-(2-hydroxyethyl)phenylacetamide (**6a**) did not undergo the α-formylation reaction even after the protection of the hydroxyl group of the ethanolamine moiety. In all the products isolated from this reaction, the ethanolamide system was modified (formation of oxazoline ring, loss of the ethanolamine moiety). We decided to protect all of the side chain with a group that could be useful in the next steps of the synthesis. Among all the protecting groups considered, we decided to mask the ethanolamine moiety as a 1,3-oxazolidine system. We speculated that 3-acyl-1,3-oxazolidine (**8a**) might rearrange under acidic conditions to the more stable 2,3-dihydro-1,3-oxazin-4-one

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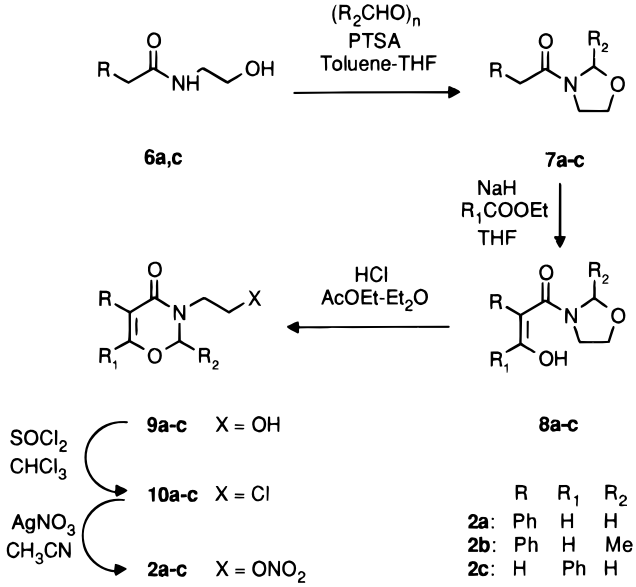
Table 1. Formylation of Amides 3 and Preparation of 2,3-Dihydro-1,3-oxazin-4-ones 5a−h

compd	R	**4**, yield (%)	**5**, yield (%)	R_1
a	nPr	48	71	H
b	iPr	75	63	H
c	cPr	71	86	H
d	cHex	84	58	H
e	Ph	70	56	H
f	CH_{2Ph}	52	72	H
g	Hex	53	75	H
h	nPr		65	Me

Scheme 2



(**9a**).[6] Therefore we synthesized **8a** by cyclization of **6a** with paraformaldehyde under acidic conditions and α-formylation (Scheme 2). According to our prediction, **8a** underwent a rearrangement reaction under acidic conditions at room temperature giving **9a**, showing that the 1,3-oxazolidine system is a good protecting group for the α-formylation reaction and that it can be used also as a formaldehyde donor for the rearrangement reaction. Reaction of alcohol **9a** with thionyl chloride gave compound **10a** which was treated with silver nitrate in refluxing acetonitrile[7] to yield the final product **2a**. Using this strategy, we also synthesized compounds **2b** and **2c**, showing that this approach could also be useful for the preparation of 6-substituted-2,3-dihydro-1,3-oxazin-4-ones such as **2c** (R_1 = Ph).

Compounds **2a−c** were totally inactive as anti-ischemic compounds in anesthetized rats[2] (ED_{50} > 100 μg/kg) compared with ITF 296 (ED_{50} = 2.1 μg/Kg). These data, combined with other observations,[8] indicated the fundamental role of the 2*H*-1,3-benzoxazin-4(3*H*)-one system in this class of organic nitrates.

In conclusion, we developed the first synthetic strategy for the synthesis of 6-unsubstituted-2,3-dihydro-1,3-oxazin-4-ones. This strategy was also used, with little modification of the synthetic pathway, for the preparation of new monocyclic organic nitrates such as **2a−c**.

(6) According to semiempirical calculation (AM1), compound **9a** was thermodynamically more stable than **8a** by about 10 Kcal/mol.

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Experimental Section

General. Melting points were determined in glass capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded respectively at 200 and 50.3 MHz. The solutions were dried over Na_2SO_4, and the solvent was removed under reduced pressure. All the compounds were purified by flash chromatography on silica gel 60 (230−400 mesh ASTM) (E. Merck & Co) using *n*-hexane−ethyl acetate (H−E) and $CHCl_3$−acetone (C−A) as eluent systems.

General Procedure for the Synthesis of α-Formyl Amide (4a−g). A solution of amide **3** (20 mmol) in THF (65 mL) was slowly added to a suspension of NaH (1.15 g, 48 mmol) in THF (65 mL). The mixture was stirred at room temperature for 30 min, then ethyl formate (8,1 mL, 100 mmol) was added, and the reaction mixture was stirred overnight at room temperature. After evaporation of the solvent at low temperature, the crude product was dissolved in aqueous NaOH (1 N) and AcOEt. The phases were separated, and the aqueous phase was acidified with aqueous HCl (1 N) and extracted with AcOEt. The crude product was purified to give pure **4**.

***N*-Propyl-3-hydroxy-2-phenylprop-2-enamide (4a)**: R_f = 0.40 (H−E 8:2); mp 81−82 °C (hexane); IR (cm^{-1}, KBr) 1720, 1640, 1630, 1610; ^1H NMR (DMSO-d_6) δ 7.45−7.10 (m, 6H), 3.10 (m, 2H), 1.48 (m, 2H), 0.87 (t, 3H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.35; H, 7.32; N, 6.67.

***N*-Isopropyl-3-hydroxy-2-phenylprop-2-enamide (4b)**: R_f = 0.40 (H−E 8:2); mp 45−46 °C (hexane); IR (cm^{-1}, KBr) 1720, 1635, 1605, 1590; ^1H NMR (DMSO-d_6) δ 8.31 (s, 1H), 7.28 (d, 2H), 7.06 (t, 2H), 6.83 (t, 1H), 3.95 (m, 1H), 1.10 (d, 6H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.43; H, 7.27; N, 6.69.

***N*-Cyclopropyl-3-hydroxy-2-phenylprop-2-enamide (4c)**: R_f = 0.35 (H−E 8:2); mp 89−91 °C (hexane); IR (cm^{-1}, KBr) 1725, 1640, 1630, 1610; ^1H NMR (DMSO-d_6) δ 7.45−7.20 (m, 6H), 2.79 (m, 1H), 0.75−0.40 (m, 4H). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.78; H, 6.49; N, 6.77.

***N*-Cyclohexyl-3-hydroxy-2-phenylprop-2-enamide (4d)**: R_f = 0.45 (H−E 9:1); mp 80−81 °C (hexane); IR (cm^{-1}, KBr) 1720, 1625, 1610, 1600; ^1H NMR (DMSO-d_6) δ 7.50−7.22 (m, 5H), 7.19 (bs, 1H), 6.85 (d, 1H), 3.77 (m, 1H), 1.93−1.44 (m, 5H), 1.44−0.96 (m, 5H). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.34; H, 7.74; N, 5.65.

***N*-Phenyl-3-hydroxy-2-phenylprop-2-enamide (4e)**: R_f = 0.30 (H−E 9:1); oil; IR (cm^{-1}, neat) 1725, 1640, 1605, 1595; ^1H NMR (DMSO-d_6) δ 7.85−6.95 (m, 11H). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.43; H, 5.46; N, 5.71.

***N*-Benzyl-3-hydroxy-2-phenylprop-2-enamide (4f)**: R_f = 0.30 (H−E 8:2); 91−93 °C (hexane); IR (cm^{-1}, KBr) 1725, 1640, 1625, 1590; ^1H NMR (DMSO-d_6) δ 7.50−7.20 (m, 11H), 4.39 (m, 2H). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.97; N, 5.53. Found: C, 75.75; H, 6.06; N, 5.38.

***N*-Hexyl-3-hydroxy-2-phenylprop-2-enamide (4g)**: R_f = 0.50 (H−E 9:1); 59−61 °C (hexane); IR (cm^{-1}, KBr) 1720, 1645, 1620, 1600; ^1H NMR (DMSO-d_6) δ 7.50−7.20 (m, 6H), 3.15 (m, 2H), 1.46 (m, 2H), 1.27 (m, 6H), 0.90 (t, 3H). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.67. Found: C, 72.69; H, 8.63; N, 5.59.

General Procedure for the Synthesis of 2,3-Dihydro-1,3-oxazin-4-ones (5a−h). A 2 N solution of HCl in Et_2O (10 mL, 20 mmol) was added to a mixture of **4** (10 mmol) and paraformaldehyde or paraldehyde (20−100 mmol) in $CHCl_3$ (50 mL). Then the mixture was stirred for 24−48 h at room temperature. The solid was filtered off, and after evaporation of the solvent, the crude product was purified to give pure **5**.

5-Phenyl-3-propyl-2,3-dihydro-1,3-oxazin-4-one (5a): R_f = 0.30 (H−E 8:2); oil; IR (cm^{-1}, neat) 1665, 1610; ^1H NMR (DMSO-d_6) δ 7.63 (s, 1H), 7.53−7.25 (m, 5H), 5.28 (s, 2H), 3.36 (m, 2H), 1.54 (m, 2H), 0.88 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 162.1, 154.9, 133.3, 128.5, 128.2, 127.2, 116.5, 70.7, 45.5, 21.6, 11.5. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.73; H, 6.95; N, 6.29.

5-Phenyl-3-isopropyl-2,3-dihydro-1,3-oxazin-4-one (5b): R_f = 0.35 (H−E 8:2); mp 71−72 °C (hexane); IR (cm^{-1}, KBr) 1655, 1615, 1605; ^1H NMR (DMSO-d_6) δ 7.62 (s, 1H), 7.54−7.25 (m, 5H), 5.26 (s, 2H), 4.59 (m, 1H), 0.62 (d, 6H); ^{13}C NMR (DMSO-d_6) δ 161.6, 154.8, 133.4, 128.6, 128.2, 127.2, 116.7, 74.2, 42.9, 20.3. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.14; H, 7.05; N, 6.39.

5-Phenyl-3-cyclopropyl-2,3-dihydro-1,3-oxazin-4-one (5c): R_f = 0.30 (H−E 7:3); mp 91−93 °C (hexane); IR (cm^{-1}, KBr) 1665, 1640, 1600; ^1H NMR (DMSO-d_6) δ 7.60 (s, 1H), 7.51 (m, 2H), 7.41−7.26 (m, 3H), 5.21 (s, 2H), 2.62 (m, 1H), 0.85-0.63 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 163.9, 155.1, 133.2, 128.7, 128.1, 127.23, 116.3, 79.4, 26.6, 7.1. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.18; N, 6.59.

5-Phenyl-3-cyclohexyl-2,3-dihydro-1,3-oxazin-4-one (5d): R_f = 0.40 (H−E 8:2); mp 94−96 °C (hexane); IR (cm^{-1}, KBr) 1640, 1620, 1605; ^1H NMR (DMSO-d_6) δ 7.61 (s, 1H), 7.53−7.24 (m, 5H), 5.25 (s, 2H), 4.18 (m, 1H), 1.83−1.03 (m, 10H); ^{13}C NMR (DMSO-d$_6$) δ 161.6, 154.8, 133.4, 128.6, 128.2, 127.2, 116.8, 74.8, 50.9, 30.3, 25.7, 25.1. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.86; H, 7.51; N, 5.39.

3,5-Diphenyl-2,3-dihydro-1,3-oxazin-4-one (5e): R_f = 0.35 (H−E 8:2); mp 141−144 °C (hexane); IR (cm^{-1}, KBr) 1660, 1620, 1600; ^1H NMR (DMSO-d_6) δ 7.82 (s, 1H), 7.58−7.25 (m, 10H), 5.69 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 161.7, 156.0, 139.5, 133.0, 129.1, 128.8, 128.3, 127.5, 126.4, 125.4, 116.7, 80.4. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.24; H, 5.05; N, 5.39.

5-Phenyl-3-benzyl-2,3-dihydro-1,3-oxazin-4-one (5f): R_f = 0.25 (H−E 8:2); mp 83−85 °C; IR (cm^{-1}, KBr) 1660, 1640, 1600; ^1H NMR (DMSO-d_6) δ 7.67 (s, 1H), 7.54 (m, 2H), 7.42−7.26 (m, 8H), 5.31 (s, 2H), 4.66 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 162.2, 155.2, 137.8, 133.1, 128.9, 128.6, 128.2, 127.7, 127.5, 127.3, 116.4, 78.6, 47.1. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.70; N, 5.28. Found: C, 76.77; H, 5.58; N, 5.19.

5-Phenyl-3-hexyl-2,3-dihydro-1,3-oxazin-4-one (5g): R_f = 0.40 (H−E 8:2); oil; IR (cm^{-1}, neat) 1660, 1640, 1600; ^1H NMR (DMSO-d_6) δ 7.62 (s, 1H), 7.50 (m, 2H), 7.39−7.24 (m, 3H), 5.27 (s, 2H), 3.40 (m, 2H), 1.51 (m, 2H), 1.29 (m, 6H), 0.88 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 162.0, 154.8, 133.3, 128.5, 128.2, 127.2, 116.5, 78.6, 43.8, 31.2, 28.2, 26.2, 22.3, 14.2. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.97; H, 8.24; N, 5.28.

2-Methyl-5-phenyl-3-propyl-2,3-dihydro-1,3-oxazin-4-one (5h): R_f = 0.35 (H−E 8:2); oil; IR (cm^{-1}, neat) 1660, 1645, 1610; ^1H NMR (DMSO-d_6) δ 7.48 (m, 2H), 7.46 (s, 1H), 7.32 (m, 3H), 5.59 (q, 1H), 3.33 (m, 2H), 1.58 (d, 3H), 1.54 (m, 2H), 0.87 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 161.3, 152.4, 133.4, 128.5, 128.1, 127.1, 115.2, 85.4, 43.9, 21.7, 18.1, 11.5. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.65; H, 7.59; N, 6.16.

General Procedure for the Synthesis of 3-Acyl-1,3-oxazolidines 7a−c. A suspension of paraformaldehyde or paraldehyde (80 mmol), N-(2-hydroxyethyl) amide **6**[9] (20 mmol), and *p*-toluenesulfonic acid (380 mg, 2 mmol) in toluene−THF 2:1 (60 mL) was refluxed for 1 h. The solid was filtered off, and the organic phase was washed with aqueous NaOH and water and finally dried. The crude product was purified to give pure **7**. ^1H NMR spectra of compounds **7a−c** are characterized by two sets of peaks due to the configurational isomers of the secondary amide.

3-(Phenylacetyl)-1,3-oxazolidine (7a): yield 80%; R_f = 0.30 (C-A 9:1); oil; ^1H NMR (DMSO-d_6) δ 7.28 (m, 5H), 4.99 (s, 0.8H), 4.83 (s, 1.2H), 4.04 (t, 1.2H), 3.98 (t, 0.8H), 3.69 (s, 1.2H), 3.60 (s, 0.8H), 3.59 (t, 1.2 H), 3.40 (t, 0.8H). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.85; H, 6.81; N, 7.25.

2-Methyl-3-(phenylacetyl)-1,3-oxazolidine (7b): yield 52%; R_f = 0.35 (C-A 9:1); oil; ^1H NMR (DMSO-d_6) δ 7.28 (m, 5H), 5.66 (q, 0.2H), 5.29 (q, 0.8H), 4.10−3.10 (m, 6H), 1.34 (d, 0.6H), 1.31 (d, 2.4H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 74.58; H, 7.82; N, 7.25. Found: C, 74.76; H, 7.72; N, 7.31.

3-Acetyl-1,3-oxazolidine (7c): yield 97%; R_f = 0.30 (C−A 8:2); oil; ^1H NMR (DMSO-d_6) δ 4.89 (s, 0.7H), 4.79 (s, 1.3H), 4.07 (t, 0.7H), 3.99 (t, 1.3H), 3.51 (t, 1.3H), 3.40 (t, 0.7H), 2.02 (s, 1.9H), 1.99 (s, 1.1H). Anal. Calcd for $C_5H_9NO_2$: C, 52.11; H, 7.88; N, 12.17. Found: C, 52.01; H, 7.93; N, 12.09.

General Procedure for the Synthesis of 3-(3-Hydroxyprop-2-enoyl)-1,3-oxazolidines 8a−c. A solution of **7** (20 mmol) in THF (65 mL) was slowly added to a suspension of NaH (530 mg, 22 mmol) in THF (65 mL) followed by ethyl formate (**8a** and **8b**) or ethyl benzoate (**8c**) (100 mmol). Then the reaction mixture was refluxed for 5 h. After evaporation of the solvent, the crude product was dissolved in aqueous HCl (1 N) and extracted with AcOEt. The crude material was purified to give pure **8**.

3-(3-Hydroxy-2-phenylprop-2-enoyl)-1,3-oxazolidine (8a): yield 81%; R_f = 0.35 (C−A 9:1); oil; ^1H NMR (DMSO-d_6) δ 7.40−7.10 (m, 6H), 4.60 (m, 2H), 4.00−3.00 (m, 4H). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.33; H, 5.71; N, 6.13.

2-Methyl-3-(3-hydroxy-2-phenylprop-2-enoyl)-1,3-oxazolidine (8b): yield 76%; R_f = 0.40 (C-A 9:1); oil; ^1H NMR (DMSO-d_6) δ 7.50−7.10 (m, 6H), 5.40−5.20 (m, 1H), 4.10−3.20 (m, 4H), 1.40−1.20 (m, 3H). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 67.50; H, 6.54; N, 6.06. Found: C, 67.42; H, 6.41; N, 6.01.

3-(3-Hydroxy-3-phenylprop-2-enoyl)-1,3-oxazolidine (8c): yield 38%; R_f = 0.40 (C−A 8:2); mp 73−78 °C (Et_2O); ^1H NMR (DMSO-d_6) δ 7.81 (d, 2H), 7.50 (m, 3H), 6.10 (m, 1H), 5.10−4.70 (m, 2H), 4.10−3.00 (m, 4H). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.53; H, 5.82; N, 6.26.

General Procedure for the Synthesis of 2,3-Dihydro-3-(2-hydroxyethyl)-1,3-oxazin-4-one (9a−c). A 2 N solution of HCl in ethyl ether (10 mL, 20 mmol) was added to a solution of **8** (10 mmol) in AcOEt (50 mL). Then the mixture was stirred for 8−24 h at room temperature. After evaporation of the solvent, the crude product was purified to give pure **9**.

2,3-Dihydro-3-(2-hydroxyethyl)-5-phenyl-1,3-oxazin-4-one (9a): yield 40%; R_f = 0.30 (H−E 1:1); oil; ^1H NMR (DMSO-d_6) δ 7.63 (s, 1H), 7.50 (d, 2H), 7.35 (m, 3H), 5.31 (s, 2H), 3.52 (m, 4H). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.85; H, 5.87; N, 6.43.

2,3-Dihydro-3-(2-hydroxyethyl)-2-methyl-5-phenyl-1,3-oxazin-4-one (9b): yield 36%; R_f = 0.40 (H−E 1:1); oil; ^1H NMR (DMSO-d_6) δ 7.50 (m, 3H), 7.31 (m, 3H), 5.62 (q, 1H), 3.68 (m, 1H), 3.57 (m, 2H), 3.31 (m, 1H), 1.64 (d, 3H). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 67.50; H, 6.54; N, 6.06. Found: C, 67.65; H, 6.71; N, 6.12.

2,3-Dihydro-3-(2-hydroxyethyl)-6-phenyl-1,3-oxazin-4-one (9c): yield 35%; R_f = 0.25 (H−E 1:1); mp 97−101 °C (Et_2O); ^1H NMR (DMSO-d_6) δ 7.79 (d, 2H), 7.50 (m, 3H), 6.07 (s, 1H), 5.39 (s, 2H), 3.50 (m, 4H). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.82; H, 5.92; N, 6.16.

General Procedure for the Synthesis of 2,3-Dihydro-3-(2-chloroethyl)-1,3-oxazin-4-one (10a−c). Thionyl chloride (700 μL, 9.6 mmol) was slowly added at 0 °C to a solution of **9** (8 mmol) in $CHCl_3$ (40 mL), and the solution was stirred at room temperature for 3 h. The solvent was removed, and the crude product was dissolved in fresh $CHCl_3$ (50 mL) and evaporated to dryness three times. Purification of the crude product gave pure **10**.

2,3-Dihydro-3-(2-chloroethyl)-5-phenyl-1,3-oxazin-4-one (10a): yield 92%; R_f = 0.30 (H−E); oil; ^1H NMR (DMSO-d_6) δ 7.63 (s, 1H), 7.50 (d, 2H), 7.35 (m, 3H), 5.33 (s, 1H), 3.79 (s, 4H). Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; Cl, 14.92; N, 5.89. Found: C, 60.35; H, 5.17; Cl, 14.73; N, 5.77.

2,3-Dihydro-3-(2-chloroethyl)-2-methyl-5-phenyl-1,3-oxazin-4-one (10b): yield 96%; R_f = 0.40 (H−E); oil; ^1H NMR (DMSO-d_6) δ 7.57 (s, 1H), 7.50 (d, 2H), 7.33 (m, 3H), 5.80 (q, 1H), 3.90 (m, 1H), 3.79 (m, 2H), 3.55 (m, 1H), 1.64 (d, 3H). Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; Cl, 14.09; N, 5.57. Found: C, 62.36; H, 5.47; Cl, 14.25; N, 5.67.

2,3-Dihydro-3-(2-chloroethyl)-6-phenyl-1,3-oxazin-4-one (10c): yield 86%; R_f = 0.35 (H−E); mp 124−127 °C (Et_2O);

(9) Prepared by mixing the corresponding ethyl esters and ethanolamine at 70 °C for several hours.

^{1}H NMR (DMSO-d_6) δ 7.81 (d, 2H), 7.54 (m, 3H), 6.04 (s, 1H), 5.38 (s, 2H), 3.80 (s, 4H). Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; Cl, 14.92; N, 5.89. Found: C, 60.46; H, 5.07; Cl, 14.68; N, 5.78.

General Procedure for the Synthesis of 2,3-Dihydro-3-(2-(nitrooxy)ethyl)-1,3-oxazin-4-ones 2a−c. A solution of **10** (5 mmol) and silver nitrate (3.4 g, 20 mmol) in acetonitrile (13 mL) was refluxed for 2 h. Then the salts were filtered off, and the solvent was evaporated under reduced pressure. The crude product was purified giving pure **2a**−**c**.

2,3-Dihydro-3-(2-(nitrooxy)ethyl)-5-phenyl-1,3-oxazin-4-one (2a): yield 32%; R_f = 0.25 (H−E 8:2); oil; IR (cm^{-1}, neat) 1640, 1630, 1600, 1280; ^{1}H NMR (DMSO-d_6) δ 7.68 (s, 1H), 7.52−7.25 (m, 5H), 5.34 (s, 2H), 4.69 (m, 2H), 3.80 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 162.7, 155.5, 133.0, 128.5, 128.2, 127.3, 116.1, 78.9, 71.9, 41.4. Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.10; H, 4.72; N, 10.30.

2,3-Dihydro-3-(2-(nitrooxy)ethyl)-2-methyl-5-phenyl-1,3-oxazin-4-one (2b): yield 66%; R_f = 0.35 (H−E 8:2); mp 48−50 °C (Et_2O); IR (cm^{-1}, KBr) 1660, 1630, 1610, 1275; ^{1}H NMR (DMSO-d_6) δ 7.55 (s, 1H), 7.52−7.26 (m, 5H), 5.66 (q, 1H), 4.70 (m, 2H), 3.79 (m, 2H), 1.62 (d, 3H); ^{13}C NMR (DMSO-d_6) δ 162.2, 153.4, 133.1, 128.5, 128.2, 127.2, 114.9, 85.7, 71.7, 39.7, 18.1. Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.42; H, 5.01; N, 9.98.

2,3-Dihydro-3-(2-(nitrooxy)ethyl)-6-phenyl-1,3-oxazin-4-one (2c): yield 77%; R_f = 0.30 (H−E 7:3); mp 100−102 °C (Et_2O); IR (cm^{-1}, KBr) 1651, 1632, 1610, 1285; ^{1}H NMR (DMSO-d_6) δ 6.09 (s, 1H), 7.84−7.44 (m, 5H), 5.41 (s, 2H), 4.68 (m, 2H), 3.77 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 164.4, 163.8, 131.7, 131.3, 129.1, 126.4, 97.8, 78.9, 71.9, 40.9. Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.34; H, 4.61; N, 10.46.

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