Synthesis of N_4-Substituted[1,3,4]oxadiazinan-2-ones Derived from Norephedrine

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[1,3,4]-Oxadiazinan-2-ones bearing substitution at the N_4-position have been synthesized from norephedrine in good yield *via N*-alkylation, nitrosation, reduction and cyclization.

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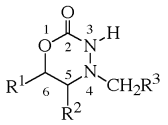
We have recently reported on the synthesis and conformational analysis of [1,3,4]-oxadiazinan-2-ones (**1**) derived from (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine [1,2]. In the course of this study, it was discovered that the pseudoephedrine based N_3-acylated [1,3,4]-oxadiazinan-2-ones are involved in complex conformational equilibria as indicated by line broadening observed in ^1H and ^{13}C NMR spectra. Based on these results, we became interested in developing other [1,3,4]-oxadiazinan-2-ones to expand our understanding of the conformational properties of this heterocycle family. In this regard, ephedrine and pseudoephedrine have limited utility in creating diverse [1,3,4]-oxadiazinan-2-ones because the N_4-position is substituted with a methyl group.



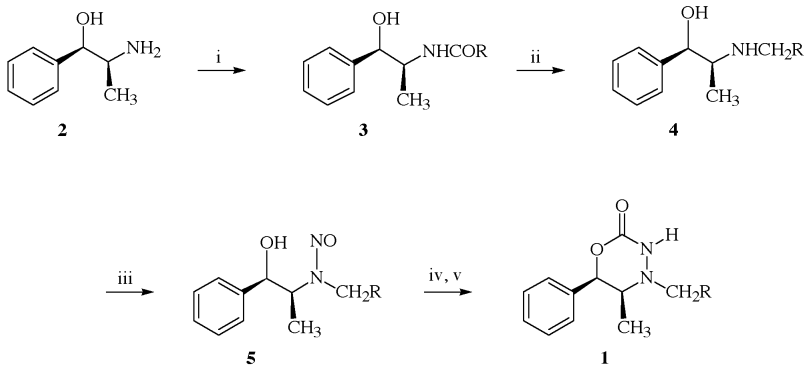
[1,3,4]-oxadiazinan-2-one (**1**)

Figure 1

In contrast, norephedrine serves as an excellent template for creating new [1,3,4]-oxadiazinan-2-ones due to the absence of substitution at nitrogen.

Norephedrine (**2**) was treated with a variety of acyl chlorides to afford the corresponding norephedrine amides **3a-f** in high yield after recrystallization (Scheme **1**) [3]. The amides were reduced with diborane generated *in situ* from $NaBH_4$ and I_2 to afford the β-aminoalcohols (**4a-f**) in high yield [4]. Subsequent *N*-nitrosation of the amine derivatives gave the desired *N*-substituted-*N*-nitrosamines **5a-f** as mixtures of diastereomeric *E*- and *Z*-rotamers. *It should be noted that the* N-*nitrosamines are potentially carcinogenic agents and should be handled with great care* [5]. For the sake of characterization of **5a-f**, the *E*-rotamer was determined to be the dominant isomer by ^1H NMR spectroscopy [6]. Ultimately, the ratio of diastereomeric *N*-nitrosamines is unimportant as this stereochemical element is removed in the subsequent reduction. Reduction of the *N*-nitrosamines was accomplished with lithium aluminum hydride [7]. This process afforded the corresponding β-hydrazino-alcohols in quantitative conversion**.** The hydrazine derivatives decomposed readily at room temperature as determined by ^1H NMR and were

Scheme 1



a) R = CH_2CH_3**; b**) R = CH_2Ph**; c**) R = $C(CH_3)_3$**; d**) R = CH_2OCH_3
e) R = CH_2OPh; **f**) R = CH_2OCH_2Ph

Table 1

entry	R	amide (**3**)	amine (**4**)	Yield (%) nitrosamine (**5**)	oxadiazinan-2-one
(**1**)					
1a	$-CH_2CH_3$	96	99	96	55
1b	$-CH_2Ph$	84	87	99	60
1c	$-C(CH_3)_3$	96	89	99	69
1d	$-CH_2OCH_3$	89	94	69	57
1e	$-CH_2OPh$	94	81	97	80
1f	$-CH_2OCH_2Ph$	88	78	84	85

cyclized without purification with 1,1'-carbonyldiimidazole (CDI) to afford [1,3,4]-oxadiazinan-2-ones **1a-f**. The collected results are summarized in Table 1.

In summary, we have prepared a series of [1,3,4]-oxadiazinan-2-ones from commercially available norephedrine in good yield. The formation of the heterocycle occurs by a reaction sequence of alkylation, nitrosation, reduction and cyclization. Studies are underway involving the application of these heterocycles as chiral auxiliaries.

EXPERIMENTAL

General Remarks.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from a potassium/sodium amalgam with benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Reactions were run under a nitrogen atmosphere. Lithium aluminum hydride was purchased from Aldrich chemicals. Flash chromatography was conducted with silica gel purchased from Selecto scientific (32-63 mesh). All ^1H and ^{13}C NMR spectra were recorded at 25 °C on a Varian spectrometer in $CDCl_3$ operating at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale) relative to tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm), and coupling constants (*J* values) are listed in hertz (Hz). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Gas chromatography was performed on a Hewlett-Packard Instrument (G1800A/GCD) with an ionization voltage of 70 eV; peaks are reported as *m/z* (% intensity relative to the base peak). Elemental analyses were conducted by either Galbraith Laboratories, Inc. Knoxville, TN or by the Microanalytical Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign.

General Procedure for the Preparation of the Amide Derivative **3**.

In a 1 L round bottom flask was placed (1*R*,2*S*)-norephedrine (5.0 g, 33 mmol) and CH_2Cl_2 (50 mL). To this reaction mixture was added aqueous NaOH (22.0 mL, 3 *M*, 66 mmol) followed by the addition of acyl chloride (35 mmol). The resulting mixture was stirred for 16 hours and treated with HCl (3 *M*) until the solution became acidic. The solution was then extracted with CH_2Cl_2 (3 x 75 mL), washed with an aqueous saturated solution of brine (100 mL), dried (Na_2SO_4) and the solvents were removed by rotary evaporation. This process afforded a white solid, which was recrystallized.

(1*R*,2*S*)-N-(2-Hydroxy-1-methyl-2-phenylethyl)-propanamide (**3a**).

Isolated product recrystallized with EtOAc-hexanes (3:1) to yield **3a** in 96% yield as white crystals. Mp: 107-108 °C; R_f = 0.56 (EtOAc). ^1H NMR ($CDCl_3$): δ 1.02 (d, 3H, J = 7.0 Hz), 1.17 (t, 2H, J = 7.7 Hz), 2.23 (q, 2H, J = 7.7 Hz), 3.41 (bs, 1H), 4.35 (dq, 1H, J = 7.1, 2.9 Hz), 4.85 (d, 1H, J = 2.6 Hz), 5.59 (bs, 1H), 7.28-7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 10.1, 14.6, 29.9, 51.2, 76.7, 126.5, 127.6, 128.3, 141.1, 174.9. IR (KBr): 3310, 2992, 1648 cm^{-1}. EI-MS, m/z (%): 132 (1), 83 (100), 77 (15).

Anal. Calc'd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.25; H, 8.22; N, 6.81.

(1*R*,2*S*)-N-(2-Hydroxy-1-methyl-2-phenylethyl)-phenylacetamide (**3b**).

Isolated product was recrystallized with EtOAc/hexanes (3:1) to yield the title compound in 84% yield as hygroscopic, feathery crystals. Mp: 138-139 °C; R_f = 0.63 (EtOAc/hexanes, 1:1). ^1H NMR ($CDCl_3$): δ 0.94 (d, 3H, J = 7.0 Hz), 3.58 (dd, 2H, J = 15.8, 7.0 Hz), 4.34 (quintet, 1H, J = 7.0), 4.78 (d, 1H, J = 2.9 Hz), 5.40 (bs, 1H), 7.19-7.37 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 15.3, 44.0, 51.3, 76.9, 126.6, 127.7, 127.9, 128.4, 129.3, 129.6, 134.8, 140.5, 172.1. IR (KBr): 3303, 3065, 1654 cm^{-1}. EI-MS, m/z (%): 237 (1, M^+), 105 (45), 56 (100).

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.43; H, 6.76; N, 4.89.

(1*R*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-trimethylacetamide (**3c**).

The title compound **3c** was obtained in 96% yield after recrystallization from ethyl acetate and hexanes. Mp: 82-84 °C; R_f = 0.12 (EtOAc/hexanes, 1:1). ^1H NMR ($CDCl_3$): δ 1.02 (d, 3H, *J* = 7.0 Hz), 1.18 (s, 9H), 4.00 (bs, 1H), 4.32 (m, 1H), 4.80 (d, 1H, *J* = 2.4 Hz), 5.68 (d, 1H, *J* = 6.6 Hz), 7.27-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.9, 27.1, 38.3, 50.4, 75.6, 125.9, 126.9, 127.7, 141.0, 178.7. IR (KBr): 3400-3100, 3297, 1652, 1547, 1117, 759, 704 cm^{-1}. EI-MS, *m/z* (%): 132 (6), 117 (100), 105 (3), 99 (75).

Anal. Calc'd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.35; H, 9.01; N, 6.17.

(1*R*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-methoxyacetamide (**3d**).

Recrystalization with EtOAc and hexanes yielded (**3d**) as a white crystalline solid in 89% yield. Mp: 84-86 °C; R_f = 0.12 (EtOAc/hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 1.06 (d, 3H, *J* = 7.2 Hz), 3.21 (bs, 1H), 3.40 (s, 3H), 3.92 (s, 2H), 4.31-4.39 (m, 1H), 4.89 (d, 1H, *J* = 2.9 Hz), 6.62 (bs, 1H), 7.27-7.34 (m, 1H), 7.35-7.36 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.2, 50.3, 59.1, 71.7, 76.0, 126.2, 127.4, 127.4, 140.8, 169.9. IR (KBr): 3400-3100, 3297, 1652, 1547, 1117, 759, 704 cm^{-1}. EI-MS, *m/z* (%): 175(25), 132 (6), 117 (100), 99 (75).

Anal. Calc'd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.51; H, 7.67; N, 6.39.

(1*R*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-phenoxyacetamide (**3e**).

The product was recrystallized from methylene chloride and hexanes to afford the title compound in 94% yield. Mp: 125-127 °C; R_f = 0.42 (EtOAc:hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 1.05 (d, 3H, *J* = 6.6 Hz), 2.52 (bs, 1H), 4.39-4.44 (m, 1H), 4.51 (s, 2H), 4.89 (d, 1H, *J* = 2.9 Hz), 6.76 (d, 1H, *J* = 8.1 Hz), 6.90-6.92 (m, 2H), 7.04 (t, 1H, *J* = 7.3 Hz), 7.26-7.36 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 14.1, 50.2, 67.0, 75.5, 114.6, 122.0, 126.1, 127.5, 128.1, 129.6, 140.5, 156.9, 168.3. IR (KBr): 3350-3100 (bs), 3326, 3066, 2993, 1654, 1244, 758, 704 cm^{-1}. HRMS Calc'd for $C_{17}H_{19}NO_3$, 285.1365. Found, 285.1359.

Anal. Calc'd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.43; H, 6.67; N, 5.12.

(1*R*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-benzyloxyacetamide (**3f**).

This process afforded a white solid which was recrystallized with EtOAc-hexanes to yield the title compound in 88% yield as a white solid. Mp: 71-72 °C; R_f = 0.42 (EtOAc:hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 0.96 (d, 3H, *J* = 7.0 Hz), 3.29 (bs, 1H), 3.91 (s, 2H), 4.24-4.26 (m, 1H), 4.46 (s, 2H), 4.78 (d, 1H, *J* = 2.9 Hz), 6.66 (d, 1H, *J* = 7.7 Hz), 7.19-7.30 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.2, 50.1, 69.1, 73.3, 75.7, 126.1, 127.3, 127.7, 128.0, 128.4, 136.6, 140.8, 169.7. IR (KBr): 3300, 2938, 1649, 1098, 757, 700 cm^{-1}.

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found C, 72.19; H, 7.11; N, 4.85.

General Procedure for the Preparation of the Amine Derivative **4**.

Into a 3-necked 5 L nitrogen purged round bottom flask equipped with a reflux condenser was placed $NaBH_4$ (11.4 g, 301 mmol) and THF (250 mL). To this stirred mixture was added the norephedrine amide (**3**) (126 mmol). A 250 mL addition funnel equipped with a pressure equalizing arm was filled with iodine (36.7 g, 144 mmol) and THF (250 mL) which was then attached to the 3-necked round bottom flask. The iodine mixture was added over a period of 30 minutes followed by heating of the resulting mixture to reflux. The mixture was maintained at reflux for 15 hours and was then cooled to room temperature followed by cautious addition of methanol (100 mL) to destroy any remaining $NaBH_4$. The solvent was then removed after all signs of $NaBH_4$ activity were gone. The resulting white solid was stirred in aqueous KOH (100 mL, 2 *M*) for 1 hour. The resulting mixture was then extracted with EtOAc (3 x 75 mL), washed with aqueous brine, dried (Na_2SO_4) and the solvent was removed.

(*1*R,2*S*)-2-Amino-*N*-propyl-1-phenyl-1-propanol (**4a**).

The resulting white solid was recrystallized with EtOAc-hexanes (1:1) to produce **4a** in 99% yield: R_f = 0.28 (1:1, EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 0.83 (d, 3H, *J* = 6.6 Hz), 0.94 (t, 3H, *J* = 7.5 Hz), 1.49-1.59 (m, 2H), 2.62-2.75 (m, 2H), 2.91-2.96 (m, 1H), 4.79 (d, 1H, *J* = 3.7 Hz), 7.22-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.7, 14.4, 23.2, 49.0, 58.4, 73.1, 126.0, 126.9, 128.0, 141.6. IR (neat): 3474, 3245, 2969, 1174 cm^{-1}. EI-MS, *m/z* (%): 190 (1), 105 (57), 86 (100), 77 (49). HRMS Calc'd for $C_{12}H_{19}NO$: 194.1545. Found: 194.1540.

(1*R*,2*S*)-2-Amino-*N*-(2-phenylethyl)-1-phenyl-1-propanol (**4b**).

The resulting white solid was recrystallized with EtOAc-hexanes (1:1) to produce the title compound in 87% yield. Mp: 75-77 °C; R_f = 0.33 (EtOAc/hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 0.79 (d, 3H, *J* = 6.6 Hz), 2.73-2.86 (m, 2H), 2.89-3.03 (m, 3H), 4.72 (d, 1H, *J* = 4.0 Hz), 7.18-7.25 (m, 4H), 7.27-7.33 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 14.8, 36.9, 48.6, 58.5, 73.3, 126.3, 126.5, 127.3, 128.3, 128.7, 128.9, 140.0, 141.5. IR (KBr): 3061, 747, 703 cm^{-1}. EI-MS, *m/z* (%): 105 (44), 77 (36), 56 (100).

Anal. Calc'd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.66; H, 8.36; N, 5.57.

(1*R*,2*S*)-2-Amino-*N*-(2,2-dimethylpropyl)-1-phenyl-1-propanol (**4c**).

The title compound was obtained in 89% yield after recrystallization from ethyl acetate and hexanes. R_f = 0.58 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 0.79 (d, 3H, *J* = 6.2 Hz), 0.94 (s, 9H), 2.47 (*AB* spin system, 2H, Δν = 63.7 Hz, *J* = 11.0 Hz), 2.88 (dq, 1H, *J* = 6.6, 4.0 Hz), 4.74 (d, 1H, *J* = 4.0 Hz), 7.23-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.8, 27.5, 31.2, 58.8, 59.3, 72.5, 125.8, 126.7, 127.8, 141.3. IR (KBr): 3416, 2954, 1494, 741, 701 cm^{-1}. HRMS Calc'd for $C_{17}H_{22}NO_2$: 222.1858. Found: 222.1857.

(1*R*,2*S*)-2-Amino-*N*-(2-methoxyethyl)-1-phenyl-1-propanol (**4d**).

The title compound was recovered as a viscous oil. Yield: 94%. Compound **4d**: ^{1}H NMR ($CDCl_3$): δ 0.83 (d, 3H, *J* = 6.6 Hz), 2.43 (bs, 1H), 2.84-2.90 (m, 2H), 2.92-2.98 (m, 2H), 3.37 (s, 3H), 3.54 (d, 2H, *J* = 4.0 Hz), 4.80 (d, 1H, *J* = 3.6 Hz), 7.33-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.2, 46.6, 58.6, 71.9, 72.8, 74.4, 126.0, 127.0, 128.0, 141.3. IR (neat): 306, 1449, 1094, 752, 703 cm^{-1}. HRMS Calc'd for $C_{12}H_{20}NO_2$ (M^+ + H): 210.1494. Found: 210.1498.

(1*R*,2*S*)-2-Amino-*N*-(2-phenoxyethyl)-1-phenyl-1-propanol (**4e**).

The title compound was recrystallized from hexanes and methylene chloride to afford a white solid in 81% yield. Mp = 90-91 °C; R_f = 0.10 (EtOAc/hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 0.86 (d, 3H, *J* = 6.6 Hz), 2.96-3.05 (m, 2H), 3.11-3.16 (m, 1H), 4.06-4.08 (m, 2H), 4.77 (d, 1H, *J* = 4.0 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 6.96 (t, 1H, *J* = 7.3 Hz), 7.23-7.33 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 14.1, 46.0, 58.3, 67.0, 73.4, 114.3, 120.7, 126.0, 126.9, 127.9, 129.3, 141.5, 158.5. IR (KBr): 3340, 3060, 2976, 1598, 1244, 757, 701 cm^{-1}. HRMS Calc'd for $C_{17}H_{22}NO_2$, 272.1651. Found, 272.1650.

Anal. Calc'd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.00; H, 7.88; N, 5.32.

(1*R*,2*S*)-2-Amino-*N*-(2-benzyloxyethyl)-1-phenyl-1-propanol (**4f**).

This process afforded a white waxy solid, which was recrystallized with EtOAc and hexanes (1:1), to yield the title compound in 78% yield. Mp: 35-40 °C (wax); R_f = 0.66 (9:1, chloroform:methanol). ^{1}H NMR ($CDCl_3$): δ 0.83 (d, 3H, *J* = 6.6 Hz), 2.76-2.90 (m, 3H), 3.29 (bs, 1H), 3.54 (t, 2H, *J* = 5.1 Hz), 4.44 (*AB* spin system, 2H, Δν = 6.1 Hz, *J* = 1.5 Hz,), 4.72 (d, 1H, *J* = 4.0), 7.18-7.33 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.0, 46.4, 58.3, 69.3, 72.9, 73.1, 125.9, 126.8, 127.6, 127.7, 127.9, 128.2, 137.9, 141.5. IR (KBr): 3302, 3302, 2936, 1649, 1101, 755, 700 cm^{-1}. HRMS Calc'd for $C_{17}H_{22}NO_2$ (M^+ + H): 286.1807. Found: 286.1807.

General Procedure for the Preparation of the *N*-Nitrosamines **5**.

In a 250 mL round bottom flask equipped with a stir bar was placed the *N*-alkylated norephedrine derivative (124 mmol) and THF (50 mL). An aqueous solution of HCl (52 mL, 2.74 *M*, 143 mmol) was then added followed by the addition of sodium nitrite (9.87 g, 143 mmol) in small portions and then stirred for 24 hours. The cloudy mixture was then diluted with a saturated aqueous solution of $NaHCO_3$ until it became basic. The reaction mixture was then extracted with EtOAc (3 x 60 mL) and washed with a saturated aqueous solution of brine (50 mL). The resulting solution was then dried ($NaSO_4$) followed by the removal of the solvent by rotary evaporation.

(1*R*,2*S*)–2-Amino-*N*-nitroso-*N*-propyl-1-phenyl-1-propanol (**5a**).

This process yielded an orange oil that was determined to be *ca.* 95% pure by the ^{1}H NMR spectrum (~4:1 ratio of the major *E*-rotamer *vs.* the minor *Z*-rotamer. R_f = 0.74 (EtOAc/hexanes, 1:1). Only the major isomer was characterized. ^{1}H NMR ($CDCl_3$): δ 0.80 (t, 3H, *J* = 7.3 Hz), 1.32-1.48 (m, 2H), 1.51 (d, 3H, *J* = 7.0 Hz), 2.76 (bs, 1H), 3.22-3.29 (m, 1H), 3.36-3.44 (m, 1H), 4.31 (quintet, 1H, *J* = 7.0 Hz), 5.11 (d, 1H, *J* = 5.1 Hz), 7.27-7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.2, 14.8, 19.7, 47.2, 65.2, 76.5, 126.3, 128.0, 128.4, 141.0. IR (neat): 3396, 2970, 1453 cm^{-1}. EI-MS, *m/z* (%): 105 (83), 77 (78), 56 (100). HRMS Calc'd for $C_{12}H_{18}N_2O_2$: 223.1447. Found: 223.1441.

(1*R*,2*S*)-2-Amino-*N*-nitroso-*N*-(2-phenylethyl)-1-phenyl-1-propanol (**5b**).

This process gave a yellow oil in nearly quantitative yield. The *N*-nitrosamine **5b** exists as a mixture of *E* and *Z*-rotamers (10:1). Only the major rotamer has been characterized. R_f = 0.80 (EtOAc/hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 1.36 (d, 3H, *J* = 7.0 Hz), 2.64-2.81 (m, 3H), 3.56-3.70 (m, 2H), 4.11-4.21 (m, 1H), 5.00 (d, 1H, *J* = 4.4 Hz), 7.15 (d, 2H, *J* = 6.8 Hz), 7.22-7.35 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 14.1, 32.5, 48.2, 66.1, 74.7, 126.0, 126.4, 127.0, 128.3, 128.7, 128.9, 129.0, 138.5. IR (neat): 3385, 3028, 1453 cm^{-1}. EI-MS, *m/z* (%): 134 (22), 105 (13), 91 (100). HRMS Calc'd for $C_{17}H_{20}N_2O_2$ (M^+ + H): 285.1603. Found: 285.1603.

(1*R*,2*S*)-2-Amino-*N*-(2,2-dimethyl)-*N*-nitroso-1-phenyl-1-propanol (**5c**).

The *N*-nitrosamine was recovered in nearly quantitative yield wherein the rotameric ratio was determined by ^{1}H NMR to be *ca.* 95:5 (*E*:*Z*). ^{1}H NMR ($CDCl_3$): δ 0.85 (s, 9H), 1.60 (d, 3H, *J* = 6.6 Hz), 2.98 (bs, 1H), 3.10 (*AX* spin system, 2H, Δν = 209 Hz, *J* = 13.2 Hz), 4.02 (dq, 1H, *J* = 6.6, 5.1 Hz), 5.21 (dd, 1H, *J* = 5.0, 2.2 Hz), 7.29-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 16.3, 28.1, 34.0, 56.8, 67.0, 76.9, 126.2, 127.6, 128.1, 140.9. IR (neat): 3389, 2959, 1454 cm^{-1}. HRMS Calc'd for $C_{14}H_{23}N_2O_2$ (M^+ + H): 251.1760. Found: 251.1753.

(1*R*,2*S*)-2-Amino-*N*-nitroso-*N*-(2-methoxyethyl)-1-phenyl-1-propanol (**5d**).

This process yielded yellow oil, which was purified by column chromatography on silica gel (EtOAc/hexanes, 35:65, column dimensions = 15.0 x 6.0 cm, to yield **5d** as yellow oil isolated as a 7:1 mixture of *E*- and *Z*-rotamers in 69% yield. R_f = 0.33 (35:65, EtOAc:hexanes). ^{1}H NMR ($CDCl_3$): δ 1.31 (d, 3H, *J* = 6.8 Hz), 3.35 (s, 3H), 3.53-3.59 (m, 2H), 3.67-3.69 (m, 1H), 3.90-3.94 (m, 1H), 4.89-4.90 (m, 1H), 5.20 (bs, 1H), 7.38-7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.9, 44.2, 58.7, 65.7, 68.8, 75.7, 125.8, 127.4, 128.1, 140.9. IR (neat): 3400-3100, 1117, 763**,** 704 cm^{-1}. HRMS Calc'd for $C_{12}H_{19}N_2O_3$ (M^+ + H): 239.1396. Found: 239.1397.

(1*R*,2*S*)-2-Amino-*N*-nitroso-*N*-(2-phenoxyethyl)-1-phenyl-1-propanol (**5e**).

The crude product was obtained in 97% yield ratio of *E*:*Z* rotomers is 8.5:1. ^{1}H NMR ($CDCl_3$): δ 1.50 (d, 3H, *J* = 7.0 Hz), 3.16 (bs, 1H), 3.68-3.74 (m, 1H), 3.91-3.99 (m, 2H), 4.05-4.10 (m, 1H), 4.69 (dq, 1H, *J* = 7.0, 4.4 Hz), 5.21 (d, 1H, *J* = 4.0 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 6.97 (t, 1H, *J* = 7.3 Hz), 7.25-7.41 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 13.9, 44.9, 63.7, 66.1, 76.3, 114.1, 121.3, 126.1, 127.8, 128.3, 129.5, 140.8, 157.7. IR (neat film): 3460, 2943, 1453, 1243, 755, 704 cm^{-1}. HRMS Calc'd for $C_{17}H_{21}N_2O_3$: 301.1552. Found: 301.1551.

(1*R*,2*S*)-2-Amino-*N*-nitroso-*N*-(2-benzyloxyethyl)-1-phenyl-1-propanol (**5f**).

This process afforded an oil which was purified by column chromatography on silica gel (EtOAc:hexanes 6:1, 14 x 6.0 cm) to yield the title compound in 84% yield as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 3H, *J* = 6.7 Hz), 3.53-3.62 (m, 2H), 3.67-3.72 (m, 1H), 3.81-3.87 (m, 1H), 3.98 (bs, 1H), 4.47 (*AB* quartet, 2H, Δν = 23.6 Hz, *J* = 14.7 Hz,), 4.76 (dq, 1H, *J* = 7.0, 3.3 Hz), 5.17 (d, 1H, *J* = 2.9 Hz), 7.25-7.36 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 12.5, 44.6, 65.7, 66.3, 73.2, 75.7, 125.9, 127.4, 127.7, 127.9, 128.1, 128.4, 136.7, 140.7. IR (KBr): 3444, 2987, 1437, 751, 698 cm^{-1}.

Anal. Calc'd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.52; H, 7.06; N, 8.90.

General Procedure for the Preparation of the [1,3,4]-Oxadiazinan-2-ones (**1**).

In a flame-dried, nitrogen purged 5 L, 3-neck round bottom flask fitted with an addition funnel and a condenser was placed lithium aluminum hydride (8.72 g, 230 mmol) and freshly distilled THF (300 mL). The mixture was then heated to reflux. The β-hydroxy-*N*-nitrosamine (77 mmol) was dissolved in freshly distilled THF (250 mL) and transferred to the addition funnel. While the mixture was at reflux the *N*-nitrosamine was added slowly over a period of 30 minutes. Once the addition was completed the reaction mixture remained under reflux for an additional 2 hours. The reaction mixture was then cooled to room temperature followed by the cautious addition of NaOH (6 *M*) until the remaining lithium aluminum hydride was consumed. The resulting mixture was diluted with a saturated aqueous

solution of sodium potassium tartrate (200 mL) and stirred for 45 minutes. The resulting mixture was then extracted with EtOAc (4 x 125 mL), washed with a saturated aqueous solution of brine (100 mL), dried (Na_2SO_4) followed by the removal of the solvent by rotary evaporation. The hydrazine was directly converted into the corresponding oxadiazinone heterocycle derivatives due to the facile decomposition.

In a flame-dried, nitrogen purged 500 mL round bottom flask was placed norephedrine hydrazine (24.0 mmol) and freshly distilled THF (100 mL). To this solution was added *p*-toluenesulfonic acid (5.10 g, 27.0 mmol) as a solid followed by the addition of 1,1'-carbonyldiimidazole (4.30 g, 27.0 mmol). After the addition was completed the resulting mixture was heated to reflux. The reaction mixture was cooled to room temperature after 3 hours followed by the addition of an aqueous saturated solution of sodium bicarbonate (50 mL). The resulting mixture was then extracted with EtOAc (3 x 50 mL) washed with a saturated aqueous solution of brine (50 mL), dried (Na_2SO_4) followed by the removal of solvent by rotary evaporation.

(5*S*,6*R*)-5-Methyl-6-phenyl-4-propyl-[1,3,4]-oxadiazinan-2-one (**1a**).

This process yielded a yellow oil which was purified by column chromatography on silica gel (EtOAc, 5 x 13.5 cm) to yield the title compound (55%) as a white solid. Mp: 114-115 °C; R_f = 0.58 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 0.92 (d, 3H, *J* = 7.1 Hz), 1.00 (t, 3H, *J* = 7.3 Hz), 1.59-1.74 (m, 2H), 2.74-2.81 (m, 1H), 3.05-3.11 (m, 1H), 3.18 (dq, 1H, *J* = 7.0, 3.3 Hz), 5.76 (d, 1H, *J* = 2.9 Hz), 7.21 (bs, 1H), 7.31-7.41 (m, 5H). ^{13}C ($CDCl_3$): δ 11.6, 11.8, 56.0, 61.1, 75.0, 125.3, 127.9, 128.6, 136.7, 152.8. IR (KBr): 3216, 2940, 1701 cm^{-1}. EI-MS, *m/z* (%): 234 (12, M^+), 117 (98), 105 (100).

Anal. Calc'd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.20; H, 7.89; N, 11.97.

(5*S*,6*R*)-5-Methyl-4-(2-phenylethyl)-6-phenyl-[1,3,4]-oxadiazinan-2-one (**1b)**.

This yielded a yellow oil which was purified by column chromatography on silica gel (EtOAc/hexanes, 1:1, R_f = 0.58, column dimensions = 5 x 13.5 cm) to yield **1b** (60 %) as an oil. R_f = 0.58 (EtOAc/hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 0.92 (d, 3H, *J* = 7.0 Hz), 2.86-2.93 (m, 1H), 2.99-3.13 (m, 2H), 3.19 (dq, 1H, *J* = 6.8, 2.9 Hz), 3.33-3.40 (m, 1H), 5.76 (d, 1H, *J* = 3.3 Hz), 6.96 (s, 1H), 7.24-7.39 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 12.0, 34.3, 56.6, 61.2, 75.5, 125.4, 126.8, 128.2, 128.8, 128.9, 129.0, 136.5, 139.1, 152.5. IR (neat): 3236, 3092, 1695 cm^{-1}. EI-MS, m/z (%): 105 (41), 77 (41), 56 (100). HRMS Calc'd: 296.1522. Found: 296.1525.

(5*S*,6*R*)-5-Methyl-4-(2,2-dimethylpropyl)-6-phenyl-[1,3,4]-oxadiazinan-2-one (**1c**).

The title compound was isolated by recrystallization from ethyl acetate and hexanes (69%)**:** Mp = 98-100 °C. ^{1}H NMR ($CDCl_3$): δ 0.92 (d, 3H, *J* = 7.0 Hz), 0.97 (s, 9H), 2.81 (*AB* spin system, 2H, Δν = 104 Hz, *J* = 13.2 Hz), 3.04 (dq, 1H, *J* = 7.0, 3.3 Hz), 5.72 (d, 1H, *J* = 3.3 Hz), 6.45 (s, 1H), 7.29-7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.9, 27.6, 32.8, 59.3, 73.6, 76.3, 125.1, 127.9, 128.5, 136.4, 151.9. IR (neat): 3243, 3065, 2978, 1701, 1599,755, 693 cm^{-1}.

Anal. Calc'd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.60; H, 8.54; N, 10.63.

(5*S*,6*R*)-5-Methyl-4-(2-methoxyethyl)-6-phenyl-[1,3,4]-oxadiazinan-2-one (**1d**).

This process yielded yellow oil, which was purified by column chromatography on silica gel (EtOAc/hexanes, 1:1) column dimensions = 11.0 x 4.8 cm, 90 fractions 3 mL ea. 46–50 contained product) to yield **1d** as yellow oil. Yield: 57%. R_f = 0.12 (EtOAc/ hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 0.95 (d, 3H, *J* = 7.3 Hz), 3.18-3.12 (m, 1H), 3.23-3.29 (m, 1H), 3.32-3.39 (m, 1H), 3.42 (s, 3H), 3.61-3.73 (m, 2H), 5.78 (d, 1H, *J* = 2.8 Hz), 6.89 (s, 1H), 7.32-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.4, 56.2, 58.1, 59.0, 70.4, 75.2, 125.1, 127.8, 128.5, 136.3, 152.0. IR (neat): 3253, 2981, 1699, 1204, 746, 700 cm^{-1}. HRMS Calc'd for $C_{13}H_{19}N_2O_3$ (M^+ + H), 251.1396. Found, 251.1391.

(5*S*,6*R*)-5-Methyl-4-(2-phenoxyethyl)-6-phenyl-[1,3,4]-oxadiazinan-2-one (**1e**).

The heterocycle was purified *via* column chromatography on silica gel (EtOAc/hexanes, 45:55) column dimensions = 15.0 x 6.5 cm) to afford a 85% yield. Mp = 99-100 ∞C; R_f = 0.32 (EtOAc/hexanes, 45:55). ^{1}H NMR ($CDCl_3$): d 0.93 (d, 3H, *J* = 7.0 Hz), 3.34-3.46 (m, 2H), 4.21-4.24 (m, 2H), 5.80 (1H, d, *J* = 2.9 Hz), 6.93-7.00 (m, 3H), 7.24-7.41 (m, 7H), 7.88 (bs, 1H). ^{13}C NMR ($CDCl_3$): d 11.7, 56.1, 57.9, 65.8, 75.2, 114.5, 121.3, 125.1, 127.9, 128.5, 129.6, 136.2, 152.2, 158.2. IR (neat film): 3243, 3065, 1701, 1599, 1244, 755, 693 cm^{-1}. HRMS Calc'd for $C_{18}H_{20}N_2O_3$, 312.1474. Found, 312.1474.

Anal. Calc'd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.04; H, 6.15; N, 9.16.

(5*S*,6*R*)-5-Methyl-4-(2-benzyloxyethyl)-6-phenyl-[1,3,4]-oxadiazinan-2-one (**1f**).

This afforded a vicious yellow oil which was purified by column chromatography on silica gel (EtOAc/hexanes, column dimensions = 15.0 x 6.5 cm) to yield the title compound in 85% yield (2.9 g, 8.8 mmol) as a yellow vicious oil. R_f = 0.26 (EtOAc/hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 0.88 (d, 3H, *J* = 7.0 Hz), 3.20-3.21 (m, 2H), 3.40-3.42 (m, 1H), 3.70-3.74 (m, 2H), 4.54 (s, 2H), 5.72 (s, 1H), 7.24-7.35 (m, 10H), 8.18 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 11.0, 54.9, 57.7, 67.5, 72.8, 74.3, 124.6, 127.2, 127.3, 127.4, 127.9, 127.9, 136.0, 137.3, 152.0. IR (neat): 3242, 2983, 1694, 1121, 749, 699 cm^{-1}. HRMS Calc'd for $C_{19}H_{22}N_2O_2$, 326.1630. Found 326.1627.

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