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Synthesis of 3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones Employing a Metal Hydride and Diethyl Carbonate: An Alternative Cyclization Method over 1,1′-Carbonyldiimidazole

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ABSTRACT

A series of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones have been synthesized from valine, leucine, ephedrine, and norephedrine. The synthesis is accomplished through a process of nitrosation, reduction, and cyclization. The cyclization protocol employed involves the use of a metal hydride (LiH or NaH) and diethyl carbonate rather than 1,1′-carbonyldiimidazole.

Key Words: 3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones cyclization; 1,1′-Diethylcarbonate; β-Amino alcohols; Oxadiazinone.

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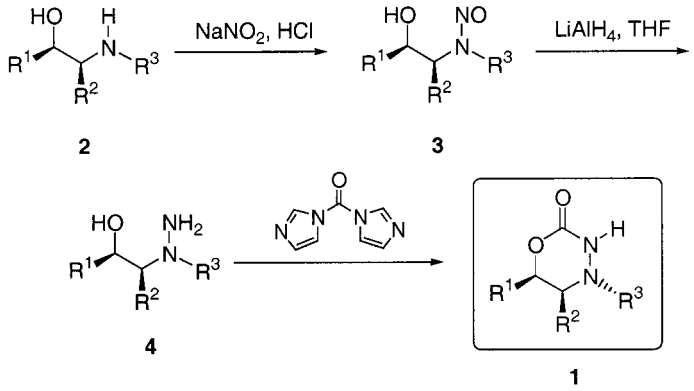
3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones (Also known as 1,3,4-oxadiazinan-2-ones. These heterocycles were first disclosed by Trepanier. Please see Ref.[1].) have been known for more than thirty years but only recently have been examined in terms of their synthesis,[2] conformational analysis,[3,4] and asymmetric application.[5] The most prevalent methodology for the synthesis of these heterocycles is based on cyclization of β-hydrazino alcohols. Typically, β-amino alcohols are nitrosated at the amino group and the corresponding *N*-nitrosamines are reduced with lithium aluminum hydride to β-hydrazino alcohols. The β-hydrazino alcohols are then cyclized with 1,1′-carbonyldiimidazole to afford the oxadiazinone (Sch. 1).[2,6]

Because of the cost of 1,1′-carbonyldiimidazole, we began to explore different cyclizing agents for the synthesis of oxadiazinones. In the process of our discovery, we determined that the use of diethyl carbonate in conjunction with a metal hydride (sodium or lithium) proved to be just as effective as 1,1′-carbonyldiimidazole. A test substrate, the β-hydrazino alcohol derived from (1*R*,2*S*)-ephedrine (**4a**), was cyclized with diethyl carbonate and lithium hydride to give the oxadiazinone **1a** in 74% yield after recrystallization (Sch. 2). This is comparable to the yield of 75% reported previously with 1,1′-carbonyldiimidazole.[2] In terms of price, diethyl carbonate has a cost of \$5/mole while CDI has a cost of \$234/mol.[7]

We became interested in expanding the scope of the cyclization by exploring other substrates. We were gratified to learn that the cyclization was also applicable to the β-hydrazino alcohol of *N*-neopentyl norephedrine (**4b**), which was cyclized to give oxadiazinone **9b** in 58% yield. This yield is nearly comparable to the cyclization of the β-hydrazino alcohol using



Scheme 1. Synthesis of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones.

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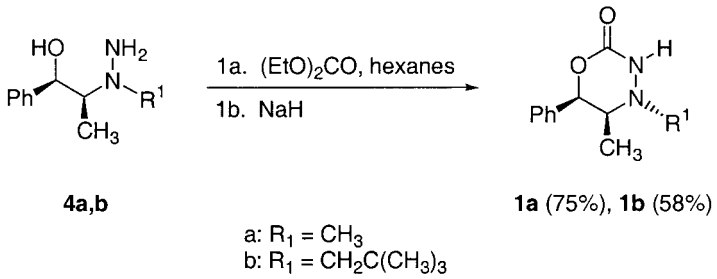
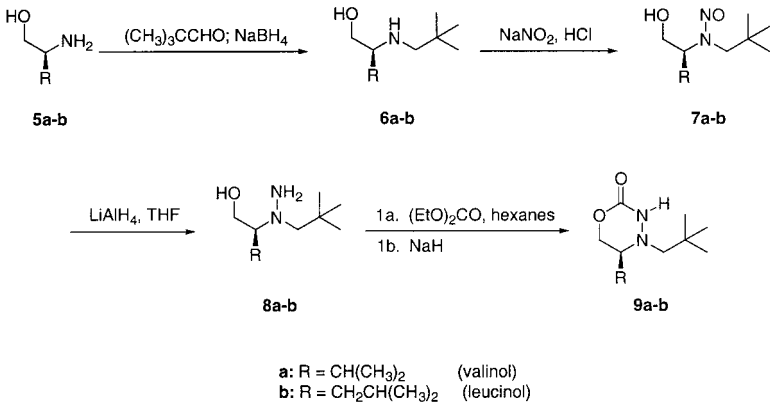


Scheme 2. Cyclization of the β-hydrazino alcohol derived from ephedrine.

1,1′-carbonyldiimidazole (69%).[2] We decided to pursue more examples derived from the α-amino acids valine and leucine.

Thus, commercially available β-amino alcohols **5a–b** were alkylated via reductive amination with trimethylacetaldehyde and sodium borohydride to afford the corresponding *N*-neopentyl-β-amino alcohols **6a–b** in high yield (Sch. 3) (for an excellent discussion on reductive amination methods, please see Ref.[8]). Subsequent *N*-nitrosation ($NaNO_2$/HCl) gave the desired *N*-neopentyl-*N*-nitrosamines **7a–b** as mixtures of diastereomeric *E*- and *Z*-diastereomers. *N*-nitrosamines are potentially carcinogenic materials and should be handled with great care. (Caution. It should be noted that many *N*-nitrosamines and their derivatives are potentially dangerous carcinogens and should be handled with due caution. For more information on *N*-nitrosamines see Ref.[9].) For the sake of characterization of **7a–b,** the *E*-diastereomer was determined to be the dominant isomer by ^{1}H NMR spectroscopy.[10]



Scheme 3. Synthesis of oxadiazinones **9a** and **9b**.

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Table 1. Synthesis of oxadiazinones **9a** and **9b**.

		Yield (%)			
Entry	R	**6**	**7**	**8**	**9**
a	$(CH_3)_2$ CH–	73	65	89	96
b	$(CH_3)_2CHCH_2$–	71	72	87	49

Reduction of the *N*-neopentyl-*N*-nitrosamines was accomplished with lithium aluminum hydride.[2,11] This process afforded the corresponding β-hydrazino-alcohols **8a–b.**

The cyclization was performed with sodium hydride and diethyl carbonate to give α-amino acid based 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones **9a** and **9b** in 96% and 49%, respectively (Table 1).

In summary, we have synthesized a series of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones using a metal hydride and diethyl carbonate to effect the cyclization.

EXPERIMENTAL

General Remarks

Tetrahydrofuran and diethyl ether were distilled from a potassium/sodium alloy with benzophenone ketyl. Methylene chloride was distilled from calcium hydride. Reactions were run under a nitrogen atmosphere. Flash chromatography was conducted with silica gel (32–63 mesh). All ^{1}H and ^{13}C NMR spectra were recorded at 25°C on a Varian spectrometer in deuteriochloroform operating at 400 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 potassium bromide pellet. 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 (percentage intensity relative to the base peak). Elemental analyses were conducted by the Microanalytical Laboratory, School of Chemical Sciences, University of Illinois, and Urbana-Champaign.

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3,4,5,6-Tetrahydro-4,5-dimethyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one: (1a)

Ephedrine hydrazine (24.0 mmol) and freshly distilled hexanes (125 mL) were combined in a 1 L flask. To this solution was added diethylcarbonate (60 mmol) and the solution was heated to reflux under nitrogen. To the reaction mixture was added LiH (25.2 mmol) and allowed to stir for 24 hr. The mixture was then cooled to room temperature, and the solvent was removed by rotary evaporation. This solid was extracted with ethyl acetate (3 × 50 mL), washed with aqueous saturated solution of sodium bicarbonate (50 mL) then an aqueous solution of brine (50 mL), dried (Na_2SO_4) followed by the removal of solvent by rotary evaporation. This process yielded the title compound as a white solid in 74% yield. This material was spectroscopically identical to the previously synthesized material.[3]

3,4,5,6-Tetrahydro-5-methyl-4-(2,2-dimethylpropyl)-6-phenyl-1,3,4-oxadiazin-2-one (1b)

The title compound was isolated by recrystallization from ethyl acetate and hexanes (69%). This material was spectroscopically identical to the previously synthesized material.[2]

General procedure for the preparation of the neopentyl aminoalcohol derivative **6**. In a 1 L round bottom flask was placed the β-amino alcohol (18.4 g, 178 mmol), ethanol (180 mL), trimethylacetylaldehyde (19.4 mL, 178 mmol) and the reaction mixture was stirred for 1 hr. To the resulting mixture was added $NaBH_4$ (12.16 g, 321.3 mmol) and it was stirred for 1 hr. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and then extracted with CH_2Cl_2 (3 × 75 mL), washed with an aqueous saturated solution of brine (100 mL), dried (Na_2SO_4) and the solvents were removed by rotary evaporation.

N-Neopentyl-valinol (6a)

Isolated product recrystallized with ethyl acetate–hexanes (3 : 1) to yield **6a** in 73% yield as a clear, colorless oil (the analytical information colected for this compound was identical to the literature; see Ref.[12]). $R_f = 0.40$ (ethyl acetate–hexanes, 3 : 7). ^{1}H NMR: δ0.88 (d, $J = 6.6$ Hz, 3H,), 0.92 (s, 9H), 0.96 (d, $J = 6.6$ Hz, 3H), 1.73–1.85 (m, 1H), 2.22 (d, $J = 11.0$ Hz, 1H), 2.35 (sextet, $J = 4.4$ Hz, 1H), 2.47 (d, $J = 11.0$ Hz, 1H), 3.27 (dd, $J = 10.3$, 7.7 Hz, 1H), 3.58 (dd, 1H, J = 10.3, 4.4 Hz). ^{13}C NMR: δ18.3, 19.5, 27.5, 28.9, 31.5,

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59.1, 60.2, 64.7. IR (neat): 3383, 2955, 1048 cm^{-1}. EI-MS, m/z (%): 174 (M^+, 34), 142 (100), 130 (51), 116 (66), 72 (80). HRMS Calcd for $C_{10}H_{23}NO$: 174.1858. Found: 174.1855.

N-Neopentyl-leucinol (6b)

The title compound was recovered in 71% yield as a clear, colorless oil. ^1H NMR: δ0.92 (s, 9H), 1.20 (quintet, $J = 7.0$ Hz, 1H), 1.39 (quintet, $J = 7.7$ Hz, 1H), 1.62 (septet, $J = 6.6$ Hz, 1H), 2.23 (d, $J = 11.4$ Hz, 1H), 2.47 (d, $J = 11.4$ Hz, 1H), 2.66 (m, 1H), 3.19 (dd, $J = 10.3$, 6.6 Hz, 1H), 3.60 (dd, $J = 10.4$, 4.4 Hz, 1H). ^{13}C NMR: δ22.6, 22.9, 24.9, 27.6, 31.4, 41.4, 57.1, 58.9 62.9. IR (neat): 3335, 2954, 1054 cm^{-1}. EI-MS, m/z (%): 188 (M^+, 17), 170 (68), 156 (100). HRMS Calcd for $C_{11}H_{25}NO$: 188.2014. Found: 188.2014.

General Procedure for the Preparation of the *N*-Nitrosamines 7

The *N*-alkylated amino alcohol **6** (124 mmol) and THF (50 mL) were combined and an aqueous solution of HCl (2.74 *M*, 143 mmol) was added followed by the addition of sodium nitrite (143 mmol) in small portions and then stirred for 24 hr. The cloudy mixture was then diluted with and saturated aqueous solution of $NaHCO_3$ until it became basic. The reaction mixture was then extracted with ethyl acetate (3×60 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 solvent by rotary evaporation.

N-Neopentyl-*N*-nitroso-valinol (7a)

This process yielded white crystals that were determined to be *ca*. 95% pure by the ^1H NMR spectrum. Mp: 78–80°C; $R_f = 0.60$ (ethyl acetate–hexanes, 1 : 1). Only the major isomer was observed. ^1H NMR ($CDCl_3$): 0.93 (s, 9H), 0.98 (d, $J = 7.0$ Hz, 3H), 1.07 (d, $J = 6.6$ Hz, 3H), 2.10–2.15 (m, 1H), 2.40–2.44 (m, 1H), 2.72 (d, $J = 12.8$ Hz, 1H), 3.63–3.68 (m, 1H), 4.13–4.21 (m, 1H), 4.27 (d, $J = 13.2$ Hz, 1H). ^{13}C NMR: δ19.5, 20.0, 28.6, 31.1, 34.9, 57.9, 62.8, 72.3. IR (KBr): 3346, 2962, 1178 cm^{-1}. EI-MS, m/z (%): 203 ($M^+ + H$, 1), 116 (32), 71 (57), 57 (100). Anal. Calcd for $C_{10}H_{22}N_2O_2$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.21; H, 10.98; N, 13.72.

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N-Neopentyl-*N*-nitroso-leucinol (7b)

The *N*-nitrosamine **7b** was recovered as a mixture of *E*- and *Z*-rotamers (10 : 1). Only the major rotamer has been characterized. $R_f = 0.52$ (ethyl acetate–hexanes, 2 : 3). ^{1}H NMR: δ0.93 (s, 9H), 0.96 (d, $J = 6.2$ Hz, 3H), 0.99 (d, $J = 6.2$ Hz, 3H), 1.64–1.74 (m, 1H), 1.91–1.97 (m, 1H), 3.13 (dd, $J = 13.2$, 1.5 Hz, 1H), 3.82 (d, $J = 13.2$ Hz, 1H), 3.99–4.13 (m, 2H). ^{13}C NMR: δ22.0, 23.2, 24.9, 28.5, 34.6, 41.0, 57.2, 64.8, 65.1. IR (KBr): 3375, 2961, 1189 cm^{-1}. EI-MS, m/z (%): 217 (M^+, 6), 128 (24), 113 (29), 74 (100), 55 (61). Anal. Calcd for $C_{10}H_{22}N_2O_2$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.21; H, 10.98; N, 13.72.

General Procedure for the Preparation of Oxadiazinones (9)

In a flame-dried, nitrogen purged 5 L, three-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 tetrahydrofuran (300 mL). The mixture was then heated to reflux. The β-hydroxy-*N*-nitrosamine (77 mmol) was dissolved in freshly distilled tetrahydrafuran (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 min. Once the addition was completed the reaction mixture remained under reflux for an additional 2 hr. The reaction mixture was then cooled to room temperature followed by the cautious addition of sodium hydroxide (6 *M*). The resulting mixture was diluted with a saturated aqueous solution of sodium potassium tartrate (200 mL) and stirred for 45 min. The resulting mixture was then extracted with ethyl acetate (4 × 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 to give product **8**. Due to the ready degradation of the hydrazines, cyclization was directly carried out to afford the corresponding oxadiazinones.

In a flame-dried, nitrogen purged 500 mL round bottom flask was placed the β-hydrazino alcohol **8** (26.8 mmol) and freshly distilled hexanes (100 mL). To this solution was added diethylcarbonate (7.92 g, 67.0 mmol) and the solution was heated to reflux. To the reaction mixture was added sodium hydride (1.18 g, 29.5 mmol) and allowed to stir for 2 hr. The mixture was then cooled to room temperature, and the solvent was removed by rotary evaporation. This solid was suspended in ethyl acetate (50 mL), washed with 1 *M* hydrochloric acid (3 × 50 mL), aqueous saturated solution of sodium bicarbonate (50 mL) then an aqueous solution of brine (50 mL), dried (Na_2SO_4) followed by the removal of solvent by rotary evaporation.

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3,4,5,6-Tetrahydro-5-isopropyl-4-neopentyl-2*H*-1,3,4-oxadiazin-2-one (9a)

This process yielded a white solid in 96% yield. Mp: 86–88°C; $R_f = 0.31$ (ethyl acetate–hexanes, 3 : 7). ^{1}H NMR: δ0.94 (s, 9H), 0.98 (d, $J = 6.6$ Hz, 3H). 1.10 (d, $J = 6.6$ Hz, 3H), 1.84–1.90 (m, 1H), 2.24–27 (m, 1H), 2.45 (d, $J = 13.5$ Hz, 1H), 2.75 (d, $J = 13.5$ Hz, 1H), 4.40 (dd, $J = 11.3$ Hz, 1H), 4.55 (dd, $J = 11.3$, 3.3 Hz, 1H), 6.31 (bs, 1H). ^{13}C: δ19.5, 20.1, 26.9, 27.7, 32.8, 64.1, 64.9, 72.6, 152.4. IR (KBr): 3244, 2957, 1704, 1301, 1104 cm^{-1}. EI-MS, m/z (%): 214 (6, M^+), 171 (38), 157 (100). Anal. Calcd for $C_{11}H_{22}N_2O_2$: C, 61.65; H, 10.35; N, 13.07. Found: C, 61.78; H, 10.52; N, 12.99.

3,4,5,6-Tetrahydro-5-isobutyl-4-neopentyl-2*H*-1,3,4-oxadiazin-2-one (9b)

This yielded a white solid that was recrystallized from ethyl acetate–hexanes to afford the title compound in 49% yield. Mp: 84–86°C; $R_f = 0.39$ (ethyl acetate–hexanes, 1 : 1). ^{1}H NMR: δ0.92 (s, 3H), 0.93 (s, 9H), 0.95 (s,3H) 1.16–1.23 (m, 1H), 1.57–1.65 (m, 1H), 1.77–1.87 (m, 1H), 2.45 (d, $J = 13.2$ Hz, 1H), 2.75 (d, $J = 13.2$ Hz, 1H), 2.85–2.89 (m, 1H), 4.12 (dd, $J = 11.0$, 2.6 Hz, 1H), 4.60 (dd, $J = 11.3$, 3.7 Hz, 1H), 7.00 (bs, 1H). ^{13}C: δ22.0, 22.9, 24.4, 27.8, 32.6, 38.8, 56.4, 67.2, 71.6, 152.0. IR (KBr): 3243, 2956, 1704, 1101 cm^{-1}. EI-MS, m/z (%): 228 (6, M^+), 171 (39), 115 (100). Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 63.51; H, 11.00; N, 11.77.

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