Dihydrobenzoxazines and Tetrahydroquinoxalines by a Tandem Reduction-Reductive Amination Reaction

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Dedicated to the Memory of our Colleague and Friend Professor Elizabeth M. Holt

A tandem reduction-reductive amination reaction has been applied to the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines and 1-acetyl-1,2,3,4-tetrahydroquinoxalines. The nitroketones required for the benzoxazine ring closures were prepared by (A) alkylation of the anion derived from 2-nitrophenol with an allylic halide or (B) nucleophilic aromatic substitution of an allylic alkoxide on 2-fluoro-1-nitrobenzene followed by ozonolysis. Precursors for the quinoxalines were prepared by alkylation of the anion of 2-nitroacetanilide with an allylic halide followed by ozonolysis. Catalytic hydrogenation of the nitroketones using 5% palladium-on-carbon in methanol then gave the target heterocycles by a reduction-reductive amination sequence. The *N*-methyl derivatives for both ring systems were easily prepared by adding 5-10 equivalents of aqueous formaldehyde prior to the reduction. The dihydrobenzoxazines were isolated in high yield following purification by chromatographic methods; tetrahydroquinoxalines were isolated in a similar manner and possessed differentiated functionality on the two nitrogens.

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Introduction.

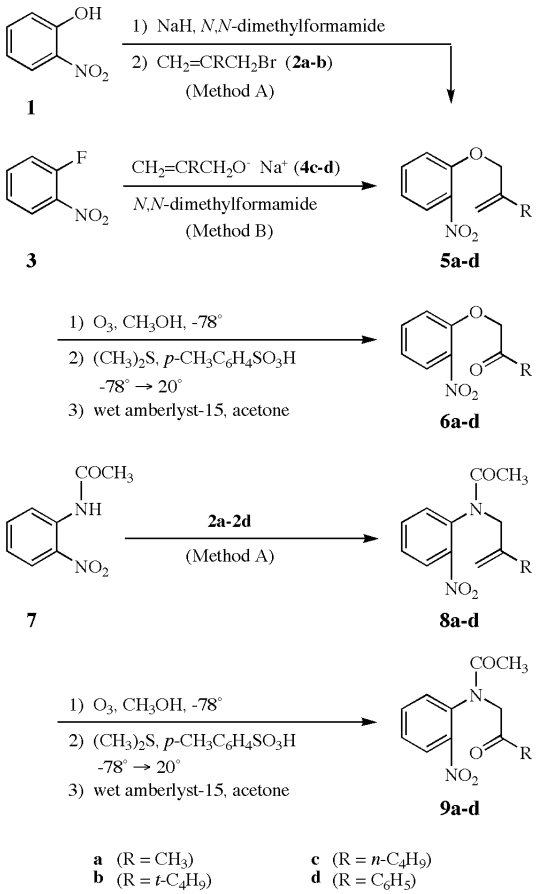
The tandem reduction-reductive amination sequence has recently proven useful and selective in the formation of a variety of heterocyclic systems [2]. As part of our effort to develop efficient new methods for the preparation of biologically active molecules, we wished to extend this methodology to the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines [3] and 1,2,3,4-tetrahydroquinoxalines [4]. Several known dihydrobenzoxazines have been shown to possess significant activity as antihypertensives [5], as serotonin receptor antagonists [6], and as neuroprotective agents [7]. Tetrahydroquinoxalines are known to possess diuretic properties [8] and have, more recently, been explored as cell adhesion agents [9]. Access to new derivatives of these structures would likely result in additional compounds with valuable biological activities. We describe here a short, high-yield synthesis of (±)-3-alkyl-3,4-dihydro-2*H*-1,4-benzoxazines and (±)-1-acetyl-3-alkyl-1,2,3,4-tetrahydroquinoxalines as well as their *N*-methyl derivatives.

Results and Discussion.

The benzoxazine precursors were prepared in two steps *via* allyl nitrophenyl ethers **5** that were available by two routes (Scheme 1). Method A, used for the preparation of **5a** and **5b**, involved deprotonation of 2-nitrophenol (**1**) and alkylation with allylic halides **2** (**a**: R = CH_3; **b**: R = *t*-C_4H_9) [10]. Method B provided **5c** and **5d** by nucleophilic aromatic substitution of 2-fluoro-1-nitrobenzene (**3**) with allylic alkoxides **4** (**c**: R = *n*-C_4H_9; **d**: R = C_6H_5) [11a]. Both of these procedures proceeded in 90-96% yields. In the second step, ozonolysis of **5a-d** followed by reductive workup and treatment with acid gave the α-(2-nitrophenoxy)ketones **6a-d** in greater than 93% yields.

Quinoxaline precursors were available using a strategy similar to Method A (Scheme 1). Deprotonation of 2-nitroacetanilide (**7**) and treatment with allylic halides **2a-d** gave the *N*-alkylated amides **8a-d** in 86-94% yields.

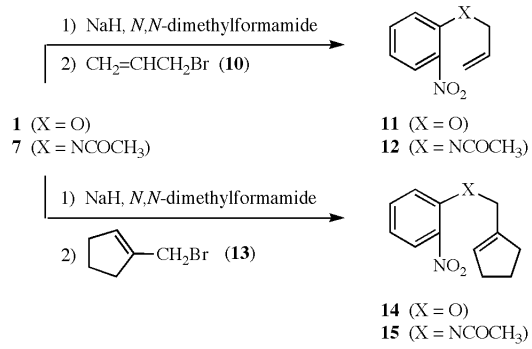
Scheme 1



Ozonolysis of **8a-d** and workup as above then delivered the ketones **9a-d** in 88-94% yields. The use of the anilide rather than the aniline permitted the use of 1:1 stoichiometric conditions [12] which gave higher yields and cleaner products. Additionally, the presence of the *N*-acetyl group precluded amine oxidation in the ozonolysis step and provided differentiated functionality on the nitrogens of the final product.

Precursors **11** and **12** for the unsubstituted parent ring systems **21** and **24-26** were synthesized by alkylation of **1** and **7** with allyl bromide (**10**) using Method A (Scheme 2). Compounds **14** and **15**, for the generation of angular-fused tricyclic structures **27** and **29**, were similarly prepared using 1-(bromomethyl)-1-cyclopentene (**13**).

Scheme 2

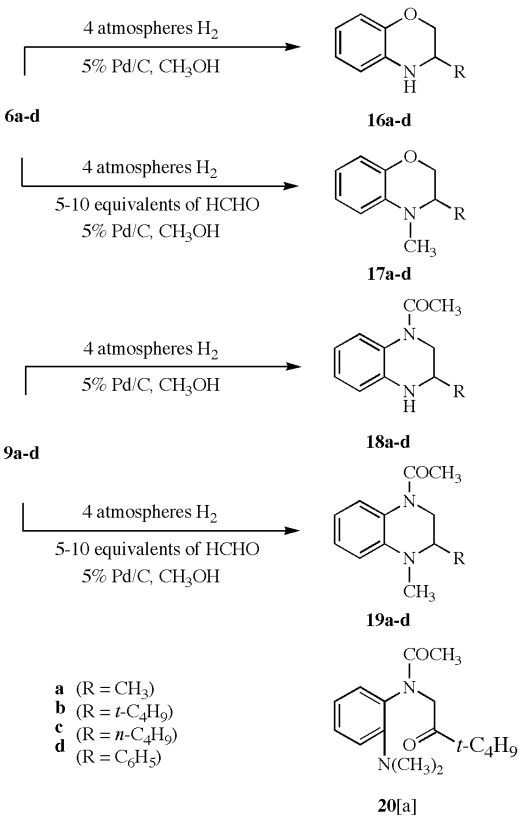


The results of our cyclization studies are summarized in Scheme 3. Hydrogenation of ketones **6** and **9** initiated a sequence involving (1) reduction of the nitro group to the hydroxylamine or amino group, (2) condensation of this nitrogen intermediate with the side chain carbonyl, and (3) reduction of the resulting imine to give the target heterocycles **16** and **18**. All of the reactions proceeded cleanly to give products that were either crystalline or easily purified by column chromatography.

Reactions to prepare the *N*-methyl derivatives **17** or **19** were performed by adding 5-10 equivalents of formaldehyde (37% in water) to the solution of **6** or **9** before hydrogenation. These transformations proceeded as above with an additional reductive amination as part of the reaction sequence. All substrates provided good yields except for the *tert*-butyl cases, **6b** and **9b**, where mixtures of methylated and unmethylated cyclization products were obtained. Increasing the amount of formaldehyde to 35 equivalents in the reaction of **9b** did not significantly increase the yield of **19b**, but instead resulted in competitive formation of the uncyclized *N*,*N*-dimethylaniline derivative **20**.

The aldehyde products from the ozonolysis of **11** and **12** were too unstable to isolate, and thus, the reductive ring closure was carried out on the crude ozonolysate. This

Scheme 3

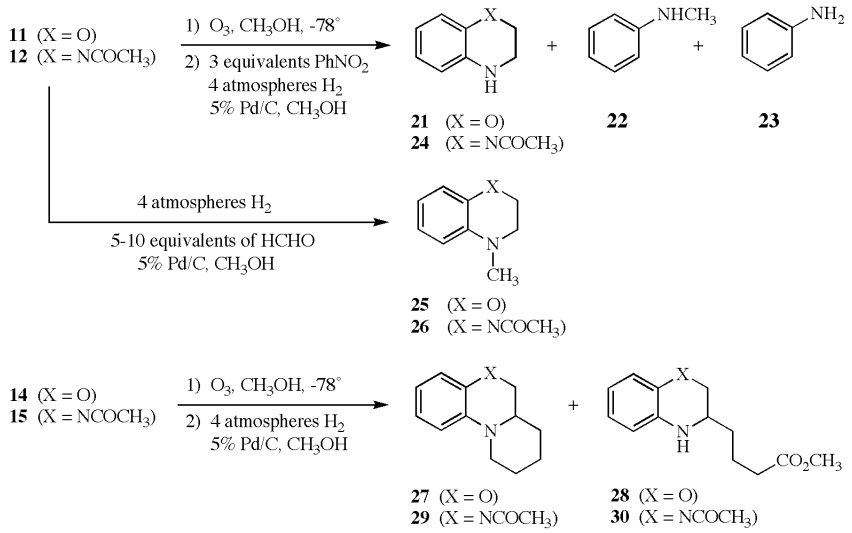


[a] Obtained from reductive cyclization of **9b** with 35 equivalents of HCHO

procedure, while more direct, was complicated by the presence of formaldehyde generated as the second ozonolysis product. To minimize reaction between the initial heterocyclic product and formaldehyde, 3 equivalents of nitrobenzene were added prior to the hydrogenation. This nitrobenzene was converted to aniline during the cyclization and served to scavenge much of the formaldehyde. Following removal of the excess aniline and *N*-methylaniline under high vacuum, chromatographic purification gave **21** and **24** in 66% and 64% yields, respectively. Finally, the *N*-methyl derivatives **25** and **26** were prepared from **11** and **12** using the standard protocol (Scheme 4).

Conversion of **14** and **15** to angular-fused heterocycles was also accomplished without isolating the intermediate aldehydes (Scheme 4). Following double bond cleavage, hydrogenation initiated a reduction-double reductive amination sequence to produce **27** and **29** in 80% and 68% yields, respectively. In each case, 10-15% of a second product (*i.e.* **28** or **30**), arising from oxidation of the aldehyde (during the ozonolysis) and a single reductive ring closure, was also produced [13]. Overall, however, this two-step sequence provided a very efficient synthesis for the angular-fused systems.

Scheme 4



The catalytic reduction of the nitroketones was carried out as described previously in methanol using 4 atmospheres of hydrogen and 20 weight percent (relative to substrate) of 5% palladium-on-carbon [2]. The presence of multiple heteroatoms in the substrates did not noticeably decrease catalyst efficiency. Competing reduction of the phenyl ketones in substrates **6d** and **9d** was not observed. Finally, in the quinoxaline synthesis, it was noted that cyclization always occurred with the side chain ketone; the less reactive amide did not participate in the reaction despite being closer to the nucleophilic aniline nitrogen.

The fact that the *N*-methylated heterocycles were formed so cleanly suggests that the reaction chronology involves six-membered ring closure prior to *N*-methylation. If this was not the case, a higher proportion of the uncyclized *N*,*N*-dimethylaniline would have been produced since formaldehyde is highly reactive in reductive aminations. Only upon addition of more than 20 equivalents of formaldehyde did measurable amounts of the dimethylaniline form. These observations suggest that intramolecular reductive amination occurs significantly faster than the intermolecular reaction in the current reductive cyclizations [14].

In summary, we have developed a simple and efficient synthesis of several new 3,4-dihydro-2*H*-1,4-benzoxazine and 1-acetyl-1,2,3,4-tetrahydroquinoxaline derivatives. Each synthesis requires three steps and affords the target heterocycle in high overall yield. The products are easily purified by crystallization or chromatography. The reaction can be extended to the synthesis of the *N*-methyl derivatives by adding 5-10 equivalents of formaldehyde to the reaction prior to the final hydrogenation step. Presumably, other simple alkyl groups could be added using different aldehydes. We are continuing to explore this cyclization strategy for the synthesis of other nitrogen heterocycles.

EXPERIMENTAL

N,*N*-Dimethylformamide, from a freshly opened bottle, was dried over 4 Å molecular sieves under nitrogen and transferred by syringe into reactions where it was used. All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates. Preparative separations were performed using flash column chromatography [15] on silica gel (grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5) or thin layer chromatography on 20-cm x 20-cm silica gel GF plates; band elution was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and were referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (J) have been given in hertz. High-resolution mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

Caution: Though we never experienced any problems, addition of 5% palladium-on-carbon to methanol can cause fires. This operation should be performed under a nitrogen atmosphere.

Representative Procedure for the Preparation of Allyl Nitroaromatic Ethers. Method A— Alkylation of 2-Nitrophenol: 2-[(2-Methyl-2-propenyl)oxy]-1-nitrobenzene (**5a**).

To a suspension of 0.26 g (11.0 mmoles) of oil-free sodium hydride in 15 mL of *N*,*N*-dimethylformamide was added 1.39 g (10.0 mmoles) of **1** in 15 mL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at room temperature for 30 minutes before a solution of 1.49 g (11.0 mmoles) of **2a** in 5 mL of *N*,*N*-dimethylformamide was added. The reaction mixture was stirred at room temperature for 6 hours, then added to 50 mL of saturated ammonium chloride and extracted with ether (three times). The combined ether extracts were washed with 1 *M* sodium hydroxide (until the aqueous washes remained colorless) and saturated sodium chloride, then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash

chromatography on a 50 cm x 2 cm silica gel column using 5% ether in hexanes to give 1.74 g (9.04 mmoles, 90%) of **5a**. The spectral data matched those reported previously [10].

2-{[2-(*tert*-Butyl)-2-propenyl]oxy}-1-nitrobenzene (**5b**).

This compound (Method A; 2.58 g, 11.0 mmoles, 88%) was isolated as a light yellow oil; ir: 1642, 1524, 1351 cm^{-1}; ^1H nmr: δ 7.84 (dd, 1H, J = 8.1, 1.8), 7.51 (ddd, 1H, J = 8.5, 7.4, 1.8), 7.07 (dd, 1H, J = 8.5, 1.2), 7.02 (ddd, 1H, J = 8.1, 7.4, 1.2), 5.26 (m, 1H), 5.14 (m, 1H), 4.71 (t, 2H, J = 1.2), 1.17 (s, 9H); ^{13}C nmr: δ 152.1, 150.5, 139.9, 134.0, 125.6, 120.2, 114.5, 110.5, 69.6, 34.8, 29.4 (3); hrms: m/z Calcd. for $C_{13}H_{17}NO_3$: 235.1208; Found: 235.1207.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96. Found: C, 66.57; H, 7.29; N, 5.91.

Method B—Nucleophilic Aromatic Substitution of 2-Fluoro-1-nitrobenzene by Allylic Alkoxides: 2-[(2-Butyl-2-propenyl)-oxy]-1-nitrobenzene (**5c**).

The alkoxide from 0.85 g (7.50 mmoles) of 2-butyl-2-propen-1-ol [16] was reacted with 0.71 g (5.00 mmoles) of **3** according to our published procedure [11a]. The crude product was chromatographed on a 50 cm x 2 cm silica gel column using 5% ether in hexanes to afford 1.13 g (4.81 mmoles, 96%) of **5c** as a light yellow oil. The spectral data matched those reported previously [11a].

2-[(2-Phenyl-2-propenyl)oxy]-1-nitrobenzene (**5d**).

This compound (Method B; 1.17 g, 4.59 mmoles, 92%) was isolated as a light yellow solid, mp 53-54° (ether-hexanes) [17]. The spectral data matched those reported previously [11a].

2-(2-Propenyloxy)-1-nitrobenzene (**11**).

This compound (Method A; 1.61 g, 9.02 mmoles, 90%) was isolated as a light yellow oil. The spectral data matched those reported previously [18].

2-(1-Cyclopentenylmethoxy)-1-nitrobenzene (**14**).

This compound (Method A; 1.02 g, 4.66 mmoles, 93%) was isolated as a light yellow oil [19]. The spectral data matched those reported previously [20].

Representative Procedure for the Alkylation of 2-Nitroacetanilide: *N*-(2-Methyl-2-propenyl)-*N*-(2-nitrophenyl)-acetamide (**8a**).

To a suspension of 0.26 g (11.0 mmoles) of oil-free sodium hydride in 15 mL of *N*,*N*-dimethylformamide was added 1.80 g (10.0 mmoles) of **7** in 15 mL of *N*,*N*-dimethylformamide. The reaction mixture was stirred for 30 minutes before a solution of 1.49 g (11.0 mmoles) of **2a** in 5 mL of *N*,*N*-dimethylformamide was added. The reaction mixture was stirred at room temperature for 8 hours, then added to 50 mL of saturated ammonium chloride and extracted with ether (three times). The combined ether layers were washed with saturated sodium chloride, dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 50 cm x 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes. The major band eluted with 30% ether in hexanes to afford 2.01 g (8.59 mmoles, 86%) of **8a** as a yellow oil; ir: 3078, 1674, 1528, 1351 cm^{-1}; ^1H nmr: δ 7.99 (dd, 1H, J = 8.1, 1.6), 7.67 (td, 1H, J = 7.8, 1.6), 7.56 (td, 1H, J = 7.8, 1.5), 7.32 (dd, 1H, J = 7.8, 1.5), 4.81(s, 1H), 4.63 (d, 1H, J = 14.8), 4.60 (s, 1H), 3.67 (d, 1H, J = 14.8), 1.90 (s, 3H), 1.76 (s, 3H); ^{13}C nmr: δ 169.7, 140.4, 133.9, 131.9, 129.4, 129.0, 125.3, 115.0, 112.7, 54.9, 22.6, 20.4; hrms: m/z Calcd. for $C_{12}H_{14}N_2O_3$: 234.1005; Found: 234.1006.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 5.98; N, 11.97. Found: C, 61.82; H, 6.07; N, 12.08.

N-[2-(*tert*-Butyl)-2-propenyl]-*N*-(2-nitrophenyl)acetamide (**8b**).

This compound (2.44 g, 8.84 mmoles, 88%) was isolated as a light yellow oil; ir: 1675, 1648, 1531, 1358 cm^{-1}; ^1H nmr (major rotamer): δ 7.97 (m, 1H), 7.64 (m, 1H), 7.55 (m, 1H), 7.44 (m, 1H), 5.24 (d, 1H, J = 16.1), 5.03 (s, 1H), 4.81 (s, 1H), 3.57 (d, 1H, J = 16.1), 1.90 (s, 3H), 0.98 (s, 9H); ^{13}C nmr (major rotamer): δ 169.9, 151.4, 142.1, 136.4, 133.7, 131.9, 127.6, 125.5, 109.3, 50.1, 35.3, 28.6 (3), 22.5; hrms: m/z Calcd. for $C_{15}H_{20}N_2O_3$: 276.1476; Found: 276.1473.

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.21; H, 7.25; N, 10.14. Found: C, 65.43; H, 7.32; N, 9.97.

N-(2-Butyl-2-propenyl)-*N*-(2-nitrophenyl)acetamide (**8c**).

This compound (1.77 g, 6.36 mmoles, 84%) was isolated as a light yellow oil; ir: 1674, 1654, 1531, 1354 cm^{-1}; ^1H nmr (major rotamer): δ 7.99 (dd, 1H, J = 8.1, 1.6), 7.66 (td, 1H, J = 7.7, 1.6), 7.55 (td, 1H, J = 8.1, 1.6), 7.31 (dd, 1H, J = 7.7, 1.6), 4.80 (s, 1H), 4.68 (d, 1H, J = 14.7), 4.61 (s, 1H), 3.69 (d, 1H, J = 14.7), 2.01 (t, 2H, J = 7.5), 1.89 (s, 3H), 1.41 (m, 2H), 1.32 (sextet, 2H, J = 7.1), 0.90 (t, 3H, J = 7.1); ^{13}C nmr (major rotamer): δ 169.9, 144.5, 136.0, 133.9, 132.0, 129.4, 128.7, 125.2, 113.8, 53.6, 33.3, 29.8, 22.6, 22.4, 13.9; hrms: m/z Calcd. for $C_{15}H_{20}N_2O_3$: 276.1474; Found: 276.1475.

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.22; H, 7.25; N, 10.14. Found: C, 65.49; H, 7.34; N, 9.91.

N-(2-Nitrophenyl)-*N*-(2-phenyl-2-propenyl)acetamide (**8d**).

This compound (3.08 g, 10.4 mmoles, 94%) was isolated as a viscous yellow oil [21]; ir: 1672, 1635, 1530, 1351 cm^{-1}; ^1H nmr (major rotamer): δ 7.96 (m, 1H), 7.47 (m, 2H), 7,40-7.28 (complex, 5H), 6.74 (m, 1H), 5.65 (dd, 1H, J = 15.0, 1.0), 5.34 (s, 1H), 4.98 (s, 1H), 3.92 (d, 1H, J = 15.0), 1.81 (s, 3H); ^{13}C nmr: δ 169.9, 143.0, 137.9, 135.0, 133.5, 132.6, 129.4, 128.7, 128.5, 128.1, 126.2, 125.4, 117.5, 50.9, 22.7; hrms: m/z Calcd. for $C_{17}H_{16}N_2O_3$: 296.1161; Found: 296.1161.

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 69.11; H, 5.50; N, 9.32.

N-(2-Nitrophenyl)-*N*-(2-propenyl)acetamide (**12**).

This compound (1.87 g, 8.51 mmoles, 85%) was isolated as a light yellow oil. The spectral data matched those reported previously [20].

N-(1-Cyclopentenylmethyl)-*N*-(2-nitrophenyl)acetamide (**15**).

This compound (3.38 g, 13.0 mmoles, 87%) was isolated as a light yellow solid, mp 77-78° (ether-petroleum ether); ir: 1671, 1527, 1353 cm^{-1}; ^1H nmr (major rotamer): δ 7.96 (dd, 1H, J = 8.1, 1.5), 7.68 (td, 1H, J = 7.7, 1.5), 7.56 (td, 1H, J = 8.1, 1.5), 7.31 (dd, 1H, J = 7.7, 1.5), 5.31 (m, 1H), 4.54 (d, 1H, J = 14.7), 4.02 (d, 1H, J = 14.7), 2.36 (m, 1H), 2.24 (m, 3H), 1.83 (m, 2H), 1.89 (s, 3H); ^{13}C nmr (major rotamer): δ 169.7, 147.4, 139.0, 136.12, 133.9, 131.8, 130.2, 129.3, 125.4, 49.1, 33.7, 32.3, 23.5, 22.6; hrms: m/z Calcd. for $C_{14}H_{16}N_2O_3$: 260.1161; Found: 260.1160.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.61; H, 6.15; N, 9.29. Found: C, 64.97; H, 6.22; N, 9.23.

Representative Procedure for the Ozonolysis of Allyl Ethers and Anilides: (2-Nitrophenoxy)-2-propanone (**6a**).

A solution of 1.00 g (5.18 mmoles) of **5a** in 150 mL of methanol at –78° was treated with ozone until thin layer chromatography indicated complete consumption of starting material. [Note: For the less soluble substrate **5d**, 150 mL of a 6:1 mixture of methanol and dichloromethane was used as the solvent.] Excess ozone was purged on a stream of dry nitrogen, and 5.08 g (6.00 mL, 84.9 mmoles) of dimethyl sulfide was added. The reaction mixture was warmed to room temperature, stirred for 4 hours and the solvent was removed under vacuum. The resulting yellow oil was dissolved in acetone, and the solution was stirred at room temperature for 12 hours with 5.00 g of wet amberlyst-15. The solvent was removed under vacuum and the product was dissolved in ether and dried (magnesium sulfate). Concentration afforded a yellow solid that was recrystallized from ether-petroleum ether to give 0.94 g (4.82 mmoles, 93%) of **6a** as a light yellow solid, mp 61-62°; ir: 1725, 1521, 1348 cm^{-1}; ^1H nmr: δ 7.91 (dd, 1H, J = 8.1, 1.5), 7.55 (ddd, 1H, J = 8.4, 7.5, 1.8), 7.12 (ddd, 1H, J = 8.1, 7.5, 1.2), 6.95 (dd, 1H, J = 8.4, 0.9), 4.63, (s, 2H), 2.38 (s, 3H); ^{13}C nmr: δ 204.9, 164.8, 151.0, 134.3, 126.1, 121.6, 114.5, 73.7, 27.0; hrms: m/z Calcd. for $C_9H_9NO_4$: 195.0531. Found: 195.0529.

Anal. Calcd. for $C_9H_9NO_4$: C, 55.38; H, 4.62; N, 7.18. Found: C, 55.54; H, 4.69; N, 7.09.

3,3-Dimethyl-1-(2-nitrophenoxy)-2-butanone (**6b**).

This compound (1.66 g, 7.00 mmoles, 98%) was isolated as a light yellow solid, mp 54-55° (ether-petroleum ether); ir: 1722, 1524, 1354 cm^{-1}; ^1H nmr: δ 7.86 (dd, 1H, J = 8.1, 1.8), 7.48 (ddd, 1H, J = 8.5, 7.5, 1.8), 7.07 (ddd, 1H, J = 8.1, 7.5, 1.2), 6.84 (dd, 1H, J = 8.5, 1.2), 5.04 (s, 2H), 1.26 (s, 9H); ^{13}C nmr: δ 208.2, 151.6, 140.4, 133.9, 125.8, 121.6, 115.1, 70.3, 43.2, 26.2 (3); hrms: m/z Calcd. for $C_{12}H_{15}NO_4$: 237.1001; Found: 237.1000.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.32; N, 5.91. Found: 61.01; H, 6.39; N, 5.82.

1-(2-Nitrophenoxy)-2-hexanone (**6c**).

This compound (1.73 g, 7.30 mmoles, 95%) was isolated as a light yellow oil that solidified on standing at 0°. The solid was triturated with petroleum ether at 0° and filtered, mp 37-38°; ir: 1724, 1524, 1351 cm^{-1}; ^1H nmr: δ 7.90 (dd, 1H, J = 8.2, 1.8), 7.54 (td, 1H, J = 7.5, 1.8), 7.11 (td, 1H, J = 7.5, 1.1), 6.95 (dd, 1H, J = 8.2, 1.1), 4.65, (s, 2H), 2.70 (t, 2H, J = 7.2), 1.62 (quintet, 2H, J = 7.2), 1.37 (sextet, 2H, J = 7.2), 0.92 (t, 3H, J = 7.2); ^{13}C nmr: δ 206.6, 151.1, 140.1, 134.3, 126.0, 121.5, 114.5, 73.5, 38.9, 25.0, 22.2, 13.8; hrms: m/z Calcd. for $C_{12}H_{15}NO_4$: 237.1001; Found: 237.0998.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.33; N, 5.91. Found: C, 60.88; H, 6.37; N, 5.86.

2-(2-Nitrophenoxy)-1-phenyl-1-ethanone (**6d**).

This compound (1.47 g, 5.72 mmoles, 98%) was isolated as a light yellow solid, mp 113-114° (ether-petroleum ether); ir: 1699, 1689, 1521, 1351 cm^{-1}; ^1H nmr: δ 8.02-7.98 (complex, 2H), 7.87 (dd, 1H, J = 8.1, 1.6), 7.64 (tt, 1H, J = 7.4, 1.3), 7.55-7.44 (complex, 3H), 7.07 (ddd, 1H, J = 8.1, 7.4, 1.2), 6.97 (dd, 1H, J = 8.5, 1.0), 5.45 (s, 2H); ^{13}C nmr: δ 193.3, 151.5, 140.3, 134.3, 134.0, 133.9, 128.9, 128.2, 125.9, 121.5, 115.2, 72.0; hrms: m/z Calcd. for $C_{14}H_{11}NO_4$: 257.0688; Found: 257.0685.

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.28; N, 5.45. Found: C, 65.52; H, 4.36; N, 5.31.

N-(2-Nitrophenyl)-*N*-(2-oxopropyl)acetamide (**9a**).

This compound (1.14 g, 4.83 mmoles, 94%) was isolated as a light yellow solid, mp 107-109° (ether-petroleum ether); ir: 1728, 1670, 1528, 1352 cm^{-1}; ^1H nmr: δ 7.96 (dd, 1H, J = 8.1, 1.6), 7.82 (dd, 1H, J = 8.0, 1.5), 7.69 (td, 1H, J = 8.0, 1.6), 7.57 (td, 1H, J = 8.1, 1.5), 5.10 (d, 1H, J = 18.0), 3.75 (d, 1H, J = 18.0), 2.18 (s, 3H), 1.85 (s, 3H); ^{13}C nmr: δ 202.1, 169.9, 147.1, 136.0, 134.2, 132.6, 129.8, 125.1, 58.7, 27.1, 21.7; hrms: m/z Calcd. for $C_{11}H_{12}N_2O_4$: 236.0728; Found: 236.0728.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 56.17; H, 5.18; N, 11.75.

N-(3,3-Dimethyl-2-oxobutyl)-*N*-(2-nitrophenyl)acetamide (**9b**).

This compound (1.83 g, 6.58 mmoles, 87%) was obtained as a light yellow solid, mp 115-117° (ether-petroleum ether); ir: 1718, 1674, 1531, 1351 cm^{-1}; ^1H nmr: δ 7.95 (dd, 1H, J = 8.0, 1.6), 7.88 (dd, 1H, J = 8.0, 1.5), 7.67 (td, 1H, J = 7.6, 1.6), 7.56 (td, 1H, J = 7.6, 1.5), 5.31 (d, 1H, J = 17.8), 3.77 (d, 1H, J = 17.8), 1.85 (s, 3H), 1.20 (s, 9H); ^{13}C nmr: δ 209.7, 169.7, 147.3, 136.3, 134.2, 132.7, 129.6, 125.0, 54.4, 43.4, 26.3 (3), 21.8; hrms: m/z Calcd. for $C_{14}H_{18}N_2O_4$: 278.1267; Found: 278.1269.

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.43; H, 6.47; N, 10.07. Found: C, 60.71; H, 6.55; N, 9.93.

N-(2-Nitrophenyl)-*N*-(2-oxohexyl)acetamide (**9c**).

This compound (0.96 g, 4.06 mmoles, 92%) was isolated as a light yellow oil that solidified on standing at 0°. The solid was triturated with petroleum ether at 0° and filtered, mp 43-45°; ir: 1728, 1674, 1531, 1351 cm^{-1}; ^1H nmr: δ 7.95 (dd, 1H, J = 8.1, 1.6), 7.85 (dd, 1H, J = 8.0, 1.5), 7.68 (td, 1H, J = 8.0, 1.6), 5.09 (d, 1H, J = 17.8), 3.70 (d, 1H, J = 17.8), 2.52 (ddd, 1H, J = 16.8, 8.2, 6.6), 2.37 (ddd, 1H, J = 16.8, 8.2, 6.6), 1.85 (s, 3H), 1.58 (m, 2H), 1.32 (sextet, 2H, J = 7.4), 0.90 (t, 3H, J = 7.4); ^{13}C nmr: δ 204.9, 169.8, 147.3, 136.2, 134.2, 132.7, 129.7, 125.1, 58.2, 39.7, 25.5, 22.2, 21.7, 13.8; hrms: m/z Calcd. for $C_{14}H_{18}N_2O_4$: 278.1267; Found: 278.1266.

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.43; H, 6.47; N, 10.07. Found: C, 60.70; H, 6.52; N, 9.96.

N-(2-Nitrophenyl)-*N*-(2-oxo-2-phenylethyl)acetamide (**9d**).

This compound (2.08 g, 6.98 mmoles, 88%) was isolated as a yellow solid, mp 88-90° (ether-petroleum ether); ir: 1699, 1669 cm^{-1}; ^1H nmr: δ 8.00-7.94 (complex, 4H), 7.70 (td, 1H, J = 7.5, 1.6), 7.56 (m, 2H), 7.47 (m, 2H), 5.84 (d, 1H, J = 17.8), 4.35 (d, 1H, J = 17.8), 1.92 (s, 3H); ^{13}C nmr: δ 193.4, 169.9, 147.2, 136.2, 134.8, 134.2, 133.7, 132.9, 129.8, 128.7, 128.0, 125.2, 55.7, 21.9; hrms: m/z Calcd. for $C_{16}H_{14}N_2O_4$: 298.0954; Found: 298.0953.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.70; N, 9.40. Found: C, 64.71; H, 4.82; N, 9.23.

Representative Procedure for the Tandem Reduction-Reductive Amination: 3-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**16a**).

To a solution of 0.50 g (2.56 mmoles) of **6a** in 150 mL of methanol in a stainless steel reaction vessel was added 125 mg of 5% palladium-on-carbon and the mixture was shaken under 4

atmospheres of hydrogen at 25° for 6 hours. [Note: For the less soluble substrate **6d**, 150 mL of a 6:1 mixture of methanol and tetrahydrofuran was used as the solvent.] The solvent was removed, the residue was diluted with ether, and the suspension was filtered through a pad of Celite topped with a layer of anhydrous magnesium sulfate to separate the catalyst. Concentration under vacuum gave a yellow oil that was purified by preparative thin layer chromatography using 25% ether in hexanes to give 0.35 g (2.35 mmoles, 92%) of **16a** as a light yellow oil; ir: 3372 cm^{-1}; ^1H nmr: δ 6.77 (m, 2H), 6.65 (td, 1H, J = 7.7, 1.8), 6.57 (dd, 1H, J = 7.7, 1.8), 4.18 (dd, 1H, J = 10.3, 2.8), 3.77 (dd, 1H, J = 10.3, 8.0), 3.65 (br s, 1H), 3.53 (m, 1H), 1.17 (d, 3H, J = 6.3); ^{13}C nmr: δ 143.6, 133.4, 121.3, 118.7, 116.4, 115.3, 70.7, 45.1, 17.6; hrms: m/z Calcd. for $C_9H_{11}NO$: 149.0841; Found: 149.0839.

Anal. Calcd. for $C_9H_{11}NO$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.44; H, 7.95; N, 8.70.

3-(*tert*-Butyl)-3,4-dihydro-2*H*-1,4-benzoxazine (**16b**).

This compound (0.44 g, 2.30 mmoles, 97%) was isolated as a white solid, mp 68-69° (ether-petroleum ether); ir: 3392 cm^{-1}; ^1H nmr: δ 6.75 (m, 2H), 6.61 (m, 2H), 4.27 (dd, 1H, J = 10.6, 2.9), 3.93 (dd, 1H, J = 10.6, 8.3), 3.77 (br s, 1H), 3.10 (dd, 1H, J = 8.3, 2.9), 0.99 (s, 9H); ^{13}C nmr: δ 143.8, 134.3, 121.3, 118.2, 116.2, 115.1, 66.5, 58.0, 32.6, 26.0 (3); hrms: m/z Calcd. for $C_{12}H_{17}NO$: 191.1310; Found: 191.1310.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.39; H, 8.90; N, 7.33. Found: C, 75.17; H, 8.83; N, 7.33.

3-Butyl-3,4-dihydro-2*H*-1,4-benzoxazine (**16c**).

This compound (0.50 g, 2.61 mmoles, 97%) was isolated as a light yellow oil; ir: 3372 cm^{-1}; ^1H nmr: δ 6.76 (m, 2H), 6.64 (td, 1H, J = 7.6, 1.8), 6.58 (dd, 1H, J = 7.8, 1.8), 4.21 (dd, 1H, J = 10.4, 2.8), 3.84 (dd, 1H, J = 10.4, 7.7), 3.73 (br s, 1H), 3.37 (m, 1H), 1.53-1.34 (complex, 6H), 0.93 (t, 3H, J = 6.9); ^{13}C nmr: δ 143.9, 133.4, 121.3, 118.6, 116.4, 115.3, 69.5, 49.6, 32.0, 27.6, 22.7, 14.0; hrms: m/z Calcd. for $C_{12}H_{17}NO$: 191.1310; Found: 191.1311.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.39; H, 8.90; N, 7.33. Found: C, 75.11; H, 8.87; N, 7.39.

3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**16d**).

This compound (0.21 g, 1.00 mmole, 76%) was isolated as a colorless oil that solidified on standing at 0°. The white solid was triturated with petroleum ether at 0° and filtered, mp 38-40°; ir: 3358 cm^{-1}; ^1H nmr: δ 7.40-7.32 (complex, 5H), 6.86-6.80 (complex, 2H), 6.78-6.64 (complex, 2H), 4.48 (dd, 1H, J = 8.6, 2.9), 4.27 (dd, 1H, J = 10.6, 2.9), 3.98 (superimposed br s, 1H and dd, 1H, J = 10.6, 8.6); ^{13}C nmr: δ 143.5, 139.1, 133.8, 128.8, 128.3, 127.1, 121.4, 118.9, 116.5, 115.3, 70.9, 54.1; hrms: m/z Calcd. for $C_{14}H_{13}NO$: 211.0997; Found: 211.0994.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.62; H, 6.16; N, 6.64. Found: C, 79.43; H, 6.13; N, 6.68.

1-Acetyl-3-methyl-1,2,3,4-tetrahydroquinoxaline (**18a**).

This compound (0.40 g, 2.09 mmoles, 82%) was isolated as an off-white solid, mp 172-174° (ether-hexanes); ir: 3345, 1640 cm^{-1}; ^1H nmr: δ 6.98 (t, 2H, J = 7.7), 6.63 (t, 1H, J = 7.7), 6.57 (dd, 1H, J = 8.2, 1.3), 4.44 (br d, 1H, J = 11.3), 3.94 (br s, 1H), 3.58 (m, 1H), 2.91 (br t, 1H, J = 8.9), 2.28 (s, 3H), 1.21 (d, 3H, J = 6.3); ^{13}C nmr: δ 169.6, 157.1, 156.9, 126.2, 124.4, 116.0, 114.1, 47.9, 44.8, 22.6, 19.9; hrms: m/z Calcd. for $C_{11}H_{14}N_2O$: 190.1107; Found: 190.1104.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.47; H, 7.37; N, 14.74. Found: C, 69.59; H, 7.41; N, 14.62.

1-Acetyl-3-(*tert*-butyl)-1,2,3,4-tetrahydroquinoxaline (**18b**).

This compound (0.39 g, 1.91 mmoles, 84%) was isolated as a light yellow solid, mp 98-99° (ether-hexanes); ir: 3365, 1644 cm^{-1}; ^1H nmr: δ 6.99 (m, 2H), 6.63 (m, 2H), 4.62 (br d, 1H, J = 10.6), 4.09 (br s, 1H) 3.14 (dd, 1H, J = 4.0, 1.3), 2.91 (br t, 1H, J = 11.5), 2.25 (s, 3H), 0.99 (s, 9H); ^{13}C nmr: δ 169.7, 138.8, 126.2, 125.0, 124.0, 115.9, 114.2, 61.0, 40.2, 33.4, 25.8 (3), 22.7; hrms: m/z Calcd. for $C_{14}H_{20}N_2O$: 232.1576; Found: 232.1574.

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.41; H, 8.62; N, 12.07. Found: C, 72.62; H, 8.69; N, 11.96.

1-Acetyl-3-butyl-1,2,3,4-tetrahydroquinoxaline (**18c**).

This compound (0.45 g, 1.94 mmoles, 90%) was isolated as a white solid, mp 68-69° (ether-hexanes); ir: 3350, 1643 cm^{-1}; ^1H nmr: δ 6.98 (t, 2H, J = 7.1), 6.63 (t, 1H, J = 7.5), 6.58 (d, 1H, J = 8.2), 4.34 (br d, 1H, J = 11.2), 4.03 (br s, 1H), 3.42 (m, 1H), 3.10 (br t, 1H, J = 10.3), 2.28 (s, 3H), 1.55-1.32 (complex, 6H), 0.93 (t, 3H, J = 6.9); ^{13}C nmr: δ 169.4, 138.0, 126.2, 124.5, 124.2, 115.8, 114.0, 52.3, 43.3, 34.1, 27.6, 22.6 (2), 13.9; hrms: m/z Calcd. for $C_{14}H_{20}N_2O$: 232.1576; Found: 232.1575.

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.41; H, 8.62; N, 12.07. Found: C, 72.58; H, 8.67; N, 11.97.

1-Acetyl-3-phenyl-1,2,3,4-tetrahydroquinoxaline (**18d**).

This compound (0.39 g, 1.54 mmoles, 92%) was isolated as a white foam; ir: 3339, 1648 cm^{-1}; ^1H nmr: δ 7.36-7.30 (complex, 5H), 7.03 (br t, 2H, J = 7.9), 6.70 (br t, 1H, J = 7.4), 6.68 (br d, 1H, J = 7.8), 4.57 (m, 2H), 4.37 (br s, 1H), 3.25 (br t, 1H, J = 10.2), 2.23 (br s, 3H); ^{13}C nmr: δ 169.5, 140.7, 137.9, 128.7, 128.1, 126.5, 126.3, 124.4, 116.3, 114.2, 56.4, 45.5, 22.4; hrms: m/z Calcd. for $C_{16}H_{16}N_2O$: 252.1263; Found: 252.1260.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.69; H, 6.77; N, 10.53. Found: C, 76.41; H, 6.68; N, 10.69.

Representative Procedure for the Tandem Reduction-Double Reductive Amination to Prepare *N*-Methyl Heterocycles: 3,4-Dimethyl-3,4-dihydro-2*H*-1,4-benzoxazine (**17a**).

A solution of 0.50 g (2.56 mmoles) of **6a** in 150 mL of methanol was ozonized as described above. The crude ozonolysate was transferred to a stainless steel reaction vessel, 1.05 g of 37% aqueous formaldehyde (0.39 g, 13.0 mmoles of formaldehyde) and 125 mg of 5% palladium-on-carbon were added and the mixture was shaken under 4 atmospheres of hydrogen at 25° for 6 hours. Workup as described above and purification by preparative thin layer chromatography using 10% ether in hexanes gave 0.38 g (2.33 mmoles, 91%) of **17a** as a light yellow oil; ir: 1602, 1505, 739 cm^{-1}; ^1H nmr: δ 6.85 (td, 1H, J = 7.7, 1.5), 6.77 (dd, 1H, J = 8.1, 1.6), 6.62 (m, 2H), 4.20 (dd, 1H, J = 10.5, 2.5), 4.00 (dd, 1H, J = 10.5, 3.4), 3.35 (m, 1H), 2.86 (s, 3H), 1.18 (d, 3H, J = 6.5); ^{13}C nmr: δ 143.6, 135.5, 121.7, 117.3, 115.6, 112.2, 69.3, 52.1, 36.1, 14.1; hrms: m/z Calcd. for $C_{10}H_{13}NO$: 163.0997; Found: 163.0995.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.77; H, 8.01; N, 8.55.

3-(*tert*-Butyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**17b**).

When the above procedure was run on 0.57 g (2.38 mmoles) of **5b**, 0.41 g of a mixture of the *N*-methylated (**17b**, 39%) and unmethylated (**16b**, 50%) products was isolated. Separation by preparative thin layer chromatography using 10% ether in hexanes gave 0.18 g (0.88 mmoles, 37%) of **17b** as a light yellow oil; ir: 1606, 1507, 739 cm^{-1}; ^1H nmr: δ 6.86 (ddd, 1H, J = 8.1, 7.2, 1.5), 6.76 (dd, 1H, J = 7.8, 1.5), 6.66 (dd, 1H, J = 8.1, 1.5), 6.57 (ddd, 1H, J = 7.8, 7.2, 1.5), 4.47 (dd, 1H, J = 11.2, 1.0), 3.76 (dd, 1H, J = 11.2, 3.4), 3.09 (s, 3H), 2.80 (dd, 1H, J = 3.4, 1.0), 0.98 (s, 9H); ^{13}C nmr: δ 143.3, 136.3, 121.6, 116.1, 115.7, 112.0, 67.4, 63.1, 43.0, 37.8, 27.8 (3); hrms: m/z Calcd. for $C_{13}H_{19}NO$: 205.1467; Found: 205.1465.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83. Found: C, 75.90; H, 9.19; N, 6.91.

3-Butyl-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**17c**).

This compound (0.38 g, 1.85 mmoles, 85%) was isolated as a light yellow oil; ir: 1606, 1503, 738 cm^{-1}; ^1H nmr: δ 6.85 (ddd, 1H, J = 7.8, 7.4, 1.6), 6.77 (dm, 1H, J = 7.5), 6.60 (td, 1H, J = 7.5, 1.6), 6.58 (d, 1H, J = 7.5), 4.19 (dd, 1H, J = 10.6, 2.2), 4.07 (dd, 1H, J = 10.6, 2.6), 3.14 (ddt, 1H, J = 8.1, 5.9, 2.4), 2.91 (s, 3H), 1.58 (m, 2H), 1.34 (m, 4H), 0.91 (t, 3H, J = 6.8); ^{13}C nmr: δ 143.5, 135.3, 121.7, 116.8, 115.6, 111.8, 66.1, 57.5, 37.3, 28.4, 28.2, 22.8, 14.1; hrms: m/z Calcd. for $C_{13}H_{19}NO$: 205.1467; Found: 205.1466.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83. Found: C, 76.19; H, 9.29; N, 6.81.

4-Methyl-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**17d**).

This compound (0.21 g, 0.93 mmoles, 72%) was isolated as a white solid, mp 96-98° (ether-petroleum ether); ir: 1606, 1500, 739, 699 cm^{-1}; ^1H nmr: δ 7.38-7.23 (complex, 5H), 6.92 (ddd, 1H, J = 8.0, 7.2, 1.5), 6.82 (dd, 1H, J = 7.9, 1.6), 6.79 (dd, 1H, J = 8.0, 1.5), 6.68 (ddd, 1H, J = 7.8, 7.2, 1.6), 4.32-4.10 (ABX, 3H: ν_A = 4.30, ν_B = 4.26, ν_X = 4.13; J_{AB} = 3.1, J_{AX} = 6.3, J_{BX} = 10.8), 2.77 (s, 3H); ^{13}C nmr: δ 144.2, 139.1, 136.9, 128.7, 127.9, 127.3, 122.0, 117.6, 116.0, 112.4, 70.1, 61.5, 36.4; hrms: m/z Calcd. for $C_{15}H_{15}NO$: 225.1154; Found: 225.1152.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.00; H, 6.67; N, 6.22. Found: C, 79.74; H, 6.59; N, 6.30.

1-Acetyl-3,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (**19a**).

This compound (0.33 g, 1.62 mmoles, 85%) was isolated as a light yellow oil; ir: 1655 cm^{-1}; ^1H nmr: δ 7.08 (apparent td, 1H, J = 8.2, 1.3), 6.97 (br, d, 1H, J = 6.8), 6.64 (m, 2H), 4.35 (br d, 1H, J = 12.5), 3.55 (m, 1H), 3.31 (br d, 1H, J = 11.8), 2.93 (s, 3H), 2.29 (s, 3H), 1.14 (d, 3H, J = 6.3); ^{13}C nmr: δ 169.5, 139.6, 126.5, 125.3, 123.7, 115.0, 110.8, 55.2, 44.3, 35.9, 22.3, 17.8; hrms: m/z Calcd. for $C_{12}H_{16}N_2O$: 204.1263; Found: 204.1261.

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.73. Found: C, 70.37; H, 7.76; N, 13.84.

1-Acetyl-3-(*tert*-butyl)-4-methyl-1,2,3,4-tetrahydroquinoxaline (**19b**).

When the above procedure was run on 0.52 g (1.87 mmoles) of **9b**, 0.36 g of a mixture of the *N*-methylated (**19b**, 35%) and unmethylated (**18b**, 44%) products was isolated. When the amount of formaldehyde was increased to 35 equivalents, 0.39 g of a mixture of **19b** (44%) and the unclosed *N,N*-dimethylaniline derivative **20** (35%) was obtained. Separation of this second mixture by preparative thin layer chromatography using 10% ether in hexanes gave 0.19 g (0.77 mmoles, 41%) of **19b** as a light yellow oil; ir: 1652 cm^{-1}; ^1H nmr: δ 7.09 (apparent td, 1H, J = 8.5, 1.5), 6.94 (br d, 1H, J = 6.3), 6.71 (dd, 1H, J = 8.5, 1.3), 6.64 (ddd, 1H, J = 7.8, 7.4, 1.3), 5.07 (br d, 1H, J = 12.5), 3.12 (s, 3H), 3.05 (dd, 1H, J = 4.4, 1.6), 2.74 (br d, 1H, J = 10.9), 2.30 (s, 3H), 0.93 (s, 9H); ^{13}C nmr: δ 169.0, 139.7, 125.7, 124.3, 122.8, 114.9, 111.9, 69.2, 44.1, 37.7 (2), 27.8 (3), 23.5; hrms: m/z Calcd. for $C_{15}H_{22}N_2O$: 246.1733; Found: 246.1730.

Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.17; H, 8.94; N, 11.38. Found: C, 73.24; H, 8.99; N, 11.23.

N-[2-(Dimethylamino)phenyl]-*N*-(3,3-dimethyl-2-oxobutyl)-acetamide (**20**).

This compound (0.17 g, 0.60 mmoles, 32%) was isolated as a light yellow oil; ir: 1721, 1662 cm^{-1}; ^1H nmr: δ 7.39 (dd, 1H, J = 7.8, 1.6), 7.24 (ddd, 1H, J = 8.2, 7.4, 1.3), 6.97 (m, 2H), 5.21 (d, 1H, J = 17.5), 4.01 (d, 1H, J = 17.5), 2.74 (s, 6H), 1.99 (s, 3H), 1.16 (s, 9H); ^{13}C nmr: δ 209.6, 171.1, 148.6, 135.1, 130.9, 128.6, 122.0, 118.8, 51.9, 43.3, 42.9 (2), 26.3 (3), 21.8; hrms: m/z Calcd. for $C_{16}H_{24}N_2O_2$: 276.1838; Found: 276.1839.

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.57; H, 8.70; N, 10.14. Found: C, 69.81; H, 8.81; N, 9.97.

1-Acetyl-3-butyl-4-methyl-1,2,3,4-tetrahydroquinoxaline (**19c**).

This compound (0.39 g, 1.58 mmoles, 80%) was isolated as a light yellow oil; ir: 1654 cm^{-1}; ^1H nmr: δ 7.08 (apparent td, 1H, J = 7.7, 1.5), 6.96 (br d, 1H, J = 7.7), 6.62 (m, 2H), 4.64 (br d, 1H, J = 12.5), 3.33 (m, 1H), 3.06 (br d, 1H, J = 12.5), 2.95 (s, 3H), 2.29 (s, 3H), 1.57 (m, 1H), 1.50-1.20 (complex, 5H), 0.91 (t, 3H, J = 6.9); ^{13}C nmr: δ 169.3, 139.3, 126.4, 125.0, 123.5, 114.7, 110.5, 60.3, 41.0, 36.9, 31.6, 28.1, 22.7, 22.3, 13.9; hrms: m/z Calcd. for $C_{15}H_{22}N_2O$: 246.1733; Found: 246.1733.

Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.17; H, 8.94; N, 11.38. Found: C, 73.46; H, 9.01; N, 11.26.

1-Acetyl-4-methyl-3-phenyl-1,2,3,4-tetrahydroquinoxaline (**19d**).

This compound (0.34 g, 1.28 mmoles, 76%) was isolated as a light yellow oil; ir: 1658 cm^{-1}; ^1H nmr: δ 7.39-7.31 (complex, 3H), 7.12-7.04 (complex, 3H), 7.00 (d, 1H, J = 7.8), 6.77 (dd, 1H, J = 8.1, 1.0), 6.70 (t, 1H, J = 7.5), 4.57 (m, 1H), 4.13 (dd, 1H, J = 12.6, 5.1), 3.86 (dd, 1H, J = 12.6, 3.7), 2.87 (s, 3H), 2.13 (s, 3H); ^{13}C nmr: δ 169.1, 140.3 (2), 128.5, 127.8, 126.7, 126.5, 125.9, 124.0, 115.5, 111.0, 63.8, 46.2, 36.7, 22.0; hrms: m/z Calcd. for $C_{17}H_{18}N_2O$: 266.1420: Found: 266.1419.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.69; H, 6.77; N, 10.53. Found: C, 76.41; H, 6.68; N, 10.69.

Representative Procedure for the Preparation of Heterocycles without Isolation of the Ozonolysis Product: 3,4-Dihydro-2*H*-1,4-benzoxazine (**21**).

A solution of 0.50 g (2.79 mmoles) of **11** in 150 mL of methanol was ozonized as described for the preparation of **6a**. The crude ozonolysate was transferred to a stainless steel reaction vessel, 3 equivalents of nitrobenzene and 200 mg of 5% palladium-on-carbon were added and the mixture was shaken under 4 atmospheres of hydrogen at 25° for 6 hours. Following workup as described above, most of the aniline and *N*-methylaniline was removed under high vacuum. Final purification by preparative thin layer chromatography using 25% ether in hexanes afforded three bands. Band 1 gave a mixture of *N*-methylaniline (**22**) and

a small amount of 4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**25**); band 2 gave aniline (**23**); and band 3 gave 0.25 g (1.85 mmoles, 66%) of **21** as a light yellow oil. The spectral data for **21** matched those reported previously [3e].

1-Acetyl-1,2,3,4-tetrahydroquinoxaline (**24**).

This compound (0.26 g, 1.48 mmoles, 64%) was isolated as a light tan oil using preparative thin layer chromatography eluted with 50% ether in hexanes; band 3; ir: 3351, 1640 cm^{-1}; ^1H nmr: δ 6.98 (br t, 2H, J = 7.5), 6.64 (td, 1H, J = 7.7, 1.3), 6.59 (dd, 1H, J = 8.2, 1.3), 4.20 (br s, 1H), 3.84 (br t, 2H, J = 4.7), 3.43 (m, 2H), 2.27 (s, 3H); ^{13}C nmr: δ 169.4, 137.9, 129.6, 126.2, 124.5, 116.0, 114.3, 42.4, 38.4, 22.6; hrms: m/z Calcd. for $C_{10}H_{12}N_2O$: 176.0950; Found: 176.0950.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.81; N, 15.91. Found: C, 68.32; H, 6.85; N, 15.87.

4-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**25**).

A solution of 0.50 g (2.79 mmoles) of **11** in 150 mL of methanol was ozonized as described for the preparation of **6a**. The crude ozonolysate was transferred to a stainless steel reaction vessel, 1.15 g of 37% aqueous formaldehyde (0.43 g, 14.2 mmol of formaldehyde) and 150 mg of 5% palladium-on carbon were added and the mixture was hydrogenated as described for the preparation of **17a**. Purification by preparative thin layer chromatography using 10% ether in hexanes gave 0.29 g (1.95 mmoles, 70%) of **25** as a light yellow oil. The spectral data matched those reported previously [3g].

1-Acetyl-4-methyl-1,2,3,4-tetrahydroquinoxaline (**26**).

This compound (0.42 g, 2.21 mmoles, 65%) was isolated as a light yellow oil; ir: 1651 cm^{-1}; ^1H nmr: δ 7.09 (apparent td, 1H, J = 7.9, 1.3), 6.98 (br d, 1H, J = 4.0), 6.67 (dd, 1H, J = 8.2, 1.2), 6.65 (td, 1H, J = 7.5, 1.2), 3.89 (t, 2H, J = 5.4), 3.37 (t, 2H, J = 5.4), 2.95 (s, 3H), 2.23 (s, 3H); ^{13}C nmr: δ 169.4, 140.0, 126.7, 125.6, 124.2, 115.4, 111.0, 50.7, 39.3, 37.8, 22.5; hrms: m/z Calcd. for $C_{11}H_{14}N_2O$: 190.1107; Found: 190.1106.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.47; H, 7.37; N, 14.74. Found: C, 69.55; H, 7.41; N, 14.66.

Ozonolysis and Cyclization of **14**.

Ozonolysis as described for the preparation of **6a** and reductive ring closure as described for the preparation of **16a** were performed on 0.60 g (2.74 mmoles) of **14**. Preparative thin layer chromatography using 10% ether in hexanes gave two major bands. Band 1 (fastest moving) contained product **27**; band 2 contained **28**.

6,6a,7,8,9,10-Hexahydropyrido[2,1-*c*][1,4]benzoxazine (**27**).

This compound (0.41 g, 2.19 mmoles, 80%) was isolated as a white solid that was triturated with petroleum ether and filtered, mp 71-72°; ir: 1602, 1499, 739 cm^{-1}; ^1H nmr: δ 6.83 (m, 2H), 6.76 (dm, 1H, J = 8.0), 6.68 (m, 1H), 4.15 (dd, 1H, J = 10.6, 2.8), 3.98 (dd, 1H, J = 10.6, 8.5), 3.82 (dm, 1H, J = 12.0), 2.94 (qt, 1H, J = 8.5, 2.8), 2.54 (td, 1H, J = 12.2, 3.1), 1.85 (m, 2H), 1.65 (m, 2H), 1.43 (qt, 1H, J = 12.7, 3.4), 1.24 (ddd, 1H, J = 16.0, 12.7, 3.4); ^{13}C nmr: δ 145.1, 136.0, 121.2, 119.0, 116.3, 113.1, 70.0, 53.3, 46.5, 27.2, 25.1, 23.2; hrms: m/z Calcd. for $C_{12}H_{15}NO$: 189.1154; Found: 189.1155.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.41. Found: C, 75.98; H, 7.99; N, 7.43.

Methyl 4-(3,4-Dihydro-2*H*-1,4-benzoxazin-3-yl)butanoate (**28**).

This compound (0.08 g, 0.35 mmoles, 13%) was isolated as a light tan solid that was triturated with petroleum ether and filtered, mp 84-85°; ir: 3372, 1735 cm^{-1}; ^1H nmr: δ 6.80-6.73 (complex, 2H), 6.68-6.57 (complex, 2H), 4.20 (dd, 1H, J = 10.5, 2.7), 3.86 (dd, 1H, J = 10.6, 7.2), 3.80 (br s, 1H), 3.68 (s, 3H), 3.39 (qd, 1H, J = 7.2, 2.7), 2.38 (t, 2H, J = 7.2), 1.76 (m, 2H), 1.53 (m, 2H); ^{13}C nmr: δ 173.7, 143.7, 133.1, 121.4, 118.7, 116.5, 115.5, 69.1, 51.6, 49.2, 33.7, 31.7, 20.8; hrms: m/z Calcd. for $C_{13}H_{17}NO_3$: 235.1208; Found: 235.1206.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96. Found: C, 66.54; H, 7.16; N, 6.02.

Ozonolysis and Cyclization of **15**.

Ozonolysis as described for the preparation of **6a** and reductive ring closure as described for the preparation of **16a** were performed on 0.60 g (2.31 mmoles) of **15**. Preparative thin layer chromatography using 10% ether in hexanes gave two major bands. Band 1 (fastest moving) contained product **29**; band 2 contained **30**.

5-Acetyl-6,6a,7,8,9,10-hexahydro-5*H*-pyrido[1,2-*a*]quinoxaline (**29**).

This compound (0.36 g, 1.57 mmoles, 68%) was isolated as a light yellow oil; ir: 1653 cm^{-1}; ^1H nmr: δ 7.05 (td, 1H, J = 7.8, 1.5), 6.96 (br d, 1H, J = 5.6), 6.84 (dd, 1H, J = 8.4,1.2), 6.67 (td, 1H, J = 7.8, 1.2), 4.31 (br d, 1H, J = 10.2), 3.94 (dm, 1H, J = 12.8), 3.31 (dd, 1H, J = 10.4, 7.8), 3.08 (m, 1H), 2.80 (td, 1H, J = 14.7, 2.4), 2.23 (s, 3H), 1.87 (dm, 1H, J = 12.4), 1.75 (dm, 2H, J = 12.4), 1.64-1.38 (complex, 2H), 1.30 (m, 1H); ^{13}C nmr: δ 169.4, 140.7, 127.3, 126.5, 124.5, 116.5, 113.0, 57.1, 47.7, 46.1, 30.1, 25.4, 23.8, 22.5; hrms: m/z Calcd. for $C_{14}H_{15}N_2O$: 230.1420; Found: 230.1420.

Anal. Calcd. for $C_{14}H_{15}N_2O$: C, 73.04; H, 6.52; N, 12.17. Found: C, 72.92; H, 6.62; N, 12.31.

Methyl 4-(1-Acetyl-1,2,3,4-tetrahydroquinoxalin-3-yl)butanoate (**30**).

This compound (0.07 g, 0.25 mmoles, 11%) was isolated as a yellow oil; ir: 3354, 1735, 1644 cm^{-1}; ^1H nmr: δ 6.98 (t, 1H, J = 7.2), 6.66 (t, 1H, J = 7.7), 6.59 (dd, 1H, J = 8.2, 1.3), 4.18 (br d, 2H, J = 8.5), 3.68 (s, 3H), 3.45 (m, 1H), 3.29 (dd, 1H, J = 12.2, 8.5), 2.37 (t, 2H, J = 7.2), 2.28 (s, 3H), 1.77 (m, 2H), 1.53 (m, 2H); ^{13}C nmr: δ 173.7, 169.5, 137.9, 126.3, 124.5, 124.2, 116.1, 114.2, 52.0, 51.6, 43.0, 33.9, 33.6, 22.5, 20.7; hrms: m/z Calcd. for $C_{15}H_{20}N_2O_3$: 276.1474; Found: 276.1473.

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.21; H, 7.25; N, 10.14. Found: C, 65.37; H, 7.22; N, 10.01.

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