TETRAHYDRO-1,5-BENZOXAZEPINES AND TETRAHYDRO-1*H*-1,5-BENZODIAZEPINES BY A TANDEM REDUCTION-REDUCTIVE AMINATION REACTION

By

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Bachelor of Science

Oklahoma State University

Stillwater, Oklahoma

2002

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
MASTER OF SCIENCE
July 2004

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PREFACE

A tandem reduction-reductive amination sequence has been developed for the synthesis of benzo-fused substituted heterocycles incorporating two heteroatoms. The heterocycles synthesized by this method are 2,3,4,5-tetrahydro-1,5-benzoxazepines and 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines. These compounds have a broad range of biological activities. The key step in the synthesis of these heterocycles is the tandem reduction-reductive amination reaction involving a catalytic reduction of an aromatic nitro group followed by an intramolecular reductive amination with a pendant ketone or aldehyde substituent. This method for synthesizing 2,3,4,5-tetrahydro-1,5-benzoxazepines and 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines has been shown to give higher yields than previous methods in the literature. The present work demonstrates that the tandem reduction-reductive amination reaction provides a new route to seven-membered heterocycles, allowing a wide variety of substitution patterns.

ACKNOWLEDGMENTS

I would like to express my thanks to Dr. R. A. Bunce, my research advisor and the chairman of my graduate committee, for his guidance of my graduate work. The instruction he gave in organic theory and laboratory technique has been invaluable to my graduate experience. I would also like to thank Dr. K. D. Berlin and Dr. Z. El Rassi for agreeing to be on my graduate advisory committee.

Thanks are also due to Dr. D. Jacobs and Dr. A. Iob for their assistance with the mass spectrometry studies of some of the compounds synthesized during the course of my graduate work.

I would also like to acknowledge Dr. S. V. Kotturi, Dr. L. B. Johnson, and L. Y. Hale, fellow graduate students in Dr. Bunce's research group. Thanks also to Matt Ackerman, Chris Smith, and Chris Knight for helping make the laboratory a more pleasant place to work.

I would like to thank the Department of Chemistry for providing a teaching assistantship to me for support during my graduate work at OSU. I would also like to express my appreciation to Carolyn, Glenda, and Cheryl in the Chemistry Department office for their assistance over the last few years.

Finally, I would like express my greatest gratitude to my friends and family, especially to my wife, Wendy H. Lewis. Their continued support for the past few years has been of great help to me in finishing this project.

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EARLY SYNTHESES OF TETRAHYDRO-1,5-BENZOXAZEPINES AND TETRAHYDRO-1*H*-1,5-BENZODIAZEPINES

Introduction

Heterocycles are important compounds for developing new drugs in the pharmaceutical industry. Most biologically active compounds have at least one heterocyclic ring as part of their structure. There will always be an interest in developing new strategies to prepare heterocycles that are more efficient or less costly than known methods. Routes to heterocycles with new substitution patterns not previously accessible are important for drug discovery. This chapter describes early syntheses of two families of heterocycles incorporating two heteroatoms, 2,3,4,5-tetrahydro-1,5-benzoxazepines and 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines.

2,3,4,5-Tetrahydro-1,5-Benzoxazepines

Members of the 1,5-benzoxazepine family of compounds have a number of pharmacological uses. Among them include uses as central nervous system depressants,[1] as orexin receptor antagonists for the treatment of obesity and sleep disorders,[2] and as angiotensin converting enzyme-inhibitors[3] for the treatment of cardiovascular disease. The pharmacological possibilities for 1,5-benzoxazepines have led to an interest in their current synthesis and possibly more improved syntheses.

The first reported method for synthesizing 2,3,4,5-tetrahydro-1,5-benzoxazepine was in 1921 by von Braun and Braunsdorf[4] (Figure 1) and started with amino ester **1**. Saponification of the ester group gave alcohol **2** and treatment with hydrochloric acid resulted in cleavage of the aryl ether as well as conversion to chloride **3**. Treatment of **3** with base then gave the desired benzoxazepine **4** by an S_N2 reaction.

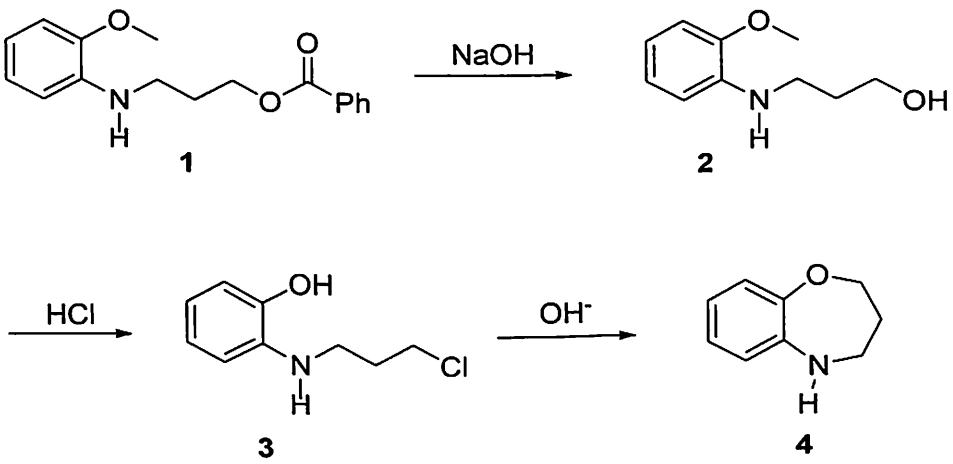


Figure 1. First reported synthesis of 2,3,4,5-tetrahydro-1,5-benzoxazepine.

The major disadvantage of this method for synthesizing benzoxazepines was the low overall yield (10%). Another potential limitation was that the halide could undergo an elimination reaction at high temperatures instead of a substitution reaction, preventing cyclization.

Sidhu, Thyagarajan and Bhalerao[5] synthesized 2,3,4,5-tetrahydro-1,5-benzoxazepine by two different methods, with the intent of improving on Braun's method. In the first approach (Figure 2), 2-aminophenol (**5**) was condensed with 3-chloropropionyl chloride to give **6**. Compound **6** was then cyclized with potassium

methoxide to give amide **7** and carbonyl reduction with lithium aluminum hydride gave the desired benzoxazepine.

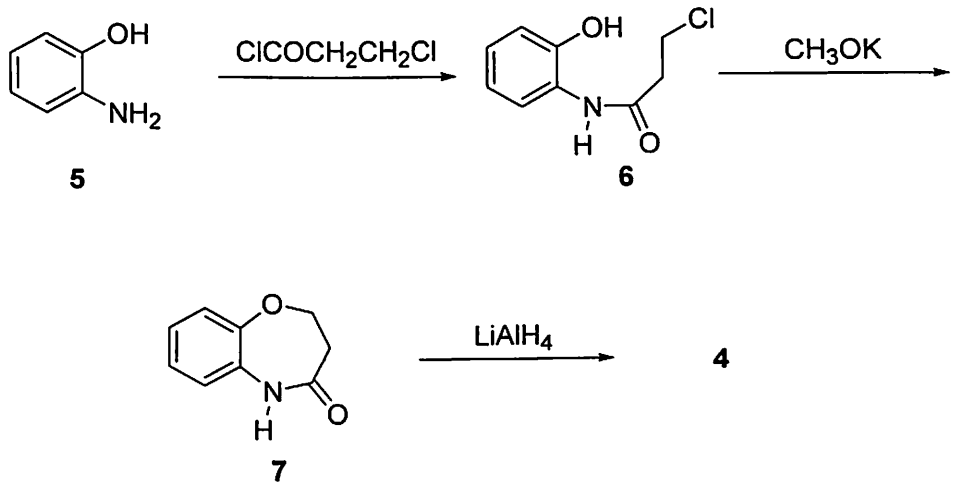


Figure 2. 1,5-Benzoxazepine by cyclization followed by amide reduction.

This method has one of the same limitations as von Braun's method, where there could be an elimination reaction, but the yield was much higher, around 55% overall yield.

The second method developed by Sidhu and co-workers also used 2-aminophenol (**5**) as the starting material (Figure 3). Alkylation of **5** at the nitrogen with 1-bromo-3-chloropropane gave **8** which was cyclized by an S_N2 reaction to give the 2,3,4,5-tetrahydro-1,5-benzoxazepine. This method could still undergo an elimination reaction, but it has fewer steps than the other syntheses.

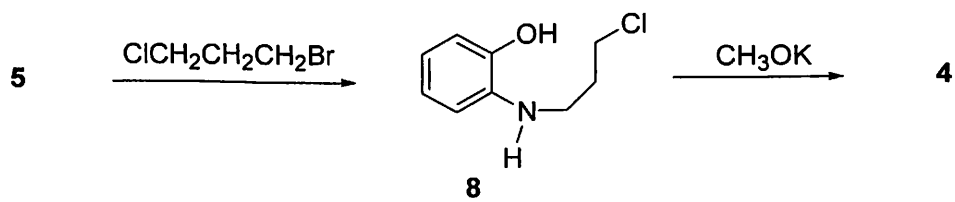
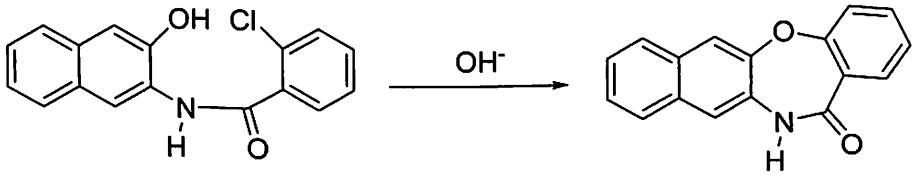


Figure 3. 1,5-Benzoxazepine by S_N2 cyclization.

Unfortunately, this synthesis only gave 40% overall yield. Thus, while the acylation method reported by Sidhu and co-workers had one extra step, it gave the desired heterocycle in higher yield.

Nagarajan and co-workers[6] synthesized a benzoxazepine by another route (Figure 4). Amide **9** was cyclized by nucleophilic aromatic substitution under basic conditions to give benzoxazepinone **10**. The amide carbonyl in **10** was then reduced to give the target heterocycle. This method suffered from two problems: (1) the starting material was not commercially available and (2) the overall yield was low.



9 **10**

Figure 4. 1,5-Dibenzoxazepinone by S_N2 cyclization.

Nour El-Din and Shawki[7] developed a strategy for synthesizing 2,3,4,5-tetrahydro-1,5-benzoxazepine that began with 2-nitrophenol (**11**) (Figure 5). The phenol was *O*-alkylated with 1-bromo-3-chloropropane to give ether **12**. The nitro group of **12** was then reduced to an amine under acidic conditions to produce the amine hydrochloride **13** which was reacted with formic acid to produce amide **14**. Finally, cyclization of **14** with potassium carbonate in the presence of copper powder gave the desired benzoxazepine.

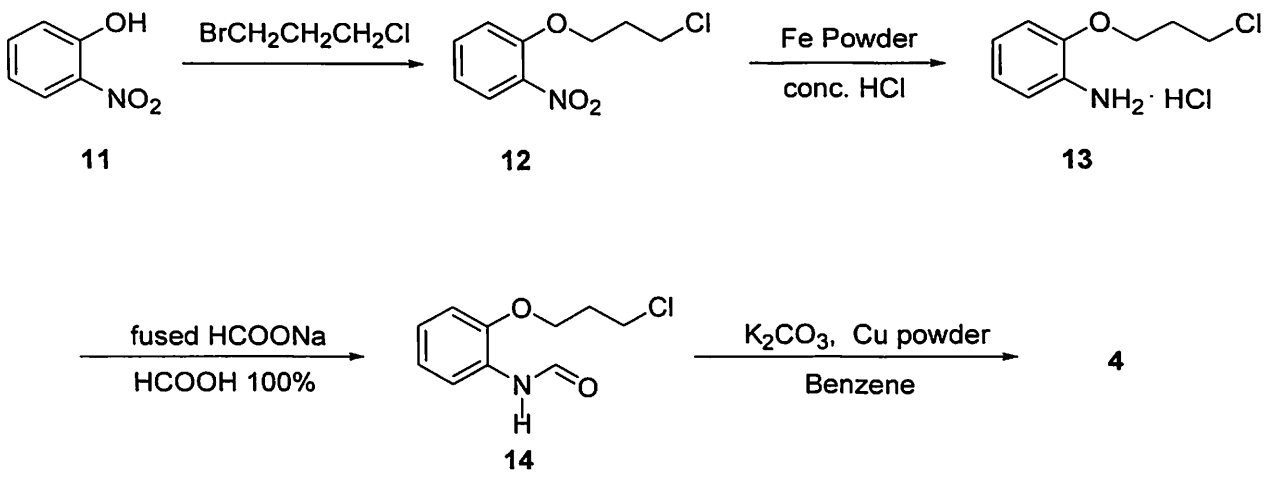


Figure 5. 1,5-Benzoxazepine from 2-nitrophenol.

When compared to the two previous methods of Sidhu and co-workers, the yield was very low (15%), making this a less attractive method for preparing benzoxazepines.

Sam[1] developed a strategy for synthesizing benzoxazepines from 3-(3-chloropropyl)benzoxazolin-2-one (**15**) (Figure 6). Compound **15** was not commercially available and had to be synthesized, but details of the procedure and yields were not reported. Compound **15** was refluxed in 2-methoxyethanol in the presence of potassium hydroxide to give 2,3,4,5-tetrahydro-1,5-benzoxazepine in 55% yield. Sam also synthesized the *N*-acylated benzoxazepine **17** by reacting **15** with pyrrolidine. This reaction proceeded in 71% yield.

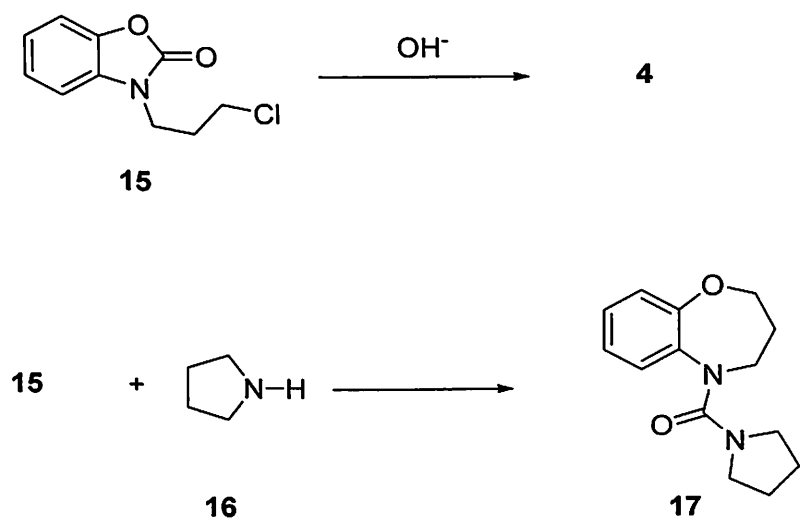


Figure 6. Cyclization to form a 1,5-benzoxazepine and an acylated 1,5-benzoxazepine.

Finally, Sebok, Levai and Timar[8] synthesized 2,3,4,5-tetrahydro-1,5-benzoxazepine through a Beckmann rearrangement (Figure 7). Benzochromanone **18** was converted to the oxime **19** in 93% yield using hydroxylamine hydrochloride and base. The oxime was then reduced with lithium aluminum hydride to give a mixture of the 4-aminochroman **20** and 2,3,4,5-tetrahydro-1,5-benzoxazepine in 8% and 38% yields, respectively. The benzoxazepine was the major product, but the yield was modest (38%). The authors also reported a case where the carbon alpha to the oxygen was substituted with two methyl groups and the carbon on the aryl group meta to the oxygen was substituted with a methoxy group. The yield for the benzoxazepine from this substrate was lowered to 25%, while the aminochroman increased to 20%. This demonstrated a limitation in the ability to substitute the benzoxazepine. As the carbon next to the oxygen is more heavily substituted, the benzoxazepine is produced in lower yield, increasing the amount of aminochroman.

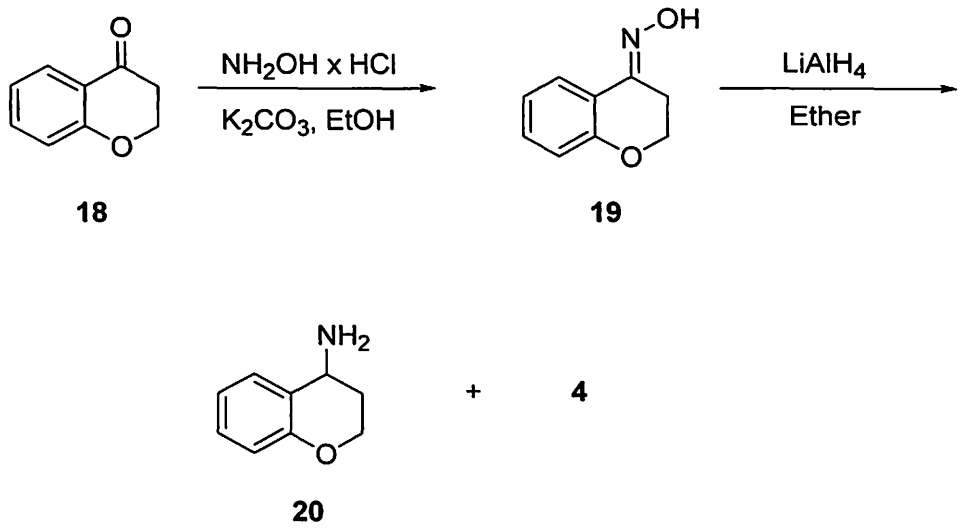


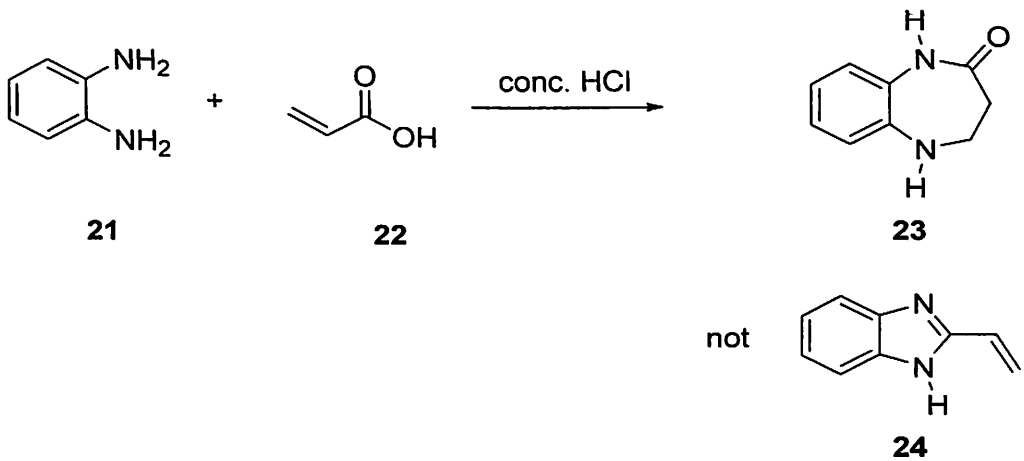
Figure 7. 2,3,4,5-Tetrahydro-1,5-benzoxazepines by Beckmann rearrangement.

2,3,4,5-Tetrahydro-1*H*-1,5-Benzodiazepines

The 1,5-benzodiazepines express a broad spectrum of biological activity. They have activity as antihypertensives because they are used as arginine vasopressin (AVP) antagonists.[9,10] AVP acts on the vasculature to produce a hypertensive effect, so a 1,5-benzodiazepine acting as an AVP antagonist is an antihypertensive. AVP also acts on the kidneys to increase water retention, so a 1,5-benzodiazepine acting as an AVP antagonist could also be used for treatment of diseases with conditions characterized by polyuria (excessive urine production). Benzodiazepines act as cholecystokinin-B (CCK-B) antagonists[11] and thus can be used as a treatment for nervous tension and anxiety.[12] 1,5-benzodiazepines have also been found to have activity as antimicrobials,[13] analgesics,[14,15] anticonvulsants,[14,15] antiaggressives,[14] antiinflammatories,[16] and antidepressants.[17] Because of the many pharmacological uses of 1,5-benzodiazepines, there is a continuing

interest in developing new and improved syntheses that yield rings bearing new substitution patterns.

In 1943, Bachman and Heisey[18] synthesized a 1,5-benzodiazepine while trying to prepare 2-vinylbenzimidazole (**24**) (Figure 8). The starting material used was 1,2-phenylenediamine (**21**). Compound **21** was reacted with acrylic acid (**22**) to give 2,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (**23**) in 67% yield. Though the authors did not reduce amide **23**, this route constitutes one of the first successful syntheses of the tetrahydro-1,5-benzodiazepine ring system.



21 **22** **23** **24**

Figure 8. 1,5-Benzodiazepinone by condensation of acrylic acid with 1,2-phenylenediamine.

Dandegaonker and Desai[19] synthesized several 1,5-benzodiazepin-2-ones by reaction of 1,2-phenylenediamene (**21**) with a series of substituted cinnamic acids. The authors proposed a mechanism (Figure 9) involving acylation of **21** followed by conjugate addition to the α,β-unsaturated amide. The target heterocycles were produced in 25-77% yields.

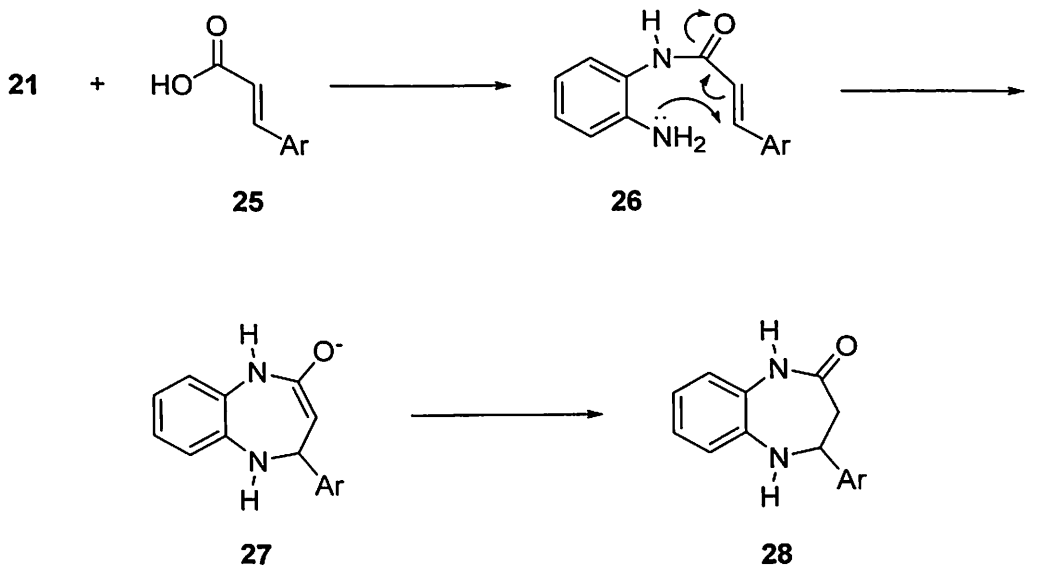
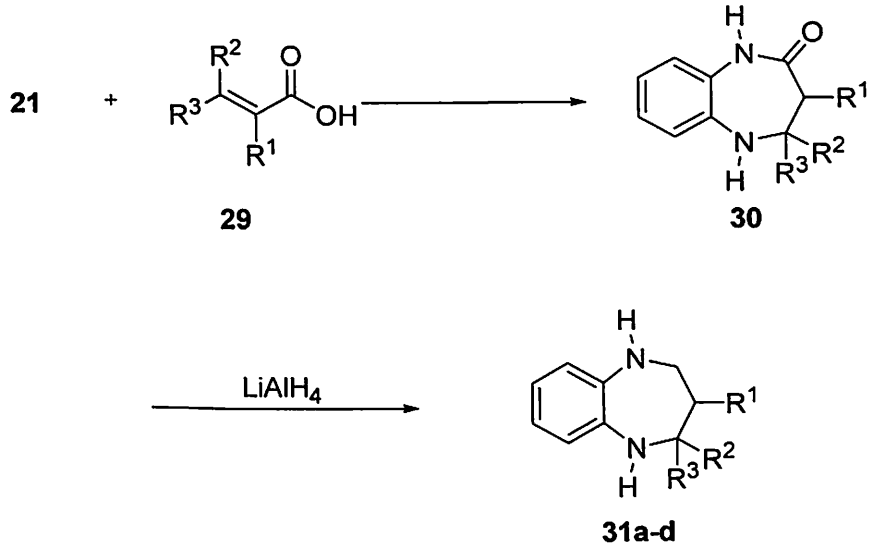


Figure 9. Mechanism for reaction of α,β-unsaturated acid with 1,2-phenylenediamine.

Hasan and co-workers[20] formed 1,5-benzodiazepines by the same method as Dandegaonker and Desai, only they varied the substitution on the aliphatic carbons of the diazepine ring by reacting 1,2-phenylenediamine with four different α,β-unsaturated acids: crotonic, methacrylic, 3,3-dimethylacrylic and acrylic acids (Figure 10). The products of these reactions would place methyl groups on two of the carbons in the diazepine ring. The amide products were converted to 1,5-benzodiazepines (**31a-d**) by reduction with lithium aluminum hydride. The final compounds were isolated in 25-40% overall yield. These yields were relatively low, and the substitution was limited to methyl groups.



31a: $R^1 = R^2 = H$ $R^3 = CH_3$
b: $R^2 = R^3 = H$ $R^1 = CH_3$
c: $R^1 = H$ $R^2 = R^3 = CH_3$
d: $R^1 = R^2 = R^3 = H$

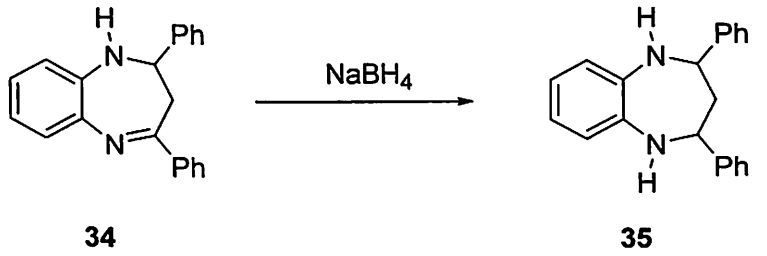
Figure 10. Condensation of various α,β-unsaturated acids with 1,2-phenylenediamine.

Zhelyazkiv and Bizhev[21] synthesized 1,5-benzodiazepines starting with α,β-unsaturated ketones rather than α,β-unsaturated acids (Figure 11). The starting material was the usual 1,2-phenylenediamine and the R groups on the α,β-unsaturated ketones

Figure 11. Condensation of α,β-unsaturated ketone with 1,2-phenylenediamine.

were either methyl or phenyl. The yields for these products were as high as 78%. Final reduction of the C=N could be carried out with sodium borohydride as Orlov and co-

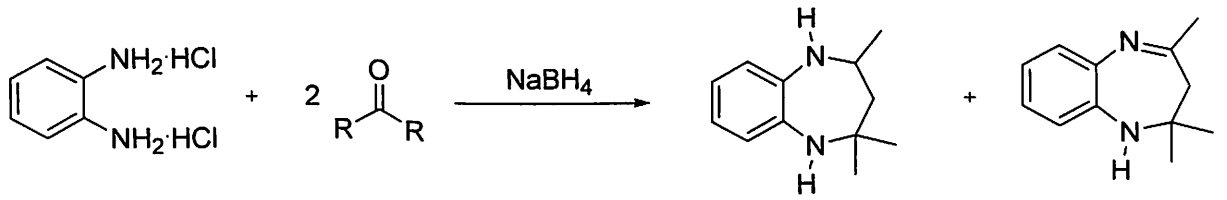
workers[22] did with a similar 1,5-benzodiazepine (Figure 12). The method of Zhelyazkov and Bizhev, however, allowed a wider variety of substitution patterns.



34 **35**

Figure 12. Reduction of C=N with $NaBH_4$.

Contreras and co-workers[23] synthesized 1,5-benzodiazepines by double reductive condensation of 1,2-phenylenediamine dihydrochloride with two equivalents of a series of symmetrical ketones (Figure 13). Reaction in the presence of sodium borohydride gave two products. The major product was the desired 1,5-benzodiazepine; the minor product had an unsaturated bond between one of the nitrogens and the adjacent carbon.



36 **37** **38** **39**

Figure 13. 1,5-Benzodiazepines by reductive condensation with two ketones.

The R groups included methyl, cyclopentyl, cyclohexyl and cycloheptyl. The desired 1,5-benzodiazepines were produced in 50-68% yield. When an aromatic ketone or aldehyde was used, the 1,5-benzodiazepines were not obtained.

Misiti, Gatta, and Landi-Vittory[24] synthesized benzodiazepines by utilizing the Schmidt reaction (Figure 14). The authors began with tetrahydroquinolin-4-one (**40**). A nitrogen was inserted adjacent to the carbonyl using the Schmidt reaction and the resulting amide was reduced to the secondary amine with lithium aluminum hydride. The Schmidt reaction yielded a mixture of two products, a 1,4-benzodiazepine and a 1,5-benzodiazepine in 80-95% yield. Unfortunately, the major product in most of the reactions was the 1,4-benzodiazepine. There were only three cases out of ten where the 1,5-benzodiazepine predominated (Table I). The 1,5-benzodiazepine was the major product only when the R^1 substituent on the nitrogen was an acyl group. Thus, the Schmidt reaction is not ideal for synthesizing 1,5-benzodiazepines, unless an acyl group is required on the nitrogen.

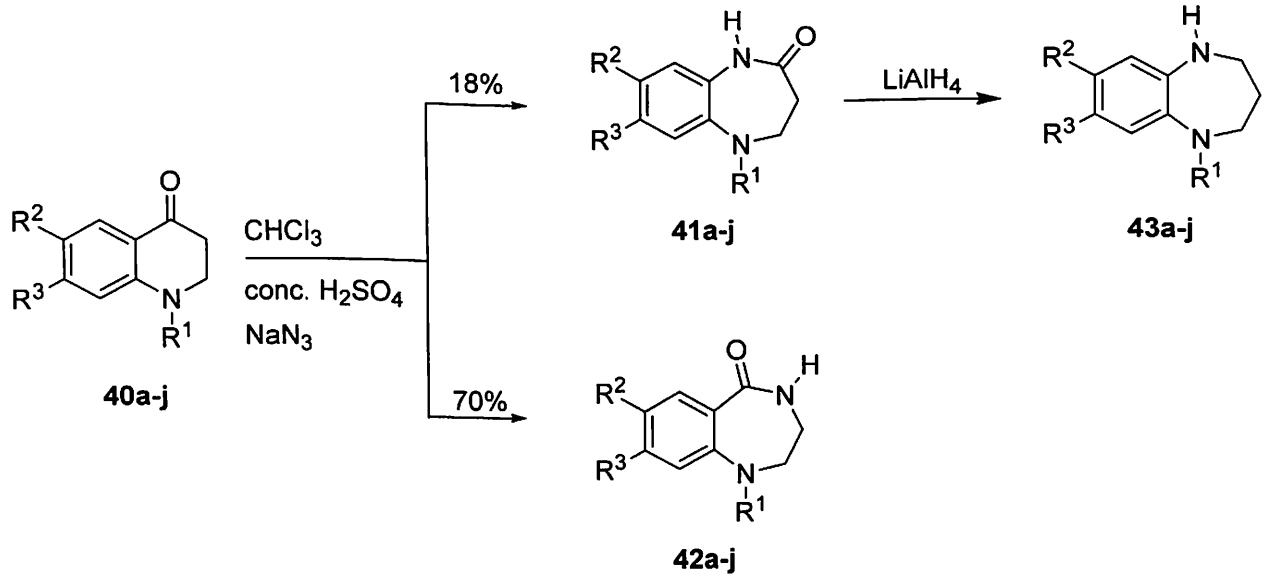


Figure 14. Benzodiazepines by the Schmidt reaction.

	1,2,3,4-tetrahdroquinolin-4-ones				isomer ratio	
	R^1	R^2	R^3	% yield	% aryl migration	% alkyl migration
40a	H	H	H	88	20	80
40b	Me	H	H	82	25	75
40c	Ph	H	H	90	5	95
40d	Ac	H	H	85	95	5
40e	H	H	OMe	95	30	70
40f	Me	H	OMe	92	35	65
40g	Ac	H	OMe	90	90	10
40h	H	Cl	H	92	35	65
40i	Me	Cl	H	91	25	75
40j	Ac	Cl	H	80	90	10

Table I. Migratory aptitudes in the Schmidt reaction of tetrahydroquinolin-4-ones.

CHAPTER II

SYNTHESIS OF 2,3,4,5-TETRAHYDRO-1,5-BENZOXAZEPINES AND 2,3,4,5-TETRAHYDRO-1*H*-1,5-BENZODIAZEPINES

Introduction

The nitro group has proven useful as a latent amine in reductive amination reactions under hydrogenation conditions.[25] Nitro groups are easily reduced to amines by catalytic hydrogenation. The resulting amines can then react with an aldehyde or ketone present in the molecule to form nitrogen heterocycles. The tandem reduction-reductive amination reaction is the reduction of an aromatic nitro group to the amine followed by reductive amination with an intramolecular aldehyde or ketone, all under hydrogenation conditions.

Prior work has shown the tandem reduction-reductive amination reaction to be useful in forming nitrogen heterocycles with more that one heteroatom. Bunce and co-workers[25] have developed a route to tetrahydrobenzoxazines and tetrahydroquinoxalines based on this strategy (Figure 15). Cyclization substrates were prepared by removal of the acidic proton from 2-nitrophenol and *N*-(2-nitrophenyl)acetamide and alkylation at the oxygen or the nitrogen, respectively, with an allylic bromide. The resulting alkene was ozonized to give the ketone or aldehyde and hydrogenation effected the tandem reduction-reductive amination to give the target heterocycles.

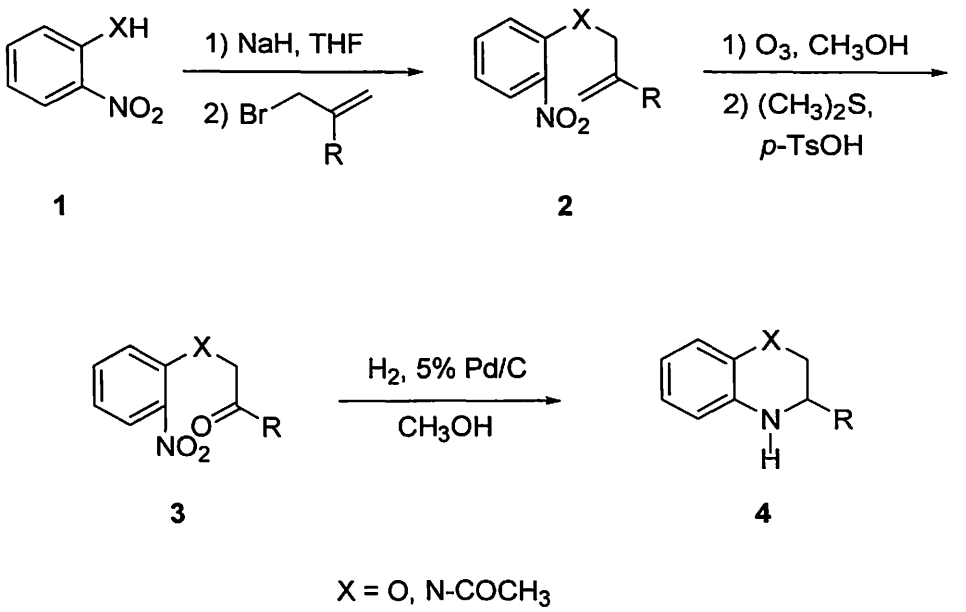
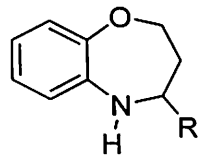


Figure 15. Synthesis of tetrahydrobenzoxazines and tetrahydroquinoxalines.

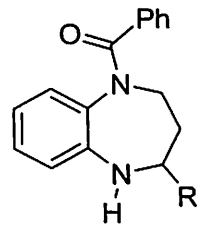
In the present work, the tandem reduction-reductive amination reaction has been extended to the synthesis of 2,3,4,5-tetrahydro-1,5-benzoxazepines and 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines (Figure 16). Members of these heterocycle families have shown a wide range of biological activity and thus may have potential as new pharmaceutical agents. The goal is the efficient preparation of these systems with new substitution patterns.



5a-e

2,3,4,5-tetrahydro-1,5-benzoxazepines

5a R = H
b R = CH_3
c R = C_4H_9
d R = *t*-C_4H_9
e R = C_6H_5



6a-b

2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines

6a R = H
b R = CH_3

Figure 16. Target molecules of the current project.

Proposed Route to 2,3,4,5-Tetrahydro-1,5-Benzoxazepines and 2,3,4,5-Tetrahydro-1*H*-1,5-Benzodiazepines

The current project for synthesizing 2,3,4,5-tetrahydro-1,5-benzoxazepines and 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines required the preparation of substrates such as **8** (Figure 17). Bunce and Johnson[26] have previously demonstrated that the tandem reduction-reductive amination reaction can be used to prepare seven-membered rings containing one heteroatom and thus the primary challenge was the synthesis of the cyclization substrates. The initial target was alkene **7**. Ozonolysis of **7** would yield the ketone **8**. Reductive cyclization of **8** would then afford the target heterocycle **9**.

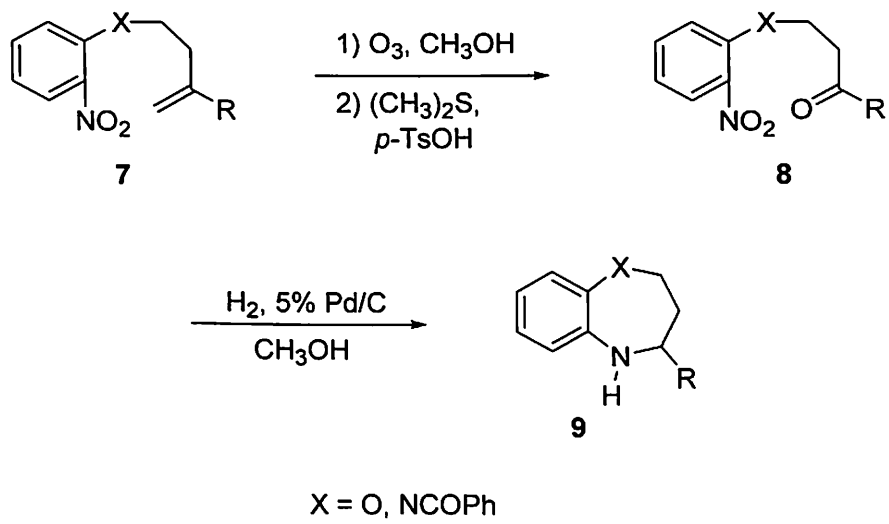


Figure 17. Proposed route to the target molecules.

The first synthetic approach to **7** involved alkylation of 2-nitrophenol (**12**) with a homoallylic halide (Figure 18). Because the homoallylic halides are less reactive than their allylic counterparts, bromide **10** was converted to iodide **11**. Deprotonation of **12** with sodium hydride in tetrahydrofuran then gave the anion which was reacted with **11**. Workup of the reaction did not afford the expected ether, however, but instead gave starting material **12**. This reaction failed because the iodide underwent an elimination reaction and 1,3-butadiene evolved out of the mixture as a gas. Similarly, attempted alkylation of amide **14** gave the same elimination process. Thus, another method for forming the required alkenes **7** was necessary. [Note: We later found that potassium carbonate in acetone could be used to alkylate the phenol, but this base was ineffective in attempts to alkylate the amide.]

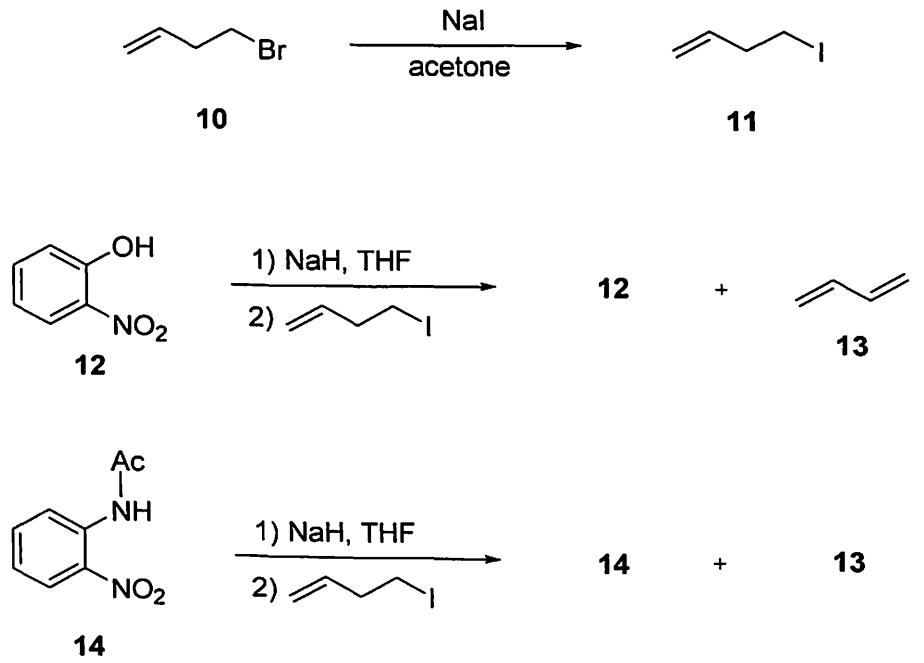


Figure 18. Attempted alkylation of 2-nitrophenol and *N*-(2-nitrophenyl)acetamide.

Synthesis of 2,3,4,5-Tetrahydro-1,5-Benzoxazepine and 2,3,4,5-Tetrahydro-1*H*-1,5-Benzodiazepine Precursors

The successful method for preparing the 1,5-benzoxazepine precursors **18a-e** was carried out in two steps. Nucleophilic aromatic substitution of the homoallylic alkoxides from **15a-e** with 2-fluoro-1-nitrobenzene[27] (**16**) afforded alkenes **17a-e** in 83-95% yield (Figure 19). Ozonolysis of these alkenes then gave the ketone substrates **18a-e** in 88-95% yield.

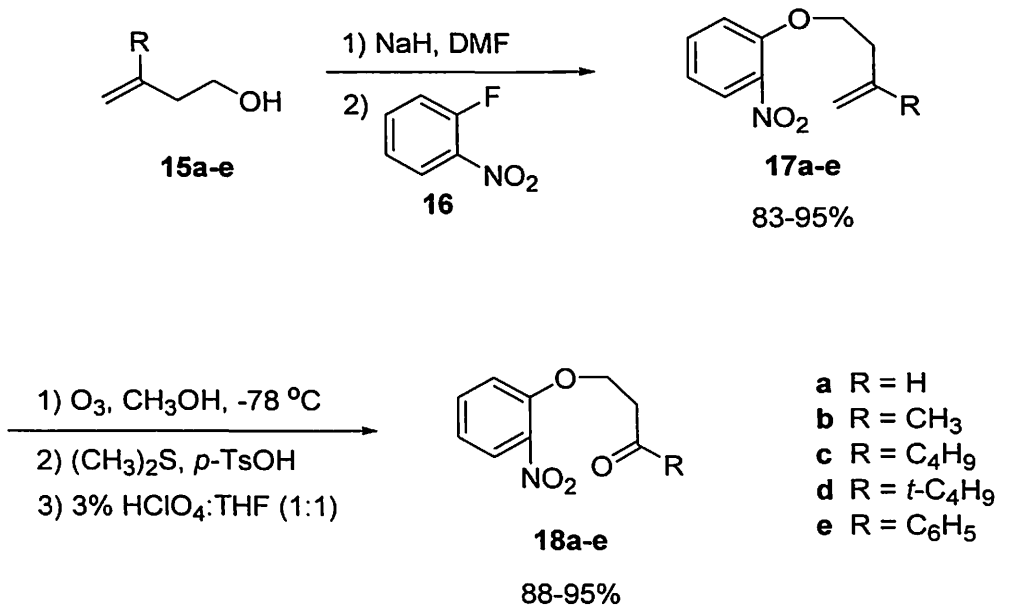


Figure 19. Synthesis of 1,5-benzoxazepine precursors.

Two of the necessary homoallylic alcohols (**15a** and **15b)** were commercially available; the others (**15c, 15d** and **15e**) required synthesis. It was decided that the required homoallylic alcohols could be most easily prepared from allylic bromides that were available from an earlier project. The synthesis of these allylic bromides is shown in Figure 20. For the *n*-butyl case, alkyne **19** was hydrobrominated[30] to give alkene **20** in 70% yield. Compound **20** was converted to its Grignard reagent and reacted with formaldehyde to give allylic alcohol **21** in 65% yield. The allylic alcohol was then treated with phosphorus tribromide to give the allylic bromide **22c** in 88% yield.[31] The *tert*-butyl case was prepared by brominating[32] alkene **23** with *N*-bromosuccinimide to give the required allylic bromide **22d** in 56% yield.

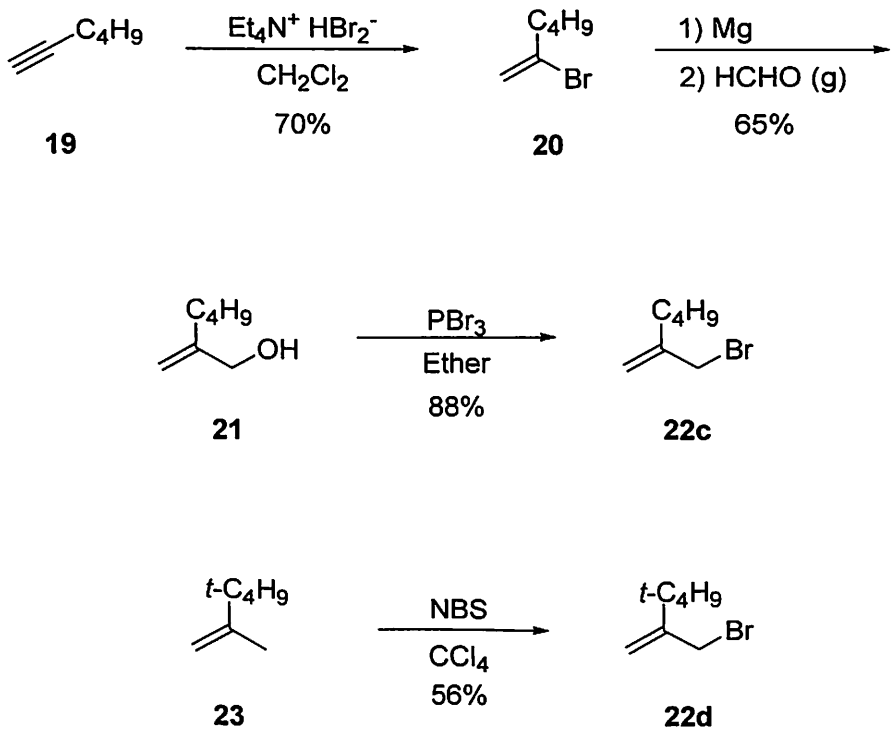


Figure 20. Synthesis of allylic bromides.

The methods by which the homoallylic alcohols were prepared from the allylic bromides are illustrated in Figure 21. The butyl and *tert*-butyl cases were synthesized by converting allylic bromides **22c-d** into Grignard reagents and reacting them with solid carbon dioxide. For this reaction it was necessary to use activated Rieke magnesium[33] to suppress coupling during the formation of the Grignard reagent. Standard Grignard conditions afforded the carboxylic acids in 20-25% yields with the bulk of the product resulting from coupling. Generation of the Grignard reagent using Rieke magnesium at 0°C, however, permitted formation of the acid products in 68-71% yield with no significant coupling of the allylic halide. The resulting carboxylic acids **24c-d** were reduced with lithium aluminum hydride to give the desired homoallylic alcohols **15c-d** in 95-96% yield. Synthesis via the carboxylic acids was superior to direct synthesis of the

alcohols by reaction with formaldehyde. The yield of the acid was higher and the product was readily purified by extraction. Finally, the phenyl case was prepared by reacting **25** with formaldehyde in acetic acid and acetic anhydride to give **26** by an ene reaction.[34] The acetate **26** was hydrolyzed to give homoallylic alcohol **15e** in 50% overall yield.

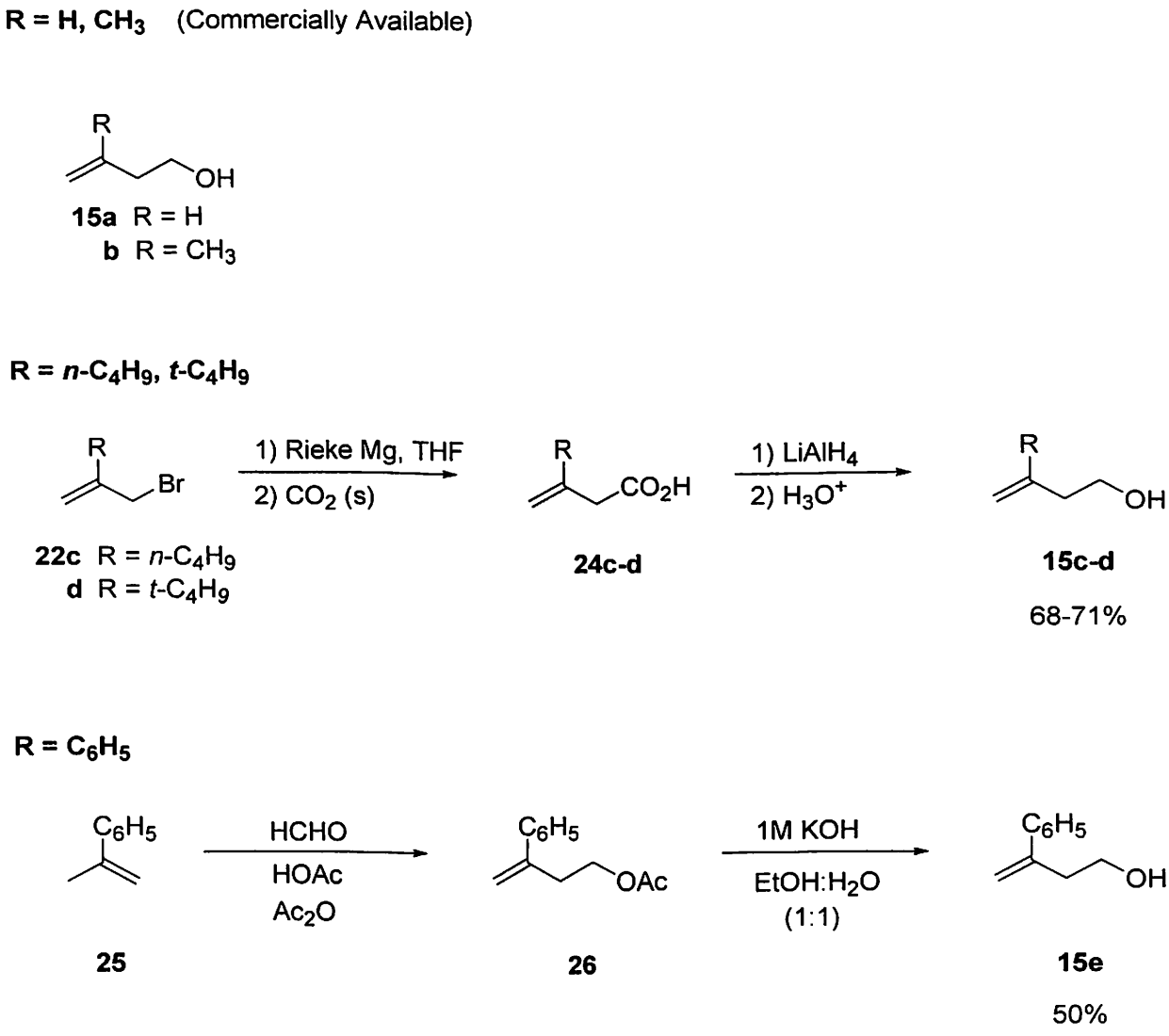


Figure 21. Synthesis of homoallylic alcohols.

The 1,5-benzodiazepine precursors required homoallylic amines as substrates. Homoallylic amines can be most easily prepared from allyl cyanides **27a** and **27b**; **27a** is

commercially available but **27b** is not. The method by which the amines were synthesized is illustrated in Figure 22. To extend the carbon chain of the allylic bromide **28b** by one carbon, **28b** was reacted with copper cyanide[35] to give **27b** in 80% yield. The cyano group of **27b** was then reduced[36] with lithium aluminum hydride/aluminum chloride to give the desired homoallylic amine **29a-b** in 50-75% yield following basic workup.

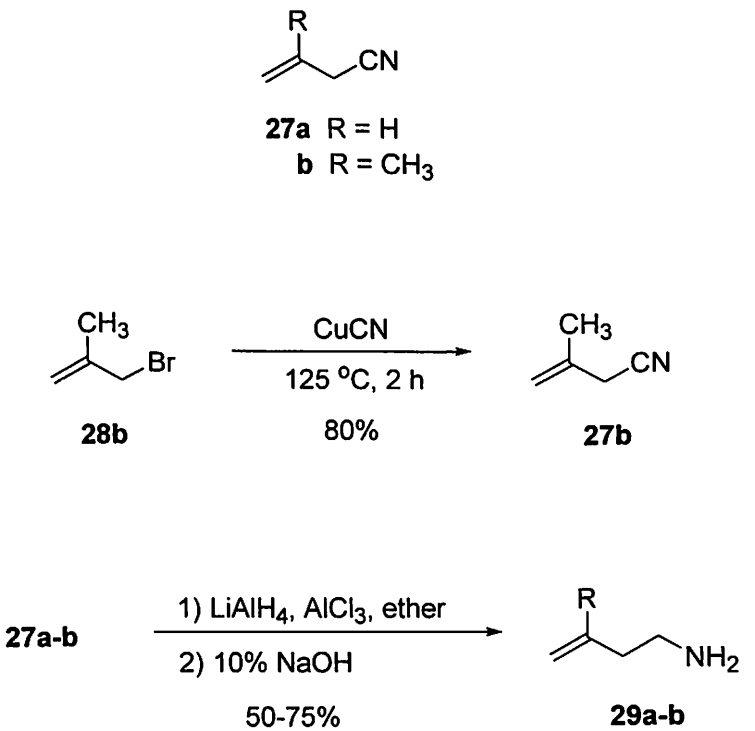


Figure 22. Synthesis of homoallylic amines.

The substrates required for synthesizing the 1,5-benzodiazepines were more difficult to prepare (Figure 23) than the substrates for the 1,5-benzoxazepines.

Homoallylic amine **29a** was reacted with 2-fluoro-1-nitrobenzene (**16**) by a nucleophilic aromatic substitution reaction to give **30a**. Acylation of this amine was necessary to

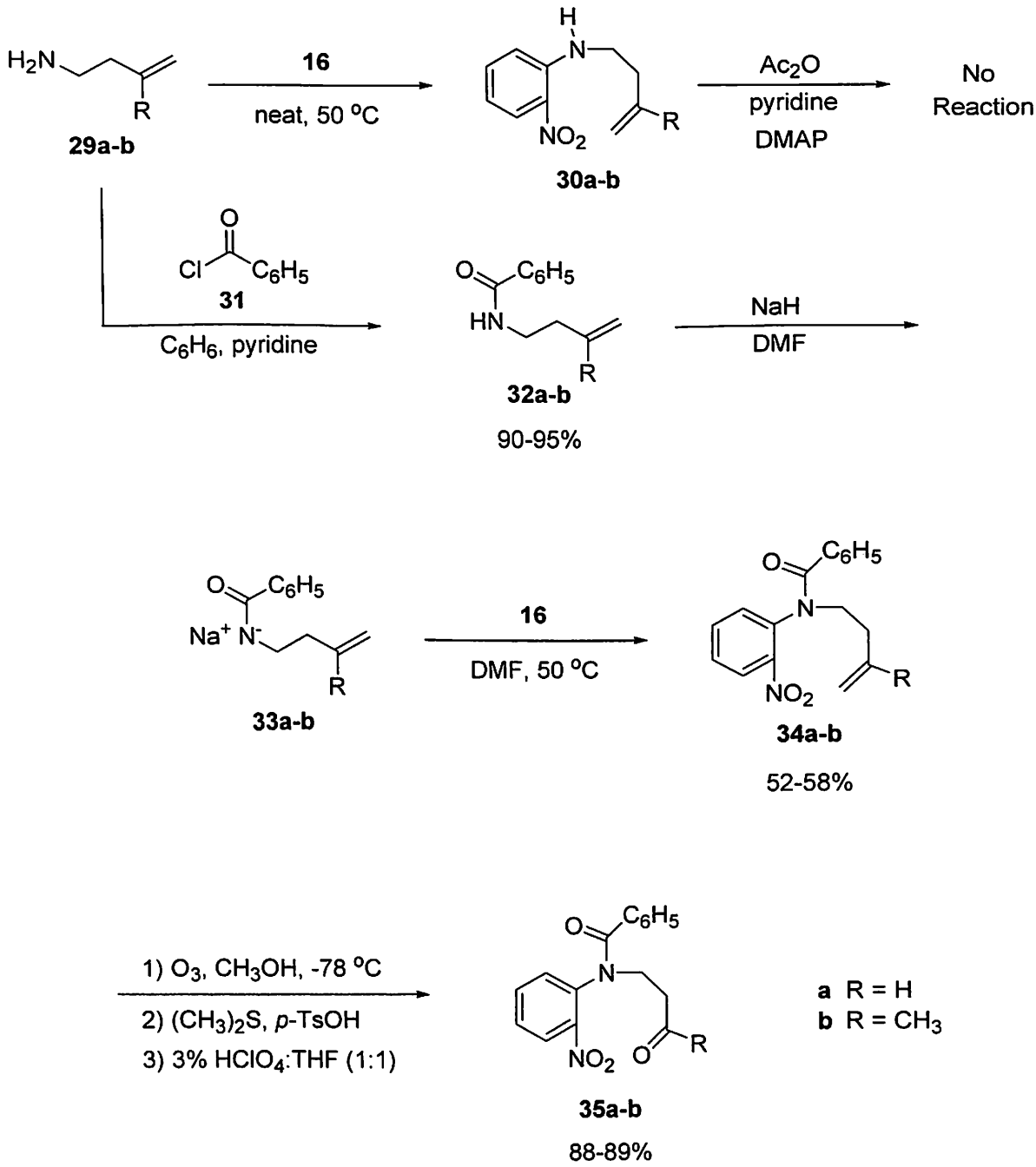


Figure 23. Synthesis of 1,5-benzodiazepine precursors.

prevent *N*-oxidation during the ozonolysis, but attempts to acylate **30a** failed. Because the first approach did not work, a new route was developed. The homoallylic amines (**29a-b**) were acylated with benzoyl chloride (**31**) to give benzamides **32a-b** in 90-95% yield.[37] Deprotonation of the benzamides with sodium hydride, followed by reaction with **16**, gave the desired substrates **34a-b** in 52-58% yield by a nucleophilic aromatic substitution.[38] To our knowledge, this is the first example of the nucleophilic aromatic substitution of a benzamide on an aromatic system. Amides **34a-b** were then ozonized to give **35a-b** in 88-95% yield.

Synthesis of 2,3,4,5-Tetrahydro-1,5-Benzoxazepines and 2,3,4,5-Tetrahydro-1*H*-1,5-Benzodiazepines by a Tandem Reduction-Reductive Reaction

The precursors **18a-e** and **35a-b** were used in the tandem reduction-reductive amination reaction to produce the target heterocycles. The results of this reaction are illustrated in Figure 24. When R = H or CH_3, the yields were high, ranging from 70-88% yield for both the 1,5-benzoxazepine and 1,5-benzodiazepine targets. The butyl, *tert*-butyl, and phenyl cases were done only for the 1,5-benzoxazepine targets. The butyl case proceeded normally to give a 78% yield of the 1,5-benzoxazepine. The *tert*-butyl and phenyl cases gave disappointing results with 37% and 0% yields, respectively.

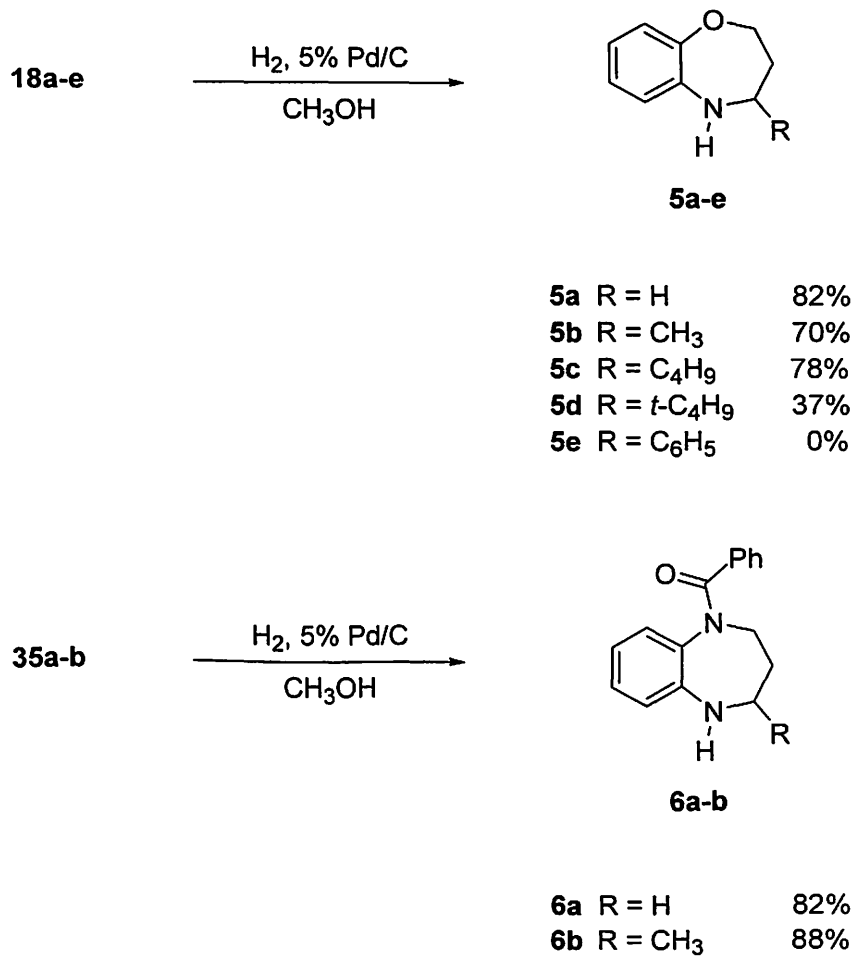


Figure 24. Results of the tandem reduction-reductive amination reaction.

The yield in the synthesis of the parent 1,5-benzoxazepine (R = H) was dependent on the concentration of the substrate (Figure 25). When the concentration of the substrate was 3.85 x 10^{-2} M, the desired target was produced in 72% yield and dimer **36** was isolated in 3.5% yield. When the concentration was reduced by a factor of three, however, the reaction gave a higher yield of the desired product (82%) and dimer formation was almost undetected. Thus, when the solution is more dilute, the chance for an intermolecular reaction decreased, and most of the product derived from the intramolecular reaction.

The *tert*-butyl case had a relatively low yield when compared to the prior cases. The reaction gave two products (Figure 25). The 1,5-benzoxazepine was produced in 37% yield and the amino ketone **37** was produced in 49% yield. Compound **37** is a result of nitro group reduction without subsequent cyclization. Presumably, reductive cyclization was precluded by the steric hindrance from the *tert*-butyl group.

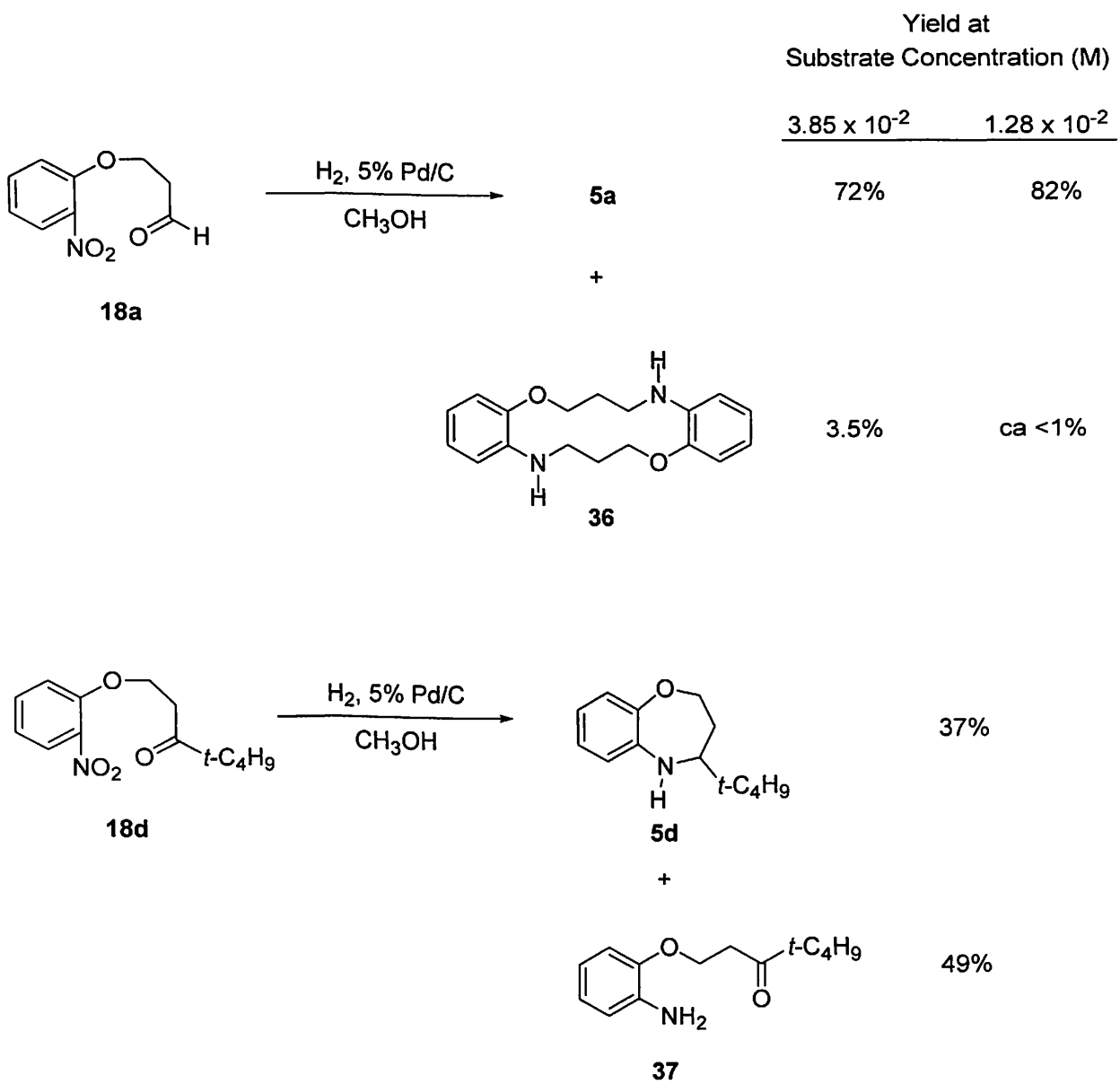


Figure 25. Results of R = H, *t*-C_4H_9 cases for 1,5-benzoxazepines.

The substrate having R = C_6H_5 gave no ring closure when the precursor was subjected to the tandem reduction-reductive amination reaction (Figure 26). Instead of the desired 1,5-benzoxazepine target, compound **38** was produced. Compound **38** is the result of both nitro and carbonyl reduction. Evidently, the phenyl ketone in **18e** is highly susceptible to reduction and was reduced before it could react with the amine. Thus, there was no cyclization. By comparison, Bunce and co-workers successfully performed a tandem reduction-reductive amination reaction on a substrate that produced a six-membered heterocycle **39**. In this reaction, the ring closure proceeded easily to give **40** in 76% yield.

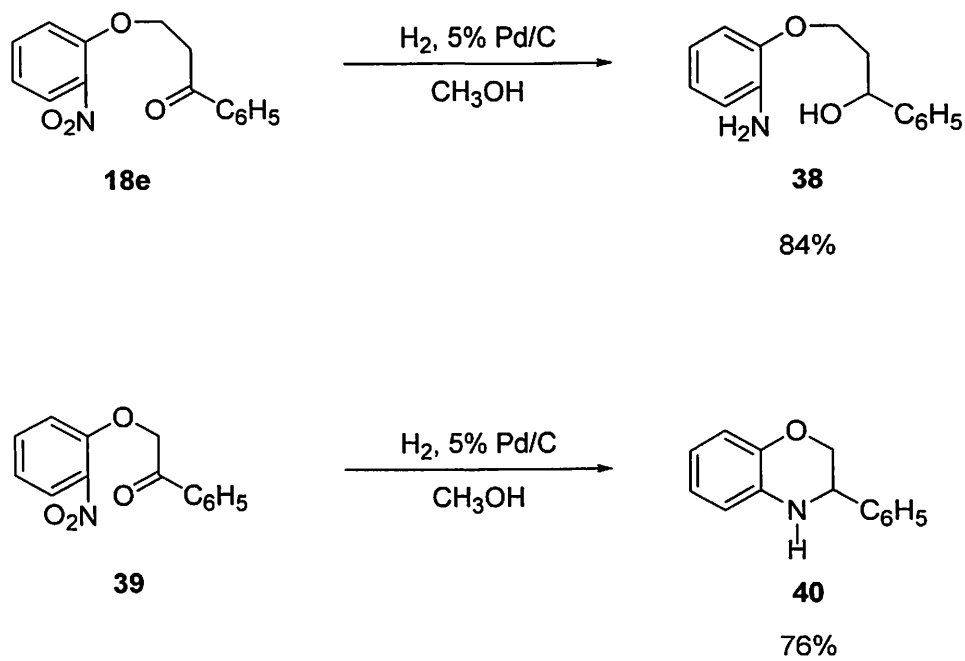


Figure 26. Tandem reduction-reductive amination: comparison of seven-membered vs. six-membered ring closure for R = C_6H_5.

A mechanism for the tandem reduction-reductive amination reaction is illustrated in Figure 27. The precursor (**18a-e, 35a-b**) first undergoes a reduction of the nitro group under catalytic hydrogenation conditions with the loss of water to give **41**. Once the nitro group is reduced to an amine, the unshared pair of electrons on the nitrogen attacks the carbonyl, closing the ring to give **42**. Elimination of water occurs to form imine (**43**) and addition of another equivalent of hydrogen gives the target molecule (**5a-e, 6a-b**).

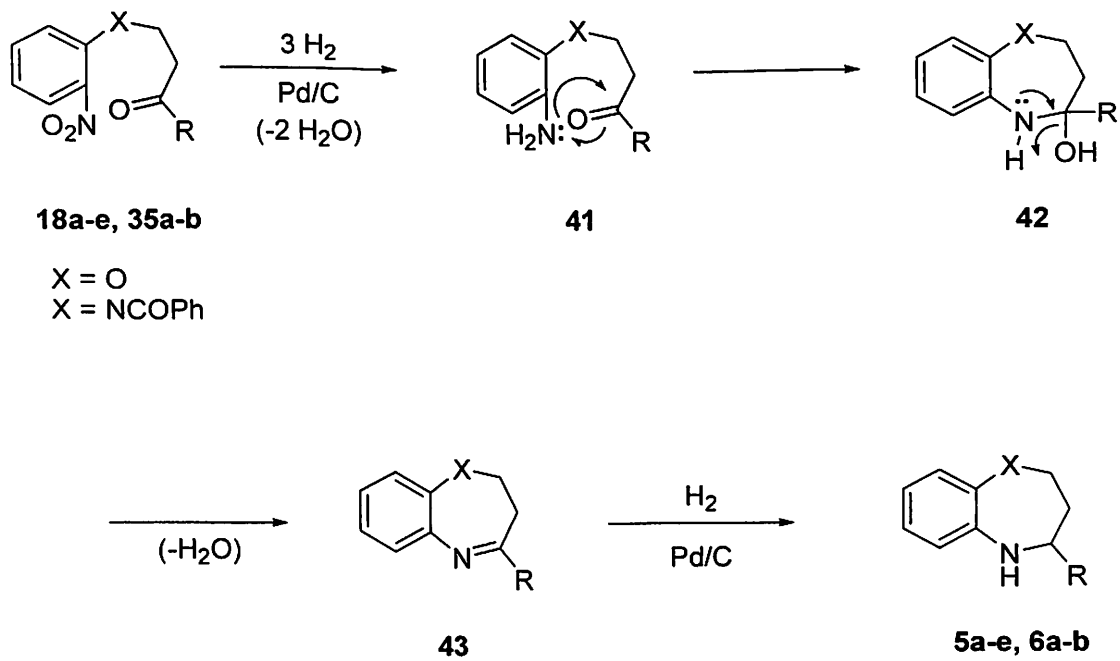


Figure 27. Mechanism for tandem reduction-reductive amination reaction.

Conclusions

A new route has been developed to two potentially valuable ring systems. From the homoallylic alcohols, 2,3,4,5-tetrahydro-1,5-benzoxazepines were synthesized in three steps with an average of 66% yield. From the homoallylic amines, 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines were synthesized in four steps with an average of

42% yield. This latter synthesis features a new approach to the synthesis of the cyclization substrates involving nucleophilic aromatic substitution of a secondary benzamide to 2-fluoro-1-nitrobenzene to install the entire prefabricated nitrogen side chain onto the aromatic ring. The tandem reduction-reductive amination reaction provides an efficient, high-yield route to seven-membered heterocycles. The larger rings are formed more slowly, however, allowing competitive reactions to intervene in some cases. The nitro group continues to prove useful as a latent amine in reductive amination reactions under hydrogenation conditions. A wider variety of substitution patterns is available using the current synthetic approach compared to prior methods.

Experimental

All reactions (except hydrogenations) were run under dry nitrogen in oven-dried glassware. The ammonium chloride (saturated), 1 M hydrochloric acid, 0.2 M sodium hydroxide, sodium bicarbonate (saturated) and sodium chloride (saturated) used in various work-up procedures were aqueous solutions. All temperatures are reported in °C. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech no. 21521) with ultraviolet detection. Preparative separations were performed using one of the following methods: (1) flash column chromatography[39] on silica gel (grade 62, 60-200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies, UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20-cm x 20-cm silica gel GF plates (Analtech no. 02015). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, repectively, using tetramethylsilane as an internal standard; coupling constants (*J*) are given in Hz. Mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

Compounds **15a** (3-buten-1-ol) and **15b** (3-methyl-3-buten-1-ol) were commercially available. Compound **15e** (3-phenyl-3-buten-1-ol) was prepared by the method of Hawkins and Thompson;[34] the physical and spectral data for **15e** matched those reported in the literature.[40] Compounds **22a** and **22b** were commercially available; compounds **22c** and **22d** were prepared as described previously.[28] Compound **27a** (allyl cyanide or 3-butenenitrile) was also commercially available.

Representative Procedure for the Preparation of 3-Butenoic Acids: 3-Butyl-3-butenoic Acid (24c). This compound was prepared on a 20-mmole scale by carbonation of the Grignard reagent from **22c** generated using activated magnesium described by Rieke and Bales.[33] A suspension of 3.80 g (40.0 mmole) of anhydrous magnesium chloride, 3.32 g (20.0 mmole) of potassium iodide and 2.72 g (70.0 mmole) of freshly cut potassium metal in 100 mL of dry tetrahydrofuran was prepared under nitrogen in a 250-mL three-necked round-bottomed flask. The mixture was refluxed with vigorous stirring for 3 hours to give a black viscous suspension. The activated magnesium was cooled to 0° and 3.54 g (20.0 mmole) of **22c** was added dropwise with vigorous stirring. Stirring was continued for 45 minutes at 0° and the Grignard reagent was transferred by cannula under nitrogen pressure to a large excess of solid carbon dioxide in a 500-mL three-necked round-bottomed flask. The reaction was stirred for 3 hours, quenched with ammonium chloride, acidified to pH 2 with 1 M hydrochloric acid and extracted with ether (three times). Purification by base extraction (0.2 M sodium hydroxide)-reacidification (1 M hydrochloric acid) afforded 1.93 g (68%) of 3-butyl-3-butenoic acid as a colorless oil. The product was carried on without further purification. IR: 3686-2287, 1710, 1646, 899 cm^{-1}; ^1H NMR: δ 11.0 (br s, 1 H), 4.96 (m, 1 H), 4.93 (m, 1 H), 3.08 (d, 2 H, J = 0.8), 2.13 (t, 2 H, J = 7.1), 1.44 (m, 2 H), 1.33 (m, 2 H), 0.91 (t, 3 H, J = 7.4); ^{13}C NMR: δ 178.2, 142.0, 114.0, 41.7, 35.5, 22.3, 13.9; MS: *m/z* 142 (M^+).

Anal. Calcd. For $C_8H_{14}O_2$: C, 67.61; H, 9.86. Found: C, 67.91; H, 9.92.

3-*tert*-Butyl-3-butenoic Acid (24d). This compound (2.02 g, 71%) was isolated as a colorless oil and was used without further purification. IR: 3467-2382, 1710, 1636,

908 cm^{-1}; ^1H NMR: δ 11.6 (br s, 1 H), 5.10 (s, 1 H), 4.93 (s, 1 H), 3.11 (s, 2 H), 1.09 (s, 9 H); ^{13}C NMR: δ 179.2, 149.8, 112.0, 38.1, 36.3, 28.8 (3); MS: *m/z* 142 (M^+).

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.61; H, 9.86. Found: C, 67.51; H, 9.92.

Representative Procedure of 3-Buten-1-ols: 3-Butyl-3-buten-1-ol (15c). Reduction of the 2.10 g (14.8 mmoles) of **24c** with 0.56 g (14.8 mmoles) of lithium aluminum hydride in 50 mL of anhydrous ether afforded the crude alcohol after workup with 5% aqueous sodium hydroxide and water. Purification by vacuum distillation afforded 1.80 g (95%) of **15c** as a colorless liquid, bp 46-48° (2 mm Hg); IR: 3338, 1643, 885 cm^{-1}; ^1H NMR: δ 4.86 (s, 1 H), 4.81 (s, 1 H), 3.71 (br t, 2 H, J = 6.6), 2.30 (t, 2 H, J = 6.3), 2.03 (t, 2 H, J = 6.9), 1.50-1.24 (complex, 5 H), 0.91 (t, 3 H, J = 7.2); ^{13}C NMR: δ 146.2, 108.5, 60.3, 39.1, 35.4, 29.9, 22.4, 13.9; MS: *m/z* 128 (M^+).

Anal. Calcd. for $C_8H_{16}O$: C, 75.00; H, 12.50. Found: C, 74.94; H, 12.55.

3-*tert*-Butyl-3-buten-1-ol (15d). This compound (1.61 g, 96%) was isolated as a colorless liquid by the same procedure used to prepare **15c**, bp 60-62° (18 mm Hg); IR: 3339, 1633, 892 cm^{-1}; ^1H NMR: δ 4.98 (s, 1 H), 4.74 (s, 1 H), 3.77 (br t, 2 H, J = 6.0), 2.35 (t, 2 H, J = 6.7), 1.59 (br s, 1 H), 1.08 (s, 9 H); ^{13}C NMR: δ 154.1, 107.8, 61.9, 36.3, 31.0, 29.3 (3); MS: *m/z* 128 (M^+).

Anal. Calcd. for $C_8H_{16}O$: C, 75.00; H, 12.50. Found: C, 75.08; H, 12.54.

Representative Procedure for the Preparation of 3-Butenyl(2-nitroaromatic) Ethers: 2-(3-butenyloxy)-1-nitrobenzene (17a). This compound was prepared on a 5.00-mmole scale by nucleophilic aromatic substitution of the alkoxide derived from 3-butyl-3-buten-1-ol with 2-fluoro-1-nitrobenzene according to the procedure of Bunce and Easton.[27] The product (0.82 g, 85%) was purified on a 40 cm x 2.5 cm silica gel column

eluted with 5% ether in hexane to give 0.82 g (85%) of **17a** as a light yellow oil. The spectral data matched those reported previously.[27]

2-(3-Methyl-3-butenyloxy)-1-nitrobenzene (17b). This compound (0.87 g, 84%) was isolated as a light yellow oil by the same procedure used to prepare **17a**; IR: 1650, 1525, 1351 cm^{-1}; ^1H NMR: δ 7.81 (dd, 1 H, J = 8.1, 1.6), 7.51 (ddd, 1 H, J = 8.4, 7.5, 1.3), 7.08 (d, 1 H, J = 8.4), 7.00 (t, 1 H, J = 8.1), 4.86 (s, 1 H), 4.81 (s, 1 H), 4.21 (t, 2 H, J = 6.8), 2.56 (t, 2 H, J = 6.8), 1.81 (s, 3 H); ^{13}C NMR: δ 152.2, 141.5, 140.0, 133.9, 125.5, 120.2, 114.5, 112.6, 68.4, 36.8, 22.8; MS: *m/z* 207 (M^+).

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.77; H, 6.28; N, 6.76. Found: C, 63.89; H, 6.34; N, 6.67.

2-(3-Butyl-3-butenyloxy)-1-nitrobenzene (17c). This compound (1.09 g, 88%) was isolated as a light yellow oil by the same procedure used to prepare **17a**; IR: 1645, 1358, 1351 cm^{-1}; ^1H NMR: δ 7.81 (dd, 1 H, J = 8.1, 1.8), 7.50 (ddd, 1 H, J = 8.5, 7.5, 1.8), 7.08 (dd, 1 H, J = 8.5, 1.0), 7.01 (ddd, 1 H, J = 8.1, 7.5, 1.2), 4.86 (s, 1 H), 4.83 (s, 1 H), 4.20 (t, 2 H, J = 6.9), 2.56 (t, 2 H, J = 6.9), 2.09 (t, 2 H, J = 7.1), 1.49-1.26 (complex, 4 H), 0.91 (t, 3 H, J = 7.1); ^{13}C NMR: δ 152.2, 145.6, 140.2, 133.9, 125.5, 120.2, 114.3, 111.3, 68.6, 36.1, 35.1, 29.8, 22.4, 13.9; MS: *m/z* 249 (M^+).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.47; H, 7.63; N, 5.62. Found: C, 67.63; H, 7.71; N, 5.47.

2-(3-*tert*-Butyl-3-butenyloxy)-1-nitrobenzene (17d). This compound (1.07 g, 86%) was isolated as a light yellow oil by the same procedure used to prepare **17a**; IR: 1638, 1526, 1354 cm^{-1}; ^1H NMR: δ 7.81 (dd, 1 H, J = 8.1, 1.8), 7.51 (ddd, 1 H, J = 8.5, 7.5, 1.8), 7.09 (dd, 1 H, J = 8.5, 1.0), 7.01 (ddd, 1 H, J = 8.1, 7.5, 1.2), 4.99 (s, 1 H), 4.78

(s, 1 H), 4.21 (t, 2 H, J = 7.5), 2.61 (t, 2 H, J = 7.5), 1.09 (s, 9 H); ^{13}C NMR: δ 153.4, 152.2, 140.2, 134.0, 125.5, 120.2, 114.5, 108.3, 69.7, 36.2, 30.4, 28.9 (3); MS (30 electron volts): *m/z* 249 (M^+).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.47; H, 7.63; N, 5,62. Found: C, 67.52; H, 7.65; N, 5.57.

2-(3-Phenyl-3-butenyloxy)-1-nitrobenzene (17e). This compound (1.21 g, 90%) was isolated as a light yellow oil by the same procedure used to prepare **17a**; IR: 1672, 1525, 1351 cm^{-1}; ^{1}H NMR: δ 7.79 (dd, 1 H, J = 8.5, 1.6), 7.48-7.42 (complex, 3 H), 7.37-7.25 (complex, 3 H), 7.01-6.96 (complex, 2 H), 5.42 (s, 1 H), 5.22 (s, 1 H), 4.17 (t, 2 H, J = 7.1), 3.06 (t, 2 H, J = 7.1); ^{13}C NMR: δ 152.1, 146.0, 143.7, 140.2, 133.9, 128.5, 127.7, 126.1, 125.5, 120.3, 115.2, 114.6, 68.3, 34.9; MS: *m/z* 269 (M^+).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.38; H, 5.58; N, 5.20. Found: C, 71.25; H, 5.53; N, 5.26.

3-Butenylamine (29a). This compound (3.15 g, 48%) was prepared by reduction of 90 mmoles of **27a** according to the procedure of Jacobson and Williard,[36] bp 75-77° (literature[41] bp 75-77°); IR: 3372, 3301, 1640, 991, 908 cm^{-1}; ^{1}H NMR: δ 5.78 (ddt, 1 H, J = 17.2, 10.3, 6.9), 5.10 (dm, 1 H, J = 17.2), 5.07 (dm, 1 H, J = 10.3), 2.76 (t, 2 H, J = 6.6), 2.20 (apparent q, 2 H, J = 6.6), 1.13 (br s, 2 H); ^{13}C NMR: δ 136.2, 116.6, 41.2, 38.1.

3-Methyl-3-butenylamine (29b). This compound (5.01 g, 64%) was prepared by reduction of 90 mmoles of **27b**[35] according to the procedure of Jacobson and Williard,[36] bp 93-95°; IR: 3365, 3290, 1647, 885 cm^{-1}; ^{1}H NMR: δ 4.84 (m, 1 H), 4.76 (m, 1 H), 2.84

(t, 2H, J = 6.6), 2.20 (t, 2 H, J = 6.6), 1.76 (m, 3 H), 1.15 (br s, 2 H); ^{13}C NMR: δ 143.2, 111.7, 41.9, 39.7, 22.1.

***N*-(3-Butenyl)benzamide (32a).** This compound was prepared on an 82-mmole scale by Schotten-Baumann benzoylation of 3-butenylamine in benzene using the procedure of Dewar and co-workers.[37] The product was isolated in 94% yield by column chromatography on silica gel eluted with 25% ether in hexanes. The spectral data matched those reported previously.[42]

***N*-(3-Methyl-3-butenyl)benzamide (32b).** This compound (3.27 g, 96%) was isolated by the same procedure used to prepare **32a**; IR: 3310, 1639, 1542, 889 cm^{-1}; ^{1}H NMR: δ 7.74 (dd, 2 H, J = 8.1, 1.3), 7.55-7.39 (complex, 3 H), 6.19 (br s, 1 H), 4.88 (m, 1 H), 4.82 (m, 1 H), 3.58 (apparent q, 2 H, J = 6.8), 2.34 (t, 2 H, J = 6.7), 1.79 (s, 3 H); ^{13}C NMR: δ 167.3, 142.7, 134.7, 131.3, 128.5, 126.8, 112.6, 37.3, 37.2, 21.9; MS: *m/z* 189 (M^+).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.41. Found: C, 76.04; H, 7.99; N, 7.35.

Representative Procedure for Nucleophilic Aromatic Substitution of Benzamides to 2-Fluoro-1-nitrobenzene: *N*-(3-Butenyl)-*N*-(2-nitrophenyl)benzamide (34a). In a 250-mL, three-necked round-bottomed flask equipped with an addition funnel, a magnetic stir bar and a condenser, 0.44 g of 60% sodium hydride in mineral oil (11.0 mmoles) was washed with hexane (three times) and suspended in 15 mL of dimethylformamide. Stirring was started and a solution of 1.75 g (10.0 mmoles) of **32a** in 15 mL of dimethylformamide was added dropwise at room temperature. The mixture was stirred for 2 h at which time a solution of 0.71 g (5.0 mmoles) of 2-fluoro-1-

nitrobenzene in 2 mL of dimethylformamide was added. The reaction became warm and turned brown in color. The reaction was stirred for 1 h at room temperature and for 24 h at 50°, then cooled, added to ammonium chloride, and extracted with ether (three times). The combined ether layers were washed with water and saturated sodium chloride, dried (magnesium sulfate), and concentrated under vacuum. The crude product was flash chromatographed on a 40 cm x 2 cm silica gel column eluted with 10-20% ether in hexane to afford 1.72 g (58%) of **34a** as a yellow oil; IR: 1657, 1528, 1348, 994, 918 cm^{-1}; ^1H NMR (not coalesced): δ 7.83 (br s, 1 H), 7.50 (br s, 1 H), 7.43-7.20 (br m, 6 H), 7.16 (br s, 1 H), 5.79 (br s, 1 H), 5.09 (br d, 1 H, J = 16.1), 5.05 (br d, 1 H, J = 9.6), 4.32 (br s, 1 H), 3.55 (m, 1 H), 2.47 (br s, 2 H); ^{13}C NMR: δ 165.6, 146.0, 137.5, 134.9, 133.7, 131.8, 129.9, 128.2 (2), 127.9 (2), 125.7, 117.1, 49.1, 32.1; MS: *m/z* 296 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 69.10; H, 5.49; N, 9.33.

***N*-(3-Methyl-3-butenyl)-*N*-2-nitrophenyl)benzamide (34b).** This compound (1.61 g, 52%) was isolated as a light yellow solid by the same procedure used to prepare **34a**, mp 65-66°; IR: 1653, 1529, 1348, 894 cm^{-1}; ^1H NMR (not coalesced): δ 7.84 (br s, 1 H), 7.51 (br s, 1 H), 7.45-7.23 (br m, 6 H), 7.14 (br s, 1 H), 4.79 (br s, 1 H), 4.73 (br s, 1 H), 4.38 (br s, 1 H), 3.59 (m, 1 H), 2.41 (br s, 2 H), 1.75 and 1.73 (2 s, 3 H); ^{13}C NMR: δ 168.4, 145.8, 142.6, 135.3, 133.7, 131.9, 130.0, 128.2 (2), 128.0 (2), 125.7, 112.1, 49.1, 35.4, 22.5; MS: *m/z* 310 (M^+).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03. Found: C, 69.79; H, 5.87; N, 8.96.

Representative Ozonolysis Procedure: 3-(2-Nitrophenoxy)propanal (18a). A solution of 0.80 g (4.14 mmole) of **17a** in 125 mL of methanol was cooled to -78° and treated with ozone until TLC indicated complete consumption of the starting material. Excess ozone was purged with a stream of dry nitrogen and the reaction was quenched at -78° by addition of 5.08 g (84.9 mmole) of dimethyl sulfide and 200 mg of *p*-toluenesulfonic acid. The resulting solution was warmed to room temperature and stirred for 8 hours, then concentrated under reduced pressure. The crude reaction mixture was diluted with ether, washed with sodium bicarbonate and sodium chloride, and dried (magnesium sulfate). Vacuum filtration and concentration under reduced pressure gave a mixture of the aldehyde and its dimethyl acetal. This mixture was dissolved in 25 mL of tetrahydrofuran, cooled to 0°, and 25 mL of 3% aqueous perchloric acid was added dropwise with stirring.[29] The solution was stirred at 0° for 1 hour and at room temperature for 4 hours, then extracted with dichloromethane (three times). The combined organic extracts were washed with sodium bicarbonate (two times) and sodium chloride, dried (magnesium sulfate), and concentrated under reduced pressure to yield 0.76 g (94%) of **18a**, which was used without further purification; IR: 2840, 2730, 1723, 1528, 1354 cm^{-1}; ^1H NMR: δ 9.89 (t, 1 H, J = 1.1), 7.83 (dd, 1 H, J = 8.1, 1.8), 7.55 (ddd, 1 H, J = 8.4, 7.4, 1.8), 7.13 (dd, 1 H, J = 8.4, 1.0), 7.06 (ddd, 1 H, J = 8.1, 7.4, 1.2), 4.44 (t, 2 H, J = 6.2), 3.02 (td, 2 H, J = 6.2, 1.1); ^{13}C NMR: δ 199.2, 151.8, 140.1, 134.1, 125.6, 120.9, 114.8, 63.4, 42.8; MS: *m/z* 195 (M^+).

Anal. Calcd. for $C_9H_9NO_4$: C, 55.38; H, 4.62; N, 7.18. Found: C, 55.51; H, 4.72; N, 7.05.

4-(2-Nitrophenoxy)-2-butanone (18b). This compound (0.77 g, 95%) was isolated by the same procedure used to prepare **18a** and purified by flash column chromatography on silica gel using 5-10% ether in hexanes. The product was a light yellow oil that solidified on cooling to 0°, mp 35-36°; IR: 1717, 1523, 1353 cm^{-1}; ^1H NMR: δ 7.82 (dd, 1 H, J = 8.1, 1.8), 7.53 (tm, 1 H, J = 8.4), 7.12 (dd, 1 H, J = 8.4, 1.0), 7.03 (ddd, 1 H, J = 8.1, 7.4, 1.2), 4.37 (t, 2 H, J = 6.2), 2.98 (t, 2 H, J = 6.2), 2.27 (s, 3 H); ^{13}C NMR: δ 206.0, 152.0, 139.8, 134.1, 125.5, 120.6, 114.7, 64.8, 42.3, 30.8; MS: *m/z* 209 (M^+).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.42; H, 5.26; N, 6.70. Found: C, 57.55, H, 5.31; N, 6.59.

1-(2-Nitrophenoxy)-3-heptanone (18c). This compound (0.75 g, 93%) was isolated as a light yellow oil by the same procedure used to prepare **18b**; IR: 1714, 1527, 1351 cm^{-1}; ^1H NMR: δ 7.81 (dd, 1 H, J = 8.1, 1.8), 7.52 (ddd, 1 H, J = 8.5, 7.5, 1.8), 7.12 (dd, 1 H, J = 8.5, 1.2), 7.03 (ddd, 1 H, J = 8.1, 7.5, 1.2), 4.37 (t, 2 H, J = 6.2), 2.95 (t, 2 H, J = 6.2), 2.53 (t, 2 H, J = 7.5), 1.60 (quintet, 2 H, J = 7.4), 1.33 (sextet, 2 H, J = 7.4), 0.92 (t, 2 H, J = 7.4); ^{13}C NMR: δ 208.5, 152.0, 140.0, 134.1, 125.5, 120.5, 114.7, 64.9, 43.5, 41.4, 25.6, 22.2, 13.8; MS: *m/z* 251 (M^+).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77; N, 5.58. Found: C, 62.07; H, 6.75; N, 5.59.

4,4-Dimethyl-1-(2-nitrophenoxy)-3-pentanone (18d). This compound (0.73 g, 91%) was isolated as a light yellow oil by the same procedure used to prepare **18b**; IR: 1710, 1527, 1354 cm^{-1}; ^1H NMR: δ 7.81 (dd, 1 H, J = 8.2, 1.8), 7.52 (ddd, 1 H, J = 8.4, 7.4, 1.8), 7.13 (dd, 1 H, J = 8.4, 1.2), 7.02 (ddd, 1 H, J = 8.2, 7.5, 1.2), 4.39 (t, 2 H, J =

6.2), 3.03 (t, 2 H, J = 6.2), 1.19 (s, 9 H); ^{13}C NMR: δ 213.0, 152.2, 140.0, 134.1, 125.5, 120.4, 114.6, 65.0, 44.3, 35.8, 26.0 (3); MS (30 electron volts): *m/z* 251 (M^+).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77; N, 5.58. Found: C, 62.28; H, 6.83; N, 5.52.

3-(2-Nitrophenoxy)-1-phenyl-1-propanone (18e). This compound (0.76 g, 94%) was isolated as a light yellow solid by the same procedure used to prepare **18b**, mp 103-105°; IR: 1684, 1525, 1352 cm^{-1}; ^{1}H NMR: δ 8.00 (dd, 1 H, J = 7.1, 1.2), 7.81 (dd, 1 H, J = 8.1, 1.8), 7.62-7.45 (complex, 4 H), 7.20 (dd, 1 H, J = 8.4, 1.0), 7.04 (ddd, 1 H, J = 8.1, 7.5, 1.2), 4.57 (t, 2 H, J = 6.6), 3.55 (t, 2 H, J = 6.6); ^{13}C NMR: δ 197.2, 152.1, 139.9, 136.4, 134.1, 133.5, 128.7, 128.1, 125.5, 120.6, 114.8, 65.1, 42.2; MS: *m/z* 271 (M^+).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.80; N, 5.17. Found: C, 66.59; H, 4.87; N, 5.05.

***N*-(2-Nitrophenyl)-*N*-(3-oxopropyl)benzamide (35a).** This compound (0.66 g, 82%) was isolated by the same procedure used to prepare **18b**. Purification was accomplished by flash column chromatography on silica gel eluted with 25% ether in hexane to give **35a** as a light yellow oil; IR: 2840, 2731, 1719, 1654, 1628, 1348 cm^{-1}; ^{1}H NMR (not coalesced): δ 9.81 (s, 1 H), 7.82 (d, 1 H, J = 7.2), 7.59 (t, 1 H, J = 7.5), 7.39 (apparent t, 2 H, J = 8.0), 7.30-7.07 (complex, 5 H), 4.36 (m, 1 H), 4.07 (quintet, 1 H, J = 6.6), 3.03 (br s, 3 H); ^{13}C NMR: δ 200.4, 170.6, 146.2, 142.6, 134.4, 134.2, 131.2, 130.3, 128.4, 128.2, 128.0, 125.7, 45.0, 42.1; MS: *m/z* 298 (M^+).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.70; N, 9.40. Found: C, 64.61; H, 4.82; N, 9.27.

***N*-(2-Nitrophenyl)-*N*-(3-oxobutyl)benzamide (35b).** This compound (0.68 g, 84%) was isolated as a light yellow solid by the same procedure used to prepare **35a**, mp 62-64°; IR: 1711, 1654, 1528, 1348 cm^{-1}; ^1H NMR (not coalesced): δ 7.78 (d, 1 H, J = 7.2), 7.60 (t, 1 H, J = 7.2), 7.44 (dd, 1 H, J = 8.0, 1.3), 7.34 (t, 1 H, J = 7.5), 7.31-7.05 (complex, 5 H), 4.20 (m, 1 H), 4.12 (m, 1 H), 3.05 (br s, 2 H), 2.16 (br s, 3 H); ^{13}C NMR: δ 208.0, 170.3, 145.7, 138.1, 134.5, 134.1, 131.0, 130.2, 128.3, 128.1, 127.9, 125.7, 46.5, 41.2, 30.0; MS: *m/z* 312 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 6.09; N, 8.97. Found: C, 65.47; H, 6.13; N, 8.93.

Representative Procedure for Reductive Ring Closure: 2,3,4,5-Tetrahydro-1,5-benzoxazepine (5a). To a solution of 750 mg (3.85 mmole) of **18a** in 300 mL of methanol was added 150 mg of 5% palladium-on-carbon and the mixture was hydrogenated in a stainless steel hydrogenation vessel under 4 atmospheres of hydrogen for 3 hours at 25°. The crude reaction mixture was concentrated, diluted with ether, and vacuum filtered through a pad of Celite 545® topped with a layer of magnesium sulfate to remove the catalyst. Concentration of the filtrate produced a light yellow oil that was purified by preparative thin layer chromatography eluted with increasing concentrations of ether in hexanes (10%) to give 470 mg (82%) of **5a** as a light yellow oil which solidified on standing at 0°, mp 35-37°; IR: 3358 cm^{-1}; ^1H NMR: δ 6.96 (dd, 1 H, J = 7.8, 1.6), 6.87 (td, 1 H, J = 7.4, 1.6), 6.79 (td, 1 H, J = 7.5, 1.8), 6.72 (dd, 1 H, J = 7.5, 1.8), 4.08 (t, 2 H, J = 5.4), 3.77 (br s, 1 H), 3.24 (t, 2 H, J = 5.6), 2.00 (m, 2 H); ^{13}C NMR: δ 150.2, 142.0, 123.4, 121.9, 120.9, 119.6, 71.5, 46.0, 31.9; MS: *m/z* 149 (M^+).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.48; H, 7.38; N, 9.40. Found: C, 72.63; H, 7.46; N, 9.32.

When the reductive ring closure was run under more concentrated conditions (3.85×10^{-2} M), **5a** was produced in 72% yield and dimer **36** was isolated in 3.5% yield, mp 254-256°; IR: 3426 cm^{-1}; ^1H NMR: δ 6.88 (td, 2 H, J = 7.7, 1.3), 6.72 (dd, 2 H, J = 8.0, 1.3), 6.65 (td, 2 H, J = 7.7, 1.5), 6.58 (dd, 2 H, J = 8.0, 1.5), 5.13 (br s, 2 H), 4.21 (t, 4 H, J = 5.0), 3.35 (q, 4 H, J = 5.0), 2.29 (quintet, 4 H, J = 5.1); ^{13}C NMR: δ 145.9, 138.0, 121.3, 116.3, 109.4, 108.7, 69.5, 44.5, 27.9; MS: *m/z* 298 (M^+).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.48; H, 7.38; N, 9.40. Found: C, 72.54; H, 7.39; N, 9.33.

(±)-4-Methyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (5b). This compound was isolated by the same procedure used to prepare **5a**. The resulting oil (473 mg, 87%) crystallized at 0° to a yellow solid that darkened on exposure to air, mp 60-62°; IR: 3351 cm^{-1}; ^1H NMR: δ 6.93 (dd, 1 H, J = 7.5, 1.6), 6.85 (td, 1 H, J = 7.4, 1.6), 6.76 (td, 1 H, J = 7.5, 1.8), 6.71 (dd, 1 H, J = 7.5, 1.8), 4.38 (ddd, 1 H, J = 12.1, 6.2, 3.8), 3.79 (ddd, 1 H, J = 11.9, 8.2, 3.5), 3.32 (m, 1 H), 3.32 (br s, 1 H), 1.96 (ddt, 1 H, J = 13.8, 6.3, 3.4), 1.78 (m, 1 H), 1.29 (d, 3 H, J = 6.5); ^{13}C NMR: δ 150.3, 140.8, 123.3, 121.7, 120.9, 119.8, 70.6, 51.6, 39.4, 22.9; MS: *m/z* 163 (M^+).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.68; H, 8.02; N, 8.56.

(±)-4-Butyl-2,3,4,5-tetrahydro-1,5-benoxazepine (5c). This compound was isolated by the same procedure used to prepare **5a** and purified by preparative thin layer chromatography eluted with 10% ether in hexanes. The resulting oil (370 mg, 90%)

crystallized at 0° to a yellow solid that darkened on exposure to air, mp 28-30°; IR: 3365 cm^{-1}; ^1H NMR: δ 6.92 (dd, 1 H, J = 7.7, 1.6), 6.85 (td, 1 H, J = 7.4, 1.6), 6.76 (td, 1 H, J = 7.5, 1.8), 6.70 (dd, 1 H, J = 7.5, 1.8), 4.39 (ddd, 1 H, J = 12.1, 7.1, 3.7), 2.02 (ddt, 1 H, J = 10.6, 7.1, 3.7), 1.74 (dddd, 1 H, J = 13.8, 11.1, 7.4, 3.8), 1.57 (m, 2 H), 1.47-1.28 (complex, 4 H), 0.93 (t, 3 H, J = 6.9); ^{13}C NMR: δ 150.1, 140.7, 123.1, 121.4, 120.8, 119.7, 70.3, 55.8, 37.4, 36.3, 28.4, 22.7, 14.0; MS: *m/z* 205 (M^+).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83. Found: C, 76.02; H, 9.23; N, 6.85.

(±)-4-*tert*-Butyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (5d). When the procedure for **5a** was run on 300 mg (1.20 mmole) of **18d**, 240 mg of a mixture of **5d** and **37** resulted. Purification by preparative thin layer chromatography eluted with 10% ether in hexanes afforded two bands. Band 1 (fastest moving) contained 90 mg (37%) of **5d** that solidified at 0° to a light yellow solid that darkened on exposure to air, mp 37-39°; IR: 3399 cm^{-1}; ^1H NMR: δ 6.87 (dd, 1 H, J = 7.7, 1.6), 6.83 (td, 1 H, J = 7.5, 1.6), 6.73 (td, 1 H, J = 7.5, 1.8), 6.66 (dd, 1 H, J = 7.5, 1.8), 4.46 (ddd, 1 H, J = 11.9, 8.2, 3.5), 3.96 (ddd, 1 H, J = 11.9, 5.6, 4.6), 3.38 (br s, 1 H), 3.07 (dd, 1 H, J = 11.1, 3.5), 2.06 (dddd, 1 H, J = 13.5, 11.9, 4.6, 3.5), 1.77 (dddd, 1 H, J = 13.5, 11.1, 5.6, 4.0), 1.02 (s, 9 H); ^{13}C NMR: δ 149.7, 140.8, 122.8, 120.8, 120.4, 119.0, 70.3, 64.6, 33.8, 31.8, 26.4 (3); MS (30 electron volts): *m/z* 205 (M^+).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83. Found: C, 76.17; H, 9.29; N, 6.80.

1-(2-Aminophenoxy)-4,4-dimethyl-3-pentanone (37). This compound (130 mg, 49%) was isolated as a light yellow oil from Band 2 (above). This oil solidified at 0° to a

light yellow solid that darkened on exposure to air, mp 37-38°; IR: 3468, 3372, 1704 cm^{-1}; ^1H NMR: δ 6.81 (m, 2 H), 6.70 (m, 2 H), 4.26 (t, 2 H, J = 6.3), 3.75 (br s, 2 H), 2.99 (t, 2 H, J = 6.3), 1.18 (s, 9 H); ^{13}C NMR: δ 213.5, 146.2, 136.6, 121.6, 118.4, 115.2, 112.6, 63.9, 44.3, 36.2, 26.1 (3); MS (30 electron volts): *m/z* 221 (M^+).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.59; H, 8.60; N, 6.33. Found: C, 70.78; H, 8.69; N, 6.19.

(±)-3-(2-Aminophenoxy)-1-phenyl-1-propanol (38). When the reductive cyclization was carried out on 400 mg of **18e** by the same procedure used to prepare **5a**, 300 mg (84%) of **38** was isolated as an oil that crystallized to a tan solid at 0°. Trituration of the solid with 1% ether in petroleum ether gave **38** as a light tan solid, mp 55-56°; IR: 3360 cm^{-1}; ^1H NMR: δ 7.40-7.20 (complex, 5 H), 6.82-6.65 (complex, 4 H), 4.97 (dd, 1 H, J = 7.8, 5.1), 4.16 (ddd, 1 H, J = 9.6, 7.1, 5.3), 4.04 (m, 1 H), 3.30 (br s, 3 H), 2.21 (m, 2 H); ^{13}C NMR: δ 146.4, 144.2, 136.2, 128.5, 127.6, 125.8, 121.4, 118.6, 115.2, 111.9, 71.9, 65.5, 38.5; MS: *m/z* 243 (M^+).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.07; H, 7.00; N, 5.76. Found: C, 74.22; H, 7.07; N, 5.65.

(±)-1-Benzoyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (6a). This compound (625 mg, 82%) was isolated as a white solid by the same procedure used to prepare **5a**, mp 137-138°; IR: 3338, 1632 cm^{-1}; ^1H NMR (not coalesced): δ 7.26 (d, 2 H, J = 6.8), 7.23-7.07 (complex, 3 H), 6.93 (td, 1 H, J = 8.0, 1.5), 6.76 (dd, 1 H, J = 8.0, 1.2), 6.54 (d, 1 H, J = 6.8), 6.50 (t, 1 H, J = 7.2), 5.10 and 5.06 (2 br s, 1 H), 3.96 (br s, 1 H), 3.58 (br s, 1 H), 3.01 (t, 1 H, J = 10.3), 2.89 (t, 1 H, J = 10.3), 2.10 (br s, 1 H), 1.97 (br s, 1 H); ^{13}C

NMR: δ 169.7, 145.7, 136.5, 134.0, 129.7, 129.3, 127.9, 127.7, 127.5, 120.5, 119.5, 46.1 (2), 29.5; MS: *m/z* 252 (M^+).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found: C, 76.23; H, 6.38; N, 11.06.

(±)-1-Benzoyl-4-methyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (6b). This compound (450 mg, 88%) was isolated as a white solid by the same procedure used to prepare **5a**, mp 124-125°; IR: 3325, 1632 cm^{-1}; ^1H NMR (not coalesced): δ 7.37 (br s, 1 H), 7.30-7.03 (complex, 3 H), 6.96 (d, 1 H, J = 7.2), 6.83 (d, 1 H, J = 7.5), 6.59 (br s, 2 H), 5.13 and 5.19 (2 br s, 0.67 H), 4.82 (br s, 0.33 H), 4.03 (br s, 0.33 H), 3.55 (br s, 0.67 H), 3.40 (br s, 0.33 H), 3.08 (br s, 0.67 H), 2.71 (br s, 0.67 H), 2.27 (br s, 0.33 H), 1.84 (br s, 2 H), 1.37 (d, 3 H, J = 6.0), 1.27 (br s, 1 H); ^{13}C NMR: δ 169.5, 145.4, 136.5, 136.0, 129.5, 129.3, 128.4, 127.7, 127.5, 120.8, 118.2, 53.1, 45.4, 37.6, 23.8; MS: *m/z* 266 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.69; H, 6.77; N, 10.52. Found: C, 76.74; H, 6.79; N, 10.47.

Acknowledgement

We wish to thank the Oklahoma Center for the Advancement of Science and Technology (HR01-015) for support of this research. Funds for the 300 and 400 MHz NMR spectrometers of the Oklahoma Statewide Shared NMR Facility were provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Partial support for our mass spectrometer by the NIH and

the Oklahoma Center for the Advancement of Science and Technology is also appreciated. Final thanks to Dr. E. J. Eisenbraun for providing 2,3,3-trimethyl-1-butene.

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