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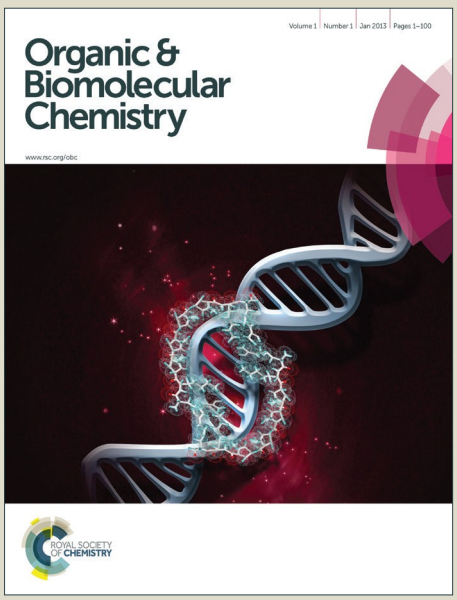

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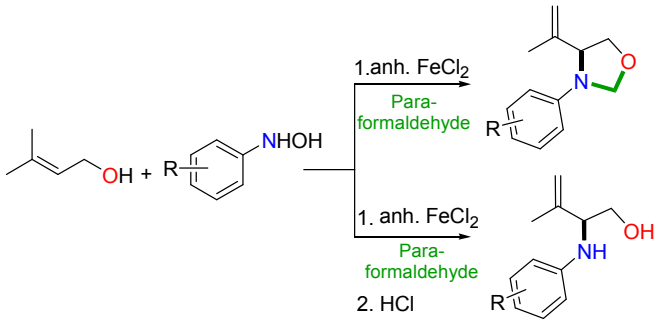

An unprecedented Fe-catalyzed oxazolidine formation was observed from the reaction of allyl alcohols with arylhydroxylamines in presence of formaldehyde or its equivalents.

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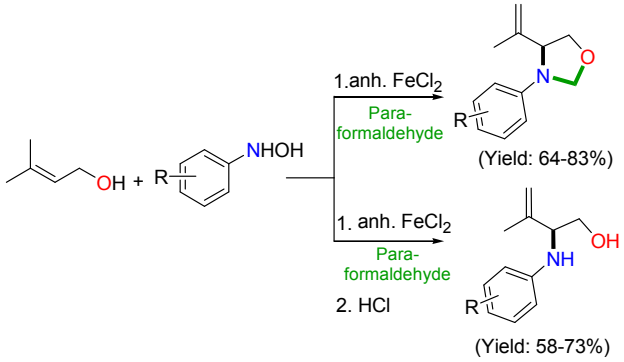
Fe-Catalyzed Synthesis of Substituted N-Aryl Oxazolidines

Siva Murru, Charles Seth Lott, Brandon McGough, Dakota M. Bernard and Radhey S. Srivastava*

Department of Chemistry, University of Louisiana at Lafayette, Lafayette, LA 70504.

rss1805@louisiana.edu

Abstract



A novel iron-catalyzed synthesis of substituted *N*-aryl oxazolidines was developed via C-N bond formation and methylenation. The reaction of aryl hydroxylamines with allyl alcohols, in the presence of formaldehyde or its equivalents, afforded variety of oxazolidine heterocycles in very good yields. This catalytic method is most effective for para-substituted aryl hydroxylamines and 3-methyl allyl alcohols. Furthermore, acid catalyzed demethylenation of oxazolidines allowed access to N-aryl amino alcohols in good yields.

Introduction

Organonitrogen compounds and nitrogen heterocycles are prevalent in natural products and biologically active molecules. Among them, oxazolidines have been utilized in organic synthesis as synthetic intermediates,[1] protecting groups,[2] and as ligands for metal catalysis.[3] Oxazolidines appear in numerous medicinally active compounds and natural products of biological significance,[4] such as quinocarcin.[4e] Similarly, N-arylated oxazolidines and oxazolidinones are found to have antibiotic activity[5] such as Linezolid (Zyvox),[5a] DuP105,[5b] DuP721.[5c] A review of the literature reveals that a number of classical methods exist for preparation of oxazoline, oxazolidine and oxazolidinone derivatives, utilizing *N*-monosubstituted 1,2-amino alcohols as starting materials.[6] However, it is difficult to prepare N-monosubstituted 1,2-amino alcohols (β-amino alcohols) via N-arylation (or alkylation) because of possible multi-substitutions. In applications such as medicine, materials, and total synthesis, β-amino alcohols play a pivotal role as a building unit.[7] Given their importance,

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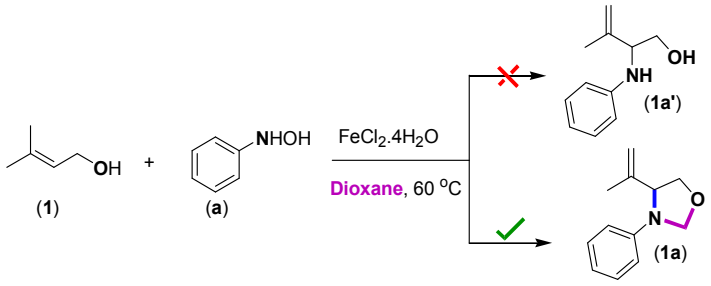
developing a direct C–H amination[8] towards synthesis of monosubstituted 1,2-amino alcohols is highly attractive.

Results and Discussion

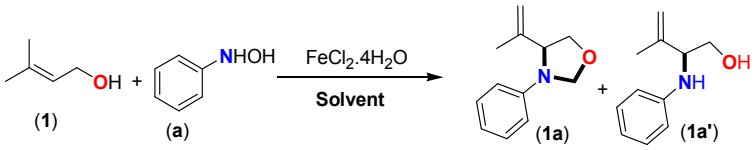
We envisioned that the C-H amination of allyl alcohols using substituted hydroxylamines as nitrogen-donors would serve as an alternate method to afford the N-monosubstituted amino alcohols. Accordingly, we have attempted to synthesize N-aryl amino alcohols starting from allyl alcohols and N-aryl hydroxylamines using our previously developed amination catalysts.[9] However, Fe-catalyzed reaction of 2-methyl-2-butenol with phenyl hydroxylamine in THF solvent didn't produce any product. Surprisingly, the same reaction performed in p-dioxane solvent yielded a product with higher mass (M+12) than the expected allyl amino alcohol. Spectroscopic analysis revealed the product to be 3-phenyl-4-propenyl-1,3-oxazolidine. (Scheme 1)



Scheme 1. Reaction of 3-methyl-2-butenol with phenyl hydroxylamine

The importance of the oxazolidine moiety, and serendipitous nature of the current reaction, led us to consider exploring the reaction further in order to develop a general synthetic method for N-arylated oxazolidines. We had initially focused on identifying the methylene group (-CH_2-) source by performing several control experiments. Thus we varied p-dioxane with other solvents as shown in Table 1. Incidentally none of these produced the oxazolidine (**1a**) or the amino alcohol (**1a'**), except for dichloromethane which produced oxazolidine (24 %). The oxazolidine formation could be due to the possible double nucleophilic substitution on dichloromethane. This observation led us to explore the possible impurities present in p-dioxane solvent.

Table 1. Screening of solvents for the reaction of 3-methyl-2-butenol with phenyl hydroxylamine



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Entry	Solvent	**1a** (%)[a,b]	**1a'** (%)[a,b]
1	p-Dioxane	65	0
2	CH_2Cl_2	24	0
3	$ClCH_2CH_2Cl$	0	0
4	THF	0	0
5	Toluene	trace	trace
6	DMF	0	trace
7	MeOH	trace	0
8	$CHCl_3$	trace	0

[a]GC yields; [b]Remaining substrate converts to azo and azoxy benzenes.

The commission on electroanalytical chemistry from IUPAC[10] reports that reagent grade dioxane obtained from different suppliers generally conform to ACS specifications[11] which includes water (~0.05%) and carbonyls (as HCHO, ~0.01%). Accordingly, we suspected that the 'methylene group' might be from the formaldehyde impurity present in p-dioxane solvent. In order to confirm our hypothesis, we performed a series of control experiments in THF solvent with a variety of formaldehyde equivalents (methylene donors) including para-formaldehyde, 1,3,5-trioxane, 1,1'-dimethoxymethane, and aqueous formaldehyde. (Table 2) Here we have observed the formation of oxazolidine product in all cases, which indicates the significance of formaldehyde (or its equivalents) in producing oxazolidine. Interestingly, these screening experiments reveal that the C-N bond formation (allylic amination) occurs only in presence of methylene ('CH_2') donors. Thus, it is evident that both allylic amination

Table 2. Screening of formaldehyde and it's equivalents for the reaction of 3-methyl-2-butenol with phenyl hydroxylamine

Entry	Reagent / Solvent	Oxazolidine (%)[a,b]
1	HCHO solution/THF	17
2	**para-formaldehyde/THF**	**68**
3	1,3,5-Trioxane/THF	45
4	Dimethoxymethane	51
5	**Dioxane**	**66**[c]
6	Dichloromethane	24

[a]GC yields; [b]Remaining substrate converts to azo and azoxy benzenes;
[c]Inconsistent results were obtained when we used p-dioxane from different suppliers.

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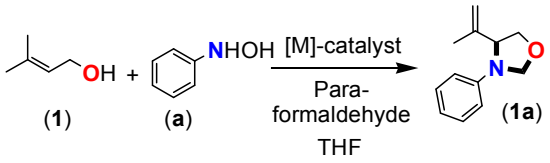
and methylenation occurs simultaneously and are synergistic. Though the paraformaldehyde-THF (entry 2, table 2) and p-dioxane (entry 5, table 2) are equally effective, the experimental results with p-dioxane vary considerably when it is used from different suppliers. Hence we chose para-formaldehyde/THF combination for the catalysts screening.

Among the various known allylic amination catalysts tested, $FeCl_3.6H_2O$, $FeCl_2.4H_2O$, anh. $FeCl_3$ and anh. $FeCl_2$ were found to be effective and afforded oxazolidine product in 56%, 68%, 78% and 84% respectively (entries 1-4, Table 3) which shows the unique catalytic activity of Fe-chloride catalysts towards oxazolidine formation. Further experimentation suggested the optimum ratios of hydroxylamine:allyl alcohol:Fe-catalyst to be 1:3:0.1. Though the reactions were faster at higher temperature, we maintained a uniform temperature of 60 ^oC for all the reactions in order to avoid the formation of side products such as azo and azoxy arenes.

Table 3. Screening of allylic amination catalysts for the reaction of 3-methyl-2-butenol with phenyl hydroxylamine



Entry	Catalyst	Oxazolidine (%)[a,b]
1	$FeCl_2.4H_2O$	68
2	**anh. $FeCl_2$**	**84**
3	anh. $FeCl_3$	78
4	$FeCl_3.6H_2O$	56
5	Fe(Pc)	9
6	$CuCl_2$	trace
7	CuCl	0
8	CuBr	0
9	Co(Pc)	trace
10	anh. $Mn(OAc)_2$	0

[a]GC yields; [b]Remaining substrate converts to azo and azoxy benzenes.

Having optimized the reaction conditions, we next evaluated the scope of the reaction using substituted aryl hydroxylamines (**a-j**) with 3-methyl-2-butenol (**1**). In general, the reactions were very clean, and the 3-aryl-4-propenyl-oxazolidine compounds were obtained in high yields under the optimized reaction conditions. As far as the oxazolidine formation is concerned, all hydroxylamines are equally effective except ortho-substituted aryl hydroxylamines (**j** and **k**). Several substituents and functional groups such as methyl (**1b**),

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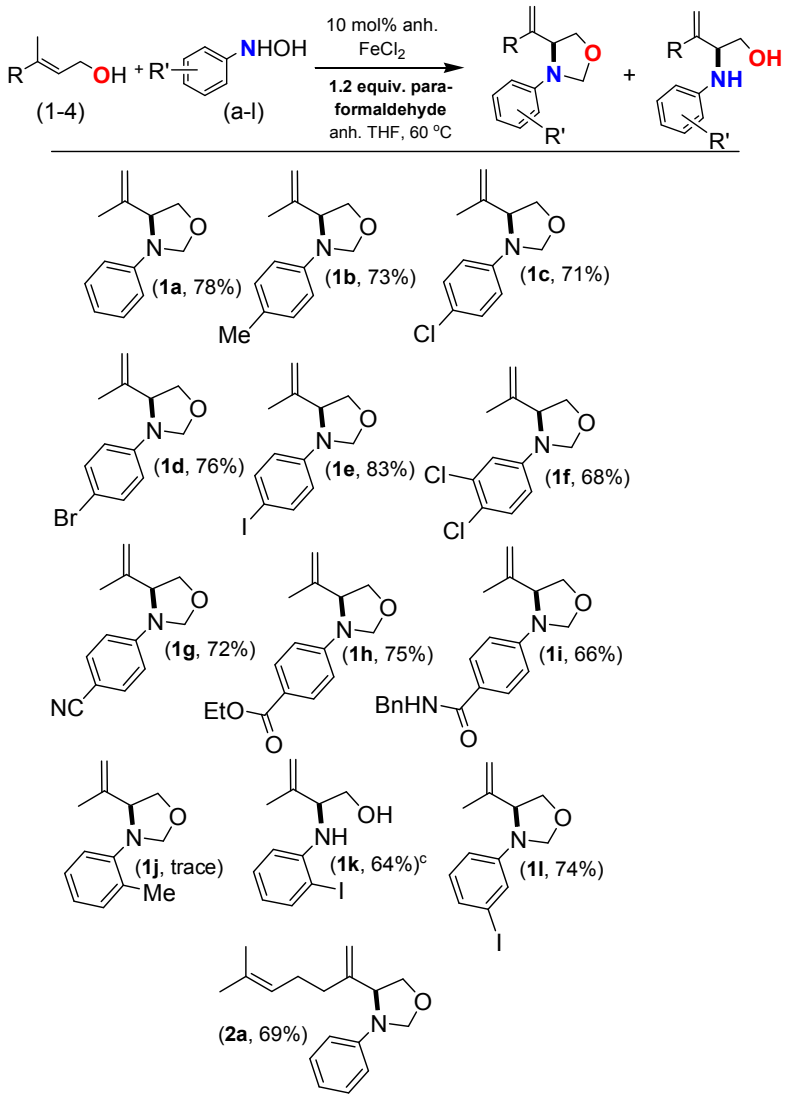
halogens (**1c**, **1d**, **1e** and **1f**), nitrile (**1g**), ester (**1h**) and amide (**1i**) were compatible for the current reaction. It should be noted here that the halogen substituted oxazolidine compounds (**1c, 1d** and **1e**) allow further elaboration on the synthesis of complex compounds via metal catalyzed coupling reactions.[12] On the other hand, *o*-Tolyl hydroxylamine (**j**) is not effective under optimized reaction conditions which might be due to steric hinderance.

Table 4. Reaction of allyl and homoallyl alcohols with aryl hydroxylamines [a,b]



[a]isolated yields; [b]associated with <5% of azo and azoxy benzenes; [c]a small amount (<10%) of oxazolidine was observed.

In order to test our hypothesis, we tested the reaction with 2-Iodo phenylhydroxylamine (**k**) where the direct formation of allyl amino alcohol (**1k**) as major product was observed. The difference in reactivity of 4-Iodo and 2-Iodo phenylhydroxylamines (**e** and **k**) could possibly be due to steric effects of ortho substitution. Later we also treated 3-Iodo

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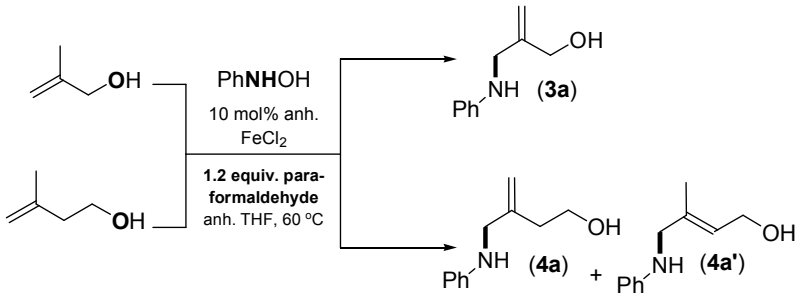
phenylhydroxylamine (**l**) with allyl alcohol (**1**) under the same reaction conditions. Surprisingly, 3-Iodo phenylhydroxylamine (**l**) did produce oxazolidine (**1l**) in very good yield. Thus from the present study, we found the following order of substituted aryl hydroxylamines' reactivity in making oxazolidines: para > meta > ortho. Success of this strategy was applied to other allyl and homo-allyl alcohols. We chose Geraniol (**2**), which is a monoterpenoid and an alcohol, as an allyl alcohol counterpart that afforded **2a** in 69% yield (table 4) and the excess Geraniol was recovered after column chromatography. Interestingly, a chemoselective reaction occurred in which only the allyl alcohol group was involved, but not the other allyl moiety. As expected, 2-methyl-2-propenol (**3**) produced the corresponding 1,3-amino alcohol (**3a**) in 21% yield. On the other hand, 3-methyl-3-butenol (**4**) afforded mixture of isomeric 1,4-amino alcohols (**4a** and **4a**') in 28% yield. (Scheme 2) However we did not observe any 6- or 7-membered *N*,*O*-heterocycles which might be due to the C-N bond formation at C-3 and C-4 positions, instead of C-2 position.



Scheme 2. Reaction of 2-methyl-2-propenol and 3-methyl-3-butenol with phenyl hydroxylamine

Our aforementioned goal was to develop a synthetic method to access N-aryl amino alcohols. Keeping that in mind, we investigated the demethylenation of the oxazolidine compounds in order to obtain allyl amino alcohols. Allyl amino alcohols are reported previously[13] via oxidative amination of allyl alcohols but they are not efficient probably because of the interference by the alcohol (-OH) group. In order to obtain the targeted amino alcohols as end products, we extended the method via demethylenation of oxazolidine products by acid treatment. In a typical experiment, 3-methyl-2-butenol (**1**) was treated with phenyl hydroxylamine (**a**) in THF using anh. $FeCl_2$ as a catalyst at 60 ^oC. After 5 hours, the solvent was removed and treated directly with conc. HCl to obtain allyl amino alcohol (**1a'**) as shown in Table 5. This seems to be a promising approach for allyl amino alcohols synthesis. Amino alcohols **1c'** and **2a'** were obtained in good yields starting from the corresponding allyl alcohols and aryl hydroxylamines (Table 5).

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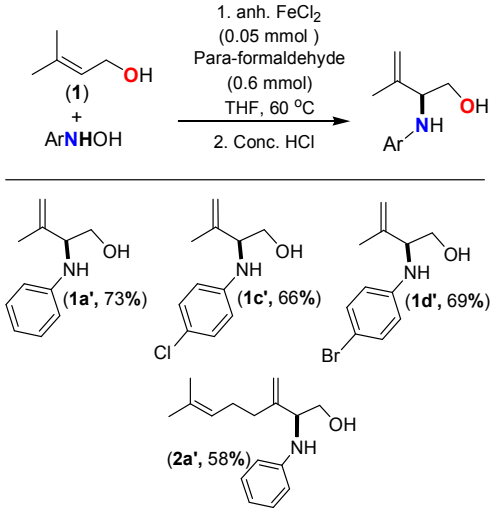
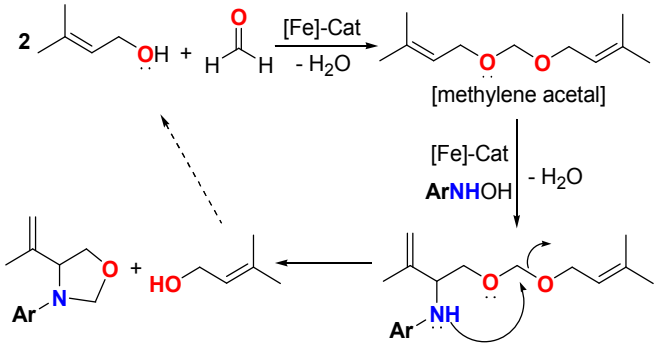
Table 5. Synthesis of allyl amino alcohols via amination and methylene bridge formation [a,b]



[a]isolated yields; [b]associated with <5% of azo and azoxy benzenes.

Having studied the synthesis of *N*-aryl oxazolidines and *N*-aryl amino alcohols, we observed that the C-N bond formation occur only in presence of paraformaldehyde or its equivalents. As we previously established, the amination reaction (C-N bond formation) involves the formation of activated nitroso-intermediates that are highly electrophilic in general.[9a,b] Consequently the allyl alcohols (-OH groups), which are nucleophilic in nature, could be detrimental to the amination reaction (C-N bond formation) via possible unwanted reaction with electrophilic nitroso compounds. However the presence of formaldehyde (or its equivalents) possibly serves as an acetal protecting group for the vulnerable alcohol (-OH) group that facilitates the new C-N bond formation via allylic C-H amination. Subsequent intramolecular nucleophilic substitution affords oxazolidines as end products along with regeneration of one equivalent of the allyl alcohol. (Scheme 3)



Scheme 3. Plausible reaction pathway for the N-aryl oxazolidine formation.

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Conclusion

We have demonstrated that 3-aryl-4-propenyl oxazolidines can be obtained from the corresponding allyl alcohols and aryl hydroxylamines in moderate to excellent yields. anh. $FeCl_2$ was found to be the most efficient catalyst for the synthesis of oxazolidines via C-N bond and methylene bridge formation. Para substituted aryl hydroxylamines favor oxazolidine formation compared to the ortho-substitution because of possible steric effects. Interestingly, Geraniol was involved in a chemo-selective reaction which afforded the corresponding oxazolidine in good yield. We have also established that the method can be extended to make allyl amino alcohols via acid catalyzed demethylenation. Further scope and asymmetric applications of the process are currently ongoing in our laboratory.

Experimental Procedures

General Procedure for the Preparation of 4-Propenyl-3-Aryl Oxazolidines: To the solution of anh. $FeCl_2$ (0.05 mmol), allyl alcohol (1.5 mmol) and para-formaldehyde (0.6 mmol) in anh. THF (5 mL), the aryl hydroxylamine (0.5 mmol) solution was added slowly in THF (5 mL) using a syringe pump over 4 hours at 60 ^{o}C while keeping the flask under inert atmosphere using nitrogen balloon. Reactions were allowed to continue for two more hours for the complete consumption of aryl hydroxylamine. Then the mixture was filtered through celite and the filtrate was concentrated to dryness. The crude product was purified over a short column of silica gel (hexane/ethyl acetate eluents) to obtain the pure oxazolidine which was then directly analyzed by GC-MS, NMR, ESI-MS and FT-IR.

General Procedure for the Synthesis of Allyl Amino Alcohols: To the propenyl oxazolidine (obtained from the previous step) in a RB flask, 2 mL of conc. HCl was added and stirred for 2 hours. Once the reaction is completed (monitored by TLC and GC-MS), the mixture was filtered through celite and the filtrate was concentrated to dryness. The crude product was purified over a short column of silica gel (hexane/ethyl acetate eluents) and the isolated pure N-aryl amino alcohol which was then confirmed the structure by GC-MS, NMR, FT-IR and HR-MS analysis.

Acknowledgments

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