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A facile preparation of various N-heterocycles using amides and olefins

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ABSTRACT

We herein report a one pot approach for the synthesis of various nitrogen containing heterocycles including: oxazolines, thiazolines, and dihydro dioxazines via the addition of amides to olefins in the presence of N-iodosuccinimide (NIS) and propionitrile at high temperatures. Thus, the reaction of aryl/heteroaryl amides, thioamides, N-hydroxybenzamide, and phenylurea with various olefins in the presence of NIS and propionitrile at 45 °C afforded the N-heterocycles in good to moderate yields. Reaction of the electron deficient tri-*O*-acetyl-D-glucal and tri-*O*-acetyl-D-galactal with benzamide and thiophene-2-carboxamide afforded the N-glycooxazolines in good yields. The newly made heterocycles were tested against various enzymes. Only 3,6-diphenyl-dihydro-1,4,2-dioxazine (**1c**) was found to moderately inhibit hexokinase II (hHK2).

Introduction

Oxazolines and thiazolines are common functional groups in many natural products. Allosamidin **1**, Trehazolin **2** (insecticides), Rilmendine **3** (antihypertensive agent), and A289099 **4** (tubulin polymerization inhibitor) are a few examples of biologically active oxazoline containing compounds (Fig. 1).[1]

Oxazolines have also been used as chiral ligands[2] and as protecting groups in natural product synthesis.[3,4] Because of their importance a great deal of effort has been put forward in the development of more efficient and cost effective methods for their chemical synthesis. In general, oxazolines and thiazolines have been prepared by reacting β-aminoalcohols with acid chlorides, carboxylic acids, nitriles, and esters.[5] More recent methodologies for the preparation of oxazolines include the reaction of a nitridomanganese complex with acid chlorides.[6] The direct preparation of oxazolines has also been accomplished via the addition of aryl and aliphatic amides to olefins in the presence of *tert*-butyl hypoiodite as the source of iodine.[7] Other iodinating reagents such as N-iodosuccinimide (NIS) were explored in the same study but poor yields were obtained and this chemistry was not further pursued. Other one-pot procedures for the preparation of oxazolines include the reaction of alkenes with N-bromosuccinimide (NBS) in the presence of nitriles and $Cu(OTf)_2$ or $Zn(OTf)_2$[8] as well as the reaction of benzenetellurinyl trifluoroacetate with boron trifluoride.[9] Both methods proceeded with good overall yields and stereoselectivity.

We have previously described the preparation of carbohydrate fused oxazolines.[10] We also successfully prepared N-glycooxazolines and N-glycothiazolines (nitrogen at the anomeric center), in one step, via the addition of amides and thioamides to benzyl protected glucal in the presence of NIS and propionitrile at 45 °C.[11] We have extended this methodology to explore the preparation of various N-heterocycles using alkenes (Scheme 1). Both electron deficient and electron rich alkenes were used in this study. Therefore, we herein report the direct synthesis of oxazolines,

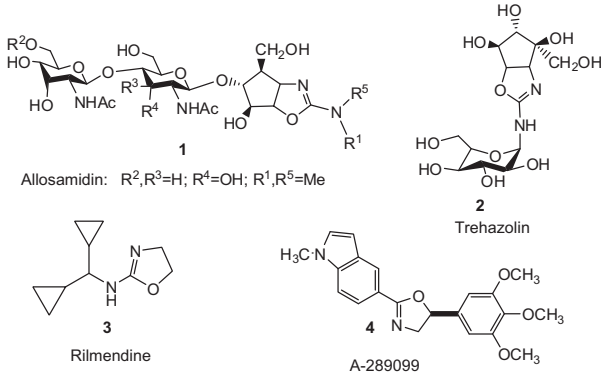

Figure 1. Biologically active oxazoline containing compounds.

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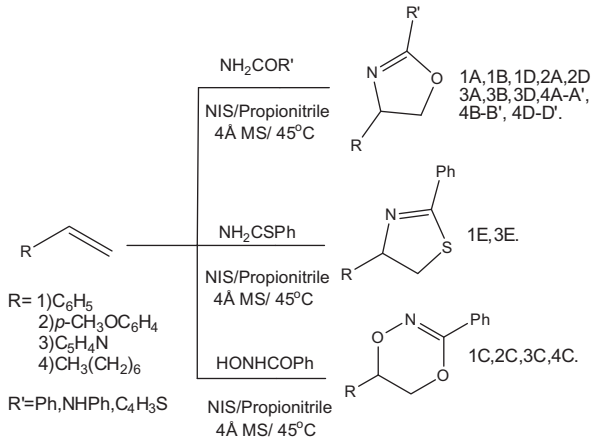


Scheme 1. Targeted N-heterocycles.

thiazolines, and the less abundant dihydro dioxazine via the addition of amides and N-hydroxyamides to alkenes and unsaturated sugars in the presence of NIS and propionitrile at 45 °C. In this study we show that access to oxazolines and other heterocycles is possible using alkenes and an excess of both NIS and the amide at 45 °C. The overall yields and stereoselectivity obtained for the formation of oxazolines when using electron rich alkenes are comparable with currently published one-pot procedures. Previously we attempted to use the electron deficient glycals, tri-*O*-acetyl-D-glucal and tri-*O*-acetyl-D-galactal in a two-step iodoamidation/cyclization to form the oxazolines. Yields were poor and mixtures of products were obtained.[10] When tri-*O*-acetyl-D-glucal, tri-*O*-acetyl-D-galactal, and tri-*O*-methyl-D-glucal were employed in the new one-pot reaction the N-glycooxazolines were obtained exclusively. Compounds **1a**, **1c**, **2a**, **2d**, **2e**, **3c** were selected to be screened against a panel of enzymes as part of Eli-Lilly's open innovation drug discovery program. All of the compounds were inactive with the exception of **1c** which exhibited moderate inhibition against hexokinase II (hHK2) with a 70% inhibition and IC_{50} >20 μM.

Results and discussion

Compounds **1a**–**e** (Table 1, entry 1) were prepared by reacting benzamide, thiophene-2-carboxamide, thiobenzamide, N-hydroxybenzamide, and phenylurea with styrene in the presence of N-iodosuccinimide (NIS).[12] Hence, styrene (1 equiv) was mixed in freshly distilled propionitrile (4.0 mL) followed by the addition of the amide (3 equiv). The mixture was heated to 45 °C until the reaction became homogenous. Pre-activated 4 Å molecular sieves powder was added to the reaction mixture to avoid inadvertent addition of water across the double bond and formation of halohydrins. Finally, NIS (2 equiv) was added to the reaction mixture. The reaction was kept at 45 °C and after 2 h TLC analysis showed complete disappearance of the starting material. The mixture was quenched with deionized water and diluted in dichloromethane (50 mL). The crude was filtered to remove the molecular sieves and subsequently washed with saturated $Na_2S_2O_3$ (100 mL) and distilled water (3 × 100 mL). Reactions were conducted in the presence and absence of light and no changes were observed in product yields. The best overall yields were obtained when 1-nonene **4** and styrene **1** were used in the reaction (Table 1, entries 1 and 4). Our NMR data for compounds **1a**[13] and **1d**[14] matched the data previously reported confirming the formation of the 2, 5-diphenyloxazoline **1a** and N, 5-diphenyl-4, 5-dihydrooxazol-2-amine **1d**. The known compounds **1b**[15] and **1c** were also obtained in good yields. However, we were only able to produce the known 2, 5-diphenylthiazoline **1e**[16] in very low yields (results not shown). When 1-nonene was reacted with benzamide a 1:1 mixture of 5-heptyl-2-phenyloxazoline **4a** and 4-heptyl-2-phenyloxazoline **4a′** were obtained in good yields (Table 1, entry 4). ^{1}H NMR of 5-heptyl-2-phenyloxazoline gave a distinct multiplet for H-5 at 4.72 ppm and a doublet of doublet for H-4 at 4.12 (dd, J = 7.0 Hz, J = 6.50 Hz, 1H, CHOCH_2N) ppm and 3.67 (dd, J = 7.5 Hz, J = 7.00 Hz, 1H, CHOCH_2N) ppm. The regioisomer 4-heptyl-2-phenyloxazoline gave a distinct doublet of doublet at 4.49 (dd, J = 8.50 Hz, J = 7.50 Hz, 1H, CHNCH_2O) ppm and 4.05 (dd, J = 8.25 Hz, J = 8.00 Hz,1H, CHNCH_2O) ppm for H-5 and a multiplet at 4.28 ppm for H-4 (Scheme 2). The same chemical shift pattern was observed for the rest of the corresponding 5-heptyl and 4-heptyl substituted oxazolines. Furthermore, 1:1 ratios were also obtained for compounds **4b**, **4b′**, **4d**, **4d′** (Table 1, entry 4). The regioisomers were easily separated by column chromatography with the exception of compounds **4d** and **4d′** that resulted in an inseparable mixture. When hydroxybenzamide was used in the reaction the dihydro-1, 4, 2-dioxazine **4c** was obtained as a single product albeit in low yields. Unfortunately very poor yields were also obtained with thiobenzamide and the preparation of **4e** was not further pursued.

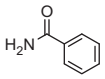
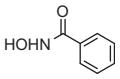
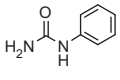
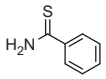
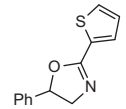
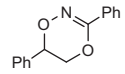
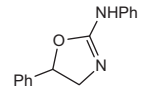
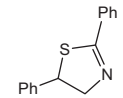
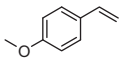
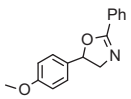
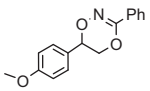
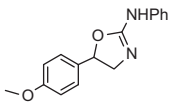
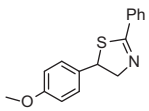
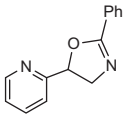
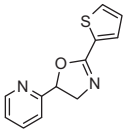
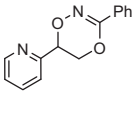
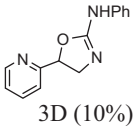
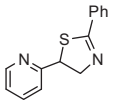
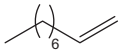
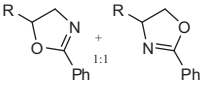
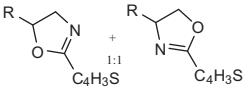
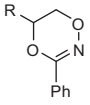
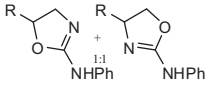
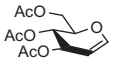
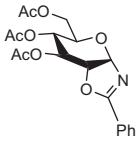
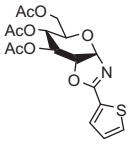
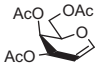
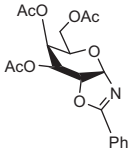
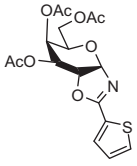
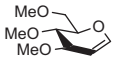
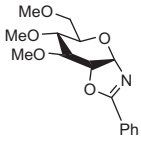
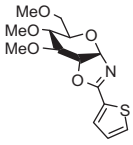
The use of vinylanisole **2** and vinylpyridine **3** allowed for the formation of the known compounds **2a**, **2e**, **3a**, **3b**, **3d**, **3e** (Table 1, entries 2 and 3).[16,17] The yields ranged from good to low, especially for compounds **2e**, **3b**, and **3d**. During the synthesis of these compounds multiple spots were observed during TLC analysis. The iodination of mono substituted benzene using NIS and acetonitrile[18] as well as NIS in the presence of trifluoroacetic acid[19] has been previously reported. It is possible that some of the byproducts obtained in these reactions may have resulted from the halogenation of the benzene ring via electrophilic aromatic substitution. We decided to test this hypothesis by mixing vinylanisole with 2.0 equiv of NIS in propionitrile at 45 °C for two hours (Scheme 3). After column chromatography ^{1}H NMR analysis confirmed the formation of compound **9** only. This result does not surprise us since the addition of the succinimide ion in the absence of a strong nucleophile has been previously reported using NIS and glucal.[20] No substitution occurred in the benzene ring and compound **9** was never isolated in any of our reaction trials with alkenes **2** and **3**.

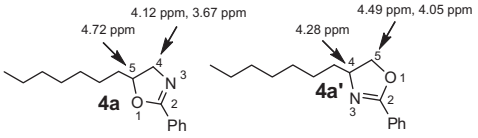
Based on these results one can envision the formation of the oxazolines and thiazolines via the addition of the nitrogen of the amide to the benzylic carbon of aryl alkenes. Migration of the nitrogen via an acyl aziridine followed by O-alkylation will lead to ring closure and formation of the 2,5-disubstituted oxazoline/thiazoline. While a free radical mechanism is possible it is not likely to occur in this case since reaction yields were not affected when conducted in the presence of light. However, the migration of amides through an aziridine intermediate is well documented.[21]

Therefore we hypothesized that the formation of the dihydro dioxazine will follow a similar pathway through the initial formation of intermediate **11** (Scheme 4). Displacement of the iodine followed by O-alkylation will lead to ring closure and formation of our target compound **13** exclusively. The electron deficient 5,6-dihydro-2*H*-pyran-2-one and trimethyl silyl acrylate were also used in this study but gave very sluggish results and their use was discontinued.

As part of our program aimed at the synthesis of novel glycosidase inhibitors we decided to revisit the direct preparation of the N-glycooxazolines using the electron deficient tri-*O*-acetyl-D-glucal **5** and tri-*O*-acetyl-D-galactal **6** (Table 1, entry 6). Acetate protecting groups are easily removed under basic conditions making them a very desirable protecting group in carbohydrate synthesis. When benzamide was used in the reaction the N-glycooxazolines **5a**, **6a** were obtained exclusively in fair yields. Similar results were obtained when thiophene-2-carboxamide was employed in the

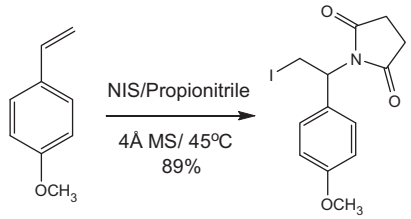
Table 1
Cyclization products

Entry	Alkene					
1		 1A (60%)	 1B (65%)	 1C (68%)	 1D (61%)	 1E (15%)
2		 2 A (68%)	NR	 2C (69%)	 2D (65%)	 2E (56%)
3		 3A (70%)	 3B (12%)	 3C (65%)	 3D (10%)	 3E (58%)
4		 4A (42%) 4A' (55%) R = HEPTYL	 4B (54%) 4 B'(45%) R = HEPTYL	 4C (25%) R = HEPTYL	 4D, 4D' (90%) R = HEPTYL	NR
5		 5A (45%)	 5B (40%)	NR	NR	NR
6		 6A (41%)	 6B (43%)	NR	NR	NR
7		 7A (80%)	 7B (85%)	NR	NR	NR



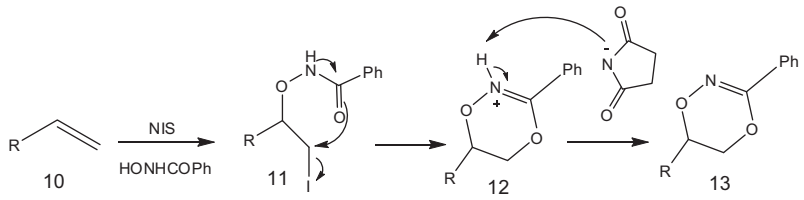
Scheme 2. Proton chemical shifts for compounds **4a** and **4a**′.

reaction resulting in compounds **5b** and **6b** (Table 1, entries 5 and 6). The formation of the N-glycooxazolines was easily confirmed using ^{1}H NMR and ^{13}C NMR where the characteristic doublet of doublet at 6.07 ppm for the anomeric proton and 94.33 ppm for the anomeric carbon was observed.[10,11] We were only successful in the addition and cyclization of these two amides. We turned



Scheme 3. Addition of succinamide to vinylanisole.

our attention to the methyl protected glucal. Methyl ethers have been used as permanent protecting groups in the chemical synthe-



Scheme 4. Possible mechanism for the formation of dihydro dioxazines using NIS.

sis of carbohydrate based natural products.[22] This eliminates a final deprotection step and is the reason why we pursued the preparation of N-glycooxazolines using this protecting group. When tri-*O*-methyl-D-glucal **7** was used in the reaction with benzamide and thiophene-2-carboxamide the N-glycooxazolines **7a** and **7b** (Table 1, entry 7) were obtained exclusively. Once again we failed to produce any carbohydrate-based heterocycles using thiobenzamide, phenylurea, or N-hydroxybenzamide.

Compounds **1a**, **1c**, **2a**, **2d**, **2e**, **3c** were screened against a panel of enzymes including hexokinase II (hHK2) as part of Eli-Lilly Pharmaceutical's open innovation drug discovery program. Hexokinase type II isoform has been shown to play a crucial role in initiating and maintaining the high glucose catabolic rate observed in malignant tumors.[23] Inhibitors of this enzyme have emerged as potential chemotherapeutic agents for the treatment of cancer.[24] Compound **1c** showed moderate activity against hHK2 with a 70% inhibition and IC50 > 20 μM (Fig. 2). The synthesis of 5,6-dihydro-1,4,2-dioxazines has been previously reported using hydroxyamides and α-bromoesters[25] as well as nitrosocarbonyl compounds with cyclic dienes.[26] The method reported in this Letter will allow for the rapid generation of small libraries of dihydro dioxazine analogues of **1c** and further test their inhibitory properties against hexokinase II. The optimization of compound **1c** is currently underway and the results will be disclosed in future publications. The % inhibition obtained for concentrations at 20 μM for all the compounds mentioned above is shown in (Fig. 2). Compound **3c** showed a 0.5% inhibition at 20 μM. Compounds **1a** and **2a** exhibited negative inhibition (−100% and −40%) respectively. These results are indicative of stimulation rather than inhibition. We intend to investigate the regioisomers of **1a** and **2a** for hexokinase II activity. Our laboratory is currently working on the chemical synthesis of such compounds using alternative procedures and the results will be reported in due time.

In summary we have achieved the direct addition and cyclization of amides and amide derivatives to aryl, heteroaryl, and aliphatic alkenes using NIS and propionitrile at 45 °C. This one pot procedure allowed for the formation of substituted oxazolines, thiazolines, and dioxazines. The reaction proceeded with a great degree of stereoselectivity when electron rich alkenes were used in the reaction with the exception of 1-nonene. The yields obtained for the preparation of oxazolines are comparable to those reported in earlier one-pot procedures. When the electron deficient tri-*O*-acetyl-D-glucal and D-galactal were reacted with benzamide and thiophene-2-carboxamide the N-glycooxazoline was obtained exclusively. Higher yields were obtained with tri-*O*-methyl-D-glucal.

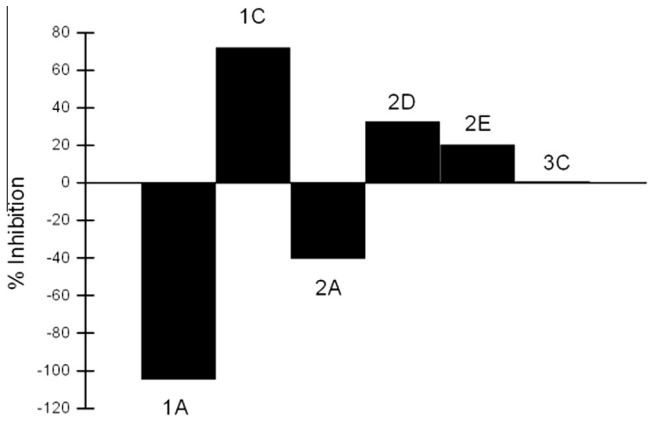


Figure 2. Hexokinase II assay.

Conclusions

The addition and cyclization of amides and amide derivatives to electron rich olefins such as: styrene, vinyl anisole, vinyl pyridine as well as 1-nonene in the presence of NIS at 45 °C are a viable alternative for the preparation of substituted oxazolines and other N-heterocycles. This reaction takes place in one step in a very short period of time with good overall yields. The addition and cyclization of amides using the electron deficient tri-*O*-acetyl-D-glucal, D-galactal, and tri-*O*-methyl-D-glucal lead to the formation of the N-glycooxazolines in good yields. Optimization of compound **1c** is currently underway in our laboratory and results will be disclosed in future publications.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.054.

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12. General procedure for the preparation of oxazolines, thiazolines, and dioxazines. The olefin (1.86 mmol) was mixed in freshly distilled propionitrile (4.0 mL) and kept under an inert N_2 atmosphere. 4 Å molecular sieves (0.01 g) were added to maintain anhydrous conditions. The amide (5.58 mmol) was added to the flask and the reaction mixture was heated to 45 °C until it became homogenous. This was followed by the addition of N-iodosuccinimide (3.72 mmol) and the flask subsequently covered with aluminum foil. The reaction mixture was stirred at 45 °C for 2 h and monitored using TLC until complete disappearance of the starting material was detected. The reaction was quenched with deionized water and the crude mixture diluted in DCM (50 mL). The mixture was washed with a saturated solution of $Na_2S_2O_3$ (100 mL) and deionized water (3 × 100 mL). The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo.
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