The Synthesis of Oxazolines Using the Vilsmeier Reagent

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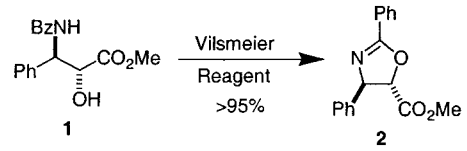
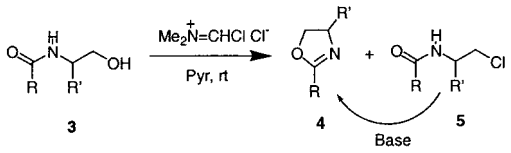
The place of oxazolines in modern day chemistry is certainly self-evident. For example, they are used in the development of chiral ligands used for asymmetric catalysis,[1] are found in natural products, are used in synthesis,[2] and provide a useful means for the protection of amino alcohols or carboxylic acids.[3]

Numerous methods for the synthesis of oxazolines have been reported. Among these are the use of thionyl chloride,[4] $SOCl_2$−AgOTf,[5] PPh_3/DEAD,[6] sulfonyl chlorides,[7−9] BF_3·Et_2O,[10] Tf_2O,[11] Tf_2O/Ph_2SO,[12] P_2O_5,[13] Et_2N-SF_3,[14] Burgess reagent,[15] Ph_3P/TEA/CCl_4,[16] Bu_2SnCl_2,[9] $POCl_3$,[17] TMSF,[18] 30% HBr, AcOH,[19] *o*-chlorophenylphosphoro-bis-(1,2,4)-triazolide,[20] and $RN_3/(PhO)_3P$.[21] Each method has its advantages and disadvantages in any given situation; therefore, no one reagent has proven totally general. Thus, the development of other methods is warranted.

Scheme 1



Scheme 2



Results and Discussion

During the course of our development of a synthesis of the paclitaxel side chain we discovered that the Vilsmeier reagent very efficiently converts the anti amido alcohol **1** to the oxazoline with inversion of configuration at the alcohol to give the oxazoline **2** in nearly quantitative yield (Scheme 1). In contrast, the use of thionyl chloride only gives a 70% yield.[22]

The facility and mildness of this transformation compared to the use of $SOCl_2$ led us to examine the generality of the process in a number of other cases. Typically, the reaction is run by slurring the Vilsmeier reagent in pyridine at room temperature and then adding the amido alcohol substrate. When other substrates were explored, we found that in most cases we obtained both the desired oxazoline **4** as well as the chloride **5** (Scheme 2). Although an inconvenience, the chloride is readily converted to the oxazoline upon treatment with DBU. Generally, it is better to isolate the mixture and then subject it to base treatment to complete oxazoline formation because this prevents the formation of very dark reaction mixtures. The dark color may be the result of excess Vilsmeier reagent reacting with the base. Little optimization work was done to define the best possible conditions for each substrate because our interest was in obtaining the oxazolines as ligands for the development of transition metal catalyzed reactions.

Table 1 gives the results we have obtained for the conversion of a series of amido alcohols to oxazolines. Generally, the yields are quite good, the exception being serine, which did not perform well in the reaction. The low yield observed was due to the formation of dehydroalanine.

During the course of this work, we have discovered that these oxazolines can be opened back to the chloride upon treatment with Pyr·HCl in pyridine (Scheme 3).[23] For example, stirring the oxazoline **4e** in pyridine with Pyr·HCl resulted in nearly complete conversion to the chloride **5e** over a 24 h period. A similar phenomenon was also observed with the ferrocenyl derivative **4a**. The relative ease with which this occurs appears substrate dependent because the phenylthio derivative **4d** required heating to 60 °C to achieve ring opening.

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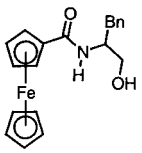
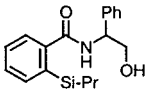
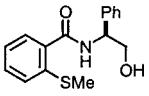
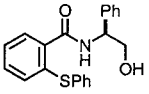
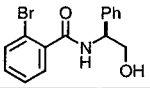
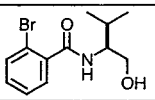
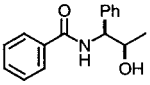
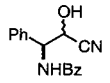
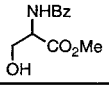
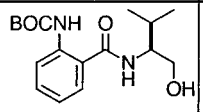
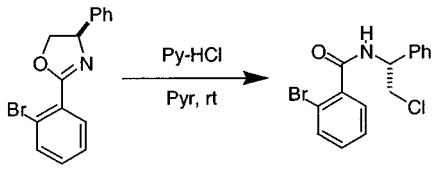
Table 1. Conversion of Amido Alcohols to Oxazolines

Entry	Substrate	Meth.	% yield	Lit. Ref.
A		B	82	25
B		B	80	New
C		B	ND	26
D		B	56	New
E		A	63	27
F		B	85	28
G		B	69	29
H		A	55	New
J		B	29	12, 30, 31
K		A	71	New

Scheme 3

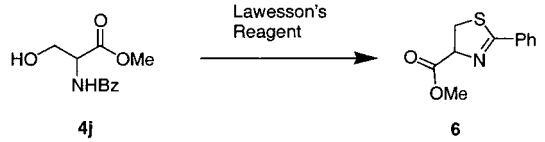


4e **5e**

We were also interested to see if the related transformation could be effected on the thioamide. Thus, treatment of the serine amide **4j** with Lawesson's reagent to convert the amide into the thioamide resulted in cyclization to give the thiazoline **6** directly (Scheme 4),[24] and thus, we abandoned any further efforts related to this transformation.

In conclusion, we have shown that the Vilsmeier reagent is effective at promoting the formation of oxazolines from amido alcohols. The low cost of the Vilsmeier reagent and the ease with which the reaction byproducts are removed by extraction makes this a very attractive method for oxazoline formation. The observation that oxazolines upon treatment with pyridine hydrochloride open the ring to give amido chlorides is new. Additionally, we found that Lawesson's reagent may be used for the direct conversion of amido alcohols to thiazolines, but the generality of this transformation has not been established.

Scheme 4



4j **6**

Experimental Section

Methyl (4*R*,5*S*)-2,4-Diphenyl-4,5-dihydro-1,3-oxazole-5-carboxylate (4l). To a flask containing 410 mg (3.20 mmol) of Vilsmeier reagent was added 4 mL of pyridine. The slurry was stirred for 5 min and the amide (488 mg, 3.2 mmol) added. After 1.5 h, TLC showed the reaction to be complete. The product was isolated with EtOAc from water to give 457 mg (99%) of the oxazoline, whose NMR was perfect: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.2 Hz, 2 H), 7.70 (m, 8 H), 5.38 (d, J = 6.6 Hz, 1 H), 4.85 (d, J = 6.6 Hz, 1 H), 3.80 (s, 3 H).

(4*S*)-4-Benzyl-2-ferrocenyl-4,5-dihydro-1,3-oxazole (4a). A solution of 345 mg (0.475 mmol) of the alcohol was dissolved in 7 mL of pyridine and treated at room temperature with 100 mg (1.6 equiv) of Vilsmeier reagent. The mixture was stirred at room temperature overnight, treated with 360 μL of DBU, and heated to 50 °C. After 1.5 h, TLC showed the disappearance of the chloride, and the product was isolated with toluene from water. Chromatography with 50% EtOAc/Hex gave an 82% yield of the oxazoline: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 4.85 (s, 2 H), 4.53 (m, 1 H), 4.44 (m, H), 4.32 (t, J = 8.88 Hz, 1 H), 4.26 (s, 9 H), 4.16 (t, J = 7.76 Hz, 1 H), 3.31 (dd, J = 4.12, 13.6 Hz, H), 2.79 (dd, J = 9.2, 13.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 137.0, 128.3, 127.6, 125.5, 70.4, 69.3, 69.0, 68.7, 68.0, 66.7, 40.8.

(4*S*)-2-[2-(Isopropylsulfanyl)phenyl]-4-phenyl-4,5-dihydro-1,3-oxazole or Isopropyl 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl Sulfide (4b). The amide (1.8 g, 5.71 mmol) in 36 mL of pyridine at room temperature was treated with 1.15 g (8.99 mmol) of Vilsmeier reagent. The solution was stirred at room temperature overnight, and the product was isolated with toluene from water to give an 85:15 mixture of the oxazoline to the chloride. The crude mixture was treated with DBU (3.8 mL) in 35 mL of THF and heated to 50 °C for 4 h. Isolation with EtOAc from water gave the crude product, which was purified by chromatography (35−50% EtOAc/Hex) to give 1.27 g (80%) of the oxazoline: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.84 Hz, 1 H), 7.33 (m, 8 H), 5.44 (dd, J = 8.32, 9.96 Hz, 1 H), 4.73 (dd, J = 8.36, 10.08 Hz, 1 H), 4.19 (t, J = 8.2 Hz, 1

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H), 3.47 (sep, J = 6.68 Hz, 1 H), 1.31 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 142.5, 138.2, 130.7, 130.5, 128.9, 128.6, 128.2, 127.4, 126.8, 124.9, 74.5, 60.3, 36.7, 22.8, 22.8, 21.0, 14.1; HRMS (FAB) calcd for $C_{18}H_{19}NOS$ + H1 198.1265, found 298.1272.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for the new oxazolines **4b**, **4d**, **4h**, and **4k** are provided and experimentals are provided for oxazolines **4k**, **4h**, **4g**, **4f**, **4e**, and **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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