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A Chemoselective, Acid Mediated Conversion of Amide Acetal to Oxazole: The Key Step in the Synthesis of Cardiovascular Drug, Ifetroban Sodium.

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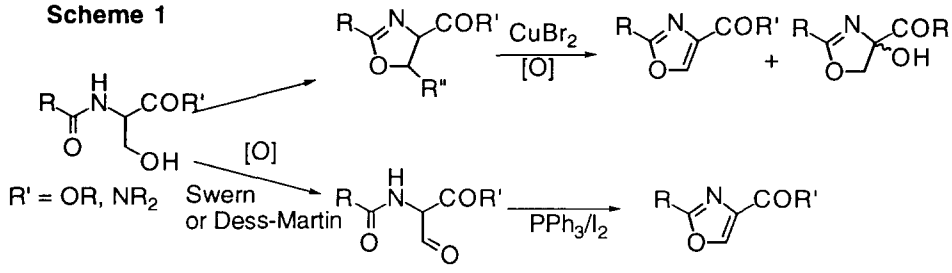
Abstract: The cyclization of acetal amide was carried out with trimethylsilyl trifluoromethanesulfonate, followed by elimination using sodium methoxide to give 2,5-disubstituted oxazole, thus completing a new route to the cardivascular drug ifetroban sodium.

The 2,4-disubstituted oxazole system occurs in various naturally occurring antivirals[1] and antibiotics.[2] The synthesis of such oxazoles from acyclic precursors in complex multifunctional molecules is a considerable synthetic challenge. Using hydroxy amides as starting material, there are two principal methodologies to prepare this heterocyclic moiety (Scheme 1). The copper bromide[3a] mediated dehydrogenation of oxazolines[3b] is the only method described to date where the yields are >80%, and has been demonstrated on scale. A recent paper[3c] describes the use of $BrCCl_3$ for dehydrogenation of oxazolines with yields > 85%. Nickel peroxide[3d] achieves the same result as copper bromide, however the yields are modest. The Wipf modification[4] of the Robinson-Gabriel approach[5] gives yields in the 60's.

Scheme 1



Each of the methods outlined in scheme 1 has its limitations. On scale, the copper bromide approach raises environmental concerns due to special handling of the waste. In addition, a stringent process control is required to prevent formation of a difficult-to-remove hydroxy oxazoline impurity. The nickel peroxide based methodology is undesirable due to usage of a large excess (>10 equiv.) of reagent, handling hazards and mediocre yields.

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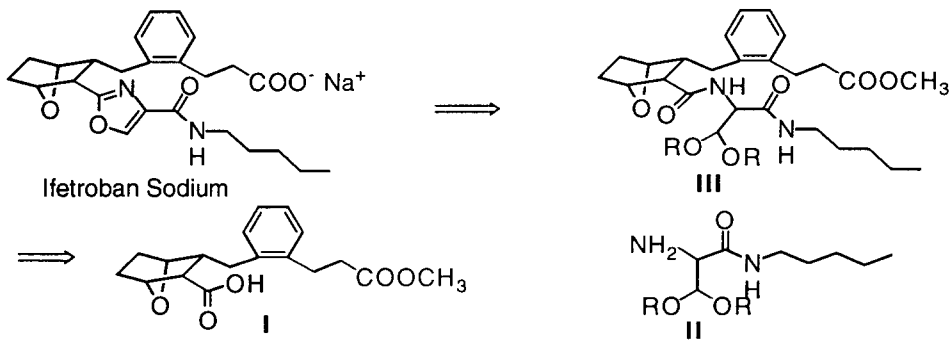
The Wipf approach gives unsatisfactory yields (<20%) when primary hydroxy amides are the precursors. In addition, both approaches involve an oxidation step which may not be compatible with other functionalities.

As part of our development efforts to improve overall yield to the cardiovascular drug candidate, Ifetroban sodium, we discovered an unprecedented, one-pot, high yielding synthesis of oxazoles, employing a Lewis acid mediated cyclization of a primary acetal amide.[6] We envisioned (Scheme 2) that this new and mild approach to the oxazole moiety would involve the following: (1) controlled coupling of the pivotal carboxylic acid **I** with the amine segment **II** having the eventual oxazole carbon distal to the nitrogen in the correct oxidation state; (2) Lewis acid mediated ring closure of **III** followed by a base catalyzed elimination to the oxazole.

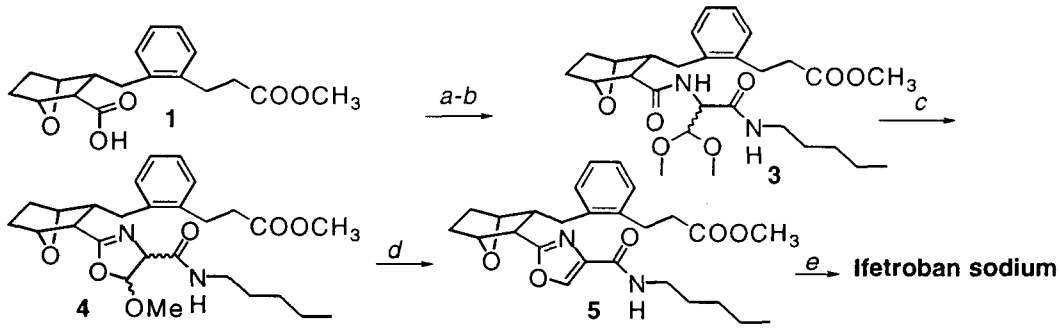
Scheme 2



The framework essential for the cyclization was synthesized as follows. The coupling of the key acid[8] **1** as its acid chloride with the acetal **2** under Schotten Baumann conditions furnished the amide acetal **3** cleanly as a mixture of two diastereomers (Scheme 3). The cyclization/elimination sequence was initiated by a Lewis acid and completed by base-mediated elimination to afford the oxazole. After extensive investigation,[9] the following protocol was adopted. Exposure of acetal **3** in 1,2-dimethoxy ethane to trimethylsilyl trifluromethanesulfonate at 40 °C gave a mixture of all four possible oxazolines **4**. This cyclization was chemoselective, since azetidinone formation with the amide nitrogen distal to the oxabicyclo ring was not observed. The driving force of aromaticity enabled the ready elimination of methanol from the crude oxazolines **4** upon their exposure to sodium methoxide at -10 °C for 1 h, without any stereochemical bias, to furnish the oxazole **5** in high yield (92 % from amide **3**) and quality. We found early on that attempted isolation of the oxazoline led to its degradation along with reversion to the acetal **3**. In terms of operational simplicity, the entire reaction from acetal **3** to the crystallization of oxazole **5** was a one-pot process, which is a significant benefit at manufacturing scale. The success of this protocol spurred further development efforts along safety and economic lines.

Inexpensive chlorosulfonic acid was successfully used instead of trimethylsilyl trifluromethanesulfonate to generate the oxazolines. Teratogenic 1,2-dimethoxyethane was replaced with methyl acetate as the solvent. The desired elimination was then carried out by an inverse addition of the oxazolines to a solution of potassium t-butoxide in t-butanol; the oxazole was isolated in 94% yield.

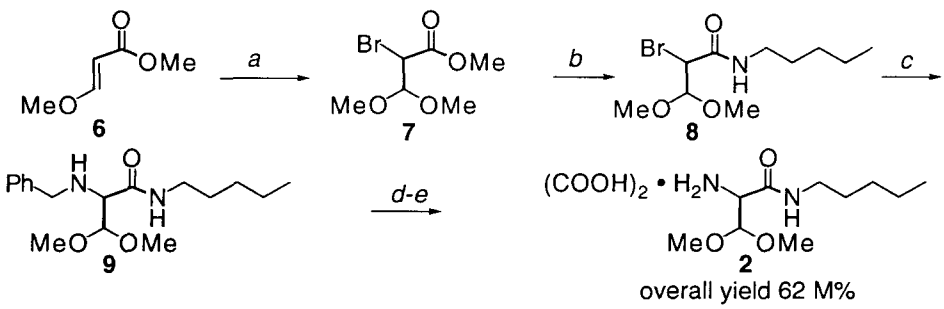
Scheme 3



[a] 1.5 equiv. Vilsmeier reagent, 20 °C, toluene. [b] 1.2 equiv. **2**, 0-10 °C, $NaHCO_3$, EtOAc, 87 M% from **1**. [c] 1.5 equiv. TMSOTf, DME, 40 °C, 2 h. or 2.1 equiv. $ClSO_3H$, MeOAc, 0 °C, 2 h. [d] 2.8 equiv. 25 wt.%NaOMe/MeOH, -10 °C, 92 M%. or addition of **3** to 5 equiv. tBuOK, tBuOH, 0 °C, 2 h. [e] NaOH, 90 M%.

As part of the development strategy, several routes[7] to the amide acetal **2** were examined and led to the high-throughput and high-yielding sequence shown in scheme 4.

Scheme 4



[a] NBS/MeOH, 5 to 20 °C, 16 h, 99 M%. [b] n-amyl amine, 5 to 20 °C, 16 h, 78 M%. [c] 3.2 equiv. benzyl amine, 110 °C, 16 h, 92 M%. [d] Perlman catalyst/H_2, MeOH, 40 °C, 25 psi, 4 h. [e] 1.1 equiv. oxalic acid, EtOAc, 20 °C, 12 h, 88 M%.

Inexpensive methoxy acrylate **6** was converted to the bromo acetal **7** with NBS/MeOH. Reaction of **7** with n-amylamine selectively afforded the bromo amide **8**, while reaction with ammonia led to the undesired a-amino amide. Nucleophilic displacement of the bromide **8** with benzyl amine furnished the protected acetal amide **9**. Finally, hydrogenolysis and isolation of the ensuing amide acetal as its oxalate salt **2** completed the synthesis of the

desired side chain. The overall yield of **5** was 45% from methoxy acrylate **6** (a seven step sequence). This new route, also known as the "oxidized side chain" route, was more cost effective than the "copper bromide" process affording Ifetroban sodium.

In summary, the present study outlines a remarkably efficient Lewis acid mediated cyclization approach to oxazoles in a complex structure. In contrast to other methods in the literature, the oxazole unit is assembled without the need for an oxidation, since the oxazole precursor is already at the proper oxidation level. The salient features are regioselective cyclization of amide acetal, ease of operation, use of environmentally friendly reagents, significant overall cost reduction and high overall yield.

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6. There is precedence for Lewis acid mediated cylization of amide glycosides to oxazolines (Kusama, T.; Soga, T.; Shioya, E.; Nakayama, K.; Nakajima, H.; Osada, Y.; Ono, Y.; Kusumoto, S.; Shiba, T.; *Chem Pharm Bull* **1990**, 38, 3366). In another instance a glycosidic oxazoline has been transformed to an oxazole (Gigg, R., Warren, C. D., *J. Chem. Soc. (C)* **1968**, 1903).
7. Three other routes to the amide acetal **5** were evaluated which will be published elsewhere.
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