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Synthesis of Fused Dihydropyrano(furano)pyridines via [4 + 2]-Cycloaddition of 5-Alkenoxy Substituted Oxazoles

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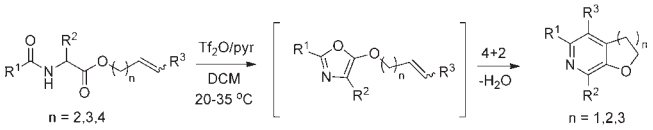
ABSTRACT



A three-step procedure to access fused pyridines has been developed utilizing inexpensive amino acids and alkenols to form the key oxazole precursors. Yields are good to excellent and provide a rapid and inexpensive route to a range of pharmacologically and biologically valuable fused pyridines with difficult to access substitution patterns.

The pyridine moiety is pervasive throughout nature as well as biologically active synthetic compounds. In particular, fused pyridine ring systems have been granted special status in the pharmaceutical arena. Having said this, the syntheses of fused pyridines have often been rather cumbersome and lengthy even for the simplest fused pyridines. An example is the dihydropyrano[2,3-*c*]pyridine **1**.

Despite the relatively simplistic looking ring system of **1**, our initial synthesis required 12 steps starting from Kojic acid. Besides the obvious length, the synthesis was plagued with several low-yielding steps, long cycle times, and cost of goods issues.

Similarly long synthetic routes to seemingly innocuous highly substituted and fused pyridines are found throughout the literature. For example, the rather simple 5-methoxy-4-methylpicolinaldehyde still required seven discrete steps from Kojic acid for its synthesis.[1] A second example, also starting from Kojic acid, assembled 2,3-dihydrofuro[2,3-*c*]pyridine-5-carbaldehyde in 10 steps and required the use of several transition metal mediated steps which can prove to be problematic to optimize should another functionality be incorporated.[2]

Tasked with developing a new route addressing these problems, we were drawn to the possibility of constructing the pyridine moiety via a [4 + 2] cycloaddition. A survey of the literature revealed a plethora of examples involving inter- and intramolecular Kondrat'eva pyridine syntheses.[3] However, we were surprised to find a dearth of examples involving intramolecular 5-alkenoxy tethered substrates. In addition, literature precedence involving 5-(alkenyloxy)-2-phenyloxazoles failed to undergo the desired [4 + 2] cycloaddition.[4] This was rather surprising as it is known that 5- (or 2)-alkoxy-substitution on the oxazole has an accelerating effect on the rate of reaction due to the increased electron density of the oxazole.[3]

(1) Kiyoto, T.; Ando, J.; Tanaka, T.; Tsutsui, Y.; Yokotani, M.; Noguchi, T.; Ushiyama, F.; Urabe, H.; Horikiri, H. WO2007138974A1, 2007.

(2) Brooks, G.; Giordano, I.; Hennessy, A. J.; Pearson, N. D. WO2007122258A1, 2007.

(3) (a) Kozikowski, A. P.; Hasan, N. M. *J. Org. Chem.* **1977**, *42*, 2039. (b) Levin, J. I.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 1397. (c) Levin, J. I.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 4325. (d) Subramanyam, C.; Noguchi, M.; Weinreb, S. M. *J. Org. Chem.* **1989**, *54*, 5580. (e) Levin, J. I.; Laakso, L. M., *Oxazoles: Synthesis, Reactivity, and Spectroscopy*; Palmer, D. C., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2003; Vol. 60, Chapter 3, pp 417. (f) Karpeiskii, M. Y.; Florent'ev, V. L. *Russ. Chem. Rev.* **1969**, *38*, 540.

(4) We are aware of only one failed report concerning oxazole cycloadditions involving substrates with the dienophile tether being incoroporated at the 5-alkoxy position; see: Padwa, A.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 399.

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Undeterred by the lack of precedence and knowing the accelerating effect of a 5-alkoxy group, we set out to explore the feasibility of utilizing a 5-alkenyloxy tethered oxazole to give the desired dihydropyrano[2,3-*c*]pyridine ring system **1** directly.

Our retrosynthesis of **1** led to the 5-(pent-4-en-1-yloxy)oxazole **2** (Figure 1). We reasoned that oxazole **2** would arise from a cyclodehydration of oxamate **3** through the use of a suitable dehydrating agent. The oxazole precursor **3** would arise ultimately from *N*-Boc-glycine (**4**) and 4-penten-1-ol (**5**).

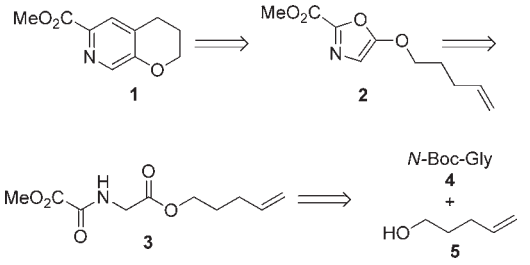


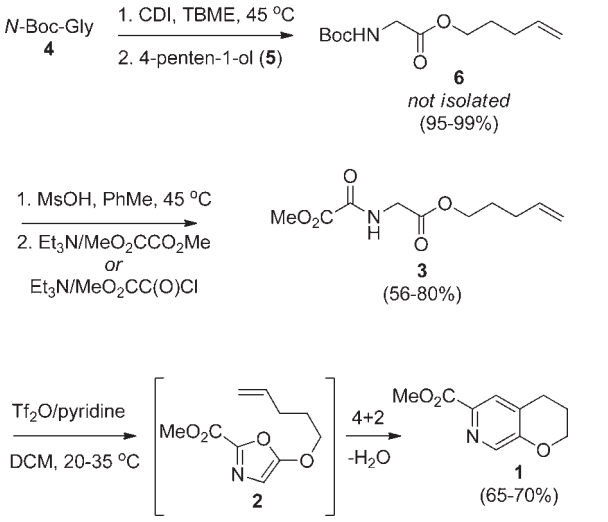
Figure 1. Retrosynthesis of dihydropyranopyridine **1**.

In the forward sense, synthesis of **3** commenced with the CDI-mediated esterification of *N*-Boc-glycine **4** with 4-penten-1-ol **5** to provide intermediate glycine ester **6** which was carried on directly without isolation (Scheme 1). Boc removal with methanesulfonic acid followed by treatment with either dimethyl oxalate or methyl chlorooxalate provided oxazole precursor **3** in 56−80% yields.[5] Treatment of **3** with triflic anhydride/pyridine in DCM led to efficient cyclodehydration to oxazole **2**.[6] Based on literature precedent we had expected to isolate and purify the oxazole **2** prior to subjecting it to the typical thermal cycloaddition conditions.[3]

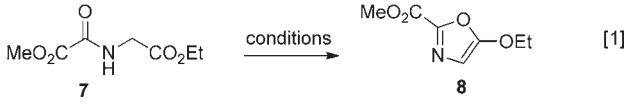
However to our delight not only did the cyclodehydration to **2** occur efficiently upon treatment with triflic anhydride/pyridine at ambient temperatures but the ensuing [4 + 2] cycloaddition and concomitant dehydration/aromatization to the desired dihydropyrano[2,3-c]pyridine **1** also occurred in a single flask reaction. *To our knowledge this is the first example of such a cascade cycloaddition/aromatization sequence occurring at ambient temperatures, under mild conditions, with a completely unactivated alkene and an oxazole*. Ultimately the new route delivered the desired pyridine **1** in a two-pot process from relatively inexpensive materials in 36−56% overall yields.

Having successfully demonstrated the viability of the key intramolecular cycloaddition we were keen to explore the substrate scope of the [4 + 2] reaction sequence. As a

Scheme 1. Synthesis of Dihydropyranopyridine **1**



first step we were hoping to replace triflic anhydride as the dehydrating agent due to cost, safety, and environmental concerns. As with the intramolecular 5-alkenoxy substituted cycloaddition, only a sparse account of dehydrating agents used to successfully form 5-alkoxy substituted oxazoles was found.[7] A screen of dehydrating agents was performed using model oxamate **7** (eq 1).



[1]

Of the reagents examined only Tf_2O/pyridine was found to give high yields of oxazole **8** in a reasonable time frame and mild conditions. Other previously reported desiccants gave no reaction, decomposition, or extremely low conversions.[8] In addition, previous reports using P_2O_5 on model oxamate **7** were also moderately successful;[6] however the mixture formed an intractable solid mass making handling and isolation on scale difficult. Interestingly, T_3P and Et_3N in either DMF or EtOAc did provide moderate conversion (60−80%) but only after extended heating (> 24 h).

With confirmation that Tf_2O/pyridine was optimal for cyclodehydration, the substrate scope was then explored (Figure 2). Employing amino acids other than glycine allowed for substitution at R_2 of the pyridine ring in high yields (**10b**−**d**).

Surprisingly, the rate of the reaction was markedly increased with the 4-alkyl substituted oxazoles (**10b** and

(5) Formation of **3** with methyl chlorooxalate in general gave higher yields and purity, whereas the dimethyloxalate invariably led to the formation of 10−20% of the undesired oxalamide via *bis*-addition. However, from a cost standpoint the use of dimethyl oxalate is much preferred.

(6) Thalhammer, A.; Mecinovic, J.; Schofield, C. J. *Tetrahedron Lett.* **2009**, *50*, 1045.

(7) See refs 2 and 4 as well as: (a) Maeda, I.; Takehara, M.; Togo, K.; Asai, S.; Yoshida, R. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1435. (b) Han, W.; Egberton, M.; Wai, J.; Zhuang, L.; Ruzek, R. D.; Perlow, D.; Isaacs, R. C.; Cameron, M.; Foster, B.; Dolling, U. H.; Hoerrner, R.; Obligado, V. E.; Neilson, L. A.; Kim, B.; Payne, L. S.; Morrisette, M. M.; Williams, P. D.; Pye, P. J.; Angelaud, R.; Mancheno, D. E.; Askin, D. WO2005087768, 2005.

(8) Unsuccessful reagents included: triphosgene/Et_3N; $COCl_2$/Et_3N; Ms_2O/Et_3N; $BF_3 \cdot OEt_2$; $SOCl_2$; $POCl_3$/pyr; $ClSO_3H$/pyr; TFAA/TFA; H_2SO_4/Ac_2O; Ph_3P/I_2/Et_3N.

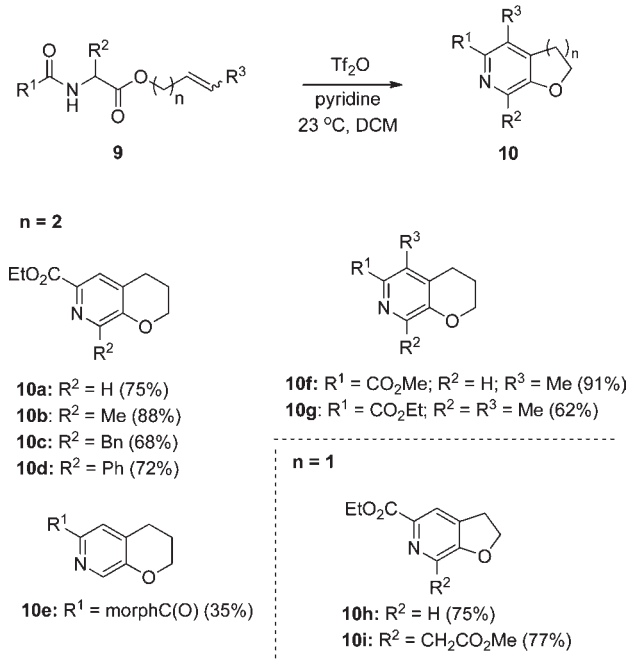
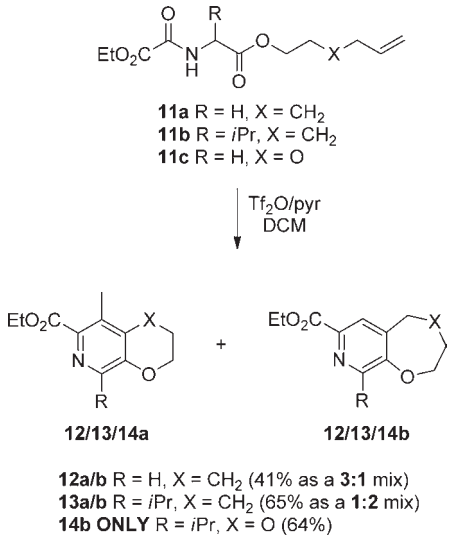


Figure 2. Substrate scope for the [4 + 2].

10c) compared to simple glycine substrates, most likely due to a further increase in the electron density of the oxazole moiety.[9] Variation at the R_1 moiety was less successful. The morpholine amide was a competent substrate to provide **10e** although the yields were only modest and not optimized further. Other R_1 substituents investigated either gave conversion to the oxazole but failed to undergo cycloaddition (R^1 = Me-, MeO-, $(MeO)_2CH$-, Ph-, Me_2N-) or failed to form oxazole (R^1 = CF_3, CCl_3) altogether. Internal alkenes (R^3 = Me) likewise were successful substrates providing tetrasubstituted pyridines **10f** (R^3 = Me).[10] A final example demonstrates the utility of the method as the pentasubstituted pyridine **10g** (R^2 = R^3 = Me) was accessed in excellent yields in only three steps with no intermediate isolations. The corresponding dihydrofuran-fused pyridines are readily obtained utilizing a butenyl tether (**10h** and **10i**).

Interestingly the seven-membered-ring homologue from the hexenyl tether **11a** was found to give two cycloaddition products whose distribution was dependent on the oxazole substitution (Scheme 2). ^{1}H NMR analysis showed that the desired tetrahydrooxepino[2,3-*c*]pyridine (**12b**, R = H) was formed as a 1:3 mixture with the dihydropyrano[2,3-

Scheme 2. Cycloaddition To Give Oxepine-Fused Pyridines



c]pyridine (**12a**) in a 41% combined yield. Whereas the 4-*i*Pr-substituted hexenyloxy oxazole arising from **11b** (R = *i*Pr) provided a reversed selectivity giving the tetrahydrooxepino[2,3-*c*]pyridine (**13b**) in a 2:1 ratio with the dihydropyrano[2,3-*c*]pyridine (**13a**) in a 65% combined yield.[11] Lastly, heteroatoms can also be incorporated into the fused ring, for example the dioxepino[5,6-*c*]pyridine (**14b**). Interestingly, this substrate (**11c**, X = O) gave exclusively the dioxepine-fused pyridine with none of the dioxane-fused product observed. If the constitutional isomers formed (**12a** and **13a**) arise from acid-catalyzed olefin isomerization, then one can explain the lack of formation of **14a** through β-alkoxy destabilization of the carbocation due to the inductive effects of the oxygen.[12]

An unexpected product was observed when the isolated oxazole **2** was submitted to thermal conditions. It was found that brief treatment of oxamide **3** with triflic anhydride followed by basic workup allowed for isolation of the oxazole **2**. When **2** was heated to 120 °C in toluene for 24 h, the ring-opened 3-hydroxypyridine **17a** was obtained in excellent yields. The benzamide (**15b**) and the *p*-nitrobenazamide (**15c**) oxazole precursors were also subjected to the cascade reaction conditions. Following oxazole formation with triflic anhydride no cycloaddition was found to occur. However, after the isolated oxazoles (**16b/c**) were heated at 120 °C for 24 h the ring-opened 3-hydroxypyridines (**17b/c**) were isolated as the only cycloadducts (Scheme 3).[13] Thus dependent upon the conditions chosen to perform the cycloaddition, complete regioselective control over which C−O bond is broken can be obtained to provide the fused dihydropyranopyridine (bond b breaks under acidic conditions) or the 3-hydroxypyridine (bond a breaks under thermal conditions) (Scheme 4).[14] It should be noted that under thermal

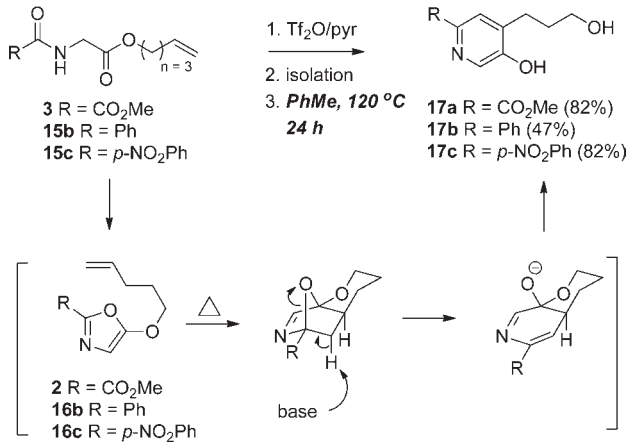
(9) The 4-alkyl substituted oxazoles proceeded to form pyridine products in 1−2 h vs 6− > 24 h for the unsubstituted oxazoles.

(10) Use of either *cis* or *trans*-4-hexen-1-ol provided similar yields and similar rates of reaction as well.

(11) At present our rationale for the 6,6- and 6,7-ring system distribution is due to simple olefin isomerization in the presence of TfOH. It is interesting to note the accelerating effect the 4-*i*Pr substituted oxazole has on the rate of the cycloaddition in which olefin isomerization is now suppressed. A similar rate enhancement was also observed in the dihydrofuran series arising from the relative rates of ring formation (5 > 6 ≫ 7).

(12) Another explanation is that olefin migration to the internal enol ether gives an alkene substrate with improper electronics to undergo the [4 + 2] cycloaddition.

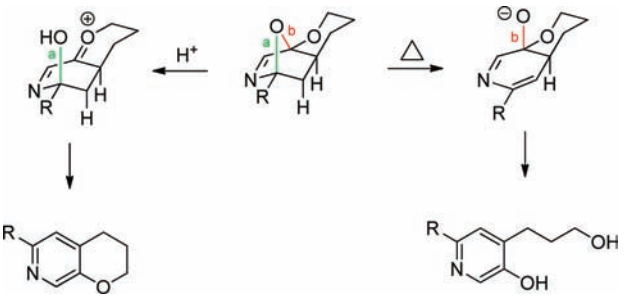
Scheme 3. Thermal Cycloaddition of Oxazoles



conditions the products (**17a**–**c**) possess the substitution pattern reported in the literature for 3-hydroxypyridines arising from intermolecular oxazole Diels–Alder reactions.[15]

In summary a novel cascade cyclodehydration/cycloaddition/aromatization sequence has been developed to access highly substituted fused pyridines in an extremely efficient, modular, and regiospecific manner. In addition, for the majority of substrates the reaction conditions required were found to be quite moderate needing only Tf_2O/pyridine at ambient temperature to induce oxazole formation and cycloaddition with completely unactivated alkenes. At this time sufficient evidence to rule out either a concerted or stepwise mechanism is not available. Future work will address this knowledge gap. In addition, it has been found that complete control of the mechanism regarding oxabicycle ring opening is obtained by switching from acidic to thermal conditions providing the fused bicyclic pyridine products or the ring-opened 3-hydroxypyridine products.

Scheme 4. Thermal vs Acidic Ring Opening



Acknowledgment. The authors thank the analytical sciences department at GlaxoSmithKline for support and analysis in structure determination.

Supporting Information Available. A general procedure along with ^1H, ^{13}C NMR and HRMS for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) Interestingly both the one carbon shorter and longer alkenyl tether homologues of **16b** reported by Padwa, A. (see ref 4) were found to be completely unreactive towards cycloaddition under a variety of conditions, returning only unreacted oxazole.

(14) An alternative mechanism in which fused pyridine product **8** simply undergoes ring opening via nucleophilic attack by adventitious water under the thermal conditions was ruled out by heating purified pyridine **1** to 120 °C in toluene for 24 h. No change in the HPLC purity or NMR profile was observed. Similarly, treating isolated oxazole **2** with Tf_2O/pyr led to exclusive formation of pyridine **1**, albeit with a slow reaction rate compared to the *in situ* method. Interestingly, treatment of pure oxazole **2** with 1 equiv of triflic acid gave an 80:20 mixture of pyridine **1** and 3-hydroxy pyridine **17a** after 3 h. It is hypothesized that adventitious water in the triflic acid lead to hydrolysis of pyridine **1**, as no attempts were made to rigorously exclude water.

(15) (a) Kondrat'eva, G. Y *Khim. Nauka Prom.* **1957**, *2*, 666. (b) Kondrat'eva, G. Y. *Chem. Abstr.* **1958**, *52*, 6345. (c) Lakhan, R.; Ternai, B. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, NY, 1974; Vol. 17, Chapter 4, p 100.