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EUROPIUM CATALYZED INTRAMOLECULAR OXAZOLE DIELS-ALDER REACTIONS FOR THE SYNTHESIS OF BENZOPYRANO[4,3-b]PYRIDINES AND BENZO[h]-1,6-NAPHTHYRIDINES

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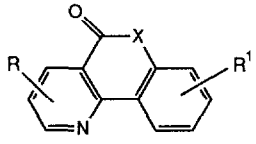
ABSTRACT: Intramolecular oxazole-olefin Diels-Alder reactions proceed, in the presence of the Lewis acid europium(fod)$_3$, to provide substituted 5H-[1]-benzopyrano[4,3-b]pyridines and benzo[h]-1,6 naphthyridines in moderate yields.

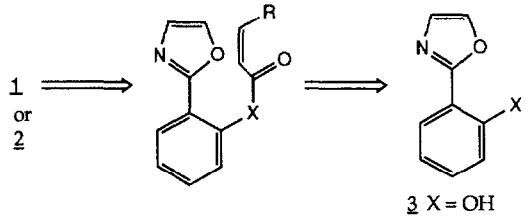
In the past several years, 5-oxo-5H-[1]-benzopyrano[4,3-b]pyridine derivatives 1 have attracted attention as pharmacologically interesting compounds.[1,2,3] These tricyclic annelated pyridines have been reported to possess inotropic, anti-allergic, analgesic and anti-inflammatory activity. The synthesis of these novel heterocycles has



1 X = O
2 X = NH

usually been accomplished through the condensation of enamines or malonic acid derivatives with substituted chromones.[1,2] More recently, Taylor has shown that these ring systems can be constructed via intramolecular cycloaddition reactions of suitably substituted triazines.[4]

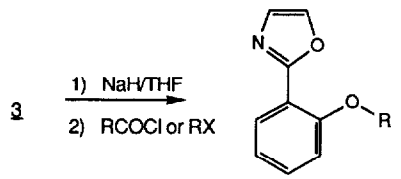
It was our intention to investigate the applicability of intramolecular oxazole-olefin Diels-Alder methodology for the synthesis of this ring system and the related nitrogen-containing compounds 2. The retro-synthetic analysis for compounds of general structure 1 and 2 is shown below:



1 or 2

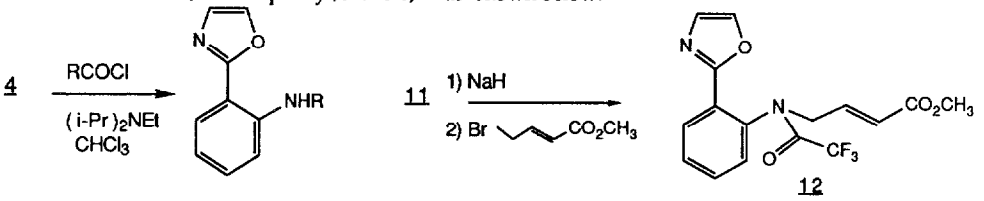
3 X = OH
4 X = NH_2

Cycloaddition reactions of oxazoles are well precedented, having first been described by Kondrat'eva in 1957.[5] Since that preliminary account, this reaction has been used on numerous occasions for the synthesis of pyridines both natural and unnatural in origin.[6] Several examples of intramolecular oxazole Diels-Alder reactions have also been published,[6,7] including one example utilizing a substituted 2-phenyl oxazole as the Diels-Alder substrate.[8] This is particularly noteworthy since 2-phenyl oxazoles are extremely unreactive heterodienes due to steric and electronic effects. The synthesis of 2-(o-hydroxyphenyl)oxazole, 3, was accomplished using a convergent four-step sequence. Thus, o-iodophenol was first acetylated with acetic anhydride/pyridine. This aryl iodide then underwent palladium catalyzed coupling with 2-tri-n-butyltin oxazole, followed by hydrolysis of the acetate to provide phenol 3 in 75% overall yield.[9] Subsequent acylation of 3 was best achieved by deprotonating the phenol with sodium hydride followed by addition of the appropriate acid chloride. Analogously, alkylation of the sodium phenoxide with the appropriate allylic bromide provided the aryl ethers 7 and 8 in good yield. This variety of olefinic side chains was chosen to investigate the electronic requirements of the dienophile in the intramolecular cycloadditions.



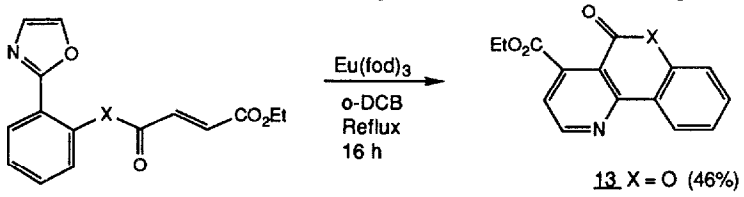
5 R = COCH = $CHCO_2Et$ (89%)
6 R = COCH = $CHCH_3$ (86%)
7 R = CH_2CH = $CHCH_3$ (49%)
8 R = CH_2CH = $CHCO_2CH_3$ (76%)

The requisite intermediates for the construction of benzonaphthyridine derivatives 2 were prepared by acylation or alkylation of the known 2-(o-aminophenyl)oxazole,[10] as shown below.



9 R = COCH=$CHCO_2Et$ (85%)
10 R = COCH=$CHCH_3$ (87%)
11 R = $COCF_3$ (89%)

Oxazole-olefin substrate 5 was chosen for our first cycloaddition attempt. Thus, the oxazole-olefin was dissolved in degassed o-dichlorobenzene (0.03M solution) and then refluxed for 16 h. Unfortunately, no reaction was observed and starting material was recovered unchanged. However, upon addition of 7 mole % of europium(fod)3 to the reaction, the



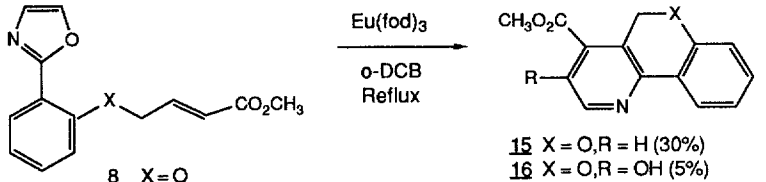
5 X = O
9 X = NH

13 X = O (46%)

14 X = NH (75%)

desired pyridine was formed in 46% yield (based on 17% yield of recovered phenol 3) after 16 h at reflux. The corresponding lactam 14 was formed from oxazole 9 in 75% yield under the same conditions. To our knowledge, this is the first example of Lewis acid catalysis in oxazole-olefin cycloaddition reactions. The only other catalyst we investigated was zinc bromide which caused decomposition of the starting materials with no apparent product formation.

Compounds 8 and 12, with mono-activated olefin side chains also underwent the desired europium catalyzed Diels-Alder reactions. In these cases, however, both the 3-unsubstituted and 3-hydroxypyridines were isolated.[8,11,12] Oxazole 8 provided a 6:1 mixture of tricyclic pyridines 15 and 16 in 35% overall yield after only 2 h in refluxing o-dichlorobenzene.[13] Oxazole 12, required 18 h in refluxing o-dichlorobenzene to give a 4.3:1 mixture of pyridines 17 and 18 in 53% overall yield. Furthermore, when nitrobenzene was used as the solvent for the cyclization of 8, the



8 X = O
12 X = NCOCF3

15 X = O,R = H (30%)
16 X = O,R = OH (5%)
17 X = NCOCF3, R = H (43%)
18 X = NCOCF3, R = OH (10%)

3-hydroxypyridine 16 was the exclusive product in 46% yield. This solvent effect was not apparent in the reactions of 5 and 9 which could never be induced to form 3-pyridinols. Only a slight increase in the yield of the 3-pyridinol was observed for the reaction of 12 in nitrobenzene (14%). It is unclear at this time why some substrates provide the 3-hydroxy substituted products and others do not.

Finally, it should be noted that oxazole-olefins 6, 7 and 10 would not undergo the desired Diels-Alder reactions. Apparently, in these intramolecular reactions, an electron-withdrawing group is required on the carbon which will occupy the 4-position of the pyridine product. This result is consistent with the activated complex proposed by Florent'ev to explain the regiochemistry of oxazole-olefin cycloadditions.[14]

Thus, in addition to investigating the scope of the intramolecular Diels-Alder reaction of substituted 2-phenyl oxazoles, we have developed a concise route to the benzopyranopyridine and benzonaphthyridine ring systems.

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12) All compounds exhibited satisfactory IR, MS, ^{1}H NMR, ^{13}C NMR and elemental analyses.
13) The increased reactivity of 8 is presumably due to both increased mobility of the olefin-containing side chain (relative to 5) and electron donation to the oxazole from the aromatic oxygen substituent. This electron donation is moderated by an α-carbonyl group in each of the other oxazole-olefin substrates.
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