Tetrahedron Letters,Vol.25,No.28,pp 2957-2960,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

THE REACTION OF 5-ACETYL-2-AMINOOXAZOLE WITH AMINES: AN APPROACH TO 1H-5-ACETYL-2-AMINOIMIDAZOLES

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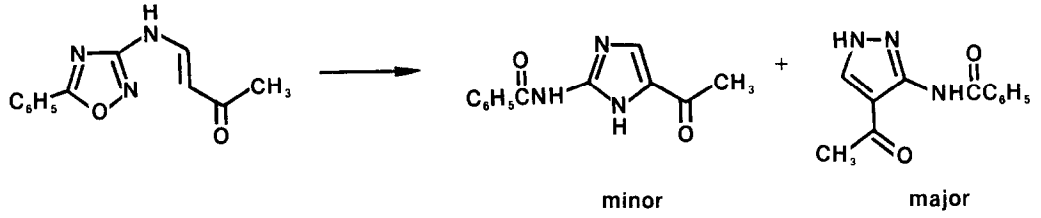
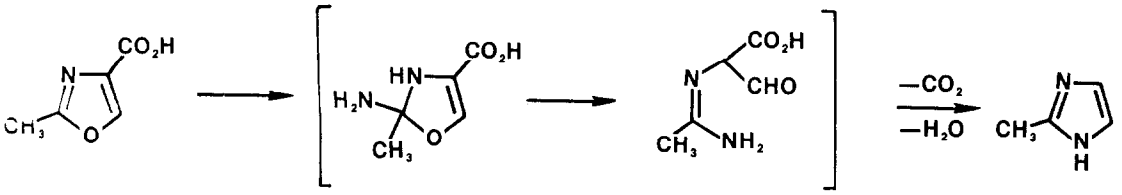
Summary: 5-Acetyl-2-aminooxazole, upon treatment with amines in the presence of water, affords good yields of 1H-5-acetyl-2-substituted aminoimidazoles, along with varying amounts of the corresponding 5-hydroxy-4-methyl-2-substituted aminopyrimidines.

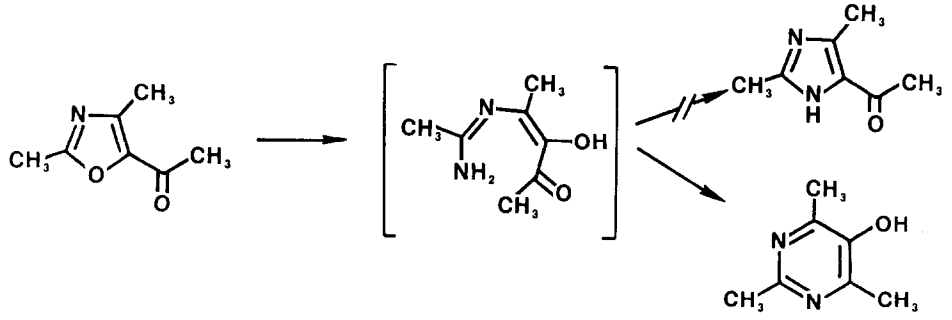
Interest in the pharmacology of histamine and histidine has recently resulted in novel synthetic methods for the synthesis of 1H-5-acetylimidazoles[1,2]. In order to pursue this area further, a general synthesis of 1H-5-acetyl-2-amino(and substituted amino)imidazoles was required. Unfortunately, previously described approaches to 1H-5-acetylimidazoles, such as the photolytic rearrangement of N-acetylimidazoles[1] or the condensation of 2-bromoacetoacetaldehyde[2] with guanidines proved unsatisfactory for the corresponding 2-aminoimidazoles. Furthermore, these difficulties were not unique. In a synthetic approach to the pseudozoanthoxanthins[3], Büchi and coworkers attempted to prepare 1H-5-acetyl-2-aminoimidazole by the 1,2,4-oxadiazole-imidazole rearrangement[4]. However, this method was of little practical use since the major product of this rearrangement was surprisingly an acetylpyrazole.



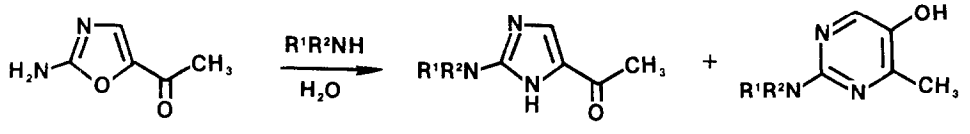
A well established synthesis of imidazoles is the rearrangement of suitably substituted oxazoles with amines[5]. For example, Cornforth[6] found that treatment of 2-methyloxazole-4-carboxylic acid with ammonia at 150° afforded 2-methylimidazole. The formation of this product undoubtedly results from nucleophilic attack at the 2-position of the oxazole, followed by ring opening, decarboxylation and subsequent ring reclosure.



It is reasonable to assume, therefore, that 1H-5-acetylimidazole should be available from the rearrangement of the appropriate 5-acetyloxazoles. However, literature precedent suggests otherwise. Reaction of 5-acetyl-2,4-dimethyloxazole with ammonia afforded exclusively 5-hydroxy-2,4,6-trimethylpyrimidine[7], a compound which results from recyclization to the six-membered ring



Despite literature claims[5] that "...the presence of a 5-acetyl group causes the reaction to follow a new pathway", this has now been found not to be a general phenomenon. In fact, 5-acetyloxazoles can be treated with amines to afford 1H-5-acetylimidazoles as the major product. Thus, reaction of 5-acetyl-2-aminooxazole (1)[2] with aqueous ethylamine affords 52% of imidazole 2a and 17% of pyrimidine 3a. Furthermore, all other amines examined gave the imidazole as the major product. Some representative examples[8] appear below.



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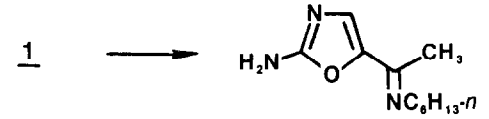
Amine	% Yield (mp °C)	
a. ethylamine	52 (198-200)	17 (100-103)
b. n-hexylamine	62 (161-162)	19 (90- 91)
c. cyclohexylamine	44 (249-251)	24 (110-112)
d. ammonia[9]	32 (210-212)	15 (202-204)
e. benzylamine	43 (200-202)	15 (109-111)
f. dimethylamine	46 (181-183)	44 (114-116)
g. pyrrolidine	48 (230-232)	35 (143-145)

Some general features on the rearrangement deserve comment. Primary amines give an imidazole/pyrimidine ratio on the order of 3:1. Secondary amines provide higher overall yields, but the product ratio approaches 1:1. t-Butylamine does not react with 1, indicating that the amine utilized must not be so hindered as to prevent nucleophilic attack at the 2-position. It should

also be noted that the presence of water is necessary in this reaction, since attempted rearrangement of 1 in neat n-hexylamine resulted in the major product (55%) being the Schiff's base 4. Inclusion of water, however, completely suppresses imine formation.



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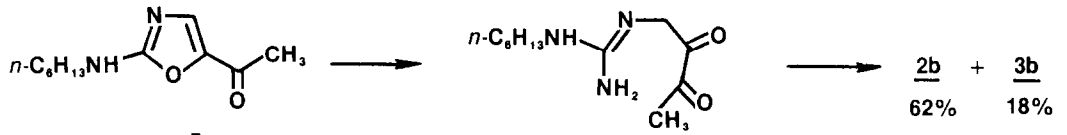
In considering the ring opening/ring reclosure mechanism of this rearrangement, it must be assumed that the same intermediate must be generated if a 5-acetyl-2-substituted aminooxazole were treated with ammonia, and thus, a similar ratio of products should be expected. In order to test this hypothesis, 5-acetyl-2-N-n-hexylaminooxazole (5) was treated with aqueous ammonia (160°, closed vessel) to afford the expected 2b and 3b in virtually identical yields to the reaction of n-hexylamine with 1.



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While this supports the proposed mechanism, it should be noted that treatment of 5-acetyl-2-N,N-dimethylaminooxazole (6) with ammonia[9] (140°, closed vessel) does not proceed as well as the reaction of 1 with dimethylamine, which occurs at room temperature. The former reaction results in 27% of 2e and 8% of 3e. The low yield and stringent conditions are due to the relatively poor nucleophilicity of ammonia, and the steric hindrance created by the N,N-dimethyl group proximal to the site of nucleophilic attack.

The difference between the reactivity of 1 and 5-acetyl-2,4-dimethyloxazole with amines is unclear but may simply stem from the presence of the 4-methyl substituent. This moiety could force the pseudo α-diketo intermediate into an enol-keto form which would enhance pyrimidine formation. Further studies to unravel the effects that substituents play on this rearrangement are now underway. Nevertheless, this work demonstrates that 5-acetyloxazoles can rearrange to imidazoles when treated with a wide variety of amines, thereby providing 1H-5-acetyl-2-aminoimidazoles, compounds of value in medicinal chemistry and natural product synthesis.

General Procedure for the Reaction of 1 with Amines: A mixture of 2.0 g (1.6 mmol) of 1, 20 ml of the appropriate amine and 4 ml of water was heated at reflux until complete consumption of 1. The mixture was concentrated and triturated with ethyl acetate. Most of the imidazole precipitated at this point. The imidazole was collected and the filtrate concentrated. Chromatography of the residue over 40 g of silica gel using 4:1 ethyl acetate:hexane as eluent afforded the less polar pyrimidine. Subsequent elution with 19:1 chloroform:methanol gave the remainder of the imidazole formed.

Acknowledgement: The authors are grateful to Professor E. J. Corey, Professor D. S. Kemp, Professor Stuart Schreiber and Dr. C. A. Lipinski for fruitful discussions of this work.

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8. All new compounds gave satisfactory spectral data and combustion analyses.

9. Some 3-5% of 1-H-5-acetyl-2-imidazolone was also formed in this reaction. This material results from water acting as the nucleophile.

(Received in USA 23 April 1984)