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THE SYNTHESIS OF 5-AMINOOXAZOLES. A NOVEL OXAZOLE TO IMIDAZOLE CONVERSION

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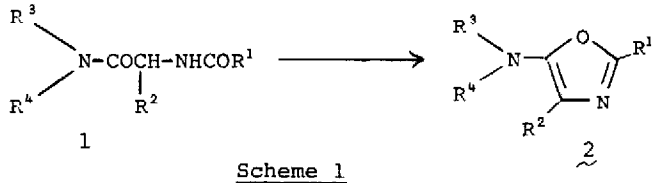
Relatively few literature reports of the preparation of substituted 5-aminooxazoles have been made[1-5]. Primary and secondary 5-aminooxazoles are unstable and readily revert to ring open forms in acid media[2,3], or undergo oxidative decomposition[6]. In contrast, tertiary amino derivatives are relatively stable to oxidative breakdown[4]. We were interested in these compounds as precursors of potential therapeutic agents, and herein report a novel rearrangement occurring during the attempted synthesis of a tertiary 5-aminooxazole.

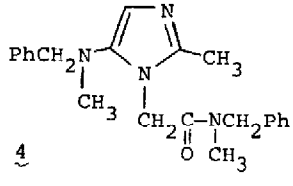
Fleury and his co-workers have prepared the tertiary amines (2) by cyclisation of the amides (1)(Scheme 1), in the presence of trifluoroacetic anhydride[4]. However, in the cases where R^2=H, the product is converted further, by electrophilic attack, into the 4-trifluoroacetyl derivatives.



1 2

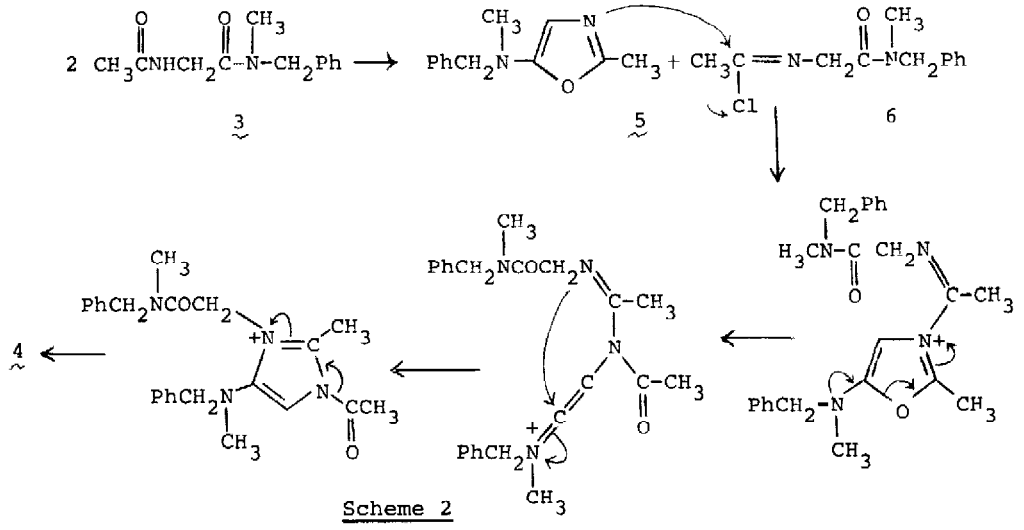
Scheme 1

Thus we prepared 2-methyl-5-morpholino-4-trifluoroacetyloxazole (2, R^1=Me, R^2=$COCF_3$, NR^3R^4=$N(CH_2CH_2)_2O$) and attempted to remove the trifluoroacetyl group by hydrolysis and subsequent decarboxylation[4].
However, only the ring open form (1) could be isolated. In considering alternative catalysts for the cyclisation reaction which would obviate the problem of substitution, we reacted the amide (3)(Scheme 2) with phosphorus oxychloride at room temperature for 16 hrs. The resulting dark oil solidified and gave, after two recrystallisations from carbon tetrachloride, white crystals m.p. 133-133.5° in 28% yield. No attempt was made to



4

maximise this recovery. The mass spectrum showed a mass ion at m/e 362 and ions at m/e 271, 180 explained by loss of two benzyl groups from the parent ion. Elemental analysis suggested an empirical formula of $C_{22}H_{26}N_4O$. A structure consistent with this data is 4, and can be rationalised by the mechanism shown in Scheme 2, the required product (5) reacting further with the iminochloride derivative (6) to yield, ultimately, an imidazole product.



Scheme 2

The proton N.M.P. spectrum confirmed this assignment, but showed an anomaly at δ2.95 where a methyl signal appeared as an apparent doublet. However, this signal collapsed to a singlet at 80°, suggesting rotamerism about the amide bond would explain this effect. The ^{13}C spectrum of 4 was also in accord with the proposed structure.

It was subsequently demonstrated that the required oxazole (5) could be isolated in 20% yield when the reaction was conducted at room temperature for a shorter period (4 hrs).

The extension of this method to the synthesis of other oxazoles is currently under investigation.

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