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A NOVEL AND EFFICIENT SYNTHESIS OF A TETRA-SUBSTITUTED IMIDAZOLE

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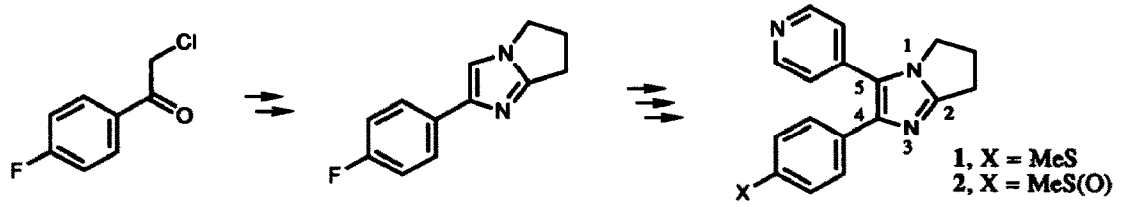
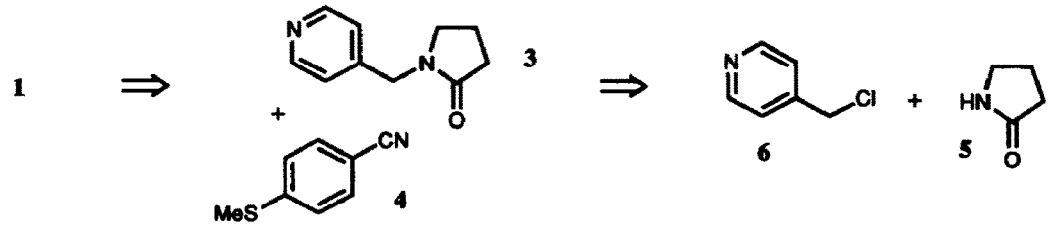
Abstract:- *A novel synthesis of a tetra-substituted imidazole is described. A key feature of the synthesis is the regioselective deprotonation of picolylpyrrolidinone 3 and the efficient reaction of this anion with an aryl nitrile to give the pyrrolidinoimidazole nucleus in a single step.*

Pyrroloimidazoles bearing 4,5-diaryl substituents, as exemplified by SK&F 105561 **1** and the corresponding pro-drug SK&F 105809 **2**, are members of a novel class of Cytokine Suppressive Anti-inflammatory drugs (CSAID's)[1] and as such are candidates for the treatment of inflammatory diseases such as arthritis and asthma.The original synthesis[2] of SK&F 105561 **1** is shown below and is based on an earlier synthetic approach



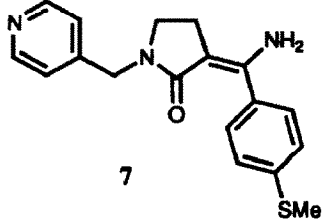
developed for an analogous series of structures.[3] This synthesis allowed the regiospecific introduction of the two aryl groups in the correct disposition with respect to the fused ring system. However, we required a shorter alternative to this eight step sequence to serve as a basis for a commercial process.

One disconnection we investigated was C_4-C_5:C_2-N_3 cleavage. The main application of this disconnection to imidazoles has involved the use of TOSMIC.[4] Whilst this has proved to be a powerful synthetic method for the construction of a variety of imidazoles, it is not applicable to products bearing C_2 or N_1 substituents. Our approach required the regioselective deprotonation of the precursor **3** at the methylene group α to the pyridine ring, rather than α to the carbonyl. We wish now to report the results of our investigation of the deprotonation of **3** and its subsequent reaction with methylthiobenzonitrile **4**.



Alkylation of 2-pyrrolidone **5** with 4-chloromethylpyridine **6** under phase transfer conditions gave the required picolylpyrrolidinone **3** in 85% yield.[5] Our initial attempts to deprotonate this compound using one equivalent of

butyllithium at -78°C, followed by addition of nitrile **4**, did give the required imidazole **1**, albeit in very low yield (10-20%). Nevertheless, this result did establish the validity of our retrosynthetic analysis. Using 2 eq of butyllithium, we obtained a 75% yield of the enamine **7**. This suggested that we had formed a dianion under these conditions. This was confirmed using *p*-fluorobenzyl bromide as the electrophile, when a 75% yield of the dialkylated compound **8** was obtained, clearly indicating the formation of a dianionic species.



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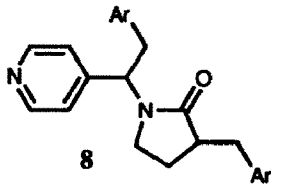

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Further optimisation of the various parameters allowed us to obtain a 45-50% yield[6] for the imidazole **1**. In particular, we found that it was necessary to reflux the reaction mixture to obtain the maximum yield of imidazole in these reactions. In our attempts to improve the reaction still further, we investigated the effect of added potassium *t*-butoxide. The use of potassium *t*-butoxide/butyllithium mixtures has been well-documented by Schlosser and others[7] to give "superbases" for the deprotonation of weakly acidic compounds. Whilst it is also generally recognised that potassium carbanions are more reactive than lithium carbanions,[8] there are relatively few reported examples where addition of potassium *t*-butoxide to a preformed anion has resulted in a dramatic change in nucleophilicity.[9] In our case, we found that addition of one equivalent of potassium *t*-butoxide to the preformed monolithio anion of **3** gave a remarkable improvement in reactivity. Not only did the reaction now go to completion at ambient temperature, rather than reflux, but the yield of product **1** increased to 85%.[6] This in turn demonstrates the high regioselectivity of the initial anion formation under these conditions.[10]

We ascribe the preferential acidity of the methylene group α to the pyridine to not only the electron withdrawing effect of the pyridine ring, but also to other factors. One is the dipole stabilisation[11] of the anion provided by the amide substituent, and the other is the so-called "complex-induced proximity effect".[12] In any event, we have demonstrated that the picolylpyrrolidinone **3** can be regioselectively deprotonated and cyclised to give a direct and efficient synthesis of the tetra-substituted imidazole **1** in a single step. Extension of this methodology to substrates analogous to **1** is under investigation, in order to define the scope of this new synthesis of imidazoles.

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6. This yield was determined by hplc assay of a solution of the crude product following work-up of the reaction.
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