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AN EASY AND STRAIGHTFORWARD ROUTE FOR THE SYNTHESIS OF DISUBSTITUTED IMIDAZOLES

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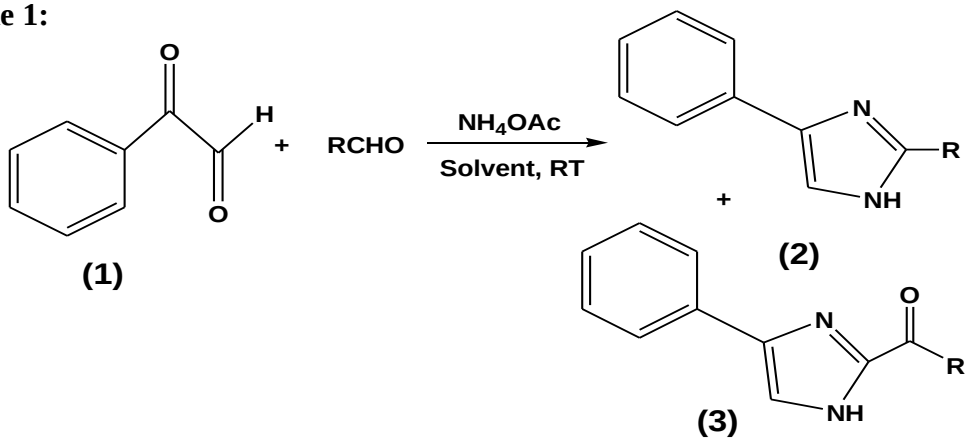
Abstract:
A simple and high-yielding procedure has been developed to synthesize disubstituted imidalozes using phenyl glyoxal monohydrate, ammonium acetate and aldehydes. This synthetic protocol allows the preparation of a variety of 2,4 (s)-disubstituted imidalozes without using any catalyst, expensive or sensitive reagents. A corresponding 2-aroyl-4(s) disubstituted imidalozes derivative has also been isolated as byproduct. The effects of solvents have also been studied.

Introduction:
Imidazoles are present in many medicinally active organic compounds and natural products. For example, amino acid histidine, the hypnotic agent etomidate, the antiulcerative agent cimetidine, the proton pump inhibitor omeprazole, the fungicide ketoconazole and the benzodiazepine antagonist flumazenil are imidazoles. For this reason, there is a need for the developing concise and rapid method for the preparation of these types of compounds.[1-4]

Results:
Although chemistry, biology and pharmacology of imidazoles are very rich, synthetic studies of these agents without any catalyst at room temperature has not been investigated. Using our methods diverse imiadazoles was prepared at room temperature without acids or acidic catalysts (**Scheme 1**).

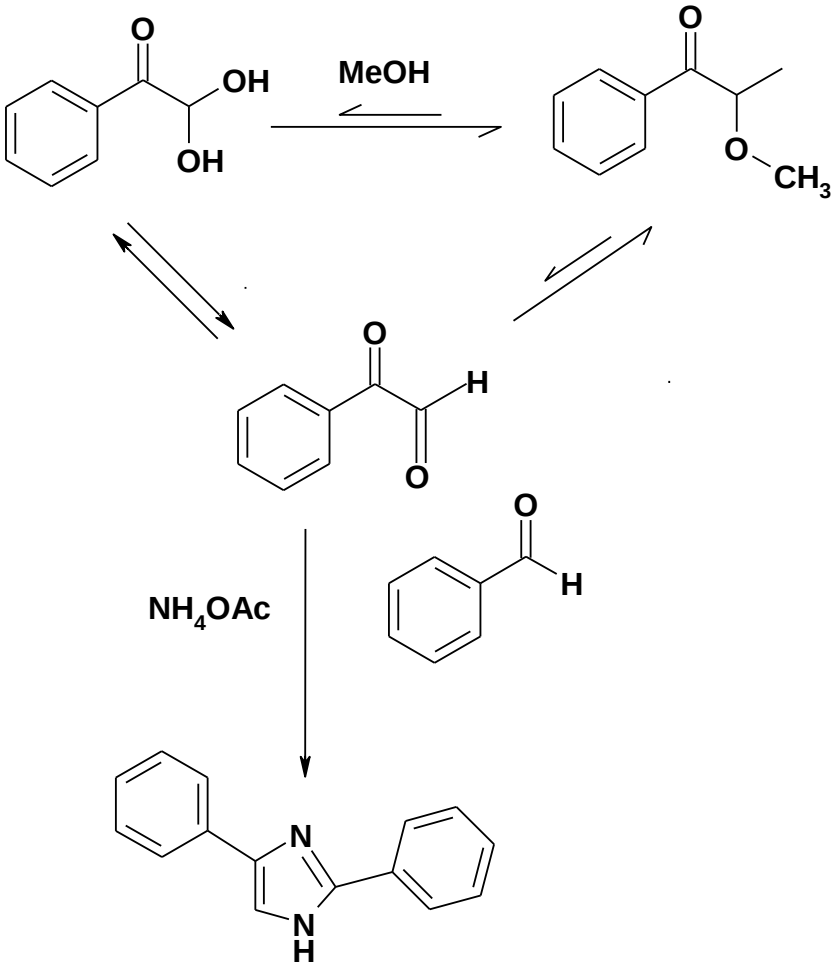
Scheme 1:



We describe herein a diverse, convergent, high yielding, environmentally friendly synthesis of functionalized imiadazoles at C-2 and C-4. Our method can be performed without using any acidic reagents or catalysts. This study reveals that the yield of the desired compound (**2**) is excellent when benzene, tetrahydrofuran and dichloromethane were used as solvent. The product ratio shifts extensively towards (**2**) when water was used as solvent but the overall yield becomes low (18%).

The mechanism of the reaction is not clear. However, a more probable route can be advanced. In the presence of methanol, we postulate that this equilibrium would be shifted toward the hemiacetal form (**Scheme 2**).

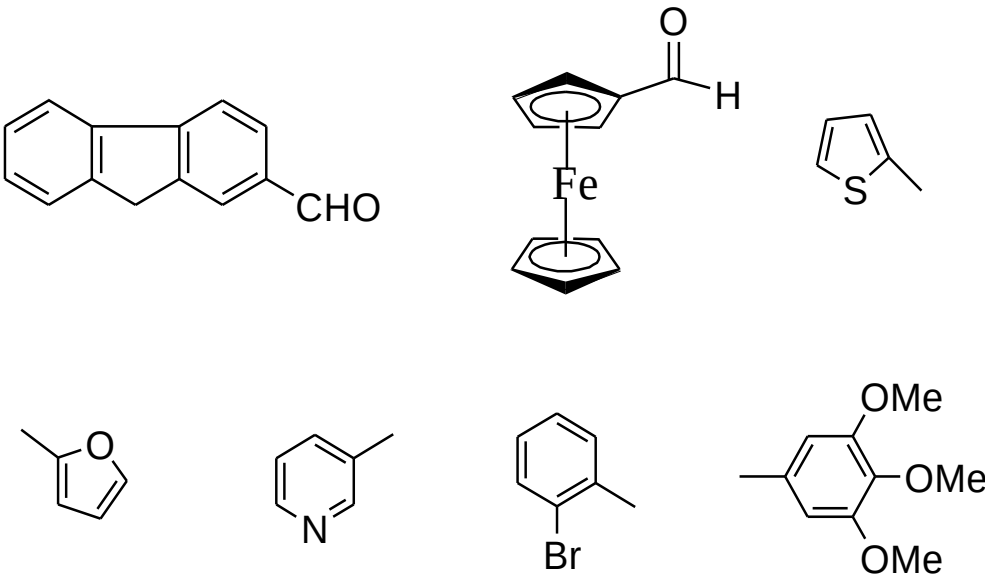
Scheme 2:



This hypothesis is confirmed by NMR studies conducted on a dicarbonyl compound in chloroform-*d* (*CDCl*$_3$), in the absence or presence of 2 equivalent of methanol. The ^{1}H NMR spectrum recorded in $CDCl_3$ without methanol shows a peak corresponding to the phenylglyoxal aldehyde group at 9.70 ppm, confirming the presence of the dicarbonyl form. This may be the

reactive species in polar solvents, for example in dichloromethane and dimethylformamide. This supports the auto-condensation and the formation of the benzoylphenylimidazole as the major cproduct. In contrast, the NMR spectrum recorded in $CDCl_3$ in presence of methanol showed a peak near the methanolic methyl chemical shift (3.51ppm) and the presence of the aldehyde peak could not be detected. This confirms the existence of the hemiacetal form and therefore, formation of the 2, 4-(5)-diphenylimidazole. This condition should favor the incorporation of benzaldehyde at the C_2 position of the imidazole ring. The data further suggests that, in other solvents, there is a competition between the aldehyde and the glyoxal for the C_2 position of the heterocyclic ring. The compounds synthesized were obtained in good yields with a simple workup and without chromatographic purification in most of the cases. Various aldehydes have been used in this study with considerable successes **(Scheme 3).**

Scheme 3:



Conclusion:

In conclusion, we have developed a simple and effective procedure for the synthesis of disubstituted imidazoles at room temperature without using any catalyst acidic mediums.

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