A SHORT REVIEW ON SYNTHESIS OF IMIDAZOLE DERIVATIVES

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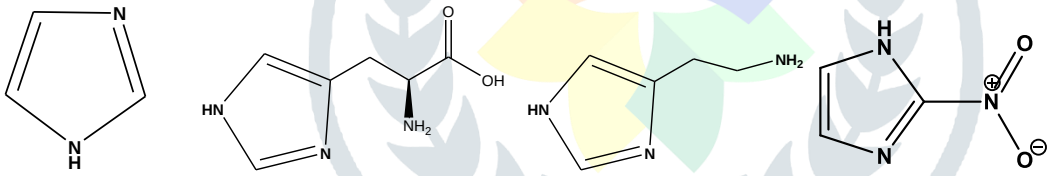
Abstract: Imidazoles containing heterocyclics are important in daily life which are essential. The imidazoles are having very broad applications in many of drugs, dyes and agrochemicals. In this review, we mainly focus on the uses of imiidazoles with some pharmacological activities and few synthetic methods.

Key word: *Imidazole, alkaloid, nitroimidazole, heterocycles.*

I. INTRODUCTION

Imidazole is an organic product that contains formula $C_3H_4N_2$. It is a "1,3-diazole," which is known as an alkaloid. Imidazole **(Fig. 1)** corresponds to the parent compound, whereas imidazoles are a family of heterocycles of identical ring structure, but with different substituents. In important biological building blocks such as histidine **(Fig. 2)**, and the related hormone histamine **(Fig.3)**, this ring system is present. Imidazole can act as a weak acid and as a base. Some medicines, such as antifungal drugs and Nitroimidazole **(Fig. 4)** contain an imidazole ring [1-5].



1 **2** **3** **4**

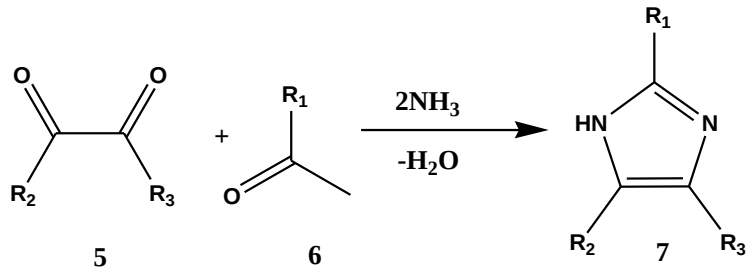
Imidazole was first synthesized by **Heinrich Debus** in 1858, but various imidazole derivatives (7) were discovered as early as the 1840s, glyoxal (5) and formaldehyde (6) were used in ammonia to form imidazole [6] as shown below. This synthesis is still used to create C-substituted imidazoles whilst producing relatively low yields.

II. General Methods of Preparation

Imidazole can be synthesized using a number of different methods. Many of these reactions can also be extended to different substituted imidazoles and imidazole derivatives simply by changing the reactant functional groups. Many methods for the synthesis of imidazoles are available, such as Debus synthesis, Radiszewski synthesis, imidazoline dehydrogenation, alpha halo ketones, Wallach synthesis, Details of the synthetic procedures are given below.

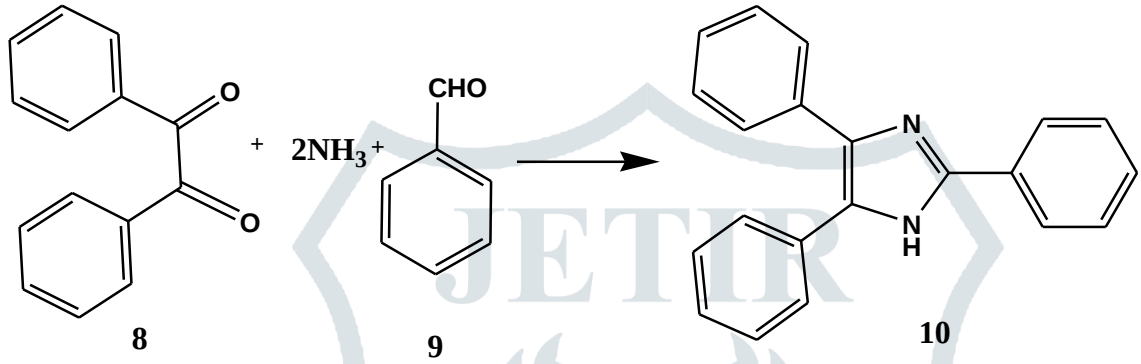
1) Debus Synthesis [6]

Debus Synthesized imidazole with ammonia using glyoxal (5) and formaldehyde (6). This synthesis is still used to produce C-substituted imidazoles though achieving relatively low yields (7).



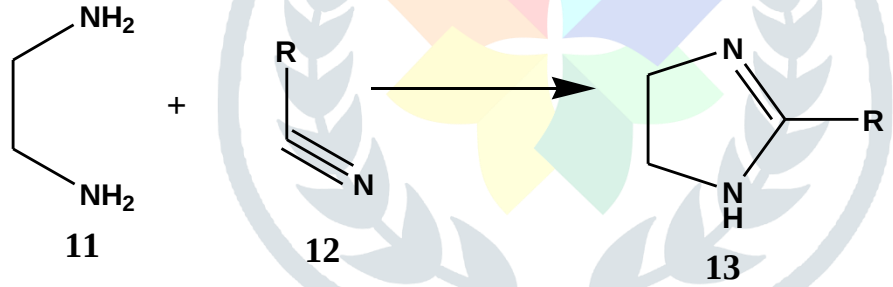
2) Radiszewski Synthesis [7-9]

Radiszewski recorded the involvement of ammonia in condensation of a dicarbonyl product, benzil (8) and α-keto aldehyde, benzaldehyde (9) or α-diketones, yield 2, 4, 5-triphenylimidazole (10).



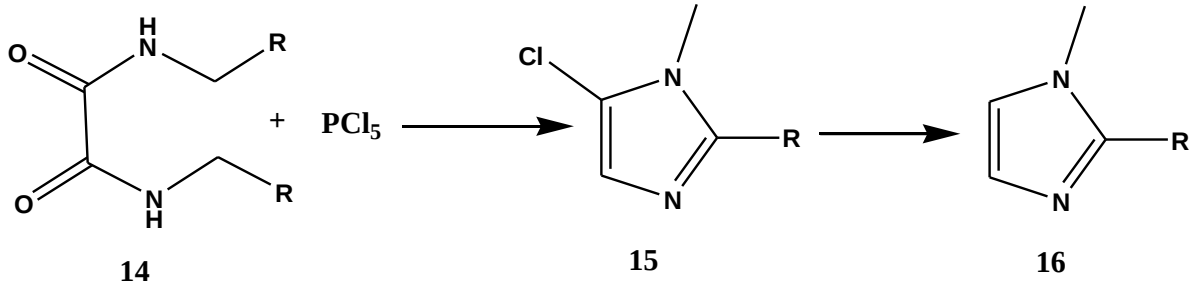
3) Dehydrogenation of Imidazoline [10]

A milder reagent barium managnates in the presence of sulphur to turn imidazolines into imidazoles. Imidazolines obtained on reaction with BaMnO4 produce 2-replaced imidazoles from 1, 2 ethanediamine (11) and alkyl nitriles (12) (13).



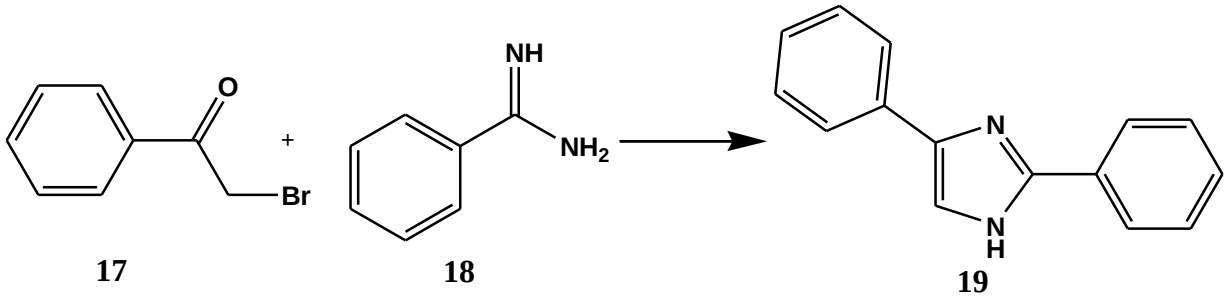
4) Wallach Synthesis [11-14]

Wallach stated that when N, N-dimethyloxamide (14) is treated with phosphorus penta chloride, a compound-containing chlorine (15) is obtained that gives N-methyl imidazole (16) upon reduction with hydroiodic acid. N-diethyloxamide is transformed to a chlorine derivative under the same scenario N, which results in 1-ethyl-methyl imidazole at reduction.



5) From α- Halo Ketone

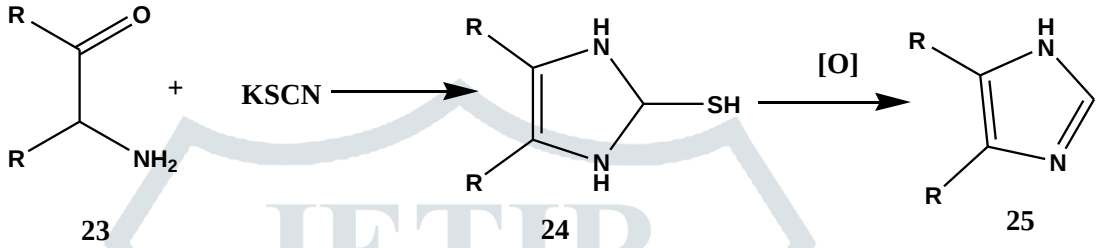
This approach is focused on an association between the ketones of the alpha halo (17) and the imidine (18). This approach was successfully applied for 2, 4- or 2, 5- biphenyl imidazole synthesis (19).



17 18 19

6) Markwald Synthesis

2-Mercaptoimidazole preparations from α-amino ketones (23) or aldehyde and potassium thiocyanate are used for the synthesis of 2-thiol substituted imidazoles (24). The sulfur can be extracted readily by a number of oxidative methods to produce the desired imidazoles (25).

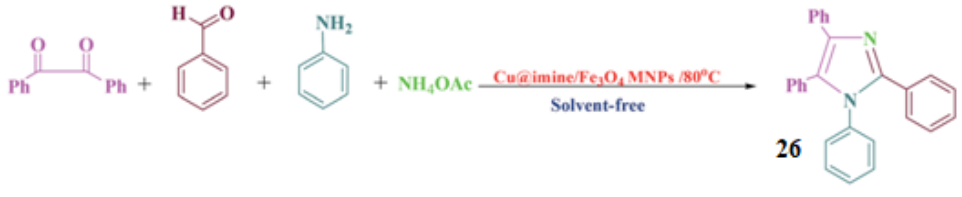


23 24 25

7) Myo Thwin method [15]

An efficient method is described for the green and rapid synthesis of biologically active polysubstituted pyrroles and 1,2,4,5-tetrasubstituted imidazoles derivatives using the catalyst Cu@imine / Fe_3O_4 MNPs under solvent-free conditions. This catalyst demonstrated strong reactivity for the synthesis of a set of different polysubstituted pyrroleum derivatives and 1,2,4,5-tetrasubstituted imidazole derivatives under appropriate reaction conditions and short periods. In fact, the catalyst was recovered and reused for six tests with no significant reduction in reactivity and yields. This approach continuously demonstrates the advantages of low catalyst activation, fast reaction times, simple product isolation and purification, high yields, and strong catalyst recoverability and recoverability compared with the recorded procedures.

Preparation of polysubstituted pyrroleum derivatives with different substituents from the reaction of aromatic aldehydes, ethyl acetoacetate, nitromethane, and aniline under solvent-free conditions utilizing Cu@imine / Fe_3O_4 MNPs as a new, environmentally friendly, reusable and promising heterogeneous nanocatalyst. While various techniques have been used to prepare polysubstituted pyrroleum derivatives, some of these approaches suffer from drawbacks such as the use of high temperature, the need for excess catalyst volumes, long reaction times, and microwave or ultrasound irradiation specifications. Hence, an improved strategy for the preparation of polysubstituted pyrrole derivatives under mild conditions of reaction is necessary.



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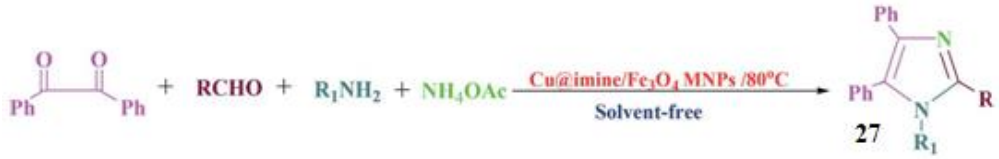

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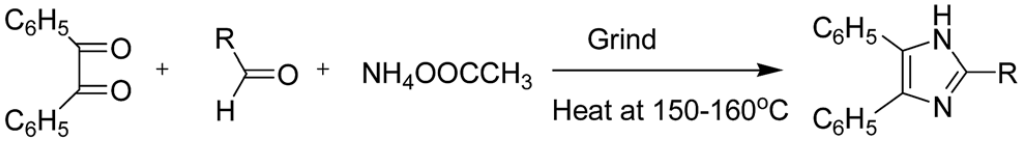
8) Kiran Pradhan method [16]

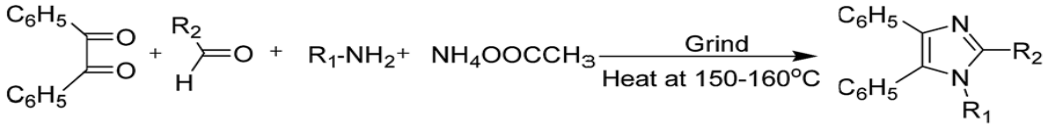
Synthesis of various imidazoles and their salts, imidazole N-oxides and 1-hydroxyimidazole 3-oxides, from sterically distinct dicarbonyl moieties provided insight into the self-catalytic activity of

carbonyl compound condensed phase reactions. For solvent-free multi-component syntheses, self-catalytic behavior was examined using a variety of methods viz., reactivity, spectroscopy, and theory. With the aid of HPLC, a comparative analysis of the kinetics of un-catalyzed and catalyzed reactions offered insights into the process. The polarizability of organized carbonyl functionalities in condensed phase contributes for the observed self-catalysis. High yields of many different imidazoles were obtained from the simply mechanical grinding and heating of MCR starting materials, even in the absence of Lewis acid catalysts.

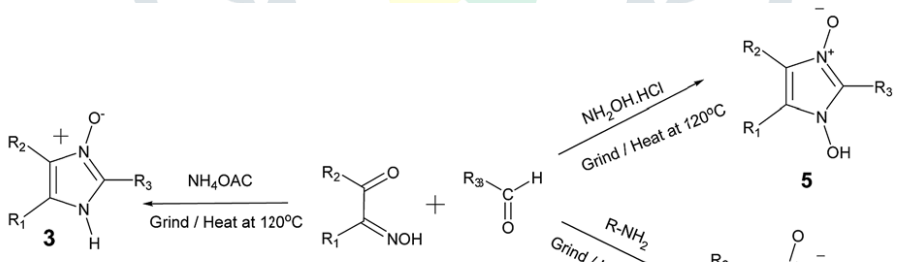
The very weak carbonyl dipole will trigger polarization in bulk, because the carbonyl bonds are strongly polarizable, and the net result is an improvement in carbonyl electrophilicity. The poor yet desirable carbonyl cluster conformation is expected to break in polar solvents owing to stronger solute– solvent interactions. Solvents therefore behave detrimental to the impact of self-catalytics. This phenomenon can be well exploited without using any catalytic material to create a self-catalytic effect.



a; R = Ph
b; R = 4-OCH_3-Ph
c; R = 2-OH-Ph
d; R = 3-NO_2-Ph
e; R = 3-OCH_3, 4-OH-Ph
f; R = 4-$N(CH_3)$-Ph
g; R = 4-OH-Ph
h; R = 2-pyridyl
i; R = H



a; R_1 = $-CH_2CH_2CH_2CH_3$ R_2 = H
b; R_1 = 4-Cl -Ph R_2 = H
c; R_1 = 4-OCH_3-Ph R_2 = H
d; R_1 = 4-OH-Ph R_2 = H
e; R_1 = 4-CH_3 -Ph R_2 = H
f; R_1 = 4-COOH-Ph R_2 = H
g; R_1 = $-CH_2COOH$ R_2 = H
h; R_1 = 2-NO2, 4-Cl-Ph R_2 = H
i; R_1 = Ph R_2 = Ph
j; R_1 = 4-OCH_3-Ph R_2 = 2-NO_2-Ph
k; R_1 = 4-OCH_3-Ph R_2 = 4-OCH_3-Ph
l; R_1 = 4-OCH_3-Ph R_2 = 4-OH-Ph



a; $R_1 = R_2 = CH_3$; R_3 = 4-OCH_3-Ph
b; $R_1 = R_2 = CH_3$; R_3 = 4-$N(CH_3)_2$-Ph
c; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph
d; $R_1 = R_2 = CH_3$; R_3 = 3-NO_2-Ph
e; $R_1 = R_2$ = Ph ; R_3 = 3-OCH_3, 4-OH-Ph
f; $R_1 = R_2$ = Ph ; R_3 = 4-OCH_3-Ph
g; $R_1 = R_2$ = Ph ; R_3 = 4-OH-Ph

a; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph
b; $R_1 = R_2 = CH_3$; R_3 = 4-OCH_3-Ph
c; $R_1 = R_2 = CH_3$; R_3 = 3-NO_2-Ph
d; $R_1 = R_2 = CH_3$; R_3 = H
e; $R_1 = R_2$ = Ph ; R_3 = 4-OCH_3-Ph

a; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph ; R = n-butyl
b; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph ; R = α–napthyl
c; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph ; R = 2-NO_2-Ph
d; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph ; R = 4-OCH_3-Ph
e; $R_1 = R_2$ = Ph ; R_3 = H ; R = 4-Cl-Ph
f; $R_1 = R_2$ = Ph ; R_3 = ethyl; R = $-CH_2COOH$
g; $R_1 = R_2$ = Ph ; R_3 = 4-OH-Ph ; R = 4-Cl-Ph

III. Conclusions: Imidazoles are available in nature in terms of biomolecules. These molecules show different types of biological activity. Therefore, a simple, economically viable method should be adoptable for the synthesis of Imidazole derivatives.

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