

REACTION STRATEGIES FOR SYNTHESIS OF IMIDAZOLE DERIVATIVES: A REVIEW

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ABSTRACT

The development of a methodical directional synthesis of complex organic molecules with the aim of obtaining the physiologically active substance with selective action takes a central position in modern synthetic organic chemistry. Imidazole derivatives are a key component in great many bioactive compounds of both natural and synthetic origin. Many scientists in the field of pharmaceutical chemistry and pharmacology have been attracted to them in recent years. This is because of the exceptional chemical properties and biological activities that they demonstrate. It is a big challenge for the scientists to modify and synthesize new imidazole derivatives.

Keywords: imidazole, synthesis, formamide, microwave

INTRODUCTION

Imidazole is an organic compound with an empirical formula $C_3H_4N_2$, shown in Fig. 1. It is a planar five-membered heterocycle with 3C and 2N in positions 1 and 3, which classified it as a "1,3 - diazole". The first name of imidazole was gluoxaline because first synthesis has been made by glyoxal and ammonia. The chemical structure of this heterocycle determines amphoteric properties, which are a prerequisite for nucleophilic and electrophilic attack. Highly stable in acid, base, thermal, reduction and oxida-

tion conditions. Imidazole possesses intramolecular hydrogen bonding. The hydrogen atom can be located in either of the two nitrogen atoms and this is a reason for its existence in two equivalent tautomeric forms. Consisting of a part of the electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring - the presence of a sextet of electrons categorizes this compound as aromatic (1).

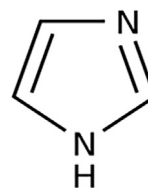


Fig. 1. Chemical structure of imidazole

Imidazole is the basic compound while imidazoles are a class of heterocycles with similar ring structure, but different substituents. Many drugs, such as antimycobacterial drugs, contain an imidazole ring fragment in their structure. Diversified imidazoles

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are biologically and pharmaceutically very important and many of their derivatives possess different activities. For example, they are used as antidiabetic, antihypertensive, and anti-inflammatory drugs.

Recent publications have drawn the attention to the potency and wide relevance of imidazole derivatives. They act as inhibitors of p38 mitogen-activated protein kinase (2), B-Raf kinase (3), activin receptor-like kinase (ALK5) transforming growth factor b1 (TGF-B1) type 1(4), cyclooxygenase-2 (COX-2) (5) and biosynthesis of interleukin-1 (IL-1) (6). Appropriately substituted imidazoles are extensively used as glucagon receptors(7), modulators of P-glycoprotein (P-gp), CB1 cannabinoid receptor antagonists (8), mediated multidrug resistance (MDR) (9), antibacterial and antitumor agents (10), and also as pesticides (11).

In summary, we can conclude that a large number of imidazoles and imidazole derivatives have been investigated for different biological and pharmacological properties. Therefore, this article aims to review the information for possible synthesis of imidazole derivatives. Imidazole can be synthesized via various methods. Many of these syntheses can also be used for the practical synthesis of different substituted imidazoles and functional groups on the reactants.

REACTION STRATEGIES FOR SYNTHESIS

In the literature several synthetic methods for 2-imidazoline have been announced starting mainly from aldehydes and ethylenediamine with NBS (12). Some methods include synthesis from carboxylic acids (13), esters (14), orthoesters (15), nitriles (13), hydroxyamides (16) and mono- or disubstituted chlorodicyanovinyl benzene (17).

Imidazole was synthesized for the first time by Heinrich Debus in 1858 although various imidazole derivatives had been discovered as early as the 1840s. Debus synthesized imidazole by using glyoxal and formaldehyde in ammonia as it is shown below on Fig. 2 (18). This synthesis produces a low yield, but it is still used as a major method for the synthesis of C-substituted imidazoles. The reaction products are 2-monosubstituted, and 2, (3,4 homo) trisubstituted imidazoles.

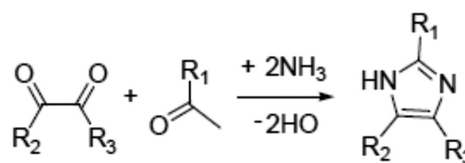


Fig. 2. Synthesis of imidazole by Heinrich Debus (H. Debus, 1858)

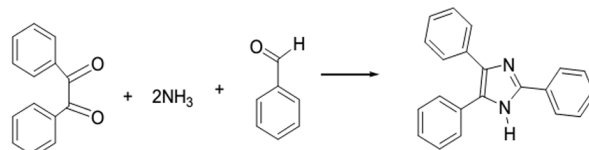


Fig. 3. Synthesis of 2, 4, 5-triphenylimidazole (E. Lunt et al., 1987)

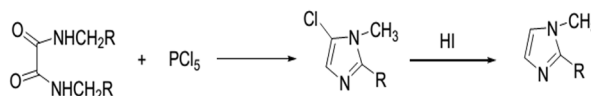


Fig. 4. Synthesis of 1-ethyl-2-methylimidazole (Na Zhao et al., 2005)

After almost one hundred years Radiszewski communicated that condensation of a benzil and α -keto aldehyde dicarbonyl compound, benzaldehyde or α -diketones in the presence of ammonia, yield 2, 4, 5-triphenyl imidazole (19-21). This synthesis is presented in Fig. 3.

Later in 1881 Wallach reported that when N, N-dimethylacetamide is treated with phosphorus pentachloride, a chlorine-containing compound is obtained. Their reduction with hydroiodic acid gives N-methyl imidazole (22-24) presented on Fig. 4.

Other scientists in the new century, Marek et al., synthesized it via a facile four-step reaction sequence starting from inexpensive and easily available N-protected amino acids (N-Cbz amino acids) shown in Fig. 5. They discovered that condensation of formamide acetate with corresponding α -bromoketones in liquid ammonia was a useful method for the synthesis of such imidazole derivatives, which are structurally related to histamine (25).

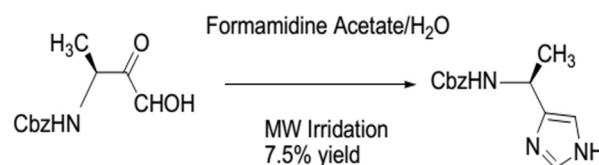


Fig. 5. Synthesis of imidazole derivatives structurally related to histamine (Marek et al., 2007)

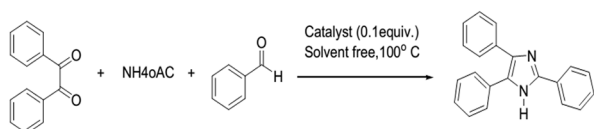


Fig. 6. Synthesis of 2, 4, 5-trisubstituted imidazoles using microwaves (Safari et al. 2010)

In present times, Safari et al. used $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ as an effective catalyst for rapid synthesis of 2,4,5-trisubstituted imidazoles, seen in Fig. 6. The reaction strategy includes condensation of benzil, aryl-aldehydes and ammonium acetate in good yields under solvent-free conditions using microwave irradiation. The microwave-assisted reactions were in accordance with reactions in conventional heating conditions (26).

In the same year, Nalage et al. described an efficient and environmentally friendly strategy for the synthesis of 2, 4, 6-triaryl-1H-imidazole in polyethylene glycol by condensing 3-methoxy-4-hydroxybenzaldehyde and benzil under microwave irradiation. The yield developed was excellent. Polyethylene glycol is reusable, nontoxic, available and inexpensive. The reaction mechanism is shown below in Fig. 7 (27).

In the same period, after one year only, a group of Indian scientists reported a synthesis method

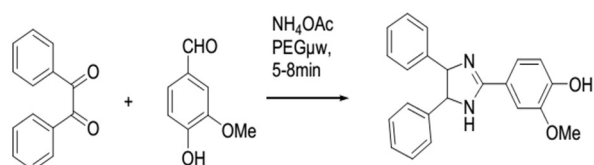


Fig. 7. Synthesis of 2, 4, 6-triaryl-1H-imidazole in polyethylene glycol (Nalage et al 2010)

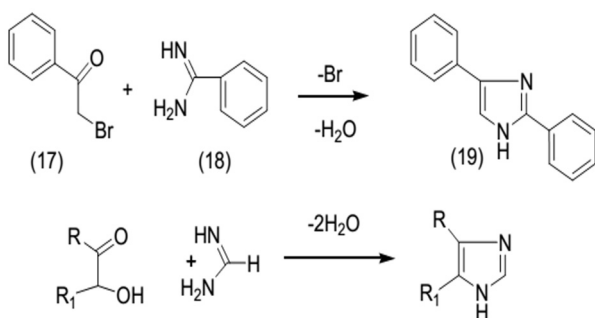


Fig. 8. Synthesis of 2,4- or 2,5- biphenyl imidazoles (Syed Sultan Qasim et al., 2011)

from α - Halo Ketone presented in Fig. 8. This method has been applied successfully for the synthesis of 2, 4- or 2, 5- biphenyl imidazole. Similar is the reaction between acyloin and amidine or alpha halo ketones to yield imidazoles (28).

The preparation of 2-mercaptoimidazoles from α -amino ketones or aldehyde and potassium thiocyanate has been used for the synthesis of 2-thiol substituted imidazoles and this method is noted as Markwald synthesis. A variety of the oxidative method can remove the sulfur and give the desired imidazoles shown in Fig. 9 (28).

The mystery of microwave heating has emerged as a valuable alternative in the synthesis of organic compounds. Synthesis of imidazole derivatives by this technique is presented in Fig. 9. Qasim et al. synthesized 2-phenanthroline derivatives. The reaction between dicarbonyl compound and p-substituted benzaldehyde is a type of acid-catalyzed reaction with excellent yields in a neutral ionic liquid, 1-methyl-3-heptylimidazolium tetrafluoroborate $[(\text{HeMIM})\text{BF}_4]$, under solvent-free and microwave-assisted conditions. This particular reaction highlights all the merits of microwave reactions like environmentally friendly, easy workup and better yield reaction (29).

Many of the steps of synthesis of novel imidazole derivatives are very valuable for the preparation of various intermediates, which can be further modified. Synthesis of imidazole ring derivatives comprises Schiff's bases, 1,3-oxazoline, oxadiazole, thiadiazole and 1, 2, 4-triazole. The projected compounds were synthesized according to Fig.11 and reaction of 2-(5-methyl-2-nitro-1H-imidazole-1-yl) ethanol

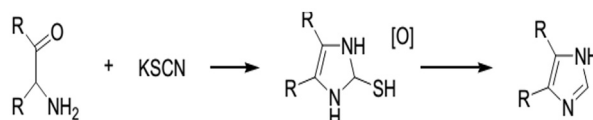


Fig. 9. Synthesis of 2-mercapto imidazoles (Syed Sultan Qasim et al., 2011)

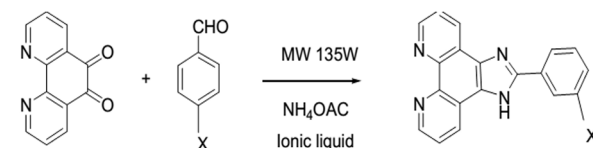


Fig. 10. Synthesis of 2- phenylimidazo [4,5-f] derivatives (Syed Sultan Qasim et al., 2011)

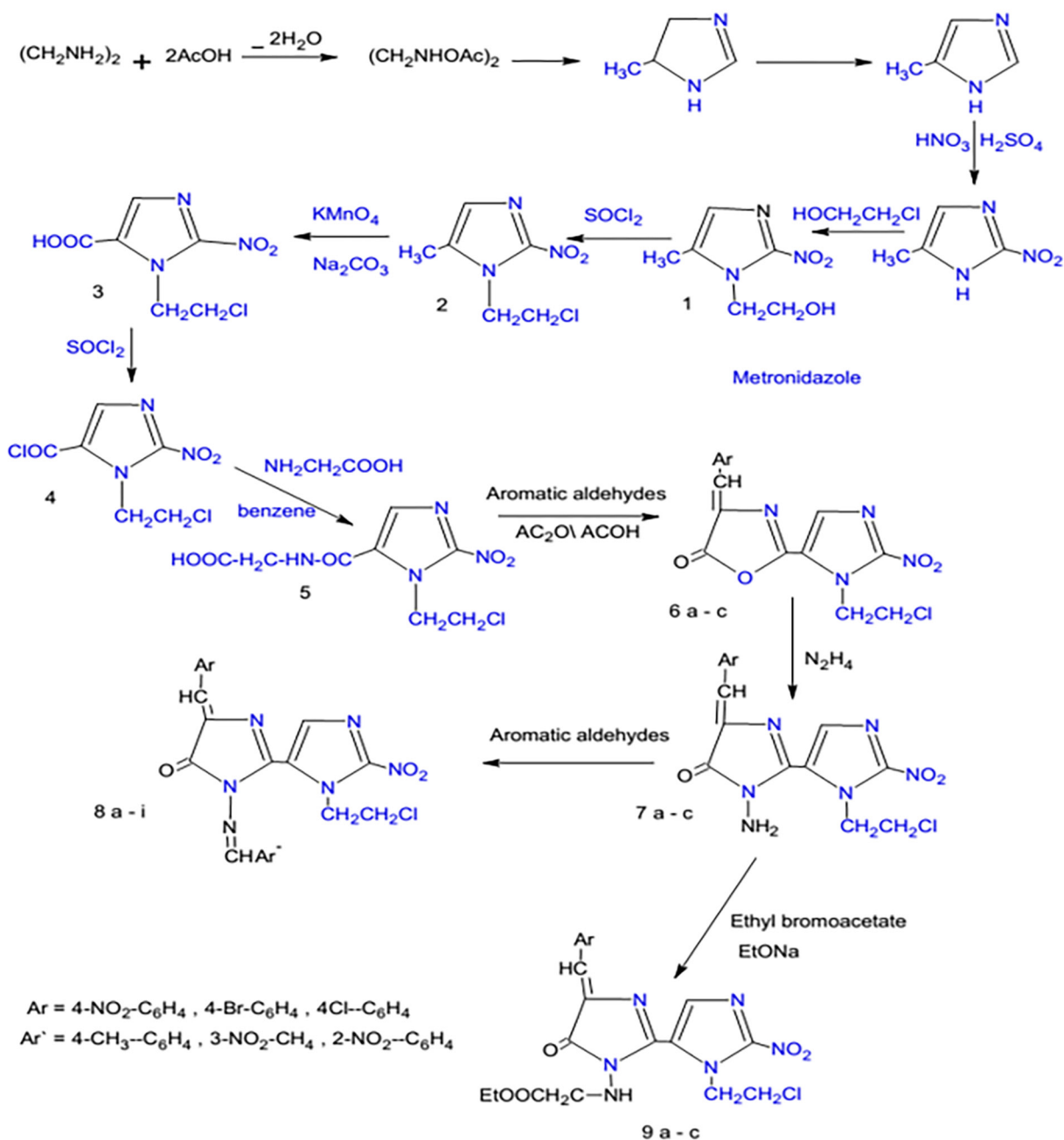


Fig. 11a. The synthesis of compounds 1 - 9a-c (Abdul Jabbar Kh. Atia et al 2009)

(metronidazole, 1) with thionyl chloride provided 1-(2-chloroethyl)-5-methyl-2-nitro-1H-imidazole (30).

The treatment of compounds 9a-c with hydrazine hydrate gave thiosemicarbazide compounds 10a-c and compounds 11a-c, accordingly. Acid hydrazides are very useful intermediates used for form-

ing some heterocyclic rings such as 1, 3, 4-oxadiazoles, 1, 3, 4-thiadiazoles and 1, 2, 4-triazoles. Another part of the compounds: 3'-(2-chloroethyl)-5-arylidene-3-[[5-mercapto-1,3,4-oxadiazol-2-yl-methyl]amino]-2'-nitro-3,5-dihydro-3'H,4H,2,4'-biimidazol-4-one and 12a-c, were synthesized in the pres-

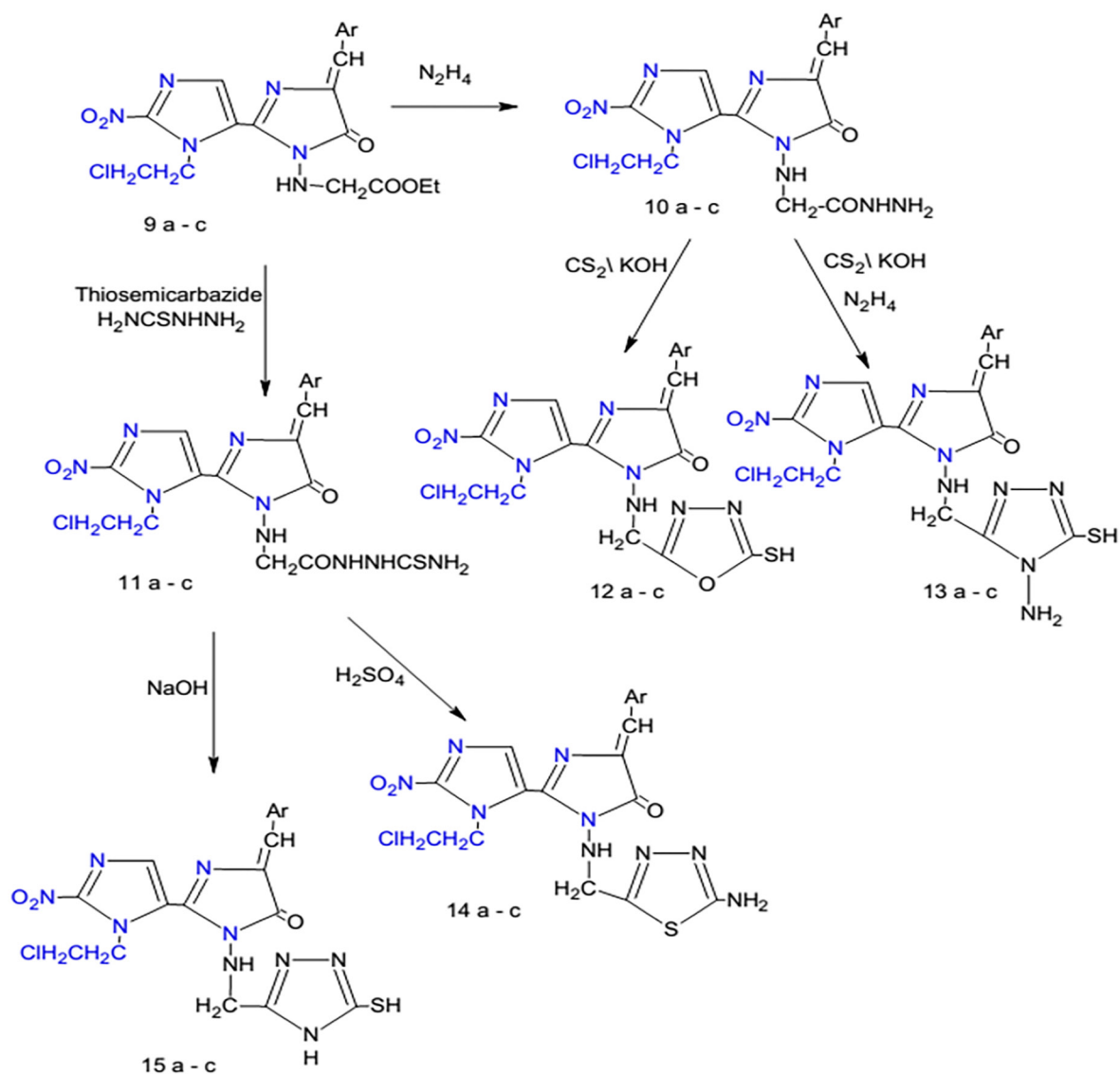


Fig. 11b. The synthesis of compounds 10-15a-c (Abdul Jabar Kh. Atia et al 2009)

ence of potassium hydroxide from the reaction between compounds 10a-c with carbon disulfide (31).

CONCLUSION

Based on the above-presented literature survey we have underlined the importance of imidazole and its synthetic derivatives. In an attempt to help the medicinal chemists or pharmacists by researches, we have presented new, easy-to-use and environmentally safe synthetic strategies. This review presents further synthetic approaches in applying the most usable strategy for obtaining a huge scope of modified

imidazoles bearing different pharmacophores, allowing structures with better effects and low toxicity.

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