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Advances in the Synthesis of Benzoazole Compounds

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Abstract: Benzozole compounds are a kind of nitrogen-containing heterocyclic compounds, which are widely used in medicine and materials, and can also be used as an important intermediate to prepare high molecular compounds. In this paper, the existing synthesis methods of benzozozole compounds are summarized, according to the reaction mechanism, which lays a foundation for the establishment of a greener, more economical and more convenient synthesis method in the future.

Keywords: Benzimidazole, Benzoxazole, Benzimidazole, Synthesis, Reaction mechanism.

1. Introduction

Benzimidazole, benzothiazole, benzoxazole and other benzoazole derivatives are common nitrogenous heterocyclic compounds, which are characterized by good biocompatibility and biodiversity, complex and variable structure, low toxicity, and are often used as important "pharmacophore" in drugs. Benzazole structures are widely used in medicine as antiviral, antibacterial, anticancer, antihistamine, anti-tuberculosis, anti-hypertension, anti - inflammatory and plant growth regulators. Because of their wide application prospect, the research and development of benzazole compounds has been widely concerned.[1]The synthesis method is particularly important.

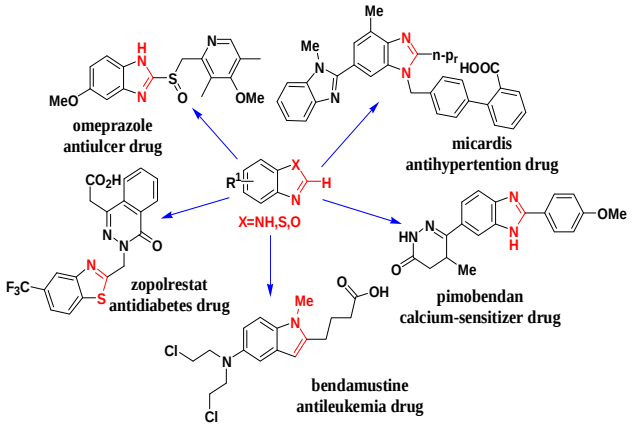

Figure 1. Representative drugs containing benzoazole skeletons

2. Review of Synthesis Methods of Benzazole Compounds

In1872, Hoebrecker first synthesized the 2,5-dimethyl - benzimidazole.They pioneered the synthesis method of benzimidazole although the yield of this reaction was not high. In 1875, the Ladenburg research group[2]studied the synthesis reaction of 4-methyl-o-phenylenediamine and acetic acid under reflux heating, and the product was benzimidazole. So far, the reaction of o-phenylenediamine and its derivatives with strong acids (such as HCl, polyphosphoric acid PPA, p-toluenesulfonic acid, mixed acid, etc.) at high temperature has become a classic preparation method of benzimidazole compounds, but the reaction conditions are harsh and the reaction time is long.

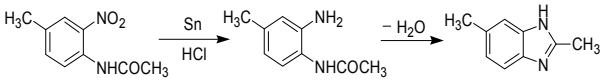

Figure 2. The synthesis method of 2,5-dimethyl benzimidazole

In 1886, Jacobson et al. [3] first synthesized benzothiazole with N-phenylthiobenzamide as raw material under the action of potassium hexacyanoferrate (III) and sodium hydroxide, and established Jacobson's ring method (Fig. 3). Jacobson uses liquid bromine as oxidant to oxidize thioamide to prepare benzothiazole. Because it is difficult to determine the amount of substances involved in the reaction with liquid bromine, by-products are often generated, and liquid bromine is highly corrosive and toxic, it does not meet the economic and environmental requirements of green chemistry.

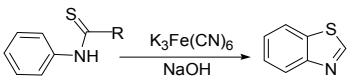

Figure 3. The synthesis of benzothiazole by N-pheny lthiophenylformamide

Since there is a method to synthesize benzimidazole and benzothiazole, the synthesis of these compounds has become a hot spot in organic synthesis. Chemists have been trying to find a more economical, efficient and green synthesis method. According to literature review, the synthesis methods of benzozole compounds are mainly as follows: First, aniline substituted by o-amino, o-mercapto and o-hydroxy is prepared by condensation reaction with carboxylic acid, nitrile and ester, which generally needs to be carried out under strong acid and high temperature conditions; Second, aniline substituted by o-amino group, o-mercapto group and o-hydroxyl group is prepared by oxidative cyclization reaction with aldehyde or alcohol, which requires stoichiometric oxidant; The third is the method of synthesizing benzimidazole by reaction of N, N-dimethylformamide (DMF) with o-mercapto, o-hydroxy and o-amino substituted aniline reported in recent years. This kind of synthesis method requires expensive reagents such as phosphorus and boron, or needs to be carried out under strong acid, strong oxidation and strong corrosion conditions, which has the disadvantages of high requirements for synthesis conditions, trivial reaction steps and low yield; As well as the recent rise in the use of CO_2 to prepare benzozole compounds, microwave radiation method to prepare benzozole compounds and other new

methods. These reactions have their own characteristics. The following is a systematic review of these synthesis methods.

(1) Condensation reaction of o-phenylenediamine with carboxylic acid, nitrile and ester.

In 2003, Chen Xingquan et al.[4]reacted with cyanamide and o-phenylenediamine as raw materials under the catalysis of NaOH to obtain 2-aminobenzimidazole with a yield of 78% - 81% (Fig. 4).

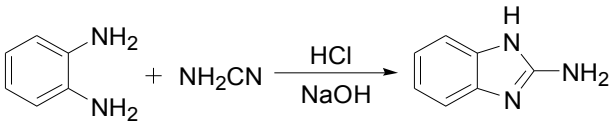

Figure 4. The synthesis of 2-aminobenzimidazole by O-phenylenediamine and cyanamide

In 2007, Zhang et al.[5]reacted with ortho pheny - lenediamine and ortho ester to obtain benzimidazole with 95% yield under the action of Lewis acid catalysts such as $ZrCl_4$, $SnCl_4 \cdot 5H_2O$, $TiCl_4$, $BF_3 \cdot Et_2O$, $ZrOCl_2 \cdot 8H_2O$, $HfCl_4$, etc.

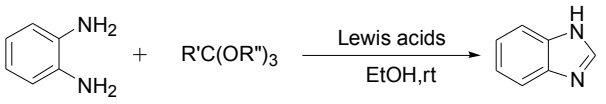

Figure 5. The synthesis of benzimidazole by O-phenylenediamine and Ortho-ester

With the condensation reaction of o-phenylenediamine with carboxylic acid, nitrile and ester, the reaction mechanism can be summarized as follows: o-phenyl -enediamine first forms N-acyl o-phenyl-enediamine intermediate with carboxylic acid, nitrile and ester, and then dehydrates and cyclizes to form benzozole compounds.

(2) Oxidative Cyclization of o-Substituted Anilines with Aldehydes and Alcohols.

In 2012, Chen et al.[6]studied the method of synthe -sizing benzimidazole with aromatic aldehydes and o-phenyl - enediamine as raw materials under $FeCl_3/Al_2O_3$ catalysis. Although the conditions of these two methods are relatively mild, they both have the disadvantage of poor selectivity (Figure 6).

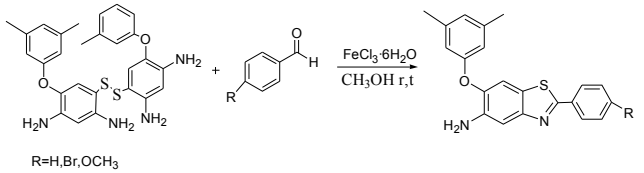

Figure 6. The synthesis of benzimidazole by O-phenylenediamine and aldehyde with metal

In 2013, Zhang Zhiwei and others[7]studied a new method of iron catalyzed synthesis of benzimidazole derivatives from disulfides: under room temperature, 2-substituted benzimidazole derivatives were synthesized in one pot with aromatic o-amino disulfides and aromatic aldehydes as raw materials under the catalysis of $FeCl_3 \cdot 6H_2O$ (Fig. 1-7).

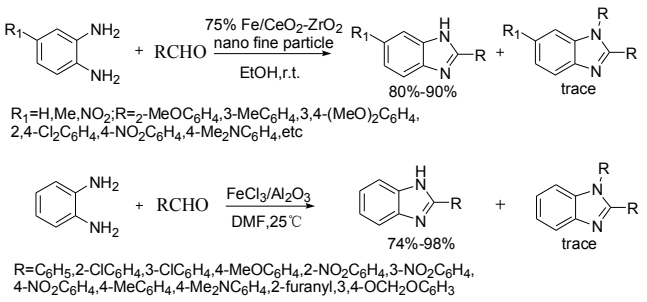

Figure 7. The synthesis of benzimidazole by aromatic amino-disulfide and aldehyde with metal

Synthesizing the oxidative cyclization reaction of o-amino and o-mercapto substituted aniline with aldehyde and alcohol, it can be concluded that the reaction mechanism is: o-amino and o-mercapto substituted aniline first forms schiff base with aldehyde, schiff base cyclizes with ortho-NH_2 to form hydrogenation intermediate, and dehydrates to form target product under the action of oxidant.

(3) Preparation of benzozoles from N, N-dimethyl - formamide (DMF).

In 2016, Liu Zhimin et al.[8]proposed a method to synthesize nitrogen containing heterocyclic compounds, which has a high yield: with o-aminothiophenol and DMF as the reaction model, under the catalysis of B $(C_6F_5)_3$, CO_2 and Et_2SiH_2 are used to promote the effect of allyl alcohol on α- For the effective hydration of hydroxy ketones, the yield of the target product benzothiazole can reach 99% at 120 □ for 24 hours (Fig. 1-8). This method combines B- $(C_6F_5)_3$ with CO_2 in the atmosphere, which can effectively promote various types of cyclization reactions. It is also suitable for the synthesis of o-phenylenediamine and its derivatives with DMF. A series of nitrogen containing heterocyclic compounds (including benzothiazole, benzoimidazole, p-quinazolone, benzoxazole) can be obtained in 68% - 99% yields. This work proposes a new method of preparing nitrogen heterocyclic compounds with metal free catalyst, and also uses carbon dioxide gas that causes greenhouse effect. However, this reaction has the disadvantages of expensive reagents and long reaction time.

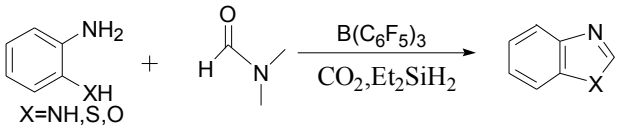

Figure 8. The synthesis of nitrogenous heterocyclic compounds by CO_2 and $B(C_6F_5)_3$

It is supposed that the possible reaction mechanism is that B $(C_6F_5)_3$ activates DMF through electrostatic action, which makes it easier for the nucleophilic reaction to form formylated intermediate A, while dimethylamine is released by DMF, which further reacts with CO_2 and silane, pushing the reaction to the right to dehydrate molecule B to form C (Fig. 9).

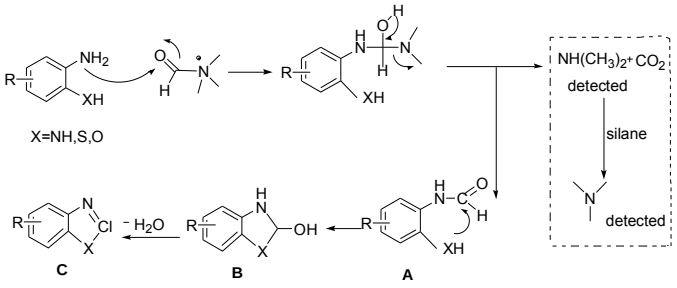

Figure 9. The reaction mechanism of nitrogenous heterocyclic compounds by CO_2 and $B(C_6F_5)_3$

(4) Preparation of Benzothiazole from Carbon Dioxide.

In 2014, Liu Zhimin, Gao Xiang and others in Liu Zhimin's research group[9]prepared benzothiazole with o-aminothiophenol and carbon dioxide as raw materials under the joint action of solvent N-methylpyrrolidone (NMP) and catalyst organic base DBN, diethylsilane (Et_2SiH_2) (Fig. 1-10). The yield of the reaction is 82%, but the reaction conditions are harsh and need to be carried out at high temperature.

The possible reaction mechanism:carbon dioxide and hydrosilane are activated by catalyst DBN (1,5-diazabicyclo [4.3.0] non-5-ene) to form an intermediate. o-aminothio - phenol further constructs carbon nitrogen double bond and carbon sulfur bond with the intermediate to form the product benzothiazole.

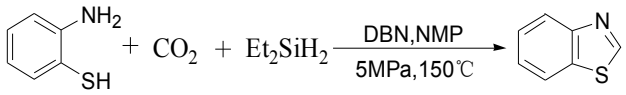

Figure 10. The synthesis of benzothiazole by O-aminobenzene and CO_2

3. Preparation of Benzozoles by Microwave Irradiation

In recent years, microwave radiation has become a widely accepted unconventional energy source in organic synthesis, and has been widely used in cycloaddition reaction, radioisotope synthesis, fullerene chemistry, polymer generation, pharmaceutical chemistry, green chemistry, etc. Microwave assisted organic synthesis, with heating speed and heating efficiency unmatched by traditional heating methods, has the advantages of mild reaction conditions, short reaction time, good reaction selectivity and high product yield. Microwave heating converts electromagnetic energy into heat energy. Energy transmission is caused by dielectric loss, which is contrary to the conduction and convection process observed in traditional heating. The amount of heat heated depends on the dielectric properties of molecules, which means that radiation and heating can be selectively absorbed. Microwave radiation makes the whole volume of materials rapidly heated at the same time, while traditional heating is to slowly transfer heat to the surface of the sample through heat conduction, and then gradually transfer it to the interior of the sample. The thermal effect observed under microwave radiation is the result of reverse heat transfer. The selective absorption of microwave radiation by polar compounds or solvents can rapidly heat the sample inside. After absorbing microwave energy, reactants can improve the reaction process and change the selectivity of the reaction.

In 2015, Kattimani et al.[10]proposed the method of synthesizing benzimidazole in 70% HCl medium using microwave heating and o-phenylenediamine and N, N-dimethylformamide (DMF) as raw materials. Moreover, it proved that this method has good universality. Different C-substituted amides were used to replace DMF to obtain 2-substituted benzimidazoles with yields of 80% - 92%. The similarities and differences between conventional heating method and microwave assisted method were compared. This method has short reaction time, simple operation and no catalyst, but it still requires the presence of strong acid (70% HCl) and harsh reaction conditions (Fig. 11).

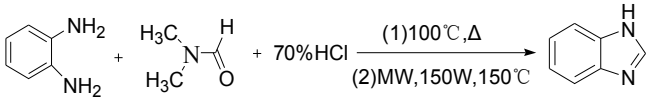

Figure 11. The synthesis of benzimidazole by O-phenylenediamine and DMF in 70% HCl

4. Conclusion

The above classification and summary of the synthesis of benzoxazole compounds (benzimidazole, benzothiazole, benzoxazole and its derivatives) are based on the reaction mechanism. Although these methods have made outstanding contributions to the synthesis of benzoxazole compounds, the current methods still have some shortcomings, such as very high requirements for reaction conditions, difficult access to raw materials, trivial reaction steps, low yield, etc. Through the summary of this paper, the basis for the next step to establish a more green, more economical and easier to operate synthesis method is laid.

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