Research Progress of Synthesis of Amine Compounds by Hydrogen Reaction

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Abstract

Amine compounds are widely used in natural products, pharmaceuticals and fine chemical products due to their wide range of activities and uses. Therefore, the development of methods for synthesizing amine compounds has been favored by chemists. Traditional synthesis methods are cumbersome, have many side reactions, and are not environmentally friendly. In recent years, a new method of synthesizing amines has been developed, namely "hydrogen borrowing reaction". They can quickly and efficiently undergo the alkylation reaction of alcohol amines or the cross-coupling reaction of amines to obtain the corresponding amination products. This article mainly reviews the research progress of the alkylation reaction of alcohol and amine, the cross-coupling reaction of amine and the three types of amine generated by nitro compound and alcohol reaction.

Keywords

Amine compounds, Hydrogenation reaction, Alkylation reaction, Cross-coupling reaction.

1. Introduction

Amine compounds are widely found in natural products, such as alkaloids, hormones, etc. At the same time, it is also an important raw material and intermediate for many chemicals such as medicine, pesticides and dyes. Therefore, the amino group is a key active group of modern 1+4 drugs, and amine compounds are also important intermediates and ligands in organic synthetic chemistry. Therefore, the synthesis method of amine compounds has always been one of the hot spots of chemists.

Traditional methods of amine synthesis include Gabriel synthesis [1], Hofmann degradation [2], reduction of nitro compounds[3], cyanamide reaction[4] and so on. These reactions have the disadvantages of cumbersome steps, environmental protection, poor atom economy, high temperature and high pressure, etc. Therefore, in recent years, a new method of synthesizing amines has been developed, called "hydrogen borrowing reaction". The by-product of this reaction is only water, which is not only very green and environmentally friendly, but also has high atomic economy, and the reaction process does not require high temperature and high pressure.

2. Introduction Various amine compounds synthesized by hydrogen reaction

The synthesis of amine compounds by hydrogen reaction can be divided into three categories: N-alkylation of alcohols and amines, cross-coupling of amines, and N-alkylation of nitro compounds.

2.1 N-alkylation of alcohol and amine

N-heterocyclic carbene has been a versatile and widely used ligand in transition metal catalyzed reactions in the past few years. The catalytic system combining iridium catalyst and carbene ligand has high activity in homogeneous catalytic reaction, which inspired us to find more convenient and highly active iridium catalyst and NHC ligand for N-alkylation of alcohol reaction.

In 2013, Jia-qi Li[5]research group discovered a highly active bidentate iridium NHC-phosphine complex catalyst, which can catalyze the N-alkylation of aromatic amines and primary alcohols under mild conditions. Some reactions can even be carried out without solvent. The reaction converts various aromatic amines into corresponding secondary amines in a high yield range, and cyclized amino alcohols can also successfully produce indole and tetrahydroquinoline, which is the first case at room temperature N-alkylation of alcohol（**Figure 1**）.

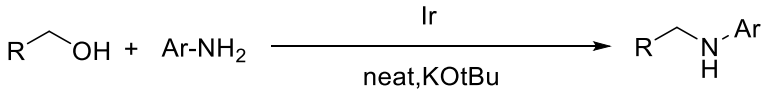

Figure 1 N-alkylation of aromatic amines and primary alcohols

Sulfonamides are widely used as antibacterial drugs, hypoglycemic agents and HIV protease inhibitors [6]. Traditional reactions to synthesize sulfonamides will generate many equivalents of harmful by-products. In recent years, the synthesis of sulfonamides by the hydrogen reaction of alcohols and amines is a good method, because it essentially produces water as a by-product, the method is highly available, easy to operate, and cost Low cost and low toxicity.Matthias Beller's[7] research group also reported a Cu-catalyzed reaction of alcohols and sulfonamides (**Figure 2**). This reaction can be carried out in air, and has high efficiency of atom economy and good production rate. The resulting product is a very useful intermediate for medicine and pesticides.

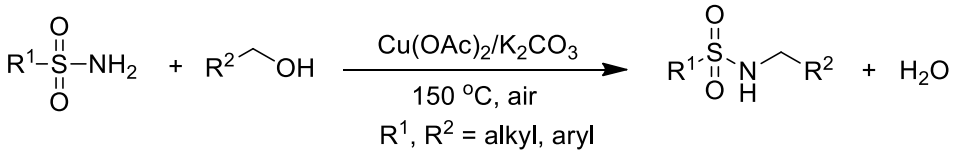

Figure 2 Cu-catalyzed reaction of alcohols and sulfonamides

2.2 Cross coupling reaction of amine

Aromatic amine compounds have played a prominent role as biologically active compounds and industrial chemicals [8]. The development of new and efficient methods for synthesizing amines has attracted great interest. In 2007 Matthias Beller[9] reported the first case of arylation of aliphatic amines and anilines. They used Shvo catalyst to catalyze the synthesis of corresponding aromatic compounds with high yields of various functionalized aniline compounds and fatty amine compounds. Amine (**Figure 3**). This reaction does not use bases and salts, which can be a good substitute for known methods to synthesize aniline and its derivatives.

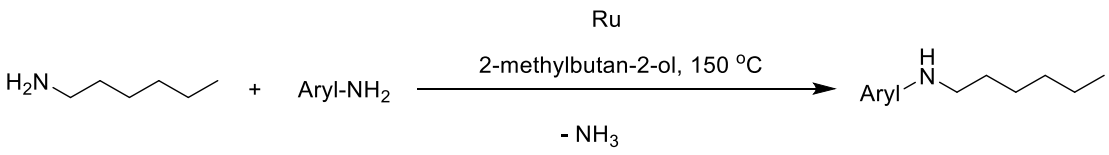

Figure 3 The arylation of aliphatic amine and aniline

Based on the relevance of biodiversity and pharmaceuticals, academic and industrial researchers are motivated to find new and improved methods for synthesizing amine derivatives. Matthias Beller's group is based on the interest in the use of salt-free synthesis of alkylamines by hydrogen reaction, and found that aromatic amines and alkylamines can synthesize N-alkyl-arylamine products in high yield. Therefore, they reported the first case of the selective synthesis of the coupling product of aromatic amines and cyclized alkylamines (such as pyrrolidine) [10]. It is interesting to note that this new type of catalytic conversion reaction involves the breaking and formation of three C-N bonds.

Matthias Beller's group used 1 mol% of Shvo catalyst to synthesize N-alkylation products of aromatic amines and cyclized alkylamines. Compound (**Figure 4**).

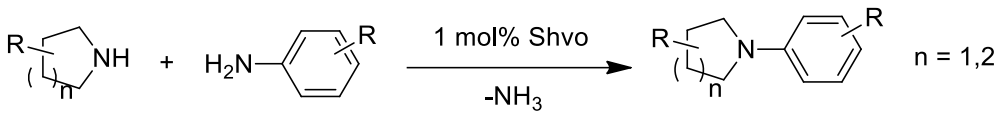

Figure 4 Synthesis of aromatic amine and alkylamine N-alkyl-arylamine

2.3 N-alkylation of nitro compounds

The reaction of directly synthesizing target molecules from the starting materials in one pot in series can simplify the separation step, reduce the use of reagents and increase the yield. In order to meet the needs of the environment, some new catalyzed series reactions have been developed in recent years [11]. Nitroaromatics and alcohols are both cheap and readily available organic compounds, and both can directly undergo amination reactions. In 2011, Shiuh-Tzung Liu [12] on the basis of the predecessors, reported a phosphine-amine divalent ruthenium complex catalyzed synthesis of secondary amines from alcohols and nitroaromatics (**Figure 5**). This method has universal applicability, high yield and significant selectivity to various nitroaromatic hydrocarbons and alcohols.

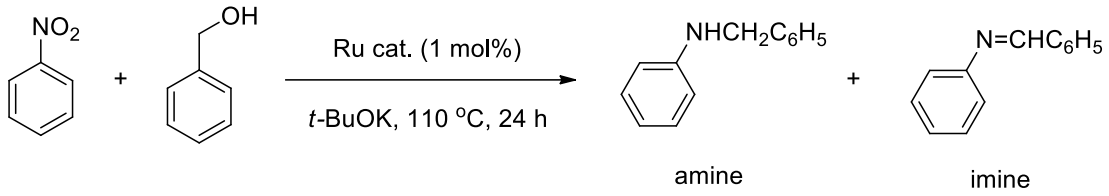

Figure 5 Reaction of alcohol and nitroaromatic

In 2013, the Feng Shi [13] research group reported a $RuCl_3$ as a catalyst, PPh_3 as a ligand, K_2CO_3 as a base, glycerol as a hydrogen source, nitrobenzene and alcohol in TFMB solvent, 130 °C, under argon atmosphere, Reaction 24h Synthesis of N-substituted amine (**Figure 6**). This reaction uses glycerin as a hydrogen source. Starting from the equivalent amounts of nitrobenzene compounds and alcohols, one-pot synthesis of mono- and di-substituted amine products is performed, and the reaction yield is also very high. This is the first controlled and selective synthesis of mono- and di-substituted amine products starting from nitrobenzene, and does not require the addition of excess alcohol as a reducing agent. This is an economical and clean one-pot synthesis of amine compounds starting from nitrobenzene. This means that biomass feedstock may be a potential source of hydrogen, and if ideal, this biomass feedstock can be used directly as a reducing agent in the synthesis of fine chemicals without the need for thermal cracking.

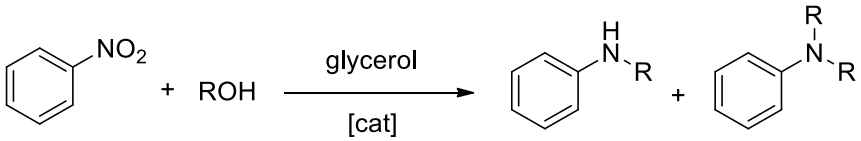

Figure 6 One-pot synthesis of amine compounds from nitrobenzene

3. Summary

Since amine compounds play an important role in biology, medicine, and fine chemicals, it is of great significance to develop a multifunctional and efficient method for synthesizing amines. Through the above literature review, we can find that the transition metal-catalyzed hydrogen borrowing reaction is a new and efficient method for synthesizing amines. In this paper, the progress of research on the synthesis of amines by hydrogen reaction is summarized by introducing the alkylation reaction of alcohol and amine, the cross-coupling reaction of amine, and the three kinds of amine compound and alcohol reaction by hydrogen reaction.

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