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Original article

Synthesis of 2,5-disubstitued benzimidazole using $SnCl_2$-catalyzed reduction system at room temperature

Li-Ping Duan [a,*], Qiang Li [a,b], Ning-Bo Wu [a], Dong-Fang Xu [b], Hao-Bing Zhang [a]

[a] National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, WHO Collaborating Centre for Malaria, Schistosomiasis, and Filariasis, Key laboratory of Parasitology and Vector Biology at National Institute of Parasitic Diseases, Shanghai 200025, China
[b] Shanghai Normal University, Shanghai 200005, China

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ABSTRACT

Stannous chloride dihydrate is used as an efficient catalyst in reductive cyclization of 2-nitro-5-substituted aniline Schiff base leading to stable 2,5-disubstitued benzimidazole derivatives in excellent yields with good purity. It provides a novel method of synthesis of 2,5-disubstitued benzimidazole under reductive system at room temperature.

1. Introduction

The benzimidazole structural motif plays very important roles in numerous pharmaceutical molecules with a wide range of biological properties including anticancer, antihistaminic, antihypertensive, antifungal, and antiviral effects [1–3]. Consequently, the synthesis of the heterocyclic nucleus has gained great importance. Many methods for the synthesis of benzimidazoles have been discovered and reported. There are two general methods for the synthesis of benzimidazoles. One is oxidative cyclodehydrogenation of aniline Schiff base with various oxidative reagents [4–6]. The other method is the coupling of a carboxylic acid with phenylenediamine under high temperature [7,8]. However, these synthetic protocols suffer from one or more disadvantages such as the use of dangerous or toxic oxide reagents, high temperature, strong acid conditions, prolonged reaction times, cumbersome multi-step processes, or the formation of side products. As a consequence, the introduction of new methods with technical improvements to overcome the limitations is still an important experimental challenge [9,10]. To the best of our knowledge, few studies have related to the synthesis of benzimidazole derivatives under reductive atmosphere [11]. The advantages of using the reduction system include mild reaction conditions, elimination of toxic oxide reagents, operational simplicity, and high yields of products.

In the last decade, stannous chloride dihydrate has gained special attention as a mild and highly chemoselective reducing agent for various organic transformations. For example, $SnCl_2{\cdot}2H_2O$ is still popularly used to selectively reduce aromatic nitro group to amino for its eco-friendly nature, affordability, high reactivity, and safety profile. A significant breakthrough in the field of reductive cylization heterocyclic compounds was based on stannous chloride dihydrate. In 2002, Bates and Li reported cyclization products produced for nitroarene reduction to aminoarene using $SnCl_2{\cdot}2H_2O$ [12]. In 2006, Roy and co-workers reported that a one-step reductive transformation of 2-(2-nitrophenyl)-3*H*-quinazolin-4-one in various alcohols furnished the desired tetracyclic product with $SnCl_2{\cdot}2H_2O$ [13]. Recently, the method of reductive cyclization of 2-nitrobenzamides with haloketones or keto acids mediated by $SnCl_2{\cdot}2H_2O$ was reported by Shi [14]. In this paper, we wish to describe a new route to synthesize benzimidazole derivatives *via* novel reductive cyclization of 2-nitro-5-substituted aniline Schiff base by $SnCl_2{\cdot}2H_2O$ at room temperature.

2. Experimental

From the starting material 2-nitro-5-substituted anilines (**1**), through the intermediate 2-nitro-5-substituted aniline Schiff bases (**2**), the target compounds 2,5-disubstitued benzimidazoles (**3a–i**) were obtained with stannous chloride dehydrate [15]. The

* Corresponding author.
E-mail address: lipingduan@yahoo.com (L.-P. Duan).

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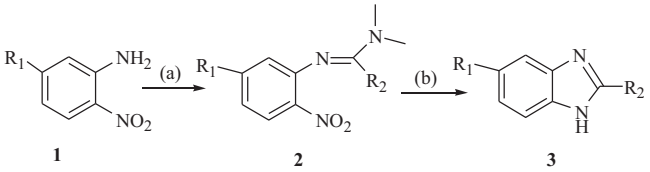

Scheme 1. Synthesis of **3**. Reaction conditions: (a) $POCl_3$, $R_2CON(CH_3)_2$, toluene, reflux; (b) $SnCl_2{\cdot}2H_2O$, ethanol, 25 °C.

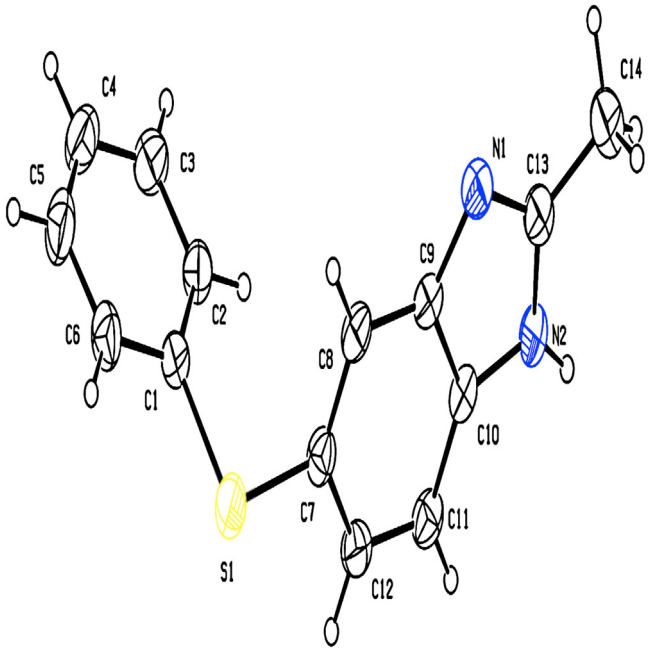

Fig. 1. Molecular structure of 2-methyl-5-phenylthio-benzimidazole.

details for the syntheses are shown in Scheme 1. The structures of **3a–i** were characterized by mass spectrometry and NMR. The molecular structure of 2-methyl-5-phenylthio-benzimidazole was confirmed by X-ray analysis (Fig. 1). The crystallographic data have been assigned the deposition numbers at the Cambridge crystallographic data Centre (CCDC945241).

Typical experimental procedure for synthesis 2,5-disubstitued benzimidazole derivatives: A solution of 2-nitro-5-substituted aniline (1 mmol), difference substituted *N*,*N*-dimethylamine

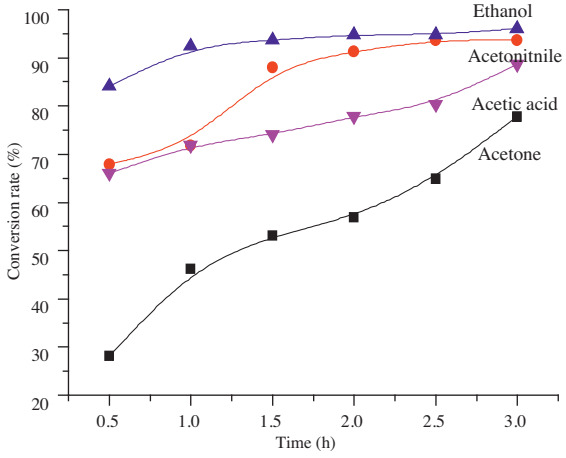

Fig. 2. Solvent effect for synthesis of 2-methylbenzimidazole using $SnCl_2{\cdot}2H_2O$ catalysts by HPLC.

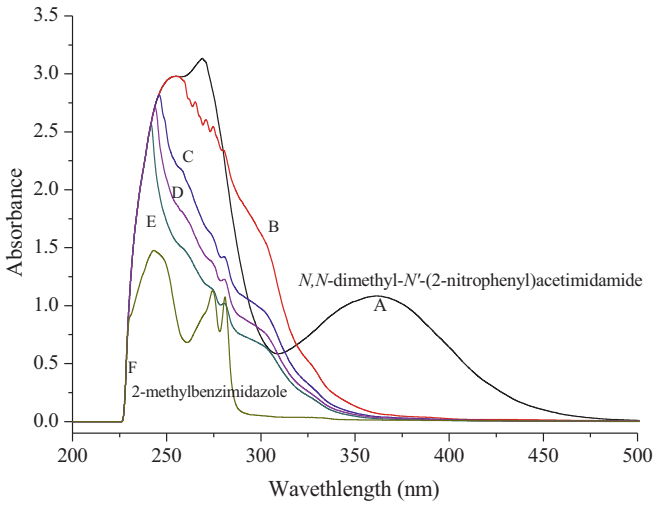

Fig. 3. The reaction process of *N*,*N*-dimethyl-*N*′-(2-nitrophenyl)acetimidamide with the addition of $SnCl_2{\cdot}2H_2O$ in ethanol at 25 °C was monitored using UV–vis spectroscopy in 1 h (the time interval is 15 min each trace in 1 h).

(1.5 mmol) and phosphorus oxychloride (2.5 mL) in toluene (10 mL) was refluxed for 4 h at 120 °C. The mixture was cooled and poured onto crushed ice, then made basic with sodium bicarbonate solution. The organic layer was washed with water, then dried over sodium sulfate and evaporated under *vacuo*. The crude material was purified by chromatography on silica gel column using ethyl acetate and petroleum ether (1 : 1 by volume) as the eluent. The solvent was removed under reduced pressure to afford the different substituted *N*,*N*-dimethyl-*N*′-(2-nitrophenyl)imidamide intermediates (**2**). Next, a mixture of **2** (1 mmol) and stannous chloride dihydrate (4 mmol) in ethanol (10 mL) was stirred at room temperature for 1 h. The solvent was removed under vacuo and the mixture was dissolved in dichloromethane and washed with sodium bicarbonate solution. The organic layer was then dried over sodium sulfate and evaporated *in vacuo*. The crude material was purified by chromatography on silica gel column using ethyl acetate and petroleum ether (1:2 by volume) as eluent. The solvent was removed under reduced pressure to give 2,5-disubstitued benzimidazoles **3**.

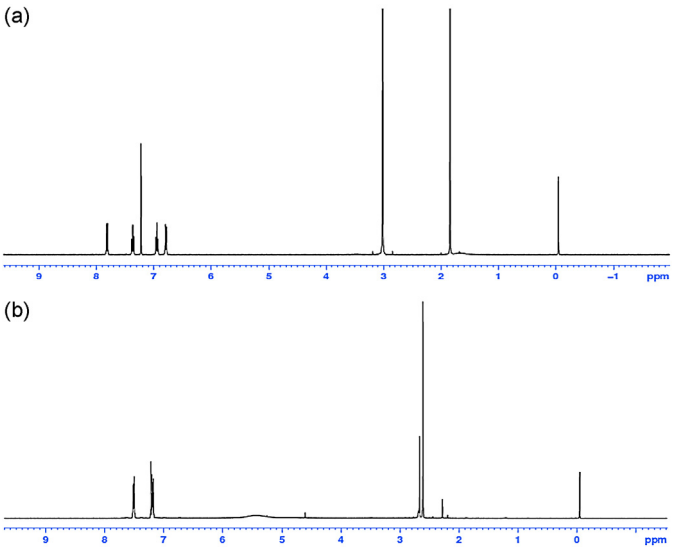

Fig. 4. ^1H NMR spectra of *N*,*N*-dimethyl-*N*′-(2-nitrophenyl)acetimidamide (a) and 2-methylbenzimidazole (b) in $CDCl_3$.