Synthesis of 5-Substituted Indole-2,3-dione

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Abstract. 4-Substituted isonitroacetanilines 2 were prepared by the reaction of 4-substituted anilines 3 with chloral hydrate and hydroxylamine hydrochloride. 5-Substituted indol-2,3-dione 1 were prepared by the cyclization of 2 in the presence of concentrated sulfuric acid. 5-Substituted indol-2,3-dione 1 is an important intermediate in many biologically active compounds. The structure was confirmed by mass spectra (MS). Furthermore, the synthetic method was optimized. The total yield of the two steps was 51-68\% (calculated from 4-substituted anilines).

Introduction

5-Substituted indol-2,3-dione (Isatin) is an endogenous compound, which is widely used in chemical industry and medical industry due to its excellent chemical and physical properties. As reported, isatin and its derivatives possess good antitumor activity, antibacterial activity, antifungal activity, anti-HIV activity. Their application in central nervous system has also been intensively studied. The substituted aniline 3 as the starting material reacted with chloral hydrate and hydroxylamine hydrochloride to form isonitroacet aniline 2\textsuperscript{[1-4]}, then the isonitroacet aniline were cyclized in the concentrated sulfuric acid and hydrolyzed to give isatins\textsuperscript{[5-7]}.

Most of the synthetic methods of 5-substituted indol-2,3-dione 1 which reported in the literature have the drawbacks such as longer synthetic route, lower yield and harmful to environment. Therefore, the optimization of the synthetic route and methods of 5-substituted indol-2,3-dione 1 is necessary.

In this study, we designed and optimized the synthetic methods for 5-substituted indol-2,3-dione 1 and make it more suitable for industrial production. The structure of 5-substituted indol-2,3-dione was shown in Fig. 1. The structures of representative compounds were shown in Fig. 2.

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\text{Fig. 1 Structure of 5-substituted indol-2,3-dione}
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Materials and methods

Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized.

Synthesis of compounds

The structures and the synthetic route were shown in Scheme 1.

Reagents and conditions: (a) Chloral hydrate, anhydrous sodium sulfate, concentrated hydrochloric acid, hydroxylamine hydrochloride, 4-fluoro aniline, 4-bromine aniline, 100°C, 1 min; (b) Concentrated sulfuric acid, ethanol, 70°C, 1 h.

General Procedure for Preparation of Compounds 2a-b

Chloral hydrate (24.8 g 0.15 mol) was dissolved in water (400 mL) and sodium sulfate (113.6 g 0.8 mol) was added slowly, vigorous stirring. 4-Substituted aniline (0.1 mol) was dissolved in water (100 mL) and the concentrated hydrochloric acid (25.1 mL 0.3 mol) was added drop-wise, then the hydroxylamine hydrochloride (31.8 g 0.45 mol) was added into the solution with stirred and then the reaction mixture was added in the reaction solution and heated to 100 °C for 1 min. After
the completion of the reaction, the solution was rapidly cooled to room temperature and was filtered, then the cake was washed with cold water (500 mL). The residue was dried naturally to obtain a powdery solid. Yield: 76-85%.

Compounds (2a-b) were synthesized from (3a-b) according to the general procedures.

*N-(4-fluoro-phenyl)-2-hydroxyimino-acetamide (2a)*
Gray solid. Yield 85%.

*N-(4-bromo-phenyl)-2-hydroxyimino-acetamide (2b)*
Yellow solid. Yield 80%.

**General Procedure for Preparation of Compounds 1a-b**
The 10V/W concentrated sulfuric acid was preheated to 50 °C, 4-substituted isonitroacetanilines (0.1 mol) was added slowly in batches with vigorous stirring maintaining the temperature between 65-75 °C for 1 h, then the mixture was heated to 80 °C for 15 min. After the completion of the reaction, the solution was cooled to room temperature and poured into crushed ice with strong stirring, the mixture then was filtered and the cake was washed with cold water to furnish crude product, the crude product was recrystallized with ethanol / water and dried to give a solid powder. Yield: 67-80%.

Compounds (1a-b) were synthesized from (2a-b) according to the general procedures.

**5-Fluoro-1H-indole-2,3-dione (1a)**
Yellow solid. Yield 77%. MS (ESI): m/z 166.2[M+H]^+.

**5-Bromo-1H-indole-2,3-dione (1b)**
Orange solid. Yield 73%. MS (ESI): m/z 226.0[M+H]^+.

**Conclusions**
In conclusion, one novel 5-substituted Indol-2,3-dione 1 was synthesized from 4-substituted aniline through two steps including amidation and cyclization. The synthetic route of 1 can be used to synthesize 5-substituted indol-2,3-dione. Its structure was confirmed by mass spectra (MS).

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