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

Dandan Zhao, Ping Wang, Tongsheng Xu, JieLian Wu, Jiajia Wang, and Shan Xu[1,a]

School of Pharmacy, Jiangxi Science & Technology Normal University, Nanchang 330013, China

[*a]shanxu9891@126.com

Keywords: 4-Substituted isonitroacetanilines, 5-Substituted indol-2,3-dione,Synthesis

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**[1-4], then the isonitroacet aniline were cyclized in the concentrated sulfuric acid and hydrolyzed to give isatins[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.

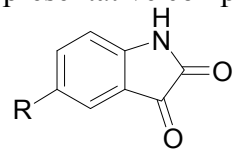
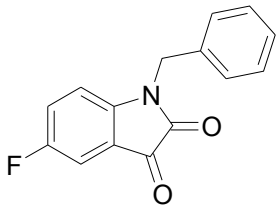
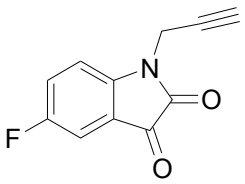


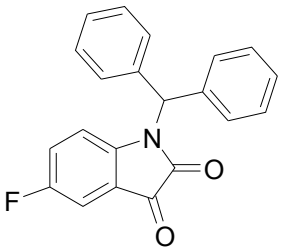
Fig. 1 Structure of 5-substituted indol-2,3-dione



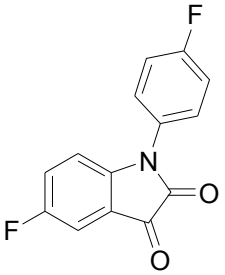
1-Benzyl-5-fluoro-1*H*-indole-2,3-dione



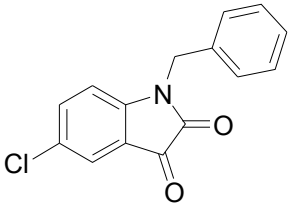
5-Fluoro-1-prop-2-ynyl-1*H*-indole-2,3-dione



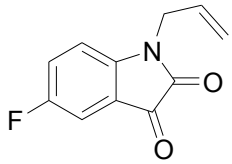
1-Benzhydryl-5-fluoro-1*H*-indole-2,3-dione



5-Fluoro-1-(4-fluoro-phenyl)-1*H*-indole-2,3-dione



1-Benzyl-5-chloro-1*H*-indole-2,3-dione



1-Allyl-5-fluoro-1*H*-indole-2,3-dione

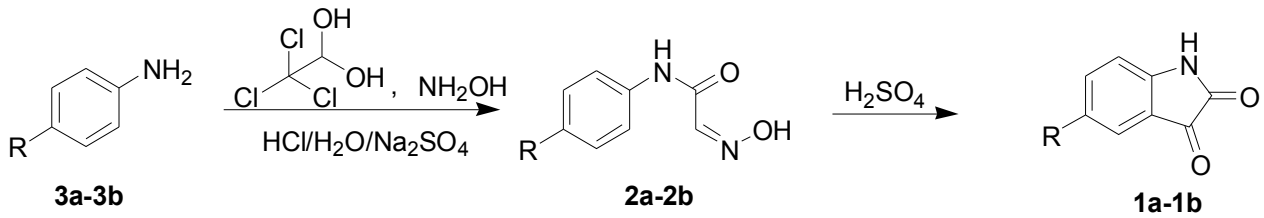
Fig. 2 Structure of representative compounds

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.



Scheme 1. The synthetic route of compound **1**

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

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 ℃ 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 ℃, 4-substituted isonitroacetanilines(0.1 mol) was added slowly in batches with vigorous stirring maintaining the temperature between 65-75 ℃ for 1h, then the mixture was heated to 80 ℃ 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-1*H*-indole-2,3-dione(1a)

Yellow solid. Yield 77%. MS (ESI): m/z 166.2$[M+H]^+$.

5-Bromo-1*H*-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).

Acknowledgments

We gratefully acknowledge the generous support provided by The National Natural Science Funds (No. 81460527), Project supported by the Natural Science Foundation of Jiangxi Province (No. 20142BAB215020) , Doctoral Scientific Research Foundation of Jiangxi Science & Technology Normal University and Program of Key Laboratory of Drug Design and Optimization, Jiangxi Science & Technology Normal University(300098010306) and College Students' Science and Technology Innovation Project of Jiangxi Province and Graduate Students' Innovation Project of Jiangxi Science & Technology Normal University(YC2014-X25).

References

[1] Yamagishi M, Yamada Y, Ozaki K, et al. Biological activities and quantitative structure-activity relationships of spiro [imidazolidine-4, 4'(1'H)-quinazoline]-2, 2', 5 (3'H)-triones as aldose reductase inhibitors[J]. Journal of medicinal chemistry, 1992, 35(11): 2085-2094.

[2] Liu H Q, Wang D C, Wu F, et al. Synthesis and biological evaluation of 5′-phenyl-3′ H-spiro-[indoline-3, 2′-[1, 3, 4] oxadiazol]-2-one analogs[J]. Chinese Chemical Letters, 2013, 24(10): 929-933.

[3] Jin K, Zhang X, Ma C, et al. Novel indoline-2, 3-dione derivatives as inhibitors of aminopeptidase N (APN)[J]. Bioorganic & medicinal chemistry, 2013, 21(9): 2663-2670.

[4] Natarajan A, Fan Y H, Chen H, et al. 3, 3-Diaryl-1, 3-dihydroindol-2-ones as antiproliferatives mediated by translation initiation inhibition[J]. Journal of medicinal chemistry, 2004, 47(8): 1882-1885.

[5] Hossain M M, Islam R M, Saha S K, et al. An efficient microwave-assisted synthesis of dihydropyrazinones and bis-benzoylketones[J]. Tetrahedron Letters, 2010, 51(8): 1155-1157.

[6] Thunuguntla S S R, Subramanya H, Kunnam S R, et al. Dihydroorotate dehydrogenase inhibitors: U.S. Patent 9,006,454[P]. 2015-4-14.

[7] Mathew V, Keshavayya J, Vaidya V P. Heterocyclic system containing bridgehead nitrogen atom: synthesis and pharmacological activities of some substituted 1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazoles[J]. European journal of medicinal chemistry, 2006, 41(9): 1048-1058.