Synthesis of 3- morpholin-4-yl-1- (4-nitrophenyl) -5,6-dihydro -1*H*-pyridin-2-one

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Keywords: 3 – Morpholin – 4 – y l – 1 - (4 – nitropheny l) - 5 , 6 – dihydro -1 *H* – pyridin -2 - one, Synthesis , Cyclopentanone oxime

Abstract. 3-Morpholin-4-yl-1-(4-nitrophenyl)-5,6-dihydro-1*H*-pyridin-2-one (**1**) is an important intermediate for the synthesis of many biologically active compounds. It was synthesized from cyclopentanone oxime (**7**) and 1-fluoro-4-nitrobenzene through three steps including rearrangement. Reaction, condensation and nucleophilic substitution reaction. The structure of the target compound **1** was confirmed by ^{1}H NMR and MS spectrum.

Introduction

Cancer is a disease caused by normal cells changing so that they grow in an uncontrolled way. Although many anti-tumor drugs and surgeries are available, the slow efficacy of the anti-tumor drugs and the cancer recurrence are still problems [1-2]. In recent years, there were many small molecule anticancer drugs had been reported. Among them, 3 – morpholin – 4 – y l – 1 - (4 – nitropheny l) – 5 , 6 – dihydro -1 *H* –pyridin -2 -one (**1**) is an significant intermediate for the synthesis of many biologically active compounds. Therefore, design and synthesis of 3- morpholin -4 –y l -1 - (4 –nitropheny l) -5, 6-dihydro-1*H*-pyridin-2-one (**1**) derivative as small molecule inhibitors played a essential role in the study of anticancer .

Many 3-morpholin-4-yl-1-(4-nitrophenyl)-5,6-dihydro-1*H*-pyridin-2-one (**1**) derivatives which exhibited potential biological activities, such as 1 - (4 – methoxypheny l)- 6 - (4 -(2 –methy l- 1-(2-oxopiperidin-1-yl)propan-2-yl)phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-c]pyridine-3-carboxamide (**2**)[3], 6 - (4 - (1 –aminocy clopropy l)phenyl)- 1 -(4 –methoxyphenyl)- 7- oxo -4,5,6,7 – tetrahydro -1 *H* –pyrazolo [3, 4-c] pyridine-3 - carboxamide (**3**) [4], 1 - (4 – methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-c]pyridine-3-carboxamide (**4**)[5], 1 – cyclopenty l- 3- ethy l-6- (4- methoxypheny l)- 1,4, 5, 6-tetrahydro- 7 *H* –pyrazolo [3, 4-c] pyridin – 7 – one (**5**) [6], 6 - (4 - (aminomethyl) phenyl) -3- (4 – methoxypheny l) -1- (trifluoromethyl) -1, 4,5,6 -tetrahydro-7 *H*-pyrazolo [3, 4-c] pyridin-7-one (**6**)[7], these 3 – morpholin -4- yl -1- (4- nitrophenyl)-5 , 6 –dihydro - 1*H* -pyridin- 2-one (**1**) derivatives showed biological activity.

Most of the synthetic methods of 3 – morpholin – 4 –y l -1- (4 –nitrophenyl) -5,6 –dihydro -1*H* –pyridin -2 -one (**1**) which reported in the literature have the drawbacks, such as lower yield [8-9]. Cyclopentanone oxime (**7**) is a key intermediate for synthesizing 3 – morpholin – 4 –yl – 1 - (4-nitrophenyl)-5,6 –dihydro -1 *H*-pyridin-2-one (**1**). The synthesis of the target compound is necessary. The structures of representative compounds were shown in Fig. 1 and Fig 2.

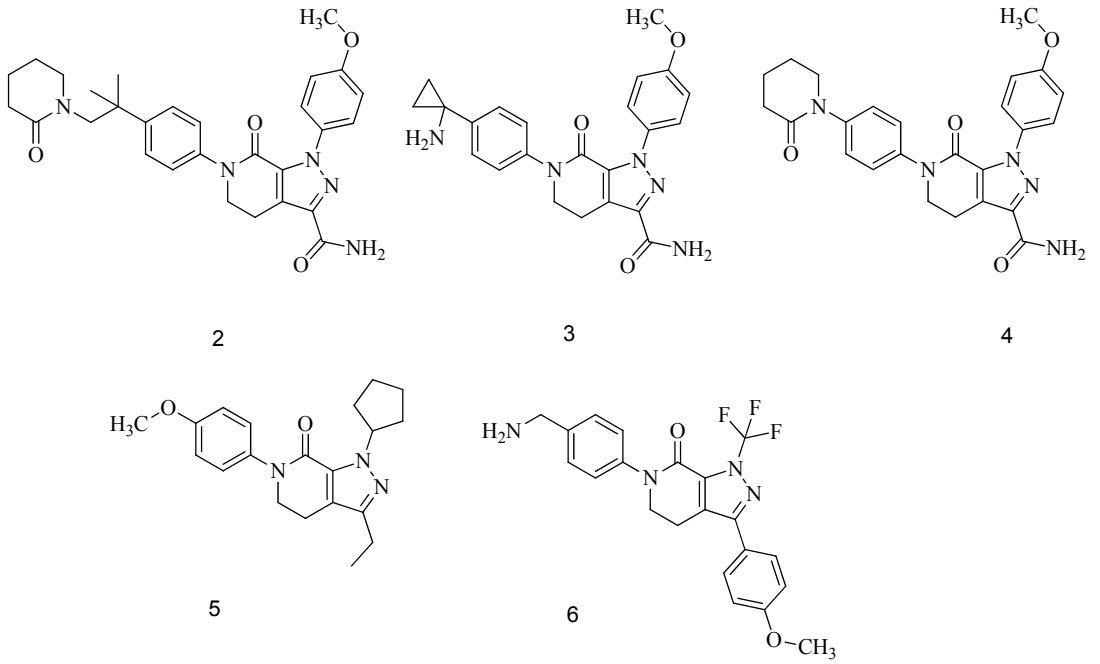


Fig.1 Structures of some drugs or active compounds containing 1-phenyl-5,6-dihydropyridin-2-one

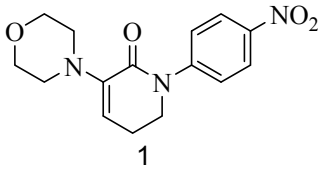


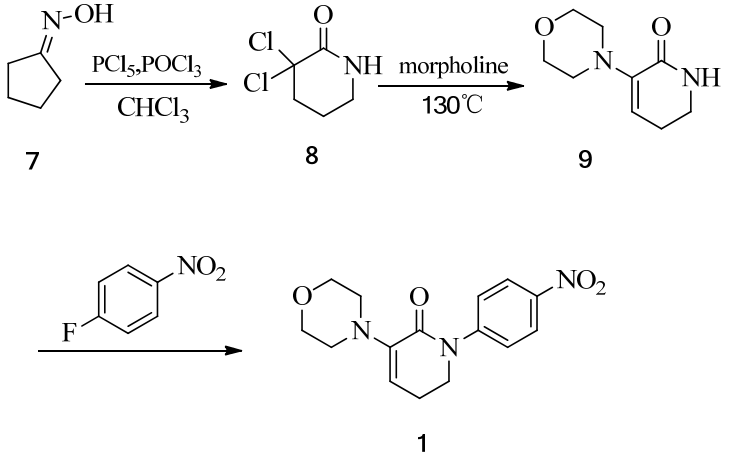
Fig. 2 Structure of the target compound 1

Materials and methods

NMR spectrum were performed using Bruker 500 MHz spectrometers (Bruker Bioscience, Billerica,MA, USA) with TMS as an internal standard.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. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China).

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) PCl_5,$CHCl_3$,$POCl_3$，70℃, 3.5 h; (b) morpholine, C_2H_5OH,130 ℃, 3 h; (c) 4-Fluoronitrobenzene, 35 ℃, 3 h.

3,3-Dichloro-piperidin-2-one (**8**)

To a solution of phosphorus pentachloride(126 g,606 mmol) and chloroform(300 mL), an appropriate amount of cyclopentanone oxime (**7**) (20 g,202 mmol) was dissolved in chloroform(200 mL) was dropped slowly at -15 ℃, then the mixture was heated to 25℃ and phosphorus oxychloride (60ml) was added to the solution. The reaction mixture then was heated to 70℃ and refluxed for 3.5 h . After the completion of the reaction (monitored by TLC). The mixture was concentrated under reduce pressure, and poured into ice water with stirred for 30 min. The solution was adjusted to pH 8 with K_2CO_3, filtered and the precipitate was washed with ethanol then the residue was dried to obtain a powdery solid (27.5g,81%). M.p. 163-165 ℃. MS：190.0,192.0,193.9 $[M+H]^+$,215.1$[M+Na]^+$.

3-Morpholin-4-yl-5,6-dihydro-1*H*-pyridin-2-one (**9**)

3,3-Dichloro-piperidin-2-one (20 g,120 mmol) (**8**) was dissolved in morpholine (60 mL) at room temperature. The reaction mixture was heated to 130℃ and refluxed for 3h. After the completion of the reaction (monitored by TLC). Cooled to room temperature, the precipitated solid was filtered. the filter cake was added to methylene chloride(100 mL), were removed by filtration. The solution was evaporated to dryness and washed with ethanol and then obtained a scream product (19.9 g,92%).M.p. 145-147℃; MS: 183 $[M+H]^+$, 205 $[M+Na]^+$.

3- Morpholin-4-yl-1- (4-nitrophenyl)-5,6-dihydro-1*H*-pyridin-2-one (**1**)

A solution of 3-morpholin-4-yl-5,6-dihydro-1*H*-pyridin-2-one (**10**) in DMF (160 mL) was stirred at room temperature, an appropriate amount of the t-BuOK (24.6 g, 219.8 mmoL) and CuI (4.2g , 22.05 mmol) were added to the reaction solution with stirred for 0.5 hours. Then an fluoronitrobenzene (17.04 g, 120.9mmol) was added to the mixture, the mixture was refluxed at 35 ℃ for 3 hours. The reaction solution was poured into ice water (200 mL ,V / m = 10: 1) and stirred for 0.5 hours, the precipitated solid was filtered and dissolved in methylene chloride(400mL), then were filtrerd. And the filtrate was evaporated to dryness so that to obtain a yellow solid (29.6 g,89%).MS:304.0$[M+H]^+$, 326.0,327.1$[M+Na]^+$. ^{1}H-NMR ($CDCl_3$,600MHz) δ:8.24 (d,2H), 7.55(d,2H), 5.75(t,1H),3.85(m,6H), 2.90(t,4H), 2.56(m,2H).

Conclusions

In conclusion, 3 – morpholin – 4 – y l -1 -(4 – nitropheny l) -5 ,6 – dihydro – 1 *H* –pyridin -2 –one (**1**) was synthesized from cyclopentanone oxime and 1-fluoro-4-nitrobenzene through three steps including rearrangement reaction, condensation and nucleophilic substitution reaction. The synthetic method of 3-morpholin-4-yl-1-(4-nitrophenyl)-5,6-dihydro-1*H*-pyridin-2-one (**1**) was optimized by changing conditions of the reaction so that can improve the yield. So the synthetic method can be used to synthesize 3 – morpholin – 4 – y l – 1 -(4 – nitrophenyl)- 5, 6-dihydro-1 *H* – pyridin - 2 -one (**1**) derivatives.

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) and Program of Key Laboratory of Drug Design and Optimization, Jiangxi Science & Technology Normal University (300098010306).

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