Synthesis of 3-(4-aminophenyl) cyclopropane-1, 1,2,2-tetracarbonitrile

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ABSTRACT: 3-(4-aminophenyl) cyclopropane-1, 1, 2, 2-tetracarbonitrile (**1**) is an important intermediate which used to synthesize NVP-BEZ-235 derivative. In this work, a rapid synthetic method for compound **1** was established. The 3-(4-aminophenyl) cyclopropane-1, 1, 2, 2-tetracarbonitrile was synthesized from the commercially available 4-nitrobenzaldehyde through three steps. The structure was confirmed by MS and ^{1}HNMR. Furthermore, the synthetic method was optimized. The total yield of the three steps was 65.25% (caculated from malononitrile).
KEYWORD: 2-(4-nitrobenzylidene)malononitrile; 3-(4-nitrophenyl)cyclopropane-1,1,2,2-tetracarbonitrile; 3-(4-aminophenyl)cyclopropane-1,1,2,2-tetracarbonitrile; Synthesis

1 INTRODUCTION

Cancer is a major public health problem in the world, which caused by the disorders of cell proliferation mechanism[1]. Developing an efficiently and safety method to treatment the malignancies has become a hot pot in nowadays. In recent years, many small molecule anticancer drugs had been reported[2-4], such as NVP-BEZ-235, 2-methyl-2-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2, 3-dihydro-1H-imidazo [4,5-c] quinolin-1-yl)phenyl) propanenitrile **(3)**, 1-(4- (3-methyl-2-oxo-8-(quinolin-3-yl)-2, 3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl)phenyl) cyclopropane-carbonitrile**(4)**[5-6]. 3- (4-aminop henyl) cyclopropane -1, 1, 2, 2 - tetracarbonitrile is the key intermediate and has a wide range of applications in the pharmaceutical and chemical fields. Some moleculers are designed and synthesized basing on 3- (4-aminop henyl) cyclopropane -1,1,2,2-tetracarbonitrile. Such as 3-(4-nitrophenyl)-2,2-dicyanocyclopropane-1,1-dicarboxylic acid diethyl ester**(5)**[7]. 2-Acetyl-2-methyl-3-(4-nitro-phenyl)-cyclopropane-1,1-dicarbonitrile**(6)**[8]. 2-Nitro-3-(4-nitro-phenyl)-cyclopropane-1,1-dicarbonitrile**(7)**[9]

The structures of the intermediate and representative compounds were shown in Fig. 1

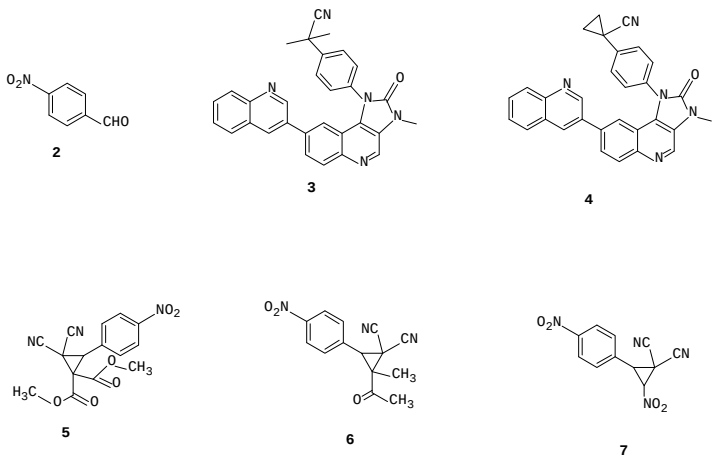


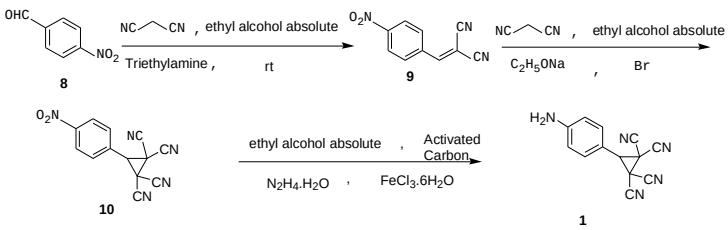
Fig.1 Structures of the intermediate and some drugs that have been reported

2 MATERIALS AND METHODS

The Melting point(M.P) of compounds was taken by X-4 type digital melting point apparatus manufactured by Beijing Tektronix, Inc. (temperature Degree without more positive).Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS. H NMR was taken by a Bruker ARX-300 NMR analyzer. TLC analysis was carried out on silica gel platesGF254 (Qin dao Hai yang Chemical, China) .All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified.

3 SYNTHESIS OF COMPOUNDS

The structures and the synthetic route were shown in Scheme 1



Scheme1. The synthetic route of compound 1

Reagents and conditions: (a) Triethylamine, ethyl alcohol absolute, rt, 4 h; (b) ethyl alcohol absolute, C_2H_5ONa, Bromine; (c)ethyl alcohol absolute, $FeCl_3 \cdot 6H_2O$, $N_2H_4 \cdot H_2O$, Activated Carbon.

3.1 *2-(4-nitrobenzylidene)malononitrile (9)*

Malononitrile was dissolved in C_2H_5OH (10mL), then it was added drop-wise to 4-nitrobenzaldehyde (3.0 g, 0.02 mol) suspension at room temperature, control the drip rate and the temperature was kept 25 ~ 27 ℃. When the addition was complete, the triethylamine(0.033mL, 0.25 nmol) was added under stirring, and keep the reaction at room temperature for 4h, After the reaction completed, the mixture was filtered off, washed with EtOH, and dried under reduced pressure to afford 2-(4- nitrobenzylidene) malononitrile(3) as yellow solid(4.0g, 93%). ^{1}H NMR (400 MHz, DMSO) δ 8.26 (d, *J* = 8.8 Hz, 2H), 8.12 (s, 1H), 8.09 (d, *J* = 8.8 Hz, 2H). M.p.163-168℃, MS: 200.1 $[M+H]^+$

3.2 *3-(4-nitrophenyl)cyclopropane-1,1,2,2-tetracarbonitrile(10)*

2-(4-nitrobenzylidene) malononitrile **(2)**(0.185g, 0.001mol) (20mL) was dissolved in C_2H_5OH (20mL), then the solution of C_2H_5ONa (0.0012mol) was added under stirring for 1 min and the bromine was added without cooling. The mixture was magnetically stirred at room temperature. After stirring for 6 h at r.t, the reaction was completed. The solid phase was filtered off, washed with warm water, and dried in desicator over P_2O_5 to isolate pure white solid (0.2g, 87%). ^{1} HNMR (400 MHz, $CDCl_3$) δ8.19 (d, *J* =8.8Hz,2H), 7.45 (d, *J* =8.8Hz, 2H), 1.7 (S,1H). M.p.232-235℃,MS:234.0 $[M+H]^+$

3.3 *3-(4-aminophenyl) cyclopropane-1, 1, 2, 2-tetracarbonitrile(1)*

3-(4-nitrophenyl)cyclopropane-1,1,2,2-tetracarbonitrile(0.2g,0.0008mol) was dissolved in anhydrous ethanol and heated to 60℃, then activated carbon(1g) and $FeCl_3 \cdot 6H_2O$ (0.43g) was added into the solution, 0.25mL $N_2H_4 \cdot H_2O$ was added and reflux for 2 h. After the reaction completed. Then the mixture was hot filtrated. The filtrate was distilled under reduced pressure to afford **1** as yellow solid (65.25%).^{1}HNMR (400 MHz, DMSO) δ 6.84(d, *J* = 8.9 Hz, 2H), δ 6.32(d, *J* = 8.9 Hz, 2H), 4.3(s,1H),1.7(s,H). M.p.192-196 ℃ ,MS:263.0 $[M+H]^+$

4 CONCLUSIONS

In conclusion, 3-(4-aminophenyl) cyclopropane-1, 1, 2, 2-tetracarbonitrile was synthesized from the commercially available 4-nitrobenzaldehyde through three steps. The synthetic method of compound **1** and the reactions conditions were optimized. Its structure was confirmed by MS and ^{1}HNMR spectrum.

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