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Synthesis of 1-(*Tert*-butyl)-3-(methyl)-4-(4-(methylthio)benzyl) piperazine-1,3-dicarboxylate

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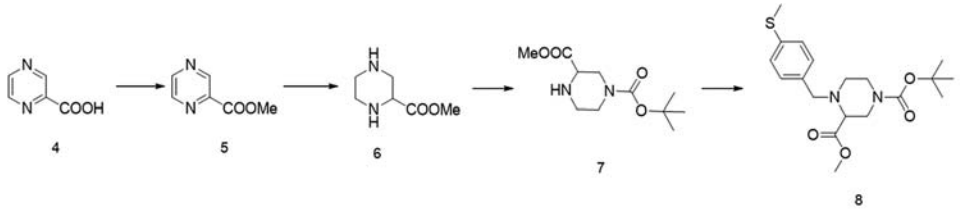
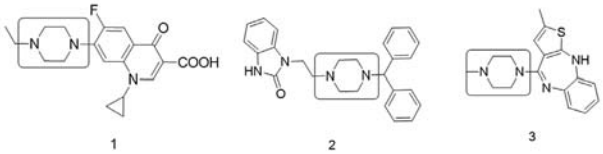
ABSTRACT 1-(*Tert*-butyl)-3-(methyl)piperazine-1,3-dicarboxylate (**7**) was synthesized by pyrazine-2-carboxylic acid (**4**) through esterification, hydrogenation reduction, and again esterification reaction. Then, 1-(*tert*-butyl)-3-(methyl)-4-(4-(methylthio)benzyl)piperazine-1,3-dicarboxylate (**8**) was prepared by electrophilic substitution reaction of **7** with 4-mercaptomethyl benzaldehyde (**9**). Their structure was confirmed by ^{1}H nuclear magnetic resonance and mass spectra.



KEY WORDS Pyrazine-2-carboxylic acid, Synthesis, 1-(*Tert*-butyl)-3-(methyl)-4-(4-(methylthio) benzyl)piperazine-1,3-dicarboxylate, Structure.

INTRODUCTION

The piperazine ring is a nitrogen-containing basic group. It has three advantages, which are, forming multiple hydrogen bonds or ionic bonds with other molecules, effectively regulating the acid-base balance constants and fat-water partition coefficients, and increasing the basicity and water solubility of the molecule. These advantages promote compounds containing piperazine ring becoming important chemical products and drug intermediates. Hence, a lot of medicines have been found in the market having piperazine in their structure such as antibacterial drugs (Enrofloxacin (**1**)),[1] antiallergic drugs (Oxatomide (**2**)),[2] and antipsychotic drugs (Olanzapine (**3**))[3].



RESULTS AND DISCUSSION

Chemical synthesis

1-(*Tert*-butyl)-3-(methyl) piperazine-1,3-dicarboxylic (**7**) was synthesized by pyrazine-2-carboxylic acid (**4**) through esterification, hydrogenation reduction, and again esterification reaction. Compound **7** on reaction with 4-mercaptomethyl benzaldehyde (**9**) resulted into **8**.

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As we all know, piperazine derivatives are synthesized by two ways: First, using piperazine ring-containing compounds, as reaction substrates synthesize piperazine derivatives[4] and second, introducing piperazine ring through hydrogenating pyrazine derivatives or coupling of two amino groups.[5,6] As a part of our research interest, we prefer the second method to synthesize a variety of heterocyclic systems with promising biological and pharmacological activities. In the present work, we propose a convenient approach which has a simple raw material, mild reaction conditions, and simple post-treatment to a new product **8** [**Scheme 1**].

EXPERIMENTAL SECTION

General

^{1}H nuclear magnetic resonance (NMR) (tetramethylsilane: δ: 0.00 as an internal standard) spectra were recorded on a Bruker 500 M spectrometer in $CDCl_3$ unless otherwise stated. Mass spectra (MS) were obtained on an Agilent 6500 instrument. All chromatographic separations were accomplished with Silica Gel 60 N (Qingdao Ocean Chemical Co., Ltd.). All samples were analyzed by high-performance liquid chromatography P230 (Dalian Elite Corporation). Most of the reagents were used without further purification unless otherwise specified. **4**, **9,** and di-*tert*-butyl dicarbonate were purchased from Shanghai Aladdin Biochemical Technology Co., Ltd.

Synthesis of pyrazine-2-carboxylic acid methyl ester (5)

$SOCl_2$ (57.51 g, 0.48 mol) was dropwise added to a stirred mixture of **4 (**30 g, 0.24 mol) and MeOH (100 mL) at 0–10°C. Then, the mixture was stirred overnight at room temperature (23°C) and concentrated under reduced pressure. The residue was adjusted with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc twice, and the combined organic phases were concentrated to give **5 (**26.4 g, 80.2% of yield, 98.2% of purity) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.85 (d, 1H), 8.78 (d, 1H), 3.96 (s, 3H). *m/z* $[M+1]^+$ 139.1 $C_6H_6N_2O_2$.

Synthesis of methyl piperazine-2-carboxylate (6)

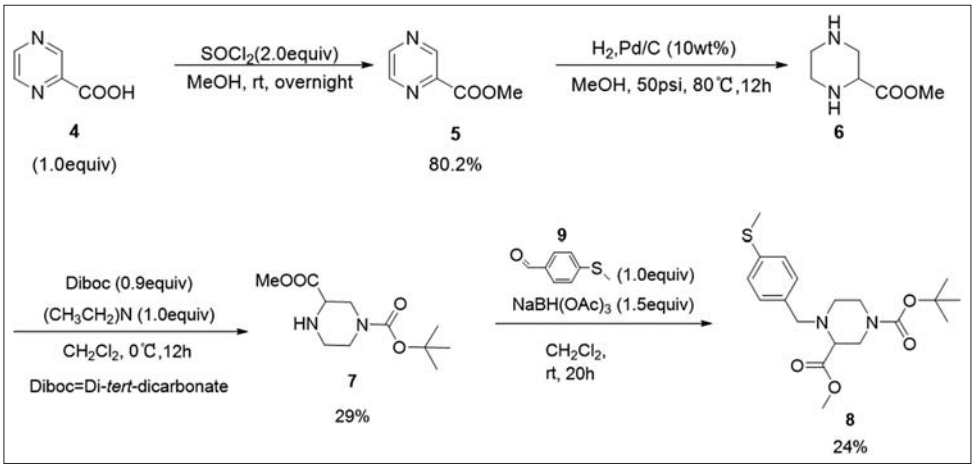
Pd/C (10%, 6 g) was added to a solution of **5 (**30 g, 0.22 mol) in methanol (250 mL) and stirred under 50 psi of hydrogen at the temperature of 80°C for 12 h. The solvent was removed under reduced pressure. Then, the crude product was used to next step without further purification (97.6% of purity). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.50–3.46 (m, 1H), 3.22–2.98 (dt, 2H), 2.93–2.76 (m, 4H), 1.38 (s, 2H). *m/z* $[M+1]^+$ 145.1 $C_6H_{12}N_2O_2$.

Synthesis of methyl 1-(tert-butyl)-3-(methyl) piperazine-1,3-dicarboxylic (7)

A solution of di-*tert*-butyl dicarbonate (13.6 g, 62.5 mmol) in dichloromethane (50 mL) was dropwise added to a stirred mixture of **6 (**10 g, 69.4 mmol), triethylamine (7.1 g, 69.4 mmol), and dichloromethane (100 mL) at 0°C over 1 h. The reaction mixture was stirred for 12 h (thin-layer chromatography, petroleum ether: ethyl acetate = 3:l). When the reaction was completed, the reaction mixture was poured into ice water (150 mL) and extracted with dichloromethane. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (petroleum ether: ethyl acetate =10:l) to afford **7 (**4.7 g, 29% of yield, 98.5% of purity) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.64 (d, 1H), 3.41–3.40 (dt, 1H), 3.01–3.00 (m, 3H), 2.78–2.67 (t, 1H), 2.19-2.15 (dt, 2H), 1.43 (dd, 9H). *m/z* $[M+1]^+$ 245.1 $C_{11}H_{20}N_2O_4$.

Synthesis of 1-(tert-butyl)-3-(methyl)-4-(4-(methylthio) benzyl)piperazine-1,3-dicarboxylate (8)

9 (17.94 g, 0.12 mol) and $NaBH(OAc)_3$ (37.48 g, 0.18 mol) were added to a stirred mixture of **7 (**30 g, 0.12 mol) in dichloromethane (200 mL) at room temperature. The reaction was maintained 20 h at room temperature and quenched with water. The organic layer was washed with water and purified by a silica gel column chromatography (petroleum ether: ethyl acetate = 100: l) to afford **8 (**11.22 g, 24% of yield, 96.8% of purity) as light yellow syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.23 (m, 4H), 3.82 (dd, 2H), 3.73



Scheme 1: Synthesis of 1-(*tert*-butyl)-3-(methyl)-4-(4-(methylthio)benzyl)piperazine-1,3-dicarboxylate

(t, 3H), 3.54 (dt, 3H), 3.28 (d, 2H), 3.01 (t, 1H), 2.48 (m, 3H), 2.33 (dd, 1H), 1.44 (s, 9H). *m/z* $[M+1]^+$ 380.9 $C_{19}H_{28}N_2O_4S$.

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