SYNTHESIS OF SOME EXTENDED HETEROCYCLIC PYRAZOLO-PYRIDAZINE DERIVATIVES BEARING (METHYLPHENYL) AMIDE MOIETY

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TÓM TẮT

TỔNG HỢP MỘT VÀI DỊ VÒNG PYRAZOLO-PYRIDAZINE CÓ CHỨA PHẦN (METHYLPHENYL) AMIDE

*Cấu trúc 3,4-Dimethyl-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one **1a-b** được sử dụng làm nguyên liệu ban đầu để tổng hợp bốn hợp chất mục tiêu **4a-d** có chứa phần (methyl)phenyl) amide qua 3 bước. Trước tiên, các dẫn xuất mang nhóm nitro **2a-b** thu được bằng phản ứng thế thân hạch của **1a-b** với 3-Nitrobenzyl bromide trong dung môi DMF. Trong bước tiếp theo, nhóm nitro được chuyển thành các hợp chất mang nhóm amin **3a-b** bằng quá trình khử thông qua tác nhân khử Tin (II) chloride monohydrate trong dung môi ethanol ở điều kiện đun hoàn lưu. Và ở bước cuối cùng, nhóm chức amin dễ dàng kết hợp với các acid chloride để tạo thành các amide tương ứng **4a-d**, các hợp chất pyrazolo-pyridazine mở rộng, với hiệu suất cao dao động từ 79-86%. Cấu trúc của các hợp chất tổng hợp đã được xác nhận dựa trên dữ liệu phổ ^{1}H-NMR.*

Keywords: *Pyrazolo-pyridazine, nucleophilic substitution reaction, reduction reaction, amide formation*

1. INTRODUCTION

The nitrogen-bearing heterocyclic compounds own a wide range of biological activities such as antimicrobial, analgesic, anticancer, antifeedant, antitubercular, antidiabetic, antifungal, antihypertensive, antiplatelet, anticonvulsant, anti-HIV, antiasthma, anti-inflammatory, antipyretic, insecticidal. They play a key role in synthetic drugs, biological processes and wide applications in medicine[1,2]. One of compound among these nitrogen-containing heterocyclic derivatives, pyrazole, which is a five membered heterocyclic ring, has been reported to ownpotential biological activities[3]. Pyridazine, another nitrogen-carrying heterocyclic derivative having 6 members, has also demonstratedto be a useful ligand for different targets in drug discovery[4].

Recent researchesillustrate that fused pyridazines, fused pyrazolesand their derivatives possess an extensive range of biological activities[5]. Thus, enormousattempts have been made to enlarge the library of pyrazolo-pyridazine derivatives. In the previous study, we reported the synthetic route of the score structure bearing pyrazolo-pyridazine, named 3,4-dimethyl-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one[6]. In this present work, in continuation of the studies on the synthesis of pyrazolo-pyridazine derivatives, the synthesis of extended pyrazolo-pyridazine compounds was reported.

2. MATERIALS AND METHODS

All chemicals were used as received from commercial sources without further purification. The reagents we have used in our synthesis works were from Aldrich Chemical

Company, Arcos Organics, TCI. The reagent grade solvents were supplied from Daejung Chemicals, Junsei Chemicals, Lancaster Synthesis, Aldrich Chemical Co., or Sigma-Aldrich Ltd. The technical grade solvents we used for flash column chromatography or extractions or even washing purposes were from Duksan Pure Chemicals or SK Chemicals. For monitoring the reactions we have used the MERK KGaA 60 F254 silica gelplates, and for flash column chromatography silica gels (particle sizedistrubution: 38-75 μm minimum 80%) were collected from Fuji Silysia Chemicals Ltd. and MERK. Visualization was accomplished with UV (254 nm). For making the solution for NMR spectroscopy we used the solvents supplied from Cambridge Isotope Laboratories and Aldrich Chemical Company. The ^{1}Hproton NMR spectra were obtained from Varian 300 MHz or Bruker 300 MHz or Bruker 500 MHz NMR spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or the internal solvent signal of deuterated solvents (^{1}H). Multiplicities are indicated by s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants *J* are reported in Hertz.

*General experimental procedure of compound **2a-b***

To a stirred solution of compound **1** (1.0 mmol, 1.0 eq) in DMF (anhydrous, 5mL) at 0 °C was added NaH (60% in oil). The mixture was stirred for 30 min, then 3-Nitrobenzyl bromide was added. After the starting material disappeared (about 30 min), the reaction mixture was quenched with cold water and extracted with EtOAc twice. The combined organic phase was washed with water twice, with brine, dried with anhydrous Na_2SO_4, filtered and concentrated. The resulted residue was purified by flash column chromatography (EtOAc:Hex, 1:1 to 2:1), which gave the desired product **2a-b** as white solids.

(2a): 3,4-Dimethyl-6-(3-nitrobenzyl)-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one

Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.57 (s, 3H), 2.65 (s, 3H), 5.45 (s, 2H), 7.49-7.53 (m, 6H), 7.79-7.82 (d, *J* = 9.0, 1H), 8.11-8.14 (d, *J* = 9.0, 1H), 8.26 (s, 1H).

(2b): 2-(4-Methoxyphenyl)-3,4-dimethyl-6-(3-nitrobenzyl)-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one

Yield: 94%. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.46 (s, 3H), 2.55 (s, 3H), 3.82 (s, 3H), 5.35 (s, 2H), 7.11-7.13 (m, 2H), 7.48-7.51 (m, 2H), 7.58-7.63 (m, 1H), 7.69-7.72 (d, *J* = 9.0, 1H), 8.09-8.12 (m, 2H).

*General experimental procedure of compound **3a-b***

To a stirred solution of compound **2** (0.5 mmol, 1.0 eq) in EtOH (10 mL) at 80 °C was added $SnCl_2.H_2O$ (5.0 eq). The reaction mixturte was stirred at 80 °C. After the starting material disappeared (about 1 h), the reaction mixture was cooled down to room temperature, neutralized with saturated $NaHCO_3$ solution at 0 °C, the resulting mixture was filtered through a celite layer. The filtrate was extracted twice with EtOAc, washed with brine, dried with anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography (EtOAc:Hex, 4:1 to 5:1), which gave the desired product **3a-b** as white solids.

(3a): 6-(3-Aminobenzyl)-3,4-dimethyl-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one

Yield: 75%. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.46 (s, 3H), 2.57 (s, 3H), 5.00 (s, 2H), 5.06 (s, 2H), 6.41 (s, 3H), 6.87-6.92 (m, 1H), 7.59 (s, 5H).

(3b): 6-(3-Aminobenzyl)-2-(4-methoxyphenyl)-3,4-dimethyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one

Yield: 94%. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.47 (s, 3H), 2.54 (s, 3H), 3.82 (s, 3H), 4.99 (s, 2H), 5.05 (s, 2H), 6.38-6.40 (m, 3H), 6.87-6.92 (m, 1H), 7.11-7.14 (m, 2H), 7.48-7.51 (m, 2H).

*General experimental procedure of compound **4a-d***

To a stirred solution of compound **3** (0.2 mmol, 1.0 eq) in DCM (5 mL) at 0 °C was added Et_3N (3.0 eq). Then acid chloride, CH_3COCl or PhCOCl, (1.1 eq) was added dropwise. The reaction mixturte was stirred at 0 °C. After the starting material disappeared (30 min), the reaction mixture was added with cold water, extracted twice with DCM, washed with brine, dried with anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography (EtOAc:Hex, 4:1 to 5:1), which gave the desired product **4a-d** as white solids.

(4a): *N*-(3-((3,4-Dimethyl-7-oxo-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-6(7*H*)-yl)methyl)phenyl)acetamide

Yield: 79%. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.96 (s, 3H), 2.46 (s, 3H), 2.58 (s, 3H), 5.17 (s, 2H), 6.90-6.93 (d, *J* = 9.0, 1H), 7.16-7.22 (m, 1H), 7.37 (s, 1H), 7.51-7.54 (d, *J* = 9.0, 1H), 7.59 (s, 5H), 9.87 (s, 1H).

(4b): *N*-(3-((3,4-Dimethyl-7-oxo-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-6(7H)-yl)methyl)phenyl)benzamide

Yield: 86%. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.46 (s, 3H), 2.58 (s, 3H), 5.22 (s, 2H), 6.99-7.01 (d, *J* = 6.0, 1H), 7.24-7.30 (m, 1H), 7.45-7.62 (m, 9H), 7.69-7.72 (d, *J* = 9.0, 1H), 7.88-7.90 (m, 2H), 10.21 (s, 1H).

(4c): *N*-(3-((2-(4-Methoxyphenyl)-3,4-dimethyl-7-oxo-2*H*-pyrazolo[3,4-*d*]pyridazin-6(7*H*)-yl)methyl)phenyl)acetamide

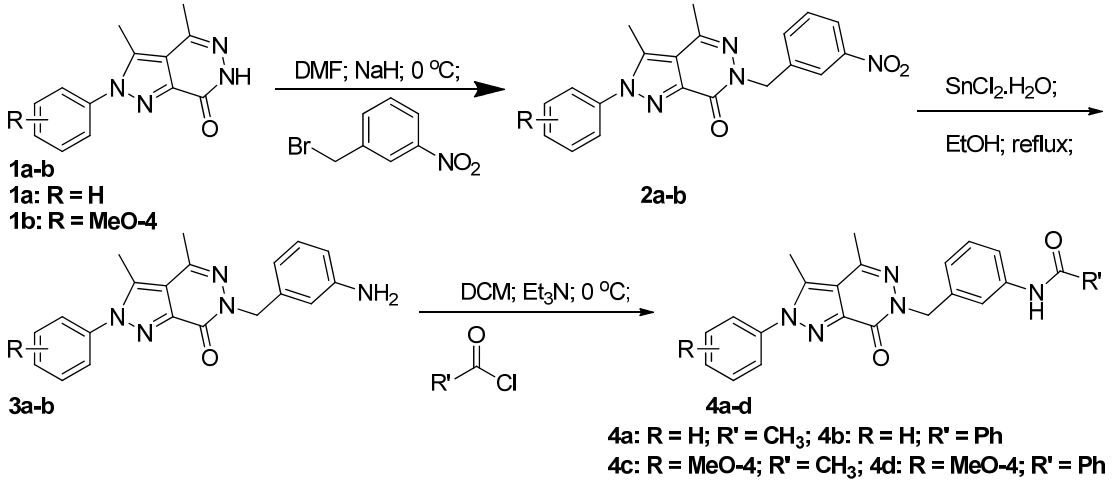
Yield: 85%. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.00 (s, 3H), 2.51 (s, 3H), 2.59 (s, 3H), 3.86 (s, 3H), 5.21 (s, 2H), 6.94-6.96 (d, *J* = 6.0, 1H), 7.15-7.25 (m, 3H), 7.40 (s, 1H), 7.52-7.57 (m, 3H), 9.89 (s, 1H).

(4d): *N*-(3-((2-(4-Methoxyphenyl)-3,4-dimethyl-7-oxo-2*H*-pyrazolo[3,4-*d*]pyridazin-6(7*H*)-yl)methyl)phenyl)benzamide

Yield: 87%. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.52 (s, 3H), 2.59 (s, 3H), 3,86 (s, 3H), 5.26 (s, 2H), 7.02-7.05 (d, *J* = 9.0, 1H), 7.14-7.17 (m, 2H), 7.28-7.33 (m, 1H), 7.48-7.55 (m, 5H), 7.66 (s, 1H), 7.73-7.76 (d, *J* = 9.0, 1H), 7.92-7.94 (m, 2H), 10.24 (s, 1H).

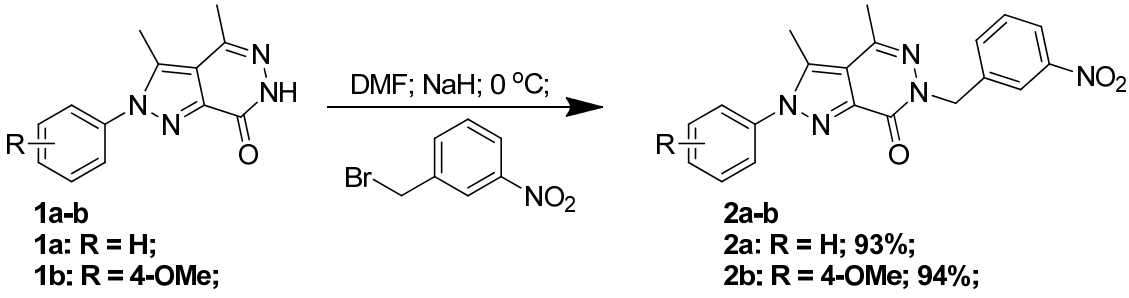
3. RESULTS AND DISCUSSION

The core structure 3,4-Dimethyl-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one **1a-b** were used as starting materials for preparation of target compounds **4a-d** in 3 steps[6]. As demonstrated in scheme 1, firstly, nitro group bearing derivatives **2a-b** were obtained by nucleophilic substitution reaction of **1** with 3-Nitrobenzyl bromide in DMF. In the next step, nitro group was converted to amine **3a-b** by reduction processusing reducing agent Tin(II) chloride monohydrate in ethanol solvent at reflux condition. The amine functional group was easily coupled with acid chloride to form desired amides **4a-d** respectively, extended pyrazolo-pyridazine compounds, in good yields.



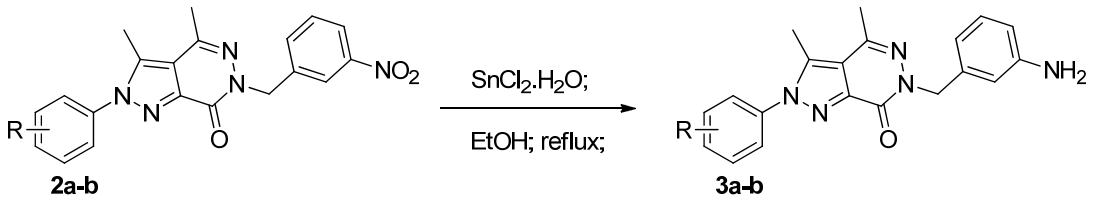
Scheme 1: General synthetic route of extended pyrazolo-pyridazin derivatives

As shown in scheme 2, the nucleophilic substitution reaction between pyrazolo-pyridazine derivative **1**, an electron rich species (the nucleophile), and 3-Nitrobenzyl bromide, an electrophilic saturated C atom attached to an electronegative group (the leaving group) in *N*,*N*-Dimethylformamide (DMF) medium undergoes very readily generating compound **2** in high yield (93 and 94% respectively). DMF is a commonly used solvent in alkylation reactions mediated by NaH. Many reactions in the literature have used these conditions with high product yields[7]. Sodium hydride is a common reagent for substrate activation in nucleophilic substitution reactions. Sodium hydride can behave both as a base and as a source of hydride. Sodium hydride is a commonly used base for deprotonation of alcohols, phenols, amides, ketones, esters and other functional groups for the promotion of their nucleophilic substitution[8]. The ^{1}H-NMR shows the signal of protons of benzyl group C_6H_5-CH_2- at δ_H 5.45 (s, 2H) of **2a** and 5.35 (s, 2H) of **2b** along with disappearance of the signal of protons of –NH.



*Scheme 2: Synthetic route of derivatives **2a-b***

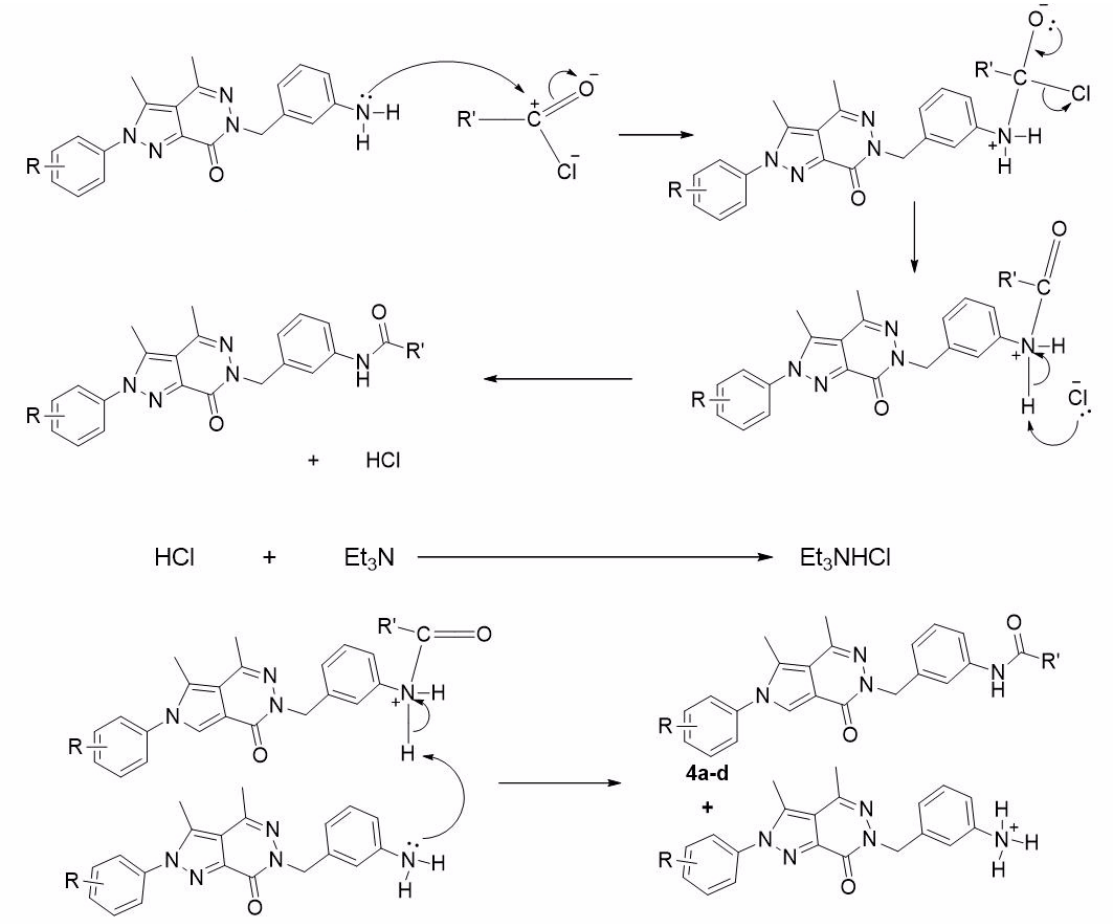
As can be seen in scheme 3, aryl amines can be readily synthesized from aryl nitro compounds via countless reduction methods. The selective reduction of aryl nitro compounds in the presence of sensitive functional groups using Tin(II) chloride have been reported as efficient methods for the synthesis of aryl amines in good yields. In addition, simple experimental procedure and purification also make the reduction of aryl nitro compounds with Tin(II) chloride advantageous over other methods of reduction.



*Scheme 3: Synthetic route of amines **3a-b***

In a typical N-acylation reaction (scheme 4), the activated form of carboxylic acid, acid halide, is used. Herein pyrazolo-pyridazine derivative **4** bearing (methyl)phenyl) amide group was prepared by reaction of aryl amine moiety of compound **3** with acid chloride in the presence of Et_3N in DCM at 0 °C. The first stage (the addition stage of the reaction) involves a nucleophilic attack on the fairly positive carbon atom by the lone pair on nitrogen atom in the amine functional group of pyrazolo-pyridazine derivative. The second

stage (the elimination stage) happens in two steps. In the first, the carbon-oxygen double bond reforms and a chloride ion is pushed off. That is followed by removal of a hydrogen ion from the nitrogen. This might happen in one of two ways: It might be removed by a chloride ion, producing HCl (which would immediately react with triethylamine to give triethylammonium chloride) or it might be removed directly by another pyrazolo-pyridazine molecule. The pyrazolo-pyridazine ammonium ion, together with the chloride ion already there, makes up the pyrazolo-pyridazine ammonium chloride formed in the reaction. A sign of proton of amide ArN-H appears at δ_H 9.8 $\rightarrow$10.3 ppm.



*Scheme 4: Plausible amide formation mechanism of pyrazolo-pyridazine derivative **4a-d***

4. CONCLUSIONS

In conclusion, we have reported that four extended heterocyclic pyrazolo-pyridazine derivatives **4a-d** bearing (methyl)phenyl) amide moiety have been successfully synthesized from two pyrazolo-pyridazine core structures in quantitative yield (79-87%) by a three-step route under mild conditions. The procedure comprised a nucleophilic substitution reaction, a reduction process of nitro group using reducing Tin(II) chloride agent, also known as stannous chloride, and followed by a route converting amine to amide. From these authentic derivatives, our further investigations will be carried out to get optimal reaction conditions for large scale synthesis and making compound library. Simultaneously, our further attention will be also focused on screening biological activities of these compounds with various targets to evaluate and find out

promising candidate for improvements leading to the increase of their activity and selectivity.

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