

## Base-Catalyzed Synthesis of Pyridopyrimidinone Derivatives

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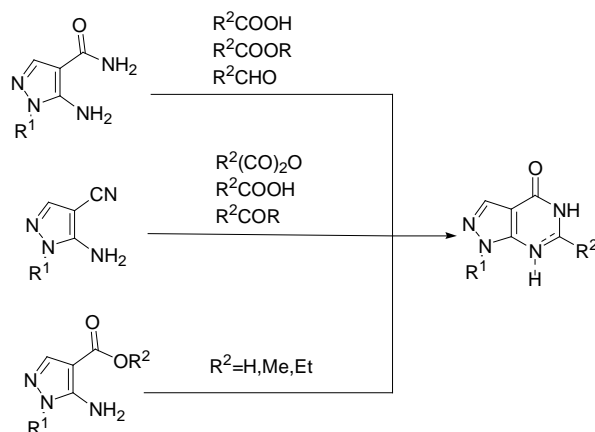
**Keywords:** 4-Cyano-5-aminopyrazole; pyridopyrimidinone derivatives; cyclocondensation; PDF conversion.

**Abstract.** Nitrogen-containing heterocyclic compounds become main trend of chemical materials gradually due to its structure diversification, high selectivity, low toxicity and other environmental-friendly characteristics. Meanwhile, it is very important in pharmaceutical research and development. Wherein, people pay more and more attention to pyrazole compounds because of its wide utility, strong efficiency and other features. In the paper, 4-cyano-5-aminopyrazole derivatives **3**, synthesized by the condensation of hydrazine and methylene malononitrile, cyclocondensation with aldehyde catalyzed by NaOH to provide pyridopyrimidinone derivatives. The structures of compounds **4** were represented by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS.

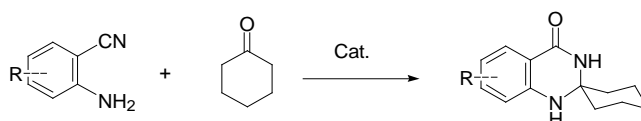
### Introduction

Pyrazolopyrimidine heterocyclic compounds have excellent biological medicine activity in the aspects of anticancer [1], diminishing inflammation [2], disinfecting [3], resisting allergy [4], resisting convulsion [5], relieving pain [6], bringing down fever [7] and calmative [8]. Some compounds containing pyrazolopyrimidine fused ring have been applied in clinical treatment, such as pirenperone used as calmative, Barmastine used as antiallergic agent. Pyrazolopyrimidine compounds are also widely used for killing insects [9], weeding [10], etc. It also has prominent effect in inhibiting dihydrofolate reductase [11].

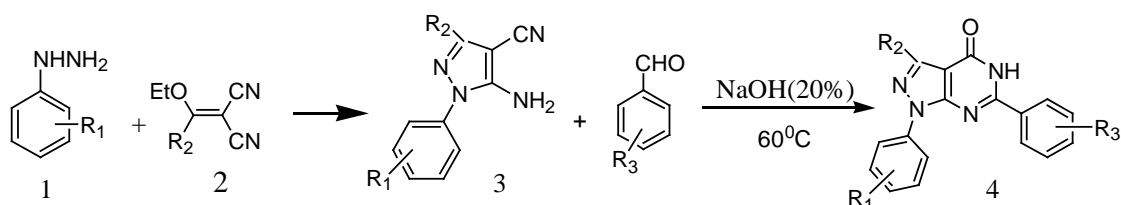
Pyrazolopyrimidinone derivatives are mainly synthesized by the following methods according to different synthetic raw materials: 1) the condensation of 5-aminopyrazole-4-amide and carboxylic acid [12], ester [13] and aldehyde [14], 2) the cyclization of 4-cyano-5-pyrazole carboxylic acid [15] or acid anhydride [16] with ketone [17], 3) the transformation of 5-pyrazole carboxylic acid or ester into pyrazolopyrimidine [18] (Scheme 1). In the previous research, we discovered that alkali can catalyze conversion of aromatic o-aminonitrile with ketone to provide pyrimidones through PDF transformation [19] (Scheme 2). In this paper, 4-cyano-5-aminopyrazole derivatives **3** were synthesized first according to literature [20], and then reacted with aldehyde through PDF conversion condensation (Scheme 3).



Scheme 1. The methods for synthesizing pyrazolo[3,4-*d*]pyrimidinones



Scheme 2. The PDF conversion of o-amino benzonitrile and ketone



Scheme 3. Synthesis of pyrazolo[3,4-*d*]pyrimidinones Experiment part

### Reagent and instrument

All reagents are commercially available except 4-cyano-5-aminopyrazole derivatives which were prepared as according to literature [20].

Melting point was determined by XT4 melting point detector (Beijing Keyi Electro-optical Factory); FTIR was determined by Nicolet Magna IR 560 infrared spectrometer (KBr, American Perkin Elmer Company). Nuclear magnetic resonance was recorded by Bruker 400 nuclear magnetic resonance spectrometer (Switzerland Bruker Company); Mass spectrum was determined by APEX IV and ZAB-HS mass spectrometer (Swiss Bruker Company).

### Experiment

**Synthesis of Pyridopyrimidinone derivatives 4:** 4-cyano-5-aminopyrazole (1 mmol), aldehyde (1.2 mmol) and 20 ml toluene were mixed in 50 mL three-neck flask. Then NaOH (0.2 mmol) was added at 60°C. After the reaction ended, the reaction mixture was poured into water (20 ml). The solution was extracted three times by ethyl acetate. Organic phase was dried with anhydrous sodium sulfate and evaporated by rotary evaporation. Crude product was washed by alcohol and then filtered. The filter cake was dried, and recrystallized from alcohol to give pure **4**.

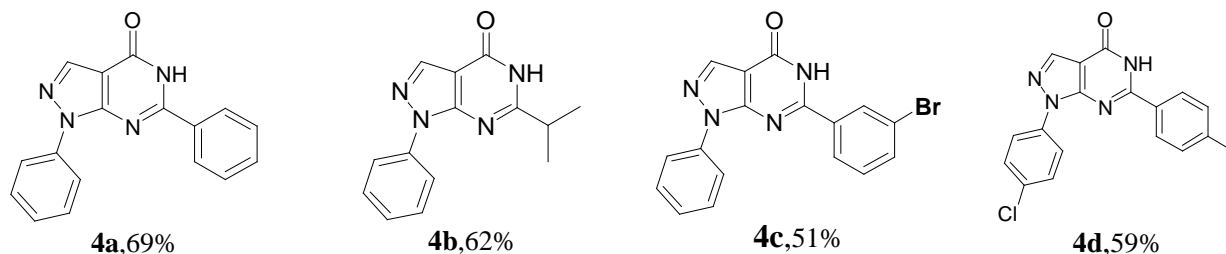
### Result and conclusion

We chose the reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitrile and benzaldehyde as a model to study the influence of different reaction conditions. As shown in Table 1, the reaction was not available without catalyst or under acid catalyst (Table1, Entries 1, 2). The catalytic properties of inorganic alkali were higher than that of organic alkal (Table1, Entries 3, 5, 6). Sodium hydroxide had the strongest catalytic effect (Table1, Entry 6). Though reaction efficiency can be improved by higher temperature, more by-products can also be produced at higher reaction temperature, so the proper temperature was 60°C. Reaction also can be affected by the amount of catalyst and 0.2 equivalent should be properly selected.

Tab.1 Optimization of reaction conditions

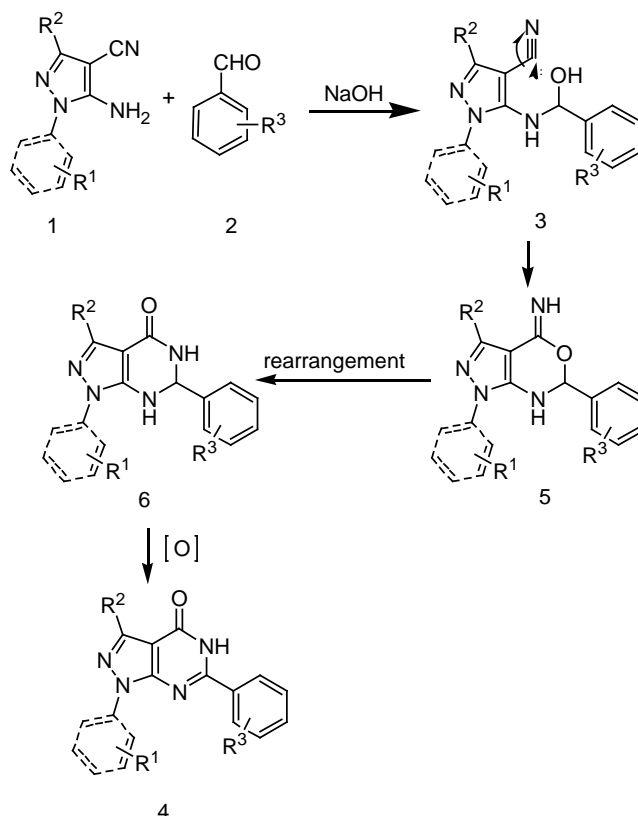
Entry	Solvent	Cat (equiv)	Temp (°C)	Yield(%)
1	PhMe	-	60	0
2	PhMe	ZnCl <sub>2</sub> (1.0)	60	0
3	PhMe	DBU (0.2)	60	0
4	PhMe	Na <sub>2</sub> CO <sub>3</sub> (0.2)	60	0
5	PhMe	KOH (0.2)	60	69
6	PhMe	NaOH (0.2)	60	86
7	PhMe	NaOH (0.4)	60	86
8	PhMe	NaOH (0.6)	60	85
9	PhMe	NaOH (0.8)	60	85

We studied a series of pyridopyrimidinone derivatives after the best reaction conditions were mastered. Aromatic aldehyde with electron withdraw group (EWG) and electron donating group (EDG) were respectively selected as reactants. The results showed that the yield of aromatic compound with EDG was higher than that of aromatic compound with EWG. We also adopted chain aldehydes in order to illustrate the universality of the reaction, and target product was also obtained with higher yield.

Tab.2 Synthesis of 4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones

**1,6-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4a):** White solid; m.p. >300°C; IR (KBr,  $\nu$ , cm<sup>-1</sup>): 3071, 1684; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) ( $\delta$ , ppm): 12.61 (s, 1H), 8.25 (s, 1H), 8.20-8.15 (m, 4H), 7.64-7.57 (m, 5H), 7.44-7.40 (m, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) ( $\delta$ , ppm): 158.7, 156.5, 152.7, 138.9, 136.5, 132.5, 132.5, 129.8, 129.2, 128.7, 127.5, 122.1, 106.5; HRMS (ESI): calcd. For C<sub>17</sub>H<sub>13</sub>N<sub>4</sub>O [M+H] 289.10839; found 289.10913.

The reaction mechanism was shown in Scheme 3. Amino of 4-cyano-5-aminopyrazole can nucleophilically attack acetaldehyde under alkaline conditions to afford **3**. Then, the intramolecular Pinner reaction of **3** formed **5**, and then **6** was obtained through rearrangement (Dimroth rearrangement [21]). Finally, **6** was converted into target product **4** under oxidant by air.



**Scheme 4** Proposed mechanism of the formation of 4.

In summary, a highly efficient synthesis of pyridopyrimidinone derivatives was established. Firstly, hydrazine and methylene malononitrile were adopted as raw materials, 4-cyano-5-aminopyrazole derivatives were synthesized under catalysis of alkali. Compounds **3** were reacted with aldehydes at 60°C in the catalyst of NaOH to give pyridopyrimidinone derivatives **4**. The method is characterized by mild condition and higher yield. The obtained products can be separated easily.

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