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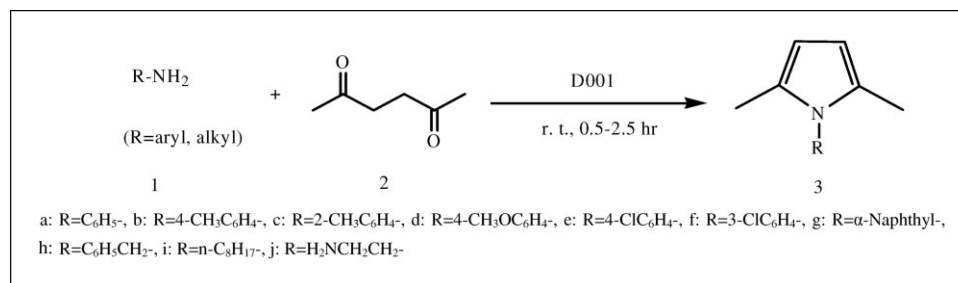
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A simple and effective Paal-Knorr condensation of 2, 5-hexanedione with most amines has been carried out at room temperature under solvent-free condition. The pyrroles were obtained in high yields and in short reaction times.

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## INTRODUCTION

Pyrroles and their derivatives are very important heterocyclic compounds. They constitute the core unit of many natural products and serve as building blocks for porphyrin synthesis [1–3]. A few substituted pyrroles have been shown to possess extensively pharmacological activities and various interesting biological activities including anticancer, antimycobacterial, and antiviral properties [4–6].

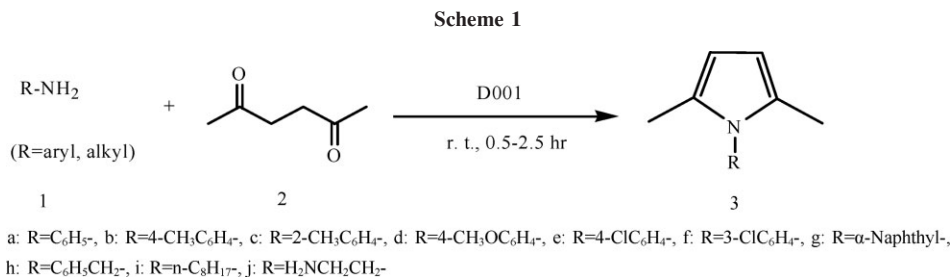
The Paal-Knorr reaction is an important method for the synthesis of substituted pyrroles. Recently, clay-catalyzed [7,8], iodine [9], aluminum oxide [10], proton acid [11,12], Lewis acid [13,14], ionic liquids [15], microwave-assisted reactions [16,17], and solvent-free reaction [18,19] have been utilized for the preparation of pyrroles under Paal-Knorr condition. However, they are not very satisfactory with regard to reaction conditions, such as the use of the toxic solvent, prolonged reaction time, violence of reaction, difficulty of separa-

tion and purification. Therefore, it is necessary to develop a simple, efficient, and more general method for the synthesis of this useful heterocyclic nucleus.

## RESULTS AND DISCUSSION

Herein, we wish to report our study on the synthesis of pyrroles by using heterogeneous catalysts. It has been observed that macroporous strongly acidic styrene resin (D001), which equals to Amberlite 200 (USA) and Lewatit SP-210 (Germany), is an efficient catalyst for construction for substituted pyrroles from amines and 2,5-diketone (Scheme 1). Our initial study was started by reacting aniline with 2,5-diketone under various catalysts. The results are summarized in Table 1.

It was found that pyrrole **3a** products (**3**, Scheme 1) were obtained in low yields by using D152 as catalyst (entries **1**, Table 1). Although reaction yields were very high when the NKC-9 and NR-50 were first performed



**Table 1**

Effect of various resin catalysts on the Paal-Knorr reaction between aniline (2.4 mmol) with 2,5-diketone (2.0 mmol).

Entry	Catalyst	Functional group	Resin type	Raw catalyst yield (3a)/% <sup>a,b,c</sup>	Recycling catalyst yield (3a)/% <sup>a,b,c</sup>
1	D152 (0.05g)	—COOH	Acrylic acid	47	31
2	D072 (0.05g)	—SO <sub>3</sub> H	Styrene	81	76
3	NKC-9 (0.05g)	—SO <sub>3</sub> H	Styrene	95	83
4	NR-50 (0.05g)	—SO <sub>3</sub> H	Nafion-vinyl	91	85
5	D001 (0.05g)	—SO <sub>3</sub> H	Styrene	90	88
6	D001 (0.1g)	—SO <sub>3</sub> H	Styrene	93	91
7	D001 (0.15g)	—SO <sub>3</sub> H	Styrene	91	90

<sup>a</sup> Products were identified by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and HRMS.<sup>b</sup> Reaction time was 1.0 h.<sup>c</sup> The reaction medium is solvent-free.

in this reaction as catalysts, the reaction yields were sharply decreased when recycling these catalysts (entries **3**, **4**, Table 1). Inspiringly, the reaction yield little reduced when recycling D001 as catalyst (entries **5**, **6**, **7**, Table 1). However, increasing amount of catalyst in excess had hardly raised yields of pyrrole **3a** (entries **7**, Table 1). After a comprehensive survey of the reaction conditions, acidic styrene resin (D001) was considered as appropriate catalysis for Paal-Knorr reaction. Subsequently, a variety of amines were examined using this method (Scheme 1). The results are listed in Table 2.

Aniline and its derivatives bearing whether electron withdraw group or electron donating group could implement Paal-Knorr reaction with 2,5-hexanedione in good yields at room temperature (entries **2**, **3**, **4**, **5**, **6**, Table 2). The position of substitution group seldom had effect on reaction yields. However, it was necessary that reaction time was prolonged when *meta*-substituted substrate was used for this reaction (entries **3**, **6**, Table 2). Moreover, naphthylamine and aliphatic amines also could afford the corresponding pyrroles under the same condi-

tion smoothly (entries **7**, **8**, **9**, **10**, Table 2). Inspiringly, when ethylene diamine was used in the present reaction, the product **3j** [1, 2-di (2, 5-dimethyl-1-pyrrole)-ethane] was formed with two units of pyrrole ring (entries **10**, Table 2).

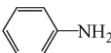

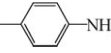
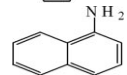
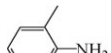
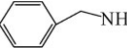
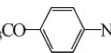
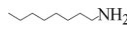
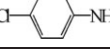
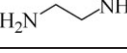
## EXPERIMENTAL

IR (Perkin-Elmer, 2000 FTIR), <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz), <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 125.7 MHz), and MS-GC (HP5890 (II)/HP 5972, EI) spectra were obtained at the Center of Analytical Configuration of University of Science and Technology of China. Flash chromatographic sheet employed was purchased from Anhui Liangchen Silicon Material Co., and all material from Aldrich and used directly as received.

**General procedure for the synthesis of pyrroles.** To a mixture of an amine (3 mmol) and hexane-2,5-dione (3 mmol) resin (D001, 100 mg) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and filtered, the organic phase washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated

**Table 2**

Resin (D001) catalyzed Paal-Knorr condensation between amines and 2,5-dione.

Entry	RNH <sub>2</sub>	Time (h)	Product <sup>a,b</sup> (Yield)/%	Ref	Entry	RNH <sub>2</sub>	Time (h)	Product <sup>a,b</sup> (Yield)/%	Ref
1		1.0	3a (93)	9	6		2.5	3f (83)	19
2		1.0	3b (89) <sup>c</sup>	19	7		1.0	3g (85) <sup>c</sup>	9
3		1.5	3c (85)	19	8		2.0	3h (91)	16
4		0.5	3d (91) <sup>c</sup>	9	9		1.5	3i (82)	3i
5		0.5	3e (87) <sup>c</sup>	19	10		2.0	3j (76)	9

<sup>a</sup> Products were identified by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and HRMS.<sup>b</sup> Isolated yields.<sup>c</sup> Reaction temp was at 60°C.

*in vacuo*. The pure products were obtained by flash chromatography on silica gel eluting with petroleum ether/EtOAc (1:4, V:V), and identified by IR,  $^1\text{H}$ -,  $^{13}\text{C}$ -NMR, and HRMS.

**1-Octyl-2,5-dimethylpyrrole (3i).** IR: 3035.2, 2983.5, 1593.6, 1466.5, 1340.2, 976.3, 810.3  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ : 5.76 (s, 2H,  $2\times\text{CH}$ ), 3.73 (t,  $J = 7.8$ , 2H,  $\text{CH}_2\text{N}$ ), 2.19 (s, 6H,  $2\times\text{CH}_3$ ), 1.68–1.74 (m, 2H,  $\text{CH}_2$ ), 1.33–1.45 (m, 12H,  $6\times\text{CH}_2$ ), 0.97 (t,  $J = 7.6$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ : 12.71, 14.21, 24.62, 30.50, 31.10, 31.59, 32.30, 35.73, 47.82, 107.66, 129.84; HRMS: calcd for  $\text{C}_{14}\text{H}_{27}\text{N}$ : 209.3707, found: 209.3695.

In conclusion, it was very appropriate that macroporous strongly acidic styrol resin (D001) was employed as catalyst for the Paal-Knorr reaction. Various amines underwent the earlier reaction with 2,5-hexanedione to produce different substituted pyrroles in high yields. The majority of reactions were carried out at room temperature and a shorter period of time (0.5–2.5 h). The reaction conditions are very mild, and no solvent was used to carry out the reaction.

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