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Chinese Chemical Letters 21 (2010) 664–668

CHINESE Chemical Letters

www.elsevier.com/locate/cclet

A convenient synthesis of pyrroles catalyzed by acidic resin under solvent-free condition

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Abstract

A convenient and effective Paal–Knorr condensations of 2,5-hexanedione with most amines have been carried out at room temperature under solvent-free condition. Macroporous strongly acidic styrol resin (D001) as a novel, efficient, cost-effective, and reusable solid acid catalyst for the synthesis of pyrroles under the same conditions. The pyrroles were obtained in high yields in short reaction times.

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Keywords: Paal-Knorr; Pyrrole; Solvent-free; Acidic resin

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]. A few substituted pyrroles have been shown to possess extensively pharmacological activities and various interesting biological activities including anticancer, antimycobacterial and antiviral properties [2].

The Paal–Knorr reaction is an important method for the synthesis of substituted yrroles. Recently, claycatalyzed [3a–c], iodine [3d], proton acid [4a–c], aluminum oxide [4d], Lewis acid [5], ionic liquids [6], microwave assisted reactions [7] and solvent-free reaction [8] 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 separation and purification. Therefore, it is necessary to develop a simple, efficient and more general method for the synthesis of this useful heterocyclic nucleus.

1. Experimental

IR (PerkinElmer, 2000 FTIR), ¹H NMR (CDCl₃, 500 MHz), ¹³C NMR (CDCl₃, 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., Ltd. and all material from Aldrich and used directly as received.

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Scheme 1. Condition and regent: (1) D001; (2) r.t., 0.5–2.5 h. a: $R = C_6H_{5^-}$, b: R = 4-CH₃C₆H₄-, c: R = 2-CH₃C₆H₄-, d: R = 4-CH₃OC₆H₄-, e: R = 4-ClC₆H₄-, f: R = 3-ClC₆H₄-, g: $R = \alpha$ -Naphthyl-, h: $C_6H_5CH_2$ -, i: R = n-C₈H₁₇-, j: $R = H_2NCH_2CH_2$ -

General procedure for the synthesis of pyrroles: to a mixture of an amine (2.4 mmol) and hexane-2,5-dione (2.0 mmol) resin (D001, 100 mg) was added. The mixture was stirred at room temperature or 60 °C and the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with CH_2Cl_2 , and filtered, the organic phase washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated 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, ¹H, ¹³C NMR and HRMS.

2. Result 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 styrol 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).

Table 1 The synthesis of pyrrole **3a** by reacting aniline (2.4 mmol) with 2,5-diketone (2.0 mmol) under different conditions.

Entry	Catalyst	Time (h)	Media	Reaction yield (3a) (%) ^{a,b}
1	1	0.5	SF ^c /r.t.	57
2	D001 (0.05 g)	0.5	SF/r.t.	88
3	D001 (0.1 g)	0.5	SF/r.t.	91
4	D001 (0.15 g)	0.5	SF/r.t.	90
5	D001 (0.1 g)	1.0	SF/r.t.	93
6	D001 (0.1 g)	1.5	SF/r.t.	93
7	D001 (0.1 g)	1.0	SF/60 °C	92

^a Products were identified by IR, ¹H NMR, ¹³C NMR and HRMS.

^b Isolated yields.

^c SF is solvent-free.

Table 2 The synthesis of pyrrole **3a** by reacting aniline (2.4 mmol) with 2,5-diketone (2.0 mmol) under various catalysts.

Entry	Reaction catalyst	Media	Yield (3a) (%) ^{a,b}
1	H ₂ SO ₄ (98%)	C ₆ H ₆ /80 °C	68.8 [4a-c]
2	4-CH ₃ C ₆ H ₄ SO ₃ H	C ₆ H ₆ /80 °C	50 [8b]
3	Montmorillonite KSF	$CH_2Cl_2/r.t.$	96 [3b]
4	Montmorillonite KSF	SF ^c /r.t	98 [3c]
5	Iodine	THF/r.t.	90 [3d]
6	NaHSO ₄ ·SiO ₂	$CH_2Cl_2/r.t.$	90 [8a]
7	Microwave	Ether	90 [7]
8	НСООН	SF/r.t.	93 [8b]
9	Sulfamic acid	SF/r.t.	92 [8c], 96 [8d]
10	Acidic styrol resin (D001, 0.1 g)	SF/r.t.	93

^a Products were identified by IR, ¹H NMR, ¹³C NMR and HRMS.

^b Reaction time was 1.0 h.

^c SF is solvent-free.

Our initial study was started by reacting aniline with 2,5-diketone under different conditions. The results are summarized in Table 1.

As shown in Table 1, the pyrrole was observed in low yield at room temperature under no catalyst (entry 1, Table 1). Augment of catalyst moderately helped to increase yields of pyrrole (entries 2–4, Table 1). It is necessary that reaction time is no less than 1 h (entry 3, 5, 6, Table 1). Raising reaction temperature had hardly increased pyrrole yield (entry 7, Table 1).

Furthermore, we compared reaction effect by using catalyst (D001) with other reported catalysts. The results are shown in Table 2.

It was found that the pyrrole was obtained in good yields by using catalyst (D001) like reported catalysts (entries 3– 9, Table 2). Besides high yield, our method has two prominent merits that the catalyst (D001) can be recycled by using hydrochloric treatment and the reaction time is shorter. After a comprehensive survey of the reaction conditions, acidic styrol resin (D001) was considered as appropriate catalysis for Paal–Knorr reaction, and used to synthesize substituted pyrroles by reacting aniline (2.4 mmol) with 2,5-diketone (2.0 mmol) at room temperature or 60 $^{\circ}$ C under solventfree. Subsequently, a variety of amines were examined using this method (Scheme 1). The results are listed in Table 3.

Table 3 Resin (D001) catalyzed Paal-Knorr condensation between amines and 2,5-dione.

Entry	RNH ₂	Time/h	Yield (%) ^{a,b}	Ref.
1	NH ₂	1.0	3a (93)	3d
2		1.0	3b (89) ^c	8
3	NH ₂	2.0	3c (85)	8
4	H ₃ CO-NH ₂	0.5	3d (91) ^c	3d
5	Cl—NH ₂	0.5	3e (87) ^c	8
6	CINH2	2.5	3f (83)	8
7	NH ₂	1.0	3g (85) [°]	3d
8	NH ₂	2.0	3h (91)	3d, 7
9	NH ₂	1.5	3i (82)	9
10	H ₂ N ^{NH} 2	2.0	3j (76)	3d

^a Products were identified by IR, ¹H NMR, ¹³C NMR and HRMS.

^b Isolated yields.

^c Reaction temp. was at 60 °C.



Scheme 2. D = acidic styrol resin (D001).

It was found that 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 1–6, Table 3). The position of substitution group seldom had effect on reaction yields, however, it was necessary that reaction time was prolonged when *ortho-* and *meta*-substituted substrate was used for this reaction (entries 3, 6, Table 3), which may be caused by increase of steric hindrance around the amino group and effect of electron withdraw respectively. Moreover, naphthylamine and aliphatic amines also could afford the corresponding pyrroles under the same condition smoothly (entries 7–10, Table 3). Inspiringly, when ethylene diamine was used in the present reaction, the product [1,2-di (2,5-dimethyl-1-pyrrole)-ethane] was formed with two units of pyrrole ring (entries 10, Table 3).

Based on our experimental results and previous reports [4a-c], we propose the following possible mechanism (Scheme 2). In the present case, it is likely that acidic styrol resin (D001) provide hydrogen ion (H⁺) to activate carbonyl group to carry out nucleophilic addition reaction with amines.

In conclusion, it was very appropriate that macroporous strongly acidic styrol resin (D001) was employed as catalyst for the Paal–Knorr reaction. This method has a merit that the catalyst (D001) can be recycled. Various amines underwent the above 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. The process is operationally simple and good to excellent yields.

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- [9] 1-Octyl-2,5-dimethylpyrrole (3i): IR: 3035.2, 2983.5, 1593.6, 1466.5, 1340.2, 976.3, 810.3 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): & 5.76 (s, 2H, 2 × CH), 3.73 (t, 2H, J = 7.8, CH₂N), 2.19 (s, 6H, 2 × CH₃), 1.68–1.74 (m, 2H, CH₂), 1.33–1.45 (m, 12H, 6 × CH₂), 0.97 (t, 3H, J = 7.6, CH₃); 13 C NMR (CDCl₃, 75 MHz): δ 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 C₁₄H₂₇N: 209.3707, found: 209.3695.