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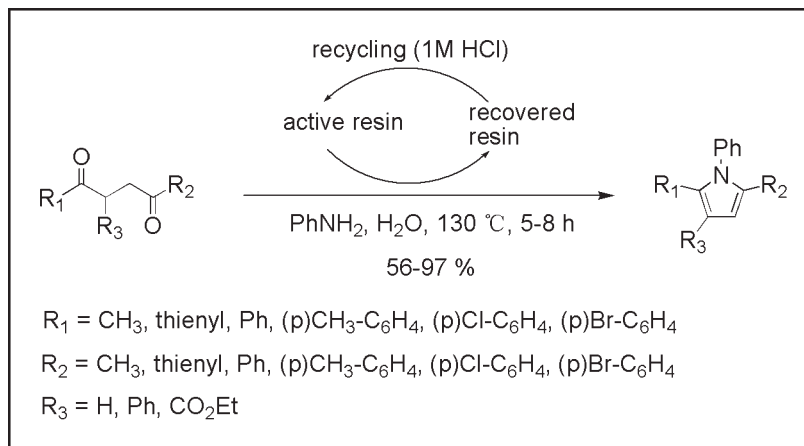
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Cationic exchange resin has been utilized for the first time as a novel and recyclable heterogeneous catalyst for the synthesis of *N*-substituted pyrroles from variety of 1,4-diketones and aniline. This simple synthesis has been accomplished with excellent yields. The recovered catalyst can be reused for subsequent runs with only a gradual decrease in activity.

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INTRODUCTION

Pyrrole rings have great importance in organic chemistry as they can be found in several natural products [1], organic materials [2], and bioactive molecules [3]. Especially, substituted pyrroles present antibacterial [4], antiviral [5], anti-inflammatory, and antioxidant activities [6]. One of the most important approaches to pyrrole synthesis is the Paal–Knorr reaction, which involves the reaction of 1,4-dicarbonyl compounds and their masked equivalents with primary amines. Generally, the most used conditions include *p*-TsOH in toluene or benzene [7], AcOH/methanol [8], TiCl₄ in toluene [5a], Ti(OPr)₄ in benzene [9], Bi(OTf)₃/[bmim]BF₄ [10], Bi(NO₃)₃ in CH₂Cl₂ [11]. However, some of these methods often suffer from certain drawbacks, such as hazardous organic solvents, metals, and high costs. As the increase environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that can avoid using harmful organic solvents and metals. Therefore, the development of green and facile methods for the synthesis of pyrroles is desirable. Besides, on the other hand, reactions in water have recently attracted significant attention because water is a cheap, safe, and non-toxic solvent [12]. In addition, if aqueous reactions can

be efficiently mediated by heterogeneous catalysts that can be recycled and reused, the result will be nearly ideal processes in terms of both greenness and simplicity [13]. Therefore, we wish to report a high-yielding and straightforward synthesis of *N*-substituted pyrroles using water as solvent and a cationic exchange resin as a recyclable heterogeneous catalyst.

RESULTS AND DISCUSSION

In our initial investigation, the condensation of aromatic 1,4-dione (**5a**) with two equivalents of aniline was carried out in 1 *M* HCl aqueous at reflux for 24 h. To our surprise, it gave furan **5d** in 100% yield instead of

Scheme 1. Condensation of **5a** with 2 equivalents of aniline under different reaction conditions.

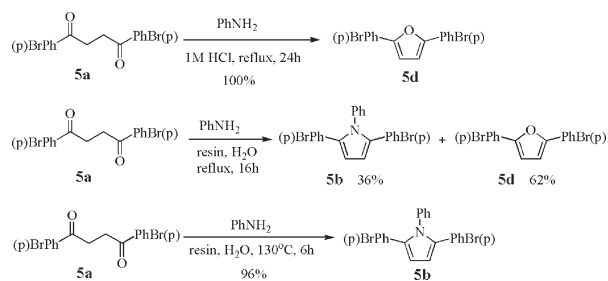
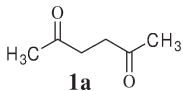
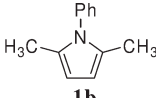
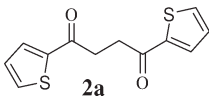
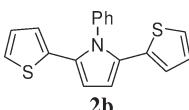
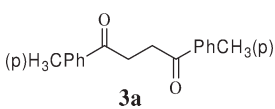
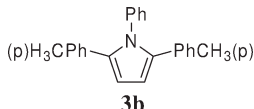
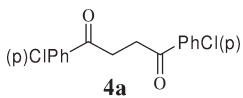
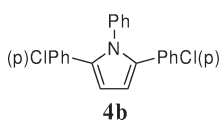
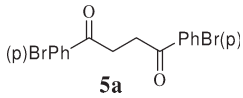
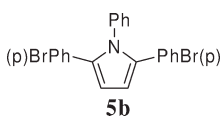
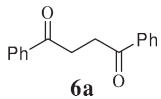
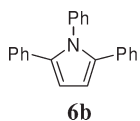
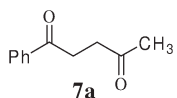
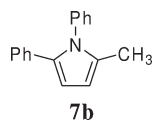
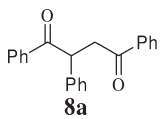
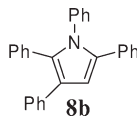
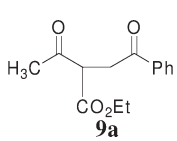
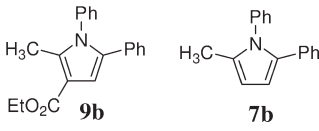


Table 1
Condensation of 1,4-diketones and aniline into pyrroles using cationic exchange resin in water.^a

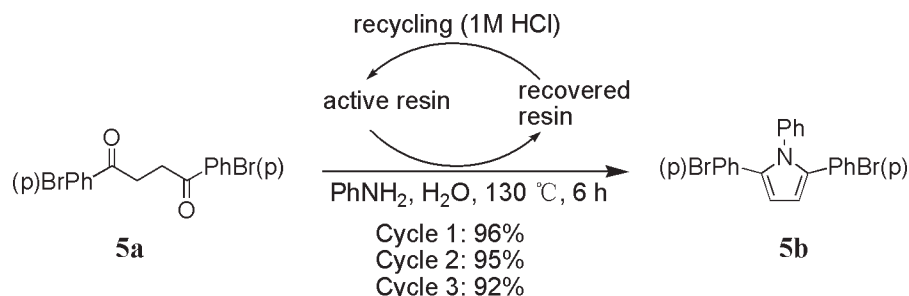
Entry	1,4-Diketone	Pyrrole	Time (h)	Yield (%) ^b	Ref.
1	 1a	 1b	5	85	[14]
2	 2a	 2b	8	95	[15]
3	 3a	 3b	6	96	[16]
4	 4a	 4b	6	95	[16]
5	 5a	 5b	6	96	[16]
6	 6a	 6b	6	94	[16]
7	 7a	 7b	5	87	[14]
8	 8a	 8b	6	97	[17]
9	 9a	 9b 7b	6	9b: 56, 7b: 34	[14,18]

^a For a typical experimental procedure see Ref. [19].

^b Refers to yield of isolated product after flash chromatography.

pyrrole **5b** (Scheme 1). Then, the reaction was performed in acidic Dowex 50 W $\times$ 8-200 (1.7 meq mL⁻¹) cationic exchange resin in water at reflux for 16 h, which provided pyrrole **5b** in 36% yield accompanied by furan **5d** in 62% yield. It suggested that the presence of cationic exchange resin can facilitate the pyrrole condensation,

while 1 M HCl aqueous only catalyzed the formation of furan. To improve the reaction rate and to observe the effect of temperature on the condensation, the reaction was carried out in a sealed tube at increased temperature. Higher temperatures than 140°C led to thermal decomposition of the resin. We therefore set the reaction at

Scheme 2. Recovery of the cationic exchange resin for recycling and use in subsequent Paal–Knorr pyrrole synthesis.

130°C; the starting material **5a** was consumed in 6 h. We pleasantly found that the reaction exclusively provided the *N*-substituted pyrrole **5b** in excellent yield of 96%. It seems that the higher temperature favors the formation of pyrrole in the presence of resin in water.

Encouraged by this new finding, we further investigated the reaction by using wide range of diketone compounds. The condensation of substituted 1,4-diketones and aniline proceeded smoothly and gave the corresponding pyrroles in good to excellent yields in water in the presence of cationic exchange resin (Table 1). The reactions were carried out in sealed tubes at 130°C. In this manner, the reactions can be run as a batch in sealed tubes within an oven without stirring. The reactions were complete in 5–8 h, and the two equivalents of amine were used to afford a valuable increase of the yields. To assess the generality of the method, variety of 1,4-dicarbonyl compounds including aromatic and aliphatic, di- and tri-substituted 1,4-dicarbonyl compounds were subjected to the condensation with aniline to give the corresponding pyrrole derivatives. When the 1,4-diphenyl-1,4-diones (**3–6a**, entries 3–6) were used, The excellent yields of 94–96% were obtained. Triphenyl 1,4-dione (**8a**, entry 8) gave the best yield of 97%. Nevertheless, methyl substituted 1,4-diones (**1a** and **7a**, entries 1 and 7) provided the products in slightly decreased yields (85 and 87%, respectively). Although 1,4-di(thienyl)butane-1,4-dione (**2a**, entry 2) required longer reaction time, the product was received in excellent yield of 95%. Interestingly, when ethyl 2-acetyl-4-oxo-4-phenylbutanoate (**9a**, entry 9) was submitted to the reaction conditions described earlier, the corresponding ester substituted pyrrole **9b** was obtained in 56% yield, accompanied by decarboxylated product pyrrole **7b** in 34% yield.

Finally, to verify that the solid catalyst could be recycled, the resin was recovered from the condensation between **5a** and aniline by filtration, reactivated it by treatment with a small amount of 1 M HCl [13] and used it in subsequent cyclizations. The reaction was performed three times using the same resin, and only a small decrease in the isolated yield of **5b** was observed. (Scheme 2).

CONCLUSION

In summary, a new catalytic protocol to synthesize pyrroles by Paal–Knorr condensation in water has been developed. Compared to previous reported methods, the present procedure avoids the use of metals and organic solvents, and instead employs cationic exchange resin as a cheap and readily available heterogeneous catalyst that is easily removed from the product mixture, which can be recycled and reused. This method has great potential for future application.

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- [18] Girolamo, C.; Gaetano D.; Anna, M. A.; Giuseppe, P.; Enrico A. *Heterocycles* 1986, 24, 3403.
- [19] Typical experimental procedure for the synthesis of *N*-substituted pyrroles. To a mixture of 1,4-diphenylbutane-1,4-dione (**6a**) (133 mg, 0.56 mmol) in H₂O (3 mL) was added cationic exchange resin (1.63 g, Dowex 50 W × 8-200) and aniline (0.12 mL, 1.12 mmol). The reaction mixture was heated at 130°C in a sealed tube for 6 h within an oven without stirring. After cooling to room temperature, the catalyst was filtered off and washed with diethyl ether. The filtrate was extracted with diethyl ether. The combined extracts were washed with water, brine, dried (Na₂SO₄), and filtered. The solvents were removed and purified by flash chromatography (petroleum ether/CH₂Cl₂ 2:1) to give compound **6b** (155 mg, 94% yield), identical to that previously reported [16].