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Sulfamic Acid as a Novel, Efficient, Cost-Effective, and Reusable Solid Acid Catalyst for the Synthesis of Pyrroles under Solvent-Free Conditions

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Abstract: Paal–Knorr condensation of 2,5-hexadione with primary amines in the presence of a catalytic amount of sulfamic acid under solvent-free conditions has been accomplished with an excellent yield. This is a very easy, rapid, and high-yielding reaction for the synthesis *N*-substituted pyrrole derivatives.

Keywords: Paal–Knorr reaction, pyrroles, solvent-free conditions, sulfamic acid

INTRODUCTION

Pyrroles are an important class of heterocyclic compounds with different biological activities.[1] Members of this family have wide applications in medicinal chemistry and are used as antimalarial, anti-inflammatory antiasthamatic, antibacterial, antihypertensive, and tyrosine kinase inhibiting agents.[2] In addition, pyrroles are found in many naturally occurring compounds such as heme, chlorophyll, and vitamin B_{12}.[3] Despite their importance from a pharmacological, industrial, and synthetic point of view, relatively few methods for their preparation have been reported.[4] Of the current methods such as Hantzsch,[5] Knorr,[6] and aza-Witting reactions,[7] the Paal–Knorr[8] reaction is one of the most simple and straightforward methods for the synthesis of *N*-substituted pyrroles. Many catalysts have

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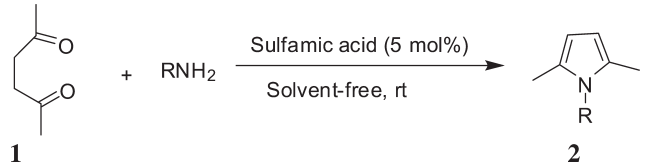
been used to promote the Paal–Knorr reaction such as $Ti(OiPr)_4$,[9] Al_2O_3,[10] $Bi(NO_3)_3$,[11] $Bi(OTf)_3$,[12] $Sc(OTf)_3$[13] montmorillonite-KSF,[14] and others.[15] No reaction is observed in the absence of catalyst. However, many of these methods have some drawbacks such as low yields of the products,[11] long reaction times,[11] harsh reactions conditions,[10] tedious workup leading to the generation of large amounts of toxic-metal-containing waste,[9] the requirement for an inert atmosphere or high temperatures,[12] and the use of stoichiometric[11] or relatively expensive reagents.[9,13] This reaction is usually carried in polar and toxic solvents such as DMSO and DMF. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the workup procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst for the synthesis of pyrroles in terms of operational simplicity, reusability, economic viability, and greater selectivity.

RESULTS AND DISCUSSION

Recently, there has been considerable interest in the use of solid acids as heterogeneous catalysts in organic synthesis.[16] Heterogeneous solid acids are more advantageous than conventional homogeneous acid catalysts because they can be easily recovered from the reaction mixture by simple filtration and reused. Sulfamic acid (H_2NSO_3H) is a common inorganic acid with mild acidity that is nonvolatile, noncorrosive, and utilized as a stable, low-cost, highly efficient green catalyst in organic synthesis.[17] It is insoluble in common organic solvents and is a commercially available, cheap reagent. In recent years, sulfamic acid has been used in many organic reactions as an efficient heterogeneous catalyst.[17] However, there are no reports of the use of sulfamic acid as a catalyst for the synthesis of pyrroles.

In continuation of our work to develop new synthetic methodologies,[18] we report herein a facile method for the synthesis of pyrroles by the condensation of 1,4-diketones with primary amines in the presence of a catalytic amount of sulfamic acid under solvent-free conditions. Accordingly, treatment of 1,4-diketone with aniline in the presence of a catalytic amount of sulfamic acid afforded 2,5-dimethyl-*N*-phenylpyrrole in 92% yield (Scheme 1). In the same manner, a variety of a amines were coupled with a 1,4-diketone in the



1 **2**

Scheme 1.

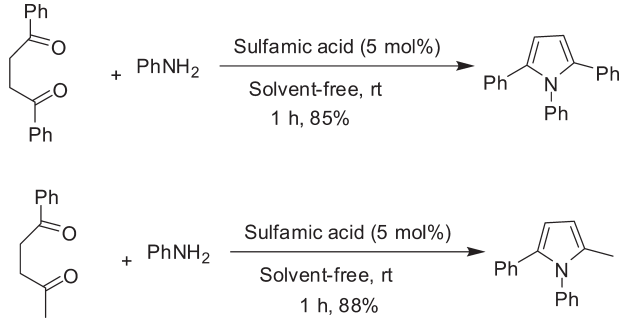
Table 1. Synthesis of pyrroles using sulfamic acid as a catalyst

Entry	Amine	Product	Time (min)	Yield[a] (%)
1	$C_6H_5NH_2$	**2a**	30	92
2	4-$NO_2C_6H_4NH_2$	**2b**	60	81
3	Furfurylamine	**2c**	35	89
4	4-$CH_3OC_6H_4NH_2$	**2d**	25	93
5	Benzyl amine	**2e**	40	87
6	*n*-Butyl amine	**2f**	75	82
7	2-Aminopyridine	**2g**	60	82
8	4-$ClC_6H_4NH_2$	**2h**	40	91
9	1-Aminonaphthalene	**2i**	90	85
10	1-Aminoanthracene	**2j**	90	88

[a]Yields refer to pure products and were characterized by comparison of their mp, IR, and ^{1}H NMR spectra with those of authentic samples.[9–14]

presence of a catalytic amount of sulfamic acid at room temperature to give the corresponding pyrroles in good to excellent yields (Table 1). We also observed that the reaction in DCM, methanol, or THF takes longer times than in the neat conditions. This acceleration is probably attributable to the concentration effect.

To extend the scope of this reaction, other substituted diketones such as 1,4-diphenylbutane-1,4-dione and 1-phenylpentane-1,4-dione were used. Clean formation of pyrroles was observed under solvent-free conditions (Scheme 2). This method does not require any other additives to promote the reaction. The reaction is fairly general, clean, and efficient. The experimental procedure is very simple. The high-yield transformation did not lead to any significant amounts of undesirable side products. Unlike previously reported methods, the present method does not require high temperatures to produce pyrrole



Scheme 2.

derivatives. The results shown in Table 1 clearly indicate the scope and generality of the reactions with respect to various aromatic, aliphatic, and heterocyclic primary amines.

EXPERIMENTAL

NMR spectra were recorded on a Bruker ARX 300 (330-MHz) instrument. Low-resolution mass spectra (EI, CI) were recorded on a Finnigan 4000 mass spectrometer. High-resolution mass spectra were recorded (HRMS, ESI) were recorded on Finnigan Mat XL 95 mass spectrometer. Melting points were recorded on Buchi R-535 apparatus and are uncorrected. All solvents and reagents were purchased from Aldrich with high quality and were used without any further purification. All yields refer to isolated products.

Typical Procedure

A mixture of hexane-2,5-dione (684 mg, 6 mmol), aniline (465 mg, 5 mmol), and sulfamic acid (25 mg, 5 mol%) was stirred at room temperature under solvent-free conditions for 30 min. After completion of the reaction, as indicated by thin-layer chromatography (TLC), the reaction mixture was diluted with diethyl ether and filtered to recover the catalyst. The ether layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (20% ethyl acetate in hexane) to afford the pure product (786 mg) in 92% yield. The recovered catalyst was washed with diethyl ether and activated at 70°C prior to reuse. The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich), which could be reused for the next reaction without losing any significant activity. The catalyst was recovered and reused three times (reaction yields: 82%, 76%, and 62%). All compounds are known and were identified by comparison with those of the authentic samples.[9–15]

Product Characterization Data

2,5-Dimethyl-1-pheny-1*H*-pyrrole (**2a**, entry 1): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 6H), 5.94 (s, 2H), 7.20–7.28 (m, 2H), 7.42–7.54 (m, 3H). HRMS calcd. for $C_{12}H_{13}N$ 171.1048; found 171.1049. Anal. calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.19; H, 7.71; N, 8.21.

1-(4-Methoxyphenyl)-2,5-dimethyl-1-H-pyrrole (**2d**, entry 4): Mp 60–61°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 6H), 3.88 (s, 3H), 5.89 (s, 2H), 6.92 (m, 2H), 7.16 (m, 2H). HRMS calcd. for $C_{13}H_{15}NO$ 201.1154; found 201.1156. Anal. calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.15; N, 6.95. Found: C, 77.52; H, 7.18; N, 6.99.

1-Benzyl-2,5-dimethyl-1*H*-pyrrole (**2e**, entry 5): Mp 43–45°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 6H), 5.04 (s, 2H), 5.89 (s, 2H), 6.90–6.95 (m, 2H), 7.20–7.41 (m, 3H). HRMS calcd. for $C_{13}H_{15}N$ 185.1205; found 185.1204. Anal. calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.32; H, 8.21; N, 7.61.

1-Butyl-2,5-dimethyl-1*H*-pyrrole (**2f**, entry 6): Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, $J = 7.2$ Hz, 3H), 1.38 (m, 2H), 1.61 (m, 2H), 2.17 (s, 6H), 3.71 (t, $J = 7.2$ Hz, 2H), 5.79 (s, 2H). HRMS calcd. for $C_{10}H_{17}N$ 151.1361; found 151.1360. Anal. calcd. for $C_{10}H_{17}N$: C, 76.41; H, 11.33; N, 9.26. Found: C, 76.43; H, 11.38; N, 9.30.

2-(2,5-Dimethyl-1*H*-pyrrol-1yl)-pyridine (**2g**, entry 7): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 6H), 5.92 (s, 2H), 7.27 (m, 2H), 7.81 (m, 1H), 8.61 (m, 1H). HRMS calcd. for $C_{11}H_{12}N_2$ 172.1000; found 172.10002. Anal. calcd. for $C_{11}H_{12}N$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.76; H, 7.05; N, 16.30.

2,5-Dimethy-1-(naphthalene-1-yl)-1*H*-pyrrole (**2i**, entry 9): Mp 120–121°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 6H), 6.01 (s, 2H), 7.15 (d, $J = 8.2$ Hz, 1H), 7.36–7.59 (m, 4H), 7.94 (d, $J = 8.2$ Hz, 2H). HRMS calcd. for $C_{16}H_{15}N$ 221.1204; found 221.1206. Anal. calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.88; H, 6.85; N, 6.31.

1-(Anthracen-1-yl)-2,5-dimethyl-1*H*-pyrrole (**2j**, entry 10): Mp 183–184°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (s, 6H), 6.04 (s, 2H), 7.35–7.59 (m, 4H), 7.71 (s, 1H), 7.92 (d, $J = 8$ Hz, 1H), 8.02 (d, $J = 7.9$ Hz, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 8.52 (s, 1H). HRMS calcd. for $C_{20}H_{17}N$ 271.1361; found 271.1362. Anal. calcd. for $C_{20}H_{17}N$: C, 88.52; H, 6.31; N, 5.16. Found: C, 88.58; H, 6.37; N, 5.20.

2-Methyl-1,5-dipheny-1*H*-pyrrole (Scheme 2): ^{1}H NMR (300-MHz, $CDCl_3$) δ 2.15 (s, 3H), 6.09 (d, $J = 3.6$ Hz, 1H), 6.32 (d, $J = 3.5$ Hz, 1H), 7.02–7.40 (m, 10 H). HRMS calcd. for $C_{17}H_{15}N$ 233.1204; found 233.1206. Anal. calcd. for $C_{17}H_{17}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.58; H, 6.54; N, 6.04.

CONCLUSION

In conclusion, we have demonstrated a mild and efficient procedure for the synthesis of pyrrole derivatives using a catalytic amount of sulfamic acid. The significant features of this method include (a) operational simplicity, (b) the use of an inexpensive and reusable catalyst, (c) high yields, and (d) short reaction times. In addition, unlike many other methods, no extra energy source such as microwave irradiation or ultrasound is needed for the success of the reaction. This procedure has a great potential for future application.

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