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Sulfamic Acid as Efficient and Reusable Catalytic System for the Synthesis of pyrrole, Furan, and Thiophene Derivatives

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ABSTRACT: *Sulfamic acid has been utilized for the first time as an efficient and reusable catalytic system for the synthesis of heteroaromatics such as pyrrole, furan, and thiophene derivatives from 1,4-diketones. This new procedure offers significant improvements in the reaction rates and yields in a shorter reaction time and a lower reaction temperature contrasted with the reported results. The recovered catalyst can be reused for subsequent runs with only a gradual decrease in activity. The most important feature is that the reaction process is homogeneous whereas the separation process is heterogeneous, which is often seen in other catalysts, and so it is a good character for technical application.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:144–148, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20389

INTRODUCTION

Heterocycles such as furan, pyrrole, and thiophene are versatile pharmacophores possessing a variety of biological activities [1]. In particular, pyrroles are found in many naturally occurring compounds such as heme, chlorophyll, and vitamin B_{12} [2]. Therefore, many synthetic methods for the preparation of pyrrole derivatives have been reported in the literature [3]. Among them, the Paal–Knorr reaction remains one of the most attractive methods for the synthesis of pyrroles [4]. The furan moiety is a core structure of many alkaloids such as kallolides and cembranolides [5]. The thiophene moiety also exists in many biologically active compounds [6]. Thus, syntheses of these heterocycles are of great importance. Generally, pyrrole, furan, and thiophene derivatives are prepared from 1,4-dicarbonyl compounds using acidic catalysts, such as zeolite [7], Ti $(OPri)_4$ [8], Al_2O_3 [9], *p*-TSA [10], layered zirconium phosphate and zirconium sulfophenyl phosphonate [11], as well as the microwave technology [12]. However, some of them often involve the use of excess amounts of acids, or hazard organic solvents, tedious workup, and large amounts of solid catalysts. Hence, an efficient and mild Paal–Knorr condensation is needed for contemporary chemical synthesis.

Sulfamic acid (NH_2SO_3H; SA) is a dry, nonvolatile, nonhygroscopic, odorless, and white crystalline solid with an outstanding physical property and stability [13]. It is commercially available and is a very cheap chemical. Recently, it was shown that SA has the prospect to be used as a substitute for conventional acidic catalytic materials because

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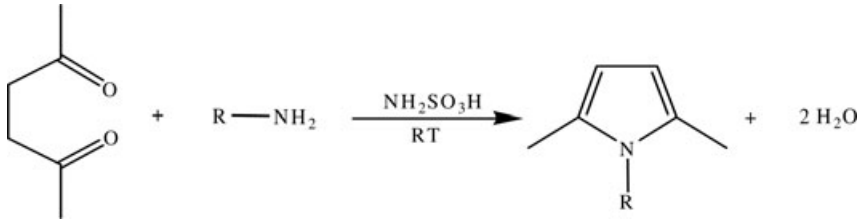


SCHEME 1 Paal–Knorr condensation for pyrrole derivatives' synthesis.

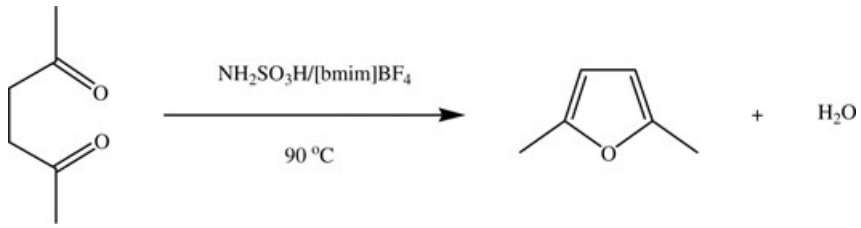
of its ease of setup, mild conditions, rapid reaction, selectivity, increased yields [14], high purity of products and low cost, compared with their homogeneous counterparts [15]. It has been used as an efficient heterogeneous acid catalyst for ketal formation or acetalization [16], deprotection of acetals [17], tetrahydropyranylation of hydroxy compounds [18], esterification of cyclic olefins with aliphatic acids under solvent-free conditions [19], the Beckmann rearrangement of ketoxime [20] in dried CH_3CN, and transesterification of β-ketoesters in ionic liquid [21].

In this paper, we report a mild and efficient method for the synthesis of pyrrole, furan, and thiophene derivatives from 1,4-diketones, using sulfamic acid as a catalyst (Schemes 1–3).

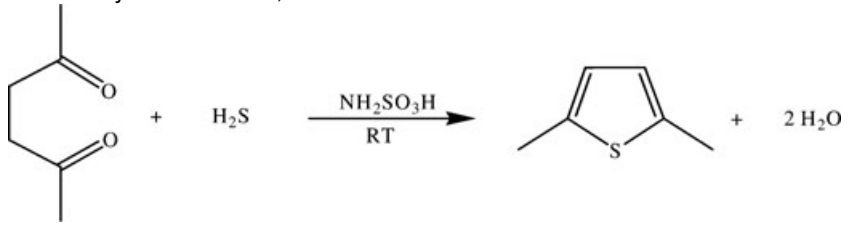
RESULTS AND DISCUSSION

To show the merits of the present work in comparison with recently reported protocols, we compared the results of the condensation of aniline and 2,5-hexanedione in the presence of montmorillonite KSF [22], zirconium phosphate [11], organoaluminum [23], bismuth nitrate [24], bis(triethylammonium) salt [25], microwave [26], Fe^{3+}-montmorillonite [27], and ionic liquids [28] with respect to the amounts of the products (Table 1). The results showed that sulfamic acid promoted the reactions more effectively than montmorillonite KSF, zirconium phosphate, organoaluminum, bismuth nitrate, and bis(triethylammonium) salt as far the amount of catalyst and reaction time were concerned. We can see that sulfamic acid was a good catalyst for pyrrole, furan, and thiophene derivatives synthesis (Tables 3 and 4).

With the best catalyst in hand, we studied the effect of other factors on this reaction. In conventional systems, an excess of amines or other substrates usually had to be used to promote the condensation [11]. From atom-economical standpoint, using nearly equimolar amounts of substrates was strongly required. Thus, we had initially treated aniline with equimolar 2,5-hexandione catalyzed by sulfamic acid in organic solvents or solventless to compare their efficiency and the results are presented in Table 2. It was found that another green solvent,



SCHEME 2 Furan derivatives synthesis from 1,4-diketones.



SCHEME 3 Thiophene derivatives synthesis from 1,4-diketones.

TABLE 1 Comparison of the Effect of Catalysts for the Condensation of 2,5-Hexandione and Aniline[a]

Entry	*Catalyst*	*Time (h)*	*Yield (%)[b]*	*Reference*
1	Monmorillonite KSF	10	96	[22]
2	Zirconium phosphate	24	56	[11]
3	Organoaluminum	12	64	[23]
4	Bismuth nitrate	10	96	[24]
5	Bis(triethylammonium) salt	4	95	[25]
6	Microwave	30 s	92	[26]
7	Fe^{3+}-Montmorillonite	3	96	[27]
8	Ionic liquids	3	96	[28]
9	Sulfamic acid	1	99	–

[a]Reaction conditions: 2,5-hexandione (1 mmol), aniline (1 mmol), sulfamic acid (10 mol%); reaction temperature: room temperature (approximately 18. °C).
[b]GC yield.

water, has also been used as reaction medium for this procedure, because of the poor solubility of substrates in water, the yield was somewhat lower than that in solventless; however, it was an exceedingly green process in organic synthesis. In addition, in the process of synthesis of furan, the best solvent was 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4). Another factor was the temperature, and the results are presented in Fig. 1. When the reaction temperature was raised, good yield was obtained soon, when the reaction reacted 1 h at 20°C, the yield was 98%. The reaction was ultimately carried out at 20°C, which met the principles of green chemistry. However, synthesis of furan derivatives needed high temperatures, which was 90°C. Thiophene derivatives' synthesis needed longer reaction times (6 h) to give good yields because the reaction was carried out in aqueous and acetonitrile (volume ratio = 1:2) mixed solutions.

To define the optimized reaction conditions, various substituted amines or 1,4-diketones underwent smooth cyclization to give the corresponding pyrrole, furan, and thiophene derivatives (Tables 3 and 4). It is well known that the reactivity of aliphatic amines was more effective when compared with

TABLE 2 Effect of Solvents on the Reaction[a]

Entry	*Solvent*	*Time (h)*	*Yield (%)[b]*
1	CH_2Cl_2	10	98
2	CH_3CN	12	82
3	H_2O	10	63
4	CH_3CH_2OH	12	85
5	CH_3OH	12	81
6	No	1	98

[a]Reaction conditions: 2,5-hexandione (1 mmol), aniline (1 mmol), sulfamic acid (10 mol%); reaction temperature: room temperature (approximately 18°C).
[b]GC yield.

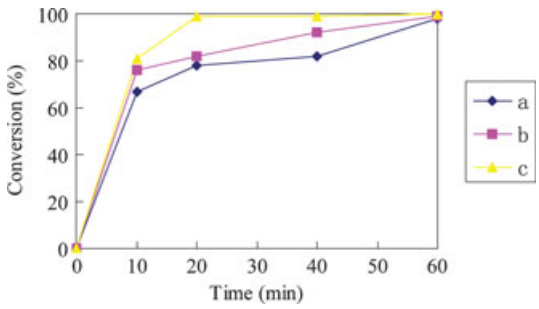


FIGURE 1 The effect of reaction temperature and time on the reaction GC yield Reaction conditions: 2,5- hexanedione (1 mmol), aniline (1 mmol), sulfamic acid (10 mol%); reaction temperature: a: 20°C; b: 40°C; c: 60°C.

that of aromatic amines, thus aliphatic amines gave higher yields and needed shorter reaction time. It was exciting that labile functionality, such as methoxy and nitro groups, was toleratable under this reaction condition. In addition, we tested diamines for the synthesis of pyrrole derivatives also with good yields, which was rarely studied (Table 3, entries 14, 15).

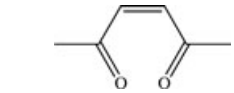
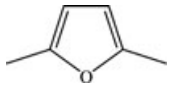
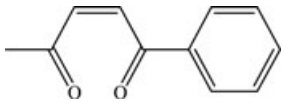
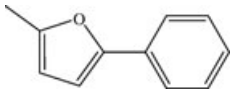
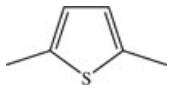
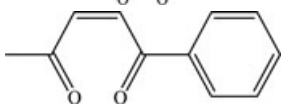
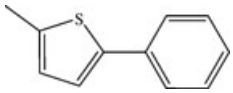
Subsequently, to show the high selectivity of the method, we studied the competitive reaction for the condensation of diamines in the presence of ketones using sulfamic acid as a catalyst at room temperature. Using this catalytic system, the highly selective conversion of diamines in the presence of 1,4-diketones was observed. Then, we studied the

TABLE 3 Yields for Pyrroles Derivatives Synthesis[a]

Entry	*R*	*Time (min)*	*Yield (%)[b]*
1	*n*-Ethyl	30	99
2	*n*-Propyl	30	99
3	*n*-Heptyl	30	98
4	*i*-Propyl	30	97
5	*n*-Butyl	30	99
6	Cyclohexyl	60	96
7	Benzyl	60	98
8	Phenyl	60	98, 95[c], 88[d]
9	4-Nitrophenyl	60	92
10	4-Methoxyphenyl	60	95, 63[d]
11	4-Ethoxyphenyl	60	96
12	4-Methylphenyl	60	98
13	2,6-Dimethylphenyl	120	93
14	1,6-Hexanediamine	90	91[f]
15	1,2-Ethylenediamine	90	92[g]
16	2-Pyridinyl	120	91

[a]Reaction conditions: 2,5-hexandione (1 mmol), amines (1 mmol), sulfamic acid (10 mol%), reaction temperature: room temperature (approximately 18°C).
[b]GC yield.
[c]Yield after catalyst reused five times.
[d]Isolated yield.
[e] Yield of the condensation of 4-methoxyaniline versus 4-nitroaniline and 2,5-hexandione in the presence of sulfamic acid.
[f] Monoadducted product.

TABLE 4 Yields of Kinds of Substances for Furan and Thiophene Derivatives Synthesis[a]

Entry	*1, 4-Diketone*	*Products*	*Time (h)*	*Yield (%)*[b]
1			4	89
2			6	91
3			6	89
4			10	87

[a]Reaction conditions: 1, 4-diketones (1 mmol), sulfamic acid (10 mol%); reaction temperature: 90°C for furan derivatives synthesis, room temperature (approximately 18°C) for thiophene derivatives synthesis.
[b]GC yield.

condensation of 4-methoxyaniline versus 4-nitroaniline and 1,4-diketones in the presence of sulfamic acid. These reactions also proceeded with high selectivity and showed the importance of electronic effects upon these reactions. From these results, we can observe that the condensation of amines in the presence of 1,4-diketones using sulfamic acid as a catalyst progresses with good selectivity and adaptability.

Finally, the recycling process was investigated starting with fresh sulfamic acid and aniline. After the reaction was completed (monitored by GC), sulfamic acid was recycled and reused in the next cycle with the same substrates. To our delight, sulfamic acid could be reused five times without the loss of the activity (Fig. 2).

CONCLUSION

In summary, we described a novel and efficient method for the synthesis of pyrrole, furan, and thiophene derivatives from 1,4-diketones using sulfamic acid as a novel and recyclable catalytic system. Compared with the classical methods, the reactions exhibited simple isolation, good yields, high selectivity, mild conditions, and nontoxic catalyst. Recovery and reuse of sulfamic acid were also satisfactory.

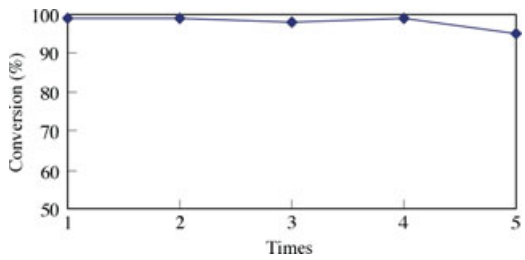


FIGURE 2 The recycle of catalyst. Reaction conditions: 2,5- hexanedione (1 mmol), aniline (1 mmol), sulfamic acid (10 mol%); reaction temperature: room temperature (approximately 18°C).

EXPERIMENTAL

General Procedure for the Synthesis of Substituted Pyrroles

A representative procedure as follows: To 2,5-hexandione (1 mmol) and amines (1 mmol) in a 10-mL round-bottom flask equipped with a magnetic stirrer, 10 mol% sulfamic acid was added. Then, the mixture was stirred at room temperature for 1 h. After the reaction, the content was extracted with diethyl ether (2 × 10 mL). The combined organic extractant was analyzed through GC/MS.

General Procedure for the Synthesis of Substituted Furan Derivatives

A representative procedure as follows: After putting 2,5-hexandione (1 mmol), sulfamic acid (10 mol%), and [bmim]BF_4 (1 mL) in a 10-mL round bottom flask equipped with a magnetic stirrer, the flask was heated at 90°C for the appropriate time. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with diethyl ether (5 × 10 mL). The combined organic layers were dried, and then concentrated in vacuum. The products were analyzed through GC/MS.

General Procedure for the Synthesis of Substituted Thiophene Derivatives

A representative procedure as follows: 2,5-hexandione (1 mmol), H_2S (30% aqueous solution,

1 mL), acetonitrile (2 mL), and sulfamic acid (10 mol%) in a 10-mL round bottom flask equipped with a magnetic stirrer were stirred at room temperature for 6 h. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (5 × 10 mL). The combined organic layers were dried, and then concentrated in vacuum. The products were analyzed through GC/MS.

ANALYTICAL DATA FOR SELECTED COMPOUNDS

1-Butyl-2,5-dimethyl-1H-pyrrole: Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 0.95 (t, $J = 7$ Hz, CH_3, 3H), 1.36 (m, CH_2, 2H), 1.58 (m, CH_2, 2H), 2.19 (s, CH_3, 6H), 3.69 (t, $J = 8.3$ Hz, CH_2, 2H), 5.78 (s, pyrrolics, 2H); GC/MS (*m*/*z*): M^+ 151, 136, 122, 108, 94; Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.38; H, 11.37; N, 9.25.

1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole: Yellow solid, mp 57–59°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 2.04 (CH_3, s, 6H), 3.88 (OCH_3, s, 3H), 5.90 (pyrrolics, s, 2H), 6.94 (PhH, d, 2H, $J = 8.89$ Hz), 7.15 (d, PhH, 2H, $J = 8.90$ Hz); GC/MS (*m*/*z*): M^+ 201, 186, 171, 159, 145, 129. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.56; H, 7.55; N, 6.94.

1-Phenyl-2,5-dimethyl-1H-pyrrole: White solid, mp 50–51°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 2.05 (CH_3, s, 6H), 5.93 (pyrrolics, s, 2H), 7.22–7.25 (PhH, m, 2H), 7.43–7.50 (PhH, m, 3H); Anal. Calcd for $C_{12}H_{13}N$: C, 84.16; H, 7.65; N, 8.18. Found: C, 79.91; H, 7.50; N, 8.02.

2,5-Dimethylfuran: Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 2.23 (CH_3, s, 6H), 5.81 (furan, s, 2H); GC/MS (*m*/*z*): M^+ 96, 81, 53, 43. Anal. Calcd for C_6H_8O: C, 75.00; H, 8.33; O, 16.67. Found: C, 74.96; H, 8.35; O, 16.70.

2,5-Dimethylthiophene: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 2.32 (CH_3, s, 6H), 6.43 (thiophene, s, 2H); GC/MS (*m*/*z*): M^+ 112, 111, 97, 77, 59, 45, 39, 27. Anal. Calcd for C_6H_8S: C, 64.29; H, 7.14; S, 28.57. Found: C, 64.32; H, 7.12; S, 28.58.

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