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Silica sulfuric acid (SSA) as a solid acid heterogeneous catalyst for one-pot synthesis of substituted pyrroles under solvent-free conditions at room temperature

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ABSTRACT

A variety of N-substituted pyrroles have been synthesized by reacting γ-diketones with amines, diamines or triamine in the presence of silica sulfuric acid (SSA) at room temperature under solvent-free conditions. The experiment protocol features simple operations, and the products are isolated in high to excellent yields (70–98%).

1. Introduction

During the recent years, the use of reusable heterogeneous catalysts has received considerable importance in organic synthesis because of their environmental, economical, and industrial aspects.[1] The development of efficient methods using recoverable and reusable catalysts is an important goal in organic synthesis. Up to now, several reusable and heterogeneous catalysts have been designed and used. One useful example of reusable heterogeneous catalysts is silica sulfuric acid (SSA), which has been widely studied in few recent years.[3] SSA is easily prepared from the treatment of silica gel with chlorosulfonic acid at room temperature.[2] It must be noted that the preparation method is simple, clean, and without work-up procedure, because HCl gas is evolved from the reaction vessel immediately.

Heterocyclic small molecules play an important role in the search for new therapeutic and drug candidates. Pyrroles are an important class of heterocyclic compounds and are structural units found in a vast array of natural products, synthetic materials, and bioactive molecules, such as heme, vitamin B12, and cytochromes.[4] Classical methods for their preparation include the Knorr,[5] Hantzsch,[6] and Paal–Knorr condensation reactions.[7–23] One of the most common approaches to pyrroles synthesis is the Paal–Knorr reaction in which 1,4-dicarbonyl compounds are converted to pyrroles in the presence of primary amines. In this reaction, the 1,4-dicarbonyl compounds provide the four carbons of the pyrroles with the possible substitutes, whereas the amine provides the nitrogen with its substituent. Many catalysts have been used for this conversion such as montmorillonite, KSF,[8] microwave irradiation,[9,10] $Bi(NO_3)_3{\cdot}5H_2O$,[11] $Sc(OTf)_3$,[12] $TolSO_3H$,[13] layered zirconium phosphate and zirconium sulfophenyl phosphonate,[14] titanium[15] or $TiCl_4/Et_3N$.[16] Some of other methods for synthesis of pyrroles include: conjugate addition reactions,[17] annulation reactions,[18,19] multi-component reactions,[20,21] and aza-Wittig reactions.[22] However, several of these methods require prolonged reaction times, use of volatile organic solvents and toxic metals.[6–10] Thus, a milder, selective, non-hazardous, inexpensive, recyclable, and eco-friendly organic catalyst is still in demand.

In continuation of our interest in synthesis of organic compounds,[23–26] we wish to report a simple, practical and efficient method for the synthesis of pyrroles from γ-diketones and primary amines catalyzed by SSA at room temperature under solvent-free conditions (Scheme 1).

Initially, we decided to explore the role of SSA for the synthesis of 2,5-dimethyl-*N*-benzylpyrrole as a model compound (Scheme 2) at room temperature using various solvents such as CH_2Cl_2, $CHCl_3$, CCl_4, CH_3CN, and EtOH (Table 1, entries 1–5). The results show that CH_3CN is a better solvent (yield 90%) than other solvents tested.

In recent years, there has been an increasing interest in reactions that proceed in the absence of solvents due to the reduced pollution, low cost, simplicity in process and handling. Therefore, we decided to test this reaction in solvent-free condition and in the presence of various catalyst ratios. We found that the reaction

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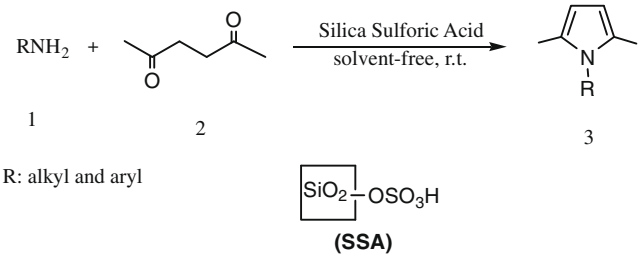


Scheme 1. Synthesis of pyrroles from γ-diketones and primary amines catalyzed by SSA room temperature under solvent-free conditions.

Table 1
The condensation reaction of acetonylacetone with benzylamine under various reaction conditions at room temperature

Entry	Solvent	Time (min)	Yield[a] (%)
1	CH_2Cl_2	15	85
2	$CHCl_3$	15	80
3	CCl_4	20	85
4	CH_3CN	15	90
5	EtOH	10	90
6	Solvent-free/(0.05 g)/grinding	10	95
7	Solvent-free/(0.10 g)/grinding	5	95
8	Solvent-free/(0.15 g)/grinding	3	98
9	Solvent-free/(0.20 g)/grinding	3	98

[a] Isolated yield.

was rapid and gave excellent yields of the products when catalyzed by SSA (3 min., 98%, entry 8).

These results promoted us to investigate the scope and generality of this new protocol for various amines (aliphatic and aromatic) under optimized conditions. In the same manner, a variety of amines were coupled with hexan-2,5-dione in the presence of a catalytic amount of SSA at room temperature in order to give the corresponding pyrroles in good to excellent yields (Table 2). The less basic aromatic amines require only slightly more time than the more basic amino compounds, and both lead to high yields of the pyrrole products.

As shown in Table 2, aromatic amines with electron-donating groups (Table 2, entries 6, 7, 10) or electron-withdrawing group (Table 2, entries 8, 9) are both effective in the Paal–Knorr reaction. The heterocyclic amines (Table 2, entry 15, 16) exhibited the same behavior of aromatic and aliphatic amines.

The reaction conditions were also applicable to di- or tri-amino substrates, in giving bipyrrole (Table 2, entries 4, 10–12, 14, 18, 19) or tripyrrole compounds (Table 2, entry 20) in excellent yields.

Finally, we examined the condensation reactions of γ-diketones with *p*-toluenesulfonylhydrazide in the presence of SSA as catalyst under solvent-free conditions (Scheme 3). *N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-4-methylbenzenesulfonamide (**3a**) were obtained with good yields (85%) when the reaction was performed at 70 °C in the presence of SSA. It is found that this condensation reaction gave **3a** in moderate yield (50%) under solvent-free conditions due to the solubility of *p*-toluenesulfonylhydrazide in γ-diketones and the yields showed significant improvement with increasing of temperature. In another case, we changed γ-diketones and the *N*-(2,5-diphenyl-1*H*-pyrrol-1-yl)-4-methylbenzenesulfonamide (**3b**) were obtained with decrease of yield (65%), which is most probably due to the electron-donating and steric effects of the phenyl groups.

The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications. Therefore, we investigated the recovery and reusability of SSA catalyst. The catalyst can be easily separated by simple filtration and re-used after washing with $CHCl_3$ and drying at 60 °C. The reusability of the catalyst was checked in the synthesis of 2,5-dimethyl-*N*-benzylpyrrole by the reaction of benzyl amine with 2,4-hexadione in the presence of SSA. As can be seen, the catalyst could be used at least five successive times without any decrease in its activity (Table 3).

A plausible mechanism is shown in Scheme 4. The carbonyl groups are first activated by the catalyst to attach amine. Cyclization and dehydration of intermediate gives the final product and releases of the catalyst for the next catalytic cycle.

In order to compare the current protocol with previously published methods for the synthesis of N-substituted pyrroles with benzyl and 2-pyridinylamine, we carried out the following studies (Table 4). These results, clearly demonstrate that SSA is a good catalyst for the preparation of *N*-alkyl and *N*-aryl-2,5-dimethylpyrroles.

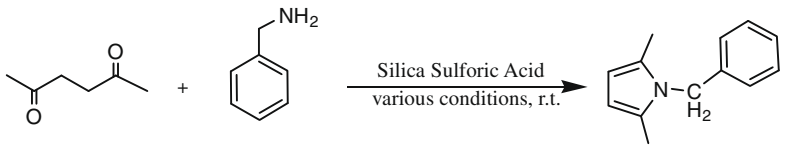
In summary, we have developed a facile and efficient method for the synthesis of N-substituted pyrroles using SSA. The advantages of the method include (i) absence of a solvent, (ii) short reaction times, (iii) high yields, (iv) easy work-up, and (v) use of little amounts of a catalyst that could be recovered and re-used.

2. Experimental section

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purifications unless otherwise stated. ^{1}H NMR spectra were recorded on a Jeol 90 MHz FT NMR spectrometer using TMS as internal standard and chemical shift are in δ (ppm). Infrared (IR) was conducted on a Perkin Elmer GX FT-IR spectrometer. All yields refer to isolated products.

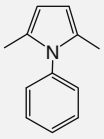
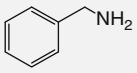
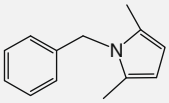
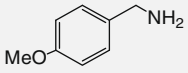
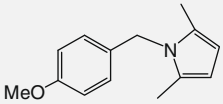
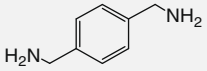
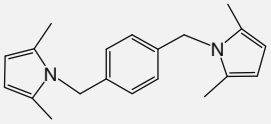
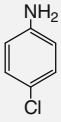
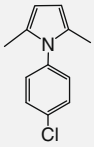
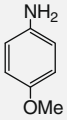
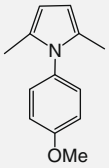
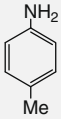
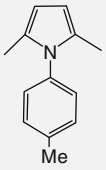
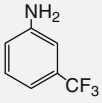
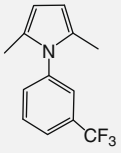
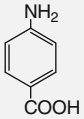
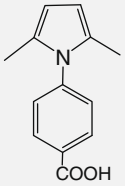
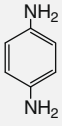
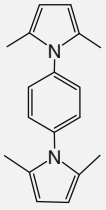
2.1. General procedure for the synthesis of pyrroles in the presence of SSA as a catalyst

To a solution of amine **1** (1 mmol) and 2,5-hexanedione **2** (1 mmol) at room temperature, catalyst (SSA) (0.15 g) was added. The mixture was allowed to stirring at this temperature for a period time specified in Table 2. The reaction was monitored by TLC (3:1 *n*-hexane/acetone). After completion of the reaction, 10 mL ethanol was added, and the catalyst was removed by filtration. Evaporation of the solvent under reduced pressure gave the products. Further purification was achieved by thin layer chromatography using *n*-hexane/acetone (70:30) as the solvent system to afford the pyrroles. The spectral and analytical data of some representative compounds are given below.



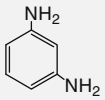
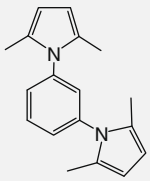
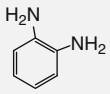
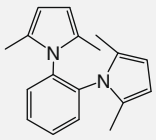
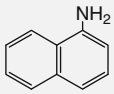
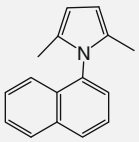
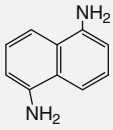
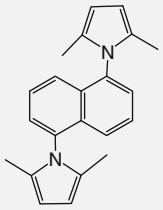
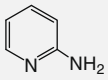
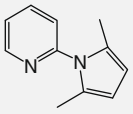
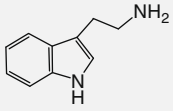
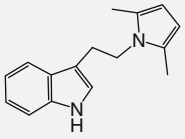
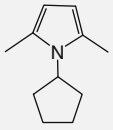
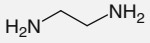
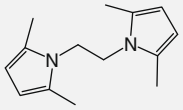
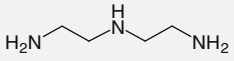
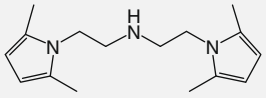
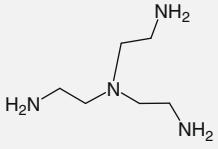
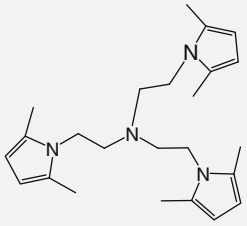
Scheme 2. The effect of SSA in the synthesis of 2,5-dimethyl-*N*-benzylpyrrole as a model compound.

Table 2
SSA-catalyzed synthesis of pyrroles under solvent-free conditions[a]

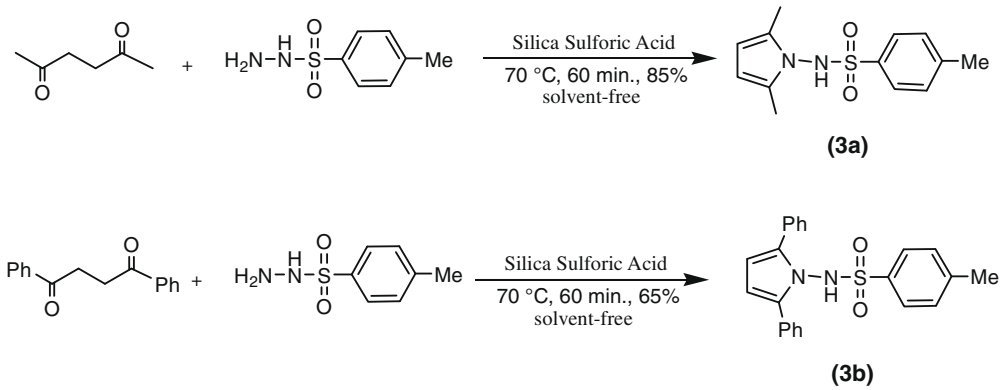
Entry	Amine (**1**)	Product[b]	Time (min)	Yield (%)
1			15	90
2			3	98
3			4	97
4			10	95
5			20	85
6			10	95
7			12	92
8			45	75
9			30	75
10			30	70

(*continued on next page*)

Table 2 (*continued*)

Entry	Amine (**1**)	Product[b]	Time (min)	Yield (%)
11			30	75
12			60	65
13			15	90
14			30	80
15			120	75
16			10	95
17			2	98
18			5	98
19			3	98
20			5	98

[a] Conditions: amine **1** (1 mmol) and 2,5-hexanedione **2** (1 mmol), catalyst (SSA) (0.15 g), rt, grinding.
[b] Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.



Scheme 3. Condensation reactions of γ-diketones with *p*-toluenesulfonylhydrazide.

Table 3
Reusability of SSA catalyst in the synthesis of 2,5-dimethyl-*N*-benzylpyrrole

Run	Time (min)	Yield (%)
1	5	98
2	5	96
3	5	95
4	5	95
5	5	90

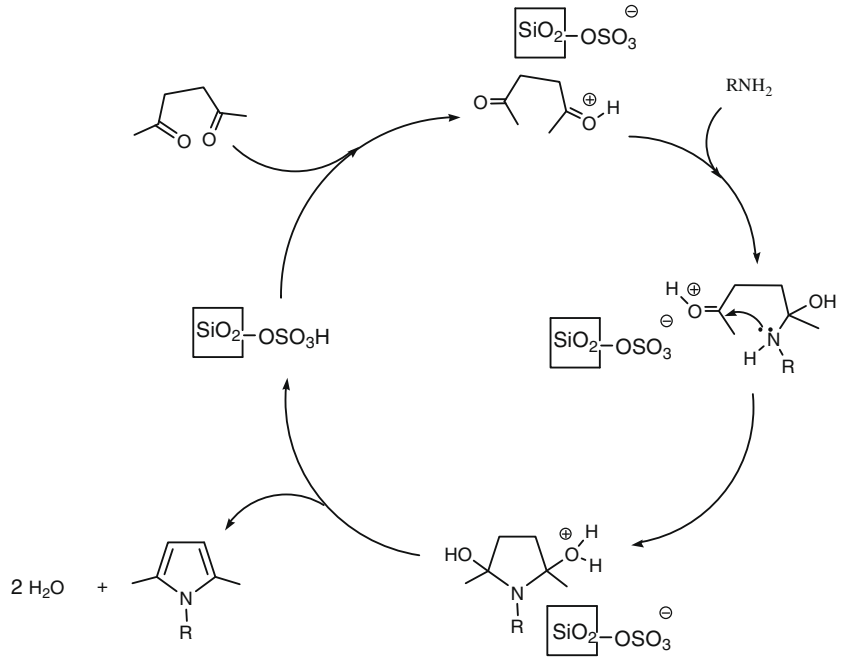
Table 4
Reaction times and yield for previously published methods

Substrate	Conditions	Reaction time	Yield (%)	Ref.
Benzylamine	SSA/solvent-free	3 min	98	–
Benzylamine	Montmorillonite, KSF	10 h	95	8
Benzylamine	I_2	0.5 h	92	8
Benzylamine	$Bi(NO_3)_3{\cdot}5H_2O$	10 h	95	11
Benzylamine	Microwave	0.5 min	90	9
Benzylamine	$Sc(OTf)_3$	30 min	94	12
Benzylamine	α-Zr$(KPO_4)_2$	2 h	78	14
1-Naphthylamine	SSA/solvent-free	15 min	90	–
1-Naphthylamine	$Sc(OTf)_3$	40 min	90	12
1-Naphthylamine	Montmorillonite, KSF	11 h	83	8
1-Naphthylamine	I_2	1 h	85	8
1-Naphthylamine	$Bi(NO_3)_3{\cdot}5H_2O$	11 h	83	11
2-Aminopyridine	SSA/solvent-free	120 min	75	–
2-Aminopyridine	$Bi(NO_3)_3{\cdot}5H_2O$	25 h	70	11
2-Aminopyridine	Montmorillonite, KSF	25 h	70	8

2.2. Analytical data for selected compounds

Compound (**4**): (cream solid, mp 197–198 °C): IR (KBr): ν_{max} 1515, 1462, 1410, 1377, 1303, 1019 cm^{-1}, ^{1}HNMR ($CDCl_3$, FT-250 MHz): δ 2.13 (s, CH_3, 12H), 4.97 (s, CH_2, 4H), 5.84 (s, pyrrolics, 4H), 6.82 (s, PhH, 4H), (Found: M^+ 292.1939. $C_{20}H_{24}N_2$ requires M, 292.1946). Anal. Calcd for $C_{20}H_{24}N_2{\cdot}0.5H_2O$: C, 78.29; H, 8.54; N, 9.96. Found: C, 79.88; H, 8.16; N, 8.97.

Compound (**12**): (brown solid, mp 110–112 °C); IR (nujol): ν_{max} 1605, 1520, 1499, 1455, 1370, 1016 cm^{-1}, ^{1}HNMR ($CDCl_3$, FT-250 MHz) δ 2.20 (s, CH_3, 12H), 5.96 (s, pyrrolics, 4H), 7.14–7.76 (m, PhH, 4H), (Found: M^+ 264.1626. $C_{18}H_{20}N_2$ requires M, 264.1635). Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.81; H, 7.57; N, 10.60. Found: C, 80.95; H, 7.42; N, 10.95.



Scheme 4. A plausible mechanism for synthesis of pyrroles.

Compound (**16**): (brown solid, mp 175–176 °C); IR (nujol): ν_{max} 3250, 3020, 1605, 1520, 1499, 1455, 1370, 1016 cm^{-1}, ^{1}HNMR ($CDCl_3$, FT-250 MHz) δ 2.24 (s, CH_3, 6H), 3.06 (t, J = 15.5 Hz, CH_2, 2H), 4.04 (t, J = 15.5 Hz, CH_2, 2H), 5.83 (s, pyrrolics, 2H), 6.87 (s, CH, 1H), 7.12–7.73 (m, PhH, 4H), 7.94 (s, NH, 1H), (Found: M^+ 238.1524. $C_{16}H_{18}N_2$ requires M, 238.1536). Anal. Calcd for $C_{16}H_{18}N_2{\cdot}H_2O$: C, 75.00; H, 7.03; N, 10.93. Found: C, 74.49; H, 6.98; N, 10.39.

Compound (**19**): (yellow solid, mp 74–75 °C); IR (nujol): ν_{max} 3312, 2915, 2854, 1663, 1571, 1517, 1463, 1404, 1377, 1298, 1121, 1108 cm^{-1}, ^{1}HNMR ($CDCl_3$, FT-250 MHz), δ 2.30 (s, CH_3, 12H), 2.70 (t, J = 18.5 Hz, CH_2, 4H), 3.75 (t, J = 18.5 Hz, CH_2, 4H), 5.70 (s, pyrrolics, 4H), (Found: M^+ 259.2048. $C_{16}H_{25}N_3$ requires M, 259.2055). Anal. Calcd for $C_{16}H_{25}N_3$: C, 74.13; H, 9.65; N, 16.21. Found: C, 73.48; H, 9.88; N, 16.07.

Compound (**20**): (pale yellow solid, mp 110–111 °C); IR (nujol): ν_{max} 3100, 2854, 2739, 1571, 1518, 1464, 1407, 1378, 1298, 1166, 1061, 1016, 745 cm^{-1}, ^{1}H NMR ($CDCl_3$, FT-90 MHz) 2.25 (s, CH_3, 18H), 2.74 (t, J = 19.7 Hz, CH_2, 6H), 3.75 (t, J = 19.7 Hz, CH_2, 6H), 5.78 (s, pyrrolics, 6H), Anal. Calcd for $C_{24}H_{36}N_4{\cdot}0.5H_2O$: C, 74.04; H, 9.51; N, 14.39. Found: C, 74.11; H, 9.67; N, 14.79.

N-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylbenzenesulfonamide (**3a**): (white solid, mp 144–145 °C); IR (nujol): ν_{max} 3320, 3090, 2850, 1578, 1520, 1464, 1410, 1370, 1310, 1160, 1052, 741 cm^{-1}, ^{1}H NMR ($CDCl_3$, FT-90 MHz) 1.80 (s, CH_3, 6H), 2.40 (s, 3H, $ArCH_3$), 5.69 (s, pyrrolics, 2H), 7.08 (s, 1H, NH), 7.33 (d, J = 8.0 Hz, 2H, ArH), 7.68 (d, J = 8.0 Hz, 2H, ArH), Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60. Found: C, 60.08; H, 6.22; N, 10.54.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.052.

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