An Efficient and Green Procedure for Synthesis of Pyrrole Derivatives by Paal–Knorr Condensation Using Sodium Dodecyl Sulfate in Aqueous Micellar

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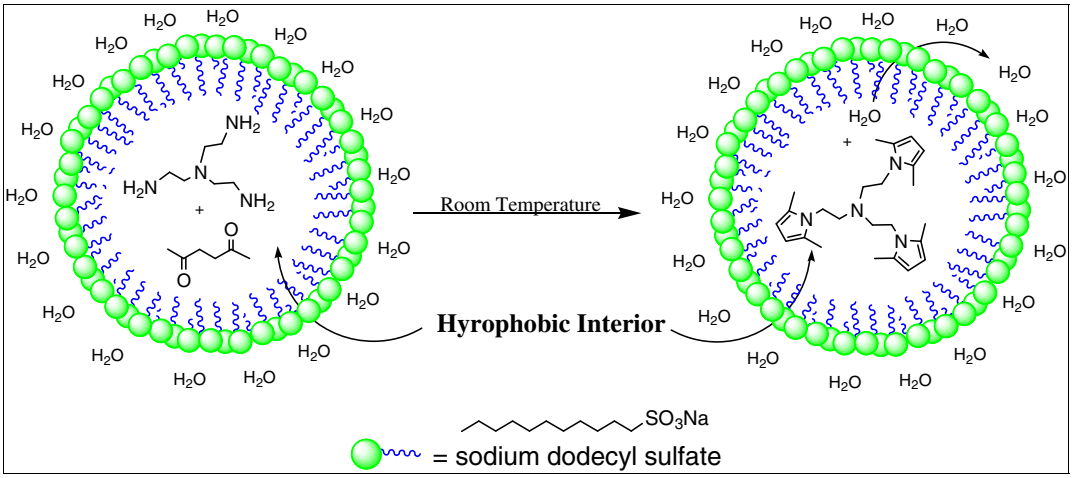

A simple, economical, and green approach to the synthesis of *N*-substituted pyrroles using sodium dodecyl sulfate as surfactant in water is described. The experiment protocol features simple operations, and the products are isolated in high to excellent yields (60–98%).

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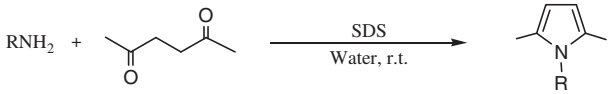
INTRODUCTION

Developing environmentally benign and economical syntheses is an area of research that is being vigorously pursued, and avoiding the use of harmful organic solvents is a fundamental strategy to achieving this. One of the most attractive alternatives to organic solvents is water, which has witnessed increasing popularity due to being inexpensive, readily available and environmentally benign. In addition, reactions in aqueous media illustrate unique reactivities and selectivities that are not usually observed in organic media [1]. However, organic reactions in water are often limited in scope due to poor solubility of the organic compounds. A possible new way to improve the solubility of substrates is the use of surface-active compounds that can form micelles [2].

Under ambient conditions, surfactant molecules can aggregate in an aqueous phase to form micelles with a hydrophobic core and a hydrophilic corona. The use of micellar surfactants as catalysts is widespread and has been investigated in detail for various reactions in aqueous solutions [3].

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 B_{12}, 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], $Bi(NO_3)_3.5H_2O$ [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], multicomponent 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, nonhazardous, inexpensive, recyclable and eco-friendly organic catalyst is still in demand.

Scheme 1. Synthesis of pyrroles from γ-diketones and primary amines using sodium dodecyl sulfate (SDS) in water.



1 2 3

R: alkyl and aryl

RESULTS AND DISCUSSION

In our continued interest in the development of a highly expedient methodology [24] for the synthesis of fine chemicals and heterocyclic compounds of biological importance, we report here a simple and efficient method for the synthesis of *N*-substituted pyrroles from reaction of γ-diketones and primary amines in aqueous micellar media, using sodium dodecyl sulfate (SDS), which simultaneously functions as a catalyst to promote the reactions and as a surfactant to assist in solubilizing the organic substrates (Scheme 1). SDS was chosen since it forms micelles in water, can solubilize organic compounds, and has been used successfully in a number of organic reactions as a catalyst.

We started this synthesis by examining the reaction of hexan-2,5-dione (1 mmol) with benzylamine (1 mmol) for the synthesis of 2,5-dimethyl-*N*-benzylpyrrole as a model reaction. As shown in Table 1, the use of SDS allowed the direct synthesis of 2,5-dimethyl-*N*-benzylpyrrole in a yield of 98% in water (5 mL) at 25°C (Table 1, Entry 2). The use of more than 10 mol % of SDS did not enhance chemical yield.

The catalytic effect of micellar SDS in this reaction can be explained as follows. In the micellar solution, γ-diketones and primary amines, which are both hydrophobic, are forced inside the hydrophobic core of the micelles, thus allowing the reaction to take place more easily (Fig. 1).

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 SDS at room temperature to give the corresponding pyrroles in good to excellent yields (Table 1). 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.

The reaction conditions were also applicable to diamino or triamino substrates, in giving bipyrrole (Table 1, Entries 4, 11–13, 15, 19, and 20) or tripyrrole compounds (Table 1, Entry 21) in excellent yields.

Finally, we examined the condensation reactions of γ-diketones with *p*-toluenesulfonylhydrazide in the presence of SDS as catalyst and surfactant in water (Scheme 2). *N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-4-methylbenzenesulfonamide (**3a**) was obtained with good yields (80%) when the reaction was performed at 100°C in the presence of SDS. 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**) was obtained with decrease of yield (55%), which is most probably due to the electron-donating and steric effects of the phenyl groups.

CONCLUSIONS

In summary, a practical and convenient synthetic method in aqueous media using SDS as the surfactant catalyst (10 mol %) has been developed for the facile synthesis of *N*-substituted pyrroles. The advantages of the method include (i) absence of organic solvent, (ii) short reaction times, (iii) high yields, (iv) easy work-up, and furthermore, this procedure is cheap, safe, and environmentally benign.

EXPERIMENTAL

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 tetramethylsilane as internal standard and chemical shift are in δ (ppm). Infrared (IR) was conducted on a Perkin-Elmer GX FTIR spectrometer. All yields refer to isolated products.

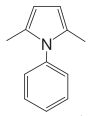
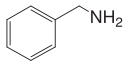
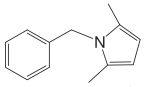
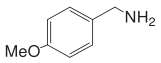
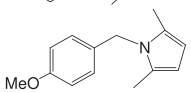
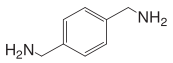
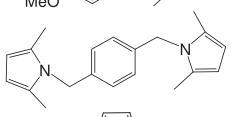
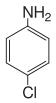
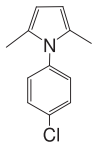
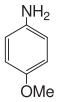
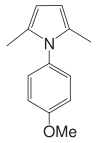
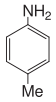
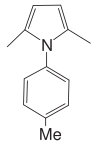
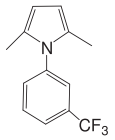
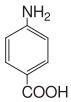
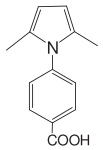
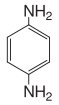
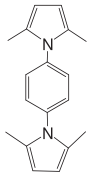
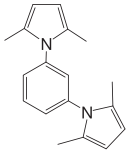
General procedure for the synthesis of pyrroles in the presence of SDS. The amine **1** (1 mmol) and 2, 5-hexanedione **2** (1 mmol) were added to a solution of SDS (10 mol %, 0.03 g) in H_2O (5 mL), and the mixture stirred at room temperature for the time given (Table 1). The progress of the reaction was monitored by TLC (eluent: 7:3 *n*-hexane-acetone). After completion of the reaction, K_2CO_3 (0.5 mmol, 0.07 g) was added to the reaction mixture, and the resulting precipitate of dodecyl sulfate filtered off. The filtrate was extracted with ethyl acetate (4 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated to give analytically pure product. When necessary, 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.

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}H-NMR ($CDCl_3$, 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 $C_{20}H_{24}N_2.0.5\ H_2O$: C, 78.29; H, 8.54; N, 9.96. Found: C, 79.88; H, 8.16; N, 8.97.

Compound (10). Pale yellow solid, mp 174–175°C; IR (nujol): ν_{max} 2400–2200, 1678, 1607, 1463, 1377, 1324, 1129, 1106 cm^{-1}; ^{1}H-NMR ($CDCl_3$, FT-250 MHz): δ 2.00 (s, CH_3,

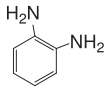
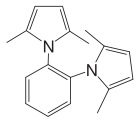
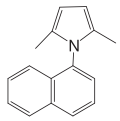
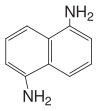
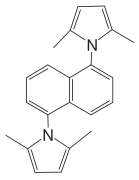
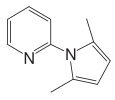
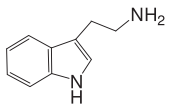
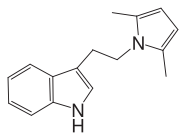
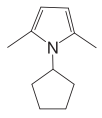
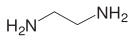
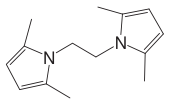
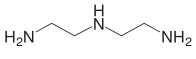
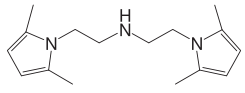
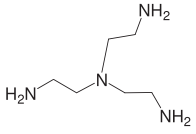
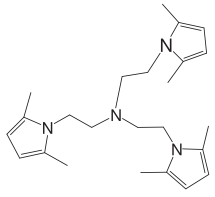
Table 1

SDS-catalyzed synthesis of pyrroles in water.

Entries	Amine (**1**)	Product[a]	Time (min)	Yield (%)
1			20	90
2			5	98
3			10	95
4			30	90
5			45	85
6			40	96
7			45	92
9			60	70
10			60	75
11			120	80
12			120	75

(*Continues*)

Table I
(Continued)

Entries	Amine (**1**)	Product[a]	Time (min)	Yield (%)
13			150	60
14			45	90
15			90	80
16			120	75
17			30	90
18			10	98
19			15	96
20			15	96
21			15	96

Conditions: amine **1** (1 mmol) and 2,5-hexanedione **2** (1 mmol), catalyst (SDS) (10 mol %), water (5 mL), and room temperature.
[a]Products were characterized from their physical properties, comparison with authentic samples, and by spectroscopic methods.

6H), 5.90 (s, pyrrolics, 2H), 7.30 (d, J = 10.1 Hz, PhH, 2H), 8.20 (d, J = 10.1 Hz, PhH, 2H), 11.39 (b, COOH, 1H); Found: M^+ 215.0946. $C_{13}H_{13}NO_2$ requires M, 215.1125; Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.55; H, 6.04; N, 6.51. Found: C, 71.84; H, 6.00; N, 6.22.

Compound (11). Pale yellow solid, mp 256–257°C; IR (KBr): ν_{max} 1514, 1463, 1378, 1310, 1211, 1001 cm^{-1}; ^{1}H-NMR ($CDCl_3$, FT-250 MHz): δ 2.10 (s, CH_3, 12H), 5.90 (s, pyrrolics, 4H), 7.25 (s, PhH, 4H); Found: M^+ 264.1626. $C_{18}H_{20}N_2$ requires M, 264.1632; Anal. Calcd for $C_{18}H_{20}N_2.H_2O$: C, 76.59; H, 7.09; N, 9.92. Found: C, 77.37; H, 6.99; N, 9.61.

Compound (12). Brown solid, mp 99–100°C; IR (nujol): ν_{max} 1600, 1521, 1499, 1459, 1377, 1321, 1006 cm^{-1}; ^{1}H-NMR ($CDCl_3$, FT-250 MHz) δ 2.10 (s, CH_3, 12H), 5.94 (s, pyrrolics, 4H), 7.12–7.68 (m, PhH, 4H); Found: M^+ 264.1626. $C_{18}H_{20}N_2$ requires M, 264.1637; Anal. Calcd for $C_{18}H_{20}N_2.0.5H_2O$: C, 79.12; H, 7.32; N, 10.25. Found: C, 79.46; H, 7.62; N, 10.75.

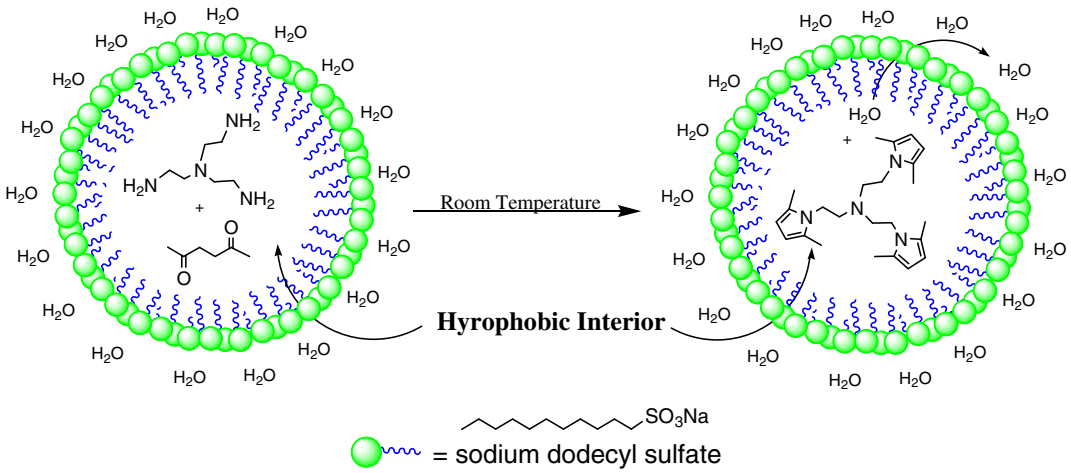
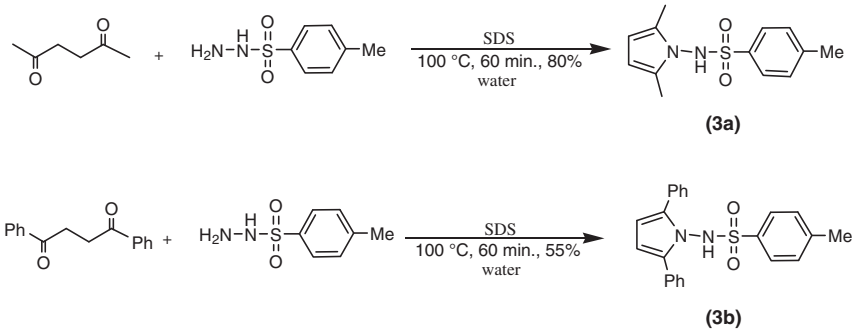


Figure 1. Proposed model for the synthesis of *N*-substituted pyrroles in water in the presence of SDS. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 2. Condensation reactions of γ-diketones with *p*-toluenesulfonylhydrazide.



Compound (13). Brown solid, mp 110–112°C; IR (nujol): ν_{max} 1605, 1520, 1499, 1455, 1370, 1016 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 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.

Compound (17). Brown solid, mp 175–176°C; IR (nujol): ν_{max} 3250, 3020, 1605, 1520, 1499, 1455, 1370, 1016 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 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 $C_{16}H_{18}N_2.H_2O$: C, 75.00; H, 7.03; N, 10.93. Found: C, 74.49; H, 6.98; N, 10.39.

Compound (20). 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}H-NMR ($CDCl_3$, 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 (21). 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 $C_{24}H_{36}N_4.0.5H_2O$: 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-90MHz) 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); Found: M^+ 264.3421. $C_{13}H_{16}N_2O_2S$ requires M, 264.3438; 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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