An Efficient Procedure for the Synthesis of Polysubstituted Pyrroles in an Ionic Liquid

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The ionic liquid 1-butyl-3-methyl-imidazolium hydrogen sulfate, [bmim]HSO_4, was used as a catalyst and reaction medium for the pyrrole synthesis, and a wide range of aliphatic, aromatic, heteroaromatic and carboxylic 1,4-diketones easily underwent condensations with aniline and ethylenediamine to form polysubstituted pyrroles. Sequential decarboxylation/Paal-Knorr pyrrole condensation was observed, which provides a new and facile approach to monoester pyrroles from 1,4-diketo-2,3-dicarboxylic acid esters.

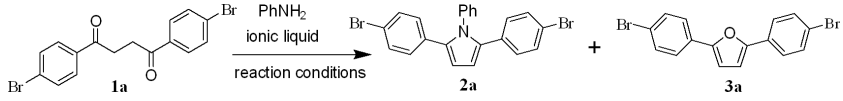
Key words: Ionic Liquid, Paal-Knorr Reaction, Polysubstituted Pyrrole, 1,4-Diketone, Decarboxylation

Introduction

Pyrrole is one of the most important heterocyclic compounds in pharmaceutical [1, 2] and material sciences [3, 4]. As a consequence, many synthetic methods are known for the construction of the pyrrole ring [5]. The most frequently used methods include conjugate addition reactions [6], transition metal-mediated reactions [7], reductive couplings [8], aza-Wittig reactions [9], multicomponent coupling reactions [10], and other multistep operations [11, 12]. Despite these extensive developments, the Paal-Knorr reaction is considered to be the most attractive method for the synthesis of pyrroles [13–15], which involves the reaction of 1,4-dicarbonyl compounds and their masked equivalents with primary amines. Although the Paal–Knorr reaction has been studied with various amines, the most often used diketone was 2,5-hexanedione, while differently substituted 1,4-diketones have been used less frequently. Thus, it is still challenging to prepare polysubstituted pyrroles with various substituents directly from readily available building blocks. Furthermore, most current methods are not applicable to sterically hindered aromatic and heteroaromatic diketones. In addition, the effect of substituents on the starting diketone has not received much attention. We recently reported the synthesis of *N*-substituted pyrroles from different 1,4-diketones and aniline by using a cation exchange resin as a recyclable heterogeneous catalyst [16]. However, further development of new methods for the preparation of pyrroles bearing various substituents is still needed in organic synthesis [17, 18].

Ionic liquids have recently emerged as environmentally benign alternatives for organic solvents [19]. However, their use in Paal-Knorr pyrrole synthesis remains largely unexplored. To the best of our knowledge, only two articles in this field have been published. Yadav and coworkers used $Bi(OTf)_3$ immobilized in [bmim]BF_4 as a catalytic system for pyrrole synthesis [20], and Wang and coworkers employed [bmim]I in the reactions of 2,5-hexanedione with different amines [21]. Hence, the development of new and convenient strategies in this field especially for the synthesis of polysubstituted pyrroles is desirable. We recently found that the ionic liquid 1-butyl-3-methyl-imidazolium hydrogen sulfate, [bmim]HSO_4, can be used as an efficient catalyst and reaction medium for furan synthesis [22]. Based on the previous study, we further explored the use of this ionic liquid in pyrrole synthesis. Herein, we wish to report a high-yield synthesis of polysubstituted pyrroles using the ionic liquid [bmim]HSO_4 as an efficient catalyst and green reaction medium for the condensation of different aliphatic, aromatic, heteroaromatic, and carboxylic diketones with aniline and ethylenediamine. Notably, a new and facile approach to monoester pyrroles from easily accessible 1,4-diketo-2,3-dicarboxylic acid esters was

Table 1. Comparison of the effect of different reaction conditions for the condensation of **1a** and aniline.



Entry	Temp. (°C)	Equiv. of aniline	Time (h)	Yield **2a** (%)[a]	Yield **3a** (%)[a]
1	50	1	36	45	47
2	50	2	36	38	56
3	100	1	12	43	54
4	100	2	12	76	17
5	150	1	6	78	10
6	150	2	3	96	0

[a] Refers to yield of isolated products after flash chromatography.

developed *via* sequential decarboxylation/Paal–Knorr pyrrole condensation.

Results and Discussion

In order to study the effect of temperature on the reaction, the condensation of the aromatic 1,4-dione **1a** with aniline was carried out in the ionic liquid [bmim]HSO_4 at 50, 100, and 150 °C (Table 1). The results have revealed that the formation of pyrrole was temperature-dependent. At lower temperature the pyrrole was only obtained in low to moderate yields, and furan was formed in a competitive reaction (Table 1, entries 1 – 4). However, at 150 °C the pyrrole was obtained as the major product after a shorter reaction time (Table 1, entry 5). Besides, use of 2 equivalents of aniline at 150 °C provided *N*-substituted pyrrole **2a** exclusively in excellent yield of 96 % (Table 1, entry 6).

To test the generality of the reaction, we further investigated the condensations of different diketone compounds and aniline in the ionic liquid [bmim]HSO_4 at 150 °C. A wide range of di-, tri- and tetra-substituted aliphatic, aromatic, heteroaromatic, and carboxylic 1,4-diketones underwent smoothly the condensation with aniline to provide *N*-substituted pyrroles in good yields (Table 2). The method was efficient and easy to carry out. The reactions were complete within 3 h. When 1,4-diphenyl-1,4-diones (**1a**, **1c**, **1d**, and **1f**, Table 2) were used, excellent yields were obtained. Triphenyl-1,4-dione **1h** and di(2-thiophenyl)-1,4-dione **1b** gave excellent yields of 97 % and 95 %, respectively (Table 2). Methyl-substituted 1,4-diones **1e** and **1g** provided the products in slightly lower yields of 88 % and 85 %, respectively. It seems that aryl-substituted 1,4-dicarbonyl compounds perform better than alkyl-substituted ones in this ionic liquid-catalyzed condensation.

Interestingly, the 2-carboxylate-substituted 1,4-diones **1i** – **1k** provided the corresponding carboxylate-substituted pyrroles **2i**, **2j**, and **2l** as major products (75 – 79 % yield), but decarboxylated pyrroles **2g**, **2k**, and **2f** were also obtained (8 – 12 % yields). However, the 2,3-dicarboxylate-substituted 1,4-diones **1l** and **1m** did not give the corresponding pyrrole dicarboxylates, and instead gave the pyrrole monoesters **2m** and **2l** as the major products in yields of 75 % and 86 %, respectively. The carboxylate-free products **2e** and **2f** were also obtained in yields of 8 % and 5 %, respectively. This provides a new and facile approach to pyrrole monoesters from easily accessible 1,4-diketo-2,3-dicarboxylates. We reasoned that the decarboxylated pyrroles were formed probably through initial decarboxylation and subsequent Paal–Knorr condensation with aniline. Otherwise, if the condensation step to form a pyrrole ring takes place before decarboxylation, the resulting conjugated system of a pyrrole carboxylate would be robust enough to prevent it from decarboxylation under the applied reaction conditions. This assumption was supported by the fact that no such transformation was observed for the carboxylate-substituted pyrrole **2j** under the given reaction conditions. In addition, it was observed that 1,4-diketo-2,3-dicarboxylates are more likely to eliminate one carboxylate group compared to monocarboxylate-substituted 1,4-diones.

To improve the scope of this ionic liquid-catalyzed method of pyrrole formation, the aliphatic amine ethylenediamine was also used (Scheme 1). The reaction was carried out in the ionic liquid at 100 °C because of the relatively low boiling point (117 °C) of ethylenediamine, and two equivalents of amine were used. A clean formation of the pyrrole **2o** was achieved in good yield of 89 % with 1,2,4-triphenyl-1,4-dione (**1h**). The product **2n** was obtained in lower yield of 74 % when 1,4-diphenyl-1,4-dione (**1f**) was used as the ketone component (Scheme 1). It is some-

Table 2. Pyrroles from the condensation of 1,4-diketones and aniline in the ionic liquid [bmim]HSO_4.

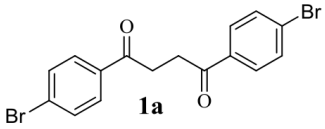
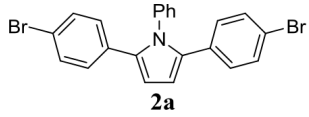
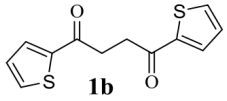
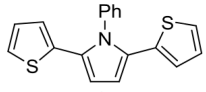
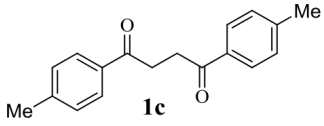
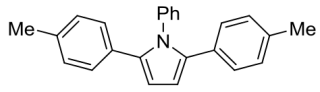
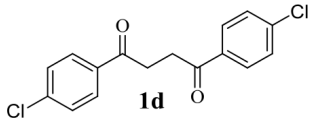
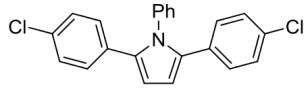
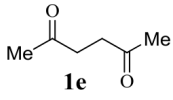
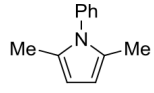
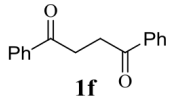
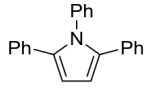
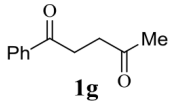
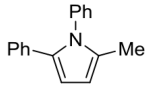
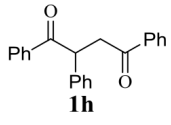
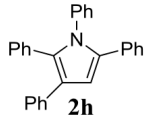
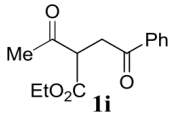
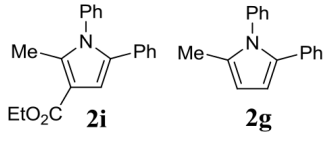
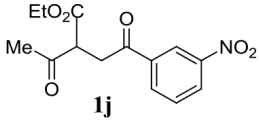
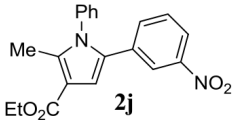
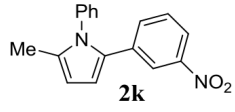
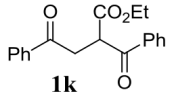
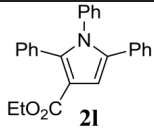
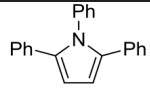
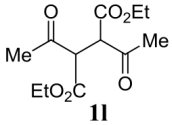
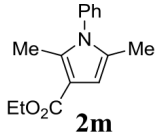
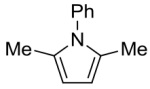
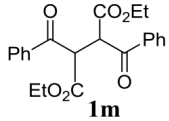
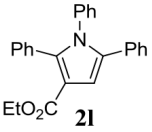
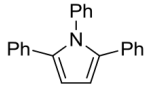
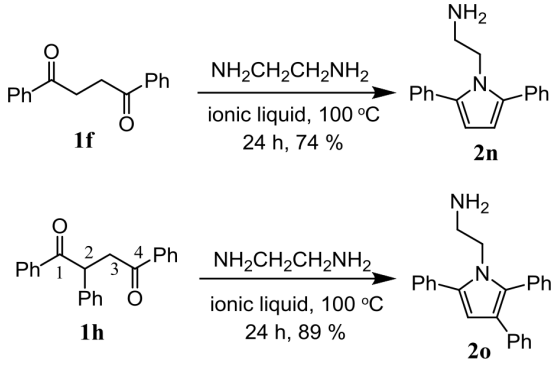
Entry	1,4-Diketone	Pyrrole	Time (h)	Yield (%)[a]
1	 **1a**	 **2a**	3	96
2	 **1b**	 **2b**	3	95
3	 **1c**	 **2c**	3	97
4	 **1d**	 **2d**	3	94
5	 **1e**	 **2e**	2	88
6	 **1f**	 **2f**	3	96
7	 **1g**	 **2g**	2	85
8	 **1h**	 **2h**	3	97
9	 **1i**	 **2i** **2g**	3	**2i**: 76 **2g**: 8
10	 **1j**	 **2j**  **2k**	3	**2j**: 79 **2k**: 11

Table 2 (continued).

Entry	1,4-Diketone	Pyrrole	Time (h)	Yield (%)[a]
11	 **1k**	 **2l**  **2f**	3	**2l**: 75 **2f**: 12
12	 **1l**	 **2m**  **2e**	3	**2m**: 75 **2e**: 8
13	 **1m**	 **2l**  **2f**	3	**2l**: 86 **2f**: 5

[a] Yield refers to isolated product after flash



Scheme 1. Condensation of diketones with ethylenediamine.

what surprising that the more hindered diketone **1h** gave a higher yield than **1f**. According to Rao and coworker's conformational analysis of **1h** [23], the two 1,4-benzoyl groups adopt a *gauche* rather than the *anti* conformation. The dihedral angle between the CO–C2 bond and the CO–C3 bond in the lowest energy conformer was 65° (the numbering of carbons is shown in Scheme 1). We think that the demand for this dihedral angle could facilitate the formation of the pyrrole ring.

During the course of the reaction, we observed that the ionic liquid turned sticky when the amine was added. This is probably due to the formation of an amine salt between the ionic liquid [bmim]HSO_4 and the amine. When the temperature was above 100 °C, the reaction mixture turned into a less viscous solution, which could be stirred smoothly. However, after the reaction was complete and the reaction mixture was cooled to r. t., it changed into curd. The addition of water was required to dissolve this curd before workup. Thus, we did not recover the ionic liquid.

Conclusion

We have developed an efficient method for the preparation of polysubstituted pyrroles with various substituents. The present method avoids the use of mineral acids and organic solvents. Instead, the ionic liquid [bmim]HSO_4 was used as a catalyst and reaction medium. The reactions were high-yielding, and the procedure is applicable to a wide range of sterically hindered aliphatic, aromatic, heteroaromatic and carboxylic diketones. Notably, the sequential decarboxylation/Paal–Knorr condensation was also investigated, which provides a new and facile approach to pyrrole monocarboxylic esters from easily accessible 1,4-diketo-2,3-dicarboxylic esters. The present procedure might be a potentially useful synthetic method for organic chemistry.

Experimental Section

*Synthesis of **2a**: Typical experimental procedure for synthesis of N-substituted pyrroles*

A solution of 1,4-bis(4-bromophenyl)butane-1,4-dione (**1a**, 75 mg, 0.2 mmol) and aniline (0.06 mL, 0.54 mmol) in 2 g (8.4 mmol) of the ionic liquid [bmim]HSO_4 was stirred at 150 °C for 3 h. After cooling to r. t., 10 mL of H_2O was added to the reaction mixture, and then thoroughly extracted with diethyl ether. The combined extracts were washed with water and brine, dried (Na_2SO_4), and filtered. The solvents were removed and the residue purified by flash chromatogra-

phy (petroleum ether / CH_2Cl_2 2 : 1) to give 2,5-bis(4-bromophenyl)-1-phenyl-1H-pyrrole **2a** as a colorless solid (82 mg, 96 % yield). M. p.: 300 – 303 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 – 7.26 (m, 7H), 7.02 – 6.99 (m, 2H), 6.91 – 6.88 (m, 4H), 6.47 (s, 2H). – ^{13}C NMR: δ = 134.88, 131.87, 131.04, 130.00, 129.05, 128.70, 127.66, 110.27. – HRMS (ESI): *m/z* = 450.9579 (calcd. 450.9571 for $C_{22}H_{15}Br_2N$, $[M]^+$).

*1-Phenyl-2,5-di(thiophen-2-yl)-1H-pyrrole (**2b**).* M. p.: 181 – 182 °C, reported [24]: 180 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 – 7.39 (m, 3H), 7.32 – 7.25 (m, 2H), 7.05 – 7.04 (m, 2H), 6.82 – 6.79 (m, 2H), 6.54 (s, 2H), 6.51 – 6.50 (m, 2H), identical to that previously reported [24].

*1-Phenyl-2,5-di(p-tolyl)-1H-pyrrole (**2c**).* M. p.: 208 – 210 °C, reported [25]: 208 – 210 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 – 6.95 (m, 13H), 6.43 (s, 2H), 2.27 (s, 6H), identical to that previously reported [25].

*2,5-Di(4-chlorophenyl)-1-phenyl-1H-pyrrole (**2d**).* M. p.: 264 – 266 °C, reported [25]: 264 – 265 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 – 7.26 (m, 2H), 7.15 – 7.12 (m, 4H), 7.01 – 6.95 (m, 7H), 6.46 (s, 2H), identical to that previously reported [25].

*2,5-Dimethyl-1-phenyl-1H-pyrrole (**2e**).* M. p.: 49 – 51 °C, reported [26]: 50 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 – 7.44 (m, 3H), 7.26 – 7.22 (m, 2H), 5.90 (s, 2H), 2.21 (s, 6H), identical to that previously reported [26].

*1,2,5-Triphenyl-1H-pyrrole (**2f**).* M. p.: 232 – 234 °C, reported [25]: 233 – 234 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 – 7.19 (m, 3H), 7.17 – 7.15 (m, 7H), 7.08 – 7.02 (m, 5H), 6.49 (s, 2H), identical to that previously reported [25].

*2-Methyl-1,5-diphenyl-1H-pyrrole (**2g**).* M. p.: 83 – 84 °C, reported [27]: 81 – 82 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 – 7.06 (m, 10H), 6.36 (s, 1H), 6.09 (s, 1H), 2.13 (s, 3H), identical to that previously reported [27].

*1,2,3,5-Tetraphenyl-1H-pyrrole (**2h**).* M. p.: 200 – 203 °C, reported [28]: 200 – 201 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 – 7.18 (m, 16H), 7.07 – 7.00 (m, 4H), 6.73 (s, 1H), identical to that previously reported [28].

*Ethyl 2-methyl-1,5-diphenyl-1H-pyrrole-3-carboxylate (**2i**).* M. p.: 99 – 101 °C, reported [29]: 99 – 100 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 – 7.04 (m, 10H), 6.80 (s, 1H), 4.35 – 4.31 (m, 2H), 2.40 (s, 3H), 1.39 – 1.36 (m, 3H), identical to that previously reported [29].

*Ethyl 2-methyl-5-(3-nitrophenyl)-1-phenyl-1H-pyrrole-3-carboxylate (**2j**).* Oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 – 7.89 (m, 2H), 7.44 – 7.17 (m, 7H), 6.95 (s, 1H), 4.37 – 4.33 (m, 2H), 2.42 (s, 3H), 1.42 – 1.37 (m, 3H), identical to that previously reported [30].

*2-Methyl-5-(3-nitrophenyl)-1-phenyl-1H-pyrrole (**2k**).* M. p.: 112 – 114 °C, reported [30]: 114 – 115 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 – 7.19 (m, 9H), 6.50 (s, 1H), 6.14 (s, 1H), 2.15 (s, 3H), identical to that previously reported [30].

*Ethyl 1,2,5-triphenyl-1H-pyrrole-3-carboxylate (**2l**).* M. p.: 132 – 134 °C, reported [31]: 130 – 131 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 – 7.09 (m, 13H), 6.94 – 6.93 (m, 3H), 4.18 – 4.16 (m, 2H), 1.26 (m, 3H), identical to that previously reported [31].

*Ethyl 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylate (**2m**).* M. p.: 45 – 47 °C, reported [32]: 45 – 46 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 – 7.18 (m, 5H), 6.37 (s, 1H), 4.29 – 4.27 (m, 2H), 2.29 (s, 3H), 1.97 (s, 3H) 1.35 (m, 3H), identical to that previously reported [32].

*2,5-Di(4-bromophenyl)furan (**3a**).* M. p.: 205 – 207 °C, reported [33]: 206 – 208 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 – 7.51 (m, 8H), 6.74 (s, 2H), identical to that previously reported [33].

*2-(2,5-Diphenyl-1H-pyrrol-1-yl)ethanamine (**2n**).* M. p.: 80 – 82 °C, reported [34]: 78 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 – 7.28 (m, 10H), 6.28 (s, 2H), 4.15 – 4.11(m, 2H), 2.43 – 2.38 (m, 2H), 0.96 (s, 2H). – ^{13}C NMR: δ = 136.94, 133.88, 128.89, 128.64, 127.08, 109.89, 48.16, 42.44. – HRMS (ESI): *m/z* = 263.1542 (calcd. 263.1548 for $C_{18}H_{19}N_2$, $[M+H]^+$).

*2-(2,3,5-Triphenyl-1H-pyrrol-1-yl)ethanamine (**2o**).* M. p.: 85 – 87 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 – 7.39 (m, 10H), 7.21 – 7.11 (m, 5H), 6.50 (s, 1H), 4.06 – 4.02 (m, 2H), 2.46 – 2.42 (m, 2H), 1.78 (s, 2H). – ^{13}C NMR: δ = 135.99, 135.44, 133.50, 132.10, 131.09, 128.95, 128.76, 128.64, 128.01, 127.72, 127.70, 127.22, 125.17, 123.31, 109.95, 47.20, 42.09. – HRMS (ESI): *m/z* = 339.1868 (calcd. 339.1861 for $C_{24}H_{23}N_2$, $[M+H]^+$).

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