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## One-pot synthesis of pyrrole derivatives from (*E*)-1,4-diaryl-2-butene-1,4-diones

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Abstract—2,5-Di- and 1,2,5-trisubstituted pyrrole derivatives can be prepared conveniently from (E)-1,4-diaryl-2-butene-1,4-diones in a one-pot operation through domino-pathways via palladium-assisted transfer hydrogenation followed by a Paal–Knorr reaction using ammonium formate and its analogs. © 2001 Elsevier Science Ltd. All rights reserved.

Pyrrole and its derivatives are ubiquitous among naturally occurring organic compounds.1 They are commonly found as structural motifs in bio-active molecules such as porphyrins, alkaloids and co-enzymes.<sup>2</sup> In view of their importance, there is a continuing interest in developing versatile synthetic routes.<sup>3</sup> Generally, pyrroles are synthesized by the condensation of 1,4-dicarbonyl compounds with primary amines. This condensation, known as the Paal-Knorr reaction, has a wide scope, permitting the synthesis of a wide variety of pyrrole derivatives.<sup>4</sup> Recently, it was found that microwaves enhance the rate of this reaction.<sup>5</sup> In this communication we wish to report a novel one-pot synthesis of 2,5-di- and 1,2,5-trisubstituted pyrrole derivatives from 2-butene-1,4-diones through domino pathways involving the reduction of a double bond followed by reductive amination-cyclization (Scheme 1).

The reaction of (E)-1,4-diphenyl-2-butene-1,4-dione **1a** with ammonium formate **2a** in the presence of palladium on carbon (10%) in methanol at reflux, resulted in the formation of known 2,5-diphenylpyrrole **3a** in 87% yield in 30 min. In this one-pot reaction, ammonium formate

was utilized for reduction of the double bond and also as a source of ammonia for reductive amination–cyclization. When the reaction was performed in polyethyleneglycol (PEG-200) in a domestic microwave oven (200 W), the reaction time was reduced to 30 s and the yield rose to 92%.<sup>6</sup> Results obtained in this study are presented in Table 1.

Even though there are several reports on the microwaveassisted rate enhancement of organic reactions in high dielectric constant solvents such as water and DMF, we are reporting here for the first time the utility of PEG-200 as a solvent in such reactions. PEG-200 is miscible with water, thereby simplifying the work-up. Furthermore, it is inexpensive and readily available in bulk quantities. We attempted the above reaction in PEG-400, ethylene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, DMF and without any solvent (Table 2). The maximum yield of the desired product was obtained when the reaction was performed in PEG-200 or tetraethylene glycol. Surprisingly, the reaction did not take place when PEG-400 was used as a solvent, possibly due to low solubility of ammonium formate.



Scheme 1. 1a:  $Ar = C_6H_5$ , 1b: Ar = 4-ClC<sub>6</sub>H<sub>4</sub>, 1c: Ar = 4-BrC<sub>6</sub>H<sub>4</sub>, 1d: Ar = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 1e: Ar = 4-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 1f: Ar = 4-Cl-3-CH<sub>3</sub>C<sub>6</sub>H<sub>3</sub>; 2a: R = H, 2b: R = n-C<sub>4</sub>H<sub>9</sub>, 2c:  $R = C_6H_5$ , 2d:  $R = CH_2C_6H_5$ ; 3a:  $Ar = C_6H_5$ , R = H; 3b: Ar = 4-ClC<sub>6</sub>H<sub>4</sub>, R = H; 3c: Ar = 4-BrC<sub>6</sub>H<sub>4</sub>, R = H; 3d: Ar = 4-Cl-3-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, R = H; 3d: Ar = 4-Cl-3-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, R = H; 3d: Ar = 4-Cl-3-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, R = H; 3e: Ar = 4-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, R = H; 3f: Ar = 4-Cl-3-CH<sub>3</sub>C<sub>6</sub>H<sub>3</sub>, R = H; 3g:  $Ar = C_6H_5$ , R = n-C<sub>4</sub>H<sub>9</sub>; 3h:  $Ar = C_6H_5$ ;  $R = C_6H_5$ ;  $R = C_6H_5$ ,  $R = C_6H_5$ .

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Table 1. Reaction of 1,4-diaryl-2-butene-1,4-diones 1a-f with ammonium formates 2a-d in PEG-200 under microwave irradiation

Entry	Ene-dione	Formate derivative	Pyrrole	Time (min) <sup>a</sup>	Yield (%) <sup>b,c</sup>
1	1a	2a	3a	0.5 (30)	92 (87)
2	1b	2a	3b	1.0 (45)	80 (60)
3	1c	2a	3c	1.0 (45)	85 (63)
4	1d	2a	3d	1.5 (45)	85 (61)
5	1e	2a	3e	2.0 (60)	89 (37)
6	1f	2a	3f	2.0 (60)	84 (23)
7	1a	2b	3g	2.0 (60)	56 (26)
8	1a	2c	3h	2.0 (60)	63 (29)
9	1a	2d	3i	2.0 (60)	60 (28)

<sup>a</sup> The number in parentheses is the reaction time in MeOH at reflux.

<sup>b</sup> Yield of isolated and purified product, yield in parentheses is from the reactions conducted in MeOH at reflux.

<sup>c</sup> All the products were characterized on the basis of analytical and spectral data, with the exception of **3f**, the other pyrrole derivatives are known compounds.<sup>7</sup>

**Table 2.** Reaction of (E)-1,4-diphenyl-2-butene-1,4-dione with ammonium formate in the presence of Pd/C in various solvents under microwave irradiation for 30 s at 200 W

Entry	Solvent	Yield (%)
1	PEG-200	92
2	PEG-400 <sup>a</sup>	No reaction
3	Ethylene glycol	50
4	Diethylene glycol	60
5	Triethylene glycol	82
6	Tetraethylene glycol	92
7	DMF <sup>a</sup>	10
8	Without solvent	25

<sup>a</sup> Ammonium formate was found to be sparingly soluble in PEG-400 and DMF.

To test the generality of the reaction, a variety of (E)-1,4-diaryl-2-butene-1,4-diones **1b**-**f** were transformed to the corresponding 2,5-diarylpyrroles **3b**-**f** (Table 1). Even when an electron-donating methoxy group was placed in the phenyl ring of the ene-dione **1e**, the yield of the substituted pyrrole **2e** was very good under the influence of microwaves (89%). When this reaction was performed in refluxing methanol the yield was only 37%. Similarly, the reaction of ene-dione **1f** using microwave irradiation furnished pyrrole derivative **3f** in 84% yield, whereas under thermal conditions the yield was only 23%.

We extended the scope of the reaction by employing different alkylammonium formates 2b-d as one of the reactive species. Thus, the reaction of *n*-butylammonium formate 2b with 1a in the presence of Pd/C under microwave irradiation in PEG-200 furnished 1-butyl-2,5-diphenyl-1*H*-pyrrole 3g in 56% yield (Table 1). Similarly, when phenylammonium formate 2c and benzylammonium formate 2d were employed, 1-phenyl-2,5-diphenylpyrrole 3h and 1-benzyl-2,5-diphenylpyrrole 3i were obtained in good yields (Table 1). To the best of our knowledge, this is the first report on the utility of alkyl/aryl ammonium formates for the reduction and amination-cyclization sequence.

Thus, we have demonstrated a simple synthesis of 2,5and 1,2,5-trisubstituted pyrroles in a one-pot operation from 1,4-diaryl-2-butene-1,4-diones via enone reduction followed by the generation of the pyrrole moiety with ammonium formate or alkyl/aryl ammonium formates. Furthermore, we have introduced PEG-200 as a convenient solvent for microwave-assisted organic reactions, which we hope, will find general use.

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- 6. In a typical experiment, ene-dione 1f (166 mg, 0.5 mmol), ammonium formate (34 mg, 5.0 mmol), 10% palladium on carbon (5.0 mg) and PEG-200 (5 mL) were taken in a conical flask and the resulting mixture was irradiated in a domestic microwave oven (BPL-Sanyo, India; mono-mode, multi-power; power source: 230 V, 50 Hz, microwave frequency: 2450 MHz) at 200 W for 2 min. After that, the mixture was cooled to room temperature, diluted with 50 mL dichloromethane (DCM) and the palladium/carbon was removed by Celite filter. The clear filtrate was washed with water (2×50 mL), saturated aqueous sodium chloride (50 mL) and dried over an-hydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was chro-

matographed on silica using hexanes/DCM as the eluent to yield pyrrole **3f** as a white solid (134.3 mg, 85%) after removal of the solvent. An analytically pure sample was obtained by recrystallization from DCM/hexanes; mp 190°C;  $\lambda_{max}$  (methanol) 335 nm;  $\nu_{max}$  3469 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 2.41$  (s, 6H), 6.53 (br s, 2H), 7.20–7.35 (m, 4H), 7.32 (br s, 2H), 8.40 (s, br, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ =19.9, 108.0, 121.8, 122.2, 123.9, 125.9, 129.3, 131.2, 136.3; MS (EI) m/z=316 (M<sup>+</sup>); Anal. calcd for C<sub>18</sub>H<sub>15</sub>Cl<sub>2</sub>N: C, 68.37; H, 4.78; N, 4.43. Found: C, 68.25; H, 4.81; N, 4.37.

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