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Facile Microwave-Mediated Transformations of 2-Butene-1,4-diones and 2-Butyne-1,4-diones to Furan Derivatives

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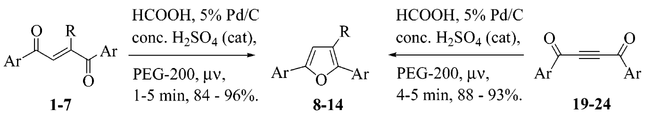
Abstract: Several di- and triarylfuran derivatives were prepared in high yields from but-2-ene-1,4-diones/but-2-yne-1,4-diones using formic acid in the presence of a catalytic amount of palladium on carbon and in poly(ethylene glycol)-200 medium in a one-pot operation under microwave irradiation (1−5 min).

The most widely used approach to furan synthesis is the Paal−Knorr method in which 1,4-dicarbonyl compounds are converted to furan derivatives via acid-mediated dehydrative cyclization.[1] In this century-old reaction, the 1,4-dicarbonyl compounds provide all the carbons as well as one oxygen necessary for the ring closure to the furan ring. For example, 2,5-diphenylfuran, the heterocycle relevant to the present study, has been prepared from 1,4-diphenylbutane-1,4-dione under dehydrative conditions by refluxing in toluene containing a catalytic amount of *p*-TSOH,[2] $ZnCl_2$ in acetic anhydride,[3] or polyphosphoric acid.[4] Even though the reaction is simple to perform, the limitation is the availability of suitably substituted 1,4-diketones. Only recently have a few good methods been developed for the synthesis of the substrate 1,4-diketones,[5] and there is still enormous scope for improvement, particularly with regard to conditions, efficiency, and applicability to a wider range of substrates.

The 1,4-diketones for the furan synthesis can be made by the hydrogenation of the corresponding enediones. We envisaged that the two steps, viz. reduction of the double bond and subsequent cyclization, could be combined in a one-pot procedure by employing a reagent that would effect both conversions. Previously, this concept was explored by treating 2-ene-1,4-diones with Lewis acids, tin(II)chloride,[6] diphosphorus tetraiodide (P_2I_4),[7] or triethyl phosphite[8] to furnish substituted furan derivatives. The main disadvantages of the above procedures were the requirement of stringent conditions, long reaction times, and lack of applicability to 2-yne-1,4-diones. We report here a facile, high-yielding, one-flask preparation of furan derivatives from 2-ene-1,4-diones and 2-yne-1,4-diones using formic acid in the presence of a catalytic amount of palladium on carbon (5%). The rationale is that formic acid decomposes at elevated temperature to hydrogen and carbon dioxide and the hydrogen generated can be used for metal-mediated hydrogenation of double or triple bonds. Formic acid also serves as a catalyst for the dehydrative cyclization of the 1,4-diketones to furan derivatives. Thus, it was expected that 2-ene or 2-yne 1,4-diketones could be transformed to furan derivatives in a one-pot operation. Recently, we reported the microwave-mediated synthesis of 2,5-di- and 1,2,5-trisubstituted pyrrole derivatives from 2-butene-1,4-diones using ammonium formate or alkylammonium formate in the presence of palladium on carbon.[9]

SCHEME 1



1, 8, 19: Ar = C_6H_5, R = H; **2, 9, 20**: Ar = 4-Cl-C_6H_4, R = H; **3, 10, 21**: Ar = 4-Br-C_6H_4, R = H; **4, 11, 22**: Ar = 4-CH_3-C_6H_4, R = H; **5, 12, 23**: Ar = 4-CH_3O-C_6H_4, R = H; **6, 13, 24**: Ar = 4-Cl-3-CH_3-C_6H_3, R = H; **7, 14**: Ar = R = C_6H_5.

TABLE 1. Microwave-Mediated Reduction−Dehydrative Cyclization of 2-Ene-1,4-diones/2-Yne-1,4-diones to Furan Derivatives

sl. no.	dione	furan	time (min)	Power (W)	yield (%)
1	**1**	**8**[a]	1.0	400	95
2	**2**	**9**[b]	3.0	400	96
3	**3**	**10**[b]	2.0	200	91
4	**4**	**11**[a]	5.0	200	96[d]
5	**5**	**12**[a]	5.0	200	96[d]
6	**6**	**13**	5.0	400	96
7	**7**	**14**[c]	5.0	200	84[d]
8	**19**	**8**	4.0	155	93
9	**20**	**9**	4.0	155	92
10	**21**	**10**	4.0	155	93
11	**22**	**11**	5.0	200	89[d]
12	**23**	**12**	5.0	200	88[d]
13	**24**	**13**	5.0	200	90[d]

[a] Reference 11. [b] Reference 16. [c] Reference 8. [d] Concentrated H_2SO_4 (5 mol %) was used.

When a two-phase reaction mixture of (*E*)-1,4-diphenyl-2-butene-1,4-dione **1**, formic acid, and catalytic palladium on carbon (5%) in poly(ethylene glycol)-200 (PEG-200) was exposed to microwaves in a domestic microwave oven at 400 W, 2,5-diphenylfuran **8** was obtained in 95% yield in 2 min (Scheme 1 and Table 1). In this transformation, formic acid acted both as a source of hydrogen and as an

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acid catalyst to promote dehydrative cyclization. Under reflux in methanol, the conversion of **1** to **8** did not take place even after 24 h, which shows that a higher temperature is required for formic acid to aid catalytic transfer hydrogenation of **1**.

Poly(ethylene glycol) was found to be a suitable solvent for performing the microwave mediated conversion of enedione **1** to **8** and an attempt was made to conduct this two-phase transformation in other solvents such as ethanol, diethylene glycol, triethylene glycol, tetraethylene glycol and PEG-400. Even though the yield of furan **8** was the same either in PEG-200 or in tetraethylene glycol, the former solvent is cheaper and readily available in bulk quantities. Moreover, a dielectric constant of around 20,[10] high boiling point (> 250 °C), ability to behave as a phase-transfer reagent,[10] and high water miscibility make PEG-200 an ideal protic solvent for microwave-mediated organic reactions. The PEG-400 is also available in bulk quantities, but its high viscosity precludes its use as a convenient solvent for microwave mediated reactions. With the present procedure, it is possible to perform the transformation of dione **1** to furan **8** on a 3 mmol scale without difficulty.

To assess the generality of the dehydrative cyclization reaction and also to evaluate the electronic influence of the aromatic ring substituents, dichloro (**2**), dibromo (**3**), dimethyl (**4**), and dimethoxy 1,4-diaryl-2-butene-1,4-dione (**5**) derivatives were subjected to the transformation to the corresponding furan derivatives **9**−**12** under microwave conditions. In their studies on the mechanistic details of the Paal−Knorr synthesis of 2,5-diarylfurans, Amarnath and Amarnath found that the rate-determining step in the reaction sequence is the attack on the protonated carbonyl group by the enol formed from the second carbonyl group.[11] Furthermore, they found that while electron-donating groups (Me or OMe) on C-4 of the phenyl rings in the 1,4-diphenyl-2-butene-1,4-diones enhance the rate of the reaction, electron-withdrawing groups (NO_2) retard the process. It was rationalized that since electron-donating groups promote both protonation of the C-1 carbonyl group and enolization of the C-4 carbonyl group, the rate of dehydrative cyclization is higher than in the cases where electron-withdrawing groups are present. Surprisingly, we observed contrasting results. When we conducted the reductive dehydrative-cyclization reaction on diketones **2** and **3** having electron-withdrawing Cl and Br groups in the C-4 position of the phenyl rings,[12] the reaction took place readily and the furan derivatives **9** and **10** were obtained in near-quantitative yields within 2 min. However, when the reaction was conducted on the diketones **4** and **5** having electron-donating Me and OMe groups, respectively, the reaction was relatively sluggish and the double bond reduced products were obtained along with furan derivatives **11** and **12**. When the same microwave-mediated reaction was conducted in the presence of a catalytic amount of concentrated sulfuric acid (5 mol %), i.e., in addition to formic acid and palladium on carbon, the reaction went to completion in 5 min to furnish 2,5-diarylfurans **11** and **12** in 95% yield. We monitored the progress of the reaction closely by TLC to differentiate the rates of hydrogenation and subsequent dehydrative cyclization. We noticed that reduction of the double bond in diketones **1**−**5** took place within 1 min to furnish the double bond hydrogenated products 1,4-diarylbutane-1,4-diones **15** (Figure 1) without any difference in the rate of hydrogenation. Subsequent dehydrative cyclization was demanding longer exposure to microwaves to form furan derivatives **11** and **12**. Thus, the reactivity of hydrogenated products **15** toward dehydrative cyclization appears to be influenced by substituents on the phenyl ring. A proposed mechanism for the Paal−Knorr conversion of enediones **1** to furans **8** is given in Figure 1. The first step is the palladium-mediated hydrogenation of **1** to furnish dione **15**. Subsequent protonation of **15** generates protonated species **16**, which undergoes enolization to furnish intermediate **17**. Since furan formation depends on the nature of the substituents on the phenyl ring, we believe that the rate-controlling step under the conditions employed is the conversion of **17** to **18**. In this step, intramolecular nucleophilic attack of the enol oxygen upon the electrophilic carbon (C-1) of the protonated carbonyl group takes place. While electron-donating Me and OMe groups render the C-1 carbonyl carbon in **17** less electrophilic, electron-withdrawing groups enhance its electrophilicity. The stronger acid catalyst, concentrated sulfuric acid, possibly aids protonation of the carbonyl oxygen in the rate-limiting step. The final step is the dehydration of **18** to furnish furan derivatives **8**−**12**.

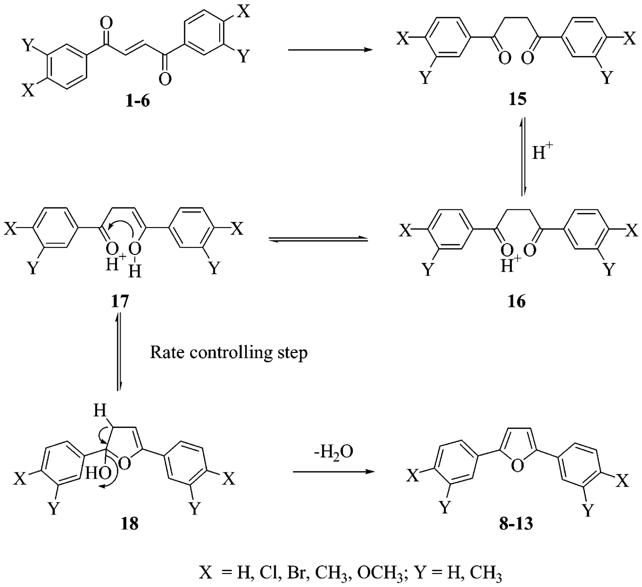

FIGURE 1.

The enedione **6** having electron-withdrawing 4-Cl and electron-donating 3-Me groups was also transformed to the hitherto unknown furan derivative **13** in 96% yield within 4 min under microwave irradiation (Scheme 1; entry 6, Table 1). In this case, a catalytic quantity of concentrated sulfuric acid was required for dehydrative-cyclization to **13**.

Extension to the enedione **7** having a bulky phenyl ring on C-2 gave the furan **14** in quantitative yield in 1 min.

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with the help of microwave heating. It appears that the hydrogenation, followed by dehydrative-cyclization of **17**, is even more facile than with enedione **1**, possibly due to conformational factors.[13]

Having established a simple method for the transformation of 2-ene-1,4-diones to the corresponding furans, we extended the scope to the one-pot reductive cyclization−dehydration of 1,4-diaryl-2-butyne-1,4-diones **19**−**24** (Scheme 1 and Table 1). Thus, the domino reaction on diones **19**−**24** took place within 2 min using formic acid in PEG-200 under microwave irradiation. While there are some isolated reports on the conversion of alkynyl monoketones to furan derivatives,[15] to the best of our knowledge, this is the first report on the conversion of 2-yne-1,4-diones to furan derivatives. Similar to the reaction of enediones **4** and **5** having electron-donating groups in the phenyl ring, ynediones **22**, **23**, and **24** also required catalytic amounts of sulfuric acid to drive the reactions toward furans **11**, **12**, and **13**, respectively (entries 11, 12, and 13; Table 1).

In this study, we have shown that 2-ene-1,4-diones and 2-yne-1,4-diones can be converted to furan derivatives conveniently using formic acid and palladium on carbon in PEG-200 under microwave irradiation. The reaction takes less than 5 min, is amenable to scale-up, and works well for the preparation of both 2,5-diaryl- and 2,3,5-triphenylfuran derivatives. In some difficult cases, a catalytic quantity of concentrated sulfuric acid is required to promote the dehydrative-cyclization step.

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Supporting Information Available: Experimental details for the synthesis of di- and triarylfurans from enediones and ynediones. Copies of IR, ^{1}H NMR, ^{13}C NMR, DEPT, and GC−MS spectra of 2,5-di(4-chloro-3-methylphenyl)furan **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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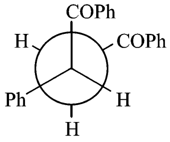
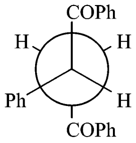
[13] Conformational analysis of the hydrogenated product of **7**, 1,2,4-triphenylbutane-1,4-dione, was performed using calculations at the AM 1 level of theory.[14] The results indicated that the two 1,4-benzoyl groups adopt gauche conformation **7a** rather than anti conformation **7b**. The dihedral angle between the CO−C-2 bond and the CO−C-3 bond in the lowest energy conformer was 65°, and this dihedral demand could facilitate furan ring formation.



7a



7b

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