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Microwave-assisted synthesis of 1,3-benzodioxole derivatives from catechol and ketones or aldehydes

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ABSTRACT

An efficient synthetic procedure for the preparation of a diverse library of 1,3-benzodioxoles was developed by applying controlled microwave heating in comparison with currently available conventional heating. Reactions were completed in less than 3 h. The isolation of product is simple, the isolated yields are good to excellent, and this method is applicable to large scale production.

1. Introduction

In many instances, protection groups that are commonly used in synthetic organic chemistry are also present in nature for completely different purposes.[1] This is certainly the case with 1,3-benzodioxoles.[2–5] Probably the most commonly known and widely used natural products with 1,3-benzodioxole moieties are safrole,[6] myristicin,[7,8] and piperin.[9] Derivatives of these natural products are used as inhibitors of mono-oxygenase enzymes,[10] pesticides or pesticide intermediates,[11] herbicides,[12] antioxidants,[13] antimicrobials,[14] and medicines.[15–17] Therefore, it should not be a surprise that there is a substantial demand for a simple and very effective method for the preparation of a wide variety of the 1,3-benzodioxole derivatives.

There are several synthetic approaches for the preparation of these important compounds. One of the most common approaches is through condensation of carbonyl compounds with catechol in the presence of an acid catalyst.[18] The applicability of this synthetic approach strongly depends on the efficiency of the acidic catalyst.[19] In particular 1,3-benzodioxoles have been prepared from the corresponding carbonyl compounds and catechol with catalysts, such as *p*-toluenesulfunic acid,[20] copper *p*-toluenesulfonate,[21] pyridinium *p*-toluenesulfonate,[22] and KSF or K-10[23] to name a few. There are also methods that utilize aggressive Lewis acid catalysts, such as phosphorus pentoxide[24] or phosphorus trichloride.[25] Clearly, there is a demand for simple and highly efficient synthetic procedures for the preparation of these valuable compounds.

Recently, we designed a microwave organic synthetic reactor[26] that allows the synthetic organic chemist to carry out organic reactions together with magnetic stirring, stable microwave power control, temperature control, and solvent refluxing.[27] This reactor design adds an advantage in performing a number of very efficient reactions over conventional synthetic methods.[28–30] Microwave-assisted reactions are particularly effective when small polar molecules are part of the reaction transformation.[31–33] One can also speculate that microwave heating should be especially effective for chemical transformations in which water is one of the reaction products. In conventional approaches, to drive the reaction to completion, the addition of water-consuming and aggressive reagents, such as phosphorus pentoxide and phosphorus trichloride, are used. We believe that the combination of simple and safe catalysts, such as acidic polymers (dowex), acidic clay (K-10), and *p*-toluenesulphonic acid, in combination with microwave heating will be a prevailing alternative approach for preparing a wide variety of 1,3-benzodioxole derivatives.

To test the validity of this assumption, we subsequently selected four different carbonyl compounds (both aliphatic and aromatic ketones and aldehydes) that have the capability of producing four different derivatives of 1,3-benzodioxoles presented in Scheme 1. Three acid catalysts (amberlite, clay K-10, and *p*-toluenesulfonic acid) and three solvents (benzene, toluene, and xylene) were selected for a comparison of the differences in conventional and microwave assisted preparation of the

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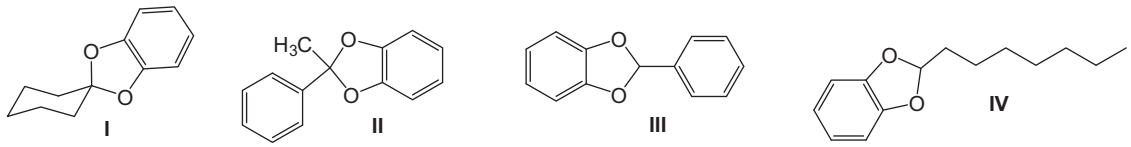
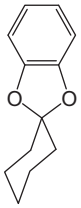
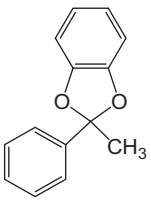
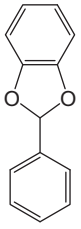
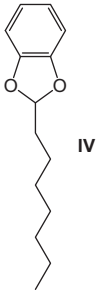


Scheme 1. Structures of selected 1,3-benzodioxoles for optimization of the reaction conditions.

1,3-benzodioxoles. Overall, 72 reactions were performed and the isolated yields of the corresponding 1,3-benzodioxoles are presented in Table 1. Microwave magnetron power was adjusted to generate vigorous solvent refluxing (400 W for benzene, 500 W for toluene, and 560 W for xylene). There were substantial differences regarding the nature of substrate, solvent, acid catalyst, and above all conventional versus microwave-assisted reactions. There was a clear improvement in using microwave heating over conventional heating in all of our studied substrates. The reaction time for microwave-assisted reactions was up to twenty times shorter than for comparable reactions under conventional heating. When the reaction time was shortened, thermal decomposition was also minimized, resulting in higher isolated yields and more simplified product purification. This was also the case for microwave-assisted reactions. The choice of the acid catalyst was also important. *p*-Toluenesulfonic acid (PTSA) continuously gave the best results in comparison to amberlite and clay K-10 (Table 1). In many instances, the solvent of choice was benzene, although comparable results were obtained with toluene as a solvent and although xylene as a solvent somewhat shortened the reaction times, the amount of thermal decomposition byproducts increased. Isolated yields were good to excellent for the aromatic and aliphatic ketones as well as aromatic aldehydes. Isolated yields were slightly lower for aliphatic aldehydes. Under both conventional

Table 1
Comparison of microwave and conventional heating in catechol carbonyl protection

Product	Solvent	Conventional			Microwave	
		Acidic catalyst	Time (min)	Yield (%)	Time (min)	Yield (%)
 I	Benzene	Dowex	1300	71	120	78
		PTSA	1440	68	120	96
		Clay K-10	1620	83	105	84
	Toluene	Dowex	1270	77	105	72
		PTSA	1440	87	105	89
		Clay K-10	1160	85	90	78
	Xylene	Dowex	1220	58	90	66
		PTSA	1200	72	90	74
		Clay K-10	1500	74	90	62
 II	Benzene	Dowex	3600	68	240	63
		PTSA	7440	58	240	59
		Clay K-10	2400	69	210	66
	Toluene	Dowex	3240	72	120	71
		PTSA	7440	71	120	91
		Clay K-10	1440	73	120	82
	Xylene	Dowex	3000	63	90	73
		PTSA	7200	76	90	79
		Clay K-10	1200	69	90	84
 III	Benzene	Dowex	1080	48	120	62
		PTSA	4200	58	120	87
		Clay K-10	900	58	120	69
	Toluene	Dowex	900	54	120	62
		PTSA	2880	80	120	84
		Clay K-10	510	65	120	74
	Xylene	Dowex	720	53	90	59
		PTSA	2400	68	90	72
		Clay K-10	450	61	90	71
 IV	Benzene	Dowex	900	34	90	28
		PTSA	1200	42	90	72
		Clay K-10	900	29	90	39
	Toluene	Dowex	780	31	90	33
		PTSA	1080	60	90	72
		Clay K-10	840	26	90	41
	Xylene	Dowex	690	22	75	25
		PTSA	900	38	75	49
		Clay K-10	600	18	75	33

and microwave heating, a considerable amount (10–30%) of the aldol condensation product was formed. However, separation of the aldol byproduct from the corresponding 1,3-benzodioxole was simple and involved filtration through a short column of silica gel. Nevertheless, the microwave-assisted preparation of 1,3-benzodioxole from aliphatic aldehydes can be optimized to about 80–85% conversion with more than 75% isolated yield.

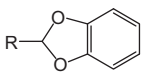
Now that the advantage of the microwave versus conventional heating was demonstrated (Table 1), we would also like to show the NMR reaction following the preparation of (**1f**) from benzaldehyde and catechol in benzene with PTSA as an acid catalyst (Fig. 1).[34] This reaction was the perfect demonstration of the efficiency and selectivity of the microwave-assisted preparation of 1,3-benzodioxoles. There was no formation of byproducts and according to ^{1}H NMR, the conversion was almost quantitative, with the isolated yield reflecting loss during isolation and purification. If xylene was used instead of benzene as the reaction medium, the reaction time shortened to 90 min (benzaldehyde is consumed) and a small amount of decomposition byproduct is formed, reflecting slightly a lower isolated yield (Table 1).

The efficiency of the microwave-assisted preparation of 1,3-benzodioxole from both aliphatic and aromatic aldehydes was demonstrated in Table 2. All reactions were performed in benzene as the reaction medium, *p*-tolunebenzoic acid (PTSA) as the acid catalyst, and the microwave heating with magnetron power of 400 W.[35] For aromatic aldehydes, the reactions were very clean but for aliphatic aldehydes the reaction must be carefully monitored because the aldol byproducts are formed. Considering these problems, benzene was the better solvent choice when using aliphatic aldehydes because benzene as a solvent presents lower amounts of the aldol product formation when compared to xylene. For aliphatic aldehydes, the optimal reaction time was between 90 and 120 min. The formation of the aldol product with aliphatic aldehydes was not a problem for 1,3-benzodioxole purification (filtration through short silica gel column) resulting that their isolated yields are in general ~10% lower than those for aromatic aldehydes (Table 2). However, aliphatic 1,3-benzodioxoles can be prepared with this method in 70–80% making it a method of choice for the preparation of these valuable compounds.

Ketones are ideal starting materials for the preparation of 1,3-benzodioxoles. They are more reactive and, therefore, the required microwave heating is shorter than in comparison with aldehydes. Contrary to the problem with aldol condensation products forming as a byproduct in the reactions with aliphatic aldehydes, when aromatic aldehydes were used, the condensation product was not present at all or the formed amount is negligible (1–2% at the most). The reaction with both aliphatic and aromatic ketones with one aliphatic group was practically quantitative. The lower isolated yields result from the loss of product during the isolation and the acid catalyst removal (Table 3). However, we were not able to prepare 2,2-diphenyl-1,3-benzodioxole from benzophenone and catechol. This was the case with several other diaromatic ketones. Aromatic substituents such as nitro, methoxy, hydroxyl, dimethylamino, and amino do not interfere with the reaction; however, they can either facilitate (electron donating group) or retard (electron withdrawing group) the reaction. This reaction was very simple and was applicable to a large-scale preparation of 1,3-benzodioxoles. Hundred gram quantities of these compounds can be prepared in research laboratories in a matter of hours. For instance, 104 g of 2-methyl-2-phenyl-1,3-benzodioxole was prepared from acetophenone and catechol in less than 3 h.[36]

In conclusion it can be stated that microwave-assisted preparation of 1,3-benzodioxole derivatives from aldehydes and ketones is superior to currently existing preparation methods. The isolated yields are generally higher and the required reaction time is significantly (up to 20 times) shorter in comparison with conventional heating. Aromatic aldehydes, aromatic-aliphatic ketones, and

Table 2
Microwave-assisted preparation of 1,3-benzodioxole from aldehydes

 **1**	Time (min)	Yield (%)
1a: R = *n*-C_3H_7	120	79
1b: R = *n*-C_4H_9	120	73
1c: R = *n*-C_7H_{15}	90	72
1d: R = *n*-C_9H_{19}	90	72
1e: R = *n*-$C_{11}H_{23}$	90	70
1f: R = C_6H_5	120	87
1g: 2-$CH_3OC_6H_4$	90	91
1h: 3-$CH_3OC_6H_5$	90	89
1i: 3-$NO_2C_6H_4$	150	79

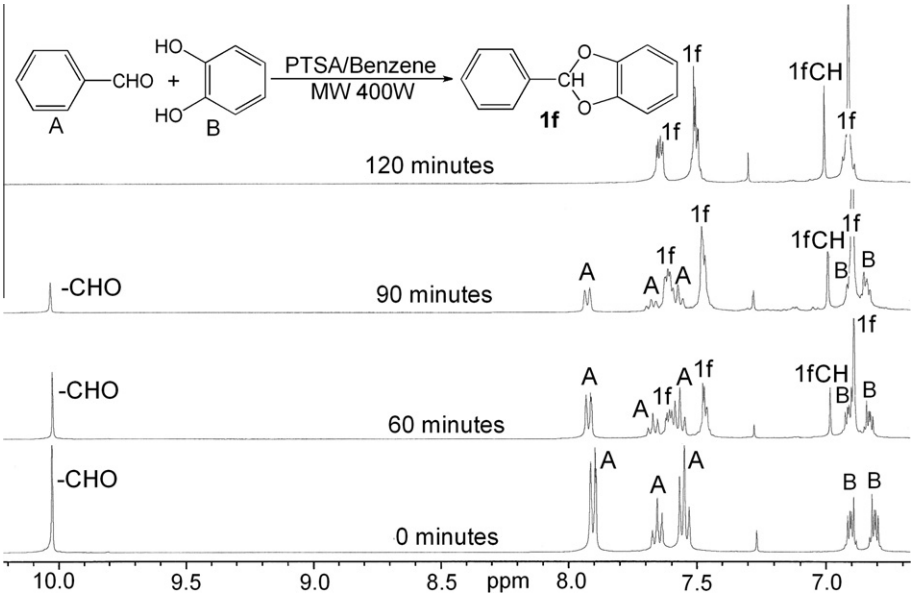
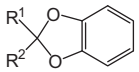


Figure 1. The NMR microwave-assisted reaction following for preparation of **1f**.

Table 3
Microwave-assisted preparation of 1,3-benzodioxole from ketones

 **2**	Time (min)	Yield (%)
2a: $R^1 = R^2 = CH_3$	120	82
2b: $R^1 = CH_3$; $R^2 = C(CH_3)_3$	60	98
2c: $R^1 = CH_3$, $R^2 = CH_2CH_3$	120	96
2d: $R^1 = R^2 = CH_2CH_3$	90	93
2e: $R^1 = CH_3$; $R^2 = n\text{-}C_6H_{13}$	60	92
2f: R^1–R^2 = –$(CH_2)_4$–	60	91
2g: R^1–R^2 = –$(CH_2)_5$–	120	96
2h: $R^1 = CH_3$; $R^2 = CH_2COCH_3$	75	86
2i: $R^1 = CH_3$; $R^2 = CH_2CH_2COCH_3$	75	89
2j: $R^1 = CH_3$; $R^2 = C_6H_5$	120	96
2k: $R^1 = CH_3$; $R^2 = 4\text{-}ClC_6H_4$	120	87
2l: $R^1 = CH_3$; $R^2 = 3,5\text{-}(CH_3)_2C_6H_4$	120	97
2m: $R^1 = CH_3$; $R^2 = CH_2CO_2C_2H_5$	120	89

aliphatic ketones are excellent starting materials; however, reaction with aliphatic aldehydes must be carefully monitored to maximize the isolated yield of the product due to formation aldol byproduct. Even in this case, isolated yield of corresponding 1,3-benzodioxole is higher than 70%. Due to its simplicity the method is applicable to a large-scale preparation of benzodioxoles.

Acknowledgment

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27. The laboratory version of our microwave has a cavity size of 21.6 cm in height, 17.30 cm wide, and 25.4 cm deep with two 2.54 cm hole on the top of the microwave for the condenser and thermometer. The magnetron (700 W) was directly wired to variable electronic autotransformer for control of the magnetron power. ECM meter (10 A) was wired to the magnetron transformer to control the microwave power. The magnetic stirrer was installed beneath the cavity for stirring the reaction mixture. The reaction temperature was measured directly with a thermometer inserted into the reaction mixture through a condenser and/or by infrared reading. For chemical reactions, a conventional microwave is not applicable due to the fact that the magnetron power cannot be controlled and, therefore, reaction mixtures are burned after several minutes of microwave irradiation. Additionally, reaction mixtures cannot be stirred and neither a condenser nor a thermometer can be added to the reaction container. For these reasons conventional as well as currently available commercial microwave laboratory reactors cannot be used effectively in organic synthetic labs. However, conventional microwaves can be used for few short reactions (maximum a few minutes) where reaction media overheating and solvent evaporation are acceptable.
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34. The NMR reaction following was performed in refluxing solvents. Samples are taken from reaction mixture at the time described in Figure 1 and the solvent was immediately removed under nitrogen flow. The solid residue was slurred in $CDCl_3$, the insoluble *p*-toluenesulfonic acid was separated by filtration, and ^1H NMR of the $CDCl_3$ filtrate was recorded on Varian Unity 400.
35. Benzene (10 ml) suspension of carbonyl compound (1 mmol), catechol (1.1 g; 1 mmol), and *p*-toluenesulfonic acid (5 mg) ws refluxed with Dean Stark trap and microwave power of 400 W for time indicated in Tables 2 and 3. Solvent was evaporated at reduced pressure. The solid residue was dissolved in hot dichloromethane–hexane (1:9; 3 ml) place on short (2 × 2 inches) silica gel column. Silica gel was washed with dichloromethane–hexane (1:9; 3 × 20 ml). The filtrates were combined and the solvent was evaporated to yield pure product.
36. Typical large-scale preparation of 1,3-benzodioxoles. Preparation of 2-methyl-2-phenylbenzo[*d*][1,3]dioxole (**2j**). A mixture of acetophenone (60 g; 0.5 mol), catechol (55 g; 0.5 mol), and *p*-toluenesulfonic acid (0.2 g) in benzene (100 ml) was refluxed under microwave heating (magnetron power of 400 W). After 2 h the amount of water collected in the dean star trap is constant and reaction mixture was cooled to room temperature and then to 10 °C with ice-water bath cooling. Formed white needle crystals were separated by filtration and dried at room temperature to afford 102 g (98%) of pure product. ^1H NMR ($CDCl_3$), δ 7.70 (2H, d, J = 7.8 HZ), 7.43 (3H, m), 6.86 (4H, m), and 2.08 (3H, s) ppm. ^{13}C NMR ($CDCl_3$) δ 147.8, 141.8, 129.4. 128.9, 125.5, 121.9, 117.1, 109.1 and 27.5 ppm.