

Efficient One-Pot 1,3-Dibromo-5,5-dimethylhydantoin (DBH)-Catalyzed Synthesis of Highly Substituted Furans

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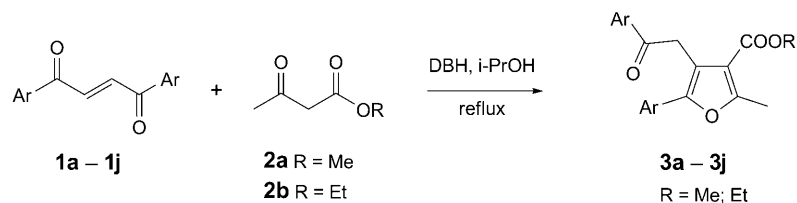
The 1,3-dibromo-5,5-dimethylhydantoin (DBH) was found to efficiently catalyze the one-pot synthesis of highly functionalized tetrasubstituted furan derivatives by the reaction of 1,4-diarylbut-2-ene-1,4-diones and acetoacetates in *i*-PrOH as the solvent at 80–90° for 3–7 h. The products were formed in high yields (82–95%) under mild and neutral conditions.

Introduction. – Substituted furan derivatives are important synthetic intermediates [1] and are found as structural units in many natural products such as in kallolides [2], cembrenolides [3], pheromones [4], and polyether antibiotics [5]. These heterocycles have found applications in many pharmaceuticals, fragrances, and dyes [6]. Furan subunits have also been used as building blocks for a large number of heterocyclic compounds and as synthons in natural-product synthesis [7]. As a consequence, the synthesis [8–11] and the applications [12–15] of furan derivatives still attract the attention of organic chemists. The most common strategy involved in the synthesis of furans is the cyclization [16] of 1,4-dicarbonyl compounds. Of the various other methods, syntheses involving transition-metal salts have recently been described for the preparation of substituted furan derivatives [17]. *Oh* and co-workers [18] have synthesized highly substituted furans *via* Pt-catalyzed hydroxy- or alkoxy-assisted cyclization of 2-(alk-1-yn-1-yl)alk-2-en-1-ones. More recently, *Jaisankar* and co-workers reported a novel method for the preparation of highly substituted furans by InCl₃-catalyzed nucleophilic addition followed by a cyclization reaction, although it was limited to specific substrate classes [19].

Results and Discussion. – In connection with our ongoing studies on 1,3-dibromo-5,5-dimethylhydantoin (= 1,3-dibromo-5,5-dimethylimidazoline-2,4-dione; DBH) as a versatile and convenient reagent used in various transformations [20–25], and also to avoid the drawbacks generally caused by the use of strong acidic media in nitrosation reactions, we wish, herein, to report on the use of DBH as a more robust and efficient catalyst in the one-pot synthesis of highly functionalized tetrasubstituted furan derivatives **3a–3j** by the reaction of 1,4-diarylbut-2-ene-1,4-diones **1a–1j** and acetoacetates **2a** or **2b** under neutral conditions (*Scheme 1* and *Table 1*).

We propose a mechanism for these reactions in three steps as shown in *Scheme 2*. Thus, the 1,4-diarylbut-2-ene-1,4-diones act as *Michael* acceptors and the acetoacetates

Scheme 1

Table 1. DBH-Catalyzed Synthesis of Furans **3a–3j**

Product ^{a)}	Ar	R	Time [h]	Yield [%] ^{b)}	M.p. [°]
3a	Ph	Me	3.4	90	92
3b	Ph	Et	4.1	92	89
3c	4-Me-C ₆ H ₄	Me	4.5	87	83
3d	4-Me-C ₆ H ₄	Et	4.2	82	80
3e	4-Br-C ₆ H ₄	Me	3.8	90	87
3f	4-Br-C ₆ H ₄	Et	5.7	95	85
3g	4-Cl-C ₆ H ₄	Me	5.1	81	96
3h	4-Cl-C ₆ H ₄	Et	5.6	88	94
3i	3-Cl-4-Me-C ₆ H ₃	Me	6.2	91	79
3j	3-Cl-4-Me-C ₆ H ₃	Et	6.8	95	77

^{a)} All the isolated products were characterized by their physical properties, by ¹H- and ¹³C-NMR and IR spectra, and by direct comparison with literature data [19]. ^{b)} Isolated yields.

as the nucleophiles resulting in a *Michael* adduct which, under the influence of DBH, forms a hemiketal which undergoes spontaneous dehydration to afford furans.

The advantages or the characteristic aspects of the method described herein, in comparison with those already reported, are the following: The yields of products are better than the perviously reported yields. In addition, the catalyst DBH is inexpensive and not moisture sensitive, and sub-molar amounts of DBH are required. Longer reaction times are required when smaller amounts of DBH are employed. It is important to note that no furan derivatives were formed when the reactions were carried out in the absence of DBH.

The role of the solvent was also investigated. Among the various solvents used, *i*-PrOH afforded the maximum yield of the furan derivative **3a** (Table 2). It is well known that reactions of this type are more efficient in polar solvents as corroborated by this study (Table 2). It was also observed that the inclusion of H₂O had very little or no influence in this reaction.

In summary, the present method is an efficient one-pot synthesis of fully substituted furans under mild conditions.

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Scheme 2

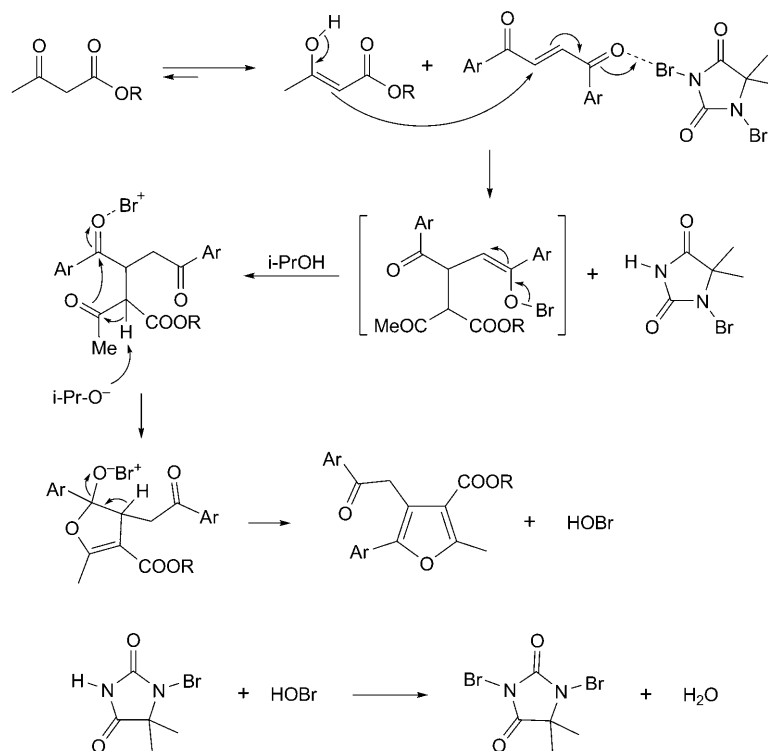


Table 2. Role of the Solvent in the Synthesis of Furan 3a

Solvent	Time [h] ^{a)}	Yield of 3a [%]
i-PrOH	3.4	90
i-PrOH/H ₂ O 6 : 4	11	65
MeOH	10	50
MeCN	18	41
CH ₂ Cl ₂	15	40
THF	14	55

^{a)} Extension of the reaction time did not improve the yield.

Experimental Part

General. Chemicals were obtained from *Merck* and *Fluka*. M.p.: *Büchi-530* melting point apparatus; uncorrected. IR Spectra: *Shimadzu-435-U-04* spectrophotometer; KBr pellets. NMR Spectra: 90-MHz-*Jeol-FT-NMR* spectrometer; CDCl₃ solns.

Typical Synthetic Procedure. To a soln. of 1,4-diphenylbut-2-ene-1,4-dione (**1a**; 236 mg, 1 mmol) and methyl acetoacetate (= methyl 3-oxobutanoate; **2a**; 128 mg, 1.1 mmol) in dry i-PrOH (7 ml) was added anh. DBH (199 mg, 0.7 mmol). The mixture was then stirred under reflux at 80–90° for 3.4 h. After complete disappearance of the starting material (monitored by TLC (petroleum ether CHCl₃ 6 : 4)), the

solvent was evaporated. The residue was then diluted with H₂O (15 ml) and extracted with CHCl₃ (4 × 15 ml), the org. layer washed with brine, dried (MgSO₄), and concentrated, and the resulting solid chromatographed (SiO₂, petroleum ether with increasing proportions of AcOEt). The eluent petroleum ether/AcOEt 96 : 4 gave a solid which was recrystallized from CHCl₃/petroleum ether 2 : 8: **3a** (300 mg, 90%). White solid. M.p. 92°.

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