Acid-catalyzed convenient transformation of 1-aryl-2-pentene-1,4-diones into polyfunctionalized furans

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Abstract

The reaction of phenylglyoxal with 2,4-pentanedione in the presence of boron trifluoride gave the unstable 3-acetyl-1-phenyl-2-pentene-1,4-dione intermediate which was converted in situ by the reaction with an excess amount of 2,4-pentanedione into new crystalline tri- and tetra-substituted furans. Other unstable 1-aryl-2-pentene-1,4-diones, which were obtained by the photooxygenation of 3-acetyl-5-aryl-2-methylfurans, were trapped by the acid-catalyzed reaction, giving polyfunctionalized furans in good yields. Treatment of the 1-phenyl-2-pentene-1,4-dione intermediate with concentrated hydrochloric acid followed by boiling ethanol quantitatively yielded a stable 2-ethoxymethylfuran via the unstable 2-chloromethylfuran. © 2000 Elsevier Science Ltd. All rights reserved.

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Furans and their derivatives are very useful as starting materials to produce pharmaceutically and industrially important compounds.[1] It is also well-known that furans are used in acid-catalyzed hydrolysis, autoxidation, Diels–Alder reaction, photocyclization, hydrogenation, substitution, and so on.[1] In connection with the photo-induced naphthalene synthesis using 5-aryl-4,5-dihydrofurans,[2] we have also investigated the photooxygenation of 3-acetyl-5-aryl-2-methylfurans in the presence of Rose Bengal.[3,4] Although the photooxygenation was complicated, we managed to isolate unstable 3-acetyl-1-aryl-2-pentene-1,4-diones **1**.[3,5] In order to scrutinize the properties of the unstable electron-deficient enediones **1**, we embarked on a study of several reactions.

First, we tried to alternatively synthesize 3-acetyl-1-phenyl-2-pentene-1,4-dione (**1a**) from phenylglyoxal and 2,4-pentanedione under normal base conditions,[6] and we found that the Knoevenagel-type condensation in the presence of pyridine gave **1a** in 87% yield (Scheme 1). On the other hand, the acid-catalyzed crossed Aldol condensation of phenylglyoxal (1 mmol) with 2,4-pentanedione (5

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mmol) in the presence of boron trifluoride (5 mmol) was a vigorous exothermic reaction, producing crystalline 3-(3-acetyl-5-phenyl-2-furyl)methyl-4-hydroxy-3-penten-2-one (**2a**, 50%) together with the desired **1a** (12%).[7] Surprisingly, the use of 10 equivalents of 2,4-pentanedione in the same reaction produced **2a** (37%) and isomeric 3-(3-acetyl-2-methyl-5-phenyl-4-furyl)-4-hydroxy-3-penten-2-one (**3a**, 56%). It seemed that the furans **2a** and **3a** were probably formed by the further reaction of **1a** with excess amounts of 2,4-pentanedione. Since the reaction not only trapped the unstable **1a**, but also afforded a novel methodology to prepare polyfunctionalized furans, we focused on the acid-catalyzed reaction of **1a** with 2,4-pentanedione.
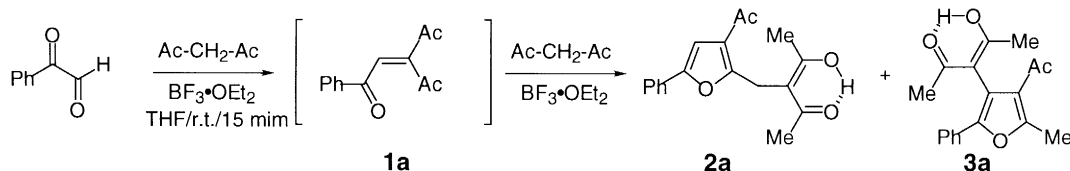
Scheme 1.

The enedione **1a** (1 mmol) was dissolved in tetrahydrofuran (3 mL) under argon, and 2,4-pentanedione (5 mmol) and a boron trifluoride diethyl ether complex (5 mmol) were added to the mixture through a septum by a microsyringe (Scheme 2). The mixture was stirred at room temperature for 30 min. The relatively mild exothermic reaction started and the yellow color of the reaction mixture turned to red although **1a** still remained. Then a further 5 mmols of 2,4-pentanedione and a boron trifluoride diethyl ether complex were added and the reaction mixture was stirred for 1.5 h. Water (20 mL) and then saturated sodium hydrogencarbonate solution (30 mL) were added to decompose the Lewis acid, and the aqueous mixture was then extracted with chloroform (30 mL×3). After separation by flash chromatography eluting with chloroform, crystalline **2a** was actually formed in 66% yield together with isomeric **3a** in 24% yield (Table 1, entry 1). It was easy to distinguish the structure of the furan **2a** from that of **3a** based on their NMR spectra.[8,9] Although both 2,4-pentanedione parts of the furans **2a** and **3a** existed as the enol form, a methylene group was substituted at the C-2$'$ carbon with no substituent present at the C-4$'$ carbon of the furan **2a**, while all of the furan ring carbons of **3a** were substituted by a methyl at the C-2$'$, an acetyl at the C-3$'$, 4-hydroxy-2-oxo-3-penten-3-yl at the C-4$'$, and a phenyl group at the C-5$'$ carbon. In addition, each R_f value of furans **2a** and **3a** was also distinguishable in the TLC spot test.
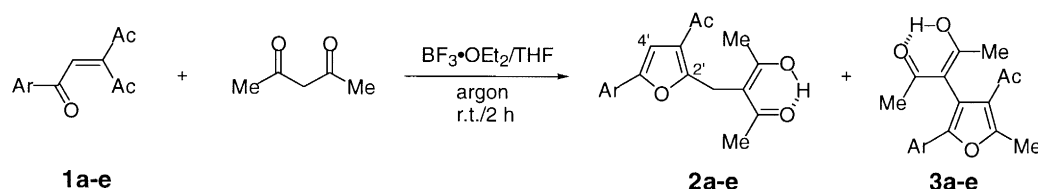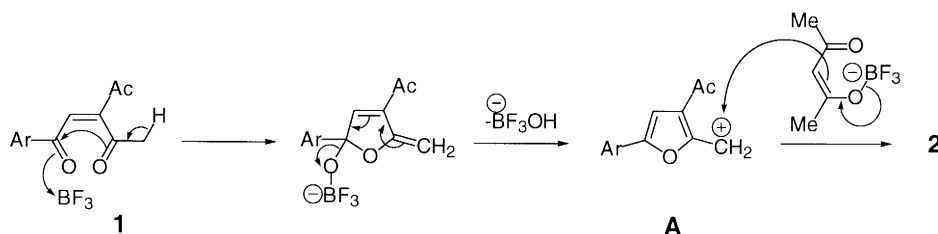

Scheme 2.

Since the unstable enedione **1a** was transformed into the corresponding very stable furans **2a** and **3a** by the acid-catalyzed reaction, we examined the reaction of other unstable enediones **1b–e** isolated by the photooxygenation of the corresponding 3-acetyl-1-aryl-2-methylfurans in 62–69% yields.[3,5] The reaction gave the expected furans **2b–e** and **3b–e** in the yields shown in Table 1 (entries 2–5). An apparent substituent effect was observed in the reaction. That is, the reaction of the phenyl, 4-fluorophenyl, or 4-chlorophenyl-substituted enediones **1a–c** mainly gave the tri-substituted furans **2a–c**, while the reaction of the 4-methylphenyl- or 4-methoxyphenyl-substituted enediones **1d,e** mainly yielded the tetra-substituted furans **3d,e**. When the enedione **1** cyclizes in the presence of boron trifluoride during the first stage, a benzyl type carbocation intermediate **A** would be formed, which would be simultaneously

Table 1

Reaction of 3-acetyl-1-aryl-2-pentene-1,4-diones **1a–e** with 2,4-pentanedione in the presence of the boron trifluoride diethyl ether complex[a]

Entry	Enedione	Product (Yield/%)[b]	
1	**1a**: Ar = Ph	**2a** (66)	**3a** (24)
2	**1b**: Ar = 4-F-C_6H_4	**2b** (53)	**3b** (23)
3	**1c**: Ar = 4-Cl-C_6H_4	**2c** (76)	**3c** (8)
4	**1d**: Ar = 4-Me-C_6H_4	**2d** (34)	**3d** (53)
5	**1e**: Ar = 4-MeO-C_6H_4	**2e** (15)	**3e** (59)

[a] The reaction was carried out in tetrahydrofuran at room temperature for 2 h under argon at the molar ratio of enedione **1**:2,4-pentanedione:boron trifluoride = 1:10:10. [b] Isolated yield based on the amount of the enedione **1** used.

attacked by 2,4-pentanedione to give **2** (Scheme 3). On the other hand, if a 2,4-pentanedione–boron trifluoride complex directly attacks the carbon at the C-2 position of **1**, the addition intermediate **B** would be formed and successive cyclization would afford **3** (Scheme 4). The substituent effect would probably depend on the electrophilicity of the aroyl carbon of the enedione **1**.
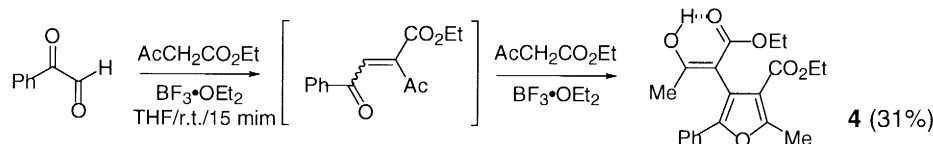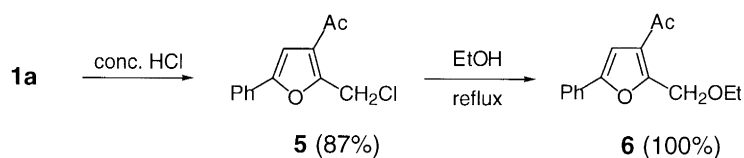

Scheme 3.
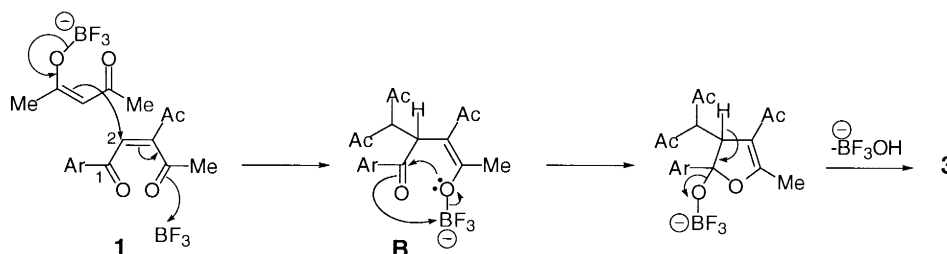
Scheme 4.

A similar acid-catalyzed crossed Aldol condensation of phenylglyoxal with ethyl 3-oxobutanoate (10 equivalents) afforded the corresponding furancarboxylate **4** (31%) along with small amounts of other poly-substituted furans (Scheme 5).

Scheme 5.

The reaction of **1a** in the presence of concentrated hydrochloric acid led to the formation of unstable 3-acetyl-2-chloromethyl-5-phenylfuran **5** which was converted to the stable 3-acetyl-2-ethoxymethyl-5-phenylfuran **6** by treatment with boiling ethanol (Scheme 6).[10]

Scheme 6.

The unstable enediones **1** were trapped by the reaction with 2,4-pentanedione in the presence of boron trifluoride and stable new furan derivatives **2** and **3** were obtained in good yields. In addition, the acid-catalyzed crossed Aldol condensation of phenylglyoxal with several 1,3-dicarbonyl compounds could apply to the synthesis of polyfunctionalized furan derivatives. Although there are many synthetic methods for furans,[11] we are assured that this reaction would be a good technique to synthesize the tri- and tetra-substituted furans.

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8. 3-(3-Acetyl-5-phenyl-2-furyl)methyl-4-hydroxy-3-penten-2-one (**2a**): R_f=0.35; colorless needles (from MeOH); mp 127°C; IR (KBr) ν 3700–3300 (OH), 1673, 1610 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 16.88 (1H, OH), 7.58 (2H, m, arom H), 7.39 (2H, m, arom H), 7.29 (1H, m, arom H), 6.85 (1H, s, H-4′), 4.12 (2H, s, -CH$_2$-), 2.49 (3H, s, Ac), 2.24 (6H, s, Ac×2); ^{13}C NMR (75 MHz, CDCl$_3$) δ 194.6 (C=O), 192.2 (2C, C-2 and C-4), 158.5 (C-2′), 152.5 (C-5′), 129.5 (arom C), 128.9 (2C), 128.2, 123.7 (2C) (arom CH), 122.4 (C-3′), 106.1 (C-3), 105.0 (C-4′), 29.4 (Ac), 26.2 (CH$_2$), 23.5 (Me×2). Anal. calcd for C$_{18}$H$_{18}$O$_4$: C, 72.47; H, 6.08. Found: C, 72.63; H, 6.08.
9. 3-(3-Acetyl-2-methyl-5-phenyl-4-furyl)-4-hydroxy-3-penten-2-one (**3a**): R_f=0.50; colorless needles (from hexane); mp 59–60°C; IR (KBr) ν 3700–3300 (OH), 1679, 1610 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 16.75 (1H, OH), 7.36 (3H, m, arom H), 7.16 (2H, m, arom H), 2.59 (3H, s, Ac), 2.00 (3H, s, Me), 1.92 (6H, s, Ac×2); ^{13}C NMR (75 MHz, CDCl$_3$) δ 196.1 (C=O), 193.7 (2C, C-2 and C-4), 158.1 (C-2′), 144.7 (C-5′), 132.9 (arom C), 129.1 (2C), 128.8 (2C), 127.9 (arom CH), 125.5 (C-4′), 123.3 (C-3′), 103.9 (C-3), 30.8 (Ac), 23.9 (Me×2), 14.5 (Me). Anal. calcd for C$_{18}$H$_{18}$O$_4$: C, 72.47; H, 6.08. Found: C, 72.66; H, 6.31.
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