Dienediones as Building Blocks of an Unfused Polyaromatic Furan Ring System with Tunable Regioselectivity

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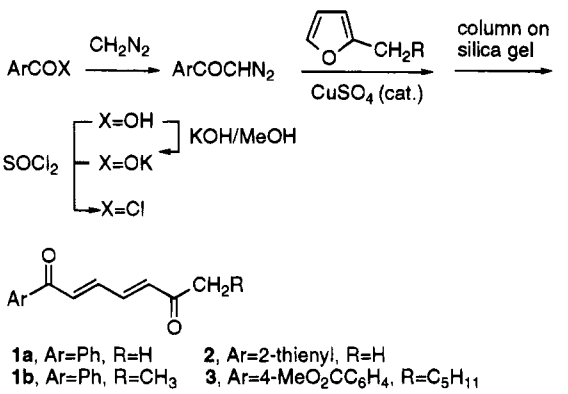
The 1,6-dioxo (*E,E*)-diene has two available sites for isomerization to the (*Z*) configuration and can undergo an intramolecular acid-catalyzed cyclization to furanonium intermediates **A** and **B**, giving two distinct regioisomeric cyclized products. With unsubstituted aryl derivatives, unfused polyaromatic furans were obtained in good yield with HCl–AcOH. Aryl groups having electron-withdrawing substituents were found to give the opposite regioselectivity. In contrast, the reaction in *p*-TsOH–CH_2Cl_2 always resulted in a mixture of regioisomeric products, irrespective of the aryl substituents. Thus, the regioselectivity in the intramolecular cyclization of 1,6-dioxo 2,4-diene can be tuned by varying the aromatic substituents and the acid conditions.

Introduction

The unfused polyaromatic furan is an important structural unit which displays a broad spectrum of biological activities, including antibacterial,[1] antifungal,[2] antidepressant,[3] antiinflammatory,[4] and spaspolytic.[5] In general, the construction of this ring system has involved the use of individual aromatic precursors, for example: (i) treatment of furan with aryldiazonium salt,[4] (ii) irradiation of furan with a high-pressure mercury lamp in aromatic solvents,[6] and (iii) nickel(II)/palladium(II)-catalyzed heteroarylation of heteroarene halide *via* cross coupling with aryl Grignard reagents or zinc halides.[7] None of the above methods is suitable for the direct preparation of arylfurans having substituents on the furan or aromatic ring. Although many methods for the construction of furan from acyclic precursors have been published,[8] preparations of unfused polyaromatic furans from acyclic precursors have rarely been prepared. The condensation of dimethylsulfonium methylide with the enol ether of acyclic β diketones having an aryl substituent was found to give arylfurans *via* the rearrangement of the epoxide intermediate.[9] Also, Padwa[10] has recently described the use of 2,3-dihalo-1-(phenylsulfonyl)-1-propene to obtain arylfurans.

Here we report a new synthesis of unfused arylfurans having substituents at both aromatic rings by an acid-catalyzed cyclization of 1,6-dioxo 2,4-diene derivatives. These new building blocks can be readily prepared by the following methods: (i) transition metal-catalyzed reaction of monosubstituted furans with aromatic diazo ketones,[11] (ii) electrophilic substitution of 1,4-bis(trimethylsilyl)buta-1,3-diene with acyl chlorides,[12] and (iii) palladium-catalyzed isomerization of ynone.[13] We have studied the scope of the reaction with respect to the aromatic rings and their substituents. We have shown that it is possible to control the regioselectivity in the reaction using either concentrated hydrochloric acid in acetic acid or anhydrous *p*-toluenesulfonic acid in dichloromethane.

Scheme 1. Preparations of 1,6-Dioxo (*E,E*)-2,4-Dienes from Diazo Ketones and Furan Derivatives



1a, Ar=Ph, R=H **2**, Ar=2-thienyl, R=H
1b, Ar=Ph, R=CH_3 **3**, Ar=4-$MeO_2CC_6H_4$, R=C_5H_{11}

Results and Discussion

Although various routes to 1,6-dioxo 2,4-diene derivatives have been reported, [11–13] **1a,b**, **2**, and **3** were synthesized according to the method of Wenkert[11] by the decomposition of aromatic diazo ketone with 2-alkylfuran in the presence of a transition metal catalyst (Scheme 1). Copper sulfate performed better than dirhodium tetraacetate as catalyst. The initial product from this reaction has been reported to be the 1,6-dioxo (*E,Z*)-2,4-diene,[11] but on the other hand, the more stable (*E,E*)-

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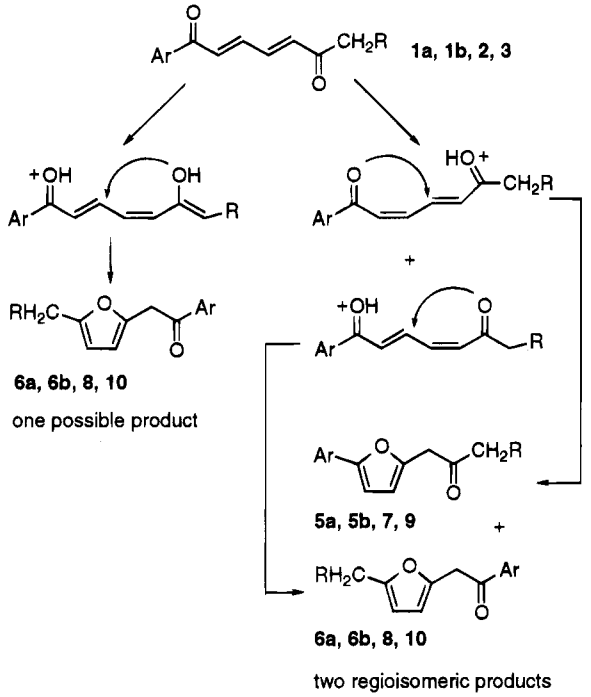
Scheme 2. Potential Mechanism for Furan Formation



diene was obtained as the major product after purification by chromatography on a silica gel column. The conformational constraint of the (*E,E*)-dienes excludes any possible intramolecular reaction.

The strategy employed for the synthesis was based on the facile isomerization of the 1,6-dioxo (*E,E*)-2,4-diene to the (*E,Z*)-diene under acidic conditions. The (*Z*) geometric requirement for the formation of a furan from a dienedione under acidic conditions has been reported.[14] Two modes of reaction exist. As described by Padwa,[10] the (*Z*)-enone having an α proton may enolize under acidic conditions and cyclize onto the (*E*)-enone to form furan. With compounds having one enolizable position, a single product would be expected by this mechanism. Another feasible mechanism is the direct nucleophilic Michael addition of the oxygen lone pair of the carbonyl function of the (*Z*)-enone to the properly aligned (*E*)-enone. The acid thus activates the (*E*)-enone toward a Michael type addition by protonation of a carbonyl group. Since two available sites for isomerization exist in the 1,6-dioxo (*E,E*)-2,4-diene, two distinct regioisomeric products are possible *via* this mechanism (Scheme 2). We set out to rigorously establish the mechanism of the reaction since the potential utility of these reactions could be realized if one could control their regiospecificity.

Reaction of 1,6-dioxo (*E,E*)-2,4-dienes having unsubstituted aryl and thienyl functions, **1a,b** and **2**, in HCl–AcOH were found to give unfused polyaromatic furans **5a,b** and **7** as major products, respectively (Table 1). With the products obtained, the regioselectivity of cyclization could not have arisen *via* enolization, followed by furan ring formation. These results clearly indicate the direct cyclization of the non-enolizable benzoyl carbonyl oxygen onto the enone. Interestingly, the reaction of **3**, which has an electron-withdrawing group on the aryl ring, gave **10** as the major product with the opposite regioselectivity. Since two available isomeric (*E,Z*)- and (*Z,E*)-dienes for

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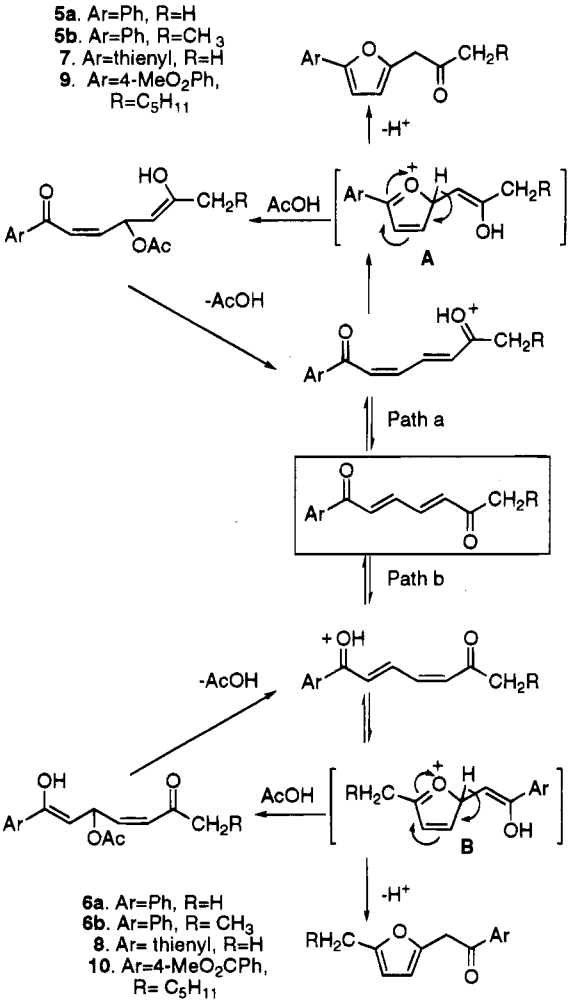
Table 1. Cyclization of Dienedione with HCl–AcOH and *p*-TsOH–CH_2Cl_2

dienedione	reaction condition	combined yield (%)	product ratio[c]
1a	HCl, ACOH[a]	68	**5a:6a** (11:1)
1a	TsOH, CH_2Cl_2[b]	69	**5a:6a** (2.08:1)
1b	HCl, ACOH	59	**5b:6b** (11:1)
1b	TsOH, CH_2Cl_2	86	**5b:6b** (2.09:1)
2	HCl, ACOH	43	**7**
2	TsOH, CH_2Cl_2	50	**7:8** (1.13:1)
3	HCl, ACOH	62	**10**
3	TsOH, CH_2Cl_2	31	**9:10** (1.55:1)

[a] The dienediones were dissolved in acetic acid, a catalytic amount of concentrated HCl was added, and the mixture was stirred overnight. [b] The dienediones were dissolved in CH_2Cl_2, a catalytic amount of *p*-TsOH was added, and the mixture was stirred overnight. [c] The chemical shift for the methylene protons differs for the isomeric products, and their ratio is determined from integration of the crude mixture prior to separation.

Scheme 3. Proposed Reaction Pathways under Reversible and Irreversible Conditions in the Formation of Furans



reaction exists, two distinct regioisomeric products are possible. The reaction pathway most likely would involve the regeneration of (*E,Z*)- and (*Z,E*)-diene from one of the two possible intermediates to give one predominant regioisomeric product. A mechanism that accounts for the regioselectivity observed is summarized in Scheme 3. It is proposed that the starting (*E,E*)-diene is in equilibrium with both the 2,4-(*E,Z*)- and 2,4-(*Z,E*)-dienes, which can cyclize to furanonium intermediates **A** (pathway a) and **B** (pathway b), respectively. Stable fur-

anonium ions are known to exist under acidic conditions.[15] Each furanonium intermediate could undergo either proton loss to form the furan or ring cleavage by nucleophilic attack. If cleavage by the acetate anion takes place prior to furan formation, the starting dienediones are obtained. Thus, equilibration between the two furanonium intermediates can occur. In unsubstituted compounds **1a,b** and **2**, the furanonium intermediate **A** is stabilized by the aromatic ring and loses a proton rapidly to give the highly conjugated arylfurans **5a,b** or thienylfuran **7** as the major products. In acetic acid, however, the more reactive furanonium intermediate **B** undergoes a nucleophilic ring cleavage to regenerate the starting material after elimination of acetic acid and equilibrates to the furanonium intermediate **A**. The opposite regioisomer **10**, obtained with **3**, can thus be rationalized in that the furanonium intermediate **A** is destabilized due to the electron-withdrawing aryl group and upon attack by acetate regenerates the starting material and equilibrates to the more stable furanonium intermediate **B**. The unusual regioselectivity for furan formation can thus be fully rationalized on the basis of the stability of the furanonium intermediates **A** and **B** and the reversiblity when acetic acid is used as solvent. The formation of products **5a,b** and **7** from the cyclization of aromatic ketones without α protons disfavors a mechanism based first on ketone−enol formation, followed by ring closure on the enone and formation of furan as described by Padwa.[10]

The role of acetic acid as a nucleophile, and its influence on the regiocontrol, can be minimized by replacing it with *p*-toluenesulfonic acid in dichloromethane. The reaction of **1a,b**, **2**, and **3** under these new acidic conditions is shown in Table 1. Interestingly, poor regioselectivity was observed in these reactions which gave mixtures of products derived from both furanonium intermediates **A** and **B**, with a slight preponderance of arylfuran or thienylfuran formation. The poor regioselectivity is attributed to the favorable formation of both the (*E,Z*)- and (*Z,E*)-diene isomers with *p*-TsOH in CH_2Cl_2 which on cyclization to the furanonium intermediates **A** and **B** can only undergo a loss of proton to give the furans. The interconversion between the two furanonium intermediates **A** and **B** cannot occur in the absence of a nucleophilic species. In this case, **3** gave both arylfurans **9** and **10**. The cyclization of dienedione with *p*-TsOH in CH_2Cl_2 is under kinetic control, while that in HCl in AcOH is under thermodynamic control.

The two furan products formed during the *p*-TsOH−CH_2Cl_2 cyclization were readily separated by chromatography. The two isomers differ in their 2,5-disubstitution pattern. Structural evidence of the two compounds can be gleened from their individual IR spectra. The unfused aromatic furan **5a** has an unconjugated ketone IR absorption at 1715 cm^{-1}, while regioisomeric **6a** has a conjugated ketone absorption at 1690 cm^{-1}. A general trend observed in the ^1H NMR spectra was a shift of the furan protons to δ 6.60 and 6.27 and an upfield shift of the methylene protons to δ 3.74 in aryl- and thienylfurans such as **5a,b**, **7**, and **9**, relative to the regioisomers **6a,b**, **8**, and **10** which showed furan proton resonances at δ 6.10 and 5.90 and methylene proton resonances at δ 4.25. The ratio of the two isomeric products can be determined from integration of the NMR spectrum of the crude mixture prior to separation.

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The regioselective formation of isomeric furans has been explained on the basis of the differing stabilities of furanonium intermediates **A** and **B**, which is especially important in the HCl−AcOH system. It has been reported that *tert*-butylfurans can form stable furanonium ions under acidic conditions,[15] which may be transformed into some unknown subsequent products. Thus, it was necessary to establish that the regioselectivity observed with HCl−AcOH was not a consequence of the instability of the minor isomer. Pure **6a** obtained after chromatographic separation from the *p*-TsOH−CH_2Cl_2 system was treated with HCl−AcOH, and it was recovered unchanged in near quantitative yield. No **5a** was obtained from **6a**, implying that **6a** does not reform the furanonium intermediate; therefore, no further equilibration occurs. The isomeric products formed appear to be stable under all of the reaction conditions.

Conclusion

These studies provide the groundwork for the rational utilization of acid-catalyzed cyclization of 1,6-dioxo 2,4-diene as a tool for the synthesis of certain aryl- or thienylfurans. Some interesting trends in reactivity are observed. For example, while HCl−AcOH provided clean regioselectivity or one major product, *p*-TsOH−CH_2Cl_2 gave a mixture of regioisomeric products. Thus, the outcome of the HCl−AcOH conditions is dependent on the thermodynamic stability of the intermediates, while that of *p*-TsOH depends on the kinetics of the reaction. The scope of this chemistry can be extended for purposes of total synthesis since 1,6-dioxo 2,4-dienes are readily available by various methods.

Experimental Section

Infrared spectra were determined in $CHCl_3$ and ^1H NMR spectra in $CDCl_3$. Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) was purchased from Aldrich. Compounds **1a,b** and **3** were prepared according to the methods of Wenkert[11] in our previous report.[16]

1-Thienyl-1,6-dioxo-2,4-heptadiene (2). This compound was synthesized previously:[16] yield of 70% as yellow solid; mp 65−66 °C; IR 1695, 1650, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.36 (1H, dd, *J* = 15.0 and 11.5 Hz), 7.78 (1H, d), 7.67 (1H, d), 7.15 (1H, d), 6.98 (1H, d, *J* = 15.0 Hz), 6.58 (1H, dd, *J* = 15 .0 and 11.5 Hz), 6.35 (1H, d, *J* = 11.5 Hz), 2.30 (3H, s); exact mass *m/z* 206.2595, calcd for $C_{11}H_{10}O_2S$ 206.2598. Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89. Found: C, 64.01; H, 4.87.

General Procedure: HCl−AcOH Cyclization Method. To a stirred solution of 2 mmol of 1,6-dioxo (*E,E*)-2,4-diene in 5 mL of AcOH was added one drop of concentrated HCl. The solution was stirred at room temperature overnight and concentrated under reduced pressure. The mixture was extracted with chloroform and purified by chromatography to afford the products. Crude ^1H NMR spectra were obtained prior to purification to determine the ratio of the isomeric products.

***p*-TsOH−CH_2Cl_2 Cyclization Method.** To a stirred solution of 2 mmol of 1,6-dioxo (*E,E*)-2,4-diene in 10 mL of dichloromethane was added 0.2 mmol of anhydrous *p*-TsOH. The solution was stirred at room temperature overnight. Dilute sodium bicarbonate solution was then added and the dichloromethane layer separated. The aqueous layer was further extracted with chloroform. The organic extract was combined and dried over sodium sulfate (anhydrous), and the solvent was evaporated in vacuo. The crude products were purified by chromatography to afford individual isomers.

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2-Phenyl-5-acetonylfuran (**5a**): brownish oil; IR 1715, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (2H, d), 7.34 (3H, m), 6.60 (lH, d, J = 3.2 Hz), 6.27 (1H, d, J = 3.2 Hz), 3.74 (2H, s) 2.18 (3H, s); exact mass 200.0838, calcd. for $C_{13}H_{12}O_2$,200.0842. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.21; H, 6.08.

2-Phenacyl-5-methylfuran (**6a**): brownish oil; IR 1690, 1601 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00 (2H, d), 7.52 (3H, d, J = 7.5 Hz, 1H), 6.08 (1H, d, J = 3.0 Hz), 5.90 (1H, d, J = 3.0Hz), 4.26 (s, 2H), 2.26 (s, 3H); exact mass 200.0847, calcd for $C_{13}H_{12}O_2$ 200.0842. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.73; H, 6.10.

4-[2′-(5′-Phenylfuryl)]butan-3-one (**5b**): brownish oil; IR 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (2H, d), 7.30 (3H, m), 6.60 (1H, d, J = 3.3 Hz), 6.27 (1H, d, J = 3.3 Hz), 3.75 (2H, s), 2.53 (2H, q), 1.06 (3H, t); MS m/z 214 (M). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.20; H, 6.57.

2-Phenacyl-5-ethylfuran (**6b**): brownish oil; IR 1684 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.01 (2H, d), 7.50 (3H, m), 6.11 (1H, d, J = 3.1 Hz), 5.91 (1H, d, J = 3.1 Hz), 4.26 (2H, s), 2.61 (2H, q), 1.19 (3H, t); MS m/z 214 (M). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.23; H, 6.37.

2-Thienyl-5-acetonylfuran (**7**): brownish oil; IR 1712 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.22–7.19 (2H, m), 7.02 (1H, dd), 6.45 (1H, d, J = 3.3 Hz), 6.25 (1H, d, J = 3.3 Hz), 3.74 (2H, s), 2.21 (3H, s); MS m/z 206 (M). Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89. Found: C, 64.29; H, 4.93.

2-Thienacyl-5-methylfuran (**8**): brownish oil; IR 1692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78 (1H, d), 7.65 (1H, d), 7.13 (1H, dd), 6.12 (1H, d, J = 3.1 Hz.), 5.91 (1H, d, J=3.1 Hz), 4.17 (2H, s), 2.26 (3H, s); MS m/z 206 (M). Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89. Found: 64.01; H, 4.94.

[2′-[5′-[4-(α-Methoxybenzoyl)]furyl]]octan-7-one (**9**): yellow solid; mp 72–73 °C; IR 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (2H, d), 7.67 (2H, d), 6.74 (1H, d, J = 3.2 Hz), 6.32 (1H, d, J = 3.2 Hz), 3.92 (3H, s), 3.78 (2H, s), 2.51 (2H, t), 1.59 (2H, brs), 1.25 (6H, brs), 0.85 (3H, t); MS m/z 328. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.30. Found: C, 73.20; H, 7.59.

2-(4-Carbomethoxyphenacyl)-5-hexylfuran (**10**): yellow solid; mp 51–52 °C; IR 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (2H, d), 8.05 (2H, d), 6.11 (1H, d, J = 2.7 Hz), 5.91 (1H, d, J = 2.7 Hz), 4.28 (2H, s), 3.95 (3H, s), 2.56 (2H, t), 1.59 (2H, brs), 1.26 (6H, brs), 0.87 (3H, t); MS m/z 328. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.30. Found: C, 73.15; H, 7.36.

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