Oxidative Aromatization of 2-Acylcyclohexane-1,3-dione Derivatives Using Iodine in Methanol

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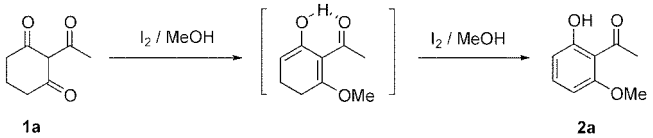
Recently, we are interested in the synthesis of *ortho*-hydroxyacetophenone derivatives.[1] We have developed an efficient method for the synthesis of these compounds from the Baylis-Hillman acetates.[1] As a continuous work we wish to report herein another synthesis of *ortho*-hydroxyacetophenone derivatives from 2-acylcyclohexane-1,3-dione derivatives by the iodine mediated oxidation procedure.

Iodine in methanol has been used as a novel reagent for the conversion of 2-cyclohexen-1-ones into the corresponding anisole derivatives.[2-5] Kotnis reported the aromatization of a wide variety of Hagemann's esters by heating with iodine and methanol to *p*-methoxybenzoates.[2a] It has also been reported that cyclohexenone can be aromatized with iodine and cerium ammonium nitrate in various alcohols.[2b] Originally, Tamura and Yoshimoto have reported the synthesis of anisole derivatives by aromatization of cyclohexeneones using iodine and methanol.[2c] Such a novel aromatization method has been used for the synthesis of natural products, successfully.[3] Hegde and co-workers have reported the aromatization of 2-cyclohexenone-4-carboxylates with iodine and sodium ethoxide to 2-iodophenols.[4] Iodine in methanol can be used for the aromatization of 1,4-dihydropyridines into pyridines[5a] and tetrahydro-4-quinolones into 2-aryl-4-methoxyquinolines.[5b] Recently, fragmentation of bicyclic diones by iodine in methanol has been reported.[6]

However, aromatization of cyclohexane-1,3-dione system has not been studied much.[3,7] Vanadium-induced synthesis of 1,3-diethoxybenzene in low yield from cyclohexane-1,3-dione was reported.[7] Iodine in methanol was used during the synthesis of natural product, rocaglamide,[3a] for the transformation of cyclohexanedione enol ether into anisole derivative. Aromatization of alkyl group-substituted cyclohexane-1,3-diones into the corresponding dimethoxyresorcinols with iodine and methanol was reported by Kotnis.[3b]

In these respects, we reasoned that we could prepare *ortho*-hydroxyacetophenone derivative **2a** from 2-acetylcyclohexane-1,3-dione (**1a**) as shown in Scheme 1. **2a** was stabilized by intramolecular hydrogen bonding and thus the hydroxyl group cannot be converted into methoxy substituent during the aromatization process.[8] As expected, **2a** was obtained in 89% isolated yield from **1a** and iodine (2.0 equiv.) in methanol under reflux condition.

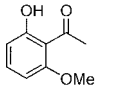
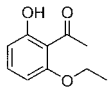
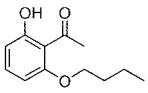
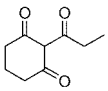
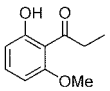
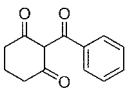
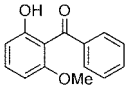
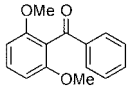
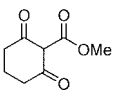
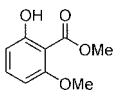
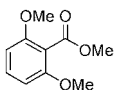
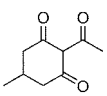
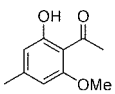
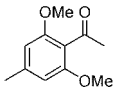
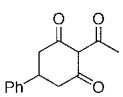
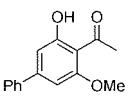
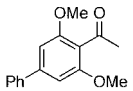


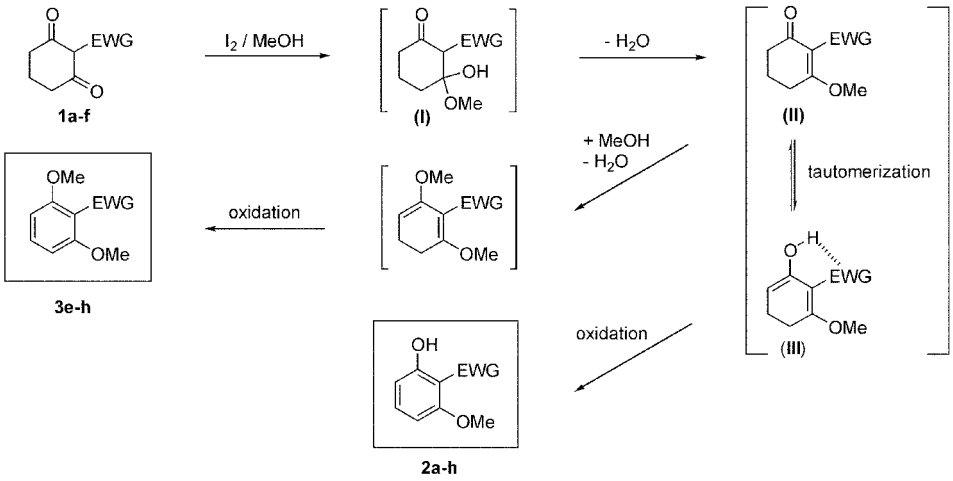
1a 2a

Scheme 1

With these results in hand, we examined the oxidative aromatization reaction of some 2-substituted cyclohexane-1,3-dione derivatives **1**. The reaction of **1a** and iodine in methanol could be extended to ethanol and *n*-butanol successfully (entries 2-3) to give **2b** and **2c**, respectively. As

Table 1. Synthesis of resorcinol derivatives from 2-substituted cyclohexane-1,3-diones

Entry	Substrate	Conditions	Products (% yield)	
1	 **1a**	I_2 (2.0 equiv.) CH_3OH, reflux, 17 h	 **2a** (89)[10a]	
2	**1a**	I_2 (2.0 equiv.) CH_3CH_2OH, reflux, 15 h	 **2b** (70)[10a]	
3	**1a**	I_2 (2.0 equiv.) *n*-BuOH, reflux, 12 h	 **2c** (41)[10a]	
4	 **1b**	I_2 (2.0 equiv.) CH_3OH, reflux, 13 h	 **2d** (79)[10b]	
5	 **1c**	I_2 (2.0 equiv.) CH_3OH, reflux, 14 h	 **2e** (28)[10c]	 **3e** (48)[10d]
6	 **1d**	I_2 (2.0 equiv.) CH_3OH, reflux, 10 h	 **2f** (49)[10c]	 **3f** (26)[10d]
7	 **1e**	I_2 (2.0 equiv.) CH_3OH, reflux, 20 h	 **2g** (63)[10e]	 **3g** (9)[10f]
8	 **1f**	I_2 (2.0 equiv.) CH_3OH, reflux, 20 h	 **2h** (50)[10g]	 **3h** (12)[11]



Scheme 2

shown in Table 1, the reaction of other cyclohexane-1,3-dione derivatives **1b-f**[9] with iodine and methanol afforded the aromatized compounds **2d-h** in good to moderate yields. Monomethoxy compounds were formed exclusively from the acetyl- and propionyl substituted starting materials **1a** and **1b**. We could not obtain dimethoxy compounds in these cases. However, for the benzoyl- (entry 5) or carbomethoxy- (entry 6) substituted **1c** and **1d**, dimethoxy- and monomethoxy compounds were produced as a mixture. This might be due to the weak hydrogen bonding in these cases compared with the acetyl- or propionyl analogs. For the 5-substituted cyclohexane-1,3-diones (entries 7-8), momo- and dimethoxy derivatives were isolated as a mixture in variable ratios also. The reason is not clear at this point.

The reaction mechanism is thought to be as follows (Scheme 2).[2d,5] (1) Formation of hemiketal **I** followed by dehydration afforded 3-methoxycyclohexene-1-one derivative **II**. The intermediate **II** might be present in equilibrium with its enol form **III**, which stabilized by the intramolecular hydrogen bonding with the oxygen atom of the EWG. (2) Iodine assisted oxidative dehydrogenation of **III** gave the desired momomethoxy compounds **2a-h**. Dimethoxy derivatives **3e-h** were formed *via* the sequential addition of methanol, dehydration followed by oxidation process from **II** as shown.

In summary, the reaction of cyclohexane-1,3-diones with electron withdrawing substituents at the 2-position with iodine in methanol afforded the corresponding monomethoxy resorcinol derivatives as the major products.

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8. The reaction of cyclohexane-1,3-dione itself in the same reaction conditions (I_2, MeOH, reflux, 4 h) afforded dimethoxy resorcinol in 74% yield.
9. Starting materials **1a-f** were prepared as follows. (1) Synthesis of *O*-acyl derivatives (70-87%) by the reaction of the corresponding cyclohexane-1,3-diones and acetyl chloride, propionyl chloride, benzoyl chloride, and methyl chloroformate in CH_2Cl_2 in the presence of Et_3N. (2) Isomerization of the initially obtained *O*-acyl derivatives into desired **1** (71-84%) by the use of KCN/Et_3N in CH_3CN as reported (For the isomerization of enol esters, see: Montres, I. F.; Burger, U. *Tetrahedron Lett*. **1996**, *37*, 1007).
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11. The synthesis of **2a** is typical. A solution of **1a** (100 mg, 0.65 mmol) and iodine (330 mg, 1.3 mmol) in methanol (5 mL) was heated at reflux for 17 h. The reaction mixture was diluted with methylene chloride and washed with aqueous $NaHSO_3$ solution and brine. After removal of solvent and flash column chromatographic separation process (hexane/ether, 40 : 1), we could obtain **2a** as a white solid, 96 mg (89%). The synthesized compounds were identified from their melting points, ^1H and ^{13}C NMR spectra and/or IR, mass spectra by comparison with the reported data (see Table for the references).[10] The selected spectroscopic data of the unknown compound **3h** is as follows: mp 131-133 °C; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H), 3.87 (s, 6H), 6.74 (s, 2H), 7.34-7.48 (m, 3H), 7.54-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 32.41, 55.96, 103.32, 119.36, 127.26, 127.98, 128.84, 141.08, 144.42, 157.06, 202.49.