

Notes

Synthesis of Anisole Derivatives from 4-Alkylidene-2-cyclohexen-1-ones with Iodine in Methanol

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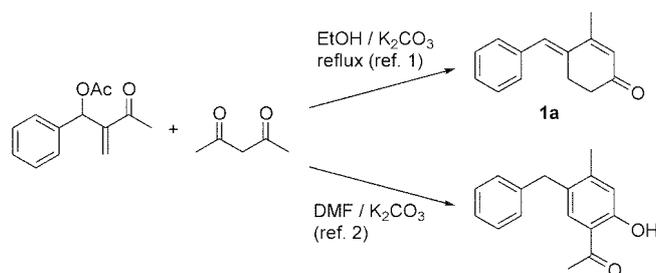
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Chamakh and Amri have reported the synthesis of 4-alkylidene-2-cyclohexen-1-ones from the reaction of Baylis-Hillman acetates and β -diketones in ethanol in the presence of K_2CO_3 (Scheme 1).¹ Recently, we have reported the facile synthesis of *ortho*-hydroxyacetophenones from the same reaction in DMF (Scheme 1).² Besides *ortho*-hydroxyacetophenones, we are recently interested in the synthesis of aromatic and heteroaromatic compounds from Baylis-Hillman adducts, which included quinolines or naphthalenes.³ In these respects, we examined the possibility of converting 4-alkylidene-2-cyclohexen-1-ones **1** to the corresponding aromatic compounds such as anisole or phenol derivatives. Suitably substituted phenol or anisole derivatives are useful as starting materials for the preparation of fragrances, dyes and pesticides, as antioxidants in oils and fats or as stabilizers of plastics.⁴

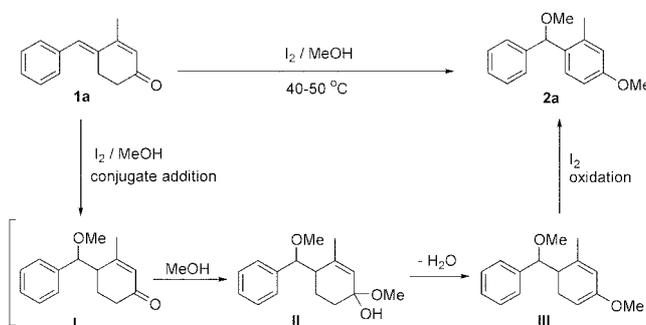


Scheme 1

Kotnis reported the aromatization of a wide variety of Hagemann's esters by heating with iodine and methanol to *p*-methoxybenzoates.^{5a} It has also been reported that cyclohexenone can be aromatized with iodine, cerium ammonium nitrate in various alcohols.^{5b} Originally, Tamura and Yoshimoto have reported the synthesis of anisole derivatives by aromatization of cyclohexenones using iodine and methanol.^{5c} Such a novel aromatization method has been used for the synthesis of natural products, successfully.⁶ Hegde and co-workers have reported the aromatization of 2-cyclohexenone-4-carboxylates with iodine and sodium ethoxide to 2-iodophenols.⁷ Iodine-methanol system can be used for the

aromatization of 1,4-dihydropyridines into pyridines^{8a} and tetrahydro-4-quinolones into 2-aryl-4-methoxyquinolines.^{8b} Recently, iodine-methanol induced fragmentation of bicyclic diones has been reported.⁹ These reports confirmed the feasibility for the synthesis of anisole derivatives from 4-alkylidene-2-cyclohexen-1-ones (Scheme 2). Exo-methylene moiety in the starting materials might have the key for the successful reaction. We thought that the initial conjugate addition of methanol could be possible to produce the intermediate **I**, which could undergo the next aromatization reaction according to the reported process.

As expected, anisole derivative **2a** was obtained in 64%



Scheme 2

isolated yield from the reaction of **1a** and iodine (1.1 equiv.) in methanol at 40-50 °C (Scheme 2). As shown in Scheme 2, the mechanism could be thought as follows. (1) Conjugate

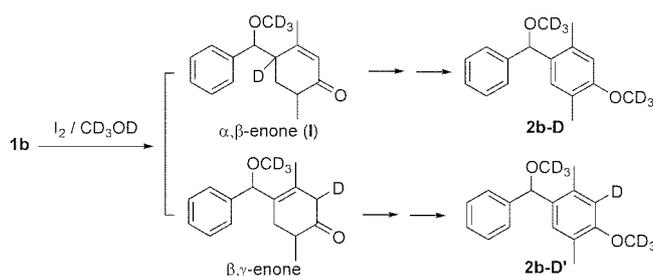
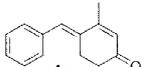
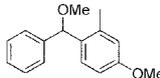
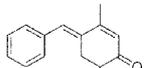
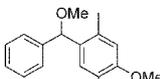
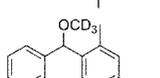
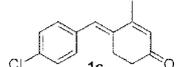
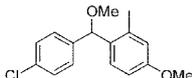
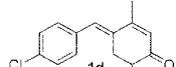
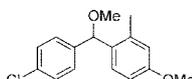
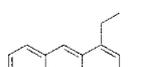
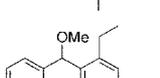
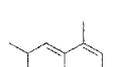
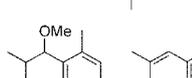
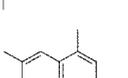
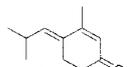
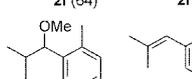
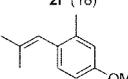


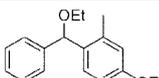
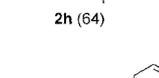
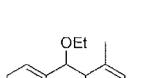
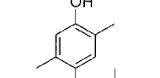
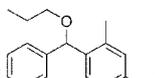
Figure 1

Table 1. Synthesis of anisoles with iodine/MeOH

entry	substrate	conditions	products (%)
1		I ₂ (1.1 equiv.) MeOH 40-50 °C, 7 h	 2a (64)
2		I ₂ (1.1 equiv.) MeOH 40-50 °C, 1 h	 2b (72)
3		I ₂ (1.1 equiv.) CD ₃ OD reflux, 1 h	 2b-D (32)
4		I ₂ (1.1 equiv.) MeOH 40-50 °C, 3 h	 2c (66)
5		I ₂ (1.1 equiv.) MeOH 40-50 °C, 2 h	 2d (81)
6		I ₂ (1.1 equiv.) MeOH 40-50 °C, 1 h	 2e (62)
7		I ₂ (1.1 equiv.) MeOH 40-50 °C, 1 h	 2f (64)  2f' (18)
8		I ₂ (1.1 equiv.) MeOH 40-50 °C, 1 h	 2g (64)  2g' (6)

addition of methanol to **1a** to give **I** (vide infra, Figure 1).¹⁰ (2) Formation of hemiketal **II** followed by dehydration into **III**.^{8b} (3) Iodine catalyzed oxidation of **III** to give the desired product **2a**.^{8a} The reaction of **1b** with iodine in deuterated methanol, CD₃OD, afforded **2b-D** in 32% isolated yield (entry 3 in Table 1).¹¹ The other plausible product **2b-D'** with deuterium at the 2-position of anisole moiety was not observed, from which we proposed the first step as the conjugate addition to generate α,β -enone derivative (Figure

Table 2. Some other results from the reaction of **1b**

entry	conditions	products (%)
1	I ₂ (1.1 equiv.) EtOH 40-50 °C, 3 h	 2h (64)
2	I ₂ (1.1 equiv.) EtOH 40-50 °C, 16 h	 2h (12)  2h' (17)  2h'' (20)
3	I ₂ (1.1 equiv.) CH ₃ CH ₂ CH ₂ OH 40-50 °C, 3 h	 2i (50)

1).^{10,11} Similar results were observed with various 4-alkylidene-2-cyclohexen-1-ones **1b-g**. Representative results are summarized in Table 1. Starting materials, 4-alkylidene-2-cyclohexen-1-ones **1a-g**, were prepared according to the Amri's procedure from the reaction of Baylis-Hillman acetates and β -diketones in ethanol in the presence of K₂CO₃.¹

The reaction of **1b** and iodine in other alcohol solvents such as ethanol or *n*-propanol gave the corresponding aromatized compounds **2h** and **2i** in moderate yields. When the reaction was performed at elevated temperature (entry 2 in Table 2) unusual compound such as **2h''** was isolated.¹² Experimental procedure and spectroscopic data of some of the synthesized compounds are summarized in experimental section.

In summary, we applied the well-known iodine-methanol system for the synthesis of highly substituted anisole derivatives. The results extended the useful aromatization method to the cyclohexenone system containing exocyclic double bond for the first time. Studies on the mechanism for the formation of some unusual compounds including **2f'**, **2g'**, **2h'** and **2h''** and the study for the synthesis of phenolic compounds selectively are underway.

Experimental Section

Typical procedure: A stirred solution of **1a** (198 mg, 1.0 mmol) and iodine (280 mg, 1.1 mmol) in methanol (3 mL) was gently heated to 40-50 °C for 7 h. The reaction mixture was poured into cold water and extracted with ether. The organic phase was washed successively with NaHSO₃ solution and brine. After removal of solvent and following column chromatographic purification (hexane/ether, 50 : 1) desired **2a** was obtained as an oil, 155 mg (64%). Spectroscopic data of **2a** was as follows. ¹H NMR (CDCl₃) δ 2.26 (s, 3H), 3.36 (s, 3H), 3.77 (s, 3H), 5.36 (s, 1H), 6.69-6.75 (m, 2H), 7.22-7.32 (m, 6H); ¹³C NMR (CDCl₃) δ 19.55, 55.11, 56.91, 82.33, 110.91, 116.18, 127.28, 127.31, 128.24, 128.38, 131.96, 137.59, 141.37, 158.78; Mass (70 eV) *m/z* (rel intensity) 77 (14), 105 (17), 149 (17), 165 (87), 211 (100), 242 (M⁺, 45).

Selected spectroscopic data of **2b-D**, **2f'** and **2h''** are as follows.

2b-D: white solid; mp 67-68 °C; ¹H NMR (CDCl₃) δ 2.17 (s, 3H), 2.26 (s, 3H), 5.36 (s, 1H), 6.59 (s, 1H), 7.12 (s, 1H), 7.22-7.31 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 15.89, 19.40, 54.44 (septet, *J*_{C-D} = 21.5 Hz), 56.06 (septet, *J*_{C-D} = 21.5 Hz), 82.07, 112.10, 123.80, 127.17, 127.20, 128.23, 129.33, 131.12, 134.37, 141.62, 156.74.

2f': oil; ¹H NMR (CDCl₃) δ 1.69 (d, *J* = 0.9 Hz, 3H), 1.88 (d, *J* = 0.9 Hz, 3H), 2.17 (s, 3H), 2.20 (s, 3H), 3.81 (s, 3H), 6.13 (br s, 1H), 6.64 (s, 1H), 6.89 (s, 1H); ¹³C NMR (CDCl₃) δ 15.73, 19.23, 19.92, 26.02, 55.29, 111.48, 122.96, 123.64, 129.81, 131.66, 134.06, 134.65, 155.94.

2h'': white solid; mp 219-220 °C (lit.¹² 229-230 °C); IR (KBr) 3344 cm⁻¹; ¹H NMR (CDCl₃ + DMSO-d₆) δ 2.04 (s, 6H), 2.07 (s, 6H), 5.45 (s, 1H), 6.42 (s, 2H), 6.62 (s, 2H), 7.00-7.31 (m, 5H), 7.39 (s, D₂O exchangeable, 2H); ¹³C NMR (CDCl₃ + DMSO-d₆) δ 15.84, 19.19, 49.00, 116.92,

120.80, 125.71, 128.01, 129.69, 131.58, 133.48, 134.72, 144.08, 152.81; Mass (70 eV) m/z (rel intensity) 195 (42), 209 (27), 255 (36), 317 (100), 332 (M^+ , 89).

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