Synthesis of 4-Methylene-2-cyclohexenones and Their Aromatization Reaction toward *para*-Methoxylmethyl Anisole Derivatives

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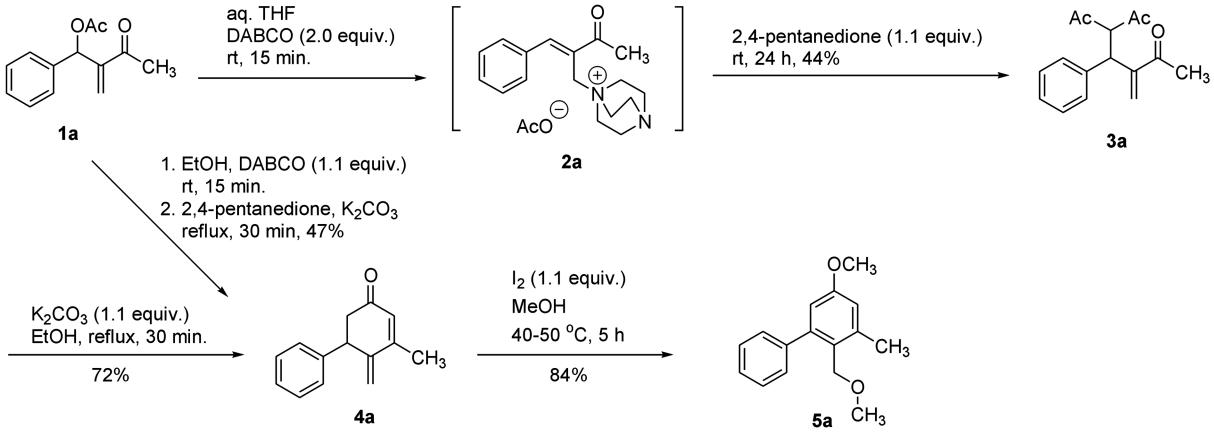
Recently, we have reported on the synthesis of anisole derivatives from 4-alkylidene-2-cyclohexene-1-ones with iodine in methanol.[1] 4-Alkylidene-2-cyclohexene-1-ones could be synthesized from the reaction of Baylis-Hillman acetates and 2,4-pentanedione according to the reported procedure by Chamakh and Amri.[2]

We and other groups have reported the selective introduction of nucleophiles at the secondary benzylic position of the Baylis-Hillman acetates via the corresponding DABCO salts.[3] Thus, we envisioned that we could prepare 4-methylene-2-cyclohexenone skeleton and *para*-methoxymethyl anisoles by combining the DABCO salt concept and the aromatization reaction with iodine in methanol.[1,3] Suitably substituted anisoles are useful as the starting materials for the fragrances, dyes and pesticides, as antioxidants in oils and fats, or as stabilizers of plastics.[4] Moreover, *para*-methoxymethyl anisoles have been used for the kinetic acetalization of diol or amino alcohol systems in the presence of DDQ[5] during the synthesis of (+)-FR900482,[5b] taxotere side chain,[5c] cyclopropyl lactone oxylipins,[5d] and erythromycin A.[5e]

Our synthetic scheme for the synthesis of 4-methylene-2-cyclohexenone skeleton and *para*-methoxymethyl anisole is shown in Scheme 1 by using **4a** and **5a** as the representative examples. The reaction of the Baylis-Hillman acetate **1a** and DABCO in aqueous THF gave the corresponding DABCO salt **2a** instantaneously as reported.[3] The reaction of the DABCO salt **2a** and 2,4-pentanedione afforded the intermediate **3a** in moderate yield (44%). During the synthesis of **3a**, some side products were produced (including dihydropyran skeleton),[6] which diminished the yield of **3a**. With the compound **3a** in our hand, we examined the next conversion toward 4-methylene-2-cyclohexeneone **4a** by using the Amri's conditions (K_2CO_3 in ethanol)[2] and we could prepare 4-methylene-2-cyclohexenone **4a** in good yield (72%).[7] The synthesis of **4a** was tried by using the modified conditions in order to improve the yield of **4a** as follows. In situ generation of the DABCO salt **2a** in ethanol and the following reaction with 2,4-pentanedione in the presence of K_2CO_3 gave **4a** in a similar isolated yield (47%) (Scheme 1).[8] The use of ethyl acetoacetate instead of 2,4-pentanedione also gave **4a** in lower yield (not shown in Scheme 1). The structure of **4a** was confirmed as shown in Table 1 by NOE experiments. As an example, irradiation of the methyl group (δ = 2.11 ppm) of **4a** showed increments of the proton at the 2-position (δ = 6.00 ppm) and one of the methylene protons (δ = 5.51 ppm) in 0.6 and 0.7%, respectively. As the final step, the reaction of **4a** and iodine (1.1 equiv.) in methanol (40-50 °C) afforded methoxymethyl anisole **5a** in good yield (84%).[9] Similarly, **5c** and **5e** were synthesized in good yields from **4b** and **4c**. As shown in Table 1, the use of ethanol as the solvent afforded the ethoxymethyl phenetole derivatives



Scheme 1

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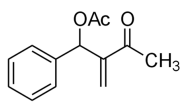
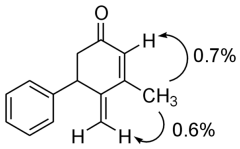
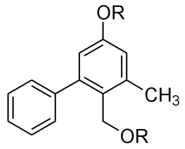
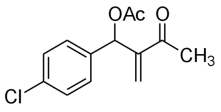
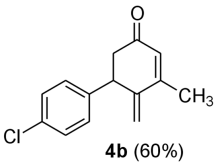
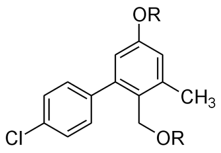
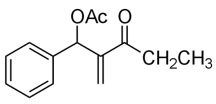
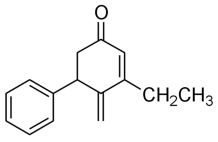
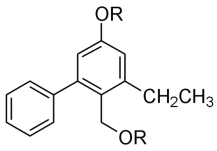
Table 1. Synthesis of 4-methylene-2-cyclohexenones **4**, 4-methoxymethyl anisoles **5a**, **5c**, **5e**, and 4-ethoxymethyl phenetoles **5b**, **5d**, **5f**

Entry	B-H acetate **1**	Conditions	Cyclohexenone **4**	Conditions	Product **5**
1 2	 **1a**	(1). DABCO (2.0 equiv.) aq. THF, rt, 15 min. (2). 2,4-pentanedione (1.1 equiv.) rt, 24 h, **3a** (44%) (3). K_2CO_3 (1.1 equiv.) EtOH, reflux, 30 min.	 **4a** (72%)	I_2 (1.1 equiv.) MeOH, 40-50 °C 5 h I_2 (1.1 equiv.) EtOH, 40-50 °C 12 h	 **5a** (R = Me, 84%) **5b** (R = Et, 77%)
3 4	 **1b**	(1). DABCO (2.0 equiv.) aq. THF, rt, 15 min. (2). 2,4-pentanedione (1.1 equiv.) rt, 24 h, **3b** (25%) (3). K_2CO_3 (1.1 equiv.) EtOH, reflux, 30 min.	 **4b** (60%)	I_2 (1.1 equiv.) MeOH, 40-50 °C 3 h I_2 (1.1 equiv.) EtOH, 40-50 °C 12 h	 **5c** (R = Me, 88%) **5d** (R = Et, 75%)
5 6	 **1c**	(1). DABCO (2.0 equiv.) aq. THF, rt, 15 min. (2). 2,4-pentanedione (1.1 equiv.) rt, 24 h, **3c** (45%) (3). K_2CO_3 (1.1 equiv.) EtOH, reflux, 30 min.	 **4c** (59%)	I_2 (1.1 equiv.) MeOH, 40-50 °C 4 h I_2 (1.1 equiv.) EtOH, 40-50 °C 12 h	 **5e** (R = Me, 78%) **5f** (R = Et, 70%)

5b, **5d**, and **5f**. When we used ethanol, somewhat longer reaction time was required.

In summary, we have developed an efficient synthetic methodology for the synthesis of 4-methylene-2-cyclohexenones, 4-methoxymethyl anisoles, and 4-ethoxymethyl phenetoles in moderate yields, starting from the Baylis-Hillman acetates.

Experimental Section

Typical procedure for the synthesis of 3a. To a stirred solution of the Baylis-Hillman acetate (**1a**, 436 mg, 2 mmol) in aq. THF (THF/H_2O = 3 : 1, 10 mL) was added DABCO (448 mg, 4 mmol) and stirred at room temperature for 15 min. To the reaction mixture 2,4-pentanedione (220 mg, 2.2 mmol) was added and stirred at room temperature for 24 h. After the normal aqueous workup and column chromatographic purification process (hexanes/ether, 4 : 1) pure **3a** was obtained, 228 mg (44%). Spectroscopic data of prepared compounds are as follows. **3a**: 44%; ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H), 2.15 (s, 3H), 2.26 (s, 3H), 4.56 (d, J = 12.6 Hz, 1H), 4.90 (d, J = 12.6 Hz, 1H), 5.93 (s, 1H), 6.13 (s, 1H), 7.17-7.27 (m, 5H). **3b**: 25%; ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H), 2.14 (s, 3H), 2.26 (s, 3H), 4.55 (d, J = 12.6 Hz, 1H), 4.88 (d, J = 12.6 Hz, 1H), 5.94 (s, 1H), 6.15 (s, 1H), 7.14-7.30 (m, 4H). **3c**: 45%; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 6.6 Hz, 3H), 1.89 (s, 3H), 2.15 (s, 3H), 2.50-2.70 (m, 2H), 4.57 (d, J = 12.6 Hz, 1H), 4.89 (d, J = 12.6 Hz, 1H), 5.86 (s, 1H), 6.09 (s, 1H), 7.15-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.04, 28.29, 30.60, 31.39, 45.07, 73.41, 123.54, 127.18, 128.24, 128.68, 138.98, 148.52, 201.28, 202.64, 202.80.

Typical procedure for the synthesis of 4a. To a stirred solution of **3a** (129 mg, 0.5 mmol) in ethanol (5 mL) was added K_2CO_3 (76 mg, 0.55 mmol) and heated to reflux for 30 min. After the normal aqueous workup and column chromatographic purification process (hexanes/ether, 10 : 1) pure **4a** was obtained, 72 mg (72%). **4a**: 72%; IR (KBr) 1666, 1585, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.11 (d, J = 1.5 Hz, 3H), 2.77 (dd, J = 16.1 and 5.5 Hz, 1H), 2.91 (dd, J = 16.1 and 9.3 Hz, 1H), 4.01-4.06 (m, 1H), 5.06 (app t, J = 1.5 Hz, 1H), 5.51 (s, 1H), 6.00 (s, 1H), 7.19-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.62, 43.74, 46.81, 117.99, 127.05, 127.86, 127.88, 128.61, 141.29, 146.05, 154.08, 198.35. **4b**: 60%; white solid, mp 99-100 °C; IR (KBr) 1658, 1585, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.11 (d, J = 1.2 Hz, 3H), 2.75 (dd, J = 16.1 and 5.6 Hz, 1H), 2.86 (dd, J = 16.1 and 9.0 Hz, 1H), 3.99-4.04 (m, 1H), 5.06 (app t, J = 1.6 Hz, 1H), 5.26 (s, 1H), 5.99 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.56, 43.55, 46.15, 118.12, 127.86, 128.72, 129.14, 132.79, 139.72, 145.57, 153.90, 197.87. **4c**: 59%; IR (KBr) 1666, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.5 Hz, 3H), 2.46 (qd, J = 7.5 and 1.2 Hz, 2H), 2.78 (dd, J = 16.2 and 5.5 Hz, 1H), 2.93 (dd, J = 16.2 and 9.1 Hz, 1H), 4.00-4.05 (m, 1H), 5.06 (app t, J = 1.2 Hz, 1H), 5.53 (s, 1H), 5.99 (s, 1H), 7.19-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.36, 25.29, 42.66, 46.23, 116.04, 124.71, 126.00, 126.83, 127.55, 140.16, 144.25, 158.38, 197.67.

Typical procedure for the synthesis of 5a. A stirred

solution of **4a** (99 mg, 0.5 mmol) and iodine (140 mg, 0.55 mmol) in methanol (3 mL) was heated to 40-50 °C during 5 h. After the normal aqueous workup and column chromatographic purification process (hexanes/ether, 20 : 1) pure **5a** was obtained, 102 mg (84%).

5a: 84%; mp 56-58 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.28 (s, 3H), 3.78 (s, 3H), 4.19 (s, 2H), 6.67 (d, J = 2.7 Hz, 1H), 6.77 (d, J = 2.7 Hz, 1H), 7.34-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.59, 55.17, 57.81, 69.32, 112.52, 115.47, 126.07, 126.98, 127.88, 129.26, 140.52, 141.65, 144.82, 158.60; Mass (70 eV) *m/z* (rel intensity) 165 (28), 196 (43), 211 (100), 242 (M^+, 57).

5b: 77%; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3H), 1.38 (t, J = 7.2 Hz, 3H), 2.45 (s, 3H), 3.42 (q, J = 7.2 Hz, 2H), 4.02 (q, J = 7.2 Hz, 2H), 4.23 (s, 2H), 6.66 (d, J = 2.7 Hz, 1H), 6.76 (d, J = 2.7 Hz, 1H), 7.33-7.44 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.82, 15.27, 19.65, 63.34, 65.50, 67.33, 113.24, 116.14, 126.10, 126.91, 127.82, 129.32, 140.43, 141.77, 144.73, 157.95; Mass (70 eV) *m/z* (rel intensity) 197 (57), 225 (100), 241 (38), 270 (M^+, 83).

5c: 88%; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.30 (s, 3H), 3.79 (s, 3H), 4.15 (s, 2H), 6.62 (d, J = 2.6 Hz, 1H), 6.77 (d, J = 2.6 Hz, 1H), 7.32-7.40 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 18.60, 54.21, 56.93, 68.25, 111.53, 114.61, 125.03, 127.08, 129.59, 132.14, 139.04, 139.69, 142.58, 157.70; Mass (70 eV) *m/z* (rel intensity) 195 (37), 209 (90), 245 (100), 276 (M^+, 77), 278 (M^++2, 27).

5d: 75%; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 6.9 Hz, 3H), 1.39 (t, J = 6.9 Hz, 3H), 2.44 (s, 3H), 3.44 (q, J = 6.9 Hz, 2H), 4.02 (q, J = 6.9 Hz, 2H), 4.19 (s, 2H), 6.61 (d, J = 2.4 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 7.36 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 14.80, 15.28, 19.64, 63.38, 65.63, 67.26, 113.24, 116.24, 126.03, 128.00, 130.62, 133.06, 140.15, 140.59, 143.48, 158.04; Mass (70 eV) *m/z* (rel intensity) 196 (47), 223 (70), 231 (43), 259 (100), 304 (M^+, 70), 306 (M^++2, 23).

5e: 78%; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3H), 2.80 (q, J = 7.5 Hz, 2H), 3.27 (s, 3H), 3.81 (s, 3H), 4.19 (s, 2H), 6.67 (d, J = 2.7 Hz, 1H), 6.82 (d, J = 2.7 Hz, 1H), 7.35-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.56, 25.87, 55.23, 57.79, 68.83, 112.43, 113.89, 125.55, 127.00, 127.88, 129.35, 141.87, 145.11, 146.49, 158.89; Mass (70 eV) *m/z* (rel intensity) 165 (37), 195 (55), 224 (100), 256 (M^+, 61).

5f: 70%; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 6.9 Hz, 3H), 1.30 (t, J = 7.5 Hz, 3H), 1.40 (t, J = 6.9 Hz, 3H), 2.80 (q, J = 7.5 Hz, 2H), 3.41 (q, J = 6.9 Hz, 2H), 4.03 (q, J = 6.9 Hz, 2H), 4.23 (s, 2H), 6.66 (d, J = 2.7 Hz, 1H), 6.81 (d, J = 2.7 Hz, 1H), 7.31-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.84, 15.28, 15.50, 25.87, 63.33, 65.46, 66.79, 113.07, 114.52, 125.55, 126.88, 127.76, 129.37, 141.96, 144.97, 146.36, 158.20; Mass (70 eV) *m/z* (rel intensity) 165 (41), 183 (43), 238 (100), 255 (30), 284 (M^+, 55).

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