

# Studies on Hydroiodination and Deconjugation of 5-Aryloxy-(thiophenyl)-3-pentyn-2-one

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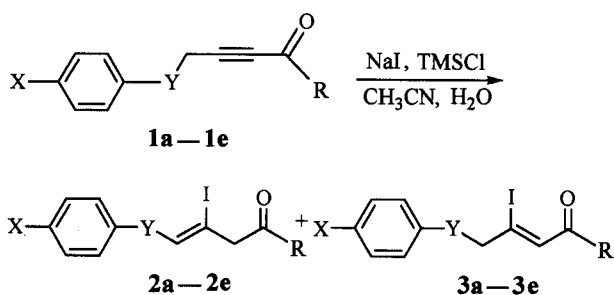
One-pot hydroiodination and deconjugation of 5-aryloxy (or thiophenyl)-3-pentyn-2-one with a reagent system of sodium iodide/trimethylsilyl chloride/water in acetonitrile at 25 °C have been described. The plausible mechanism was discussed. The reaction provided a simple and useful method for the preparation of (*Z*)- $\beta$ -substituted  $\beta, \gamma$ -enones and (*Z*)- $\beta$ -substituted  $\alpha, \beta$ -unsaturated ketones.

**Keywords**  $\beta$ -substituted  $\beta, \gamma$ -enone, hydroiodination, deconjugation

The synthesis of  $\beta$ -substituted  $\beta, \gamma$ -enones is still a synthetic challenge due to the easy migration of carbon-carbon double bond from the  $\beta, \gamma$ -position to the  $\alpha, \beta$ -position.<sup>1,2</sup> Most of the earlier known methods for isomerization or deconjugation of  $\alpha, \beta$ -unsaturated carbonyl compounds involved a base<sup>3-5</sup> or were done under photochemical conditions.<sup>6</sup> Recently, Ma *et al.*<sup>7</sup> reported that hydrohalogenation reaction of 1,2-allenyl ketones with metal halides could afford  $\beta$ -substituted  $\beta, \gamma$ -enones. Luo *et al.*<sup>8</sup> reported that the reaction of conjugated acetylenic ketones with hydrogen iodide *in situ* generated from sodium iodide/trimethylsilyl chloride/water, then with the organozinc compounds in the presence of palladium catalyst, brought about various substituted  $\beta, \gamma$ -enones. Under NaI/TMSCl/H<sub>2</sub>O/CH<sub>3</sub>CN system, conjugated acetylenic ketones gave (*Z*)- $\beta$ -iodo- $\beta, \gamma$ -enones with a purity of 95% as the hydroiodination product.<sup>9</sup> However, the hydrohalogenation of  $\gamma$ -heteroatom conjugated acetylenic ketones has not been reported in the literature. We now report that the preparation of conjugated (*3Z*)-5-aryloxy-

(or thiophenyl)-4-iodo-3-penten-2-one and deconjugated (*4Z*)-5-aryloxy (or thiophenyl)-4-iodo-4-penten-2-one from 5-aryloxy (or thiophenyl)-3-pentyn-2-one at room temperature (Scheme 1).

Scheme 1



R = 3,4,5-trimethoxyphenyl or CH<sub>3</sub>

X = H or F; Y = O or S

The results are summarized in Table 1. The *Z*-configuration of the double bond was determined by 2D NOESY (phase sensitive) <sup>1</sup>H NMR spectral analyses. Water has a dramatic effect on the reaction. In the absence of water, 5-phenoxy-3-pentyl-2-one was recovered with more than 75% after 3 h under the reaction conditions of TMSCl/NaI/CH<sub>3</sub>CN system. The reaction afforded the deconjugated product **2** in 25% yield and the conjugated iodinated ketone **3** in 39% yield with 1 equiv. of H<sub>2</sub>O, meanwhile, (*E*)-5-phenoxy-4-iodo-3-pentene-2-one was obtained in 23% yield.

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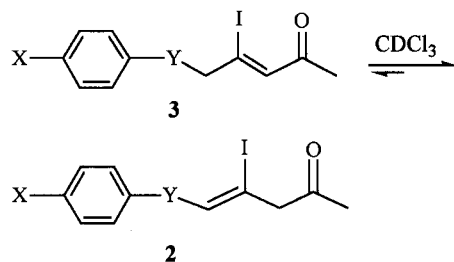
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**Table 1** Hydroiodination of 5-aryloxy(thiophenyl)-3-pentyn-2-one<sup>a</sup>

Entry	X	Y	R	Yield of <b>3</b> (%)	Yield of <b>2</b> (%)
<b>1a</b>	H	O	CH <sub>3</sub>	15	65
<b>1b</b>	F	O	CH <sub>3</sub>	18	61
<b>1c</b>	H	O	3,4,5-trimethoxyphenyl	17	62
<b>1d</b>	F	O	3,4,5-trimethoxyphenyl	13	64
<b>1e</b>	H	S	CH <sub>3</sub>	25	53

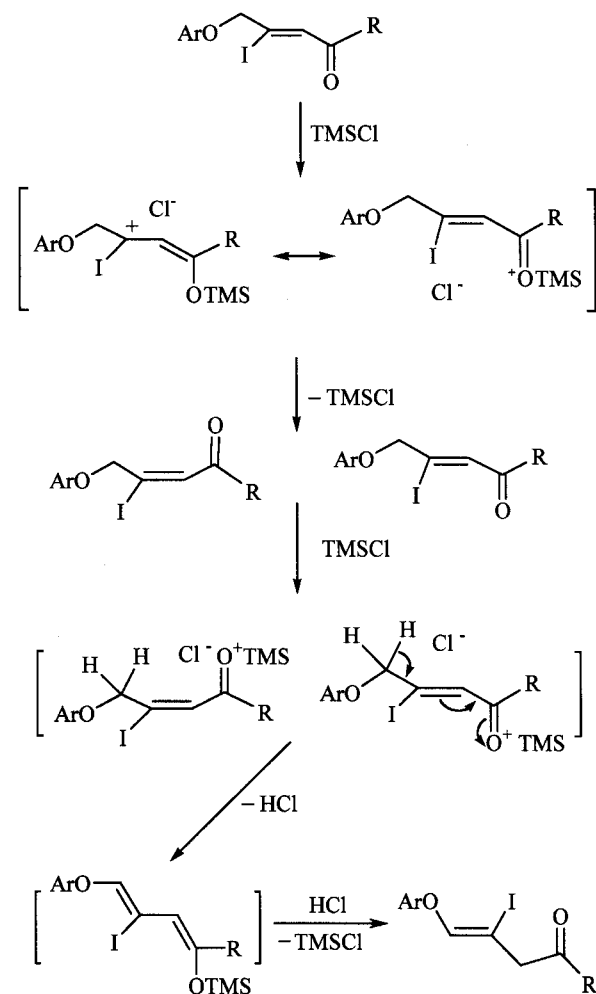
<sup>a</sup> Reaction condition:  $t = 25\text{ }^{\circ}\text{C}$ ; time = 3 h.

When 2 equiv. of H<sub>2</sub>O were added in the reaction, conjugated (*Z*)- and (*E*)-**3** became the major product, while the deconjugated product **2** could be isolated only in trace amount (< 5%). TMSCl played an important role in the hydroiodination. Without TMSCl only starting material **1** was recovered ( $\leq 90\%$ ) under NaI/CH<sub>3</sub>CN/H<sub>2</sub>O system. We also observed that in CDCl<sub>3</sub> the conjugated product **3** could be partially converted to deconjugated **2** (**3**:**2** = 1:1).

**Fig. 1** Conversion of conjugated product **3**.

The stability of conjugated isomer was increased obviously by neutralizing CDCl<sub>3</sub> with sodium hydroxide. Thus, we assumed that the presence of 0.2 mol of excess TMSCl which acts as a Lewis acid may be responsible for the formation of deconjugated product. The possible mechanism<sup>10</sup> for this reaction is shown in Scheme 2. TMSCl acts a Lewis acid to activate (*Z*)-enone to form silyl enol ether allylic cation intermediates. The chloride anion acts as a base to abstract one of the allylic protons to form HCl and the silyl dienol ether intermediate. Since the allylic protons in the (*Z*)-isomer have less steric hindrance than that of (*E*)-isomer, they are more easily to be accessed than that of the (*E*)-isomer by the chloride anion. Thus, the process of deconjugation for the (*Z*)-isomer was faster than the (*E*)-isomer. Since the coexistence of

HCl and the silyl dienol ether is inevitable, the subsequent kinetic protonation of the silyl dienol ether with HCl to form the deconjugated product and TMSCl is very fast. The Cl<sup>-</sup> is a weak base so that phenoxy group and the iodo substituent are on the *syn* position of the C—C single bond to allow the proton abstraction. The following double bond migration and protonation should give (*Z*)-form of the deconjugated product.

**Scheme 2**

## Experimental

Precoated silica gel 60F-254 on aluminum plates made by EM chemical company was used for thin layer chromatography. Purification of products by column chromatography was carried out with EM silica gel 60 (70—230 mesh ASTM). All materials were used without further purification. IR spectra were recorded on a Perkin-

Elmer 882 infrared spectrometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AC200, AC300 or AMX400 spectrometer; chemical shifts were reported in ppm relative to  $\text{Me}_4\text{Si}$ . MS spectra were obtained on an HP 5971, Fisons MD800 GC/MS or VG 70-250S spectrometer. HRMS were obtained on a VG 70-250S spectrometer. Elemental analyses were performed on a Perkin-Elmer EA-2400.

*General procedure for the hydroiodination of 5-aryloxy-(thiophenyl)-3-pentyn-2-one*

To a solution of anhydrous sodium iodide (0.68 g, 4.5 mmol) in  $\text{CH}_3\text{CN}$  (3 mL) in a dry flask under nitrogen atmosphere was added  $\text{TMSCl}$  (0.46 mL, 3.6 mmol) and the mixture was stirred at r.t. for 20 min. A dry syringe was used to inject 0.5 equiv. of water into the flask. The reaction mixture was stirred for another 10 min at r.t. One equiv. of **1** (3 mmol) was added quickly into the flask with a dry syringe. After stirring for another 4 h, the reaction mixture was quenched with saturated solution of sodium thiosulfate and extracted with ethyl acetate (10 mL  $\times$  3). The organic layer was dried over magnesium sulfate followed by filtration and concentration. The crude product was purified by chromatography (silica gel, ethyl acetate/hexane = 1/10, V/V).

*(4Z)-5-Phenoxy-4-iodo-4-penten-2-one (2a)*

Oil, 0.59 g, 65% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.21 (s, 3H), 3.65 (s, 2H), 6.73 (s, 1H), 7.0—7.38 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 29.29, 51.77, 73.37, 116.75, 123.68, 129.61, 146.39, 156.04, 204.70; IR (film)  $\nu$ : 1716, 1590, 1490, 1226, 1162, 755  $\text{cm}^{-1}$ ; MS  $m/z$  (%): 302 ( $\text{M}^+$ , 30), 259 (30), 131 (5). HRMS calcd for  $\text{C}_{11}\text{H}_{11}\text{O}_2\text{I}$ : 301.9804, found 301.9822.

*(3Z)-5-Phenoxy-4-iodo-3-penten-2-one (3a)*

Colorless oil, 0.14 g, 15% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.27 (s, 3H), 4.75 (s, 2H), 7.14 (t,  $J = 1.5$  Hz, 1H), 6.88 (d,  $J = 7.4$  Hz, 2H), 7.01 (t,  $J = 7.4$  Hz, 1H), 7.30 (t,  $J = 7.4$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 31.58, 76.85, 109.26, 114.80, 121.87, 129.52, 129.65, 157.21, 195.76; IR (film)  $\nu$ : 1755, 1684, 1584, 1491, 1135, 1177, 754  $\text{cm}^{-1}$ ; MS  $m/z$  (%): 302 ( $\text{M}^+$ , 9), 259 (7), 174 (51), 132 (63), 94 (100). Anal. calcd for  $\text{C}_{11}\text{H}_{11}\text{O}_2\text{I}$ : C 43.73, H 3.67; found C 43.85, H 3.78.

*(4Z)-5-(4-Fluorophenoxy)-4-iodo-4-penten-2-one*

(**2b**) 0.59 g, 61% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.24 (s, 3H), 3.67 (s, 2H), 6.67 (s, 1H), 7.0—7.05 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 29.51, 51.88, 73.37, 77.42, 116.28 (d,  $J = 23$  Hz), 118.32, 118.44, 146.81, 152.36, 159.03 (d,  $J = 241$  Hz), 204.48; IR (film)  $\nu$ : 1716, 1652, 1498, 1241, 1203, 831  $\text{cm}^{-1}$ ; MS  $m/z$  (%): 320 ( $\text{M}^+$ , 78), 277 (30), 122 (100), 83 (48). HRMS calcd for  $\text{C}_{11}\text{H}_{10}\text{O}_2\text{FI}$ : 319.9710, found 319.9722.

*(3Z)-5-(4-Fluorophenoxy)-4-iodo-3-penten-2-one (3b)* 0.17 g, 18% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.42 (s, 3H), 4.86 (d,  $J = 1.2$  Hz, 2H), 6.95—7.40 (m, 4H), 7.27 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 31.57, 77.58, 108.93, 115.91, 116.28, 124.14, 129.71, 154.40 (d,  $J = 152$  Hz), 160.18, 195.80; IR (film)  $\nu$ : 1697, 1504, 1434, 1196, 1023  $\text{cm}^{-1}$ ; MS  $m/z$  (%): 320 ( $\text{M}^+$ , 7), 277 (13), 193 (48), 150 (63), 112 (100). Anal. calcd for  $\text{C}_{11}\text{H}_{10}\text{O}_2\text{FI}$ : C 41.27, H 3.15; found C 41.40, H 3.33.

*(2Z)-4-phenoxy-3-iodo-1-(3,4,5-trimethoxyphenyl)-2-buten-1-one (3c)* 0.23 g, 17% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.77 (s, 6H), 3.93 (s, 3H), 4.86 (s, 2H), 6.95—7.40 (m, 5H), 7.59 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 56.04, 60.80, 76.24, 105.64, 109.86, 114.6, 121.74, 128.63, 129.70, 131.63, 142.92, 152.99, 157.10, 188.72; IR (film)  $\nu$ : 1658, 1581, 1408, 1127, 1000, 757  $\text{cm}^{-1}$ ; MS  $m/z$  (%): 455 ( $\text{M}^+$ , 72), 328 (35), 235 (33), 196 (76), 155 (100). HRMS calcd for  $\text{C}_{19}\text{H}_{19}\text{O}_5\text{I}$ : 454.0277, found 454.0282.

*(3Z)-4-Phenoxy-3-iodo-1-(3,4,5-trimethoxyphenyl)-3-buten-1-one (2c)* 0.84 g, 62% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.92 (s, 6H), 3.93 (s, 3H), 4.20 (s, 2H), 6.74 (s, 1H), 7.03 (d,  $J = 7$  Hz, 2H), 7.10 (t,  $J = 7$  Hz, 1H), 7.33 (t,  $J = 7$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 37.71, 46.90, 56.36, 60.95, 73.76, 105.66, 106.07, 115.26, 116.94, 123.74, 129.73, 131.44, 146.55, 153.11, 156.33, 194.72; IR (film)  $\nu$ : 1678, 1581, 1491, 1337, 1228, 1126, 754  $\text{cm}^{-1}$ ; MS  $m/z$  (%): 454 ( $\text{M}^+$ , 34), 328 (46), 235 (36), 196 (100). HRMS calcd for  $\text{C}_{19}\text{H}_{19}\text{O}_5\text{I}$ : 454.0277, found 454.0285.

*(2Z)-4-(4-Fluorophenoxy)-3-iodo-1-(3,4,5-trimethoxyphenyl)-2-buten-1-one (3d)* 0.20 g, 14% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.81 (s, 6H), 3.90 (s, 3H), 4.85 (s, 2H), 6.9—7.0 (m, 4H), 7.08 (s, 2H), 7.58 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 56.43,

61.25, 76.38, 112.34, 114.64 (d,  $J = 28$  Hz), 117.25 (d,  $J = 8$  Hz), 135.69, 139.68, 144.39, 153.97, 154.63, 157.29 (d,  $J = 272$  Hz), 186.37; IR (film)  $\nu$ : 1664, 1575, 1504, 1331, 1203, 1126  $\text{cm}^{-1}$ . HRFABMS calcd for  $\text{C}_{19}\text{H}_{19}\text{O}_5\text{FI}$ : 473.0261 ( $\text{MH}^+$ ), found 473.0240.

(3*Z*)-4-(4-Fluorophenoxy)-3-iodo-1-(3,4,5-trimethoxyphenyl)-3-buten-1-one (**2d**) 0.91 g, 64% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.93 (s, 9H), 4.20 (s, 2H), 6.68 (s, 1H), 7.01 (d,  $J = 6.2$  Hz, 4H), 7.26 (s, 2H); IR (film)  $\nu$ : 1670, 1581, 1500, 1337, 1201, 1120, 833  $\text{cm}^{-1}$ ; MS  $m/z$  (%): 472 ( $\text{M}^+$ , 4), 344 (22), 234 (18), 219 (23), 206 (36), 195 (100), 191 (66). HRMS calcd for  $\text{C}_{19}\text{H}_{18}\text{FIO}_5$  472.0813, found 472.0179.

(4*Z*)-4-Iodo-5-phenylthio-4-penten-2-one (**2e**) Oil, 0.51 g, 53% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.20 (s, 3H), 3.74 (s, 2H), 6.84 (s, 1H), 7.26—7.46 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 29.47, 58.24, 90.11, 127.79, 129.03, 129.18, 130.85, 130.68, 133.57, 137.67, 203.95; IR ( $\text{CHCl}_3$ )  $\nu$ : 1716, 1579, 1475, 1354, 1156, 740  $\text{cm}^{-1}$ ; FABMS  $m/z$ : 318 ( $\text{M}^+$ ). Anal. calcd for  $\text{C}_{11}\text{H}_{11}\text{OIS}$ : C 41.52, H 3.48; found C 41.65, H 3.59.

(3*Z*)-4-Iodo-5-phenylthio-3-penten-2-one (**3e**) Oil, 0.24 g, 25% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.13 (s, 3H), 3.94 (s, 2H), 6.54 (s, 1H), 7.23—7.41 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 30.71, 47.69, 110.00, 127.59, 129.13, 129.65, 131.59, 133.71, 140.11, 195.81; IR (film)  $\nu$ : 1703, 1575, 1478, 1177  $\text{cm}^{-1}$ .

FABMS  $m/z$ : 318 ( $\text{M}^+$ ). HRMS calcd for  $\text{C}_{11}\text{H}_{11}\text{OIS}$ : 317.9575, found 317.9583.

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