# Synthesis of Iodoenol Lactone Derivatives from the Baylis-Hillman Adducts Using Iodolactonization Protocol

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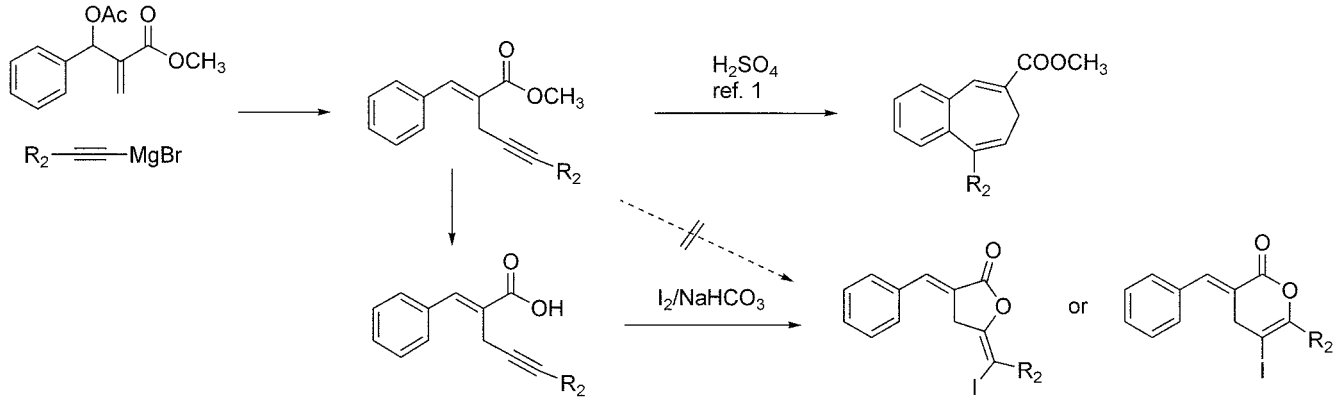
Recently, we have reported the preparation of benzocycloheptene derivatives from the intramolecular Friedel-Crafts reaction of triple bond-tethered methyl cinnamates.[1] In the reaction, we could not obtain any lactone derivatives, which could be formed via the intramolecular attack of the oxygen atom of ester moiety to the activated triple bond by the acid catalyst (Scheme 1).

We think that there may be a certain competition between arene moiety and ester group as nucleophiles toward the activated triple bond. From the previous results we concluded that the arene moiety is more nucleophilic than the oxygen atom of ester toward the *in-situ* generated vinyl cation.[1] In order to increase the nucleophilicity of the oxygen atom of ester group we decided to hydrolyze the ester into acid and to examine the feasibility of iodolactonization in the presence of $NaHCO_3$ as shown in Scheme 1. From the reaction, we could expect the formation of two types of lactones, 5-membered iodoenol lactone[2] or 6-membered $\alpha$-pyrone.[3]

Iodoenol lactone derivatives have been studied extensively due to their usefulness as synthetic intermediates and their biological activities.[2] Low molecular weight $\alpha$-pyrones have been shown to be potent HIV-1 protease inhibitors.[3d] Recently, Larock and Rossi have reported an elegant synthesis of isocoumarins and $\alpha$-pyrones *via* electrophilic cyclization.[2-4] We were stimulated by their works and envisioned that we could synthesize suitably substituted $\alpha$-pyrones or iodoenol lactone derivatives starting from the Baylis-Hillman adducts as mentioned in Scheme 1.

The starting material **1** was prepared from Baylis-Hillman acetate according to our previous paper.[1] Base hydrolysis of **1** was carried out using LiOH in aqueous THF at room temperature to give **2** in 53-69% yields. The use of KOH or NaOH was less efficient. With **2** in our hands, we initially examined the reaction with iodine in the presence of $NaHCO_3$ in $CH_3CN$, which is a typical condition for the iodolactonization.[5] Unfortunately, complex mixtures were observed on TLC. Among the various conditions, we finally found that the use of THF as solvent afforded the desired iodoenol lactones **3** in moderate to good yields (56-90%).[6] The formation of **3** can be explained as iodolactonization involving iodonium intermediate (**I**) *via* 5-*exo*-*dig* manner as shown in Scheme 2.[2a,b] We could not find nor isolate the corresponding six-membered $\alpha$-pyrones, which can be formed *via* 6-*endo*-*dig* fashion.[2a,b]

As the other electrophile source we examined $H_2SO_4$ and *N*-bromosuccinimide (NBS) in order to check the possibility for the synthesis of proton- or bromine-attached enol lactones. Fortunately, desired compounds were synthesized in moderate yields. As shown in Scheme 3, bromolactonization of **2a** (THF, NBS, $NaHCO_3$) gave the bromoenol lactone **4** in 72% yield. Sulfuric acid-mediated cyclization of **2c** in acetonitrile afforded enol lactone **5** in 53% yield at




**Scheme 1**

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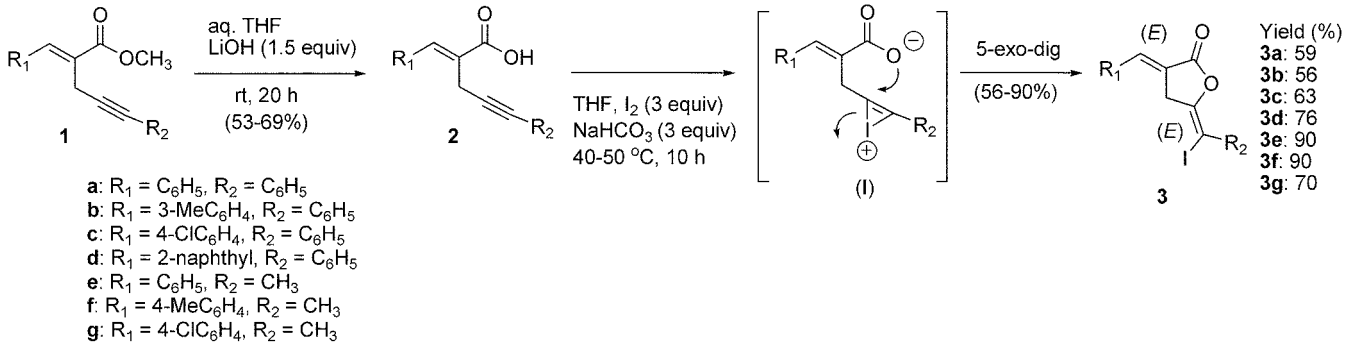
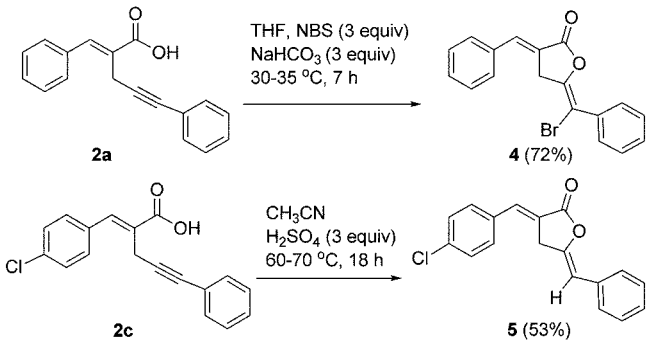



**Scheme 2**




**Scheme 3**

elevated temperature.[7] However, the prepared compounds were somewhat unstable. After 1-2 days at room temperature, we could find some impurities on TLC. Thus, taking of $^1$H NMR, $^{13}$C NMR, and IR spectra were carried out directly.

Structure identification of **3a-g**, **4**, and **5** was carried out by comparison with the reported IR, $^1$H, and $^{13}$C NMR data.[2,3] Especially, the absorption peak of carbonyl group (1766-1786 cm$^{-1}$ for **3a-g**) gave the unequivocal evidence for the structure as 5-membered iodoenol lactone. The carbonyl absorption peak of five-membered lactone derivatives appeared at around 1766-1786 cm$^{-1}$, while for the six-membered $\alpha$-pyrone derivatives in the ranges of 1717-1740 cm$^{-1}$.[2d] The configuration of the two double bonds of **3** is thought to be as *E* based on the previous papers.[8]

Further transformation of the iodoenol lactones and evaluation of their biological activities are under progress.

## Experimental Section

**Typical procedure for the preparation of 2a and 3a.** To a stirred solution of **1a**[1] (276 mg, 1.0 mmol) in aq. THF (2 mL, $H_2O$/THF = 1 : 4) was added LiOH monohydrate (63 mg, 1.5 mmol) and stirred at room temperature for 20 h. After the usual aqueous workup and flash column chromatographic separation (hexanes/EtOAc, 9 : 1) process we obtained **2a** as clear oil, 155 mg (59%).

**2a**: IR (neat) 1685 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.63 (s, 2H), 7.25-7.65 (m, 10H), 7.95 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.52, 81.13, 86.79, 123.52, 126.93, 127.84, 128.15, 128.71, 129.45, 129.95, 131.75, 134.68, 142.85, 172.02.

To a stirred solution of **2a** (262 mg, 1.0 mmol) in THF (6 mL) was added successively iodine (762 mg, 3.0 mmol) and $NaHCO_3$ (252 mg, 3.0 mmol) and the reaction mixture was heated to 40-50 °C for 10 h. After the usual aqueous workup and flash column chromatographic separation (hexanes/ether, 98 : 2) process we obtained **3a** as clear oil, 230 mg (59%).

**3a**: IR (neat) 1786, 1651 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.99 (d, *J* = 3.0 Hz, 2H), 7.22-7.58 (m, 10H), 7.67 (t, *J* = 3.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 37.77, 77.08, 121.84, 128.17, 128.24, 129.22, 129.82, 130.45, 130.73, 133.89, 137.61, 138.44, 146.24, 170.09. Other compounds were synthesized analogously and their spectroscopic data are as follows.

**3b**: IR (neat) 1782, 1655 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.36 (s, 3H), 3.92 (d, *J* = 2.7 Hz, 2H), 7.15-7.52 (m, 9H), 7.56 (t, *J* = 2.7 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.45, 37.80, 77.20, 121.54, 127.23, 128.17, 128.22, 129.08, 129.83, 131.52, 131.60, 133.87, 137.63, 138.68, 138.95, 146.34, 170.16.

**3c**: IR (neat) 1778, 1654 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.97 (d, *J* = 3.0 Hz, 2H), 7.21-7.57 (m, 9H), 7.62 (t, *J* = 3.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 37.91, 77.43, 122.71, 128.44, 128.56, 129.81, 130.04, 131.75, 132.57, 137.13, 137.18, 137.76, 146.14, 170.06.

**3d**: IR (neat) 1774, 1647 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.07 (d, *J* = 3.0 Hz, 2H), 7.23-7.96 (m, 11H), 7.81 (t, *J* = 3.0 Hz, 1H), 8.02 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 38.09, 77.33, 122.04, 126.12, 127.28, 128.02, 128.26, 128.42, 128.48, 129.06, 129.26, 130.08, 131.64, 132.24, 133.36, 134.21, 137.86, 138.79, 146.52, 170.38.

**3e**: IR (neat) 1770, 1685, 1651 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.44 (t, *J* = 1.8 Hz, 3H), 3.69 (m, 2H), 7.34-7.46 (m, 5H), 7.55 (t, *J* = 3.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 24.84, 36.13, 74.50, 122.74, 129.37, 130.58, 130.78, 134.15, 138.19, 145.71, 170.28.

**3f**: IR (neat) 1778, 1685, 1655 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.33 (s, 3H), 2.43 (t, *J* = 1.8 Hz, 3H), 3.64 (br s, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.50 (t, *J* = 2.7 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.84, 24.88, 36.23, 73.38, 121.54, 130.18, 130.71, 131.52, 138.26, 141.53, 145.95, 170.53.

**3g**: IR (neat) 1766 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.45 (t, *J* =

1.8 Hz, 3H), 3.65-3.69 (m, 2H), 7.39 (s, 4H), 7.50 (t, $J$ = 3.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 24.86, 36.07, 73.80, 123.39, 129.73, 131.68, 132.63, 136.74, 136.96, 145.43, 170.05.

**4**: IR (neat) 1782, 1647 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.03 (d, $J$ = 3.0 Hz, 2H), 7.25-7.70 (m, 11H); $^{13}$C NMR ($CDCl_3$) $\delta$ 34.88, 103.34, 121.15, 128.47, 128.69, 129.35, 129.49, 130.75, 131.04, 134.16, 135.12, 138.92, 144.45, 169.87.

**5**: IR (neat) 1716, 1604 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.50 (dd, $J$ = 4.2 and 2.7 Hz, 2H), 5.65 (t, $J$ = 4.2 Hz, 1H), 7.27-7.59 (m, 9H), 7.88 (t, $J$ = 2.7 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 25.94, 97.67, 122.89, 124.52, 128.50, 129.00 (2C by $^1$H-$^{13}$C COSY), 131.58, 132.49, 133.20, 135.68, 140.94, 148.80, 163.96.

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6. The trials for the synthesis of iodoenol lactones **3** directly from the ester derivatives **1** were not efficient under such conditions of $I_2$/LiI/AcOH or $I_2$/$NaHCO_3$/$CH_3CN$ systems.
7. Trials for the synthesis of enol lactone **5** from **2c** was completely failed when we used $Sc(OTf)_3$ in $CH_2Cl_2$ or $ZnBr_2$ in $CH_3CN$.
8. The *E*-configuration of the arylidene double bond at the 3-position of **3** is same as those of **1** or **2**.[1] The configuration of the iodovinyl moiety at the 5-position might be also *E* based on the previous literature.[2,4d]