# Formation of Lactones in the Heck Reaction

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The Heck reaction of methyl 2-bromobenzoate with methyl acrylate gave a mixture of alkene **1** and lactone **9**. Acrylonitrile and methyl 2-bromobenzoate gave lactone **10**. Ethyl 2-bromobenzoate and methyl acrylate or acrylonitrile gave the alkenes **2** and **4** respectively.

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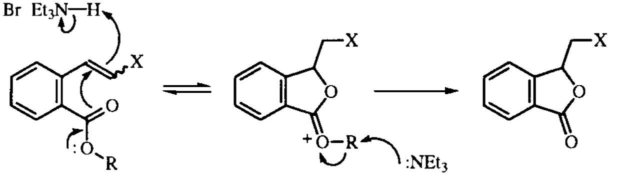
The Heck reaction is a well known and versatile palladium mediated coupling reaction from which arylalkene derivatives can be formed by the reaction of an aryl halide with an alkene in the presence of a base and a phosphine [1,2]. The synthesis of the *E* arylalkene derivative **1** from methyl 2-bromobenzoate and methyl acrylate at 100° illustrates this reaction [3].

We required compound **1** as a synthetic intermediate and reacted methyl 2-bromobenzoate with methyl acrylate in dimethylformamide (DMF) solution at reflux (isomantle) in the presence of triethylamine and catalytic quantities of palladium acetate and triphenylphosphine and noticed the formation of a second product under these reaction conditions when the progress of the reaction was monitored by gc-ms. The molecular weight and fragmentation pattern of the second product suggested that it had the lactone structure **9**. Distillation of the crude reaction product under reduced pressure gave a 3:2 mixture of compound **1** and lactone **9** (40% yield). With the less volatile and more nucleophilic tripropylamine as the base, a 1:4 ratio of compound **1** to lactone **9** was obtained. The identity of compound **1** was established by comparison of its proton nmr signals with those of an authentic sample [3]. An authentic sample of lactone **9** was prepared by treating the commercially available acid **8** with dimethyl sulphate under basic conditions and the proton nmr signals of the resulting ester **9** were identical to those of the second product in the Heck reaction mixture. The presence of lactone **9** in the Heck reaction was therefore established. Lactone **9** is probably formed by the mechanism depicted in the Scheme in which cyclisation of the alkene **1** occurs to give the intermediate **7** which is then demethylated by the action of triethylamine (or tripropylamine) to yield the lactone **9**. In support of this mechanism compound **1** was converted into lactone **9** under the reaction conditions. An alternative mechanism in which alkene **1** is demethylated giving carboxylic acid **5** which subsequently cyclises to lactone **9** has not been excluded but related compounds such as the diacid **6** have been reported to undergo a similar cyclisation when heated [4]. If acid **5** was formed in this reaction it would almost certainly cyclise under the reaction conditions to give the lactone **9** and would not therefore be detected and identified as a reaction intermediate.

Scheme



| | R | X |
|---|---|---|
| **1** | Me | $CO_2Me$ |
| **2** | Et | $CO_2Me$ |
| **3** | Me | CN |
| **4** | Et | CN |
| **5** | H | $CO_2Me$ |
| **6** | H | $CO_2H$ |

**7**

**8** X = $CO_2H$
**9** X = $CO_2Me$
**10** X = CN

An alternative method for preventing the transformation of intermediates **7** into lactone products would be to use an ester which is more resistant to dealkylation. Ethyl 2-bromobenzoate was therefore reacted with methyl acrylate under similar reaction conditions as those described above and the diester **2** (92% yield) was formed exclusively.

The reaction of acrylonitrile with methyl and ethyl 2-bromobenzoate was also investigated. In the former case, lactone **10** [4] (92% yield) was formed *via* the initially formed alkene **3** as expected and in the latter case only the alkene **4** (80% yield) was produced as an 1:3 mixture of *Z* and *E* isomers.

## EXPERIMENTAL

Proton nmr spectra were determined at 90 MHz in deuteriochloroform solution. Infra red spectra were recorded as liquid films.

### Methyl 3-(2-Carboxymethylphenyl)propenoate **1** and 1-Oxo-3-carboxymethylmethyl-1,3-dihydrobenzo[*c*]furan **9**.

A mixture of methyl 2-bromobenzoate (10.76 g), methyl acrylate (6 ml), triethylamine (6.31 g), triphenylphosphine (0.50 g) and palladium acetate (0.10 g) in DMF (40 ml) were heated at vigorous reflux (isomantle) for 6 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and poured into water. The mixture was extracted several times with dichloromethane and the combined organic extracts were washed several times with dilute hydrochloric acid and then water, dried (magnesium sulfate) and evaporated. The residue was distilled under reduced pressure giving firstly a forerun of methyl 2-bromobenzoate (1.90 g) and then a mixture 2.54 g (40%) of compounds **1** and **9** in the ratio 3:2 as an oil, bp 156-162° (2.5 mm Hg). The identity of the distillate was established by comparison of its $^1$H nmr spectrum with those of authentic samples of compounds **1** [3] and **9** (see below).

In a similar experiment with tripropylamine as the base, a 1:4 ratio of compounds **1** and **9** was obtained.

### 1-Oxo-3-carboxymethylmethyl-1,3-dihydrobenzo[*c*]furan **9**.

A mixture of acid **8** (5.0 g), potassium carbonate (4.70 g) and dimethyl sulphate (3.28 g) in acetone (100 ml) was heated at reflux with stirring for 5 hours. The reaction mixture was allowed to cool to room temperature, poured into water and extracted with ether. The combined organic extracts were washed with potassium hydrogen carbonate solution and then with water, dried (magnesium sulfate) and evaporated giving compound **9**, 3.64 g (68%) as a colorless oil; ir: ν 1764 (broad) cm$^{-1}$; $^1$H nmr: δ 7.75 (4H, m, ArH), 5.90 (1H, t, J = 7 Hz, >CH-), 3.75 (3H, s, -OMe) and 2.95 (2H, d, J = 7 Hz, >CH$_2$) ppm.

*Anal.* Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 64.0; H, 4.95.

### Methyl 3-(2-Carboxyethylphenyl)propenoate **2**.

In a similar manner to that described above for the preparation of compounds **1** and **9**, ethyl 2-bromobenzoate and methyl acrylate gave compound **2** (67%), bp 160-168° (2.0 mm Hg); ir: ν 3070, 2990, 2950, 2900, 2840, 1720 and 1275 cm$^{-1}$; $^1$H nmr: δ 8.45 (1H, d, J = 18 Hz, -CH=), 7.55 (4H, m, ArH), 6.30 (1H, d, J = 18 Hz, ArH), 4.40 (2H, q, J = 9 Hz, -CH$_2$-), 3.82 (3H, s, -OMe) and 1.42 (3H, t, J = 9 Hz, -Me) ppm.

*Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.0. Found: C, 66.55; H, 6.0.

### 1-Oxo-3-cyanomethyl-1,3-dihydrobenzo[*c*]furan **10**.

In a similar manner to that described above for the preparation of compounds **1** and **9**, methyl 2-bromobenzoate and acrylonitrile gave compound **10** (92%), mp 116-119° (from ethanol), lit mp 113° [4].

### 1-Cyano-2-(2-carboxyethylphenyl)ethene **4**.

In a similar manner to that described above for the preparation of compounds **1** and **9**, ethyl 2-bromobenzoate and acrylonitrile gave compound **4** (80%) as a 1:3 mixture of *Z* and *E* isomers after chromatography over silica gel eluting with dichloromethane. Compound **4** had; ir: ν 3065, 2980, 2220, 1715 and 1275 cm$^{-1}$; $^1$H nmr: δ 8.30 (1H, d, J = 17 Hz, -CH=), 7.68 (4H, m, ArH), 5.80 (1H, d, J = 17 Hz, -CH=), 4.40 (2H, q, J = 7 Hz, >CH$_2$) and 1.45 (3H, J = 7 Hz, -Me) ppm [5].

*Anal.* Calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.8; H, 5.6; N, 7.2.

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[5] These chemical shifts are for the *E* isomer. A signal at δ 5.55 (d, J = 12 Hz) was attributed to the *Z* isomer.