# A FACILE SYNTHESIS OF 4-ARYLBUTYROLACTONES VIA THE PALLADIUM-CATALYZED ARYLATION OF 1,3-DIOXEP-5-ENE

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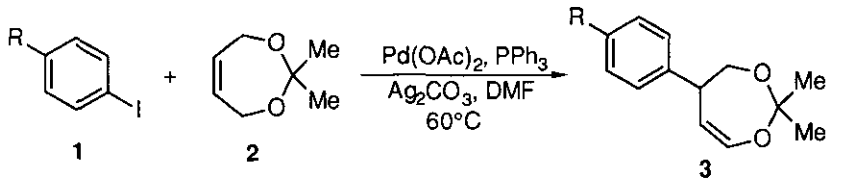
Abstract - 1,3-Dioxep-5-ene was arylated by using Heck reaction, and the arylated 1,3-dioxep-4-ene derivatives were easily converted into 4-arylbutyrolactones, intermediates for the synthesis of natural products and biological active compounds.

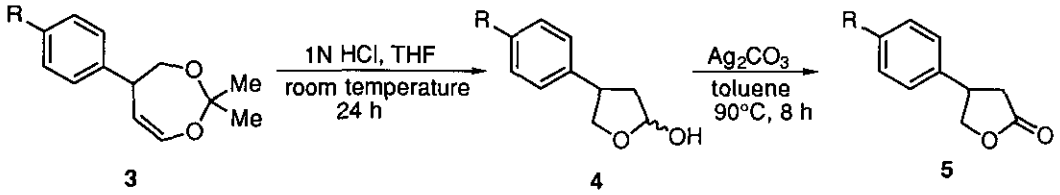
Heck reaction is one of the most excellent synthetic procedures for carbon-carbon bond formation.[1] Not only terminal olefins but also cyclic olefins can be arylated by the catalytic action of a palladium complex. As an extention of our work[2] on the Heck reaction using heterocyclic olefins,[3] our interest was focused on the use of the seven-membered heterocyclic olefin, 1,3-dioxep-5-ene.[4] Among the various conditions for the coupling reaction of cyclic olefins,[5] the use of $Ag_2CO_3$[6] as a base gave satisfactory results. As shown below, iodobenzenes (**1a-d**) with various functional groups reacted smoothly with **2** to give 6-aryl-1,3-dioxep-4-ene derivatives (**3a-d**) in good yields. Only 4-nitroiodobenzene (**1e**) gave the product (**3e**) in somewhat low yield.




**1** **2** **3**

| 3 | R | time (h) | yield (%) |
|---|---|---|---|
| **a** | H | 24 | 65 |
| **b** | Me | 24 | 72 |
| **c** | OMe | 24 | 70 |
| **d** | COOEt | 48 | 66 |
| **e** | $NO_2$ | 72 | 25 |

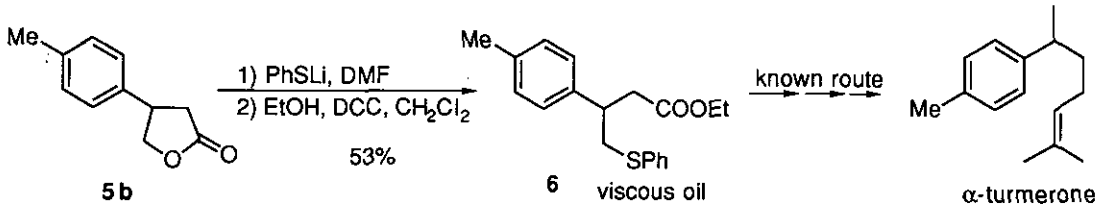
Next, the transformation of the cross coupling products (**3**) into butyrolactones (**5**) was investigated. The arylated dioxep-4-ene derivatives (**3**) were hydrolyzed by treating with 1N HCl-THF to form hemiacetals (**4**) which were easily oxidized to the 4-arylbutyrolactone derivatives (**5**) with $Ag_2CO_3$ in toluene in good yields.




**3** **4** **5**

| **5** | R | yield (%) | mp or bp (mmHg) |
|---|---|---|---|
| **a** | H | 55 | 135-140°C (2) |
| **b** | Me | 58 | 43-45°C |
| **c** | OMe | 61 | 68-71°C |
| **d** | COOEt | 56 | 77-79°C |
| **e** | $NO_2$ | 53 | 112-114°C |

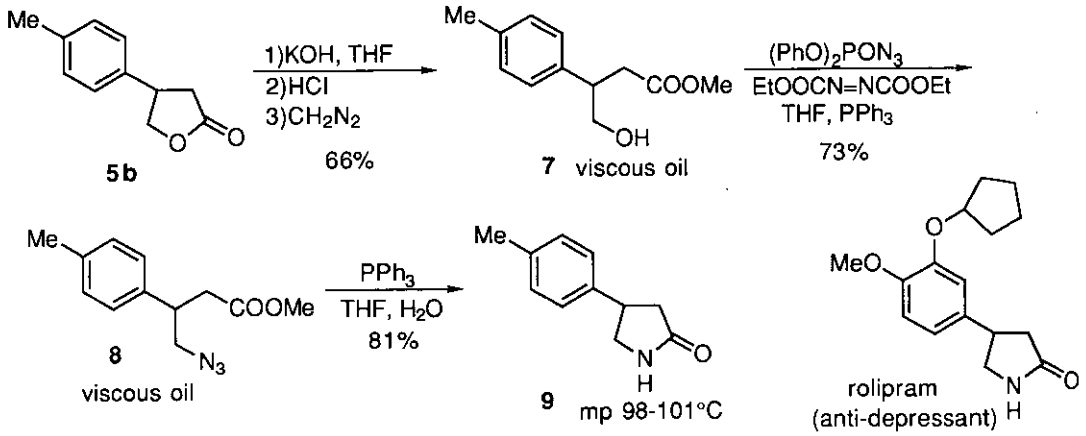
Some transformations of the 4-arylbutyrolactones (**5**) were examined for the syntheses of natural products and biologically active compounds. Firstly the butyrolactone (**5b**) was treated with lithium phenylmercaptide in DMF, and the obtained acid was esterified to give the sulfide ester (**6**). The conversion of this sulfide ester to α-turmerone has already been reported by Takano *et al.*[7] The sulfide ester is also a useful intermediate for the other bisabolane sesquiterpenes.




**5b** **6** viscous oil α-turmerone

In connection with our interest in the synthesis of anti-depressant rolipram, the transformation of the lactone (**5b**) into the corresponding lactam was examined. Hydrolysis of the butyrolactone (**5b**) with 3N KOH in THF followed by esterification with diazomethane gave hydroxy ester (**7**). The ester (**7**) was converted into the azide (**8**) using Mitsunobu reaction with DPPA. The azide (**8**) was reduced by treating with $PPh_3$ in aquaous THF and during the reaction the cyclization accompanied to give the five-membered lactam (**9**). The synthesis of rolipram using this manner is under way.

The present study provides a facile method for construction of butyrolactone or butyrolactam moiety on aromatic rings and the method is considered to be widely applicable for the syntheses of other biologically interesting com pounds containing such heterocycles.

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8 Typical Procedure: **6-*p*-Tolyl-1,3-dioxep-4-ene(3b)** : A mixture of *p*-iodotoluene (436 mg, 2 mmol), 1,3-dioxep-5-ene (1.28 g, 10 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol) , $PPh_3$ (32 mg, 0.12 mmol), $Ag_2CO_3$ (1.10 g, 4 mmol), and DMF (1ml) was stirred at 60°C for 24 h. After reaction, the mixture was diluted with ether (30 ml), filtered, and washed with $H_2O$ (10 ml). The aqueous layer was extracted with additinal $Et_2O$ (10 ml x2). The combined organic phases were washed with brine (10 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual material was subjected to $SiO_2$ column

chromatography using n-hexane/AcOEt (9:1) as an eluent to give colorless oil (314 mg, 72%). $^1$H Nmr ($CDCl_3$) δ: 7.16 (d, *J*=8.6 Hz, 2H), 7.12 (d, *J*=8.6 Hz, 2H), 6.33 (dd, *J*=6.7, 1.8 Hz, 1H), 4.94-4.91 (m, 1H), 3.95 (dd, *J*=11.6, 9.8 Hz, 1H), 3.83-3.79 (m, 1H), 3.70-3.67 (m, 1H), 2.32 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H).

9 **5b**: $^1$H Nmr ($CDCl_3$) δ: 7.17 (d, *J*=7.9 Hz, 2H), 7.12 (d, *J*=7.9 Hz, 2H), 4.65 (t, *J*=8.5 Hz, 1H), 4.24 (t, *J*=8.5 Hz, 1H), 3.79-3.71 (m, 1H), 2.90 (dd, *J*=17.7, 9.1 Hz, 1H), 2.65 (dd, *J*=17.7, 9.1 Hz, 1H), 2.15 (s, 3H). Ir ($CHCl_3$) ν: 1780 $cm^{-1}$.

10 **9**: $^1$H Nmr ($CDCl_3$) δ: 7.15 (s, 4H), 6.29 (br s, 1H), 3.79-3.63 (m, 2H), 3.39 (dd, *J*=8.8, 7.3 Hz, 1H), 2.71 (dd, *J*=16.8, 8.8 Hz, 1H), 2.48 (dd, *J*=16.8, 8.8 Hz, 1H), 2.34 (s, 3H). Ir ($CHCl_3$) ν: 3440, 1695 $cm^{-1}$.

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