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SYNTHESIS OF BENZOFURANS, TETRAHYDROBENZOPYRANS, AND RELATED CYCLIC ETHERS VIA CYCLIC CARBOPALLADATION[1,†]

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Abstract - Treatment of a variety of alkenyl ethers (**1-8**) derived from o-iodophenol, o-iodobenzyl alcohol, and (Z)-3-iodoallyl alcohols with a catalytic amount of $Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$ in the presence of NEt_3 in refluxing CH_3CN gives the corresponding cyclic ethers in good yields.

The intramolecular Heck reaction,[2] i.e., cyclic carbopalladation of olefins containing aryl and alkenyl halides followed by dehydropalladation, has been widely applied to the synthesis of nitrogen heterocycles.[3] More recently, its application to the synthesis of carbocycles[4] has emerged as an attractive methodology. Surprisingly, little attention has been paid to the synthesis of oxygen heterocycles by this methodology.[5] We now report that treatment of a variety of alkenyl ethers (**1-8**) derived from o-iodophenols, o-iodobenzyl alcohol, and (Z)-3-iodoallyl alcohols with a catalytic amount of Pd-PPh_3 complex, *e.g.*, $Pd(PPh_3)_4$ *or* $Cl_2Pd(PPh_3)_2$, in the presence of a base, e.g., NEt_3, in refluxing CH_3CN induces cyclization-elimination to give the corresponding cyclic ethers in good yields. The experimental results are summarized in Eq 1-8.

The following observations and interpretations are noteworthy. First, the isolated yields of the products ranged from 60-97% except for the preparation of **14b** and **15b**, which was performed on a 0.29 mmol scale. Various Pd-containing complexes including $Pd(PPh_3)_4$, $Cl_2Pd(PPh_3)_2$, and $Pd(dba)_2$ appear to be satisfactory catalysts, and the selection of a catalyst in Eq 1-8 was entirely arbitrary. Secondly, the position of the double bond which must be formed via dehydropalladation is somewhat unpredictable. Thus, **9** and **10** were formed as ca. 3/1 mixtures under the conditions used. Examination of the reaction mixtures by GLC clearly indicated that **10** were the kinetically favored products. No attempts to convert **10** into **9** were made. Under comparable conditions, **2** was cleanly converted into **11**, whereas **12** consisted mainly of two regioisomers. There was little or no indication for the formation of the corresponding benzofuran in this case. The regiochemistry

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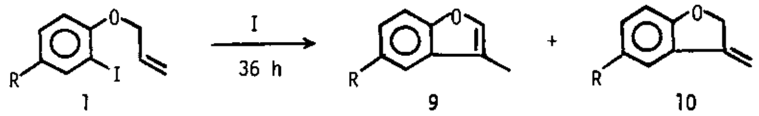
[†] This paper is dedicated to Professor Sir D. H. R. Barton on the occasion of his 70th birthday.

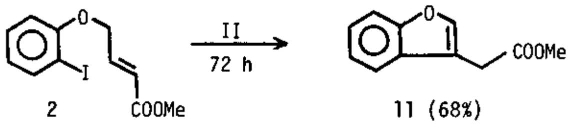
in Eq 2 is completely opposite to that observed in the corresponding reaction of methyl (*E*)-5-(*o*-iodophenyl)-2-pentenoate which produced exclusively the corresponding exocyclic alkene.[4d] The products derived from **4** were essentially 1/1 mixtures of **14** and **15**. The combined amount of the other regiosiomers was <10%. The ratio of the two possible regioisomers **16** and **17** was 1/3. Whereas **18** was isomerically >95% pure, **19** is a mixture of 3 isomers, none of which has the same regiochemistry as **18**. The formation of **20** is >95% regioselective.[6] While it is not possible to provide satisfactory explanations for all of the regiochemical results, the presumed syn stereochemical requirement for carbopalladation and dehydropalladation is clearly reflected in some results. Thirdly, ring fusion in **12**, **14a**, **15a**, and **19**, is almost completely cis, as judged by ^{1}H and ^{13}C nmr analysis of partially hydrogenated products **13**, **21**, and **22**. Fourthly, the preparation of **1-8** involves the Williamson ether synthesis using appropriate alkali metal oxides of *o*-iodophenols, cyclohexenols, 1-cyclohexenylmethanol, and an allylic alcohol **23**, prepared by the treatment of 2-nonyn-1-ol with MeMgBr followed by iodinolysis.[6] In the synthesis of **7**, however, the reaction of the lithio derivative of **23** with 3-bromo-1-cyclohexene led to a low yield of **7**. On the other hand, the reaction of lithium 2-cyclohexenoate with **24** provided **7** in nearly quantitative yield.

The following procedure for the conversion of **6** into **18** is representative. To a suspension of NaH (22 mg, 0.55 mmol) in THF (3 ml) was added 140 mg (0.5 mmol) of (*Z*)-3-iodo-2-methyl-2-nonenol, prepared by successive treatment of 2-nonynol with MeMgBr (3 equiv) in ether and I_2 in THF.[7] After the reaction was stirred for 2 h at 25°C, HMPA (1 ml) and then allyl bromide (0.13 ml, 1.5 mmol) were slowly added. After 4 h, the reaction mixture was quenched with water, extracted with ether, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give 121 mg (75% yield) of **6**: ^{1}H Nmr ($CDCl_3$, Me_4Si) δ 0.89 (t, *J* = 6 Hz, 3 H), 1.30 (s, 6 H), 1.51 (t, *J* = 6 Hz, 2 H), 1.86 (s, 3 H), 2.59 (t, *J* = 7 Hz, 2 H), 3.93 (t, *J* = 1 Hz, 2 H), 4.14 (s, 2 H), 5.19 (d, *J* = 10 Hz, 1 H), 5.30 (d, *J* = 17 Hz, 1 H), 5.9 (m, 1 H); ir (neat) 1650 (w), 1460 (m), 1080 (s), 990 (m), 925 (s) cm^{-1}. To a solution of allyl (*Z*)-3-iodo-2-methyl-2-nonenyl ether (**6**) (191 mg, 0.592 mmol) in THF (1 ml) and CH_3CN (1 ml) were added $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) and triethylamine (0.12 ml, 0.9 mmol). After the reaction mixture had been refluxed for 16 h, it was quenched with water, extracted with ether, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and chromatographed on silica gel (99:1 pentane-ether) to give 111 mg (97%) of **18**: ^{1}H Nmr ($CDCl_3$, Me_4Si) δ 0.90 (t, *J* = 7 Hz, 3 H), 1.2-1.45 (m, 8 H), 1.66 (s, 3 H), 2.26 (t, *J* = 8 Hz, 2 H), 4.09 (s, 2 H), 4.20 (s, 2 H), 4.72 (s, 1 H), 4.92 (s, 1 H); ^{13}C nmr ($CDCl_3$) δ 14.06, 14.85, 22.63, 26.91, 28.70, 29.60, 31.74, 70.30, 70.37, 105.04, 129.55, 131.96, 139.68; ir (neat) 1640 (m), 1608 (s), 1250 (s), 1225 (s), 1100 (s), 1000 (s), 965 (s), 870 (s), 800 (s) cm^{-1}.



(1)

a: R = H. b: R = Me. 9/10 = 3/1. **9a** + **10a** (60%). **9b** + **10b** (81%)



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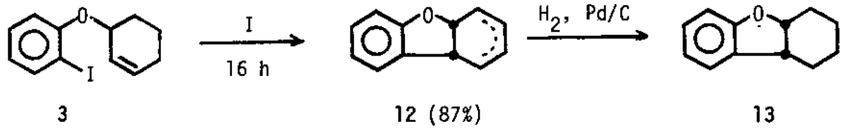

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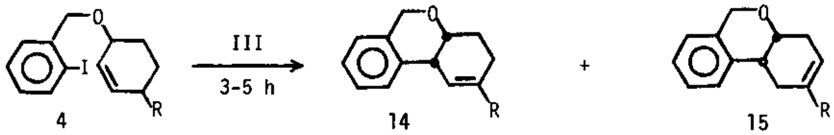
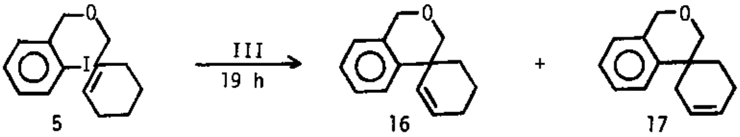


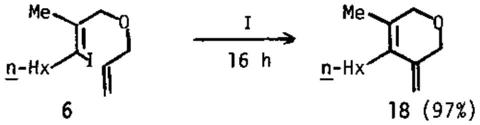
(4)

a: R = H. b: R = tert-Bu. 14/15 = 1/1. **14a** + **15a** (74%). **14b** + **15b** (50%)

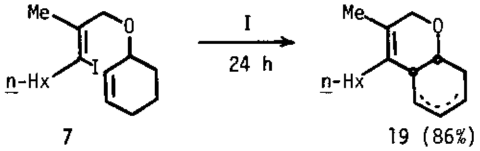


(5)

16/17 = 1/3. 16 + 17 (85%)



(6)



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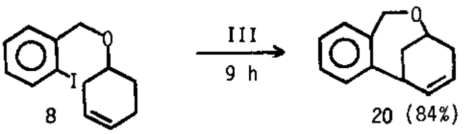
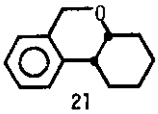


(8)

I = Pd(PPh$_3$)$_4$ (5 mol %), NEt$_3$ (1.5 equiv), CH$_3$CN-THF, reflux. II = Pd(dba)$_2$ (5 mol %), NEt$_3$ (1.5 equiv), CH$_3$CN-THF, reflux. III = Cl$_2$Pd(PPh$_3$)$_2$ (5 mol %), NEt$_3$ (1.5 equiv), CH$_3$CN, reflux.



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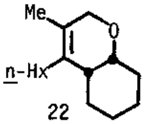

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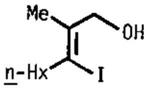

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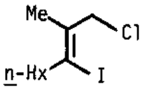

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