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Palladium-Catalyzed Reaction of 2-Vinyl-2,3-dihydrobenzofurans and Chroman with Nucleophiles

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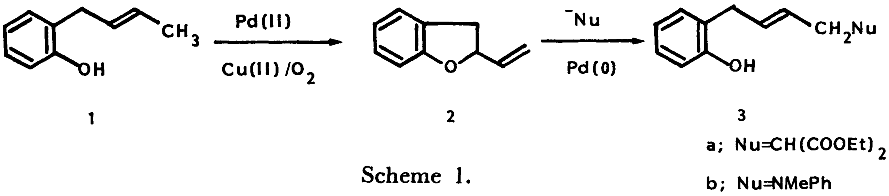
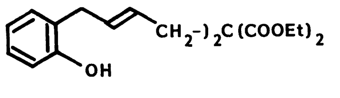
Reaction of 2,3-dihydro-2-vinylbenzofuran with nucleophiles ($NaCH(COOEt)_2$ and $PhNHCH_3$) in the presence of palladium catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PR_3)_2$ (R=Ph and Et) gives 2-(2-butenyl)phenols (46—76% yields) in which nucleophiles are incorporated into the methyl group of the butenyl moiety. 2-Vinylchroman undergoes the same type of reaction where only the palladium complex bearing PEt_3 ligand is effective. The effectiveness of PEt_3 ligand is also observed in the reaction of 2,3-dihydro-2-isopropenylbenzofuran with diethyl sodiomalonate leading to 3-ethoxycarbonyl-4-(2-methyl-1-propenyl)-2-chromanone.

Palladium (II)-catalyzed cyclization of 2-(*trans*-2-butenyl)phenol(**1**) gives 2-vinyl-2,3-dihydrobenzofuran (**2**).[1] Since the vinyl compound has a structural unit of allylic ether, it is expected to react with nucleophiles in the presence of palladium(0) catalysts such as $Pd(PPh_3)_4$.[2] This will lead to functionalization of the methyl group in the butenyl moiety of **1** (Scheme 1). Described herein is the realization of the expectation, and an application of this procedure to 2-(*trans*-3-pentenyl)phenol (**8**) (Scheme 2).



Scheme 1.

The reaction of vinylbenzofuran **2** with diethyl sodiomalonate (1.2 equiv) in the presence of 3 mol% of $Pd(PPh_3)_4$ (THF-toluene, 110 °C, 4 h) gives a 76% yield of 4-substituted 2-butenylphenol **3a** along with its dimer **4** (10%). Palladium(II) complexes such as $PdCl_2(PR_3)_2$ (R=Ph and Et) are comparatively effective in promoting the reaction, in which palladium(0) species is generated in situ by the reduction of $PdCl_2$ complexes with excess diethyl sodiomalonate.[3] Diazopalladium(II) complex, $[PhC(N_2)]_2Pd(PEt_3)_2$ (**5**),[4] which upon heating generates $Pd(PEt_3)_2$, also serves as the catalyst to give **3a** (69%). Deethoxycarbonylation ($NaCN/LiI\cdot H_2O/DMSO$, 160 °C) of **3a** afford **6** (75%), resulting in two carbon homologation of the butenyl moiety of **1**.



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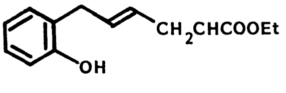

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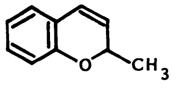

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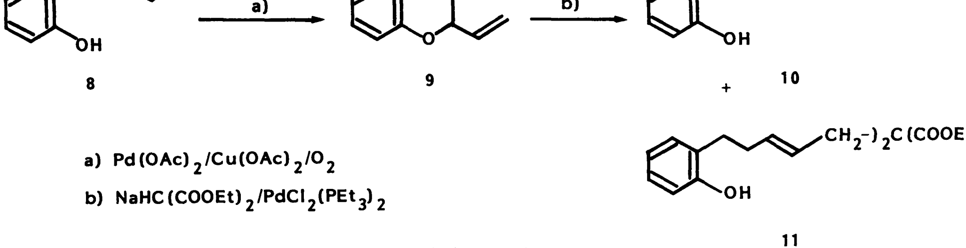
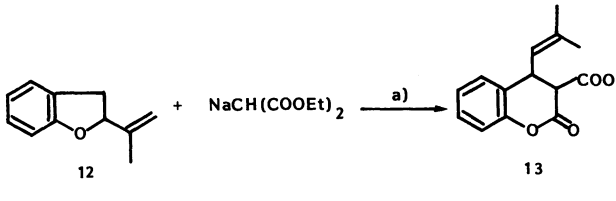
Treatment of **2** with *N*-methylaniline (1.3 equiv) in the presence of $Pd(PPh_3)_4$ (3 mol%) in THF–toluene at 120 °C for 3 h gives **3b** in 46% yield (Scheme 1). The use of complex **5** bearing PEt_3 ligand affords a trace amount of **3b**. In this case, the substrate **2** largely rearranges into 2-methyl-2*H*-chromene (**7**) (46%).

2-Vinychroman (**9**), which is readily prepared by Pd(II)-catalyzed cyclization of 2-(*trans*-3-pentenyl)-phenol (**8**), undergoes the same type of alkylation with diethyl sodiomalonate (Scheme 2). In this case,



Scheme 2.

however, only the palladium complex bearing PEt_3 is effective; no reaction takes place with $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$, while $PdCl_2(PEt_3)_2$ affords a 63% yield of **10** along with its dimer **11** (10%). Since PEt_3 complexes are more nucleophilic than PPh_3 complexes,[5] the oxidative addition of Pd(0) into the C–O bond must be the rate-determining step in this alkylation.[6] The effectiveness of PEt_3 ligand is also observed in the reaction of dihydrobenzofuran **12** with diethyl sodiomalonate leading to coumarin **13**.



a) $PdCl_2(PEt_3)_2$ or **5**

Thus, **13** is obtained in 54—64% yields with $PdCl_2(PEt_3)_2$ or **5**, while no reaction occurs with $Pd(PPh_3)_4$. In the reaction pathways shown in Scheme 3, **13** is assumed to be formed via isomerization of the intermediate π-allyl complex **14** to **15**.

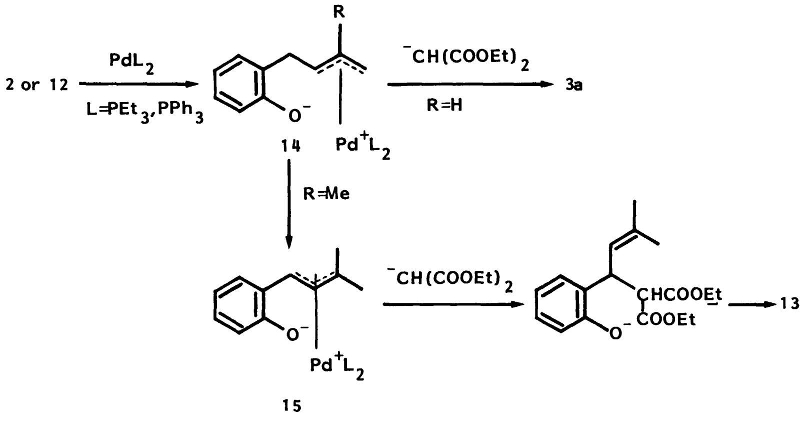
Experimental

2-(*trans*-2-Butenyl)phenol (**1**) was prepared by C-alkylation of phenol with *trans*-1-chloro-2-butene (Tokyo Kasei).[1] 2-(*trans*-3-Pentenyl)phenol (**8**) was synthesized by the reaction of *o*-methoxybenzylmagnesium chloride with *trans*-2-butenyl diethyl phosphate[7] followed by demethylation.[8] The preparation of 2-isopropenyl-2,3-dihydrobenzofuran (**12**) was carried out by the reported procedure.[9]

Palladium(II)-Catalyzed Cyclization of 1 and 8. The reaction was performed by using substrate **1** or **8** (2.5 mmol), $Pd(OAc)_2$ (56.5 mg, 0.25 mmol), and $Cu(OAc)_2$ (45.0 mg, 0.25 mmol) in anhydrous MeOH (5 mL) under O_2 atmosphere (1 atm, balloon) at 36 °C. After usual workup,[1] the cyclized product was isolated by distillation followed by preparative TLC (SiO_2, hexane). **2**: Yield 62%; R_f=0.27. **9**:[10] Yield 57%; R_f=0.41.

Palladium-Catalyzed Alkylation of 2, 9, and 12 with Diethyl Sodiomalonate. Into a suspension of NaH (48 mg, 1.20 mmol) in dry THF (4 mL) was added diethyl sodiomalonate (240 mg, 1.50 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. The resultant solution was then added by syringe to a solution of palladium catalyst (0.03 mmol) and vinyl compound **2**, **9**, or **12** (1 mmol) in dry toluene at room temperature, and the mixture was heated at 110 °C for 4 h. After cooling, the reaction was quenched by addition of water (10 mL) and ether (10 mL). The aqueous layer was neutralized by 2 M HCl(1 M=1 mol dm^{-3}) and extracted with ether (10 mL×3). The combined ethereal layer was washed with brine (20 mL×2) and dried over $MgSO_4$. Removal of the solvent followed by preparative TLC (SiO_2, hexane-EtOAc=7:3) gave the alkylated products. Their spectral and analytical data are listed below. The isolated yields of **3a** and **4** are 76 and 10% with $Pd(PPh_3)_4$, 56 and 19% with $PdCl_2(PPh_3)_2$, and 68 and 15% with $PdCl_2(PEt_3)_2$, respectively. Those of **10** and **11** are 63 and 10% with $PdCl_2(PEt_3)_2$ and 54 and 20% with $[PhC(N_2)]_2Pd(PEt_3)_2$ (**5**), respectively. The yield of **13** are 64 and 54%, with $PdCl_2(PEt_3)_2$ and **5**, respectively.

2-[*trans*-5,5-Bis(ethoxycarbonyl)-2-pentenyl]phenol (3a). R_f=0.34; bp 154—155 °C (1 mmHg); IR (neat) 3450, 3000, 1730 (C=O), 1600, 1040, and 965 (*trans* -CH=CH-) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.20 (6H, t, *J*=7 Hz, Me), 2.60 (2H, dd, *J*=8 and 6 Hz, $ArCH_2$-), 3.25—3.27 (3H, m, -CH- and $-CH_2C$=C), 4.14 (4H, q, *J*=7 Hz, $-OCH_2CH_3$), 5.17—6.00 (2H, m, -CH=CH-), 6.21—6.65 (1H, br s, OH), and 6.65—7.21 (4H, m, ArH). MS, *m/z* 306 (M^+). Deethoxycarbonylation of **3** by the reported procedure[11] gave 2-(*trans*-5-ethoxycarbonyl-2-pentenyl)phenol (**6**) in 75% yield;



Scheme 3.

bp 115—116 °C (1 mmHg); IR (neat) 3400, 1730, 1710, 965 (*trans* -CH=CH-) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ=1.16 (3H, t, *J*=7 Hz, Me), 2.32 (4H, m, $-CH_2CH_2-$), 3.63 (2H, d, *J*=5 Hz, $ArCH_2-$), 4.15 (2H, q, *J*=7 Hz, $-OCH_2CH_3$), 5.23—5.98 (2H, m, -CH=CH-). Found: C, 71.89; H, 7.69%. Calcd for $C_{14}H_{18}O_3$; C, 71.77; H, 7.74%.

(2*E*,7*E*)-1,9-Bis(2-hydroxyphenyl)-5,5-bis(ethoxycarbonyl)-2,7-nonadiene (4). R_f=0.17; IR (neat) 3450, 3000, 1725 (C=O). 1040, and 980 (*trans* -CH=CH-) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ=1.16 (6H, t, *J*=7 Hz, Me), 2.60 (4H, d, *J*=6 Hz, $-CH_2C=C-$), 4.10 (4H, q, *J*=7 Hz, $-OCH_2CH_3$), 5.22 (2H, br s, OH), 5.12—5.91 (4H, m, -CH=CH-), and 6.33—6.86 (8H, m, ArH).

2-[*trans*-6,6-Bis(ethoxycarbonyl)-3-hexenyl]phenol (10). R_f=0.30; IR (neat) 3450, 3000, 1740 (C=O), 1240, and 980 (*trans* -CH=CH-) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ=1.25 (6H, t, *J*=7 Hz, Me), 2.01—2.91 (6H, m, $-CH_2CH_2-$ and $-CH_2C=C$), 3.40 (1H, t, *J*=7 Hz, -CH-), 5.05 (1H, br s, OH), 5.15—5.88 (2H, m, -CH=CH-), 6.65—7.42 (4H, m, ArH).

Found: C, 67.60; H, 7.74%. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55%.

(3*E*,8*E*)-1,11-Bis(2-hydroxyphenyl)-6,6-bis(ethoxycarbonyl)-3,8-undecadiene (11). R_f=0.54; IR ($CHCl_3$), 3450, 2980, 1750, 1730, 1030, and 970 (trans -CH=CH-) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ=1.21 (6H, t, *J*=7 Hz, Me), 2.08—2.86 (12H, m, $-CH_2CH_2-$ and $-CH_2C=C$), 4.14 (4H, q, *J*=7 Hz, $-OCH_2CH_3$), 4.98—5.80 (4H, m, -CH=CH-), and 6.60—7.34 (8H, m, ArH). The OH proton was unable to be assigned unambiguously. MS, *m/z* 481 (M$^+$).

3-Ethoxycarbonyl-4-(2-methyl-1-propenyl)coumarin (13). R_f=0.75; IR (neat) 1775 (C=O), 1740 (C=O), 1588, 1485, 1452, 1135, 1032, and 755 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ=1.21 (3H, *J*=7 Hz, Me), 1.77 (3H, d, *J*=1.5 Hz, Me), 1.79 (3H, d, *J*=1.5 Hz, Me), 3.45 (1H, d, *J*=10 Hz, H-3), 4.17 (2H, q, *J*=7 Hz, $-OCH_2CH_3$), 4.35 (td, *J*=10 and ≈1 Hz, H-4), 4.95 (1H, dm, *J*=10 and 1—1.5 Hz, -CHC=C-), and 7.11 (4H, m, ArH). The coupling of $J_{3,4}$=10 Hz suggests the *trans* configuration between the H-3 and H-4 protons.

Found: C, 69.92; H, 6.52%, M$^+$, 274. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61%; M, 274.

Amination of 2 with *N*-Methylaniline. To a solution of $Pd(PPh_3)_4$ (39.5 mg, 0.034 mmol) in toluene (1 mL) were added successively **2** (173 mg, 1.2 mmol) and a solution of *N*-methylaniline (164 mg, 1.53 mmol) in dry THF (1 mL) at room temperature. The mixture was then heated at 120 °C with stirring for 3 h, and cooled to room temperature. Removal of the solvent followed by preparative TLC (SiO_2, $CHCl_3$-acetone=95:5) afforded **3b** in 46% yield. The same treatment of **2** with **5** gave **7** in 46% yield.

[*trans*-4-(*N*-Methylanilino)-2-butenyl]phenol (3b): R_f=0.45 (SiO_2, $CHCl_3$-acetone=19:1); IR (neat) 3380, 3035, 1920, 1800, 1700, 1600, 1500, 1232, 970, 745, 694 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ=2.73 (3H, s, N-Me), 3.27 (2H, d, *J*=5.0 Hz, CH_2), 3.76 (2H, d, *J*=4.0 Hz, $N-CH_2-$), 4.86—5.14 (1H, br, OH), 5.06—5.98 (2H, m, -CH=CH-), 6.44—7.19 (9H, m, ArH).

Found: C, 80.70; H, 7.57; N, 5.59%. Calcd for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53%.

The spectral properties of **7** have been already reported.[12]

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