

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

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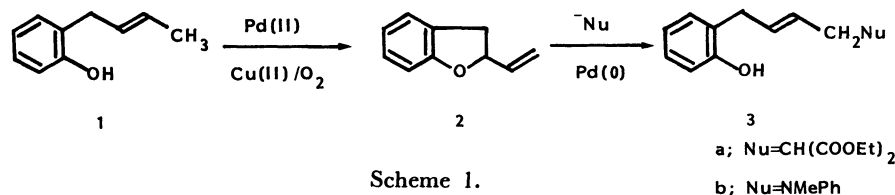
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(Received February 6, 1986)

Reaction of 2,3-dihydro-2-vinylbenzofuran with nucleophiles ($\text{NaCH}(\text{COOEt})_2$ and PhNHCH_3) in the presence of palladium catalysts such as $\text{Pd}(\text{PPh}_3)_4$ and $\text{PdCl}_2(\text{PR}_3)_2$ ($\text{R}=\text{Ph}$ 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 $\text{Pd}(\text{PPh}_3)_4$.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

reduction of PdCl_2 complexes with excess diethyl sodiomalonate.³⁾ Diazopalladium(II) complex, $[\text{PhC}(\text{N}_2)]_2\text{Pd}(\text{PEt}_3)_2$ (**5**),⁴⁾ which upon heating generates $\text{Pd}(\text{PEt}_3)_2$, also serves as the catalyst to give **3a** (69%). Deethoxycarbonylation ($\text{NaCN}/\text{Li}\cdot\text{H}_2\text{O}/\text{DMSO}$, 160 °C) of **3a** afford **6** (75%), resulting in two carbon homologation of the butenyl moiety of **1**.

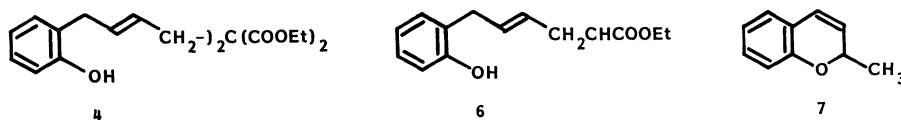


expectation, and an application of this procedure to 2-(*trans*-3-pentenyl)phenol (**8**) (Scheme 2).

The reaction of vinylbenzofuran **2** with diethyl sodiomalonate (1.2 equiv) in the presence of 3 mol% of $\text{Pd}(\text{PPh}_3)_4$ (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

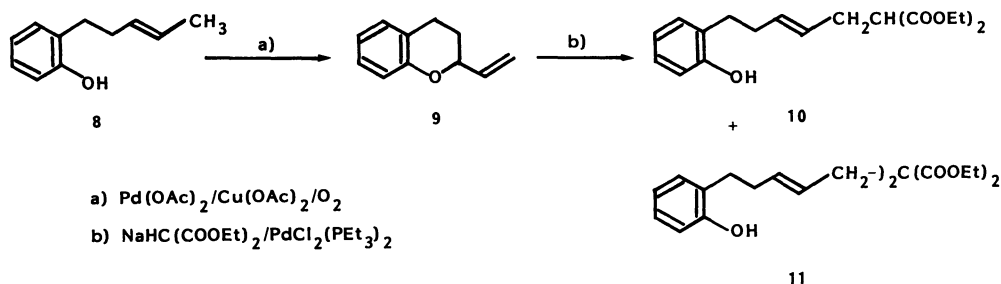
Treatment of **2** with *N*-methylaniline (1.3 equiv) in the presence of $\text{Pd}(\text{PPh}_3)_4$ (3 mol%) in THF-toluene at 120 °C for 3 h gives **3b** in 46% yield (Scheme 1). The use of complex **5** bearing PEt_3 ligand affords a trace amount of **3b**. In this case, the substrate **2** largely rearranges into 2-methyl-2*H*-chromene (**7**) (46%).

2-Vinychroman (**9**), which is readily prepared by



$\text{PdCl}_2(\text{PR}_3)_2$ ($\text{R}=\text{Ph}$ and Et) are comparatively effective in promoting the reaction, in which palladium(0) species is generated in situ by the

$\text{Pd}(\text{II})$ -catalyzed cyclization of 2-(*trans*-3-pentenyl)phenol (**8**), undergoes the same type of alkylation with diethyl sodiomalonate (Scheme 2). In this case,

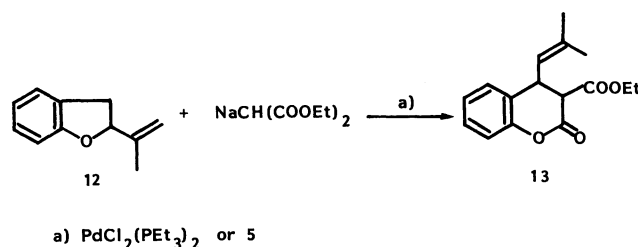


Scheme 2.

however, only the palladium complex bearing PEt_3 is effective; no reaction takes place with $\text{Pd}(\text{PPh}_3)_4$ and $\text{PdCl}_2(\text{PPh}_3)_2$, while $\text{PdCl}_2(\text{PEt}_3)_2$ 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 $\text{Pd}(0)$ 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**.

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



Thus, **13** is obtained in 54–64% yields with $\text{PdCl}_2(\text{PEt}_3)_2$ or **5**, while no reaction occurs with $\text{Pd}(\text{PPh}_3)_4$. 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**.

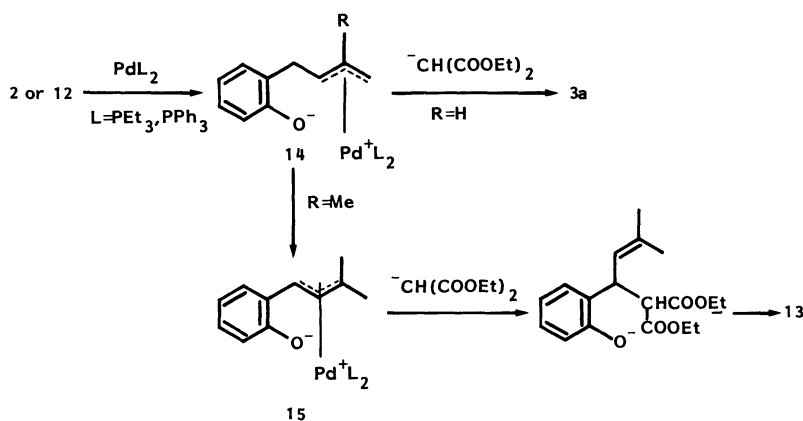
Experimental

2-(*trans*-2-Butenyl)phenol (**1**) was prepared by C-alkylation of phenol with *trans*-1-chloro-2-butene (Tokyo Kasei).¹¹ 2-(*trans*-3-Pentenyl)phenol (**8**) was synthesized by the reaction of *o*-methoxybenzylmagnesium chloride with *trans*-2-butenyl diethyl phosphate⁷ followed by demethylation.⁹ 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), $\text{Pd}(\text{OAc})_2$ (56.5 mg, 0.25 mmol), and $\text{Cu}(\text{OAc})_2$ (45.0 mg, 0.25 mmol) in anhydrous MeOH (5 mL) under O_2 atmosphere (1 atm, balloon) at 36°C . After usual workup,¹¹ the cyclized product was isolated by distillation followed by

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 $\times$ 3). The combined ethereal layer was washed with brine (20 mL $\times$ 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 $\text{Pd}(\text{PPh}_3)_4$, 56 and 19% with $\text{PdCl}_2(\text{PPh}_3)_2$, and 68 and 15% with $\text{PdCl}_2(\text{PEt}_3)_2$, respectively. Those of **10** and **11** are 63 and 10% with $\text{PdCl}_2(\text{PEt}_3)_2$ and 54 and 20% with $[\text{PhC}(\text{N}_2)]_2\text{Pd}(\text{PEt}_3)_2$ (**5**), respectively. The yield of **13** are 64 and 54%, with $\text{PdCl}_2(\text{PEt}_3)_2$ and **5**, respectively.

2-[*trans*-5,5-Bis(ethoxycarbonyl)-2-pentenyl]phenol (3a). $R_f=0.34$; bp $154\text{--}155^\circ\text{C}$ (1 mmHg); IR (neat) 3450, 3000, 1730 ($\text{C}=\text{O}$), 1600, 1040, and 965 (*trans* $-\text{CH}=\text{CH}-$) cm^{-1} ; ^1H NMR (60 MHz, CDCl_3) $\delta=1.20$ (6H, t, $J=7$ Hz, Me), 2.60 (2H, dd, $J=8$ and 6 Hz, ArCH_2-), 3.25–3.27 (3H, m, $-\text{CH}-$ and $-\text{CH}_2\text{C}=\text{C}-$), 4.14 (4H, q, $J=7$ Hz, $-\text{OCH}_2\text{CH}_3$), 5.17–6.00 (2H, m, $-\text{CH}=\text{CH}-$), 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 procedure¹¹ 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} ; ^1H NMR (60 MHz, CDCl_3) δ =1.16 (3H, t, J =7 Hz, Me), 2.32 (4H, m, -CH₂CH₂-), 3.63 (2H, d, J =5 Hz, ArCH₂-), 4.15 (2H, q, J =7 Hz, -OCH₂CH₃), 5.23–5.98 (2H, m, -CH=CH-). Found: C, 71.89; H, 7.69%. Calcd for C₁₄H₁₈O₃; 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} ; ^1H NMR (60 MHz, CDCl_3) δ =1.16 (6H, t, J =7 Hz, Me), 2.60 (4H, d, J =6 Hz, -CH₂C=C-), 4.10 (4H, q, J =7 Hz, -OCH₂CH₃), 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} ; ^1H NMR (60 MHz, CDCl_3) δ =1.25 (6H, t, J =7 Hz, Me), 2.01–2.91 (6H, m, -CH₂CH₂- and -CH₂C=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 C₁₈H₂₄O₅; 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} ; ^1H NMR (60 MHz, CDCl_3) δ =1.21 (6H, t, J =7 Hz, Me), 2.08–2.86 (12H, m, -CH₂CH₂- and -CH₂C=C), 4.14 (4H, q, J =7 Hz, -OCH₂CH₃), 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} ; ^1H 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, -OCH₂CH₃), 4.35 (td, J =10 and $\approx$ 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 C₁₆H₁₈O₄; C, 70.06; H, 6.61%; M , 274.

Amination of 2 with *N*-Methylaniline. To a solution of Pd(PPh₃)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 (SiO₂, 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 (SiO₂, CHCl_3 -acetone=19:1); IR (neat) 3380, 3035, 1920, 1800, 1700, 1600, 1500, 1232, 970, 745, 694 cm^{-1} ; ^1H NMR (60 MHz, CDCl_3) δ =2.73 (3H, s, N-Me), 3.27 (2H, d, J =5.0 Hz, CH₂), 3.76 (2H, d, J =4.0 Hz, N-CH₂-), 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 C₁₇H₁₉ON: C, 80.57; H, 7.56; N, 5.53%.

The spectral properties of 7 have been already reported.¹²⁾

References

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