Syntheses of Steroidal Vinyl Ethers Using Palladium Acetate−Phenanthroline as Catalyst

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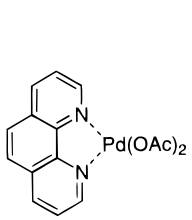
Mercuric salts of carboxylic acids are common catalysts for the preparation of vinyl ethers from alcohols and alkyl vinyl ethers.[1] This catalyst has two major drawbacks, especially in large-scale syntheses: (1) trace quantities of mercury find their way through several steps of a reaction sequence[2] and (2) disposal of waste stream effluents containing mercury is difficult and costly. Recently, Gassman et al.[3] found that vinyl ethers may be prepared from ketals of enolizable ketones using trimethylsilyl triflate/*N*,*N*-diisopropylamine, and Dujardin et al.[4] have used this approach to prepare vinyl ethers from mixed ketals. In an analogous reaction, Katz and co-workers[5] used trimethylsilyl chloride/benzoic acid/pyridine to effect loss of an alcohol from a ketal to yield a vinyl ether. Additionally, prop-1-enyl ethers can be prepared by isomerization of the corresponding *O*-allyl ethers.[6]

We have prepared steroid C_{17}-cyclopropyl ethers from their corresponding vinyl ethers. For preparation of smaller quantities of these vinyl ethers, we used either mercuric acetate or mercuric trifluoroacetate as the catalyst.[7] For larger preparations we investigated other catalyst systems. McKeon et al.[8,9] have described the use of palladium-based catalysts to effect transetherification of vinyl ethers. Specifically, these authors described the use of bis(acetato)(1,10-phenanthroline-N^1,N^{10})palladium (**1**) as a catalyst.[10] We report here the successful use of catalyst **1** for the syntheses of primary and secondary steroidal *O*-vinyl ethers **3** from the corresponding alcohols **2** and the subsequent formation of cyclopropyl ethers **4**.

The reaction, eq 1, is effected by simply stirring an alcohol **2** and 2.5−3.5 mol % of **1** in ethyl vinyl ether (a cosolvent such as dichloromethane can be used) at ambient temperature. When the transetherification is complete, the reaction mixture is placed on a silica gel flash column and the product is eluted. For large-scale reactions, removal of the solvent(s) is appropriate prior to purification. The yields for this conversion are moderate to good (13−79%). Estrone did not transetherify under these conditions. We did not explore the reasons for this inactivity, but it may be due to the phenolic nature of the hydroxyl group or to the lack of solubility of estrone in ethyl vinyl ether/dichloromethane. The lowest yield obtained was for the primary alcohol **2B**. By way of comparison, when this alcohol was treated with ethyl vinyl ether in the presence of $Hg(OCOCF_3)_2$, the desired **3B** was obtained in 53% yield along with the mixed ketal **5** (25%).



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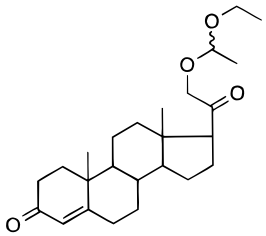

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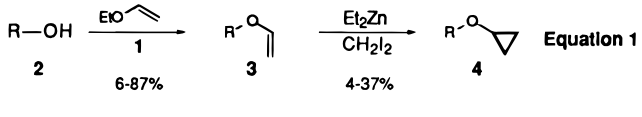
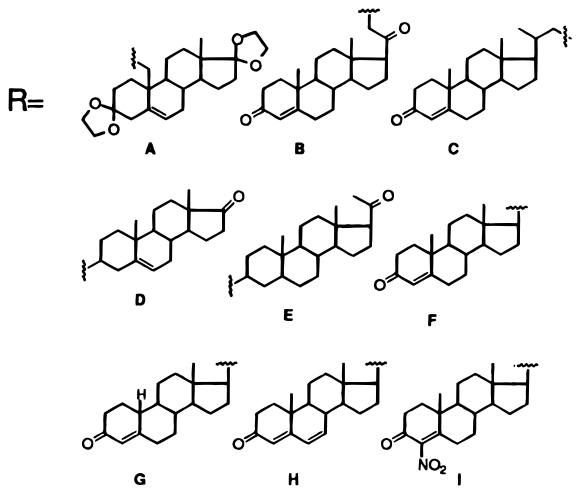
We explored briefly the effect of catalyst purity on the conversion of alcohols to vinyl ethers. As shown in Table 1, it is not necessary to use recrystallized complex **1**; crude catalyst gives equivalent results. Going one step further, use of catalyst formed *in situ* gave similar yields. Thus, for convenience the reaction may be run by adding 1,10-phenanthroline and palladium acetate to ethyl vinyl ether followed by the alcohol.

Cyclopropanation of selected vinyl ethers (**3F**,**H**,**I** eq 1) was accomplished using a modified Simmons−Smith reaction (diethylzinc−diiodomethane). Cyclopropanation of the nuclear double bonds was not observed.





In conclusion, we have developed a general synthesis of vinyl ethers which employs a palladium-based catalyst rather than mercury salts.

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(1) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828−2833.
(2) Benson, H. D., personal communication. See also Ruddick, P. L.; Reese, P. B. *J. Chem. Res. Synop.* **1994**, 442−443.
(3) Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449−1457.
(4) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653−1656.
(5) Willmore, N. D.; Hoic, D. A.; Katz, T. J. *J. Org. Chem.* **1994**, *59*, 1889−1891.
(6) Mereyala, H. B.; Guntha, S. *Tetrahedron Lett.* **1993,** *34*, 6929−6930.
(7) Angelastro, M. R.; Marquart, A. L.; Weintraub, P. M.; Gates, C. A.; Laughlin, M. E.; Blohm, T. R.; Peet, N. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 91−100.
(8) McKeon, J. E.; Fitton, P.; Griswold, A. A. *Tetrahedron* **1972**, *28*, 227−232.
(9) McKeon, J. E.; Fitton, P.; Griswold, A. A. *Tetrahedron* **1972**, *28*, 233−238.
(10) After our work was completed, Taylor reported the use of sodium tetrachloropalladate chloride in the vinyl acetate exchange to give an *N*-vinylformamide. See: Taylor, E. C.; Yoon, C.; Hamby, J. H. *J. Org. Chem.* **1994**, *59*, 7092−7095.

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Table 1. Study of Catalyst

	isolated product (g)	% yield
recrystallized	3.85−4.29[a]	70.5−78.6
uncrystallized	3.95−4.10[a]	72.3−75.1
in situ formed catalyst	4.29[b]	78.6

[a] Testosterone (5.01 g, 17. 4 mmol) in ethyl vinyl ether (25 mL) and dichloromethane (5 mL) containing the appropriate catalyst (0.125 g) was stirred at room temperature for 4 days followed by the usual workup. [b] The reaction was run as above except that phenanthroline (0.146 g) and palladium acetate (0.81 g) were first added to the ethyl vinyl ether−dichloromethane medium and stirred for 15 min prior to addition of the steroid.

Experimental Section[11]

3β-(Cyclopropyloxy)androst-5-en-17β-ol (2J). To a solution of ketone **4D** (1.36 g, 4.14 mmol) in 95% ethanol was added $NaBH_4$ (0.58 g, 15.3 mmol). After 90 min, the reaction was diluted with H_2O (50 mL) and cautiously made acidic with 10% HCl. The resulting precipitate was collected by filtration, washed with H_2O, and crystallized from aqueous Me_2CO to give **2J** (0.93 g, 67.4%): mp 105−106 °C; MS (CI) 331 (3), 273 (100); ^{1}H NMR ($CDCl_3$) δ 0.42−0.59 (m, 4H), 0.77 (s, 3H), 1.01 (s), 3.25−3.38 (m, 2H), 3.59−3.69 (m, 1H), 5.33−5.39 (m, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 79.03, 81.56, 121.21, 141.06; IR (KBr) 3281 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O$: C, 79.95; H, 10.37. Found: C, 79.17; H, 10.17.

Procedure for Vinylation of Alcohols 2. 17β-(1-Ethenyloxy)androst-4-en-3-one (3F). A mixture of testosterone (50.0 g, 173.3 mmol), 1,10-phenanthroline−palladium acetate complex (2.10 g, 5.20 mmol), ethyl vinyl ether (250 mL), and dichloromethane (150 mL) were stirred at ambient temperature for 4 days. (Complete solution was effected by this time.) The reaction mixture was poured directly onto a column of silica gel (9 cm × 19 cm) prepared in hexane−20% ethyl acetate and flash chromatographed using the same solvent. The product-containing fractions (3−5, 1 L each) were combined and concentrated to a white solid (43.3 g, 79.4%). Crystallization from hexane gave an analytical sample of **3F**: MS (CI) 315 (100); ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.20 (s, 3H), 3.74 (t, 1H), 3.95 (dd, 1H), 4.26 (dd, 1H), 5.73 (s, 1H), 6.34 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 87.85, 88.00, 123.87, 151.71, 170.97, 199.39; IR (KBr) 1666, 1637, 1614 cm^{-1}. Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.55; H, 9.88.

19-(1-Ethenyloxy)androst-5-ene-3,17-dione bisethylene ketal (3A): 74.4%; mp 88−89 °C (aqueous Me_2CO); MS (CI) 417 (100); ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3H), 3.66 (d, 1H), 3.81−4.03 (complex m, 10H), 4.17 (dd, 1H), 5.08−5.13 (m, 1H), 6.50 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 86.10, 109.11, 119.44, 125.66, 135.51, 151.76; IR (KBr) 1615 cm^{-1}. Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.02; H, 8.57.

21-(1-Ethenyloxy)pregn-4-ene-3,20-dione (3B): 87.3%; mp 142−143 °C (Me_2CO/Et_3N); MS (CI) 357 (100); ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 3H), 1.17 (s), 2.73 (t, 1H), 4.07−4.18 (m, 2H), 4.19 + 4.26 (d + d, 2H), 5.72 (s, 1H), 6.47 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 87.89, 123.94, 150.77, 170.68, 199.29, 206.60; IR (KBr) 1707, 1661, 1620, 1203 cm^{-1}. Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.51; H, 8.98.

21-(1-Ethenyloxy)-20-methylpregn-4-en-3-one (3C): 85.0%; MS (CI) 357 (100); ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3H), 1.05 (d), 1.19 (s), 3.42 (dd, 1H), 3.63 (dd, 1H), 3.94 (dd, 1H), 4.04 (dd, 1H), 5.73 (s, 1H), 6.46 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 85.90, 123.77, 152.23, 171.40, 199.50; IR (KBr) 1680, 1620, 1198 cm^{-1}. Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 81.09; H, 10.15.

3-(1-Ethenyloxy)androst-5-en-17-one (3D): 70.6%; mp 146−148 °C (Me_2CO/Et_3N); MS (CI) 315 (12), 271 (100); ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 3H), 1.06 (s), 3.58 (m, 1H), 4.00 (dd, 1H), 4.30 (dd, 1H), 5.37−5.43 (m, 1H), 6.34 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 78.86, 88.33, 121.40, 140.46, 150.35, 220.91; IR (KBr) 1738, 1630, 1175, 1071 cm^{-1}. Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.36; H, 10.07.

3-(1-Ethenyloxy)-5α-pregnan-20-one (3E): 5.9%; mp 85−87 °C (aqueous Me_2CO); MS (CI) 345 (35), 301 (100); ^{1}H NMR ($CDCl_3$) δ 0.63 (s, 3H), 0.82 (s, 3H), 2.12 (t, 1H), 2.64−2.75 (m, 1H), 3.98 (dd, 1H), 4.29 (dd, 1H), 6.33 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 78.76, 88.11, 150.57, 209.52; IR (KBr) 1701, 1634 cm^{-1}. Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.34; H, 10.49.

5α-Pregnan-20-one: 5.3%; mp 132−133 °C (MeOH); MS (CI) 303 (100); ^{1}H NMR ($CDCl_3$) δ 0.60 (s, 3H), 0.78 (s, 3H), 2.11 (s), 2.52 (t, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 209.69; IR (KBr) 1705 cm^{-1}. Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 82.59; H, 11.09.

17β-(1-Ethenyloxy)estr-4-en-3-one (3G): 80.2%; mp 140−141 °C (Me_2CO/Et_3N); MS (CI) 301 (100); ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H), 3.76 (t, 1H), 3.95 (d 1H), 4.28 (d, 1H), 5.83 (s, 1H), 6.34 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 87.83, 88.05, 124.54, 151.67, 166.34, 199.71; IR (KBr) 1670, 1613, 1196 cm^{-1}. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.91; H, 9.49.

17β-(1-Ethenyloxy)androsta-4,6-dien-3-one (3H): 5.6%; mp 75−76 °C (hex); MS (CI) 313 (100); ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.09 (s, 3H), 3.75 (dd 1H), 3.94 (dd, 1H), 4.24 (dd, 1H), 5.65 (s, 1H), 6.05−6.15 (m, 2H), 6.32 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 87.57, 87.96, 123.68, 140.04, 151.57, 163.38, 199.32; IR (KBr) 1670, 1615, 1194 cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.73; H, 9.02.

17β-(1-Ethenyloxy)-4-nitroandrost-4-en-3-one (3I): 74.1%; MS (CI) 360 (100); ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H), 1.31 (s), 3.74 (t, 1H), 3.97 (dd, 1H), 4.27 (dd, 1H), 6.34 (dd, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 87.69, 88.02, 146.27, 151.60, 160.41, 187.40; IR (KBr) 1693, 1630, 1533 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.09; H, 7.98; N, 3.86.

21-(1-Ethenyloxy)pregn-4-ene-3,20-dione (3B). A solution of recovered 21-hydroxyprogesterone (13.6g, 41.1 mmole), mercuric trifluoracetate (0.63 g), ethyl vinyl ether (100 mL), and dichloromethane (50 mL) was stirred at room temperature for 5 d. The reaction mixture was poured onto a column of silica gel prepared in hexane−25% ethyl acetate and flash chromatographed. The desired product **3B** (7.78 g, 52.9%) eluted first. A second material then eluted from the column (4.16 g, 25.1%) which was identified as **21-[(1-ethoxyethyl)oxy]pregn-4-en-3-one (5):** mp 64−66 °C; MS (FAB) 403 (100); ^{1}H NMR ($CDCl_3$) δ 0.63 (s, 3H), 1.09−1.14 + 1.12 (m + s), 1.28 (dd), 3.39−3.49 + 3.52−3.62 (m + m, 2H), 4.01 + 4.10 (dd + d, 2H), 4.67−4.75 (m, 1H), 5.66 (s, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 99.08, 99.55, 123.77, 170.63, 170.64, 199.13; IR (KBr) 1723, 1709, 1674, 1616 cm^{-1}. Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.49; H, 9.38.

Procedure for the Cyclopropanation of Vinyl Ethers 3. 17β-(Cyclopropyloxy)androst-4-en-3-one (4F). To a solution of **3F** (37.56 g, 119 mmol) in Et_2O (900 mL) under a nitrogen atmosphere was added 1 M Et_2Zn/hexane (240 mL, 240 mmol), and then a solution of CH_2I_2 (66.7 g, 248 mmol) in Et_2O (75 mL) was slowly added. The reaction mixture was heated at reflux temperature for 18 h and then cooled to room temperature. A second portion of Et_2Zn/hexane (120 mL) was added followed by more CH_2I_2 (33.4 g) in Et_2O (50 mL). After being refluxed for 5 h, the reaction mixture was cooled to room temperature, and the excess reagent was *cautiously* decomposed by dropwise addition of saturated NH_4OAc (75 mL). After the mixture was diluted with Et_2O (500 mL), the organic layer was separated, washed with saturated NH_4OAc (2 × 200 mL) and with saturated NaCl (200 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was dissolved in MeOH (400 mL)−H_2O (10 mL)−10% HCl (1 mL) and stirred for 2.5 h at ambient temperature. Et_3N (10 mL) was added, and the solvents were removed on a rotary evaporator. The residue was

(11) Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. TLC analyses were performed with Merck DC-F_{254} or Analtech GHLF silica gel plates, with visualization by alkaline permanganate and UV irradiation. Flash chromatography was performed with Merck silica gel 60 (0.040−0.063 mm). NMR spectra were recorded on Varian VXR-300, Unity 300, Unity 400, or Gemini-300 spectrometers in $CDCl_3$. ^{1}H and ^{13}C NMR signals are reported in ppm from tetramethylsilane. IR spectra were recorded on a Perkin-Elmer Model 1800 or Mattson Galaxy 5020 FT-IR spectrophotometer. MS data were collected at 70 eV on a Finnigan MAT 4600 or Mat TSQ-700 or VG Analytical Limited ZAB2-SE mass spectrophotometer. Combustion analyses were performed using a Perkin-Elmer Model 2400 elemental analyzer. The organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 prior to solvent removal on a rotary evaporator.

purified by flash chromatography (silica gel, hexane−20% EtOAc) to give the title compound as an oil, **4F** (14.7 g, 37.5%), which crystallized on standing. It was recrystallized from aqueous MeOH: MS (CI) 329 (100); ^{1}H NMR ($CDCl_3$) δ 0.38−0.61 (m, 4H), 0.80 (s, 3H), 1.19 (s), 3.26−3.33 (m, 1H), 3.44 (t, 1H), 5.73 (s, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 88.88, 123.81, 171.23, 199.47; IR (KBr) 1676, 1616 cm^{-1}. Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 79.49; H, 9.64.

17β-(Cyclopropyloxy)androsta-4,6-dien-3-one (4H): 4.4%; MS (CI) 327 (100); ^{1}H NMR ($CDCl_3$) δ 0.38−0.59 (m, 4H), 0.83 (s, 3H), 1.10 (s), 3.26−3.32 (m, 1H), 3.46 (t, 1H), 5.66 (s, 1H), 6.10 (s, 2H); ^{13}C NMR ($CDCl_3$) downfield only δ 88.56, 123.61, 127.95, 140.51, 163.75, 199.58; IR (KBr) 1720, 1665, 1618, 1584 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2$.0.75$(CH_3)_2CO$: C, 78.71; H, 9.40. Found: C, 78.68; H, 9.02.

17β-(Cyclopropyloxy)-4-nitroandrost-4-en-3-one[12] **(4I):** 27.4%; MS (CI) 374 (100); ^{1}H NMR ($CDCl_3$) δ 0.38−0.61, 0.80 (s, 3H), 1.29 (s), 3.25−3.33 (m, 1H), 3.44 (t, 1H); ^{13}C NMR ($CDCl_3$) downfield only δ 88.63, 146.65, 160.62, 187.44; IR (KBr) 1695, 1622, 1535, 1373 cm^{-1}. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.85; H, 8.37; N, 3.75. Found: C, 70.83; H, 8.34; N, 3.70.

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(12) Curran, T. T.; Flynn, G. A.; Rudisell, D. E.; Weintraub, P. M. *Tetrahedron Lett.* **1995**, *36*, 4761−4764.