## Synthesis of 2H-1-Benzopyrans by Pd-Catalyzed Cyclization of o-Allylic Phenols

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Derivatives of 2H-1-benzopyran (1), also known as chromenes, are prominent natural products of many genera of the *Asteraceae* possessing a wide range of valuable physiological activities.<sup>1</sup> They are also useful intermediates in the synthesis of complex natural products, such as pterocarpans.<sup>2</sup>



The synthesis of 2H-1-benzopyrans is of considerable current interest.<sup>3</sup> Most pertinent to the present research are synthetic methods involving (1) the palladium-catalyzed coupling of *o*-iodophenols and tertiary allylic alcohols,<sup>4</sup> (2) the iodoetherification<sup>5</sup> or selenoetherification<sup>6</sup> of *o*-allylic phenols and subsequent elimination, and (3) the direct oxidation of *o*-allylic phenols by DDQ<sup>7</sup> or potassium dichromate-Adogen 464.<sup>7u</sup> While all of these methods afford good yields of 2,2-disubstituted 2H-1-benzopyrans and iodoetherification or direct oxidation afford 2-aryl-2H-1-benzopyrans as well, none of these methods has been reported to work on phenols possessing a wide variety of substitution patterns in the allylic side chain.

The cyclization of o-allylic phenols by palladium(II) salts has been reported to produce a variety of cyclic ethers. Phenols bearing a simple allyl, 2-butenyl or cinnamyl group react with NaOMe and stoichiometric amounts of PdCl<sub>2</sub>(PhCN)<sub>2</sub>, stoichiometric Pd(OAc)<sub>2</sub>, or catalytic Pd(OAc)<sub>2</sub> plus Cu(OAc)<sub>2</sub>•H<sub>2</sub>O to afford exclusively 5membered ring products.8 However, 2-(2-butenyl)phenol has been reported to react directly with PdCl<sub>2</sub> in methanol to produce a mixture of 5- and 6-membered ring ethers in low yield. While the yields are improved using Pd(OAc)<sub>2</sub>, only 5-membered ring products are obtained.<sup>8</sup> Analogous reactions on 2-(3-methyl-2-butenyl)phenol afford predominantly 6-membered ring ethers using PdCl<sub>2</sub> and a mixture of 5and 6-membered ring ethers when PdCl<sub>2</sub> plus NaOAc or Pd(OAc)<sub>2</sub> alone are employed.9 A mixture of 5-membered ring double bond isomers has been observed in the reaction of 2-(2-cycloalkenyl)phenols and Pd(OAc)<sub>2</sub>.<sup>10</sup> The latter process could be made catalytic if run under 1 atm of O2. Finally, early attempts to effect the enantioselective cyclization of 2-(2-butenyl)phenol using chiral  $\pi$ -allylpalladium catalysts in the presence of O2 and Cu(OAc)2 afforded mixtures of 5membered ring ethers with low enantioselectivities,11 but recently 2-(2,3-dimethyl-2-butenyl)phenol and 2-(3,4-dimethyl-3-pentenyl)phenol have been cyclized to the corresponding 5- and 6-membered ring ethers respectively with high enantioselectivities using 10 mol % Pd(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub>, a chiral ligand and benzoquinone.<sup>12</sup>

We have observed that the use of an appropriate Pd catalyst under the right reaction conditions will very cleanly produce high yields of 2H-1benzopyrans *from a wide variety of o-allylic phenols* and that *air* can be employed as the sole reoxidant for palladium (eq 1).



We<sup>13</sup> and others<sup>14</sup> have previously shown that catalytic amounts of palladium acetate in the presence of oxygen and DMSO provides an excellent Pd(II) catalyst for the cyclization of functionalized alkenes and the conversion of enol silanes to enones. While this catalyst system proved unsatisfactory for the synthesis of 2H-1-benzopyrans, further optimization has afforded reaction conditions which provide exclusively the 6-membered ring ethers in high yields. Optimal conditions for the cyclization of *o*-allylic phenols (0.5 mmol) require heating 5 mol % Pd(dba)<sub>2</sub> (dba = dibenzylideneacetone) and KHCO<sub>3</sub> (0.55 mmol) in 9:1 DMSO/water (10 ml) for 3 days at 60 °C in the presence of *air*.

The choice of Pd catalyst, base and solvent system are critical to the clean formation of the 6-membered ring ether in high yields. The reaction of *o*-allylphenol and PdCl<sub>2</sub> gave exclusively 5-membered ring 2-methylbenzofuran, while Pd(OAc)<sub>2</sub> and Pd(dba)<sub>2</sub> afforded exclusively 2H-1-benzopyran. While Pd(dba)<sub>2</sub> has usually been employed as the catalyst, Pd(OAc)<sub>2</sub> provided faster and cleaner reactions for electron-deficient phenols (see entries 9 and 10 in Table 1). Carbonate bases afforded only the 6-membered ring ether, while acetate

## Table 1. Palladium-Catalyzed Cyclization of o-Allylic Phenols<sup>a</sup>







a See the text and supplemental information for the detailed procedure.

- b Yields refer to isolated compounds purified by
- c from tography. c 5 mol % Pd(OAc)<sub>2</sub> is used in place of Pd(dba)<sub>2</sub>.
- d Temperature is 40 °C.
- e Room temperature; 34:66 ratio of 6:5 membered rings.

bases gave mixtures of 5 and 6-membered ring ethers. To our surprise, small scale reactions run in the presence of *air* actually gave higher yields than those run under  $O_2$ , although they took longer to reach completion. This appears to be the first efficient use of *air* as the sole reoxidant for palladium. However, on larger scale reactions (10 mmol), better results were obtained using 1 atm of  $O_2$ .

Employing our optimal procedure, we have examined the cyclization of a wide variety of *o*-allylic phenols (Table 1). Unlike much previous methodology for the synthesis of 2H-1-benzopyrans and particularly the processes cited in references 4-6, our process provides good yields of 2H-1-benzopyrans substituted in a variety of positions about the aromatic ring or the pyran ring. However, electron-withdrawing groups *para* to the OH group significantly lower the yield of cyclic ether (entries 9 and 10). It is noteworthy that the cyclization of 2-(2cyclohexenyl)phenol under our reaction conditions produced exclusively a single tetrahydrodibenzofuran product in high yield (entry 12), since the stoichiometric use of Pd(OAc)<sub>2</sub> is reported to produce regioisomers.<sup>10</sup> While 1-allyl-2-naphthol cyclized cleanly to the corresponding 6-membered ring ether (entry 13), the corresponding prenyl derivative afforded a mixture of 5- and 6-membered ring ethers (entry 14). This is quite surprising, since the corresponding phenol (entry 4) affords solely the 2H-1-benzopyran. No more than traces of 5membered ring ethers were observed in any of the other reactions. This methodology has also proven useful for the synthesis of precocene-II (6,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran, entry 11)<sup>15</sup> and 6cyano-2,2-dimethyl-2H-1-benzopyran (entry 10), an important intermediate for the synthesis of benzopyran potassium channel openers,<sup>16</sup> as well as flav-3-enes (entry 5) and neoflav-3-enes (entry 6).

The mechanism of this cyclization is not presently known. Two options appear reasonable. The allylic phenol may be directly converted to an aryl-substituted  $\pi$ -allylpalladium intermediate, which then undergoes Pd substitution at the remote end of the allylic system to afford the observed 6-membered ring products and Pd(0). Subsequent oxidation of palladium regenerates the requisite Pd(II) catalyst. The formation of  $\pi$ -allylpalladium intermediates directly from alkenes and nucleophilic substitution of such compounds are both well known processes.<sup>17</sup> Alternatively, these reactions may be proceeding via oxypalladation, subsequent palladium hydride beta elimination, and Pd(0) reoxidation; again all are well known processes.<sup>17a-c</sup> Both mechanisms have been suggested by us previously to explain the products of the Pd(II)-catalyzed cyclization of *o*-allylic tosylanilides.<sup>13c</sup>

In summary, a wide variety of 2H-1-benzopyrans can now be prepared by the Pd-catalyzed cyclization of *o*-allylic phenols. The process is highly regioselective, accommodates a variety of substitution patterns in the aryl ring and allylic moiety, proceeds in good to excellent yields and utilizes *air* as the sole reoxidant for palladium. The mechanism of this process appears to involve either direct  $\pi$ -allylpalladium formation or oxypalladation.

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## References

- (a) Dean, F. M. "The Total Synthesis of Naturally Occurring Oxygen Ring Compounds," ApSimon, J., Ed.; Wiley Interscience: New York, 1973; Vol. 1, p 467. (b) Ellis, G. P. "Chromenes, Chromanones, and Chromones," John Wiley and Sons: New York, 1977. (c) Passreiter, C. M.; Willuhn, G.; Steigel, A.; Matthiesen, U. *Phytochemistry* **1992**, *31*, 1070; (d) Merlini, L. *Adv. Heterocyl. Chem.* **1975**, *18*, 159.
- (2) (a) Narkhede, D. D.; Iyer, P. R.; Iyer, C. S. R. *Tetrahedron* 1990, 46, 2031. (b) Engler, T. A.; Lynch, K. O., Jr.; Reddy, J. P.; Gregory, G. S. *Bioorg. Med. Chem. Lett.* 1993, 3, 1229.
- (3) (a) Billeret, D.; Blondeau, D.; Sliwa, H. *Synthesis* 1993, 881, and references cited therein. (b) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.; Guiry, P. J. *Tetrahedron Lett.* 1990, *31*, 7449.
- (4) Garcías, X.; Ballester, P.; Saá, J. M. *Tetrahedron Lett.* 1991, *32*, 7739.
- (5) (a) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron Lett.* **1979**, 2545. (b) Jurd, L.; Manners, G. D. *Synthesis* **1980**, 618.
- (6) Clive, D. L. J.; Chittattu, G.; Curtis, N. J.; Kiel, W. A.; Wong, C. K. J. Chem. Soc., Chem. Commun. 1977, 725.

- (a) Cardillo, G.; Cricchio, R.; Merlini, L. Tetrahedron 1968, 24, (7)4825. (b) Mechoulam, R.; Yagnitinsky, B.; Gaoni, Y. J. Am. Chem. Soc. 1968, 90, 2418. (c) Cardillo, G.; Cricchio, R.; Merlini, L.; Nasini, G. Gazz. Chim. Ital. 1969, 99, 308. (d) Nozoe, S.; Suzuki, K.T. Tetrahedron Lett. 1969, 29, 2457. (e) Jain, A. C.; Lal, P.; Seshadri, T. R. Tetrahedron 1970, 26, 1977. (f) Hlubucek, J.; Ritchie, E.; Taylor, W. C. Aust. J. Chem. 1970, 23, 1881. (g) Jain, A. C.; Khanna, V. K.; Lal, P.; Seshadri, T. R. Ind. J. Chem. 1970, 8, 480. (h) Bajwa, B. S.; Khanna, P. L.; Seshadri, T. R. Ind. J. Chem. 1971, 9, 1322. (i) Bala, K. R.; Seshadri, T. R. Phytochemistry 1971, 10, 1131. (j) Steck, W. Can. J. Chem. 1971, 49, 2297. (k) Carpenter, I.; McGarry, E. J.; Scheinmann, F. J. Chem. Soc. C 1971, 3783. (1) Jain, A. C.; Jain, S. M. Tetrahedron Lett. 1972, 28, 759. (m) Deshpande, V.H.; Rama Rao, A. V.; Srinivasan, R.; Venkataraman K. Ind. J. Chem 1972, 10, 681. (n) Jain, A. C.; Jain, S. M. Tetrahedron 1972, 28, 981. (o) Anand, S. M.; Jain, A. C. Tetrahedron 1972, 28, 987. (p) Jain, A. C.; Jain, S. M. Tetrahedron 1972, 28, 5063. (g) Meikle, T.; Stevens, R. Tetrahedron Lett. 1972, 4787. (r) Jain, A. C.; Zutshi, M. K. Aust. J. Chem. 1973, 26, 641. (s) Monache, F. D.; De Lima, O. G.; De Mello, J. F.; Monache, G. D.; Marini-Bettòlo, G. B. Gazz. Chim. Ital. 1973, 103, 779. (t) Jain, A. C.; Jain, S. M. Tetrahedron 1973, 29, 2803. (u) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J. Chem. Soc., Chem. Commun. 1979, 836.
- (8) (a) Hosokawa, T.; Ohkata, H.; Moritani, I. *Bull. Chem. Soc. Jpn.* 1975, 48, 1533. (b) Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett.* 1973, 739.
- (9) Hosokawa, T.; Yamashita, S.; Murahashi, S.; Sonoda, A. Bull. Chem. Soc. Jpn. 1976, 49, 3662.
- (10) Hosokawa, T.; Miyagi, S.; Murahashi, S.; Sonada, A. J. Org. Chem. 1978, 43, 2752.

- (11) (a) Hosakawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. J. Am. Chem. Soc. 1981, 103, 2318. (b) Hosokawa, T.; Imada, Y.; Murahashi, S.-I. Bull. Chem. Soc. Jpn. 1985, 58, 3282. (c) Hosokawa, T.; Okuda, C.; Murahashi, S.-I. J. Org. Chem. 1985, 50, 1282.
- (12) Uozumi, Y.; Kato, K.; Hayashi, T. J. Am. Chem. Soc. 1997, 119, 5063.
- (13) (a) Larock, R. C.; Hightower, T. R. J. Org. Chem. 1993, 58, 5298.
  (b) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. Tetrahedron Lett. 1995, 36, 2423. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. J. Org. Chem. 1996, 61, 3584.
- (14) (a) van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. J. Chem. Soc., Chem. Commun. 1994, 357.
  (b) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. Tetrahedron Lett. 1994, 35, 9281. (c) Rönn, M.; Bäckvall, J.; Andersson, P. G. Tetrahedron Lett. 1995, 36, 7749.
- (15) (a) Tiabi, M.; Zamarlik, H. *Tetrahedron Lett.* 1991, *32*, 7251.
  (b) Timár, T.; Jászberényi, J. C. *J. Heterocycl. Chem.* 1988, *25*, 871.
- (16) North, J. T.; Kronenthal, D. R.; Pullockaran, A. J.; Real, S. D.; Chen, H. Y. J. Org. Chem. 1995, 60, 3397.
- (17) (a) Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer: Berlin, Heidelberg, New York; 1980. (b) Heck, R. F. "Palladium Reagents in Organic Synthesis"; Academic Press: New York, 1985. (c) Tsuji, J. "Palladium Reagents and Catalysts: Innovations in Organic Synthesis", John Wiley & Sons: Chichester, New York, Brisbane, Toronto, Singapore; 1995. (d) van der Schaaf, P. A.; Sutter, J.-P.; Grellier, M.; van Mier, G. P. M.; Spek, A. L.; van Koten, G.; Pfeffer, M. J. Am. Chem. Soc. 1994, 116, 5134.