Synthesis of Unsaturated Lactones via Palladium-Catalyzed Cyclization of Alkenoic Acids

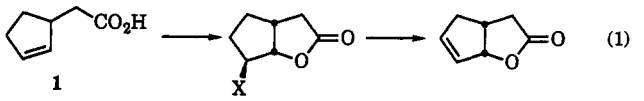
Richard C. Larock* and Timothy R. Hightower

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received July 19, 1993®

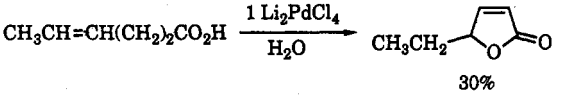
Summary: Acyclic and cyclic, aliphatic or aromatic, 4- or 5-alkenoic acids cyclize in high yield to 5- or 6-membered unsaturated lactones using 5 mol % $Pd(OAc)_2$, 2 equiv of NaOAc, and 1 atm of O_2.

The cyclization of alkenoic acids to unsaturated lactones[1] is a very valuable synthetic transformation most commonly effected by two-step processes involving either halolactonization–dehydrohalogenation[2] (eq 1, X = Br, I), selenolactonization–oxidation[2c,d,g,3] (eq 1, X = SeR), or sulfenolactonization–oxidation (eq 1, X = SR).[3b,g,4] The halolactonization process requires 1 equiv of halogenating agent and a relatively strong base to effect elimination,[2i] and the latter step is known to generate the starting alkenoic acid on occasions.[2a] Selenolactonization requires stoichiometric amounts of oxidants and toxic selenium reagents and generates toxic side products. The corresponding sulfur process requires stoichiometric amounts of relatively unstable sulfur reagents, as well as a base, gives dirtier reactions and lower yields, and requires high temperatures to effect elimination.

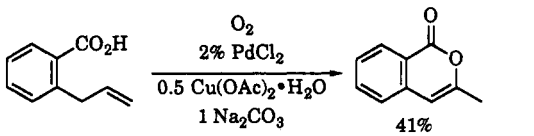


(1)

It appeared to us that analogous chemistry might be effected in one synthetic step employing only catalytic amounts of palladium via acyloxypalladation and subsequent, immediate, room-temperature palladium hydride elimination (eq 1, X = PdOAc).[5] While there are a number of examples of the intramolecular acyloxypalladation of alkenoic acids to form lactones,[6] including the low-yield cyclizations of 4-alkenoic acids to butenolides (eq 2)[7] and



(2)



(3)

o-(2-alkenyl)benzoic acids to isocoumarins (eq 3),[8] this approach has not been developed as a good, general, catalytic route to unsaturated lactones. We now report an experimentally simple, very mild, but versatile, palladium-catalyzed procedure to effect just such a conversion.

Initial model studies employing carboxylic acid 1 and 1 equiv of $Pd(OAc)_2$ in a variety of polar solvents proved successful, with the best results being obtained in DMSO (80% yield). Since the palladium hydride presumably generated during this process is expected to rapidly decompose to Pd(0), a reoxidant is required if the process is to be catalytic in palladium. This was effectively accomplished by employing 5 mol % $Pd(OAc)_2$ in the presence of 2 equiv of $Cu(OAc)_2$ under an atmosphere of oxygen in DMSO (57% yield). Still better results were achieved by adding 2 equiv of NaOAc (80% yield). We subsequently observed that even better yields could be achieved by reducing the amount of $Cu(OAc)_2$ to 10 mol % (90% yield) or omitting it completely (86% yield). *Oxygen alone is remarkably efficient in reoxidizing palladium under our reaction conditions.*

This latter method proved very efficient for the cyclization of a wide variety of alkenoic acids as noted in Table I. Monocyclic, fused, and bridged bicyclic, and spirocyclic lactones bearing 5- or 6-membered rings are all formed readily. Mono-, di-, and trisubstituted alkenes can be employed in this process. However, preliminary attempts to close 4-, 7-, and 12-membered rings have thus

® Abstract published in *Advance ACS Abstracts*, September 1, 1993.

(1) For a general review of electrophilic heteroatom cyclizations, see: Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Pergamon: Oxford, New York, Seoul, Tokyo, 1991; Vol. 4, pp 363–421.

(2) (a) Klein, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611. (b) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972; pp 441–2. (c) Barrish, J. C.; Wovkulich, P. M.; Tang, P. C.; Batcho, A. D.; Uskoković, M. R. *Tetrahedron Lett.* **1990**, *31*, 2235. (d) Bartlett, P. A; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317. (e) Mulzer, J. *Organic Synthesis Highlights*; VCH: Weinheim, New York, Basel, Cambridge, 1991; pp 158–64. (f) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3B, Chapter 6. (g) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114. (h) Staninets, V. I.; Shulov, E. A. *Russ. Chem. Rev.* **1971**, *40*, 272. (i) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171. (j) Trost, B. M.; Timko, J. M.; Stanton, J. L. *J. Chem. Soc., Chem. Commun.* **1978**, 436.

(3) (a) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429. (b) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884. (c) Huckstep, M. R.; Taylor, R. J. K.; Caton, M. P. L. *Tetrahedron Lett.* **1986**, *27*, 5919. (d) Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097. (e) Clive, D. L. J.; Russell, C. G.; Chittattu, G.; Singh, A. *Tetrahedron* **1980**, *36*, 1399. (f) Clive, D. L. J.; Chittattu, G. *J. Chem. Soc., Chem. Commun.* **1977**, 484. (g) de Moura Campos, M.; Petragnani, N. *Chem. Ber.* **1960**, *93*, 317. (h) Nicolaou, K. C.; Lysenko, Z. *J. Am. Chem. Soc.* **1977**, *99*, 3185. (i) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704. (j) Clive, D. L. J.; Chittattu, G.; Wong, C. K. *Can. J. Chem.* **1977**, *55*, 3894. (k) Pearson, A. J.; Kole, S. L.; Ray, T. *J. Am. Chem. Soc.* **1984**, *106*, 6060. (l) Polniaszek, R. P.; Stevens, R. V. *J. Org. Chem.* **1986**, *51*, 3023. (m) Konstantinović, R.; Mihailović, M. Lj. *Tetrahedron Lett.* **1987**, *28*, 6511. (n) Murata, S.; Suzuki, T. *Chem. Lett.* **1987**, 849. (o) Hoye, T. R.; Kurth, M. J. *Tetrahedron Lett.* **1983**, *24*, 4769. (p) Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. *Tetrahedron Lett.* **1979**, 4801. (q) Miyachi, N.; Satoh, H.; Shibasaki, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2049. (r) Vukićević, R.; Konstantinović, S.; Mihailović, M. Lj. *Tetrahedron* **1991**, *47*, 859.

(4) (a) Nicolaou, K. C.; Lysenko, Z. *J. Chem. Soc., Chem. Commun.* **1977**, 293. (b) Trost, B. M.; Ochiai, M.; McDougal, P. G. *J. Am. Chem. Soc.* **1978**, *100*, 7103. (c) O'Malley, G. J.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6159. (d) Tuladhar, S. M.; Fallis, A. G. *Tetrahedron Lett.* **1987**, *28*, 523.

(5) For a general review of the reactions of metal-activated alkenes with heteroatom nucleophiles, see: Hegedus, L. S. *Comprehensive Organic Synthesis*; Pergamon: Oxford, New York, Seoul, Tokyo, 1991; Vol. 4, pp 551–569.

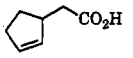
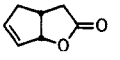
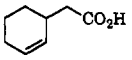
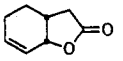
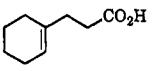
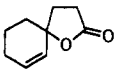
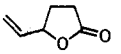
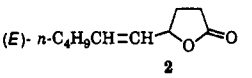
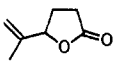
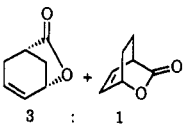
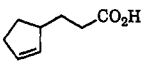
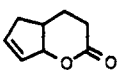
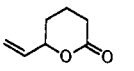
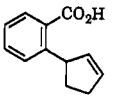
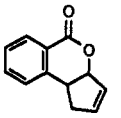
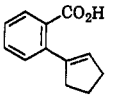
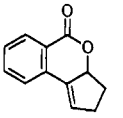
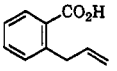
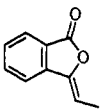
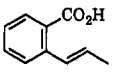
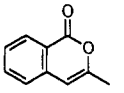
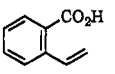
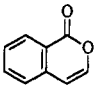
(6) (a) Izumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1673. (b) Tamaru, Y.; Higashimura, H.; Naka, K.; Hojo, M.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1045. (c) Bäckvall, J.-E.; Andersson, P. G.; Vågberg, J. O. *Tetrahedron Lett.* **1989**, *30*, 137.

(7) Kasahara, A.; Izumi, T.; Sato, K.; Maemura, M.; Hayasaka, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1899.

(8) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.

0022-3263/93/1958-5298$04.00/0

Table I. Palladium-Catalyzed Cyclization of Alkenoic Acids to Unsaturated Lactones[a]

entry	alkenoic acid	time (h), T (°C)	product(s)[b]	% isolated yield (ratio)
1		24, 25		86
2		24, 25		90
3		24, 80		91
4	(*E*)-$CH_3CH{=}CH(CH_2)_2CO_2H$	48, 25		81
5	(*E*)-*n*-$C_5H_{11}CH{=}CH(CH_2)_2CO_2H$	48, 25	 **2**	78
6	(*Z*)-*n*-$C_5H_{11}CH{=}CH(CH_2)_2CO_2H$	72, 25	**2**	81
7	$(CH_3)_2C{=}CH(CH_2)_2CO_2H$	168, 25		82
8		36, 80	 3 : 1	56
9		24, 80		87
10	(*E*)-$CH_3CH{=}CH(CH_2)_3CO_2H$	48, 80		68
11		72, 25		82
12		72, 25		80
13		72, 80		71
14		48, 80		78
15		48, 25		90

[a] All reactions were run using 0.5 mmol of alkenoic acid, 1.0 mmol of NaOAc, and 5 mol % of $Pd(OAc)_2$ in 10 mL of DMSO under 1 atm of oxygen. [b] All new products gave appropriate ^1H and ^{13}C NMR, IR, and mass spectral analysis data.

far failed. No cyclization has been observed for 3-butenoic acid or 4-pentenoic acid, although these substrates undergo halo-, seleno-, and sulfenolactonization and have previously been cyclized by Li_2PdCl_4 (see eq 2) to the corresponding butenolides.[7] While the 5-*endo-trig* halo-[2a] and selenolactonization[3b] of 1-cyclopenteneacetic acid and 1-cyclohexeneacetic acid have been successful, the palladium-catalyzed cyclization of these systems fails, presumably due to the strain present in the organopalladium intermediate and the reversibility of the acyloxypalladation reaction.[9]

The relative reactivity of the alkenes generally follows the order: disubstituted > trisubstituted > monosubstituted. There appears to be a fine balance between the effects of electron density and steric hindrance. In general, five-membered rings are more easily closed than six-membered rings (compare entries 1 and 9).

The products of several of these palladium cyclization reactions are quite surprising. First, the cyclization of 3-cyclohexenecarboxylic acid is observed to give two bicyclic lactones (entry 8), while previous work on iodo-,[2j] sulfeno-,[3b] and selenolactonization[3h,3p] of this acid afforded the [3.2.1]bicyclic lactone almost exclusively. As noted earlier, (*E*)-4-hexenoic acid reacts with Li_2PdCl_4 to afford the butenolide (eq 2),[7] but under our conditions only the vinyl valerolactone is formed (entry 4). Analogous results are observed for (*E*)- and (*Z*)-4-decenoic acid (entries 5 and 6). Note that only the (*E*)-alkene is formed in the latter two reactions. While the cyclization of *o*-(2-cyclopentenyl)benzoic acid affords the anticipated product

(entry 11), *o*-(1-cyclopentenyl)benzoic acid produced solely the product of apparent 6-*endo*-*trig* cyclization and subsequent exocyclic palladium hydride elimination (entry 12). No phthalide or isocoumarin product was observed. On the other hand, 5-methyl-4-hexenoic acid cyclizes cleanly to the 5-membered ring lactone under our conditions (entry 7) but affords the 5- and 6-membered ring lactones upon selenolactonization.[3n]

The cyclization of *o*-allylbenzoic acid was even more surprising. Hegedus and co-workers have previously cyclized this substrate to 3-methylisocoumarin using either stoichiometric amounts of $PdCl_2 \cdot 2CH_3CN$ plus Na_2CO_3 or 2 mol % $PdCl_2 \cdot 2CH_3CN$ in the presence of $Cu(OAc)_2 \cdot H_2O$, Na_2CO_3, and O_2 (eq 3).[8] To our great surprise, we observed only the *Z*-phthalide product in high yield (entry 13). This appears to be a particularly useful route to the naturally-occurring 3-alkylidenephthalide ring system.[10] Formation of the 5-membered ring lactone suggested that perhaps the starting acid was first isomerizing to *o*-(1-propenyl)benzoic acid which then affords the observed product. However, cyclization of the latter substrate afforded only 3-methylisocoumarin (entry 14). It appears that the phthalide product of entry 13 arises by π-allylpalladium formation,[11] intramolecular carboxylate displacement of palladium, and subsequent double-bond isomerization. It is possible that other products, particularly those of entries 8 and 12, are also being formed by similar π-allylpalladium processes.

While 2-vinylbenzoic acid has been cyclized previously by palladium chloride to afford a 3:1 mixture of isocoumarin and 3-methylene phthalide,[8] under our conditions the isocoumarin is the sole product isolated in 90% yield (entry 15). It is quite clear that the mechanism of our palladium acetate-catalyzed process is significantly different from that of the palladium chloride based methodology reported previously.

Acknowledgment. We gratefully acknowledge the National Institutes of Health and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous financial support and Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for the palladium acetate.

Supplementary Material Available: General experimental procedure and spectral data for all new compounds (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) (a) Henry, P. M. *Adv. Organomet. Chem.* **1975**, *13*, 365. (b) Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1966**, *88*, 2054. (c) Henry, P. M. *Acc. Chem. Res.* **1973**, *6*, 13. (d) Henry, P. M.; Ward, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 1494. (e) Henry, P. M. *J. Am. Chem. Soc.* **1971**, *93*, 3853.

(10) Mali, R. S.; Patil, S. R.; Kulkarni, B. K.; Yeola, S. N. *Ind. J. Chem.* **1990**, *29B*, 319.

(11) (a) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572. (b) Godleski, S. A. *Comprehensive Organic Synthesis*; Pergamon: Oxford, New York, Seoul, Tokyo, 1991; Vol. 4, pp 585–661.