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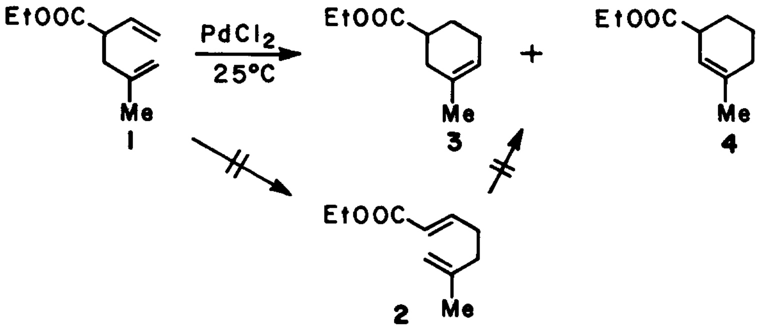
PALLADIUM DICHLORIDE-PROMOTED CYCLIZATIONS OF 1,5-DIENES. A NEW METHOD FOR FORMING CYCLOHEXENES.[1]

Larry E. Overman* and Alfred F. Renaldo
Department of Chemistry, University of California
Irvine, California 92717

Summary: 1,5-Hexadienes, which are substituted with electron-withdrawing groups at carbon-3, undergo regioselective rearrangement to cyclohexenes upon treatment with palladium dichloride.

The formation of oxidized methyl cyclopentenes from the reaction of palladium(II) salts with 1,5-dienes has been described by several investigators.[2] In this Letter, we report that certain acyclic 1,5-dienes cyclize with good regioselectivity to give cyclohexenes when treated under mild conditions with palladium dichloride. To our knowledge,[3,4] this molecular rearrangement is unprecedented, and provides a new method for preparing cyclohexenes, albeit in modest yields.

Reaction of ethyl 2-ethenyl-4-methyl-4-pentenoate (1)[5,6] with 0.2 equiv of bis(acetonitrile)palladium dichloride (25°C, THF), standard conditions previously employed by us to effect the Cope rearrangement of acyclic 1,5-dienes,[1,7] did not yield Cope product 2. This treatment provided the cyclized products 3 and 4 in low yields and returned large amounts of the starting diene 1. When 1 equiv of bis(acetonitrile)palladium dichloride was employed and the reaction was quenched after 1 hr with excess KCN, cyclohexenes 3 and 4 were isolated in a 4:1 ratio and 40% yield. Cyclohexene 3 was identical



with the minor Diels-Alder adduct formed from isoprene and ethyl acrylate,[8] while the structure of 4 was confirmed by its preparation[9] from 3-methylbenzoic acid. Treatment of Cope product 2 (prepared from 1 by thermal rearrangement at 195°C) under identical conditions did not afford 3 and 4 and returned 2 unchanged. Similarly, cyclohexenes 3 and 4 were not produced when 1 was treated with acid catalysts.[10]

Since the rearrangement of 1 to cyclohexenes 3 and 4 should be catalytic in palladium(II), we investigated a variety of reaction conditions, quenching agents, co-oxidants, and palladium(II) salts in an attempt to optimize this transformation. Unfortunately, we have not yet succeeded in obtaining reasonable yields of cyclized products under catalytic conditions.[11] However, the regioselectivity of the cyclization could be improved by quenching[12] the reaction of 1 and bis(acetonitrile)palladium dichloride [or the more soluble salt, bis(hexanenitrile)palladium dichloride][13] with silica gel. Chormatographic purification then provided cyclohexene 3 in 53% yield. Capillary GC analysis of the crude cyclization product showed that less than 5% of 4 was produced under these conditions. The similar cyclization of a variety of 1,5-dienes, which contain electron-withdrawing substituents at C-3, is summarized in the Table.[12] The cyclohexenes produced in this way showed diagnostic AB quartets for an isolated allylic methylene group and a broad signal for one vinylic hydrogen in the 250 MHz ^{1}H NMR spectra.

It is important to stress that the cyclization reactions reported here are limited in scope. If an electron-withdrawing group is not present, dienes related in structure to those shown in the Table undergo clean palladium dichloride-catalyzed Cope rearrangement under similar conditions.[7] Even moving the electron-withdrawing group by one carbon directs the reaction totally down the catalyzed Cope rearrangement manifold.[14] Nonetheless, since the cyclohexenes shown in the Table are not readily available by Diels-Alder construction, palladium(II)-promoted diene cyclizations may have applications in organic synthesis.

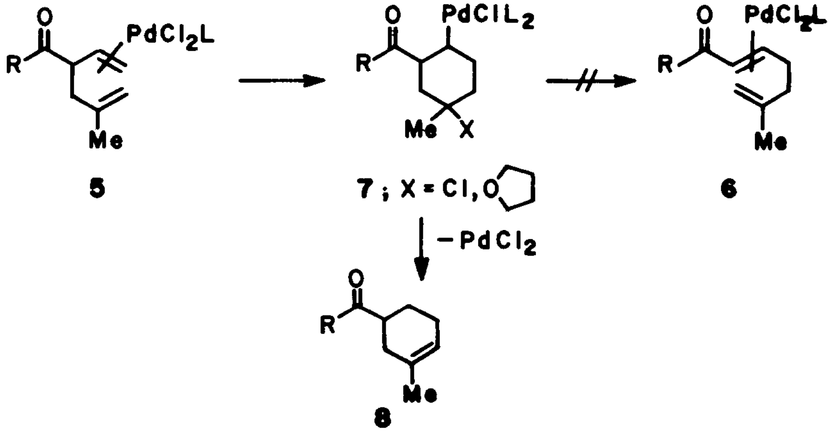
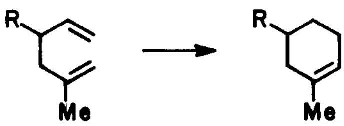
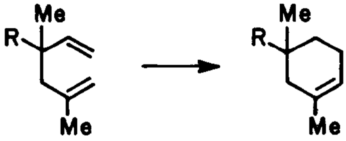
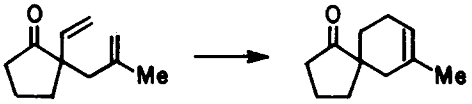


TABLE: CYCLOHEXENES FROM 1,5-DIENES.[12]

Reaction		Conditions Temp, Time	Yield
	$\mathrm{R} = \overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OEt}$	25°C, 1h	53%
	$\mathrm{R} = \mathrm{C{\equiv}N}$	25°C, 2h	30%
	$\mathrm{R} = \overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OEt}$	66°C, 0.8h	30%
	$\mathrm{R} = \overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Ph}$	66°C, 0.8h	44%
	$\mathrm{R} = \overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Me}$	66°C, 0.8h	35%
		66°C, 0.8h	22%
		66°C, 0.8h	21%

The reluctance of dienes such as 1 to undergo palladium(II)-catalyzed Cope rearrangements,[1,7] can be rationalized by the relative instability of palladium dichloride alkene complex 6.[15] We suggest that cyclohexenes 8 arise from cyclization of 5 to 7. Because of the electron-withdrawing substituent, 7 does not fragment[1] to Cope product 6, but rather is transformed by a sequence whose mechanism is currently unclear to cyclohexene 8.

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References and Notes

1. Catalyzed Sigmatropic Rearrangements. 7. For part 6, see: Overman, L.E.; Jacobsen, E.J. *J. Am. Chem. Soc.* *1982*, *104*, 7225-7231.
2. See, *inter alia*: (a) Adachi, N.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Bull. Chem. Soc. Jpn.* *1975*, *48*, 521-525. (b) Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem. Int. Ed. Engl.* *1979*, *18*, 866-867.
3. Oxidative cyclizations of 2-trimethylsilyloxy-1,5-dienes[4a] and 5-methyleneecyclooctene[4b] with palladium(II) salts to give six-membered ring products have been described, as have related oxidative cyclizations with mercury(II) salts.[4c]
4. Cf. (a) Ito, Y.; Aoyama, H.; Saegusa, T. *J. Am. Chem. Soc.* *1980*, *102*, 4519-4521; Kende, A.S.; Roth, B.; Sanfilippo, P.J. *Ibid*. *1982*, *104*, 1784-1785. (b) Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem. Int. Ed. Engl.* *1979*, *18*, 867-868. (c) Julia, M.; Fourneron, J.-D. *J. Chem. Res.* *(M)* *1978*, 5401.
5. Prepared from ethyl crotonate and 3-iodo-2-methylpropene by the general procedure of Schlessinger.[6] Other starting dienes were prepared in related fashions.
6. Herrmann, J.L.; Kieczykowski, G.R.; Schlessinger, R.H.; *Tetrahedron Lett.* *1973*, 2433-2436.
7. Overman, L.E.; Knoll, F.M. *J. Am. Chem. Soc.* *1980*, *102*, 865-867.
8. Hennis, H.E. *J. Org. Chem.* *1963*, *28*, 2570-2572
9. Birch reduction, followed by esterification and selective hydrogenation of the disubstituted double-bond in the presence of *tris*(triphenylphosphine)rhodium chloride.
10. For example, treatment (25°C, 32 h) of **1** with CF_3COOH (2 equiv) gave no **3** or **4** (capillary GC analysis), although > 80% of **1** was consumed under these conditions.
11. Apparently, the by-products of unknown structure which are produced in these reactions consume the palladium(II) catalyst.
12. Cyclizations were conducted at 0.1 *M* in THF using 1.0 equiv of bis(hexanenitrile)palladium dichloride. After the reaction was judged complete by GC analysis, silica gel (1 g/50 mmol of $PdCl_2$) was added, the mixture was concentrated, the residue was layered on top of a silica gel chromatography column, and the product was eluted with mixtures of hexane and ethyl acetate. New compounds showed IR, 250 MHz ^1H NMR, ^{13}C NMR, and high resolution mass spectra consistent with their assigned structures.
13. Prepared by dissolving $PdCl_2$ in hot hexanenitrile and precipitating the resulting complex at room temperature by adding ether.
14. Overman, L.E.; Renaldo, A.F. to be published.
15. Cf. Kurosawa, H.; Majima, T.; Asada, N. *J. Am. Chem. Soc.* *1980*, *102*, 6996-7003; and references cited therein.

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