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ONE-POT SYNTHESIS OF TETRAHYDROFURAN DERIVATIVES FROM ALLYLIC ALCOHOLS AND VINYL ETHERS BY MEANS OF PALLADIUM(II) ACETATE

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Summary: Treatment of a mixture of allylic alcohol and vinyl ether in the presence of $Pd(OAc)_2$ provides 2-alkoxy-4-alkenyltetrahydrofuran in good yield.

The palladium(II)-mediated intramolecular cycloalkenylation reaction between enol ethers and alkenes has become a general synthetic method for alicyclic compounds.[1] Here we wish to report that $Pd(OAc)_2$ promotes intermolecular cycloalkenylation reaction between allylic alcohols and vinyl ethers to give tetrahydrofuran derivatives in a single step. The formation of tetrahydrofurans could be explained by assuming an intermediate palladium compound **1**, which undergoes intramolecular olefin insertion followed by β-elimination of palladium hydride from palladium complex **2**.

A typical procedure for the preparation of 2-butoxy-4-vinyltetrahydrofuran (**3a**) is illustrated as follows. To a solution of crotyl alcohol (72 mg, 1.0 mmol) in butyl vinyl ether (3 ml, 10 mmol), $Pd(OAc)_2$ (0.23 g, 1.0 mmol) was added and the resulting mixture was stirred at 25°C for 2h. The mixture was diluted with hexane (20 ml) and pyridine (0.2 g) was added. After stirring at 25°C for additional 10 min, the precipitated palladium residue was filtered off and filtrate was concentrated in vacuo. Purification of the residual oil by silica gel column chromatography gave 2-butoxy-4-vinyltetrahydrofuran **3a** (0.13 g, cis:trans = 1:1)[2] in 74% yield. The other results are summarized in Table 1.[3,4]

The new reaction has following characteristics. (1) Tetrahydrofurans are formed in preference to dihydropyran derivatives with an exception of the reaction of cinnamyl alcohol which gives six-membered ring exclusively. (2) In the case of methallyl alcohol, β-elimination of palladium hydride can

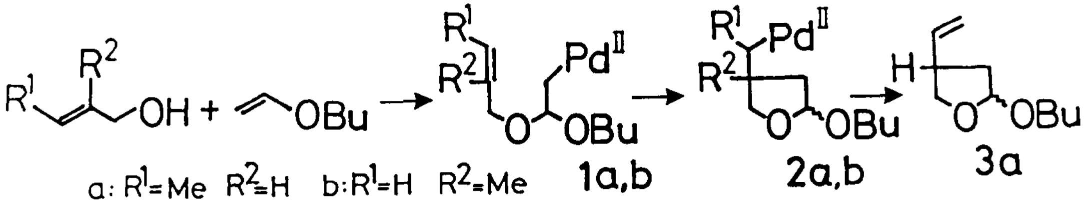
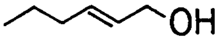
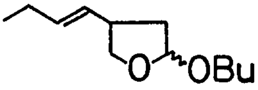
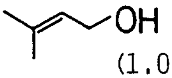
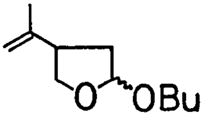
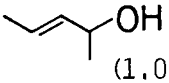
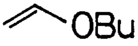
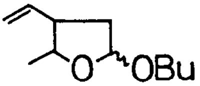
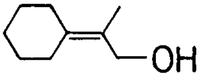
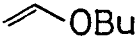
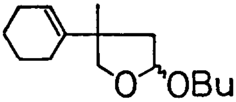
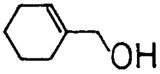
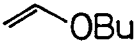
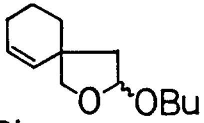
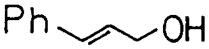
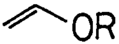
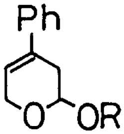
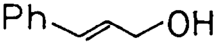
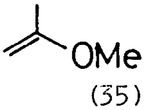
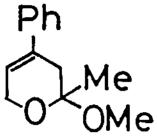
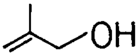
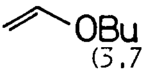
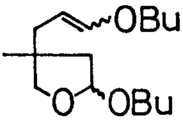
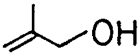
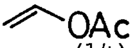
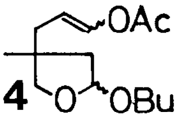
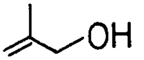
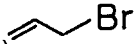
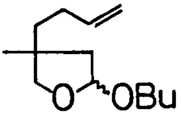
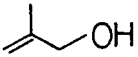
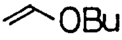
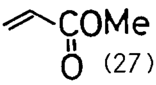
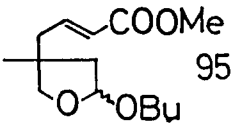


Table 1. Palladium(II)-Promoted Tetrahydrofuran Synthesis[a)]

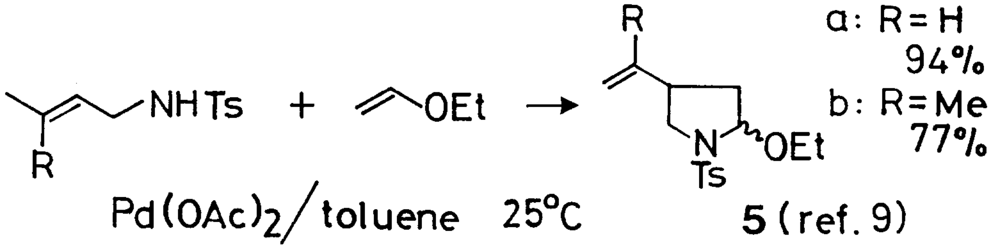
Entry	Allylic Alcohol (mmol)	Vinyl Ether (mmol)	Product	Y(%)[b)]
1	 (1.0)	 (10)		94
2	 (1.0)	 (6.5)[c)]		81
3	 (1.0)	 (16)		75
4	 (1.0)	 (3.7)[c)]		55
5	 (1.0)	 (3.0)[c)]		47
6	 (1.0)	 (10)		R Et 88 Bu 63
7	 (1.0)	 (35)		54[d)]
8	 (1.0)	 (3.7)[c)]		31
9	 (1.8)	 (2.7)[c)]  (14)	 4	90
10	 (1.4)	 (7.0)[c)]  (21)		81
11	 (2.6)	 (6.6)[c)]  (27)		95

Footnotes of Table 1.

a) Reactions were performed at 25°C using one mmol of $Pd(OAc)_2$. b) Isolated yields based on $Pd(OAc)_2$ employed. c) Toluene (5 ml) was used as a solvent. In other cases, vinyl ether was used as a solvent. d) Noncyclized product, $PhCH=CHCH_2OC(Me)_2OMe$ was also obtained in 27% yield.

not be occurred from the intermediary palladium complex **2b**, thus the second butyl vinyl ether molecule reacts with **2b** to afford 2-butoxy-4-methyl-4-(3-butoxy-2-propenyl)tetrahydrofuran (Entry 8). It was anticipated that olefins such as enol acetate, allyl bromide, and methyl acrylate act as third component instead of butyl vinyl ether. This was indeed the case and these olefins reacted with the complex **2b** by the addition-elimination process to give the corresponding adducts (Entries 9,[5] 10, and 11).[6] (3) The use of $Pd(OAc)_2$ was essential for the formation of furan derivatives. The use of $PdCl_2$ or $PdCl_2(CH_3CN)_2$ resulted in the formation of acetal[7] without any contamination by cyclized product. In the reactions with $PdCl_2$ or $PdCl_2(CH_3CN)_2$, hydrogen chloride is generated in situ along with the formation of the complex **1** and cleaves C-Pd bond of the complex **1** to give acetal and regenerate $PdCl_2$ catalyst. This bond breaking could be avoided by the addition of base to the reaction mixture. Thus, treatment of a solution of methallyl alcohol (1.0 mmol), butyl vinyl ether (5.0 mmol), and allyl bromide (10 mmol) in ^{t}BuOH (5 ml) with $PdCl_2(CH_3CN)_2$ (1.0 mmol) in the presence of potassium acetate (10 mmol) gave 2-butoxy-4-methyl-4-(3-butenyl)tetrahydrofuran in 85% yield.[8] (4) The amount of $Pd(OAc)_2$ can be reduced to 0.3 molar equivalent in the presence of $Cu(OAc)_2$. For instance, treatment of an acetonitrile solution of 2-hexene-1-ol (1.0 mmol) and butyl vinyl ether (3.4 mmol) in the presence of $Pd(OAc)_2$ (0.3 mmol) and $Cu(OAc)_2$ (2.5 mmol) provided 2-butoxy-4-(1-butenyl)tetrahydrofuran in 90% yield after stirring at 25°C for 20 h.

The reaction was successfully applied to the synthesis of pyrrolidine derivative from the corresponding allylic tosylamide.



5 (ref. 9)

References and Notes

1. Y. Ito, H. Aoyama, T. Hirao, A. Mochizuki, and T. Saegusa, J. Am. Chem. Soc., **101**, 494 (1979); A. S. Kende and D. J. Wustrow, Tetrahedron Lett., **26**, 5411 (1985).

2. **3a** (cis/trans = 1/1): Bp 75°C (bath temp, 25 Torr); IR (neat) 1643, 1347, 1098, 1070, 1032, 1010, 994, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, J = 7.1 Hz, 3H), 1.3-1.7 (m, 4H), 1.7-1.9 (m, 1H), 2.07 (dd, J = 12.5, 7.8 Hz, 0.5 Hz), 2.2-2.4 (m, 0.5H), 2.7-3.0 (m, 0.5H), 3.0-3.2 (m, 0.5H), 3.3-3.5 (m, 1H), 3.5-3.8 (m, 2H), 3.95 (dd, J = 7.9, 8.2 Hz, 0.5H), 4.07 (dd, J = 8.2, 8.2 Hz, 0.5H), 5.0-5.2 (m, 3H), 5.7-5.9 (m, 1H). Found: C, 70.80; H, 10.86%. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%. Hydrogenation of **3a** followed by oxidation (mCPBA: P. A. Grieco, T. Oguri, and Y. Yokoyama, *Tetrahedron Lett.*, **1978**, 419) provided β-ethyl-γ-butyrolactone which was identical with an authentic sample (J.-M. Surzur and P. Teissier, *Bull. Soc. Chim. Fr.*, **1970**, 653).
3. Other products in Table 1 are also mixture of cis and trans isomers (cis/trans = 1/1).
4. Allyl alcohol provided 2-butoxy-4-methylenetetrahydrofuran in only 10% yield along with the undefined complex mixture on treatment with $Pd(OAc)_2$ in butyl vinyl ether.
5. 2-Butoxy-4-methyl-4(3-acetoxy-2-propenyl)tetrahydrofuran (**4**): Bp 130°C (bath temp, 1.0 Torr); IR (neat) 1757, 1672, 1215, 1098, 1073, 1032, 934, 904 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, J = 7.3 Hz, 3H), 1.05 (s, 1.5H), 1.06 (s, 1.5H), 1.3-2.0 (m, 7H), 2.12 (s, 1.5H), 2.15 (s, 1.5H), 2.18 (d, J = 8.2 Hz, 0.5H), 2.35 (d, J = 7.5 Hz, 0.5H), 3.3-3.8 (m, 4H), 5.1-5.3 (m, 1H), 5.43 (dt, J = 12.5, 8.1 Hz, 1H), 7.1-7.2 (m, 1H). Found: C, 65.34; H, 9.58%. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44%.
6. In the case of crotyl alcohol, the third component such as allyl bromide did not participate in the reaction and the ordinary compound **3a** was obtained in good yield. Thus, the β-elimination of palladium hydride from comlex **2a** took place much faster than the addition of Pd-C bond to the olefin.
7. $PdCl_2(COD)$ catalyzed reaction of alcohol and 2-benzyloxy-1-propene has been reported for a protecting method of hydroxyl groups. T. Mukaiyama, M. Ohshima, and M. Murakami, *Chem. Lett.*, **1984**, 265; M. Ohshima, M. Murakami, and T. Mukaiyama, *ibid.*, **1984**, 1535.
8. The reaction between lithium alkoxide, $PhCH=CHCH_2OLi$, and ethyl vinyl ether also enabled us to use $PdCl_2(CH_3CN)_2$ instead of $Pd(OAc)_2$ and provided the corresponding dihydropyran derivative in 99% yield.
9. **5b** (isomeric ratio: 36/64): IR (neat) 1649, 1598, 1442, 1343, 1165, 814, 707, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.18 (t, J = 6.8 Hz, 1.1H), 1.20 (t, J = 7.1 Hz, 1.9H), 1.3-1.5 (m, 1H), 1.8-2.4 (m, 1.36H), 2.43 (s, 3H), 2.93 (dd, J = 9.0, 10.3 Hz, 0.64H), 3.1-3.3 (m, 1H), 3.5-3.7 (m, 2H), 3.7-4.0 (m, 1H), 4.63 (bs, 1H), 4.71 (bs, 1H), 5.21 (d, J = 5.0 Hz, 0.64H), 5.33 (dd, J = 4.0, 5.9 Hz, 0.36H), 7.32 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1.28H), 7.77 (d, J = 8.1 Hz, 0.72H). Found: C, 62.07; H, 7.61; N, 4.39%. Calcd for $C_{16}H_{23}O_3SN$: C, 62.11; H, 7.49; N, 4.53%.

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