Pergamon

Tetrahedron, Vol. 52, No. 37, pp. 12291-12298, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00715-6

Palladium Catalysed Conversion of Vinyl Bromo Allylic Alcohols into Vinylic Carbonyl Compounds and Oxidation of Secondary Alcohols to Ketones[1,2]

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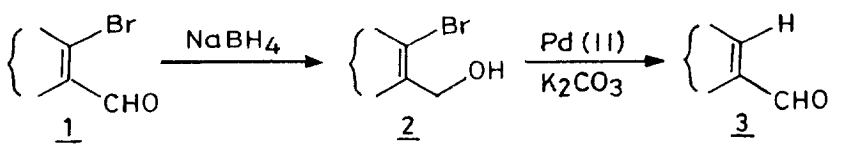
Abstract: A variety of vinyl bromo allylic alcohols are converted into the corresponding vinylic carbonyl compounds and secondary alcohols are oxidised into ketones upon treatment with palladium acetate in the presence of potassium carbonate under the typical Heck reaction conditions.

The Heck reaction [3], which involves palladium catalysed C-C bond formations, has been very useful in contemporary organic synthesis[4]. Formation of aryl palladium (or vinyl palladium) complex as a result of oxidative addition of palladium (0) to an aryl halide (or a vinyl halide), followed by their addition across a double bond are the initial key steps in the Heck reaction. This reaction, although originally and mainly used in an intermolecular fashion, has been found to work well in intramolecular fashion also.[5]

A few years ago Tsuji et al.[6] reported an interesting observation where CCl_4 and $BrCCl_3$ were found to react with allylic alcohols to afford γ,γ,γ-trichloro ketones in high yields. During their studies related to the mechanism of this reaction Tsuji et al.[7] found that halohydrins were intermediates which eventually led to the final ketones under similar reaction conditions. Here too, oxidative addition of palladium to the carbon-halogen bond of halohydrins was the initial key step. Subsequent β-hydride elimination forming ketones most probably constituted the next key step. In view of these observations of Tsuji et al. and the fact that vinyl halides undergo oxidative addition to palladium (cf. Heck reaction) we reasoned that appropriately substituted alcohols having a vinylic halide moiety should undergo oxidation to the corresponding vinylic carbonyls with the loss of the halogen atom (Scheme 1). In this communication we wish to report that

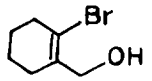
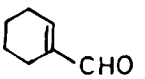
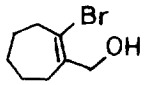
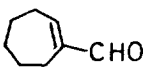
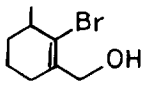
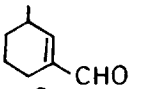
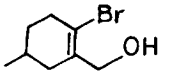
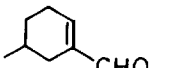
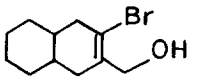
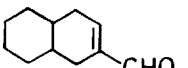
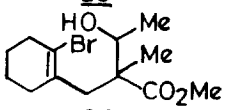
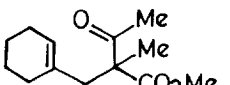
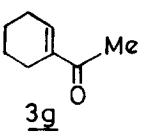
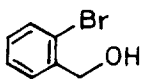
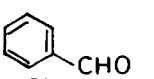


1 2 3

SCHEME - 1

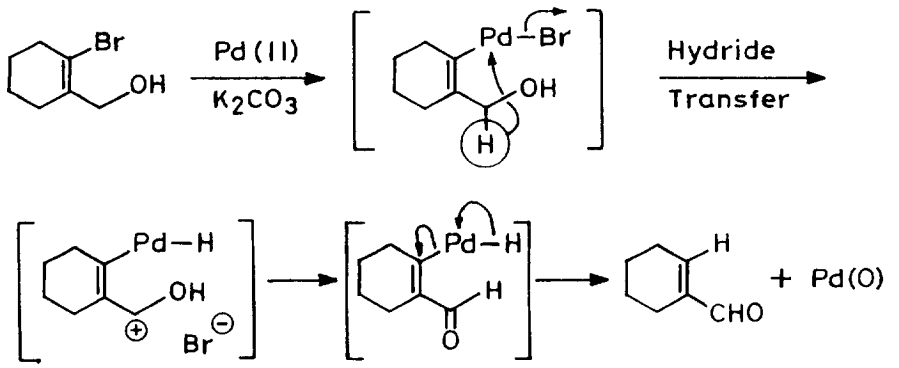
a variety of vinyl bromo allylic alcohols undergo a facile conversion to the corresponding vinylic carbonyl

Table 1: Palladium Catalysed Conversion of Vinyl Bromo Allylic Alcohols to Vinylic Carbonyl Compounds

Entry	Substrate	Product	Reaction Time (hrs)	% Yield
1	 2a	 3a	6[a]	85
2	 2b	 3b	8[a]	89
3	 2c	 3c	8[a]	61
4	 2d	 3d	8[a]	57
5	 2e	 3e	10[a]	61
6	 2f	 3f	10[a]	32
7	 2g	 3g	10[b]	76
8	 2h	 3h	10[a]	94

a: Refluxed in benzene b: Refluxed in toluene

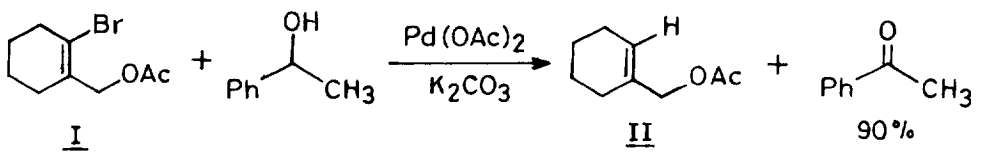
compounds (cf. Table 1) under the Heck reaction conditions [$Pd(OAc)_2$, K_2CO_3, benzene, reflux]. At the same time an ω-hydroxy vinyl bromide **2f**[8] (cf. entry 6, Table 1) also underwent oxidation to the corresponding ketone **3f** albeit in low yield. Further, it was also found that o-bromo benzyl alcohol underwent smooth transformation to benzaldehyde under similar conditions. This indicates that these reactions clearly involve Heck type palladium complex followed by oxidative (very likely intramolecular) conversion to carbonyl compounds (Scheme 2).



SCHEME -2

In an effort to study if this reaction could also be used to oxidise alcohols in an intermolecular fashion[9] we have found that only secondary alcohols get oxidised to ketones with vinyl bromo allyl acetate **I** under these conditions. The corresponding reduced product viz. **II** (Scheme 3) was isolated from the reaction mixture in every case. A variety of alcohols were oxidised in this manner (Table 2) in excellent yields.

In an attempt to further improve the yields of the products some other bases such as NaH and Et_3N were employed but the best results were obtained using K_2CO_3. Likewise, preformed Pd(0) catalyst viz. $Pd[(Ph_3P)_4]$ was found to be less effective than Pd(II). Change of solvent from benzene to acetonitrile,



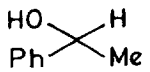
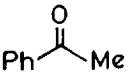
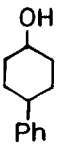
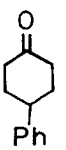
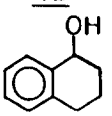
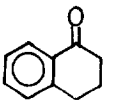
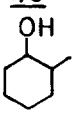
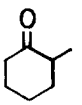
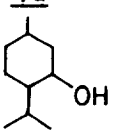
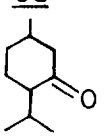
SCHEME - 3

acetonitrile-water mixture or DMF also did not make any appreciable changes, although the use of toluene, in place of benzene, in some cases (Tables 1 and 2) did improve the yield.

These reactions basically involve metal catalysed transfer hydrogenations[10]. However, to our knowledge, such transfer hydrogenation in an intramolecular fashion using palladium catalyst is not reported in the literature. We believe that such types of transfer hydrogenations both in intra (Scheme 2) as well as intermolecular (Scheme 3) fashions are useful additions to this area of research.

In view of the importance of vinylic carbonyl compounds we expect that the present method of their synthesis will find use in organic synthesis, particularly so since vinyl bromo allylic alcohols are readily available from the corresponding ketones using Vilsmeier-Haack reacion[11] and sodium borohydride reduction reaction sequence.

Table 2 : Palladium Catalysed Oxidation of Secondary Alcohols to Ketones

Entry	Substrate	Product	Reaction Time (hrs)	% Yield
1	 4a	 5a	11[a]	90
2	 4b	 5b	7[a]	98
3	 4c	 5c	8[a]	90
4	 4d	 5d	8[b]	88
5	 4e	 5e	15[b]	84

a : Refluxed in benzene b: Refluxed in toluene

EXPERIMENTAL:

General:

^{1}H NMR spectra were recorded on Jeol JNM-PMX 60 SI and Bruker WP 80 spectrometers with Me_4Si as internal standard. IR spectra were recorded on Perkin-Elmer 1320 spectrophotometer. Mass spectra were recorded at 70 eV on a Jeol MS-300 D mass spectrometer. Chloroform and dichloromethane were distilled over P_2O_5 and stored over 4 A^0 molecular sieves prior to use. Tetrahydrofuran (THF), benzene and toluene were distilled over sodium-benzophenone. N,N-Dimethylformamide (DMF) was subjected to azeotropic removal of benzene-water, stored over activated alumina and finally distilled and stored over 4 A^0 molecular sieves. Potassium carbonate was activated by heating in an oven prior to use.

All the experiments mentioned below have also been carried out on larger than 1 mmol scale (upto about 5 mmol) with practically no difference in the final yields or the product distribution. However, for uniformity we have given below the details of 1 mmol based data.

General procedure for the preparation of vinyl bromo aldehydes 1a-1e: Compound **1a** was prepared according to literature procedure[11]. The same procedure was adopted to obtain **1b** from cycloheptanone, **1c** from 2-methylcyclohexanone, **1d** from 4-methylcyclohexanone and **1e** from decahydro-2-naphthalone.

1-Carboxaldehyde-2-bromo cycloheptene 1b: Yield 58%. IR(neat): 3350, 2740, 1680, 1605, 1390 cm^{-1}. ^1H NMR (CCl_4): δ 1.7-1.9 (m, 6H, methylenes), 2.2-2.4 (m, 2H, allylic), 2.7-2.9 (m, 2H, allylic), 9.6 (s, 1H, -CHO).

1-Carboxaldehyde-2-bromo 3-methyl cyclohexene 1c: Yield 54%. IR (CCl_4): 2940, 1675, 1615, 1205, 770 cm^{-1}. ^1H NMR (CCl_4): δ 0.75-1.1 (d, 3H, $-CH_3$), 1.1-2.75 (m, 7H, methine, methylenes and allylic), 9.9 (s, 1H, -CHO).

1-Carboxaldehyde-2-bromo-5-methyl cyclohexene 1d: Yield 55%. IR (CCl_4): 2940, 1680, 1615, 1205, 770 cm^{-1} . ^1H NMR (CCl_4): δ 0.9-1.1 (d, 3H, $-CH_3$), 1.1-2.0 (m, 3H, methine and methylene), 2.1-2.45 (m, 2H, allylic), 2.5-3.0 (m, 2H, allylic), 9.9 (s, 1H, -CHO).

2-Carboxaldehyde-3-bromo-2,3-dehydro decahydronaphthalene 1e: Yield 55%. IR (CCl_4): 2940, 1680, 1635, 1450, 1175, 900, 800, 700 cm^{-1}. ^1H NMR (CCl_4): δ 0.7-2.0 (m, 10H, 4 x CH_2 s, 2 methine protons), 2.0-2.8 (m, 4H, allylic methylenes), 9.9 (s, 1H, -CHO).

General procedure for the reduction of vinyl bromo aldehydes (1a-1e): Sodium borohydride (1 mmol) was added in portions to a stirred solution of vinyl bromo aldehyde (1 mmol) in methanol (4 ml) at -20 ^0C. After the completion of the reaction (TLC monitoring) methanol was removed under reduced pressure and the usual work up was carried out with diethyl ether (3 x 20 ml) which yielded the crude alcohol. Purification by column chromatography (eluent: petroleum ether: ethyl acetate/ 90:10) afforded the pure product.

1-Methanol-2-bromo cyclohexene 2a: Yield 87%. IR and ^1H NMR spectral data of this bromo alcohol was in complete agreement with its literature[12] data.

1-Methanol-2-bromo cycloheptene 2b: Yield: 89%. IR (neat): 3310, 2930, 2860, 2840, 1650, 1445, 1330, 1250, 1175, 970, 800 cm^{-1}. ^1H NMR (CCl_4): δ 1.25-2.0 (m, 6H, methylenes), 2.0-2.65 (m, 5H, allylic, -OH), 4.1 (s, 2H, $-\underline{CH_2}OH$).

1-Methanol-2-bromo-3-methyl cyclohexene 2c: Yield 89%. IR (CCl_4): 3310, 2930, 1650, 1450, 1335, 1010, 790 cm^{-1}. ^1H NMR (CCl_4): δ 0.75-1.1 (d, 3H, $-CH_3$), 1.1-2.7 (m, 8H, methine, methylenes, allylic and -OH), 4.0 (s, 2H, $-C\underline{H_2}OH$).

1-Methanol-2-bromo-5-methyl cyclohexene 2d: Yield 83%. IR (CCl_4): 3330, 2930, 1645, 1440, 1000 cm^{-1}. ^1H NMR (CCl_4): δ 0.75-1.0 (d, 3H, $-CH_3$), 1.0-1.9 (m, 3H, methylene and methine), 2.0-2.65 (m, 5H, allylic and -OH), 4.0 (s, 2H, $-C\underline{H_2}OH$).

2-Methanol-3-bromo-2,3-dehydro decahydronaphthalene 2e: Yield 80%. IR (CCl_4): 3355, 2940, 2870, 1630, 1445, 1025, 770 cm^{-1}. ^1H NMR (CCl_4): δ 0.75-2.1 (m, 10H, 4 x CH_2 s and 2 methines), 2.1-2.8 (m, 5H, allylic and -OH), 4.15 (s, 2H, $-\underline{CH_2}OH$).

Preparation of 3-Carbomethoxy-3-methyl-4-(2-bromo-1-cyclohexenyl) butane-2-ol 2f: To a stirred solution of NaH (24 mg, 1 mmol) in dry THF (3 ml) was added a solution of α-methyl methyl acetoacetate[13] (130 mg, 1 mmol) under argon atmosphere and stirring continued for 45 min. The reaction mixture was then cooled (5 ^0C) and a solution of vinyl bromo allyl bromide[14,8] **III** (254 mg, 1 mmol) in THF (2 ml) was added dropwise. After 4 hr of stirring at this temperature the solvent was removed under reduced pressure and the residue treated with water (10 ml). Extraction with ether (3 x 15 ml) followed by usual work up led to a crude product whose purification by column chromatography afforded the pure keto bromide **IV**[8]. Yield: 133 mg (44%). IR (CCl_4): 2935, 2860, 1705, 1640, 1430, 1345, 1230, 1110, 962, 770 cm^{-1}. ^1H NMR (CCl_4): δ 1.3 (s, 3H, $-CH_3$), 1.5-2.0 (m, 4H, non allylic ring methylenes), 2.1 (s, 3H, $-COCH_3$), 2.3 (s, 2H, side chain allylic methylene), 2.35-3.0 (m, 4H, allylic ring methylenes), 3.7 (s, 3H, $-OCH_3$). Mass spectrum: m/z 302, 304.

Reduction of this keto bromide **IV** with $NaBH_4$ in methanol under usual conditions led to the formation of **2f**. Yield: 114 mg (85%). IR (CCl_4): 3360, 2935, 2860, 1640, 1430, 1345, 1230, 1110, 962, 770 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 (s, 3H, $-CH_3$), 1.3-1.4 [d, 3H, $-CH(\underline{CH_3})$, J = 6.3 Hz], 1.5-1.85 (m, 4H, non allylic ring methylenes), 2.1 (s, 2H, side chain allylic methylene), 2.4-3.0 (m, 5H, allylic ring methylenes and -OH) 3.85 (s, 3H, $-COOCH_3$), 3.9-4.3 (m, 1H, methine).

1-(2-Bromocyclohexenyl) ethanol 2g: To a solution of vinyl bromo aldehyde **1a** (189 mg, 1mmol) in dry ether (3 ml) was added CH_3Li (1.2 ml of 1.0 M solution in THF) at 0 ^0C and the reaction mixture was stirred for 3 hrs. It was then diluted with a saturated solution of NH_4Cl (10 ml) and then worked up with ether in the usual manner. The crude product so obtained was purified by column chromatography (eluent: petroleum ether:ethyl acetate/ 90:10) to yield pure **2g**. Yield: 170 mg (83 %). IR (CCl_4): 3440, 2940, 1610, 820 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (d, 3H, $-CH_3$, J = 6 Hz), 1.0-1.4 (m, 4H, non allylic ring methylenes), 1.6-1.9 (m, 2H, methine and -OH), 2.05-2.45 (m, 4H, allylic ring methylenes). Mass spectrum: m/z 188, 186 (M^+-18).

General procedure for the oxidative debromination of vinylic bromo alcohols 2a-2h: Palladium acetate (20 mg), Ph_3P (40 mg) and anhydrous K_2CO_3 (138 mg, 1 mmol) were added to a stirred solution of a vinylic

bromo alcohol (1 mmol) in dry benzene (3 ml) and the resultant mixture was refluxed under argon atmosphere for the time mentioned in the Table 1. The reaction mixture was filtered through a thin pad of celite and the filtrate concentrated under reduced pressure to obtain the crude vinylic aldehyde which was purified by column chromatography (eluent: petroleum ether:ethyl acetate) to yield the pure product. The carbonyl compounds so obtained were characterised by spectral means and where known (**3a**[15], **3b**[16], **3c**[17], **3d**[17]) compared with the literature data.

2-Carboxaldehyde-2,3-dehydro decahydronaphthalene 3c: Yield 61%. IR (CCl_4): 2940, 2720, 1680, 1635, 1450, 1370, 1175, 1020, 900, 800, 760, 700 cm^{-1}. ^1H NMR (CCl_4): δ 0.7-2.0 (m, 10H, 4 x CH_2s and 2 methines), 2.0-2.5 (m, 4H, allylic), 6.3-6.65 (br s, 1H, olefinic), 9.45 (s, 1H, -CHO).

Methyl[(1-methyl-1-acetyl)-2-(1-cyclohexenyl)] propionate 3f: Yield 32%. IR(CCl_4): 2935, 2860, 1705, 1640, 1430, 1345, 1230, 1110, 962, 770 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.3 (s, 3H, -CH_3), 1.5-2.1 (m, 4H, non allylic ring methylenes), 2.2 (s, 3H, -$COCH_3$), 2.25 (s, 2H, side chain allylic methylene), 2.45-2.75 (m, 4H, ring allylic methylenes), 3.85 (s, 3H, -$COOCH_3$), 5.4-5.6 (br s, 1H, olefinic). Mass spectrum: m/z 224. Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.20; H, 8.57 %.

The spectral data of compounds **3g**[18] and **3h** was comparable with the literature values.

General procedure for the oxidation of secondary alcohols 4a-4e to ketones 5a-5e: To a solution of an alcohol (1 mmol) and vinyl bromo allyl acetate **1**[19] (233 mg, 1 mmol) in benezene (or toluene) (3 ml) was added $Pd(OAc)_2$ (20 mg), K_2CO_3 (138 mg, 1 mmol) and Ph_3P (40 mg) and the resultant mixture was refluxed under argon atmosphere for the time given in Table 2. The reaction mixture was then filtered through a thin pad of celite and the solvent removed under vacuum. Purification of the crude product by column chromatography (eluent: petroleum ether: ethyl acetate) led to pure ketones which gave satisfactory spectral and analytical data.

ACKNOWLEDGEMENT: We thank the Department of Science and Technology and the Council of Scientific and Industrial Research, New Delhi for financial assistance.

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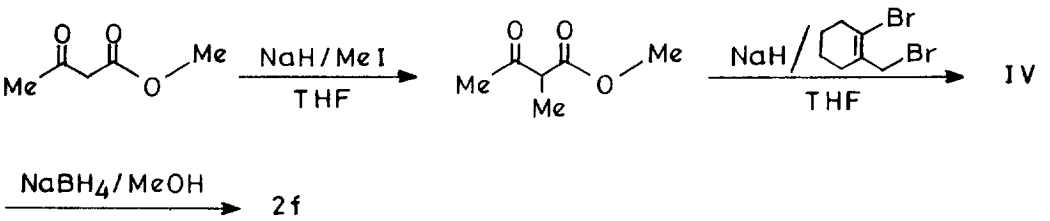
8. Compound **2f** was synthesised through a sequence of reactions as shown below:



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19. Compound **I** was prepared by the acetylation of **2a** in 89 % yield. IR (CCl_4): 2940, 1730, 1650, 1230, 1025, 780 cm^{-1}. ^1H NMR (CCl_4): δ 1.5-1.9 (m, 4H, non allylic ring methylenes), 2.0 (s, 3H, $-OCOCH_3$), 2.0-2.7 (m, 4H, allylic ring methylenes), 4.7 (s, 2H, side chain allylic methylene). Mass spectrum: m/z 190, 188 (M^+-43). Anal. Calcd. for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62. Found: C, 46.81; H, 5.03 %.

(*Received in UK* 24 *June* 1996; *revised* 26 *July* 1996; *accepted* 1 *August* 1996)