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Palladium-Catalyzed Synthesis of Allylic Thioacetates. A Convenient Access to Allylic Thiols

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Abstract: Palladium(0)-catalyzed alkylation of various allylic acetates and carbonates by potassium thioacetate allowed an easy access to allylic thioacetates in rather good yields. The reaction was regioselective with substitution at the less hindered side of the intermediate π-allyl system, and diastereoselective with net retention of configuration.

Keywords: Palladium; alkylation; potassium thioacetate; allylic thioester.

INTRODUCTION

Palladium(0)-catalyzed allylic alkylation is now a common tool in organic synthesis. This wide application is due to the facile reaction of the allylic substrates and the very high stereo- and chemoselectivity generally observed in this reaction.[1] While carbon, oxygen and nitrogen nucleophiles are commonly used in this catalytic reaction in the presence of phosphine-palladium complexes, sulfur nucleophiles are not so common in such a reaction. Bosnisch obtained allyl alkyl sulfides from *O*-allyl *S*-alkyl dithiocarbonate substrates in the presence of palladium(0) in rather good yields.[2] Silylated thiols reacted also with allylic carbonates to give the corresponding allyl alkyl sulfides.[3] We[4] and Moreno-Mañas[5] have shown that thiols reacted cleanly and quantitatively with allylic carbonates in the presence of a catalytic amount of palladium(0) to give the corresponding allylic alkyl thiols, and more recently an asymmetric version of this methodology was described.[6]

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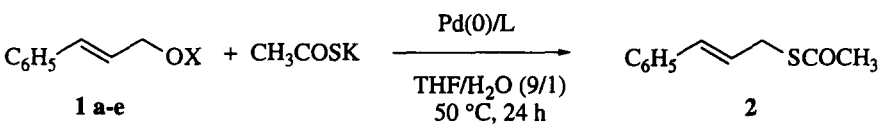
The use of sodium salts of carboxylic acids as nucleophiles in palladium-catalyzed alkylation reaction has also been described.[7] However there is no example of the use of salts of thiocarboxylic acids in this reaction. Our continuing interest in the palladium-catalyzed formation of sulfur-carbon bond was spurred by the idea that salts of thiocarboxylic acids could be good nucleophiles in such a reaction, leading to the formation of allylic thiocarboxylic esters; since these substrates could be saponified very easily into thiols, this methodology would be a very convenient access to allylic thiols. We describe in this paper the use of potassium thioacetate as the nucleophile in the palladium alkylation reaction.

RESULTS AND DISCUSSION

Firstly substitution of various cinnamyl compounds with potassium thioacetate was carried out using palladium complexes combined with various ligands as the catalyst in order to compare the reactivity of these allylic compounds and the different palladium-complexes (Scheme 1).



1 a-e **2**

a X = $CO_2C_2H_5$
b X = $COCH_3$
c X = COC_6H_5
d X = $PO(OC_2H_5)_2$
e X = C_6H_5

Scheme 1

As shown in Table 1, reaction of cinnamyl ethyl carbonate **1a** with potassium thioacetate proceeded quantitatively in a THF/H_2O (9/1) mixture in the presence of $Pd_2(dba)_3$-$CHCl_3$ associated with various ligands to give the allylic thioester **2** in good yields after column chromatography (Table 1, entries 1-8), whatever the ligand used [PPh_3, 1,2-bis(diphenylphosphino)ethane or dppe, 1,3-bis(diphenylphosphino)propane or dppp, 1,4-bis(diphenylphosphino)butane or dppb, 1,5-bis(diphenylphosphino)pentane or dpppe, 1,6-bis(diphenylphosphino)hexane or dpph and 1,1'-bis(diphenylphosphino)ferrocene or dppf]. $Pd(OAc)_2$ (Table 1, entry 9) or $Pd(acac)_2$ (Table1, entry 10) were as efficient as $Pd_2(dba)_3$ catalyst precursor, although $PdCl_2$ or $Pd(CN)_2$ gave no reaction at all (Table 1, entries 11 and 12).

Alkylation of cinnamyl acetate **1b**, cinnamyl benzoate **1c** and cinnamyl diethyl phosphate **1d** also occurred quantitatively (Table 1, entries 13-15); on the other hand, cinnamyl phenyl ether **1e** seemed less reactive (Table 1, entry 16).

In order to compare the reactivities of cinnamyl derivatives **1a-e**, some competitive reactions were carried out (Table 2). When carbonate **1a** (1 equiv) and acetate **1b** (1 equiv) were reacted with potassium thioacetate (1 equiv) in the presence of palladium(0)-dppb catalyst, carbonate **1a** was quantitatively alkylated, although acetate **1b** was recovered unchanged (Table 2, entry 1). The same behaviour was observed using benzoate **1c** instead of acetate **1b** (Table 2, entry 2). Reaction of a 1:1 mixture of acetate **1b** and benzoate **1c** proceeded at 50 °C to give quantitatively the alkylated product **2**, 38% of **1b** and 62% of **1c** being recovered.

Table 1. Palladium-Catalyzed Substitution of Cinnamyl Derivatives by Potassium Thioacetate.[a]

Entry	Substrate	Catalyst	Conversion % (Yield %)[b]
1	**1a**	$Pd_2(dba)_3$ + 8 PPh_3	100 (69)[c]
2	**1a**	$Pd_2(dba)_3$ + 4 dppe	100 (68)
3	**1a**	$Pd_2(dba)_3$ + 4 dppp	100 (82)
4	**1a**	$Pd_2(dba)_3$ + 4 dppb	100 (85)
5	**1a**	$Pd_2(dba)_3$ + 4 dpppe	100 (90)
6	**1a**	$Pd_2(dba)_3$ + 4 dpph	100 (82)
7	**1a**	$Pd_2(dba)_3$ + 4 dppf	100 (74)
8	**1a**	$Pd(OAc)_2$ + 4 PPh_3	100 (81)
9	**1a**	$Pd(acac)_2$ + 4 PPh_3	100 (87)
10	**1a**	$PdCl_2$ + 4 PPh_3	0
11	**1a**	$Pd(CN)_2$ + 4 PPh_3	0
12	**1b**	$Pd_2(dba)_3$ + 4 dppb	100 (87)
13	**1c**	$Pd_2(dba)_3$ + 4 dppb	100 (84)
14	**1d**	$Pd_2(dba)_3$ + 4 dppb	100 (71)
15	**1e**	$Pd_2(dba)_3$ + 4 dppb	95 (38)

[a] [1]:[CH_3COSK]:[Pd] = 25:35:1; [1] = 0.25 mol.l^{-1}; solvent THF:H_2O (9:1); 50 °C; 24 h. [b] Conversion determined by G. C.; chemical yield of pure product after column chromatography and not optimized. [c] The same result was obtained using a ratio [Pd]:[PPh_3] = 4

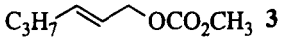
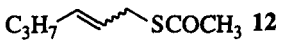
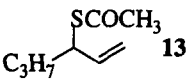
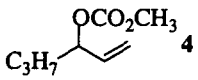
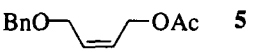
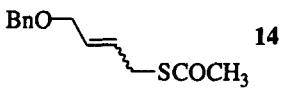
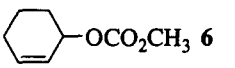
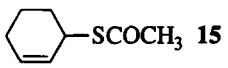
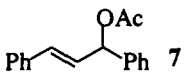
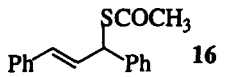
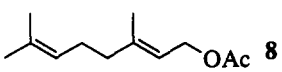
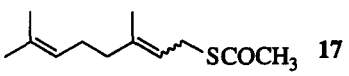
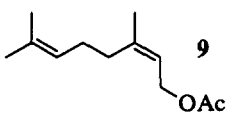
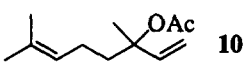
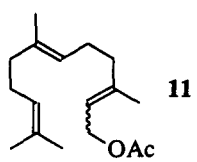
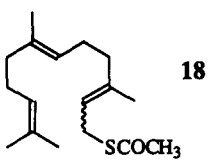
Table 2. Competitive Palladium-Catalyzed Substitution Using Potassium Thioacetate.[a]

Entry	Substrates (ratio)	Products (%)[b]
1	**1a** + **1b** (1:1)	**2** (100 %) + **1b** (100 %)
2	**1a** + **1c** (1:1)	**2** (100 %) + **1c** (100 %)
3	**1b** + **1c** (1:1)	**2** (100 %) + **1b** (38 %) + **1c** (62 %)
4	**1b** + **1d** (1:1)	**2** (100 %) + **1b** (100 %)

[a] [1]:[CH_3COSK]:[$Pd_2(dba)_3$]:[dppb] = 40:20:0.5:2; [1] = 0.25 mol.l^{-1}; solvent THF:H_2O (9:1); 50 °C; 24 h. [b] Determined by G. C.

This means that cinnamyl acetate **1b** is more reactive than cinnamyl benzoate **1c**. Finally reaction of a 1:1 mixture of acetate **1b** and phosphate **1d** gave the alkylated product **2**, acetate **1b** being recovered quantitatively at the end of the reaction.and **4** reacted with CH_3COSK to give almost identical mixtures of regio and stereoisomeric allylic thioesters **12** and **13** (Table 3, entries 1 and 2). The more substituted alkene **12** is predominant (95% vs 5%), a mixture of *E* and *Z* isomers being obtained as shown by the NMR spectrum of the mixture. We observed the chemical shifts for the allylic carbons of the major isomer at higher field (δ 31.4

Table 3. Palladium-Catalyzed Substitution of Allylic Acetates and Carbonates by Potassium Thioacetate.[a]

Entry	Allylic substrate	Product(s)	Yield %[b] (ratio)[c]
1	 **3**	 **12** (*E/Z* : 77/23) +  **13**	68 (95/5)
2	 **4**	**12** (*E/Z* : 86/14) + **13**	51 (95/5)
3	 **5**	 **14** (*E/Z* : 88/12)	56
4	 **6**	 **15**	70
5	 **7**	 **16**	22
6	 **8**	 **17** (*E/Z* : 94/6)	79
7	 **9**	**17** (*E/Z* : 17/86)	68
8	 **10**	**17** (*E/Z* : 56/44)	91
9	 **11**	 **18**	57

[a] [Substrate]:[CH_3COSK]:[$Pd_2(dba)_3$]:[dppb] = 25:35:0.5:2; [substrate] = 0.25 mol.l^{-1}; solvent THF:H_2O (9:1); 50 °C; 24 h.
[b] Chemical yield of pure product after column chromatography and not optimized. [c] Determined by NMR and GC.

and 34.3 ppm) than those of the minor isomer (δ 22.5 and 29.2 ppm), characteristic of a *E* and *Z* stereochemistry, respectively. The branched allylic thioester **13** was also characterized by ^{13}C-NMR, the signal of the allylic carbon appearing at δ 46.3 ppm.

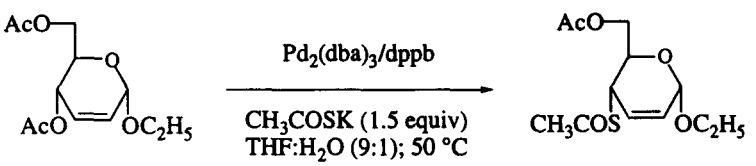
The *Z* allylic carbonate **5** gave a 88/12 mixture of *E* and *Z* allylic thioesters **14** (Table 3, entry 3), whose configuration was mainly based on ^{13}C-NMR data. The signals of the allylic carbons corresponding to the major isomer are at lower field (δ 30.8 and 69.9 ppm) than those corresponding to the minor isomer (δ 26.4 and 65.5 ppm).

Cyclohexyl ethyl carbonate **6** is also alkylated to give the corresponding thioester **15** in good yield (Table 3, entry 4), although acetate **7** was alkylated in low yield (Table 3, entry 5).

The reaction of geranyl acetate **8**, neryl acetate **9** and linalyl acetate **10** under these conditions gave a mixture of geranyl and neryl thioester **17** in 79, 68 and 91% yield, respectively (Table 3, entries 6-8). Surprisingly, geranyl acetate **8** gave a 94/6 mixture of **17** *(E)* and **17** *(Z)* and **18**, although neryl acetate **9** gave a 14/86 mixture, and linalyl acetate **9** a 55/45 mixture. Following the reaction by gas chromatography showed that the reaction was quite fast and that the *E/Z* ratio was the same throughout the process; this could be due to a very fast alkylation process compared to the $\sigma \rightleftharpoons \pi \rightleftharpoons \sigma$ equilibrium and probably a poisoning of the catalyst at the end of the reaction.

Finally the reaction was extended to farnesyl acetate **11** to give farnesyl thioacetate **18** in 57% yield (Table 3, entry 9).

In order to gain an insight into the stereochemistry of this reaction, the unsaturated acetate **19** was used as the π-allyl precursor (Scheme 2). Unsaturated carbohydrate **20** was obtained as the sole product in 73% yield. The *trans* stereochemistry of compound **20** was determined from the ^{1}H-NMR spectrum with a coupling constant $J_{4,5}$ = 10.7 Hz, characteristic of a *trans* relationship between H-4 and H-5. So the reaction occured with an overall retention of configuration as usually observed with soft nucleophiles.



19 **20**

Scheme 2

CONCLUSION

Reaction of potassium thioacetate with allylic carbonates or acetates in the presence of a palladium(0)-complex provides allylic thioacetates in quite good yields. The reaction is regioselective with the formation of the less substituted allylic thioacetate, and stereospecific with overall retention of configuration. Since these compounds could be saponified without racemization, this methodology is a very valuable solution to the preparation of allylic thiols.

EXPERIMENTAL PART

All reactions that involved palladium complexes were carried out under a nitrogen atmosphere in Schlenk tubes. Column chromatography was performed on silica gel, Merck, grade 60 (230-400 mesh, 60 Å). GC analyses were recorded with a capillary gas chromatograph GIRDEL DELSI 330 equipped with a capillary column OV 101 (25 m x 0.32 mm). All compounds were characterized through their ^{1}H- and ^{13}C-NMR spectra, using $CDCl_3$ as the solvent and Me_4Si or chloroform-d_1 as internal standard; carbon multiplicities were obtained from DEPT experiments. The following chemicals were from commercial sources and used as received: $Pd_2(dba)_3$-$CHCl_3$, $Pd(OAc)_2$, $PdCl_2$, $Pd(CN)_2$, CH_3COSK, cinnamyl acetate, *(E)*-2-hexen-1-ol, 1-hexen-3-ol, *(Z)*-4-benzyloxy-2-buten-1-ol, 2-cyclohexen-1-ol, geranyl acetate, neryl acetate, linalyl acetate, farnesyl acetate, ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside, PPh_3, dppe, dppp, dppb, dpppe, dpph and dppf. The alcohols were converted to the corresponding acetate, carbonate, benzoate, phosphate or phenyl ether in good yields using standard procedures. Thioesters **2**[8], **15**[9] and **18**[10] have already been described.

General procedure for the palladium-catalyzed reaction of potassium thioacetate with allylic substrates. A mixture of palladium complex $Pd_2(dba)_3$-$CHCl_3$ (2 mol%) and the monophosphine (16 mol%) or the diphosphine (8 mol%) was stirred in THF (8 mL) for 0.5 h. Potassium thioacetate (3.5 mmol) in 2 mL H_2O was added, followed by the allylic substrate (2.5 mmol). The reaction mixture was stirred at 50 °C for the indicated time. The solvent was evaporated and the residue was purified by column chromatography on silica gel to give the desired product(s).

(E)- and (Z)-Thioacetic acid S-(hex-2-enyl)ester 12 and thioacetic acid S-[3-(n-propyl)prop-2-enyl] ester 13. These compounds were characterized in the mixture. ^{1}H-NMR (300 MHz): δ 0.88 (t, 3H, J = 7.3 Hz, CH_3 of *E*-**12**), 0.94 (t, 3H, J = 7.3 Hz, CH_3 of *Z*-**12**), 1.30-1.45 (m, 2H, CH_2), 1.98 (dt, 2H, J = 7.0 and 7.0 Hz, CH_2-CH= of *E*-**12**), 2.08 (dt, 2H, J = 7.0 and 7.0 Hz, CH_2-CH= of *Z*-**12**), 2.40 (s, 3H, CH_3), 3.49 (bd, 2H, J = 7.0 Hz, CH_2S of *E*-**12**), 3.56 (bd, 2H, J = 7.2 Hz, CH_2S of *Z*-**12**), 5.08 (d, 1H, J = 10.3 Hz, CH_2=CH- of **13**), 5.21 (d, 1H, J = 16.9 Hz, CH_2=CH- of **13**), 5.30-5.60 (m, 1H, -CH=), 5.60-5.75 (m, 1H, -CH=), 580-5.90 (m, 1H, -CH=CH_2 of **13**). ^{13}C-NMR (50 MHz): for *E*-**12** δ 13.5, 22.2, 30.4, 31.4, 34.3, 124.5, 134.5 and 195.4; for *Z*-**12** δ 13.7, 22.5, 26.2, 29.2, 30.3, 123.7, 133.7 and 195.4; for **13** δ 14.0, 20.1, 30.4, 36.0, 46.3, 115.89, 137.8 and 195.3. Anal. Calcd. for $C_8H_{14}OS$: C, 60.73; H, 8.85. Found: C, 60.16; H, 8.89.

(E)- and (Z)-Thioacetic S-[(4-benzyloxy)but-2-enyl)] ester 14. Characterized as a *E/Z* mixture. ^{1}H-NMR (200 MHz): δ 2.32 (s, 3H, CH_3), 3.53 (d, 2H, J = 5.9 Hz, CH_2S), 3.98 (d, 2H, J = 5.0 Hz, CH_2O of *E*-**14**), 4.15 (d, 2H, J = 6.5 Hz, CH_2O of *Z*-**14**), 4.48 (s, 2H, OCH_2Ph of *E*-**14**), 4.51 (s, 2H, OCH_2Ph of *Z*-**14**), 5.62-5.85 (m, 2H, =CH-), 7.25-7.33 (m, 5H, C_6H_5). ^{13}C-NMR (50 MHz): for *E*-**14** δ 30.4, 30.8, 69.9, 72.1, 127.5, 127.7, 128.4, 130.1 and 194.9; for *Z*-**14** δ 26.4, 30.4, 65.5, 72.3, 127.5, 127.7, 128.0, 128.4, 129.6, 138.2 and 194.9. Anal. calcd for $C_{13}H_{16}O_2S$: C, 66.08, H, 6.77. Found: C, 65.90; H, 6.94.

(E)-Thioacetic acid S-(1,3-diphenylallyl) ester 16. ^{1}H-NMR (200 MHz): δ 2.3 (s, 3H, CH_3), 5.46 (d, 1H, *J* = 7.1 Hz, CHS), 6.45 (dd, 1H, *J* = 15.7 and 7.1 Hz, -CH=), 6.61 (d, 1H, *J* = 15.7, -CH=), 7.10-7.50 (m, 10H, C_6H_5). ^{13}C-NMR (50 MHz): δ 30.4, 50.4, 126.5, 126.6, 127.5, 128.4, 128.7, 131.8, 136.5 and 201.6.

Thioacetic acid S-geranyl ester and thioacetic acid S-neryl ester 17. These compounds were characterized in the mixture. ^{1}H-NMR (300 MHz): δ 1.59 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.95-2.10 (m, 4H, CH_2-CH=), 2.30 (s, 3H, $COCH_3$), 3.50 (d, 2H, *J* = 7.7 Hz, CH_2S), 5.00-5.30 (m, 2H, =CH-). ^{13}C-NMR (50 MHz): for *(E)*-**17** δ 16.1, 17.6, 25.6, 26.5, 27.3, 30.2, 39.5, 118.4, 123.8, 139.5, 139.9, 195.6; for *(E)*-**17** δ 17.6, 23.3, 25.6, 26.4, 27.3, 30.2, 31.9, 119.14, 123.8, 131.95, 140.0, 195.6.

Ethyl 6-acetoxy-4-thioacetoxy-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranoside 20. R_f 0.44 (petroleum ether: ethyl acetate 4:1). ^{1}H-NMR (200 MHz): δ 1.25 (t, 3H, *J* = 7.1 Hz, CH_3), 2.10 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.57 (dq, 1H, *J* = 9.6 and 7.0 Hz, OCH_2-), 3.82 (dq, 1H, *J* = 9.6 and 7.0 Hz, OCH_2-), 4.02 (ddd, 1H, *J* = 10.7, 5.2 and 2.1 Hz, H-5), 4.16 (dd, 1H, *J* = 12.2 and 2.1 Hz, H-6), 4.30 (dd, 1H, *J* = 12.2 and 5.2 Hz, H-6), 4.35 (bd, 1H, *J* = 10.7 Hz, H-4), 5.05 (s, 1H, H-1), 5.83 (s, 2H, H-2, H-3). ^{13}C-NMR (50 MHz): δ 15.3, 20.8, 30.5, 38;0, 63.6, 63.9, 68.3, 93.9, 127.2, 130.4, 170.8, 193.5. Anal. Calc. for $C_{12}H_{18}O_5S$: C, 52.54; H, 6.56. Found: C, 52.57; H, 6.75.

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