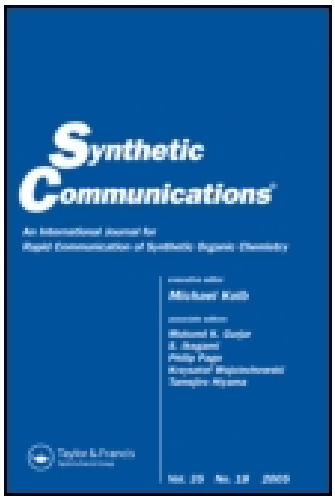

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PALLADIUM(0)-CATALYZED SYNTHESIS OF 2-PHENYL-2H-CHROMENE

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ABSTRACT

2-Phenyl-*2H*-chromene is obtained in quite good yield starting from 3-[(2-*tert*-butyldimethylsilyl)oxyphenyl]prop-2-enal. Condensation of this aldehyde with phenyl magnesium bromide, followed by the acetylation of the alcohol obtained, and then intramolecular cyclization in the presence of a palladium catalyst gave the phenylchromene in an overall 34% yield.

Key Words: 2*H*-Chromene; Palladium; Cyclization; Allylic acetate

INTRODUCTION

Flav-3-enes are useful intermediates in the synthesis of the parent flavans, flavan-3,4-diols and flavylium salts.[1] They are easily isomerized

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into flav-2-enes that are precursors of biflavonoïds.[2] 4-Aryloxyflavans and 4-aryloxyflavonoïds, whose structures are known to occur in some natural products, could also be obtained from flav-3-enes.[3]

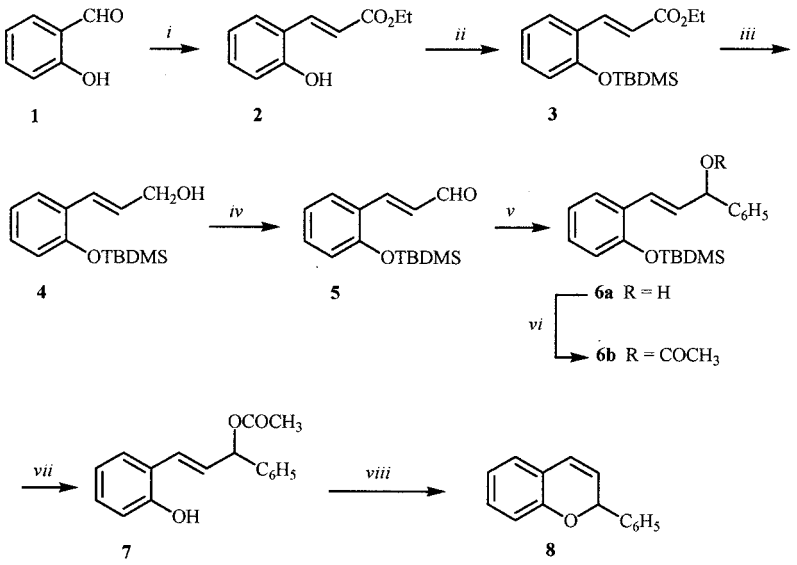
2-Phenyl-*2H*-chromene was first obtained by reduction of 2′-hydroxychalcone in isopropanol.[1] Dehalogenation of halogenoflavanes gave also the corresponding 2-phenyl-*2H*-chromene.[2–5] Various aryl propargyl ethers have been thermally cyclized via a Claisen rearrangement into the corresponding 2-aryl-*2H*-chromenes.[6] More recently a palladium(II)-catalyzed cyclization of various *o*-allylic phenols to substituted *2H*-benzopyrans was published by Larock et al.[7]

We have recently shown that allylic ethers could be conveniently prepared in high yields and under very mild conditions via palladium(0)-catalyzed *O*-alkylation of allylic carbonates or acetates with alcohols and phenols.[8,9] This procedure was particularly efficient for the formation of oxygenated heterocyclic compounds.[10–15] We described in this paper the application of this very simple procedure for the synthesis of 2-phenyl-*2H*-chromene.

DISCUSSION

The sequence for the preparation of 2-phenyl-*2H*-chromene (**8**) is shown in Sch. 1. Wittig reaction between 2-hydroxybenzaldehyde (**1**) and the stabilized ylide $Ph_3P{=}CHCO_2Et$ in benzene according to the literature procedure[16] afforded hydroxy ester **2** in 99% yield as a *E*/*Z* mixture (70/30). Reaction of the (*E*)-hydroxy ester **2**, obtained by column chromatography, with *tert*-butyldimethylsilyl chloride in DMF in the presence of imidazole gave compound **3** in 96% yield. Transformation of ester **3** into aldehyde **5** was performed in two steps; reduction of the ester **3** with Dibal in toluene, followed by oxidation with MnO_2 in CH_2Cl_2 afforded the aldehyde **5** in 82% yield. It is to be noticed that this aldehyde **5** could also be obtained by a Wittig condensation between 2-hydroxybenzaldehyde and $Ph_3P{=}CHCHO$ in benzene[17] (44% yield) followed by the reaction with *tert*-butyldimethylsilyl chloride in DMF in the presence of imidazole (64% yield). However this Wittig reaction gave many by-products.

Reaction of the Grignard reagent obtained from C_6H_5Br and magnesium on aldehyde **5** afforded the allylic benzylic alcohol **6a** in 79%. However, since this alcohol is very unstable, the crude product was reacted directly with acetyl chloride in CH_2Cl_2 in the presence of pyridine to give the corresponding acetate **6b** (76% yield). Deprotection of the hydroxyl function of compound **6a** in the presence of $Bu_4NF.H_2O$ afforded the hydroxyacetate **7**, which was directly cyclized in the presence of a palladium catalyst, obtained



Scheme 1. Reagents and conditions: (*i*) $Ph_3P{=}CHCO_2Et$, C_6H_6, 99%,Ref. [16]; (*ii*) TBDMSCl, imidazole, DMF; (*iii*) Dibal, toluene; (*iv*) MnO_2, CH_2Cl_2; (*v*) C_6H_5MgBr, diethylether; (*vi*) CH_3COCl, C_5H_5N, CH_2Cl_2; (*vii*) $Bu_4NF{\cdot}H_2O$, THF; (*viii*) $Pd_2(dba)_3$, dppb, THF.

from $Pd_2(dba)_3$ and dppb or 1,4-*bis*(diphenylphosphino)butane in THF to give the expected 2-phenyl-*2H*-chromene **8**. It is to be noticed that the overall chemical yield from the aldehyde **5** to the phenyl chromene **8** is 34%.

CONCLUSION

In conclusion, we have devised a new access to 2-phenyl-*2H*-chromene occuring under very mild conditions. This palladium-catalyzed synthesis can be extended to the preparation of various 2-alkyl-*2H*-chromenes as well as functionalized 2-aryl-*2H*-chromenes. Work is currently under progress in these directions.

EXPERIMENTAL

All manipulations involving palladium-catalysis were carried out in Schlenk tubes under an inert atmosphere. Tetrahydrofuran was distilled

from sodium/benzophenone. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-Gemini 200 or Brücker AM 300 spectrometers in $CDCl_3$. Chemical shifts are reported on the δ scale with the reference to tetramethylsilane as the internal standard. TLC was done using Merck silica gel 60 F_{254} precoated aluminium-backed plates, 0.2 mm thickness. Visualisation was by UV or by spraying with 10% sulphuric acid and then heating. Column chromatography was carried out using Merck silica gel (Kieselgel 60 70–230 mesh).

Ethyl (*E*)-3-[(2-*tert*-butyldimethylsilyl)oxyphenyl]prop-2-enoate (3): A solution of *t*-$BuMe_2SiCl$ (3.6 g, 23.2 mmol) and imidazole (3.6 g, 52.9 mmol) in DMF (30 mL) was added at room temperature to a solution of ethyl (*E*)-3-(2-hydroxyphenyl)prop-2-enoate[16] (**2**) (4.0 g, 21 mmol) in DMF (15 mL). After being stirred at 25°C for 24 h, water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (5×30 mL). The organic phases are washed with NaOH 5% (5×30 mL), then with H_2O (5×40 mL), and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the residue by flash-chromatography using petroleum ether/ethyl acetate (7 : 1) as the eluent gave 6.2 g of compound **3** as an oil (yield 96%). $R_f = 0.38$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.23 (s, 6H, SiMe), 1.05 (s, 9H, CMe_3), 1.33 (t, $J = 7.2$ Hz, 3H, CH_3), 4.25 (q, $J = 7.2$ Hz, 2H, OCH_2), 6.38 (d, $J =$ 16.2 Hz, 1H, =CH-), 6.84 (dd, $J = 7.9$, 1.1 Hz, 1H, H_{arom}), 6.98 (ddd, $J =$ 7.9, 7.4, 1.1 Hz, 1H, H_{arom}), 7.26 (ddd, $J = 7.9$, 7.4, 1.8 Hz, 1H, H_{arom}), 7.55 (dd, $J = 7.9$, 1.8 Hz, 1H, H_{arom}), 8.09 (d, $J = 16.2$ Hz, 1H, -CH=); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: −4.2, 14.4, 18.4, 25.8, 60.3, 117.8, 120.0, 121.6, 126.0, 127.3, 131.3, 139.9, 154.6, 167.2. Anal. calcd for $C_{17}H_{26}O_3Si$ (306.48): C 66.63, H 8.56, found: C 66.63, H 8.54.

(*E*)-3-[(2-*tert*-Butyldimethylsilyl)oxyphenyl]prop-2-enol (4): A solution of ester **3** (3.0 g, 9.8 mmol) in toluene (60 mL) was slowly added at −78°C to a solution of Dibal 1.5 M in toluene (16.3 mL, 24.5 mmol). After being stirred at −78°C for 2 h, methanol (20 mL) was added, and the solution acidified by HCl 1 N (20 mL). The solution was extracted with CH_2Cl_2 (5×30 mL), and the organic phase dried over Na_2SO_4. Evaporation of the solvent followed by purification of the residue by flash-chromatography using petroleum ether/ethyl acetate (4 : 1) as the eluent gave 2.44 g of compound **4** as an oil (yield 94%). $R_f = 0.42$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.23 (s, 6H, SiMe), 1.05 (s, 9H, CMe_3), 1.55 (bs, 1H, OH), 4.32 (d, $J = 6.1$ Hz, 2H, CH_2OH), 6.31 (dt, $J = 16.0$, 6.1 Hz, 1H, =CH-), 6.80 (dd, $J = 8.1$, 0.9 Hz, 1H, H_{arom}), 6.93 (ddd, $J = 7.7$, 7.3, 0.9 Hz, 1H, H_{arom}), 6.95 (d, $J = 16.0$ Hz, 1H, -CH=), 7.13 (ddd, $J = 8.1$, 7.3, 1.8 Hz, 1H, H_{arom}), 7.47 (dd, $J = 7.7$, 1.8 Hz, 1H, H_{arom}); ^{13}C NMR (75.5 MHz , $CDCl_3$) δ: −4.1, 18.4, 25.9, 64.3, 119.7, 121.5, 126.5, 126.6, 128.1, 128.4, 128.6, 153.0.

Anal. calcd for $C_{15}H_{24}O_2Si$ (264.45): C 68.14, H 9.16, found: C 67.91, H 8.66.

(*E*)-3-[(2-*tert*-Butyldimethylsilyl)oxyphenyl]prop-2-enal (5): *Method A*: A mixture of 3-[(2-*t*-butylmethylsilyl)oxyphenyl]prop-2-enol **4** (4.49 g, 17.0 mmol) and MnO_2 85% (53.0 g, 0.52 mol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 3 h. After filtration of the solid on Celite and evaporation of the solvent, the residue was purified by flash-chromatography using petroleum ether/ethyl acetate (8 : 1) as the eluent to give 3.97 g of compound **5** as an oil (yield 89%). *Method B*: A solution of *t*-$BuMe_2SiCl$ (2.24g, 14.8 mmol) and imidazole (2.3 g, 33.7 mmol) in DMF (15 mL) was added at room temperature to a solution of (*E*)-3-(2-hydroxyphenyl)prop-2-enal[17] (2.0 g, 13.5 mmol) in DMF (15 mL). After being stirred at 25°C for 24 h, water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (5×30 mL). The organic phases are washed with NaOH 5% (3×30 mL), then with H_2O (7×40 mL), and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the residue by flash-chromatography using petroleum ether/ethyl acetate (8 : 1) as the eluent gave 2.25 g of compound **5** as an oil (yield 64%). $R_f = 0.35$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.25 (s, 6H, SiMe), 1.05 (s, 9H, CMe_3), 6.70 (dd, $J = 16.2$, 7.7 Hz, 1H, =CH-), 6.88 (dd, $J = 8.1$, 0.7 Hz, 1H, H_{arom}), 7.01 (ddd, $J = 7.7$, 7.4, 0.7 Hz, 1H, H_{arom}), 7.32 (ddd, $J = 8.1$, 7.4, 1.7 Hz, 1H, H_{arom}), 7.55 (dd, $J = 7.7$, 1.7 Hz, 1H, H_{arom}), 7.89 (d, $J = 16.2$ Hz, 1H, -CH=), 9.67 (d, $J = 7.7$ Hz, 1H, CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: −4.1, 18.4, 25.8, 119.9, 121.7, 125.5, 127.8, 128.3, 132.5, 148.3, 154.9, 194.0. Anal. calcd for $C_{15}H_{22}O_2Si$ (262.43): C 68.67, H 8.46, found: C 68.55, H 8.62.

(*E*)-3-[(2-*tert*-Butyldimethylsilyl)oxyphenyl]-1-phenylprop-2-enol (6a): A solution of compound **5** (2.0 g, 7.6 mmol) in diethylether (5 mL) was slowly added at 0°C to a solution of the Grignard reagent obtained from bromobenzene (3.6 g, 22.3 mmol) and Mg (0.56 g, 22.3 at.g) in diethylether (100 mL). After being stirred at 25°C for 24 h, a saturated aqueous ammonium chloride solution (60 mL) was added, the mixture was extracted with diethylether (3×20 mL), and the organic phase was dried over Na_2SO_4. Evaporation of the solvent gave the crude alcohol **6a** which was used without further purification. $R_f = 0.56$ (eluent petroleum ether/ethyl acetate 7 : 1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.18 (s, 3H, SiMe), 0.19 (s, 3H, SiMe), 0.99 (s, 9H, CMe_3), 2.02 (bs, 1H, OH), 5.38 (d, $J = 6.5$ Hz, 1H, CHOH), 6.35 (dd, $J = 16.0$, 6.5 Hz, 1H, =CH-), 6.95 (d, $J = 16.0$ Hz, 1H, -CH=), 6.70–7.50 (m, 9H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: −4.2, −4.1, 18.4, 25.9, 75.6, 119.6, 121.4, 126.2, 126.4, 126.6, 127.7, 127.9, 128.6, 128.7, 131.5, 143.0, 153.1.

Acetic Acid (*E*)-3-[(2-*tert*-butyldimethylsilyl)oxyphenyl]-1-phenylprop-2-enol ester (6b): To a solution of crude alcohol **6a** (1.7 g, 6.5 mmol) and pyridine (2.1 mL, 25.9 mmol) in CH_2Cl_2 (25 mL) was slowly added at 0°C

acetyl chloride (1.89 mL, 25.9 mmol). After being stirred at 25°C for 24 h, an aqueous saturated copper sulfate solution (20 mL) was added, the mixture was extracted with diethylether (3×15 mL), and the organic phase was dried over Na_2SO_4. Evaporation of the solvent gave 1.7 g of the crude acetate **6b** (yield 76%) which was used without further purification for the next step. $R_f = 0.45$ (eluent petroleum ether/ethyl acetate 12 : 1 + 1% Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.19 (s, 3H, SiMe), 0.20 (s, 3H, SiMe), 0.99 (s, 9H, CMe_3), 2.14 (s, 3H, CH_3), 6.32 (dd, $J = 15.9$, 5.9 Hz, 1H, =CH-), 6.47 (d, $J = 5.9$ Hz, 1H, CHO), 6.70–7.50 (m, 10H, -CH=, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: −4.2, −4.1, 18.4, 21.4, 25.9, 76.4, 119.7, 121.4, 126.6, 127.3, 127.5, 127.6, 127.7, 128.2, 128.7, 128.9, 139.5, 153.1, 170.0.

Acetic Acid (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-enol ester (7): To a solution of crude acetate **6b** (1.19 g, 4.6 mmol) in THF (25 mL) was added a solution of $Bu_4NF.H_2O$ (1.63 g, 62.4 mmol). After being stirred at 25°C for 1 h, the solvent was evaporated and the residue treated with diethylether (50 mL). The diethylether solution was washed with water (3×20 mL) and dried over Na_2SO_4. Evaporation of the solvent gave 0.76 g of the crude acetate **7** (yield 76%) which was used without further purification for the next step.

Synthesis of 2-phenyl-*2H*-chromene (8): The catalytic system was prepared by stirring for 0.5 h in a Schlenk tube under argon Pd_2dba_3 [or dipalladiumtris(dibenzylideneacetone)] (51.2 mg, 0.056 mmol) and 1,4-*bis*(diphenylphosphino)butane or dppb (95.5 mg, 0.224 mmol) in tetrahydrofuran (7 mL). This solution was added under argon to a Schlenk tube containing the acetate **7** (300 mg, 1.12 mmol) and Et_3N (0.23 mL, 1.68 mmol) in THF (7 mL). After being stirred for 24 h, the solvent was evaporated and the residue purified by flash-chromatography using petroleum ether/ethyl acetate (15 : 1) as the eluent to give 73.7 mg of 2-phenyl-*2H*-chromene (yield 76%). $R_f = 0.36$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.82 (dd, $J = 9.9$, 3.3 Hz, 1H, =CH-), 5.94 (bs, 1H, OCH), 6.56 (dd, $J = 9.9$, 0.9 Hz, 1H, -CH=), 6.70–7.50 (m, 9H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 77.3, 116.1, 121.3, 121.4, 124.1, 125.0, 126.7, 128.5, 128.7, 129.6, 140.9, 153.3. These values are in quite agreement with the literature.[18]

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