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Designing a catalytic synthesis of 4-methylcoumarin from *ortho*-iodophenyl 3-butenoate: ring closure and isomerization control

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Abstract

The palladium-catalyzed ring closure of *ortho*-iodophenyl 3-butenoate to 4-methylcoumarin is in competition with the isomerization to the 2-butenoic ester; the latter reaction has been controlled by the appropriate use of ligands, solvents and neutralizing agents to the point that quantitative yields of the cyclic compound have been attained.

Keywords: Coumarin; Palladium; Catalysis; Cyclization

1. Introduction

We recently reported the synthesis of 4-methylcoumarin **2** from *o*-iodophenyl 3-butenoate **1**, catalyzed by palladium(0) complexes (Scheme 1) [1].

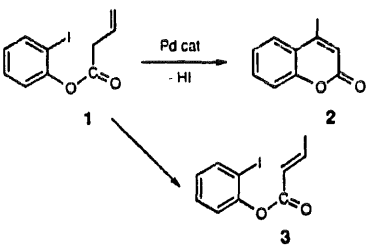
Although several palladium-catalyzed ring-forming reactions starting from *ortho* bifunctional aromatics had been described (for examples see Ref. [2]) the title synthesis offered special difficulties. In particular we had to overcome the strong tendency towards double bond isomerization to the internal position of the butenoic chain (compound **3**), which is favoured by both medium basicity and hydridopalladium species (Scheme 1).

To prevent undesired reactions we worked in a non-polar solvent such as anisole, in the presence of potassium butyrate as neutralizing agent, using palladium(0) bis(dibenzylideneacetone) plus two molecules of triphenylphosphine as catalyst, at 80 °C. Under these conditions the yield was still unsatisfactory, but the presence of carbon monoxide at atmospheric pressure and of benzonitrile in an excess of 10–20 molecules per molecule of palladium complex turned out to be beneficial and the yield rose to 85%. We felt, however, that in view of the many steps involved the reaction should be better understood in order to find more efficient methods.

2. Results and discussion

Complex **4** (P = PPh_3) [1], corresponding to the initial oxidative addition step, was investigated by ^1H NMR. The butenoic chain turned out to be non-coordinated, no significant change in the absorptions of the vinyl protons being noticed (for a similar situation see Ref. [3]) in respect to the free ligand. Complex **5** (P–P = bis(diphenylphosphino)ferrocene, dppf), prepared from (dba)(dppf)Pd (dba = dibenzylideneacetone) and *o*-iodophenyl 3-butenoate **1** showed a similar behaviour in the ^1H NMR spectrum (Scheme 2).

As monitored by NMR, on heating in $C_6D_5CD_3$ at 50 °C these complexes gave only a small amount of 4-methylcoumarin **2**, the main reactions being double



Scheme 1.

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bond shift to the internal position as in **6** and formation of benzofuranone **7**, probably through formation of an allylpalladium bond (Scheme 2).

At 80°C the reaction leading to 4-methylcoumarin **2** was predominant, but the undesired reactions occurred as well. Separately prepared complex **6** gave benzofuranone **7** (Scheme 2).

These reactions also took place in the catalytic process if **4** or **5** were used as catalysts. That a palladium hydride is responsible for an isomerization process which is independent of the one promoted by basicity is known from the literature [4]. In this connection we checked the behaviour of *o*-iodophenyl 3-butenyl ether in respect to cyclization as reported for the corresponding bromide [5]. This ether remained unchanged under our basic conditions in the absence of catalyst, but it gave extensive isomerization to the 2-butenyl ether when $Pd(PPh_3)_4$ was used as catalyst, thus pointing to $HPd(PPh_3)_2I$ intermediacy.

To prevent undesired reactions we tested the effect of triphenylphosphine addition to the catalyst. The neutralizing agent was potassium butyrate, containing 20% potassium bicarbonate, a mixture empirically found to be better than potassium butyrate alone. As shown in Table 1, although the excess of phosphine slowed down the formation of 4-methylcoumarin **2**, it blocked the formation of the isomerized product **3**, thus allowing complete selectivity to be attained. The excess of triphenylphosphine is likely to be useful not only for preventing the formation of **3** and **7**, but also for accelerating the final reduction to palladium(0) by stabilization of the latter in respect to the palladium hydride species that could cause double bond shift in the 3-butenoic chain. Addition of 1 mol of chelating phosphines (bis(diphenylphosphino)ethane = dppe, bis(diphenylphosphino)propane = dppp, bis(diphenylphosphino)butane = dppb, bis(diphenylphosphino)ferrocene = dppf) led to low yields of **2** and extensive isomerization with dppe, while satisfactory yields of **2** were attained with dppp, dppb and dppf. Only the latter, however, effectively prevented isomerization to **3**.

Table 1
Reactions of *o*-iodophenyl 3-butenoate **1** in anisole at 80°C for 24h in the presence of a palladium catalyst (substrate to catalyst ratio 20), potassium butyrate/potassium bicarbonate 4:1 and CO (atmospheric pressure) and benzonitrile (12 mol per mol catalyst) as promoters

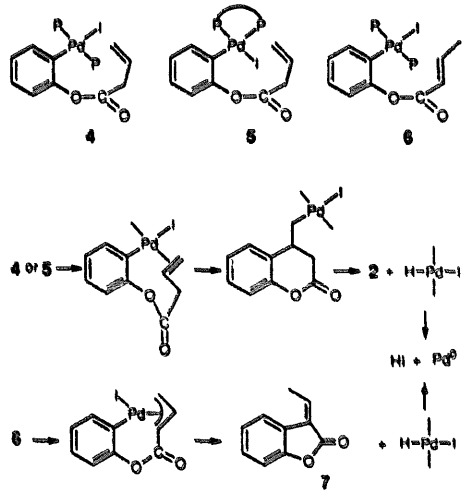
Catalyst	Added phosphine (mol/mol Pd)	Conversion [a] (%)	Yield [a]		
			2	3	7
4	—	84	44	31	9
$Pd(dba)_2$	$2PPh_3$	94	85	9	—
$Pd(PPh_3)_4$	—	80	70	10	—
$Pd(PPh_3)_4$	$2PPh_3$	54	54	—	—
$Pd(PPh_3)_4$	dppe	56	6	50	
$Pd(PPh_3)_4$	dppp	65	52	13	
$Pd(PPh_3)_4$	dppb	76	64	12	—
$Pd(PPh_3)_4$	dppf	62	62	--	--

[a] Conversions and yields were determined by NMR spectroscopy of the crude material; the signals of the methyl protons of coumarin (**2**), *o*-iodophenyl (*E*)-2-butenoate (**3**) and benzofuranone (**7**) and those of the methylene protons of *o*-iodophenyl 3-butenoate (**1**) were used to determine the integration value.

To clarify the role of anion replacement and dissociation we also used an excess of tetraalkylammonium iodide under the reaction conditions. The reaction was slowed down remarkably and so the iodide replacement with a poorly coordinating anion appeared the step to be accelerated. On the other side it is known that double bond insertion is favoured by cationic palladium complexes [6]. Silver and tallium salts can be advantageously used to this end [7]. Accordingly the use of silver acetate or carbonate allowed us to obtain a quantitative reaction without the need for using carbon monoxide and benzonitrile. The latter acted as promoters in the reaction based on the butyrate–anisole system, probably because they favoured the anion dissociative process (CO) and accelerated the insertion step (benzonitrile). In view of the positive results obtained with silver compounds no further investigation on the role of promoters was carried out.

At this point we reasoned that the use of expensive reagents such as the silver-based ones could be avoided by adopting conditions more favourable to iodide replacement, at the same time taking into account the need for not too basic reaction conditions. We thus passed to the use of magnesium oxide with dimethylformamide (DMF) as reaction medium. The result with $Pd(PPh_3)_4$ was an 85% yield of 4-methylcoumarin and 14% of *o*-iodophenyl (*E*)-2-butenoate, simply working under dinitrogen. The addition of two molecules of PPh_3 to the catalyst led to a decrease of the yield of 4-methylcoumarin and to the formation of a large amount of *o*-idophenyl (*E*)-2-butenoate (Table 2).

Since the presence of the isomerized product can likely be attributed to the fact that the main reaction was



Scheme 2.

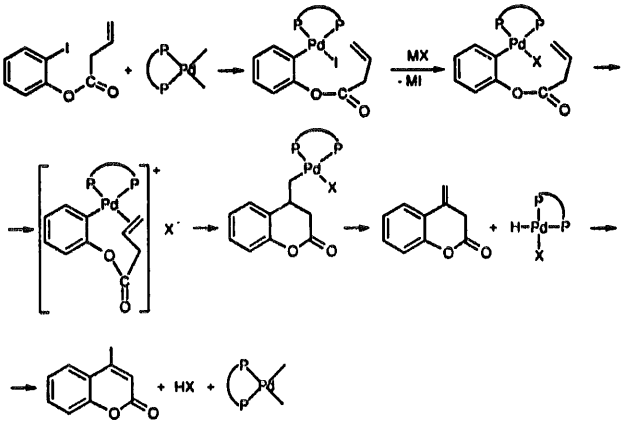
Table 2
Reactions of *o*-iodophenyl 3-butenoate **1** in DMF with $Pd(PPh_3)_4$ as catalyst, MgO as neutralizing agent and without added benzonitrile under N_2, other conditions the same as in Table 1

Ligand in excess (mol/mol Pd)	Yield	
	2	3
—	85	14
$2PPh_3$	70	30
dppf	100	—

not sufficiently fast to overcome the competing isomerization, we added a chelating diphosphine, dppf, to the tetrakis(triphenylphosphine)palladium complex. The choice of dppf was based on (a) the assumption that non-chelating phosphines had first to rearrange from the *trans* to the *cis* position to allow double bond coordination *cis* to the aryl group as required for insertion, and (b) the observation of the behaviour of chelating phosphines in the reaction in anisole (Table 1) where the addition of dppf to $Pd(PPh_3)_4$ blocked the isomerization, while dppe addition slowed down the formation of **2** remarkably. Even with silver acetate in anisole, dppe gave a significant amount of isomerized product **3**. The effect of dppe is probably related to the requirements for insertion [8]: a chelating phosphine forming a small angle with palladium favours elimination less than those forming a larger angle and migratory insertion can be regarded as a similar process inasmuch as it too implies the departure of the migrating group from the metal. On the basis of these considerations we used dppf [9] in conjunction with $Pd(PPh_3)_4$ under the conditions of the reaction in DMF–MgO and obtained a quantitative yield of 4-methylcoumarin.

The course of the reaction in the presence of the dppf ligand can now be viewed as involving the steps shown in Scheme 3 (M = metal, X = anion at oxygen).

In conclusion, the competition between isomerization and cyclization can be made to be won by the latter if ligands, bases and anions are chosen appropriately.



Scheme 3.

4-Methylcoumarin can thus be obtained catalytically in quantitative yield under mild conditions.

3. Experimental section

All reagents were commercial products (Inalco, C. Erba and Aldrich) and were used without further purification. Organometallic reactions were carried out under dinitrogen or carbon monoxide by use of conventional Schlenk techniques. Solvents were dried and degassed before use. ^1H NMR spectra were recorded on either a Bruker AC-300 or an AC-100 spectrometer and are referenced to residual protonic solvents with chemical shifts reported as δ (ppm) from TMS. Gas chromatography (GC) was carried out with a C. Erba HRGC 5300 instrument equipped with a 30 m SE 30 capillary column and a Hewlett-Packard 3394 integrator.

Potassium butyrate, containing 20% potassium bicarbonate, was prepared from butyric acid and potassium bicarbonate. Tetrakis(triphenylphosphine)palladium [10], bis(dibenzylideneacetone)palladium [11] and *trans*-$PdI(o\text{-}C_6H_4OCOCH_2CH{=}CH_2)(PPh_3)_2$ (**4**) [1] were prepared according to published procedures. *o*-Iodophenyl 3-butenyl ether was synthesized in almost quantitative yield from *o*-iodophenol and 4-bromo-1-butene in aqueous solution of NaOH following a procedure reported in the literature [12].

3.1. Preparation of o-iodophenyl 3-butenoate (1) and (E)-2-butenoate (3)

The compounds were prepared according to standard procedures by acylation of *o*-iodophenol with the corresponding butenoyl chloride. Yields were ca. 70% in both cases.

1. ^1H NMR ($CDCl_3$): δ 7.83 (d, 1H), 7.37 (dd, 1H), 7.11 (d, 1H), 6.99 (dd, 1H) (aryl group), 6.09 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, $CH{=}CH_2$), 5.33 (dq, J = 17.1, 1.4 Hz, 1H, $=CH_2$), 5.30 (dq, J = 10.2, 1.4 Hz, 1H, $=CH_2$), 3.43 (dt, J = 6.9, 1.4 Hz, 2H, $CH_2CH{=}CH_2$).

3. ^1H NMR ($CDCl_3$): δ 7.83 (d, 1H), 7.36 (dd, 1H), 7.27 (dq, J = 15.5, 6.9 Hz, 1H, $=CHCH_3$), 7.12 (d, 1H), 6.97 (dd, 1H), 6.09 (dq, J = 15.5, 1.7 Hz, 1H, $CH{=}CHCH_3$), 2.00 (dd, J = 6.9, 1.7 Hz, 3H, CH_3).

3.2. Preparation of [1,1'-bis(diphenylphosphino)ferrocene](η²-dibenzylideneacetone)palladium(0)

The procedure is an extension of the one described by Herrmann et al. [13] for the preparation of analogous tertiary phosphine complexes.

In a 50 ml Schlenk-type flask were introduced, under dinitrogen, 0.1 g (0.174 mmol) of $Pd(dba)_2$ and 0.106 g

(0.191 mmol) of dppf in 10 ml of dry and degassed toluene. The solution was stirred at room temperature and after 10 min there was a change of colour from brown to orange. Stirring was continued for 2.5 h then the solution was filtered on Celite under dinitrogen to eliminate traces of palladium metal, thus obtaining a clear orange solution. The solvent was removed under vacuum and the solid residue was washed several times with a cold solution of diethyl ether and dried under vacuum. (dba)(dppf)Pd was thus obtained as an intensely yellow coloured solid (0.118 g, 76%).

^{1}H NMR ($C_6D_5CD_3$): δ 7.85–7.65 (m, 4H), 7.20–6.90 (m, 28H) (phenyl groups of dppf and dba + uncoordinated olefinic group), 4.32 (brs, 2H), 4.10 (brs, 2H), 4.03 (s, 2H), 3.90 (brs, 2H), 3.56 (brs, 1H), 3.32 (brs, 1H) (coordinated olefinic group and Cp).

3.3. Synthesis of 3-butenoic ester of o-hydroxyphenyl[1,1'-bis(diphenylphosphino)ferrocene]palladium iodide (5)

(dba)(dppf)Pd (0.118 g, 0.132 mmol) was treated with 20 ml of toluene to obtain an orange–red solution. On adding 0.057 g (0.198 mmol) of *o*-iodophenyl 3-butenoate in 2 ml of toluene the solution became straw-yellow. After stirring for 20 min the solvent was removed under vacuum and the residual solid was washed several times with cold diethyl ether until the extracts were no longer coloured. The solid was then dried under vacuum (0.069 g, 55%).

^{1}H NMR ($C_6D_5CD_3$): δ 8.36 (m, 4H), 7.80 (m, 2H), 7.60–6.42 (m, 18H) (phenyl groups of dppf and aryl ligand), 6.32 (ddt, 1H, J = 17.1, 10.3, 6.9 Hz, CH=CH_2), 5.51 (s, 1H, Cp), 5.25 (dq, J = 17.1, 1.4 Hz, 1H, =CH_2), 5.20 (dq, J = 10.3, 1.4 Hz, 1H, =CH_2), 4.50 (s, 1H), 4.30 (s, 1H), 4.13 (s, 1H), 3.73 (s, 1H), 3.57 (s, 1H), 3.50 (s, 1H) (Cp), 3.36 (dt, J = 6.9, 1.4 Hz, 2H, CH_2–CH=), 3.26 (s, 1H, Cp).

3.4. Synthesis of (E)-2-butenoic ester of trans o-hydroxyphenylbis(triphenylphosphine)palladium iodide (6)

The preparation was of the same type as that of the 3-butenoic ester previously described [1], with the difference that (*E*)-2-butenoic ester of *o*-iodophenol was employed. Yield 71%.

^{1}H NMR ($CDCl_3$): δ 7.60–7.50 (m, 12H), 7.30 (m, 6H), 7.27–7.18 (m, 12H) (PPh_3 ligands), 6.93 (dq, J = 15.4, 6.9 Hz, 1H, =$CHCH_3$), 6.53 (d, 1H), 6.39 (t, 1H), 6.25 (d, 1H), 6.02 (t, 1H) (aryl ligand), 6.04 (dq, partially overlapping with the signal at 6.02, 1H, J = 15.4, 1.7 Hz, OCH=), 2.07 (dd, J = 6.9, 1.7 Hz, 3H, CH_3).

3.5. General procedure for the cyclization reaction

(a) Reactions in anisole with potassium butyrate. The palladium complex was placed in a 25 ml flask together with the base (potassium butyrate with 20% potassium bicarbonate) under dinitrogen, then the iodophenyl ester and benzonitrile, dissolved in anisole, were added. Dinitrogen was replaced by carbon monoxide and the mixture was stirred magnetically at 80 °C for 24 h. After cooling at room temperature the mixture was added to methylene chloride and washed with sodium bicarbonate and water. The organic phase was dried over sodium sulphate, filtered and evaporated to dryness under vacuum. The resulting residue was dissolved in deuterated chloroform and analyzed by NMR spectroscopy.

(b) Reactions in anisole with silver acetate. $Pd(PPh_3)_4$, *o*-iodophenyl 3-butenoate and silver acetate were reacted in 1:20:20 molar ratio, in anisole under dinitrogen, according to procedure (a) but without adding any other compound.

(c) Reactions in DMF with magnesium oxide. The procedure was analogous to that described in (b), with the difference that DMF was used in place of anisole and magnesium oxide in place of silver acetate.

Pure 4-methylcoumarin **2** was obtained in 96% yield by flash chromatography (SiO_2) using 9:1 *n*-hexane/ethyl acetate as the eluent starting from 150 mg (0.52 mmol) of *o*-iodophenyl-3-butenoate, 30 mg (0.026 mmol) of $Pd(PPh_3)_4$ and 89 mg (0.53 mmol) of silver acetate in 4 ml of anisole and using either procedure (b) or procedure (c). In the latter case 23 mg (0.57 mmol) of MgO and 14 mg (0.026 mmol) of dppf were used in 5 ml of DMF. The catalytic efficiency thus corresponds to 20 mol per mol of Pd, but no attempt has been made to optimize it.

3.6. E-Ethylidenebenzofuranone 7 [14]

This compound (M^+ 160) was obtained in 12% yield, together with 4-methylcoumarin **2** (12%) and *o*-iodophenyl (*E*)-2-butenoate **3** (50%) from a reaction carried out according to procedure (a), using $Pd(dba)_2$ + 2 mol PPh_3 as catalyst in the absence of CO and benzonitrile as promoters. The same compound **7** was observed by ^{1}H NMR on heating complex **6** in $CDCl_3$ at 50 °C. The activated methyl protons were clearly recognized at δ 2.30, corresponding to the *E* (*trans*) compound described in the literature [14] as distinguished from the *Z* (*cis*) one which absorbs at δ 2.15.

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