Palladium-Catalyzed Double-Bond Migration in the Homoisoflavone System

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(Received April 13, 1994)

Synopsis. 3-Benzylidene-4-chromanones were converted to 3-benzylchromones in HMPA at 200 °C in excellent yields. The reaction was irreversible and efficiently promoted by palladium catalysts in a remarkably shortened reaction time (3 h), compared with the existing procedure (24 h).

Recently, our studies concerning flavonoids have been extended so as to include a group of homoisoflavones, a less significant member. The first one, eucomin (**1**) (Scheme 1), was isolated by Boehler and Tamm in 1967 from bulbs of *Eucomis bicolor* Bak.[1] Among this class of compounds, there are three types of fundamental framework, namely, the *exo*-type (**2a**, and **3a**, (*E*)- and (*Z*)-3-benzylidene-4-chromanone, respectively) and the *endo*-type (**4a**, 3-benzylchromone) (Scheme 1). Although (*Z*)-isomers (**3**) exclusively occur in living plants,[2] those synthesized in the laboratory are almost (*E*)-isomers (**2**). While **2** can be readily obtained by the condensation of 4-chromanones with benzaldehydes,[3] **4** can be produced with difficulty from 2'-hydroxy-chalcones via four steps.[4,5] In 1977, Andrieux and his co-workers reported that **2a** isomerized into **4a** through a rhodium-catalyzed double-bond migration in essentially quantitative yield at 70 °C.[6] We thus attempted this *exo*-cyclic–*endo*-cyclic double-bond migration for the purpose of preparing **4a** from **2a**, according to all of the same procedures that they reported. However, in spite of several runs, **4a** was not obtain in over 60% yield, while always leaving a significant amount of the substrate. In this case, a perfect isolation of **4a** by column chromatography could not be achieved, due to a very small difference between the R_f-values of **2a** and **4a** in a TLC analysis.

In order to establish an alternative route starting from **2** toward **4**, we carried out several trial- and error-experiments. We could succeed in obtaining good results by heating **2** with palladium-catalysts at 200 °C in hexamethylphosphoric triamide (HMPA) (Eq. 1, in Scheme 1).

Results and Discussion

For this type of migration, the classical methods usually require drastic conditions, i.e., strong acids and bases or high-temperature heterogeneous catalysts.[7] At first, **2a** was heated at 200—250 °C under nonsolvent conditions in a nitrogen atmosphere, but obtaining poor results (Table 1). The low total recoveries of **2a** and **4a** may be mainly due to thermal degradation of **2a**, because **4a** was almost completely recovered in a blank test with heating at 250 °C for 5 h. We next conducted the reaction in an aprotic polar solvent, such as DMSO or HMPA, under various conditions, and obtained some interesting results (summarized in Table 2).

The following observations and interpretations may be worth noting: (1) In runs using DMSO as a solvent at the reflux temperature (Runs 1—5), all of the yields of **4a** were very low. Although the results were stoichiometrically reasonable in the absence of Pd-catalysts (Runs 1 and 2), some degradation was observed in their presence. This is presumably due to the instabilities of the Pd intermediates formed with the substrate and/or product under these conditions. (2) In runs conducted in HMPA (Runs 6—14), all of the conversions of **2a** were complete at above 200 °C. While HMPA shows a slightly stronger basicity than does DMSO, compounds of type **2** are known to be unstable in a basic medium. Thus, the competitive degradation of **2a** may have been faster than the migration of the double bond at the reflux temperature in the absence of a Pd catalyst (Runs 6 and 7). However, the addition of a Pd catalyst improved the yield of **4a** appreciably (Run
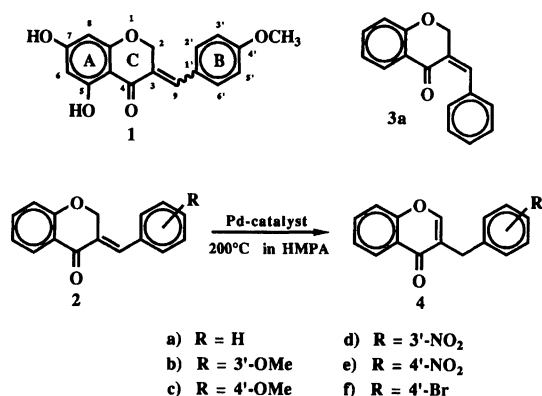
Scheme 1.

Table 1. Thermal Isomerization of 2a into 4a[a]

Run	Temp	Time	Conv. of 2a[b]	Yield[c]
	°C	h	%	%
1	200	5	37	8
2	200	10	37	7
3	250	5	62	20
4	250	10	72	23

a) All the reactions were carried out under the nitrogen atmosphere, using 0.5 mmol of **2a** in a silicone oil bath adjusted at the temperature shown. b) Conversion of **2a**. c) Determined by GLC-analyses based on **2a**, after the dissolution with 25 mL of chloroform, using pentadecane as an internal standard.

Table 2. The Isomerization of **2a** into **4a** in Solution

Run	Solvent[a]	Temp °C	Time h	Catalyst[b]	Conv. of **2a**[c] %	Yield[d] %
1	DMSO	Reflux	5		12	8
2	DMSO	Reflux	16		16	11
3	DMSO	Reflux	6	$PdCl_2$[e]	27	9
4	DMSO	Reflux	6	$PdCl_2(dppf)$	35	10
5	DMSO	Reflux	6	$Pd(PPh_3)_4$	47	16
6	HMPA	Reflux	7		100	13
7	HMPA	Reflux	3		100	12
8	HMPA	Reflux	3	$Pd(PPh_3)_4$	100	39
9	HMPA	200	3		100	61
10	HMPA	200	3	$PdCl_2$	100	76
11	HMPA	200	3	$Pd(OAc)_2$	100	75
12	HMPA	200	3	$PdCl_2(dppf)$	100	49
13	HMPA	200	3	$Pd(PPh_3)_4$	100	84
14	HMPA	200	3	$RhCl_3 \cdot 3H_2O$	100	59
15	HMPA	150	3		34	11
16	HMPA	150	3	$Pd(PPh_3)_4$	31	17

a) 25 mL of solvent was added in every case. b) 3 mol% was added against substrate, unless otherwise stated. c) Conversion of 1 mmol of **2a**. d) GLC yield based on **2a**. e) 10 mol% was added.

8). (3) When the reactions were carried out at 200 °C in HMPA, the yields of **4a** increased remarkably, giving the best result in the run using tetrakis (triphenylphosphine)palladium [$Pd(PPh_3)_4$] as a catalyst (Run 13, 84%). The lowest efficiency of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium [$PdCl_2(dppf)$] is probably due to a lower capability of ligand dissociation compared to [$Pd(PPh_3)_4$], and/or to a steric factor attributed to the bulky ferrocene moiety, though still not clear in detail. (4) In order to clarify the effect of rhodium on this migration,[6] $RhCl_3 \cdot 3H_2O$ was used as a catalyst under the same conditions, to also give the desired product in a yield of below 60% (Run 14). (5) When the reaction was carried out at 150 °C, the yields of **4a** decreased extremely, contaminated with a substantial amount of substrate (Runs 15 and 16).

To investigate the substituent effect on this reaction, derivatives of **2a** with several kinds of substituents on the B-ring were examined at 200 °C in HMPA in the presence of $PdCl_2$ or [$Pd(PPh_3)_4$]. The obtained results are summarized in Table 3. As shown in the table, no explicit substituent effect was observed except for the Br derivative, in which a appreciable amount of debromo-reduced product (ca. 25%) was observed in the GLC-analysis, probably attributed to the insertion of the Pd catalyst into the C–Br bond.

2-Benzylidenetetralone and 2-benzylideneindanone, whose structures are analogous to that of **2a**, were also tested under the same conditions, but failed to obtain the desired products. It is reasonable to consider that the *exo*-form is energetically more stable than the *endo*-form in the former, and that the thermal degradation and/or ring fission ascribed to the ring strain occurs exceedingly under these conditions in the latter.

Although a large number of reports concerning the

Table 3. The Isomerization of Substituted 3-Benzylidene-4-chromanones (**2b**—**2f**) into the Corresponding 3-Benzylchromones (**4b**—**4f**)[a]

Substrate	R	Catalyst[b]	Conv. of **2** %	Yield[c] %
2b	3'-OMe	$PdCl_2$	100	76
		$Pd(PPh_3)_4$	100	80
2c	4'-OMe	$PdCl_2$	100	58
		$Pd(PPh_3)_4$	100	43
2d	3'-NO_2	$PdCl_2$	100	69
		$Pd(PPh_3)_4$	100	63
2e	4'-NO_2	$PdCl_2$	100	64
		$Pd(PPh_3)_4$	100	36
2f	4'-Br	$PdCl_2$	100	25
		$Pd(PPh_3)_4$	100	10

a) All the reactions were conducted under the nitrogen atmosphere at 200 °C in 25 mL of HMPA, using 1 mmol of substrate. b) $PdCl_2$: 10 mol%, $Pd(PPh_3)_4$: 3 mol%. c) GLC yields based on substrates.

exo-cyclic–*endo*-cyclic double-bond migration have hitherto been presented,[8,9] very long reaction times have generally been required (24 h—3 d). On the other hand, Leonard et al.[10] have described the isomerization of dibenzylidene-4-piperidones to the corresponding dibenzyl-4-piridones using the Pd-carbon catalyst at 194—195 °C in ethylene glycol, and have obtained the desired products in excellent yields after one-half hour. We then examined their procedure for **2a** and gained **4a** in 90% yield.

We believe that the present method is another practical one for preparing **4** from **2** as well as the above-cited procedure, though its reaction mechanism is not still clear in detail, since the reaction time was remarkably shortened and an isolation of product is very easy

through the complete conversion of the substrate in column chromatography.

Experimental

All of the melting points are uncorrected. The IR and mass spectra were recorded on the same instruments that we previously reported.[11] ^{1}H NMR spectra were obtained with a JEOL-EX270 Fourier Transform NMR spectrometer (270 MHz). GLC analyses were performed on a Hitachi-263-30 instrument using Silicone SE-30 (2 m) on Uniport B.

Materials and Reagents. PdCl$_2$, Pd(OAc)$_2$, RhCl$_3$·3H$_2$O, and solvents were all commercially available grades and were used without further purification. [Pd-(PPh$_3$)$_4$][12] and [PdCl$_2$(dppf)][13] were prepared following literature procedures. 3-Benzylidene-4-chromanones, prepared by a known procedure,[3] and 3-benzylchromones, isolated in the present reactions, are identified on the basis of values given in the literatures,[6,14,15] except for the following derivatives.

3-(m-Methoxybenzylidene)-4-chromanone (2b): Mp 82.0—83.0 °C; IR (KBr) 1675cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=3.85 (s, 3H, OCH$_3$), 5.34, 5.35, (s, s, 2H, (C$_2$-H)×2), 6.84—7.53 (m, 7H, aromatic), 7.85 (s, 1H, C$_9$-H), 8.03 (dd, J=7.9 and 1.3 Hz, 1H, C$_5$-H). MS Found: m/z 266.0952. Calcd for C$_{17}$H$_{14}$O$_3$: M, 266.0943.

3-(m-Nitrobenzylidene)-4-chromanone (2d): Mp 174.0—176.0 °C; IR (KBr) 1675cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=5.32, 5.33 (s, s, 2H, (C$_2$-H)×2), 6.98—8.30 (m, 7H, aromatic), 7.87 (s, 1H, C$_9$-H), 8.04 (dd, J=8.1 and 1.5 Hz, 1H, C$_5$-H). MS Found: m/z 281.0682. Calcd for C$_{16}$H$_{11}$NO$_4$: M, 281.0688.

3-(p-Nitrobenzylidene)-4-chromanone (2e): Mp 226.0—227.0 °C; IR (KBr) 1675cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=5.34, 5.35 (s, s, 2H, (C$_2$-H)×2), 6.97—8.32 (m, 8H, aromatic), 7.81 (s, 1H, C$_9$-H). MS Found: m/z 281.0679. Calcd for C$_{16}$H$_{11}$NO$_4$: M, 281.0688.

3-(p-Bromobenzylidene)-4-chromanone (2f): Mp 166.0—168.0 °C; IR (KBr) 1675cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=5.30, 5.31 (s, s, 2H, (C$_2$-H)×2), 6.96—7.61 (m, 7H, aromatic), 7.79 (s, 1H, C$_9$-H), 8.02 (dd, J=7.9 and 1.7 Hz, 1H, C$_5$-H). MS Found: m/z 313.9947. Calcd for C$_{16}$H$_{11}$BrO$_2$: M, 313.9942.

3-(m-Methoxybenzyl)chromone (4b): Mp 76.0—77.0 °C; IR (KBr) 1645cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ= 3.79 (s, 3H, OCH$_3$), 3.80 (s, 2H, benzylic CH$_2$), 6.76—7.68 (m, 7H, aromatic), 7.64 (s, 1H, C$_2$-H), 8.24 (dd, J=7.9 and 1.7 Hz, 1H, C$_5$-H). MS Found: m/z 266.0935. Calcd for C$_{17}$H$_{14}$O$_3$: M, 266.0943.

3-(m-Nitrobenzyl)chromone (4d): Mp 131.5—133.0 °C; IR (KBr) 1645cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=3.90 (s, 2H, benzylic CH$_2$), 7.26—8.15 (m, 7H, aromatic), 7.84 (s, 1H, C$_2$-H), 8.21 (dd, J=7.9 and 1.8 Hz, 1H, C$_5$-H). MS Found: m/z 281.0696. Calcd for C$_{16}$H$_{11}$NO$_4$: M, 281.0688.

3-(p-Nitrobenzyl)chromone (4e): Mp 175.0—176.0 °C; IR (KBr) 1640cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=3.90 (s, 2H, benzylic CH$_2$), 7.23—8.18 (m, 7H, aromatic), 7.81 (s, 1H, C$_2$-H), 8.21 (dd, J=7.9 and 1.7 Hz, 1H, C$_5$-H). MS Found: m/z 281.0669. Calcd for C$_{16}$H$_{11}$NO$_4$: M, 281.0688.

3-(p-Bromobenzyl)chromone (4f): Mp 155.0—156.9°C; IR (KBr) 1640cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ= 3.76 (s, 2H, benzylic CH$_2$), 7.17—7.66 (m, 7H, aromatic),

7.66 (s, 1H, C$_2$-H), 8.22 (dd, J=7.9 and 1.7 Hz, 1H, C$_5$-H). MS Found: m/z 313.9967. Calcd for C$_{16}$H$_{11}$BrO$_2$: M, 313.9942.

General Procedure. A 50 mL two-necked round-bottomed flask equipped with a reflux condenser, a septum inlet, and a magnetic stirring bar was charged with (E)-3-benzylidene-4-chromanone (2a, 1.0 mmol) and [Pd(PPh$_3$)$_4$] (0.036 g, 0.03 mmol) or PdCl$_2$ (0.017 g, 0.1 mmol). The flask was flushed with dry nitrogen and filled with 25 mL of HMPA through the septum inlet with a hypodermic syringe. The mixture was heated with stirring for 3 h in an oil bath adjusted at 200 °C. The reaction solution was then cooled to room temperature, and diluted with a large amount of water. The products were extracted with dichloromethane, washed with water several times and finally brine, and dried over anhydrous Na$_2$SO$_4$. After filtration, the solution was condensed to ca. 25 mL by an evaporator, followed by a GLC analysis. 4a was isolated from the residual solution by silica-gel column chromatography using a mixture of benzene and ether (4:1) as an eluent, and recrystallized from hexane and a small amount of benzene.

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