norcamphor favored concerted transfer of the syn C(7) hydrogen to the carbonyl carbon as α-cleavage occurred, and that this process was faster than the common biradical disproportionation pathway.[8] This suggestion would be difficult to reconcile with our present findings, which would require that remote alkyl substitution on the rigid norbornane skeleton strongly influence the rate of the proposed concerted transfer of hydrogen. While further studies with various stereospecifically substituted norcamphors are certainly desirable to support this conclusion, it seems clear from our results that no special mechanism is necessary to account for the product specificity observed with norcamphor.

Experimental Section

Materials and Equipment. Unless noted otherwise below, these were the same as we have described previously.[3] NMR spectra were obtained at 60 MHz unless otherwise indicated.

Photolysis of 4-Methylnorcamphor (8). A 120-mg sample of 8[4] in 40 mL of benzene containing 1.2 mL of methanol was degassed for 15 min with N_2 and then irradiated through Pyrex for 8 h. Most of the solvent was removed by distillation through a Vigreux column and the products were isolated by preparative VPC on a 25 ft × 0.25 in. 25% DEGS column to give, in order of elution, 1-methylcyclopent-2-en-1-acetaldehyde (**12**) and 1-methylcyclopent-3-en-1-acetaldehyde (**13**) in the ratio 3:1.

Characterization data for **12:** IR 3040 (w), 2940 (s), 2850 (m), 2720 (m), 1725 (s), 1450 cm^{-1} (m); NMR δ 1.17 (s, 3 H), 1.48–1.97 (m, 2 H), 2.10–2.60 with d, J = 3 Hz, at 2.37 (m, 4 H), 5.63 (s, 2 H), 9.70 (t, J = 3 Hz, 1 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.62; H, 9.73.

Characterization data for **13:** IR 3045 (m), 2945 (s), 2830 (s), 2720 (m), 1725 (s), 1615 (w), 1435 (w), 1375 (w), 670 cm^{-1} (m); NMR δ 1.12 (s, 3 H), 2.1–2.5 with s at 2.30 and d, J = 3 Hz, at 2.38 (m, 6 H), 5.60 (s, 2 H), 9.72 (t, J = 3 Hz, 1 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.39; H, 9.66.

Photolysis of 1-Isopropylnorcamphor (9). Irradiation of 77 mg of 9[2] for 7 h and workup under conditions described above for photolysis of 8 gave these products, isolated by preparative VPC on an 9 ft × 0.25 in. 15% DEGS column, in order of elution: 3-isopropylcyclopent-2-en-1-acetaldehyde (**14**) and 3-isopropylcyclopent-3-en-1-acetaldehyde (**15**) in the ratio 13:1.

Characterization data for **14:** IR 3035 (w), 2955 (s), 2860 (m), 2700 (m), 1725 (s), 1640 (w), 1470 (m), 1380 (m), 1365 cm^{-1} (m); NMR δ 1.03 (d, J = 7 Hz, 6 H), 1.18–2.58 (m, 7 H), 3.05 (m, 1 H), 5.22 (m, 1 H), 9.67 (t, J = 2 Hz, 1 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.08; H, 10.67.

Characterization data for **15:** IR 3035 (w), 2955 (s), 2700 (m), 1725 (s), 1650 (w), 1470 (m), 1380 (m), 1375 cm^{-1} (m); NMR (220 MHz) δ 1.00 (d, J = 7 Hz, 6 H), 1.80–2.82 (m, 8 H), 5.18 (m, 1 H), 9.64 (t, J = 3 Hz, 1 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.11; H, 10.48.

Determination of Quantum Yields. Benzene solutions of the VPC purified norcamphor derivatives were prepared to give an absorbance at 313 nm of 0.502–0.553 (0.035–0.037 M). Aliquots (4 mL) of these solutions were degassed in three freeze–thaw cycles, sealed in identical Pyrex tubes, and irradiated with a Hanovia Model L 450-W mercury lamp in a merry-go-round apparatus for 15 min (4–5% conversion). The product yields were determined by calibrated VPC on an 8 ft × 0.25 in. 3% DEGS column.

Acknowledgements. We thank Mr. S. T. Bella for microanalyses and both the National Science Foundation (Grant CHE74-21436) and The Rockefeller Foundation (Grant RF 70095) for support of this research. NMR spectra at 220 MHz were obtained on an instrument at The Rockefeller University and operated by a consortium supported in part by NSF Grant PCM74-12247.

Registry No.—**8,** 49664-72-4; **9,** 59247-60-8; **12,** 61436-67-7; **13,** 61394-30-7; **14,** 61394-31-8; **15,** 61394-32-9.

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Synthesis of Isocoumarins, Dihydroisocoumarins, and Isoquinolones via π-Allylnickel Halide and π-Olefin–Palladium Complexes

Donald E. Korte, Louis S. Hegedus,* and Ronald K. Wirth

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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2-Bromobenzoic esters were treated with π-(2-methoxyallyl)nickel bromide to produce 2-acetonylbenzoic esters. These were cyclized to isocoumarins by treatment with NaH/*tert*-butyl alcohol, or to dihydroisocoumarins by treatment with $NaBH_4$. The sodium salts of 2-bromobenzoic acids were reacted with a variety of π-allylnickel halide complexes to produce 2-allylbenzoic acids. These were cyclized to isocoumarins by treatment with palladium chloride. In a similar fashion isoquinolones were prepared from 2-allylbenzamides. This cyclization is thought to proceed by a palladium-assisted nucleophilic attack on the olefin of the allyl group.

Isocoumarins[1] (1*H*-2-benzopyran-1-one, **1**) are a class of naturally occurring lactones which display a wide range of biological activity.[2] They have been prepared by cyclization of homophthalic acid derivatives,[3] 2-vinylbenzoic acid derivatives,[4] 2-carboxybenzyl ketones[5] (available primarily from the Hurtley reaction),[6] by the ortholithiation of *N*-methyl-

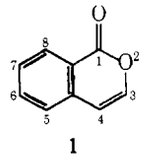

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Table I. Reaction of π-(2-Methoxyallyl)nickel Bromide with 2-Haloaromatic Esters

Substrate	Time, h	Temp, °C	Product	Yield, %[a]
Methyl ester of				
2-Bromobenzoic acid	16	50	Methyl 2-acetonylbenzoate (**2a**)	93
2-Bromo-4,5-dimethoxybenzoic acid	42	55	Methyl 2-acetonyl-4,5-dimethoxybenzoate (**2b**)	97
2-Iodo-4-chlorobenzoic acid	40	0–25	Methyl 2-acetonyl-4-chlorobenzoate (**2c**)	68
2-Bromo-3-pyridinecarboxylic acid	100	50	Methyl 2-acetonyl-3-pyridinecarboxylate (**6**)	78

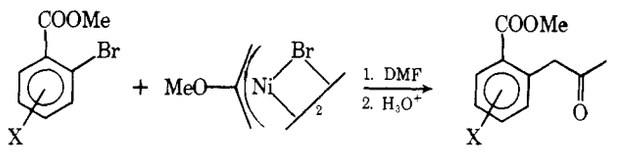
[a] Yields are of isolated, purified product.

Table II. Reaction of π-Allylnickel Bromide Complexes with Aromatic Halides[a]

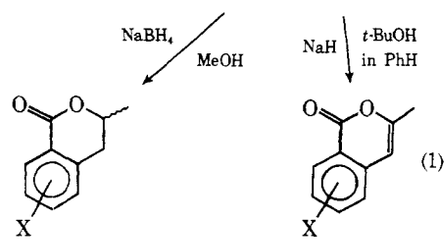
Substrate	Nickel complex	Time, h	Product	Yield,[b] %
Sodium salt of				
2-Bromobenzoic acid	π-Allylnickel bromide	96	2-(2-Propenyl)benzoic acid (**4a**)	76
2-Bromobenzoic acid	π-Crotylnickel bromide	96	2-(2-Butenyl)benzoic acid (**4b**)	91
2-Bromobenzoic acid	π-(1,1-Dimethylallyl)nickel bromide	90	2-(3-Methyl-2-butenyl)benzoic acid (**4c**)	87
2-Bromobenzoic acid	π-(2-Methallyl)nickel bromide	120	2-(2-Methyl-2-propenyl)benzoic acid	71
2-Iodo-4-chlorobenzoic acid	π-Allylnickel bromide	120	2-(2-Propenyl)-4-chlorobenzoic acid (**4d**)	*c*
2-Iodo-4-chlorobenzoic acid	π-Crotylnickel bromide	96	2-(2-Butenyl)-4-chlorobenzoic acid (**4e**)	*c*
2-Bromo-5-methoxybenzoic acid	π-Allylnickel bromide	96	2-(2-Propenyl)-5-methoxybenzoic acid (**4f**)	*c*
2-Bromobenzamide	π-Allylnickel bromide	90	2-(2-Propenyl)benzamide	59
2-Bromo-*N*-methylbenzamide	π-Allylnickel bromide	70	2-(2-Propenyl)-*N*-methylbenzamide	70

[a] All reactions were carried out at 50 °C using 1.5 mmol of nickel complex/mmol of substrate in DMF. [b] Reported yields are of isolated products purified by preparative layer chromatography. [c] These compounds were not isolated. Cyclization to the isocoumarin was carried out on the crude reaction mixture (see Table V).

benzamides,[7] and by the oxidation of isochromans.[8] These methods frequently suffer from requiring difficult to prepare starting materials and/or severe conditions for cyclization. We have recently developed methods, using π-allylnickel halide complexes[9] for the facile introduction of the acetonyl group into aromatic substrates,[10] and for palladium assisted cyclization of 2-allylanilines to 2-alkylindoles.[11] Herein we report the extension of the newly developed methods to the synthesis of isocoumarins, dihydroisocoumarins, and isoquinolones. The approaches are summarized in eq 1 and 2.

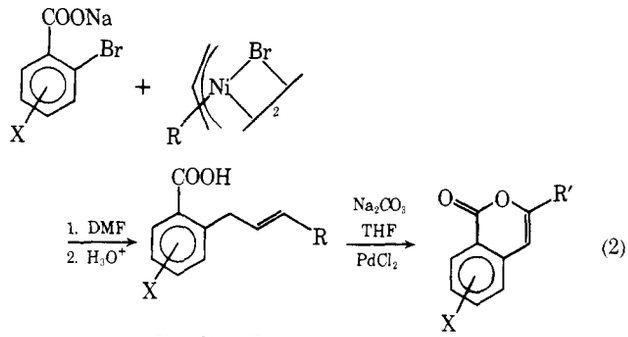


2a, X = H
b, X = 4,5-di-OMe
c, X = 4-Cl



3'a, X = H
b, X = 6,7-diOMe
c, X = 6-Cl

3a, X = H
b, X = 6,7-di-OMe
c, X = 6-Cl



(2)

4a, X = R = H
b, X = H; R = Me
c, X = H; R = $(Me)_2$
d, X = 4-Cl; R = H
e, X = 4-Cl; R = Me
f, X = 5-OMe; R = H

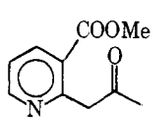
5a, X = H; R' = Me
b, X = H; R' = Et
c, X = H; R' = *i*-Pr
d, X = 6-Cl; R' = Me
e, X = 6-Cl; R' = Et
f, X = 7-OMe; R' = Me

Results

Preparation of Substrates for Cyclization. Treatment of several substituted methyl 2-bromobenzoates with π-(2-methoxyallyl)nickel bromide produced the corresponding methyl 2-acetonylbenzoates in good yield (Table I). The reaction proceeded under mild conditions (50 °C, DMF) and displayed the specificity typical for π-allylnickel halide complexes.[10,11] With methyl 2-iodo-4-chlorobenzoate, reaction took place exclusively at the iodide, leaving the chloride untouched. The heteroaromatic bromo ester methyl 2-bromo-3-pyridinecarboxylate also reacted cleanly. Thus, this procedure provides a mild and specific synthetic approach to

Table III. Preparation of 3-Methylisocoumarins from 2-Acetonyl Esters

Substrate	Product	Yield, %[a]
Methyl 2-acetonylbenzoate	3-Methylisocoumarin (**3a**)	81
Methyl 2-acetonyl-4,5-dimethoxybenzoate	3-Methyl-6,7-dimethoxyisocoumarin (**3b**)	67
Methyl 2-acetonyl-4-chlorobenzoate	3-Methyl-6-chloroisocoumarin (**3c**)	71
Methyl 2-acetonyl-3-pyridinecarboxylate (**6**)	7-Methyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (**7**)	61



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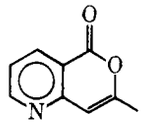

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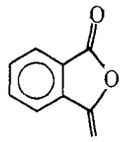
[a] Reported yields are for pure, isolated products.

Table IV. Preparation of Dihydroisocoumarins from Methyl 2-Acetonylbenzoates

Substrate	Product	Yield, %[a]
Methyl 2-acetonylbenzoate	(±)-3-Methyl-3,4-dihydroisocoumarin (**3'a**)	75
Methyl 2-acetonyl-4,5-dimethoxybenzoate	(±)-3-Methyl-3,4-dihydro-6,7-dimethoxyisocoumarin (**3'b**)	81
Methyl 2-acetonyl-4-chlorobenzoate	(±)-3-Methyl-6-chloro-3,4-dihydroisocoumarin (**3'c**)	94

[a] Reported yields are for pure, isolated products.



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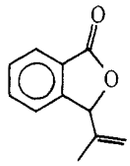

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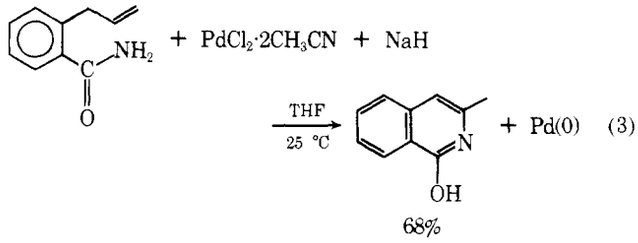
2-acetonylbenzoic esters from readily available starting materials.

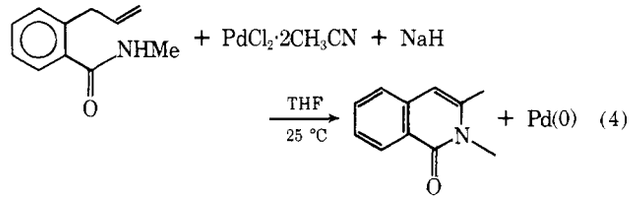
Attempts to prepare 2-allylbenzoic acids, for conversion to isocoumarins as in eq 2, by the reaction of 2-bromobenzoic acids with π-allylnickel halides met with limited success. While 2-bromobenzoic acid reacted with π-allylnickel bromide to give a fair (49%) yield of 2-(2-propenyl)benzoic acid, π-crotyl-, π-cyclohexenyl-, and π-(1,1-dimethylallyl)nickel bromide produced primarily benzoic acid from 2-bromobenzoic acid, with little allyl transfer being observed. In contrast, 4-bromobenzoic acid reacted cleanly with π-crotylnickel bromide to produce 4-(2-butenyl)benzoic acid in good yield. To circumvent this problem, the 2-bromobenzoic acids were converted to their sodium salts prior to reaction with the π-allylnickel bromide complexes. In this fashion high yields of 2-allylbenzoic acids were obtained (Table II) for later conversion to isocoumarins. In several cases these allyl acids were not purified. Rather cyclization was carried out on crude reaction mixtures to give a high-yield, one-pot conversion of 2-bromobenzoic acids to isocoumarins. The conversion of 2-bromobenzamide to 2-(2-propenyl)benzamide, for cyclization to an isoquinolone, was carried out in a similar fashion.

Cyclization Studies. The optimum conditions for the cyclization of 2-acetonylbenzoates to 3-methylisocoumarins (eq 1) was treatment with 2 equiv of NaH in refluxing benzene (16 h) with a catalytic amount of *tert*-butyl alcohol (Table III). The presence of halogen, methoxy, or heterocyclic nitrogen did not interfere with the cyclization. Treatment of methyl 2-acetonylbenzoate with 4 equiv of NaH in refluxing benzene (2 h) produced a 1:1 mixture of 3-methylisocoumarin and 1,3-dihydroxynaphthalene, resulting from C-acylation rather than O-acylation. Reductive cyclization of several methyl 2-acetonylbenzoates using excess $NaBH_4$ in methanol[5] produced racemic 3-methyl-3,4-dihydroisocoumarins in good yield (Table IV). Again, methoxy or halogen substituents did not interfere.

Isocoumarins were also synthesized from 2-alkenylbenzoic acids, using a palladium assisted cyclization reaction (eq 2) involving nucleophilic attack of carboxylate on the Pd-complexed olefin (vide infra). These results are summarized in Table V. With two exceptions, isocoumarins were the sole cyclic products. With 2-vinylbenzoic acid, a small amount of the five-membered-ring lactone **8** was obtained in addition to the major product, isocoumarin. In contrast the five-membered-ring lactone **9** was the sole cyclic product from the reaction of 2-(2-methyl-2-propenyl)benzoic acid. The presence of chloride or methoxide groups in the benzene ring did not interfere with cyclization. Purification of the alkenylbenzoic acids prior to cyclization was not necessary, since contaminants from the allylation reaction did not interfere with the cyclization. The cyclization could be made *catalytic* with regard to palladium by the addition of cupric acetate and O_2 to provide a means for oxidation of the Pd(0) produced in the cyclization step.

Dihydroisocoumarins were available by the above procedure by simply exposing the cyclization reaction mixture to an atmosphere of H_2 after cyclization was complete, utilizing the Pd metal precipitate present as catalyst. In this fashion 3,4-dihydroisocoumarin was produced from 2-vinylbenzoic acid in 65% yield, as was 3-methyl-3,4-dihydroisocoumarin from 2-(2-propenyl)benzoic acid in 68% yield. Finally 2-(2-propenyl)benzamide was converted to 3-methylisocarbostyril (eq 3) and 2-(2-propenyl)-*N*-methylbenzamide to 3-methyl-*N*-methylisoquinolone (eq 4) by treatment with $PdCl_2$ and NaH in THF.





Discussion

The reaction of π-(2-methoxyallyl)nickel bromide with 2-bromobenzoic esters to produce 2-acetonylbenzoic esters proceeded without complication, and displayed the reactivity and selectivity common to other π-allylnickel halide complexes.[9,10] The success of this reaction with methyl 2-bromo-3-pyridinecarboxylate is of note because the behavior of bromopyridines, with their ability to strongly coordinate to nickel during the course of the reaction, toward these nickel complexes was previously unknown. Although coordination

Table V. Preparation of Isocoumarins from 2-Alkenylbenzoic Acids[a]

Substrate	Time, h	Product	Yield,[b] %
2-(2-Propenyl)benzoic acid (**4a**)	3	3-Methylisocoumarin (**5a**)	86
2-(2-Propenyl)benzoic acid[b]	119	3-Methylisocoumarin (**5a**)	41 (1900)[c]
2-(2-Butenyl)benzoic acid (**4b**)	3	3-Ethylisocoumarin (**5b**)	86
2-(3-Methyl-2-butenyl)benzoic acid (**4c**)	4	3-Isopropylisocoumarin (**5c**)	96
2-(2-Propenyl)-4-chlorobenzoic acid (**4d**)[d]	4	3-Methyl-6-chloroisocoumarin (**5d**)	63[c]
2-(2-Butenyl)-4-chlorobenzoic acid (**4e**)[d]	4	3-Ethyl-6-chloroisocoumarin (**5e**)	54[e]
2-(2-Propenyl)-5-methoxybenzoic acid (**4f**)[d]	3	3-Methyl-7-methoxyisocoumarin (**5f**)	65[f]
2-Vinylbenzoic acid	3	Isocoumarin (**1**)	62
		3-Methylene phthalide (**8**)	21
2-(2-Methyl-2-propenyl) benzoic acid	5	**9**	31

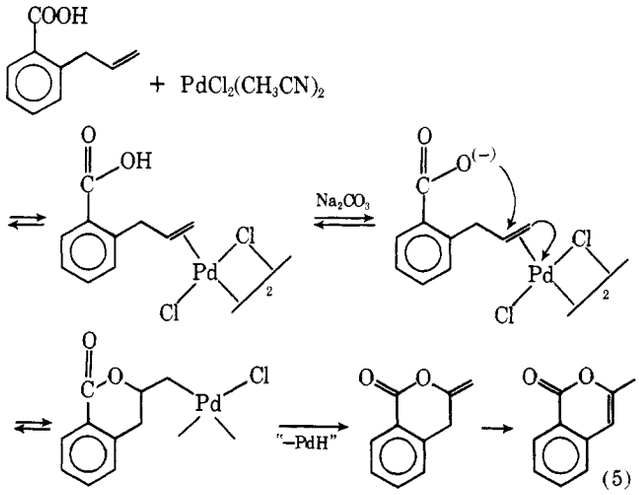
[a] Unless otherwise noted, all reactions were run using a stoichiometric amount of $PdCl_2 \cdot 2CH_3CN$. [b] Reported yields are of isolated, purified products. [c] Yield based on $PdCl_2 \cdot 2CH_3CN$, present in catalytic amounts. [d] This material was used without purification as obtained in Table II. [e] Yield is based on sodium 2-iodo-4-chlorobenzoate. [f] Yield is based on sodium 2-bromo-5-methoxybenzoate.

of the pyridine to the π-allylnickel halide complex, as evidenced by an immediate color change upon addition of substrate, apparently does occur, this coordination does not interfere with the allyl transfer. The yield of methyl 2-acetonyl-3-pyridinecarboxylate is probably somewhat higher than reported, since this product is quite water soluble and some difficulty in isolation was experienced. Both the base-catalyzed cyclization of these substrates to 3-methylisocoumarins (Table III) and the reductive cyclization to 3-methyl-3,4-dihydroisocoumarins (Table IV) were carried out in a routine fashion and require little comment. Both procedures resulted in high-yield production of the desired products.

Although aliphatic bromo acids, such as bromoacetic acid and 11-bromoundecanoic acid, react cleanly with π-allylnickel halide complexes to produce the corresponding allyl acids,[13] 2-bromobenzoic acid underwent primarily reductive debromination to produce benzoic acid upon reaction with a variety of π-allylnickel halide complexes. That benzoic acid is *not* produced in the reaction of 4-bromobenzoic acid with π-crotylnickel bromide suggests that the debromination of 2-bromobenzoic acid results from an intramolecular proton transfer from the carboxylic acid to the 2 position of the aromatic ring during reaction. Since radical anions are thought to be intermediates in the reaction of π-allylnickel halides with organic halides,[14] this is not unlikely. The problem of debromination was surmounted by converting the 2-bromobenzoic acids to their sodium salts prior to reaction with the nickel complexes. In this fashion, a number of substituted 2-allylbenzoic acids were prepared in high yield (Table II).

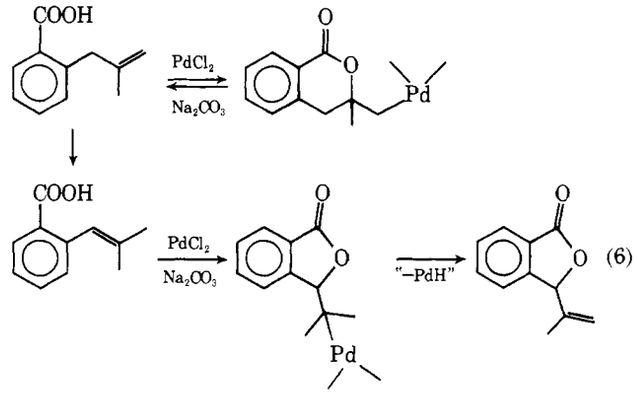
Palladium(II) has frequently been used to activate simple carbon–carbon double bonds to undergo attack by a variety of nucleophiles. The well-known Wacker process for the conversion of ethylene to acetaldehyde has as a key step the nucleophilic attack of palladium complexed ethylene by water. Other nucleophiles including acetate, chloride, and alkoxide as well as alcohols[15] and amines[16] react with Pd(II) complexed olefins. Several intramolecular versions of this reaction have also been developed. Thus 2-allylphenols were converted to benzofurans,[17] 2-allylanilines to indoles,[11] α,β-unsaturated ketoximes to isoxazoles,[18] *o*-hydroxychalcones to flavones,[19] and $\alpha,\beta,\gamma,\delta$-unsaturated carboxylic acids to α-pyrones,[20] by treatment with some form of Pd(II) and some base to generate a nucleophilic heteroatom.

Treatment of a number of 2-allylbenzoic acids with $PdCl_2(CH_3CN)_2$ and sodium carbonate in THF (eq 2) led to production of 2-alkylisocoumarins in high yield (Table V). The reaction is thought to proceed as in eq 5, involving coordination of the olefin to Pd(II), generation of free carboxylate by sodium carbonate, attack of carboxylate on this Pd(II) complex olefin to produce the ring closure and a σ-alkyl palladium



(5)

complex, followed by elimination of PdH and rearrangement to the observed isocoumarin. This mechanism is similar to that proposed for formation of indoles from 2-allylanilines,[11] and benzofurans from 2-allylphenols.[17] The stereochemistry of the ring closure and the state of coordination of the carboxylate group prior to attack are not known. Amines[21] and methoxide[22] have been shown to add to Pd(II) complexed olefins in a trans fashion, without prior coordination, while hydride[23] adds cis and is coordinated prior to attack. Chloride is known to attack by either mechanism, depending on concentration.[24] With all substrates but 2-vinylbenzoic acid, six-membered-ring lactones are the sole cyclized products when β-elimination is possible. It thus appears that the degree of substitution of the carbon atom to which palladium is bonded prior to β-elimination is of little consequence in determining the ring size of the product. With 2-(2-methyl-2-propenyl)benzoic acid, cyclization to the six-membered-ring lactone would result in a complex lacking β hydrogens, making β-elimination to product impossible (eq 6). The observed



(6)

product apparently results from an initial double bond rearrangement followed by ring closure. Since Pd(II) assisted additions to olefins are often reversible,[25] and since Pd(II) catalyzed double bond migrations are well known,[26] this is a reasonable assumption. Closure to a seven-membered ring would produce a σ-alkylpalladium complex which could β-eliminate. However, this was not observed.

As with other systems involving Pd(II) which produce materials that are not easily oxidized, the conversion of 2-allylbenzoic acids to 3-methylisocoumarins can be made catalytic in Pd(II) by providing a means of reoxidizing the Pd(0) produced in the elimination step. In this case cupric acetate and oxygen were used. Although using 2% $PdCl_2$ catalyst led to 1900% yield of isocoumarin (based on catalyst), the reaction was rather slow, and the yield of isocoumarin based on 2-allylbenzoic acid was rather low (41%). However, no attempt to optimize this catalytic reaction was made. Only the feasibility of developing a catalytic system was demonstrated.

Summary

The synthetic approaches to isocoumarins, dihydroisocoumarins, and isoquinolones presented above are among the mildest and most tolerant of functionality yet developed. The reaction of π-(2-methoxyallyl)nickel bromide with 2-haloaromatic esters provides direct access to 2-acetonylaromatic esters from readily available starting materials, for subsequent conversion to isocoumarins and dihydroisocoumarins by standard methods. The Pd(II) cyclization of 2-allyl aromatic acid derivatives to isocoumarins, dihydroisocoumarins, and isoquinolones is also very mild, tolerant of functionality, and of general utility. In most instances these new methods are a marked improvement over existing methods, and should find application in the synthesis of complex molecules.

Experimental Section

General. All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken on either Varian Associates Model A-60A or T-60 60 MHz spectrometers or a JEOL MH 100 spectrometer. Me_4Si was used as the internal standard and absorptions are expressed in parts per million (δ). Infrared (IR) spectra were recorded on a Perkin-Elmer Model 337 or Model 267 spectrometer. Absorptions are reported in microns. Analytical thin layer chromatography (TLC) was performed using Brinkmann precoated silica gel F-254 plates (0.25 mm). Preparative layer chromatography was carried out using 20 × 20 cm plates coated with Brinkmann silica gel PF-254 (2.0 mm). Products were visualized with ultraviolet light. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, Ind.

Materials. All solvents were freshly distilled and stored under an argon atmosphere. Immediately prior to use they were degassed and saturated with argon. DMF (Mallinckrodt) was distilled from CaH_2 under reduced pressure at 15–20 mmHg. Benzene (thiophene-free) was distilled at atmospheric pressure and stored over Linde type 4A molecular sieves. THF was refluxed over $LiAlH_4$ and distilled at atmospheric pressure under nitrogen. 2-Iodo-4-chlorobenzoic acid was prepared by diazotization of 4-chloroanthranilic acid.[27] 2-Bromo-5-methoxybenzoic acid was prepared by bromination of 3-methoxybenzoic acid.[28] 2-Bromo-3-pyridinecarboxylic acid was prepared via diazotization,[29] followed by oxidation[30] of 2-amino-3-picoline. 2-Bromo-4,5-dimethoxybenzoic acid was prepared by the bromination and oxidation[31] of veratraldehyde. Conversion of these acids to the corresponding salts was accomplished by reaction with an equimolar amount of sodium methoxide in methanol, followed by precipitation with ether or hexane–ether. Esterifications were performed via the method of Brewster and Ciotti.[32] 2-Vinylbenzoic acid was prepared from 2-bromostyrene (Columbia Chemical Co.) by treatment of the corresponding Grignard reagent with carbon dioxide.[33] 2-Bromobenzamide and 2-bromo-*N*-methylbenzamide were prepared by treatment of 2-bromobenzoyl chloride[34] with aqueous ammonia and methylamine, respectively, by the method of Vogel.[35] Sodium hydride and potassium hydride were purchased as oil dispersions from Alfa Inorganics. Nickel carbonyl was purchased from Matheson in 1-lb lecture bottles. π-(2-Methoxyallyl)nickel bromide was prepared by the method of Hegedus and Stiverson.[10] All other nickel complexes were prepared by the method of Semmelhack and Helquist,[36] except that in the case of π-(1,1-dimethylallyl)nickel bromide, the reaction was carried out at reflux rather than at 70 °C. All of the nickel complexes were stored under argon at −20 °C until just prior to use. Transfers of the complexes were performed in a nitrogen-filled glove bag.

General Procedure for the Reaction of 2-Haloaromatic Acid Derivatives with π-Allylnickel Bromide Complexes. Reactions were carried out in a 50-mL one-neck flask with side arm containing a magnetic stirring bar and fitted with a serum cap and stopcock. The reaction flask was flushed several times with argon and placed in a nitrogen-filled glove bag containing the nickel complex. The desired amount of the complex was transferred to the reaction flask and dissolved in argon-saturated DMF (10 mL solvent/mmol complex), producing a deep red solution. The substrate (1.5 mmol/mmol nickel complex) was weighed out in a separate 50-mL one-neck flask with side arm. The flask was then fitted with a serum cap and stopcock and flushed with argon. Argon-saturated DMF was added via syringe to dissolve the substrate and the resulting solution added via syringe to the nickel complex. With substrates which were not very soluble in DMF, the flask containing the substrate was fitted with a stir bar prior to addition of solvent, and the solution of nickel complex added to the slurry of substrate. In all cases the reaction mixture was stirred at ca. 50 °C until the red color of the nickel complex disappeared. The resulting dark green solution was poured into a separatory funnel containing 50 mL of 1.2 N HCl, saturated with NaCl, and extracted with 4 × 50 mL of ether. The combined ether extracts were washed with 6 × 25 mL of saturated aqueous NaCl to ensure removal of DMF. The ether layer was then dried with anhydrous $MgSO_4$ and solvent removed by rotary evaporator. The resulting crude product was purified by preparative layer chromatography.

Reaction of 2-Haloaromatic Esters with π-(2-Methoxyallyl)nickel Bromide. A. Methyl 2-Acetonylbenzoate (2a). To a solution of the nickel complex (0.46 g, 1.10 mmol, in 10 mL of DMF) was added methyl 2-bromobenzoate (0.35 g, 1.64 mmol, in 10 mL of DMF) and the mixture stirred at 52 °C for 16 h. After routine isolation the material was purified by preparative layer chromatography (1:1 hexane–ether).

The R_f 0.24 band contained 0.26 g (81%) of pale yellow oil: NMR ($CDCl_3$) δ 2.17 (s, 3, $COCH_3$), 3.90 (s, 3, $COOCH_3$), 4.10 (s, 2, $-CH_2-$), 7.40 (m, 1 H, ArH), 8.10 (m, 1 H, ArH); IR (neat) 3.23–3.50 (m, C–H), 5.80 (vs, aromatic ester), 5.83 (vs, saturated acyclic ketone), 5.99 (m), 6.21 (m, aromatic C=C), 6.21 (m, aromatic C=C), 6.33 (m, aromatic C=C), 6.67 (m), 6.90 (s), 6.94 (s), 7.35 (s), 7.52 (s), 7.69 (sh), 7.87 (s), 8.40 (m), 8.62 (s, methyl ester), 8.77 (s), 9.26 (s), 9.52 (m), 10.42 (m), 12.50 (m), 13.51 (s, 4 adjacent ArH), 14.29 (s), 15.25 (m), 15.87 μ (m). A portion was molecularly distilled at 0.05 mmHg and submitted for analysis. Anal. ($C_{11}H_{12}O_3$): C, H.

B. Methyl 2-Acetonyl-4,5-dimethoxybenzoate (2b). To a solution of the nickel complex (0.34 g, 0.84 mmol, in 10 mL of DMF) was added methyl 2-bromo-4,5-dimethoxybenzoate (0.32 g, 1.15 mmol, in 10 mL of DMF) and the mixture stirred at 55 °C for 42 h. After routine isolation and purification by preparative layer chromatography (1:10 hexane–ether, two developments, R_f 0.28) 0.29 g (97%) of white solid was obtained: 100-MHz NMR (acetone-d_6) δ 2.12 (s, 3, $-COCH_3$), 3.76 (s, 3, $-COOCH_3$), 3.80 (s, 3, $-OCH_3$), 3.82 (s, 3, $-OCH_3$), 4.04 (s, 2, $-CH_2-$), 6.82 (s, 1, ArH), 7.50 (s, 1, ArH); IR (paraffin oil) 5.81 (vs, aromatic ester carbonyl), 5.85 (vs, saturated acyclic ketone), 6.21 (m, aromatic C=C), 6.33 (m, aromatic C=C), 6.54 (s), 6.92 (m), 7.35 (s), 7.58 (m), 7.72 (m), 7.81 (s, aromatic ester C–O), 8.16 (s), 8.44 (m), 8.55 (s), 8.62 (sh, methyl ester), 10.00 (m), 11.24 (m), 12.82 μ (m). A portion was recrystallized from ether (white needles, mp 118–119 °C) and submitted for analysis. Anal. ($C_{13}H_{16}O_5$): C, H.

C. Methyl 2-Acetonyl-4-chlorobenzoate (2c). To a solution of the nickel complex (0.78 g, 1.86 mmol, in 15 mL of DMF) was added methyl 2-iodo-4-chlorobenzoate (0.71 g, 2.40 mmol, in 15 mL of DMF) and the mixture stirred at 0 °C for 40 h, slowly warming to room temperature in the process. After routine isolation and purification by preparative layer chromatography (1:1 hexane–ether, R_f 0.44), 0.37 g (68%) of pale yellow oil was obtained: NMR ($CDCl_3$) δ 2.25 (s, 3, $-COCH_3$), 3.84 (s, 3, $-COOCH_3$), 4.08 (s, 2, $-CH_2-$), 7.25 (m, 2, ArH), 8.00 (d, J = 4 Hz, 1, ArH); IR (neat) 3.13–3.50 (br, C–H), 5.81 (br, vs, aromatic ester, acyclic saturated ketone carbonyls), 6.25 (s, aromatic C=C), 6.37 (s, aromatic C=C), 6.73 (m), 6.99 (s), 7.38 (s), 7.52 (m), 7.69 (sh), 7.94 (vs), 8.40 (m), 8.62 (s), 9.05 (vs), 9.26 (s), 11.24 (s, isolated ArH), 11.90 (m, 2 adjacent ArH), 12.99 μ (s). Anal. ($C_{11}H_{11}ClO_3$): C, H, Cl.

D. Methyl 2-Acetonyl-3-pyridinecarboxylate (6). To a solution of the nickel complex (0.46 g, 1.10 mmol, in 12 mL of DMF) was added

methyl 2-bromo-3-pyridinecarboxylate (0.36 g, 1.65 mmol, in 12 mL of DMF) and the reaction mixture stirred at 50 °C for 100 h. After this time, 15 mL of 1.2 N HCl was added and the mixture stirred for about 1 h to hydrolyze the enol ether. After neutralization with Na_2CO_3, the organics were extracted with 3 × 75 mL of chloroform and dried over $MgSO_4$. Chloroform was removed by rotary evaporator and the DMF removed at 0.05 mmHg to leave an oily residue.

Purification of this crude product by preparative layer chromatography (1:5 hexane–ether, two developments, R_f 0.27) gave 0.24 g (78%) of **6**, a bright yellow oil: NMR ($CDCl_3$) δ 2.32 (s, 3, $COCH_3$), 3.90 (s, 3, $COOCH_3$), 4.45 (s, 2, $-CH_2-$), 7.38, 8.40, 8.80 (AMX, 3, ArH); IR (neat) 2.70–3.13 (w), 3.23–3.51 (m, C–H), 5.80 (vs, aromatic ester carbonyl), 6.02 (m, acyclic saturated ketone carbonyl), 6.10 (m), 6.29 (s), 6.35 (s), 6.90 (s), 6.97 (s), 7.35 (s), 7.55 (m), 7.84 (vs, aromatic ester C–O), 8.62 (s, methyl ester), 8.81 (s), 9.26 (vs), 9.39 (m), 10.36 (m), 12.25 (m), 12.50 (m), 13.33 μ (s). A portion was molecularly distilled at 0.05 mmHg. Anal. ($C_{10}H_{11}NO_3$): C, H, N.

Reaction of 2-Haloaromatic Acid Salts with π-Allylnickel Complexes. A. 2-(2-Propenyl)benzoic Acid (4a). To a solution of π-allylnickel bromide (0.56 g, 1.6 mmol, in 15 mL of DMF) was added sodium 2-bromobenzoate (0.52 g, 2.3 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 96 h. After routine isolation and purification by preparative layer chromatography (28:12:1 hexane–ether–formic acid, R_f 0.38), 0.28 g (76%) of white solid (mp 83–84 °C) was obtained: NMR ($CDCl_3$) δ 3.86 (d, J = 6 Hz, 2, $-CH_2-$), 5.07 (m, 2, $-C{=}CH_2$), 6.09 (m, 1, $-C{=}CH-$), 7.40 (m, 3, ArH), 8.00 (m, 1, ArH), 13.61 (s, 1, –COOH); IR (paraffin oil) 3.72–3.98 (br, OH), 5.92 (vs, aromatic –COOH carbonyl), 6.25 (s, aromatic C=C), 6.35 (m, aromatic C=C), 6.76 (m), 7.14 (m), 7.69 (m), 7.87 (s), 9.30 (m), 10.20 (m), 11.11 (s), 13.07 (s), 15.18 (m), 15.38 μ (m). Anal. ($C_{10}H_{10}O_2$): C, H.

B. *cis,trans*-2-(2-Butenyl)benzoic Acid (4b). To a solution of π-crotyl nickel bromide (0.55 g, 1.43 mmol, in 15 mL of DMF) was added sodium 2-bromobenzoate (0.48 g, 2.14 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 96 h. After routine isolation and purification by preparative layer chromatography (28:12:1 hexane–ether–formic acid, R_f 0.52) 0.34 g (91%) of white solid (mp 89–90 °C) was obtained: NMR ($CDCl_3$) δ 1.68 (d, J = 4 Hz, 3, $C{=}CCH_3$), 3.78 (d, J = 5 Hz, 2, $C{=}CCH_2$), 5.60 (m, 2, HC=CH), 7.39 (m, 3, ArH), 8.10 (m, 1, ArH), 12.87 (s, 1, –COOH); IR (paraffin oil) 3.74–3.94 (br, OH), 5.93 (vs, aromatic –COOH carbonyl), 6.37 (m, aromatic C=C), 6.73 (w), 6.87 (m), 7.09 (m), 7.63 (m), 7.87 (m), 9.26 (w), 10.31 (m), 10.93 (m), 13.79 μ (m). Anal. ($C_{11}H_{12}O_2$): C, H.

C. 2-(3-Methyl-2-butenyl)benzoic Acid (4c). To a solution of π-(1,1-dimethylallyl)nickel bromide (0.45 g, 1.09 mmol, in 10 mL of DMF) was added sodium 2-bromobeenzoate (0.36 g, 1.62 mmol, in 10 mL of DMF) and the mixture stirred at 50 °C for 90 h. After isolation and purification as in B, the R_f 0.41 band contained 0.27 g (87%) of the desired product as a white solid: NMR ($CDCl_3$) δ 1.95 (s, 6, $-CH_3$), 3.82 (d, J = 7 Hz, 2, $-CH_2-$), 5.40 (m, 1, C=CH), 7.40 (m, 3, ArH), 8.15 (m, 1, ArH), 12.70 (s, 1, –COOH); IR (paraffin oil) 3.70–3.95 (br, OH), 5.95 (vs, aromatic –COOH carbonyl), 6.33 (m), 6.71 (w), 6.90 (m), 7.09 (m), 7.66 (m), 7.84 (m), 9.26 (m), 10.75 (m), 13.51 μ (m).

D. 2-(2-Methyl-2-propenyl)benzoic Acid. To a solution of π-(2-methylallyl)nickel bromide (0.56 g, 1.43 mmol, in 15 mL of DMF) was added sodium 2-bromobenzoate (0.47 g, 2.13 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 120 h. After routine isolation and purification by preparative layer chromatography (28:12:1 hexane–ether–formic acid, R_f 0.42) 0.27 g (71%) of white solid (mp 66–67 °C) was obtained: NMR ($CDCl_3$) δ 1.80 (s, 3, $-CH_3$), 3.84 (s, 2, $-CH_2-$), 4.94 (m, 2, $C{=}CH_2$), 7.40 (m, 3, ArH), 8.15 (m, 1, ArH), 11.70 (s, 1, –COOH); IR (paraffin oil) 3.70–4.17 (br, OH), 5.90 (vs, aromatic –COOH carbonyl), 6.35 (s, aromatic C=C), 6.71 (s), 6.90 (s), 7.09 (s), 7.27 (m), 7.63 (s), 7.84 (s), 7.94 (m), 9.26 (m), 11.11 (s), 12.66 (m), 13.70 μ s). Anal. ($C_{11}H_{12}O_2$): C, H.

E. 2-(2-Propenyl)-4-Chlorobenzoic Acid (4d). To a solution of π-allylnickel bromide (0.43 g, 1.20 mmol, in 10 mL of DMF) was added sodium 2-iodo-4-chlorobenzoate (0.54 g, 1.79 mmol, in 10 mL of DMF) and the mixture stirred at 50 °C for 120 h. The crude product (0.38 g), a mixture of the desired compound and a small amount of unreacted starting material, was not readily separated by preparative layer chromatography. This mixture was used below.

F. 2-(2-Butenyl)-4-chlorobenzoic Acid (4e). To a solution of π-(crotyl)nickel bromide (0.58 g, 1.50 mmol, in 15 mL of DMF) was added sodium 2-iodo-4-chlorobenzoate (0.68 g, 2.24 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 111 h. The crude product (0.48 g), a mixture of the desired compound and a small amount of unreacted starting material, was not readily separable by preparative layer chromatography. This mixture was used below.

G. 2-(2-Propenyl)-5-methoxybenzoic Acid (4f). To a slurry of sodium 2-bromo-5-methoxybenzoate (0.67 g, 2.64 mmol, in 15 mL of DMF) was added π-allylnickel bromide (0.64 g, 1.77 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 96 h. The crude product (0.48 g), a mixture of the desired compound and a small amount of unreacted starting material, was not readily separable by preparative layer chromatography. This mixture was used below.

Reaction of 2-Bromobenzamides with π-Allylnickel Bromide. A. 2-(2-Propenyl)benzamide. To a solution of the nickel complex (0.68 g, 1.90 mmol, in 15 mL of DMF) was added 2-bromobenzamide (0.57 g, 2.83 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 90 h. The reaction mixture was then mixed with 30 mL of 1.2 N HCl and extracted with 4 × 50 mL of chloroform. The combined chloroform extracts were dried with $MgSO_4$ and volatiles removed via rotary evaporator. Most of the DMF was removed by evaporation at 0.05 mmHg. The residue was dissolved in 50 mL of ether, washed with 3 × 10 mL of saturated aqueous NaCl, and dried with $MgSO_4$. Upon removal of solvent the resulting crude product was purified by preparative layer chromatography (5:5:1 hexane–ether–formic acid, R_f 0.49) to give 0.27 g (59%) of a white solid (mp 122–123 °C): NMR ($CDCl_3$) δ 3.58 (d, J = 6 Hz, 2, $-CH_2-$), 5.02 (m, 2, $C{=}CH_2$), 6.08 (m, 1, $-CH{=}C-$), 6.08 (br, 2, $-NH_2$), 7.31 (m, 4, ArH); IR (paraffin oil) 2.94 (vs, $-NH_2$), 3.23 (w, monosubstituted alkene), 3.33 (w, monosubstituted alkene), 6.06 (vs, primary amide carbonyl, amide I), 6.15 (s, primary amide N–H bend, amide II), 6.25 (m, aromatic C=C), 6.33 (m, aromatic C=C), 6.99 (m), 7.17 (s), 8.77 (m), 10.00 (m), 10.99 (m), 12.99 (m, 4 adjacent ArH), 15.38 μ (m). Anal. ($C_{10}H_{11}NO$): C, H, N.

B. 2-(2-Propenyl)-*N*-methylbenzamide. To a solution of π-allylnickel bromide (0.42 g, 1.17 mmol, in 15 mL of DMF) was added 2-bromo-*N*-methylbenzamide (0.37 g, 1.73 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 70 h. After routine isolation and purification by preparative layer chromatography (5:5:1 hexane–ether–formic acid, two developments, R_f 0.52) 0.21 g (70%) of a white solid (mp 55–57 °C) was obtained: NMR ($CDCl_3$) δ 2.84 (d, 3, NCH_3), 3.61 (d, J = 6 Hz, 2, $-CH_2-$), 5.00 (m, 2, $-C{=}CH_2$), 5.95 (m, 1, $-CH{=}C-$), 6.98 (br, 1, NH), 7.08 (m, 4, ArH); IR (neat) 3.03 (s, N–H), 3.24 (w, monosubstituted alkene), 3.36 (w, C–H), 6.10 (s, secondary amide carbonyl, amide I), 6.23 (m), 6.45 (s, secondary amide N–H bend, amide II), 7.07 (m), 7.52 (m), 7.87 (m), 8.47 (w), 9.09 (m), 9.76 (m), 10.99 (m), 12.50 (m), 13.33 (m, 4 adjacent ArH), 14.29 μ (m).

General Procedure for the Preparation of 3-Methylisocoumarins from 2-Acetonylaromatic Esters. A twofold excess of NaH (as a 50% dispersion) was weighed out in a 50-mL three-neck flask. After addition of a magnetic stirring bar, the flask was fitted with a serum cap, stopper, and stopcock, and the system flushed with argon. The NaH dispersion was washed twice with argon-saturated hexane and the residue pumped to dryness. The system was then filled with argon and the desired amount of argon-saturated benzene added. Under a slow stream of argon, the serum cap was replaced by a reflux condensor and the substrate, followed by 3–4 drops of *tert*-butyl alcohol, added via syringe through the condensor. The resulting mixture was then refluxed overnight, cooled to room temperature, and poured into 50 mL of 1.2 N HCl which was previously saturated with NaCl. The aqueous layer was separated and extracted with 3 × 50 mL of ether and the combined organic extracts dried over anhydrous $MgSO_4$. After removal of solvent via rotary evaporator, the crude product was purified by preparative layer chromatography.

A. 3-Methylisocoumarin (3a). Using the procedure described above, methyl 2-acetonylbenzoate (0.19 g, 1.0 mmol), NaH (0.05 g, 2.0 mmol), and 2 drops of *tert*-butyl alcohol in 30 mL of benzene were refluxed for 19 h. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.56), 0.13 g (81%) of a white, crystalline solid (mp 71–71.5 °C)[3a] was obtained with NMR and IR spectra identical with those reported for this compound prepared by a different route.[38]

B. 3-Methyl-6,7-dimethoxyisocoumarin (3b). Methyl 2-acetonyl-4,5-dimethoxybenzoate (0.26 g, 1.02 mmol), NaH (0.05 g, 2.04 mmol), and 2 drops of *tert*-butyl alcohol in 27 mL of benzene was refluxed for 79 h. After routine isolation and purification by preparative layer chromatography (20:1 chloroform–methanol, R_f 0.67) 0.15 g (67%) of a pale yellow solid (mp 134–135 °C)[5] was obtained: NMR (acetone-d_6) δ 2.22 (s, 3, $-CH_3$), 3.93 (s, 3, $-OCH_3$), 3.96 (s, 3, $-OCH_3$), 6.34 (s, 1, CH=C), 6.92 (s, 1, ArH), 7.50 (s, 1, ArH); IR (paraffin oil) 5.88 (vs, α,β-unsaturated δ-lactone carbonyl), 6.02 (m, cyclic six-membered vinyl ether C=C stretch), 6.21 (m), 6.37 (m), 6.64 (s), 7.22 (m), 7.38 (m), 7.91 (s), 8.06 (m, asymmetric C–O–C stretch), 8.26 (m), 8.58 (m), 8.77 (m), 9.35 (s, symmetric C–O–C stretch), 9.90 (m), 10.20 (w), 11.36 (m), 10.90 (w), 12.82 (w), 13.07 μ (m).

C. 3-Methyl-6-chloroisocoumarin (3c). Methyl 2-acetonyl-4-chlorobenzoate (0.30 g, 1.34 mmol), NaH (0.07 g, 2.68 mmol), and 2 drops of *tert*-butyl alcohol in 30 mL of benzene were refluxed for 24 h. After routine isolation and purification by preparative layer

chromatography (20:1 benzene–ether, R_f 0.42) 0.19 g (71%) of colorless needles (mp 154–155 °C) was obtained. This compound was identical in all respects with that prepared from 2-(2-propenyl)-4-chlorobenzoic acid (see below).

D. 7-Methyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (7). Methyl 2-acetonyl-3-pyridinecarboxylate (0.12 g, 0.63 mmol), NaH (0.03 g, 1.26 mmol), and 2 drops of *tert*-butyl alcohol were refluxed in 35 mL of benzene for 24.5 h. The reaction mixture was then cooled to room temperature and acidified with 1.2 N HCl. The resulting mixture was made basic with Na_2CO_3, the aqueous layer saturated with NaCl, and the organic layer separated. Extraction of the aqueous layer with 3 × 50 mL of ether, drying of the organic layers with $MgSO_4$, and removal of solvent gave the crude product which was recrystallized from petroleum ether to give 62 mg (61%) of **7** as bright yellow crystals (mp 105–106 °C): NMR ($CDCl_3$) δ 2.40 (s, 3, $-CH_3$), 6.61 (s, 1, CH=C), 7.40, 8.52, 9.10 (AMX, 3, ArH); IR (paraffin oil) 5.75 (s, α,β-unsaturated δ-lactone carbonyl), 5.80 (sh), 6.02 (s, six-membered cyclic vinyl ether C=C), 6.29 (m, aromatic C=C), 6.39 (m, aromatic C=C), 6.76 (vs), 7.66 (m), 7.84 (m), 8.23 (m), 8.70 (m), 9.39 (m), 9.57 (m), 10.36 (m), 11.90 (m), 12.99 (m), 14.08 μ. Anal. ($C_9H_7NO_2$): C, H, N.

General Procedure for the Preparation of 3-Methyl-3,4-dihydroisocoumarins from 2-Acetonylaromatic Esters. The method of Tirodkar and Usgaonkar[5] was used without alteration.

Reaction of 2-Acetonylaromatic Esters with Sodium Borohydride. A. (±)-3-Methyl-3,4-dihydroisocoumarin (3'a). Methyl 2-acetonylbenzoate (0.31 g, 1.61 mmol) and $NaBH_4$ (0.20 g, 5.34 mmol) were stirred at 25 °C in 10 mL of methanol for 2 h. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.44) 0.20 g (75%) of pale yellow oil was obtained which was identical with the product described below prepared in a different manner.

B. (±)-3-Methyl-6,7-dimethoxy-3,4-dihydroisocoumarin (3'b). Methyl 2-acetonyl-4,5-dimethoxybenzoate (0.30 g, 1.19 mmol) and $NaBH_4$ (0.20 g, 5.24 mmol) were stirred at 25 °C in 10 mL of methanol for 2 h. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.35) 0.21 g (81%) of white solid (mp 105–106 °C, lit.[5] 104–105 °C) was obtained: NMR (acetone-d_6) δ 1.46 (d, J = 6 Hz, 3, $-CH_3$), 2.90 (d, J = 6 Hz, 3, $-CH_3$), 3.84 (s, 3, $-OCH_3$), 3.88 (s, 3, $-OCH_3$), 4.68 (m, 1, C–H), 6.94 (s, 1, ArH), 7.44 (s, 1, ArH); IR (paraffin oil) 5.83 (vs, α,β-unsaturated γ-lactone carbonyl), 6.21 (m), 6.60 (s), 7.33 (m), 7.60 (s), 7.84 (s), 8.00 (m, asymmetric C–O–C stretch), 8.20 (m), 8.55 (m), 9.30 (vs, symmetric C–O–C stretch), 11.30 (m), 12.20 (w), 12.90 μ (m).

C. (±)-3-Methyl-6-chloro-3,4-dihydroisocoumarin (3'c). Methyl 2-acetonyl-4-chlorobenzoate (0.14 g, 0.62 mmol) and $NaBH_4$ (0.08 g, 2.05 mmol) were stirred in 10 mL of methanol at 25 °C for 2 h. After routine isolation and purification by preparative layer chromatography (28:12:1 hexane–ether–formic acid, R_f 0.20) 0.11 g (94%) of white solid (mp 84–85.5 °C) was obtained: NMR (acetone-d_6) δ 1.49 (d, J = 6 Hz, 3, $-CH_3$), 3.07 (m, 2, $-CH_2-$), 4.74 (m, 1, CH=C), 7.44 (m, 2, ArH), 8.00 (d, J = 4 Hz, 1, ArH); IR (paraffin oil) 5.81 (vs, α,β-unsaturated δ-lactone carbonyl), 5.85 (sh), 6.25 (s), 7.46 (m), 7.84 (s), 8.10 (w), 8.70 (w), 8.93 (m), 9.13 (m), 9.39 (w), 9.66 (m), 10.47 (m), 11.43 (w), 11.70 (m), 11.90 (w), 12.99 (m), 14.71 μ (m). Anal. ($C_{10}H_9ClO_2$): C, H, Cl.

General Procedure for the Preparation of Isocoumarins from 2-Alkenylbenzoic Acids. The desired acid in THF (10 mL/mmol) was stirred with a slight excess of $PdCl_2{\cdot}2CH_3CN$ at 25 °C for 5–10 min, after which time a homogeneous brown solution resulted. Anhydrous Na_2CO_3 (0.5 mmol excess) was added and the resulting mixture stirred at 25 °C for 3–4 h. The reaction mixture was then filtered to remove palladium metal, and the solvent stripped by rotary evaporator to yield a crude product which was purified by preparative layer chromatography.

Reaction of 2-Alkenylbenzoic Acids with Palladium Chloride and Sodium Carbonate. A. 3-Methylisocoumarin (5a). To a stirred solution of 2-(2-propenyl)benzoic acid (0.20 g, 1.23 mmol) and $PdCl_2{\cdot}2CH_3CN$ (0.32 g, 1.24 mmol) in 15 mL of THF was added Na_2CO_3 (0.19 g, 1.78 mmol) and the resulting mixture stirred at 25 °C for 3 h. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.69) 0.17 g (86%) of white solid was obtained identical in all respects with material prepared as above, and by yet a different route.[38]

B. 3-Ethylisocoumarin (5b). The reaction was run as in A using 2-(2-butenyl)benzoic acid (0.18 g, 1.0 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.26 g, 1.0 mmol), and Na_2CO_3 (0.16 g, 1.50 mmol) in 10 mL of THF. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.64) 0.15 g (86%) of a colorless solid (mp 76–77 °C, lit. 76–77 °C)[3e] was obtained: NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3, $-CH_3$), 2.60 (q, J = 7 Hz, 2, $-CH_2-$), 6.32 (s, 1, $-C$=CH), 7.50 (m, 3, ArH), 8.22 (m, 1, ArH); IR (paraffin oil) 5.68 (sh, γ,δ-unsaturated δ-lactone carbonyl), 5.80 (s, α,β-unsaturated δ-lactone carbonyl), 6.02 (s, six-membered cyclic vinyl ether C=C stretch), 6.23 (m), 6.37 (m), 6.76 (s), 7.52 (m), 7.81 (m), 8.33 (m), 8.62 (s), 8.77 (m), 9.26 (m), 9.62 (m), 9.71 (s), 10.64 (m), 12.05 (s), 13.07 (s), 14.60 μ (s).

C. 3-(Isopropyl)isocoumarin (5c). The reaction was run as in A using 2-(3-methyl-2-butenyl)benzoic acid (0.17 g, 0.88 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.23 g, 0.88 mmol), and Na_2CO_3 (0.11 g, 1.0 mmol) in 12 mL of THF, except that the mixture was stirred for 4 h. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.67) 0.16 g (96%) of a pale yellow oil was obtained: NMR ($CDCl_3$) δ 1.29 (d, J = 7 Hz, 6, $-CH_3$), 2.80 (m, 1, CH), 6.25 (s, 1, C=CH), 7.50 (m, 3, ArH), 8.22 (m, 1, ArH); IR (neat) 3.23–3.45 (s, C–H), 5.76 (s, α,β-unsaturated δ-lactone carbonyl), 6.02 (s, six-membered cyclic vinyl ether C=C), 6.21 (m), 6.35 (m), 6.71 (s), 6.85 (m), 7.35 (m), 7.46 (m), 7.52 (m), 7.63 (m), 8.00 (m), 8.26 (m), 8.62 (m), 8.85 (s), 9.01 (m), 9.30 (s), 9.52 (m), 9.80 (s), 10.42 (s), 11.36 (m), 12.05 (m), 13.16 (s, four adjacent ArH), 14.49 μ (s). Anal. ($C_{12}H_{12}O_2$): C, H.

D. 3-Methyl-6-chloroisocoumarin (5d). The reaction was run as in A using the crude product obtained above (0.31 g, ca. 1.55 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.40 g, 1.55 mmol), and Na_2CO_3 (0.20 g, 1.91 mmol) in 15 mL of THF, except that the mixture was stirred for 4 h. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.67) 0.18 g (63% from sodium 2-iodo-4-chlorobenzoate) of white solid (mp 155–156 °C) was obtained: NMR ($CDCl_3$) δ 2.34 (s, 3, $-CH_3$), 6.25 (s, 1, C=CH), 7.40 (m, 3, ArH), 8.22 (m, 1, ArH); IR (paraffin oil) 5.68 (vs, γ,δ-unsaturated δ-lactone carbonyl), 5.90 (w), 6.02 (s, cyclic six-membered vinyl ether C=C stretch), 6.23 (s), 6.41 (m), 6.78 (m), 7.09 (m), 7.19 (m), 7.46 (s), 7.60 (m), 8.62 (s), 9.17 (m), 9.48 (m), 10.00 (m), 10.20 (m), 11.11 (m), 11.36 (m), 11.56 (m), 11.90 (m), 12.27 (m), 12.90 (m), 14.71 μ (m). Anal. ($C_{10}H_7ClO_2$): C, H, Cl.

E. 3-Ethyl-6-chloroisocoumarin (5e). The reaction was run as in D, using the crude product obtained above (0.45 g, ca. 2.12 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.55 g, 2.12 mmol), and Na_2CO_3 (0.27 g, 2.53 mmol) in 20 mL of THF. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.70) 0.23 g (54% from sodium 2-iodo-4-chlorobenzoate) of white solid (mp 94–95 °C) was obtained: NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3, $-CH_3$), 2.62 (q, J = 7 Hz, 2, $-CH_2-$), 6.25 (s, 1, C=CH), 7.40 (m, 3 H, ArH), 8.20 (d, J = 9 Hz, 1, ArH); IR (paraffin oil) 5.70 (s), 5.81 (vs, α,β-unsaturated δ-lactone carbonyl), 5.92 (w), 6.02 (w, cyclic six-membered vinyl ether C=C stretch), 6.25 (m), 6.41 (w), 7.33 (m), 7.58 (w), 8.06 (w), 8.70 (m), 9.26 (m), 9.71 (m), 10.70 (w), 11.24 (w), 12.99 μ (m). Anal. ($C_{11}H_9ClO_2$): C, H, Cl.

F. 3-Methyl-7-methoxyisocoumarin (5f). The reaction was run as in A using crude 2-(2-propenyl)-5-methoxybenzoic acid (0.40 g, ca. 1.5 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.39 g, 1.51 mmol), and Na_2CO_3 (0.21 g, 2.0 mmol) in 10 mL of THF. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.61) 0.28 g (65% from sodium 2-bromo-5-methoxybenzoate) of a pale yellow solid (mp 93–94 °C, lit.[5] 93–94 °C) was obtained: NMR ($CDCl_3$) δ 2.30 (s, 3, $-CH_3$), 3.94 (s, 3, $-OCH_3$), 6.26 (s, 1, C=CH), 7.31 (d, J = 2 Hz, 2, ArH), 7.50 (s, 1, ArH); IR (paraffin oil) 5.62 (w), 5.75 (sh), 5.81 (s, α,β-unsaturated δ-lactone carbonyl), 6.02 (m, cyclic six-membered vinyl ether C=C stretch), 6.17 (m), 6.67 (s), 6.85 (m), 7.41 (s), 7.75 (m), 7.81 (m), 8.06 (s), 8.62 (m), 9.39 (s), 9.71 (s), 10.26 (m), 11.24 (m), 11.83 (s), 12.90 (m), 14.29 μ (m).

G. Isocoumarin (1). To a stirred solution of 2-vinylbenzoic acid (0.22 g, 1.46 mmol) and $PdCl_2{\cdot}2CH_3CN$ (0.38 g, 1.46 mmol) in 10 mL of THF was added Na_2CO_3 (0.16 g, 1.47 mmol) and the resulting mixture stirred for 2 h at 25 °C. An additional portion (0.08 g, 0.75 mmol) of Na_2CO_3 was added and the reaction mixture stirred for an additional 1 h. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether) two major products were obtained.

Compound 1: R_f 0.59; 45 mg (21%) of yellow solid; NMR ($CDCl_3$) δ 5.28 (s, 2, $C=CH_2$), 7.78 (m, 4, ArH); IR (paraffin oil) 5.56 (sh, five-membered unsaturated lactone carbonyl, due to double bond adjacent to –O–), 5.62 (s, five-membered unsaturated lactone carbonyl), 5.71 (sh, five-membered unsaturated lactone carbonyl due to double bond adjacent to carbonyl), 5.78 (sh), 5.99 (s, alkene adjacent to –O–), 6.76 (s), 7.43 (m), 7.84 (s), 8.40 (w), 8.99 (m), 9.13 (m), 9.90 (s), 10.53 (s), 11.30 (m), 11.63 (m), 12.90 (m), 13.05 (s), 14.49 μ (s). From spectral data, this compound is 3-methylenephthalide (**8**). Upon reduction (H_2/Pd) the δ 5.28 singlet was replaced by signals at δ 1.75 (d, J = 7 Hz, 3, CH_3), 5.60 (q, J = 7 Hz, 1, CH), 7.50 (m, 4, ArH).

Compound 2: R_f 0.47; 0.13 g (62%) of a pale yellow solid (mp 46–47

°C, lit.[39] 46–47 °C); with IR and NMR spectra identical with those reported for isocoumarin.[39]

H. (±)-3-(Isopropenyl)phthalide (9). A slurry of 2-(2-propenyl)benzoic acid (0.21 g, 1.21 mmol) and $PdCl_2$·$2CH_3CN$ (0.32 g, 1.23 mmol) was stirred in 15 mL of THF at 25 °C for 1 h. Na_2CO_3 (0.16 g, 1.56 mmol) was then added and the mixture stirred for an additional 4 h. After routine isolation and purification by preparative layer chromatography (22:3 benzene–ether, R_f 0.52), 0.07 g (31%) of **9**, a white solid (mp 56–57 °C), was obtained: NMR ($CDCl_3$) δ 1.78 (d, J = 1 Hz, 3, $-CH_3$), 5.32 (m, 2, $C{=}CH_2$), 5.87 (s, 1, CH), 7.64 (m, 4, ArH); IR (paraffin oil) 5.65 (vs, α,β-unsaturated γ-lactone carbonyl), 6.21 (m), 6.23 (m), -6.80 (s), 7.69 (s), 7.81 (s), 8.26 (m), 9.01 (m), 9.13 (m), 9.35 (s), 9.85 (m), 10.00 (m), 10.36 (s), 12.50 μ (w).

Preparation of 3-Methylisocoumarin Using a Catalytic Amount of Palladium Chloride. A slurry of 2-(2-propenyl)benzoic acid (0.30 g, 1.86 mmol), $PdCl_2$·$2CH_3CN$ (0.011 g, 0.04 mmol), $Cu(OAc)_2$·H_2O (0.19 g, 0.93 mmol), and Na_2CO_3 (0.21 g, 2.00 mmol) in 25 mL of THF was refluxed for 119 h. Oxygen was bubbled through the mixture during the entire period. Saturated aqueous Na_2SO_3 (50 mL) was added to destroy any peroxides, and the organic products extracted with 5 × 40 mL of ether and dried with $MgSO_4$. Removal of solvent by rotary evaporator gave the crude product which was purified by preparative layer chromatography (20:1 benzene–ether, R_f 0.55) to give 0.12 g (1900% based on palladium chloride, 41% based on the alkenyl acid) of 3-methylisocoumarin.

(±)-3-Methyl-3,4-dihydroisocoumarin via $PdCl_2$ Cyclization. A slurry of 2-(2-propenyl)benzoic acid (0.24 g, 1.49 mmol), $PdCl_2$·$2CH_3CN$ (0.39 g, 1.49 mmol), and Na_2CO_3 (0.21 g, 2.0 mmol) in 15 mL of THF was stirred at 25 °C for 5 h. A hydrogen-filled balloon was then affixed and the reaction mixture was stirred at 50 °C for 16 h. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.58) 0.16 g (65%) of pale yellow oil was obtained: NMR ($CDCl_3$) δ 1.46 (d, J = 7 Hz, 3, $-CH_3$), 2.91 (d, J = 7 Hz, 2, $-CH_2-$), 4.57 (m, 1, CH), 7.26 (m, 3, ArH), 8.00 (m, 1, ArH); IR (neat) 3.27–3.56 (m, C–H), 5.81 (vs, α,β-unsaturated δ-lactone carbonyl), 6.23 (m), 6.87 (m), 7.25 (m), 7.41 (m), 7.84 (vs), 8.10 (s, C–O), 8.97 (s, C–O), 9.26 (m), 9.62 (m), 9.76 (m), 10.53 (m), 11.25 (m), 12.58 (m), 13.61 (s, four adjacent ArH), 14.08 (m), 14.71 μ (m). Anal. ($C_{10}H_{10}O_2$): C, H.

Reaction of 2-Alkenylbenzamides with Palladium Chloride and Sodium Hydride. A. 3-Methylisocarbostyril. 2-(2-Propenyl)-benzamide (0.16 g, 1.0 mmol), $PdCl_2$·$2CH_3CN$ (0.26 g, 1.0 mmol), and NaH (0.04 g, 1.65 mmol) in 12 mL of THF was stirred at 25 °C for 4 h. After routine isolation and purification by preparative layer chromatography (triethylamine, R_f 0.57) 0.11 g (68%) of white solid was obtained with identical IR, NMR spectra, and melting point with authentic material.[38]

B. 3-Methyl-*N*-methylisoquinolone. 2-(2-Propenyl)-*N*-methylbenzamide (0.16 g, 0.90 mmol), $PdCl_2$·$2CH_3CN$ (0.24 g, 0.93 mmol), and NaH (0.03 g, 1.25 mmol) in 10 mL of THF was stirred at 25 °C for 4 h. After routine isolation and purification by preparative layer chromatography (10:1 chloroform–methanol, R_f 0.48) 0.14 g (91%) of a colorless solid (mp 102–103 °C, lit.[40] 102–103 °C) was obtained: NMR ($CDCl_3$) δ 2.39 (s, 3, CCH_3), 3.54 (s, 3, NCH_3), 6.31 (s, 1, C=CH), 7.76 (m, 4, ArH); IR (paraffin oil) 6.06 (s, α,β-unsaturated δ-lactam), 6.15 (s), 6.21 (m), 6.71 (m), 7.04 (m), 7.43 (m), 7.63 (m), 7.75 (m), 8.62 (m), 9.62 (w), 9.90 (w), 11.36 (w), 12.05 (m), 13.25 (m), 14.49 μ (m).

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