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Synthesis of heterocycles via carbonylation or olefination of organopalladium intermediates

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SYNTHESIS OF HETEROCYCLES VIA CARBONYLATION OR OLEFINATION OF ORGANOPALLADIUM INTERMEDIATES

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Synthesis of heterocycles via carbonylation or olefination of organopalladium intermediates

by

Constance Anne Fellows

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I. GENERAL INTRODUCTORY NOTE

Synthetic organic chemists who prepare biologically active compounds for medicinal or agricultural purposes normally use naturally occurring compounds of known activity as a starting point. Total syntheses of these compounds are developed, and structural analogs are made in the hope of finding even more potent agents with fewer undesirable side effects. The industrial research chemist must then find ways of simplifying and streamlining his procedures so that these compound classes can be produced cheaply and in high volume for testing and for eventual marketing. Here one can invoke the guiding maxim of Nobel laureate H. C. Brown, who believes that nature is basically simple [1]. There are many ways of simplifying synthetic routes, and often the judicious use of catalysts can accomplish this.

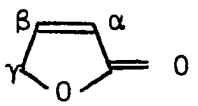
Since many classes of biologically active compounds include oxygen-containing ring systems [2], we have attempted to develop a unified synthetic strategy for the production of certain ring systems using a palladium catalyst. The following chapters of this dissertation will describe the syntheses of these various heterocycles. First, butenolides were prepared by mercuration and carbonylation of propargylic alcohols; the carbonylations were effected using a catalytic amount of palladium chloride. Second, phthalides and

3,4-dihydroisocoumarins were prepared by thallation and palladium chloride-catalyzed carbonylation of benzyl and β-phenethyl alcohols. Similarly, cyclic aryl acid anhydrides and imides were made by thallation and subsequent carbonylation of the corresponding aryl acids and amides. Finally, the production of isocoumarins, benzoxepins, and other heterocycles by thallation and palladium-assisted olefination of aryl substrates was explored. For most of the compound classes studied, our method, which employs organometallic intermediates, is significantly shorter and more efficient than most older methods.

II. SYNTHESIS OF β-CHLORO-$\Delta^{\alpha,\beta}$-BUTENOLIDES VIA MERCURATION-CARBONYLATION OF PROPARGYLIC ALCOHOLS

A. Introduction

Unsaturated five-membered ring lactones occur in many natural products [2]. They have been called "butenolides" since 1898 [3], with Greek letters used to denote the position of the double bond. Thus, compound 1 is $\Delta^{\alpha,\beta}$-butenolide, while 2 is $\Delta^{\beta,\gamma}$-butenolide. Many authors also use the term



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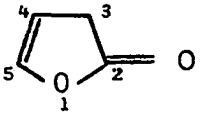
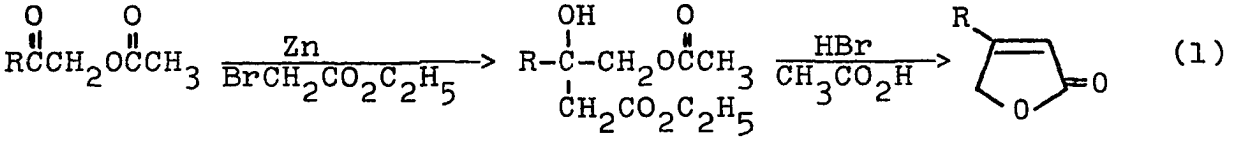


2

"crotonolactones". To avoid confusion, Chemical Abstracts recently adopted the furanone nomenclature; they list compound 1 as 2(5H)-furanone, and 2 as 2(3H)-furanone. Two extensive reviews have detailed the syntheses and reactions of such furanones [4,5]. The Reformatsky reaction of acetoxy ketones or acetylenic carbonyl compounds with bromoacetic ester appears to be the most widely used route to 2(5H)-furanones (eqs. 1,2). There are literally dozens of other



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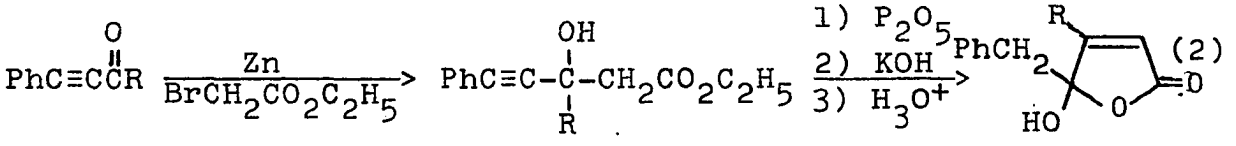
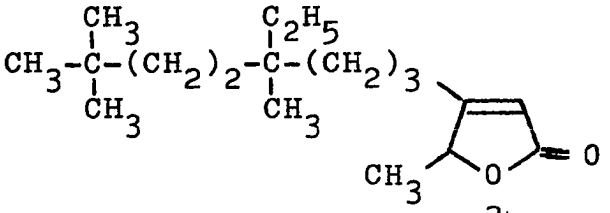


(2)

methods for the synthesis of furanones, including thermal rearrangements, Darzens-type condensations [4,5], and the carbonylation of acetylenes [6,7]; these are covered exhaustively in the reviews mentioned.

Butenolides are found in many different plant species, ranging from the simple metabolites of molds and yeasts [8] to the steroidal glycosides extracted from the foxglove (Digitalis) and from members of other plant families [9]. Amongst animals, sponges [10] and insects [11] are known to produce butenolides. Butenolides exhibit an unusually wide range of biological activity, which some examples will illustrate. Compound 3 is a patented insecticide [12].



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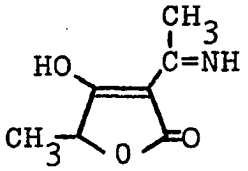
Effective lethal doses range from 0.1 µg to 25 µg per insect. Compound 4, 3-(α-iminoethyl)-5-methyl-tetronic acid, is a chlorophyll inhibitor and herbicide [13,14]. Cucumber and



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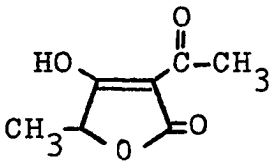
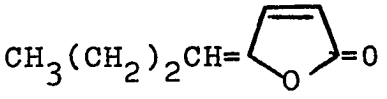


5

wheat seeds treated with 4 failed to develop normally, producing yellow leaves. These later turned white, and the plants died. However, 3-acetyl-5-methyl-tetronic acid, 5, actually stimulates seedling development in wheat [14]. Certain butenolides show marked antifungal activity [15], for example, compounds 6-9, and some are especially useful for



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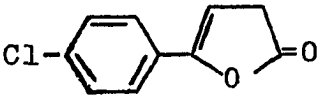

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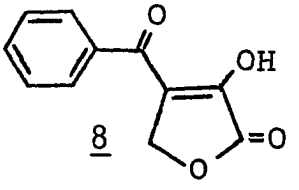

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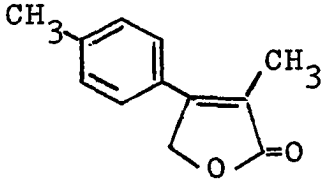
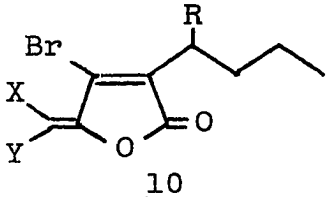


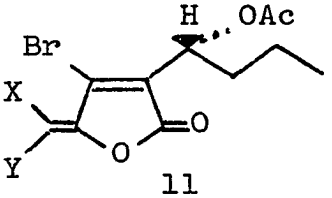
9

controlling fungus diseases in plants. Compound 9 prevents rice blast infections [16]. Recently a new class of halogenated butenolides 10 has been isolated from the red seaweed Delisea fimbriata [17,18]. The most active of these, acetoxyfimbrolides 11, show significant antifungal and



10

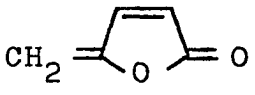
R = OAc, OH, H
X,Y = H, Cl, Br, I



11

X,Y = H, Cl, Br, I

antimicrobial activity. Other butenolides are powerful antibiotics. Protoanemonin, 12, shows antibacterial activity against Gram-positive, Gram-negative, and acid-fast bacteria, while penicillic acid, 13, is fifty times more powerful than penicillin against Gram-negative bacteria; compound 14 is thirty times as active in this respect as 13 [19]. Vitamin C,



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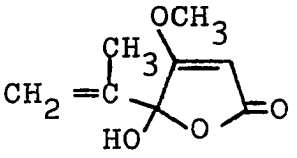

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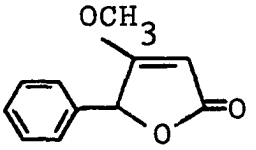
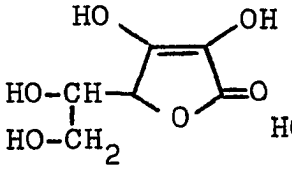


14

15, is probably the most important naturally occurring butenolide [8]. Quite recently, the novel iridoid-type glucoside antitumor agent penstemide, 16, was isolated from Penstemon Deutus Dougl. ex Lindl. (Scrophulariaceae). Possessing an unusual spiro butenolide structure, it is closely related to the antibiotic plumericin, 17 [20].



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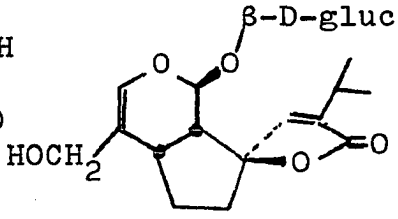

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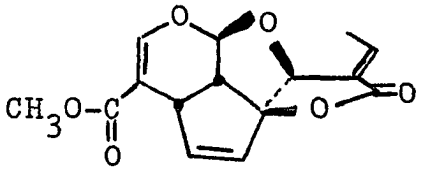
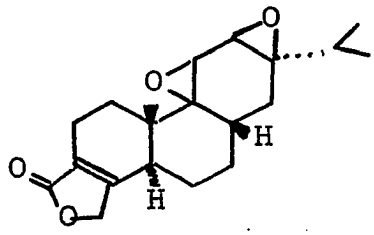


17

Cytotoxic agent stemolide, 18, [21,22] contains a butenolide ring, as do the antileukemic agents triptolide, 19, and tripdiolide, 20 [23-25]. Compounds 21 [26], 22, and 23 [27]



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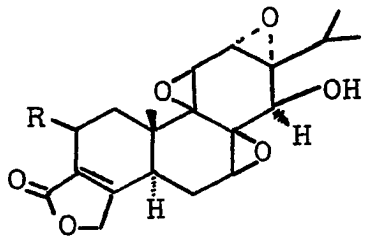
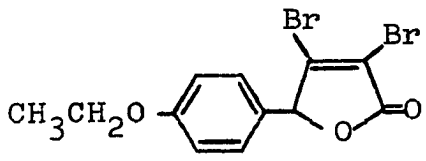


19, R = H

20, R = OH

show antineoplastic activity. Amongst the most interesting



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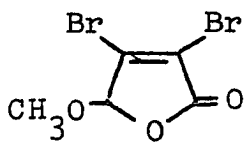

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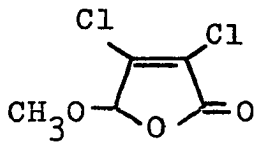
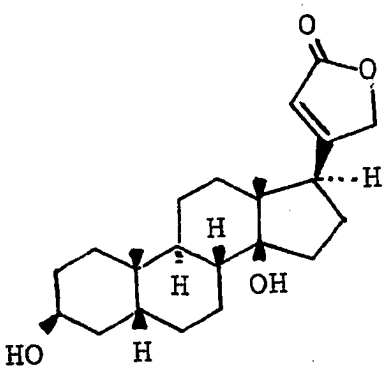


23

butenolides are the cardiotonic glycosides, which increase the intensity but decrease the rate of heartbeat. Their steroidal aglycons (genins) are usually convulsive poisons. The cardiac glycosides or their aglycons are called cardenolides. For example, extracts of Digitalis purpurea and Digitalis lanata yield a number of physiologically active glycosides, many of which gave digitoxigenin, 24, as

the aglycon. The chemistry of strophanthidin (3β,5β,14β-trihydroxy-19-oxo-5β-card-20(22)-enolide), 25, the aglycon from Strophanthus glycosides, is perhaps the best studied



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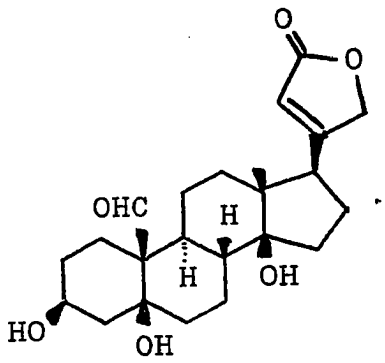
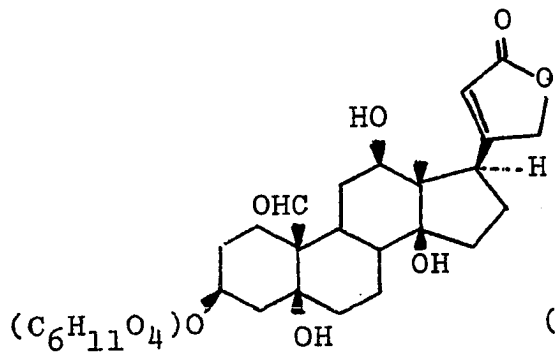


25

of these compounds [9]. Convallotoxin, the α-L-rhamnopyranoside of strophanthidin, is the most potent known cardenolide, and is obtained from lily of the valley. Two other similar compounds, antiarin, 26, and ouabain, 27, were long used by various tribes as arrow poisons. Antiarin is found in the



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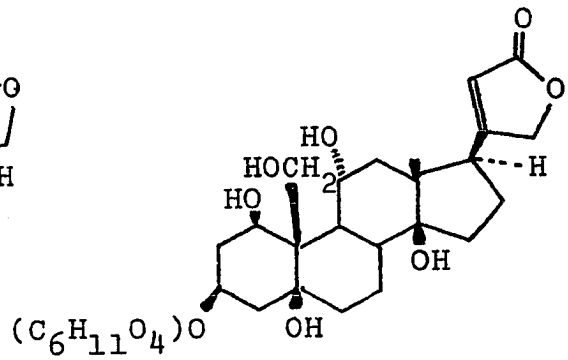
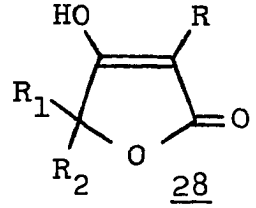


27

latex of the upas tree, Antiaris toxicaria, native to Malaya, and ouabain is found in the ouabaio tree, native to south Africa [9]. Certain insects manufacture cardenolides as chemical weapons [28]. Since butenolides are found in so many different biologically active compounds, especially in the cardenolides and the tetronic acids [8], 28, it is not



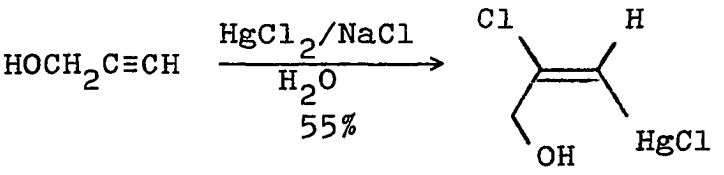
28

surprising that there has been considerable research effort directed towards the synthesis of these compounds [4,5,29-33]. We have examined the carbonylation of vinylmercurials derived from propargylic alcohols and found this to provide a novel new route to butenolides.

B. Results and Discussion

1. Preparation and carbonylation of β-chloro-γ-hydroxyvinylmercurials

In 1949, Nesmeyanov and Kochetkov reported that propargyl alcohol and certain substituted propargylic alcohols will react readily with saturated aqueous solutions of mercuric chloride and sodium chloride to give the trans addition products, β-chloro-γ-hydroxyvinylmercurials (eq. 3) [34]. More recently, Larock reported that palladium-promoted



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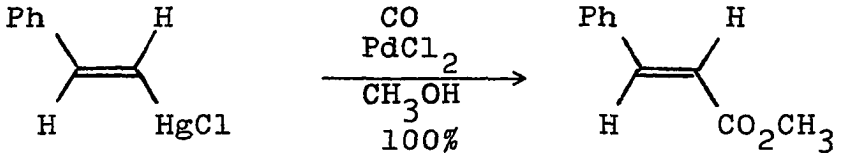
carbonylation of such vinylmercurials affords α,β-unsaturated esters and lactones in high yields (eqs. 4,5) [35]. The



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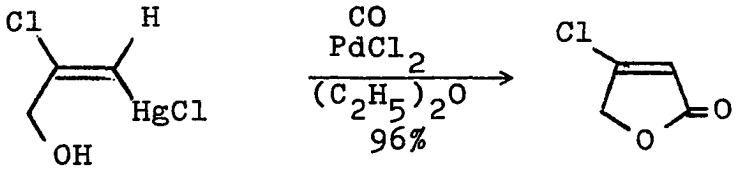
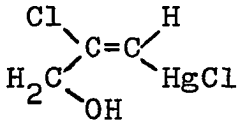
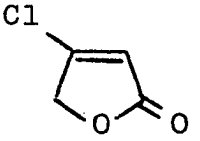
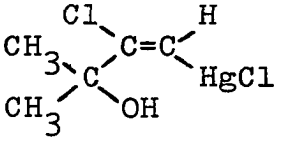
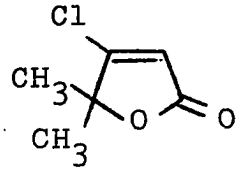
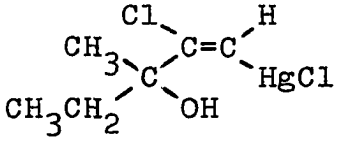
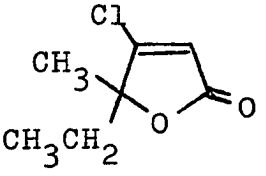
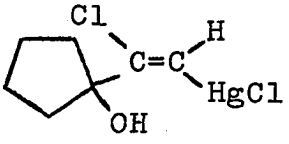
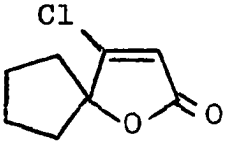
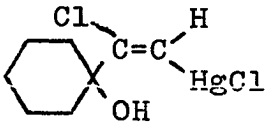
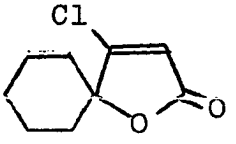


(5)

full scope of both the mercuration and the carbonylation reactions was examined by Dr. Bernhard Riefling, who used numerous propargylic alcohols and various carbonylation conditions [36,37]. Although many mercuration reactions failed, and the yields were often low, the mild reaction conditions and great ease with which the reactions could be run encouraged further examination of this route to butenolides. Riefling's results are summarized in Table I.

Preparation of the hydroxyvinylmercuric chloride derived from 1-ethynylcycloheptanol (entry 6 in Table I) (eq. 6) caused considerable trouble for Riefling, in that it was

Table I. Synthesis of butenolides via carbonylation[a]

Entry	Mercurial	Butenolide	MgO[b]	% Yield[c]
1			-	(96)[d]
2			- +	92 99(88)
3			+	98
4			+	99
5			- +	58 95(92)

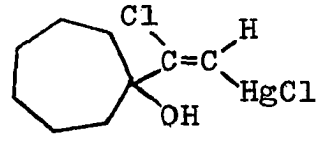
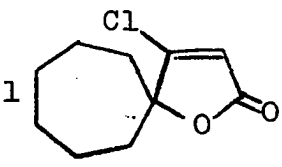
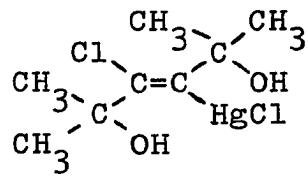
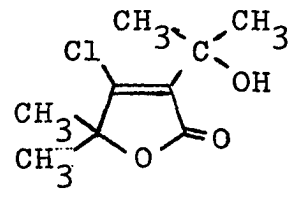
[a]One mmol mercurial, one mmol $PdCl_2$, 2 mmol LiCl, 10 ml THF, 5°C, 24 hr.

[b]One mmol or none.

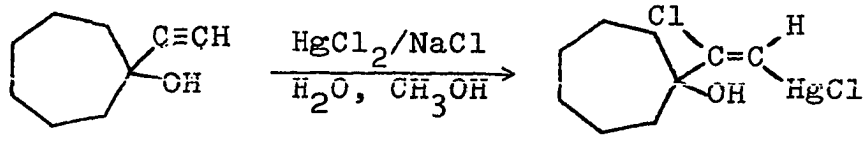
[c]Yields determined by GLC using an internal standard (isolated yields on a five mmol scale).

[d]See reference 35.

Table I. (Continued)

Entry	Mercurial	Butenolide	MgO[b]	% Yield[c]
6			+	81
7			+	94[e]

[e]Reaction run at reflux.



(6)

nearly impossible to isolate this material as a crystalline compound. The problem appeared to be due to the insolubility of the starting alcohol in the saturated $HgCl_2/NaCl$ solution, even when methanol was used as a co-solvent. Further experimentation showed that the problem could be solved if larger quantities of methanol were used to dissolve the

cycloheptanol, and then correspondingly larger amounts of the saturated aqueous solution were employed to render the vinylmercurial insoluble. Crystalline vinylmercurial was isolated successfully in this fashion.

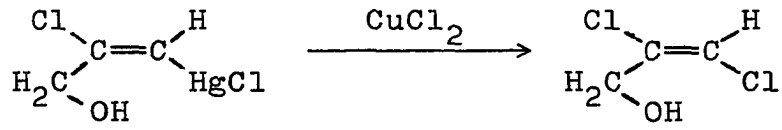
Riefling's experiments showed that carbonylations were best run in a cold room at 0-5°C, using one equivalent of palladium chloride, two equivalents of anhydrous lithium chloride, and one atmosphere of carbon monoxide, and that carbonylation proceeded well in most any solvent. Tetrahydrofuran (THF) was used for most reactions because of the greater solubility of the mercurials in this solvent. Examination of the effect of several solvents on the overall yield and the rate of lactone formation demonstrated that solvent polarity made little difference in the former, but dramatically affected the latter. The more polar solvents gave faster reactions; for example, upon carbonylation of the mercurial derived from 2-methyl-3-butyn-2-ol (entry 2 in Table I), a 99% yield was obtained in methanol after only four hours at 5°C, while an 82% yield was obtained in hexane only after 52 hours at room temperature.

Addition of certain inorganic bases and drying agents such as potassium carbonate, calcium oxide, and magnesium oxide greatly increased the yields of lactones obtained from tertiary propargyl alcohols (see entry 5 in Table I). There are two plausible explanations why the yields were lower

without these reagents. The first is that the one equivalent of HCl generated during lactonization reacted with the tertiary allylic alcohol present in the starting material. The second assumes that palladium chloride so strongly coordinated to the alcohol group that it was no longer able to undergo rapid transmetallation with the mercurial moiety. The inorganic bases either reacted with the HCl or coordinated the hydroxy group more strongly, freeing the palladium for transmetallation. The generality of this carbonylation procedure using magnesium oxide was then investigated.

2. Palladium chloride-catalyzed carbonylation

The synthetic utility of the reaction described above was vastly increased by developing a procedure catalytic in palladium. In his previous work with propargyl alcohol, Larock [35] obtained a 96% yield of β-chloro-$\Delta^{\alpha,\beta}$-butenolide in ether on a 10 mmol scale using only 1% (0.01 equivalent) of palladium chloride using anhydrous cupric chloride as a reoxidant for the palladium. Unfortunately, running the reaction on a larger (50 mmol) scale required a longer reaction time, significantly cutting down the yield (78%). Presumably, this occurs because cupric chloride reacts with vinylmercurials in polar solvents to give trans-dichloro olefins; in THF, acetone, and methanol he found that the major product was E-2,3-dichloro-2-propen-1-ol (eq. 7). By using a

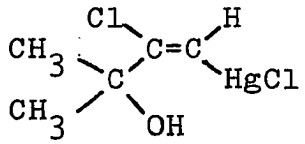
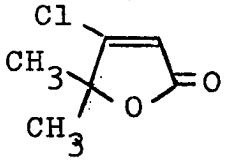
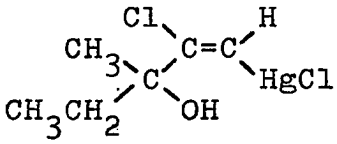
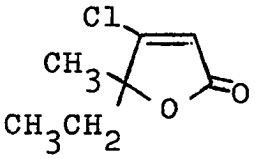
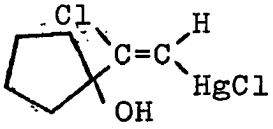
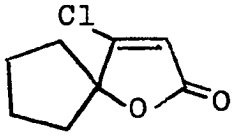
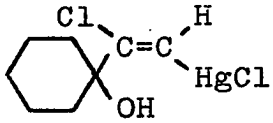
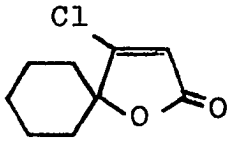
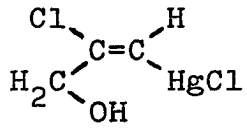
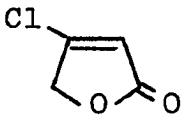


(7)

less polar solvent, benzene, we prevented this side reaction. Our yields are shown in Table II. In general, using 10% (0.1 equivalent) of palladium chloride worked best. The more highly substituted mercurials shown in the table gave much better yields when one equivalent of magnesium oxide was added, especially at very low palladium chloride concentrations. For example, the mercurial derived from 2-methyl-3-butyn-2-ol (entry 1 in Table II) gave a 96% yield of the corresponding butenolide with 10% palladium chloride catalyst, but only 57% with 1% palladium chloride. However, adding magnesium oxide increased our yield to 99%. We found that the unsubstituted mercurial gave best results when no magnesium oxide was used, perhaps because the γ-hydrogens of β-chloro-$\Delta^{\alpha,\beta}$-butenolide are extremely sensitive to bases [38].

Several other topics were studied briefly. It was found earlier [35] that carbonylation of the unsubstituted mercurial (entry 5 in Table II) could be effected using catalytic amounts of palladium on carbon, if cupric chloride were again used as reoxidant. We attempted to apply this to a substituted mercurial (eq. 8). However, this catalyst was

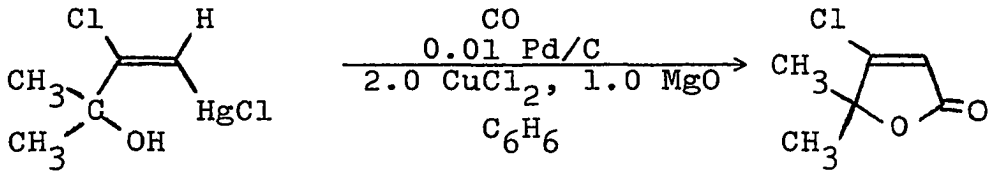
Table II. Palladium catalyzed carbonylation[a]

Entry	Mercurial	% $PdCl_2$ Catalyst	Reaction Time (hr)	Butenolide	% Yield[b]
1		10	4		96[c]
		1	23		57[c]
		1	46		99
2		10	24		100
		1	120		57
3		10	19		93
		1	72		90
4		10	19		100(81)
		1	72		54
		1	432		77
5		10	18		74[c]
		1	72		45[c]
		1	40		3

[a]One mmol mercurial, 2 mmol anhydrous $CuCl_2$, 1 mmol MgO, 10 ml benzene at room temperature.

[b]GLC analysis using an internal standard (isolated, recrystallized yield).

[c]No MgO present.

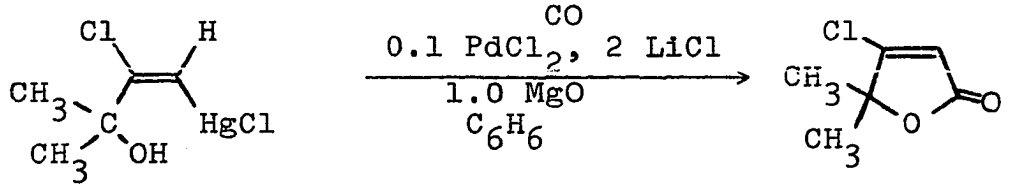


(8)

less effective than palladium chloride (entry 1 in Table II), as only a 49% yield of butenolide was obtained using 1% palladium on carbon, and a 54% yield was obtained using 5% palladium on carbon.

A very short study was done to determine the time necessary for optimal yields in the carbonylation reaction. When 1% palladium chloride was employed, two or more days were required for optimal yields (Table II). However, when 10% palladium chloride was used, the reaction went much faster (Table III).

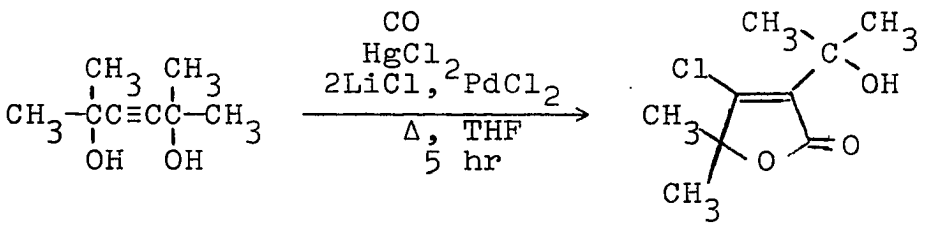
Table III. Rate of butenolide formation using 10% $PdCl_2$



Approximate Temperature, °C	Reaction Time, Hr	% Yield[a]
22	2	6
22	6	60
22	22	96
30	4	96
30	8	∿100

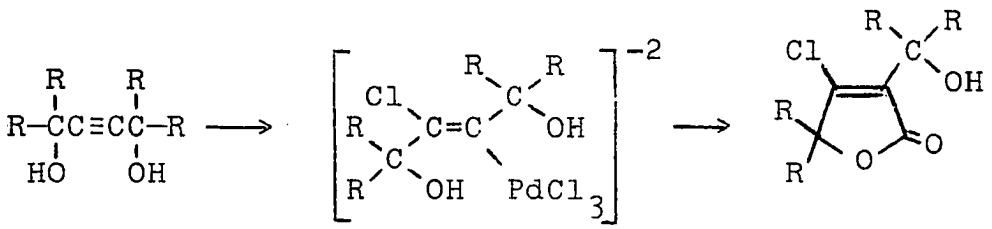
[a]GLC analysis using an internal standard.

In one case that Riefling studied, isolation of the intermediate mercurial was not necessary (eq. 9) [37]. He



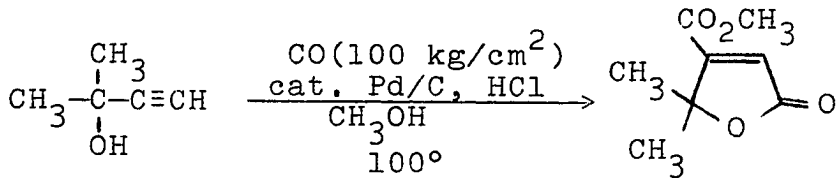
(9)

obtained a 92% yield of the butenolide simply by refluxing the acetylenic diol with the reagent normally employed, and a 70% yield by refluxing the mixture for 20 hours without any mercuric chloride at all. Evidently, dilithium tetrachloropalladate adds directly to the acetylene in a trans manner to give an intermediate vinylpalladium compound which is subsequently carbonylated and lactonized (eq. 10). This is



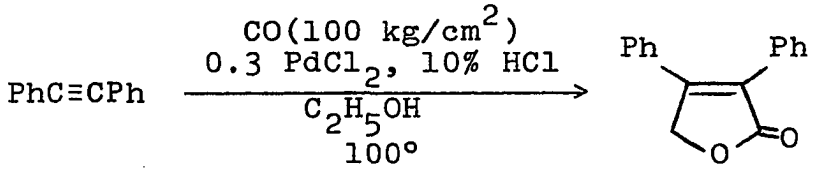
(10)

not surprising, in view of earlier literature precedent by Tsuji for the direct palladation-carbonylation of propargylic alcohols (eq. 11) [6]. Most likely other intermediates are



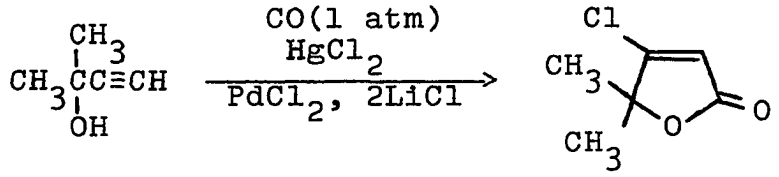
(11)

involved here, as the carboxy butenolide is formed rather than the chlorobutenolide. An internal acetylene can also be carbonylated at both ends, as in another case observed by Tsuji (eq. 12), where is obtained a 66% yield of α,β-



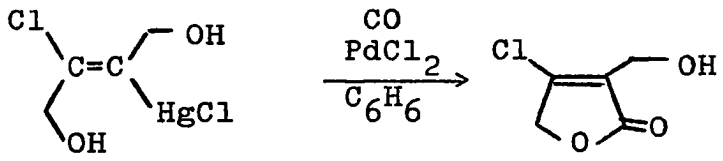
(12)

diphenyl-$\Delta^{\alpha,\beta}$-butenolide [7]. Attempts to apply our direct carbonylation reaction to 2-methyl-3-butyn-2-ol (eq. 13)



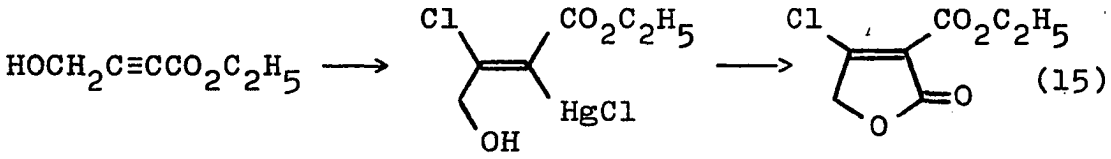
(13)

failed for the most part. When a catalytic amount of palladium chloride was used, no butenolide was observed. Only 3% of the desired product was obtained by using a stoichiometric amount of palladium chloride and refluxing the mixture overnight in pentane-benzene (9:1). Changing the solvent did not help, as no butenolide was seen when pentane, hexane, or methanol were used as solvents. Perhaps the reaction under these conditions is peculiar to tertiary acetylenic diols. In fact, attempts to cyclize the mercurial made from the corresponding primary acetylenic diol failed completely (eq. 14).



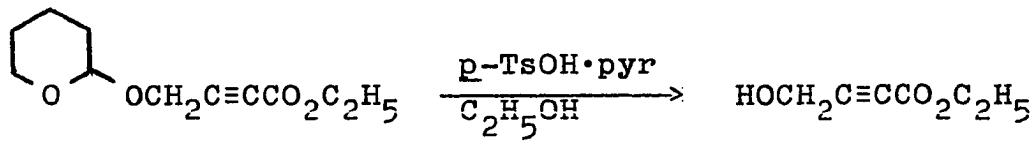
(14)

One other mercuration-carbonylation sequence was attempted (eq. 15). Work was hampered by a shortage of the



(15)

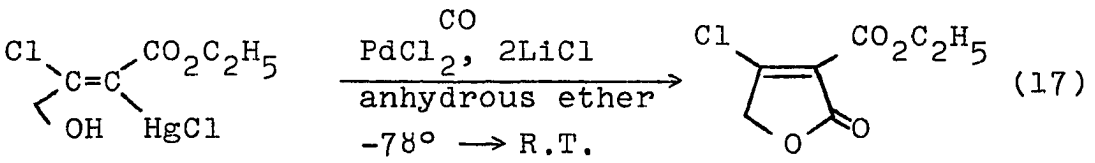
starting material, the tetrahydropyranyl ether of ethyl-4-hydroxy-2-butynoate, as only one gram was readily available. The tetrahydropyranyl ether was removed smoothly with pyridinium p-toluenesulfonate, affording a 93% yield of ethyl-4-hydroxy-2-butynoate (eq. 16) [39]. The hydroxy ester was



(16)

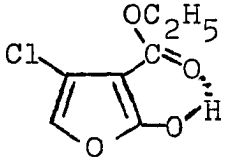
mercurated in the usual fashion affording a 36% yield of purified mercurial, which melted sharply at 157-157.5°C. The infrared spectrum (KBr pellet) showed a complete absence of the acetylenic C-C stretch at 2215 cm^{-1} present in the starting material. Other pertinent absorptions included bands at 3400-3360 cm^{-1} (OH), 1670 cm^{-1} (C=O, ester),

1620 cm^{-1} (C=C), and 1245, 1220 cm^{-1} (conjugated ester). Carbonylation and lactonization were attempted next (eq. 17).



(17)

A white solid was isolated (79% crude yield, if it is indeed the product), but there was so little material that purification and full characterization were impossible. The infrared spectrum (KBr pellet) was diffuse and nearly meaningless. Although two carbonyl absorptions were seen (1760 cm^{-1} and 1710-1670 cm^{-1}), and a carbon-carbon double bond stretch was observed (1618 cm^{-1}), a large, broad absorption at 3300-3240 cm^{-1} cast grave doubts upon the lactone structure. It is entirely possible that the product formed was not the desired lactone, but rather the tautomeric furan 29. Indeed, an NMR spectrum of the product, run nearly



29

two years after the reaction was done, showed a vinylic proton signal at δ6.5 ppm, an exchangeable proton signal at δ6.6-6.9 ppm, and the ethyl ester pattern. The sample was

badly decomposed, and many impurity peaks were present, so that one could not rule out completely the presence of some of the desired lactone. Preparation of such 3-substituted 4-chloro-2(5H)-furanones by this route is now being thoroughly explored by Chih-Ling Liu.

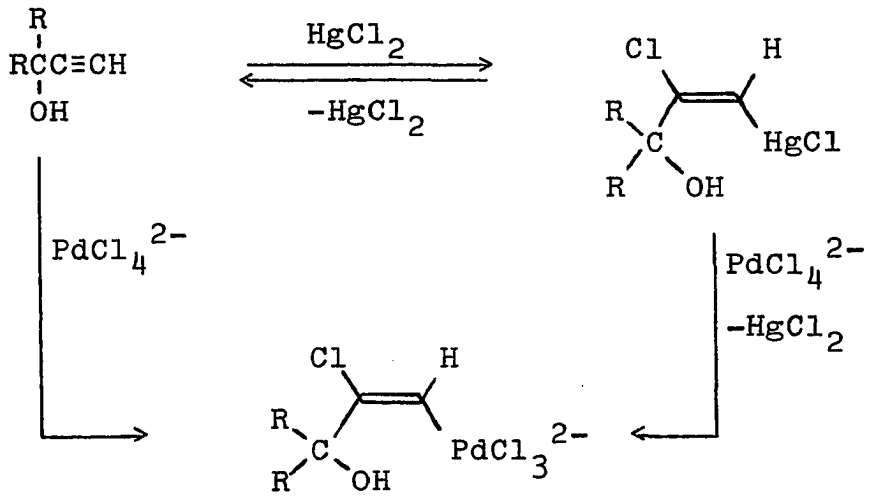
3. Mechanism

Reports concerning the addition products of mercuric chloride to acetylene and to aliphatic terminal acetylenes have appeared in the literature for more than eighty years [40-42]. However, very little is known about the mechanism of mercuric chloride addition to propargylic alcohols. Evidently, the mercuric chloride coordinates initially with the alcohol oxygen, which holds it in the vicinity of the triple bond and facilitates addition [37]. One reason for the stability of these addition products may be due to coordination of the mercury with the oxygen after the E-β-chloro-γ-hydroxyvinylmercuric chlorides are formed.

Since the vinyl mercurials are isolated by filtration, the yields obtained are entirely dependent upon the insolubility of the mercurials in the aqueous reaction medium. The more symmetrical primary and tertiary alcohols produced insoluble products, while secondary alcohols, possessing a chiral center, did not.

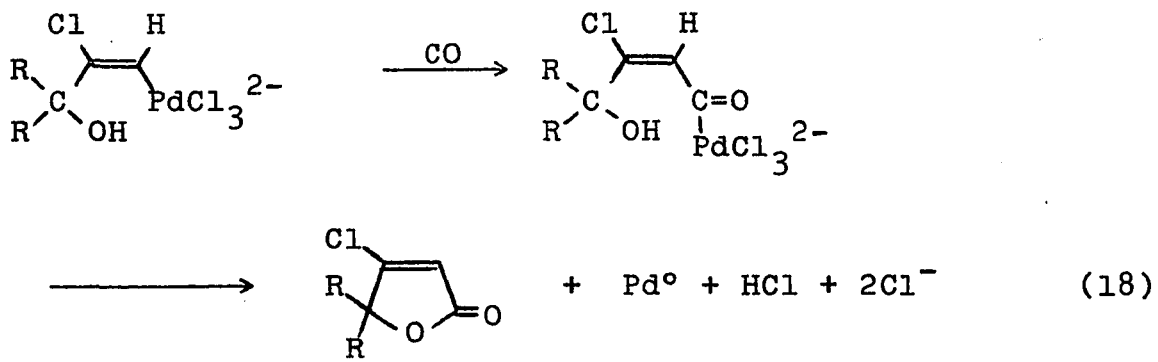
Palladation can proceed by two possible pathways (Scheme I). The most likely route is by a transmetallation

Scheme I



reaction between the vinylmercurial and dissolved palladium salt [43]. In one case described earlier, it was shown that the palladium salt can add directly to the propargylic alcohol, but this reaction proceeded at a much slower rate than when mercuric chloride was present. It is possible that preformed vinylmercurials decompose reversibly to the initial propargylic alcohols, which then add the palladium salt, but in view of the relative rates cited above and the failure of other "direct" reaction attempts, this pathway is probably a minor one. The transmetallation reaction with alkylmercurials has been shown to proceed with retention of configuration [44].

The carbonylation of vinylpalladium compounds has been known for a long time [45], and it, too, proceeds with stereochemical retention of configuration [46]. In our case, the intermediate vinylpalladium species most likely undergoes prior coordination of the carbon monoxide ligand to palladium followed by intramolecular rearrangement to an acyl species, which decomposes to the products with concomitant reduction of palladium (eq. 18). In the catalytic reactions, the



(18)

cupric chloride reoxidizes the palladium(0) to palladium(II), as in the Wacker process (eq. 19) [47].

$$Pd^{\circ} + 2CuCl_2 \longrightarrow PdCl_2 + Cu_2Cl_2 \qquad (19)$$

C. Conclusion

Mercuric chloride adds to primary and tertiary propargylic alcohols to give E-β-chloro-γ-hydroxyvinylmercuric chlorides, which then can be carbonylated in near quantitative yield. The palladium-promoted carbonylations

can be performed either with an equivalent amount of palladium chloride in any of a variety of solvents at 5°C, or with 10% palladium chloride and two equivalents of anhydrous cupric chloride at room temperature in benzene.

Although the mercuration reactions generally give poor yields, the great ease with which they are run is in keeping with the tenet that nature is simple. The final products, β-chloro-$\Delta^{\alpha,\beta}$-butenolides, bear a close structural resemblance to the naturally occurring fimbrolides 10, which have significant antifungal and antimicrobiol activity, and to the halogenated antineoplastic agents 21-23. The spiro butenolides (entries 4, 5, and 6 in Table I) have the same ring junction as the antitumor agent penstemide, 16. Work on the production of α-substituted β-chloro-$\Delta^{\alpha,\beta}$-butenolides is being continued by another member of Professor Larock's group and several of our butenolides are presently undergoing biological testing.

D. Experimental Section

1. Reagents

All chemicals were used directly as obtained unless otherwise indicated. Propargyl alcohol, 1-ethynylcyclopentanol, and 3-methyl-1-pentyn-3-ol were purchased from Aldrich, and 2-methyl-3-butyn-2-ol and 1-ethynylcycloheptanol from Farchan. Benzene and magnesium oxide were used directly

as obtained from Fisher. The palladium chloride was generously supplied by Matthey Bishop, Inc. Mercuric chloride and anhydrous lithium chloride were purchased from Fisher and J. T. Baker, respectively. Cupric chloride (hydrated) was obtained from J. T. Baker and dried in a drying oven overnight at 130° before use. Carbon monoxide was purchased from Matheson Gas Products.

The infrared spectra were recorded on a Beckman IR-4250 infrared spectrophotometer, and NMR spectra on a Varian Associates A-60 NMR spectrometer. GLC analyses were performed using a Varian Aerograph Model 920 gas chromatograph. Elemental analyses were performed by Galbraith Laboratories, Inc.

2. Mercuration of a propargylic alcohol

1-(E-1-Chloro-2-chloromercuriethenyl)cycloheptanol was prepared on a 35 mmol scale as follows. A saturated aqueous solution of mercuric chloride and sodium chloride (125 ml) was placed in a water bath and 5 g of 1-ethynylcycloheptanol dissolved in 50 ml MeOH was added. Then, 50 ml $HgCl_2$/NaCl solution was added and the water bath was cooled to 0°C. The mixture was stirred at 0°C all day and kept refrigerated at -5°C overnight. The next day the mixture was allowed to warm up to room temperature, and then the precipitate was collected by vacuum filtration and washed with a small amount

of cold water. The solid was dried overnight at 0°C in a vacuum desiccator, then ground up and dried one more day. The resulting powder was extracted with warm benzene and filtered by gravity. The filtrate was concentrated, mixed with a little Skelly B, and cooled to give product. This β-chloro-γ-hydroxyvinylmercurial was obtained in crude yield 29% or 17% isolated yield; mp 136-137°C; ^{1}H NMR (acetone-d_6) δ1.4-2.4 (m, 12, CH_2), 5.07 (s, 1, OH), and 6.10 (s, 1, vinyl). Anal. calcd. for $C_9H_{14}Cl_2HgO$: C, 26.38; H, 3.44. Found: C, 26.48; H, 3.49.

The other β-chloro-γ-hydroxyvinylmercurials were prepared as described by us earlier [37].

3. Palladium catalyzed carbonylation

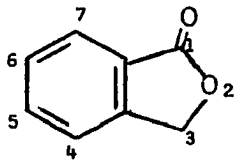
The 1 mmol scale catalytic carbonylation reactions summarized in Table II were carried out as follows. Two mmol anhydrous cupric chloride, the appropriate amounts of palladium chloride (0.01 or 0.10 mmol) and magnesium oxide (usually 1 mmol), and 5 ml benzene were added to a round bottom flask with septum inlet. After flushing with carbon monoxide and attaching a balloon full of carbon monoxide, 5 additional ml of benzene containing 1 mmol of mercurial was added and the flask was stirred at room temperature for the appropriate length of time. An internal standard was then added and the reaction analyzed by GLC. To determine the

isolated yield of 4-chloro-5,5-pentamethylene-2(5H)-furanone on a 1 mmol scale, the catalytic carbonylation reaction was set up as described above, and stirred 19 hr at room temperature. Then, 1 ml saturated ammonium chloride, 15 ml ether, and charcoal were added. The mixture was stirred under carbon monoxide for 90 minutes longer, and the resulting suspension was filtered, washed with two 25 ml portions of saturated potassium carbonate, and dried over anhydrous sodium sulfate. Evaporation of the ether gave 0.3 g (112%) crude product, which was then recrystallized from Skelly B in 81% isolated yield.

III. SYNTHESIS OF AROMATIC ESTERS, LACTONES, AND OTHER HETEROCYCLES VIA THALLATION-CARBONYLATION OF ARENES

A. Introduction

The aromatic lactones called phthalides (30; 3H-isobenzofuran-1-ones) and 3,4-dihydroisocoumarins (31; 3,4-dihydro-1H-2-benzopyran-1-ones) comprise another large class



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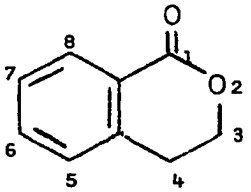
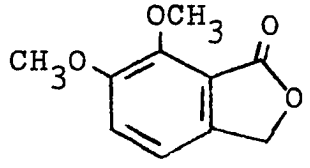


31

of naturally occurring, physiologically active compounds. Phthalides occur in a variety of plants, including the penicillium molds [2]. Meconin, 32, is found in small quantities in the opium poppy and in the root of Hydrastis canadensis [48], and was first isolated as long ago as 1832



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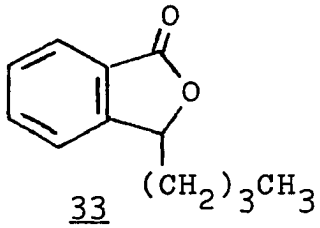

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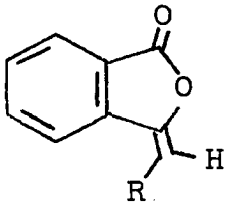
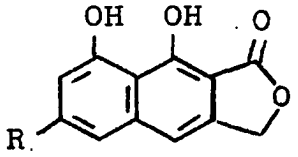


34, R = $CH(CH_3)_2$

35, R = $CH_2CH(CH_3)_2$

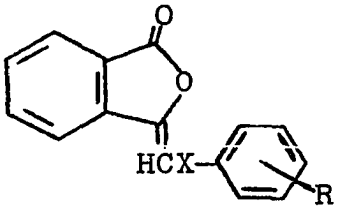
[49]. Compound 33, 3-n-butyl phthalide, is one of the major odor components of celery essential oil, and reportedly has sedative effects on mice [50]. E-3-Isobutylidene-(34) and E-3-(3-methylbutylidene)-phthalide (35) are also flavor and odor components of celery [51]. Compounds 36 and 37, α- and β-sorigenin, aglycons of materials isolated from the bark



36, R = OCH_3

37, R = H

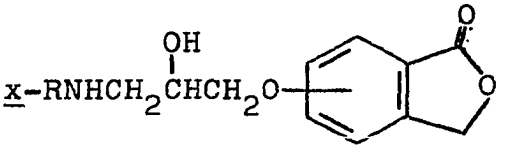
of Rhamus japonica, were the first examples of natural products with a naphthalene nucleus [52]. Certain synthetic phthalides show significant biological activity. Benzylidene-phthalides 38 have fungistatic, bacteriostatic, and herbicidal activity [53], whereas phthalide aminopropyl ethers 39 have



X = O, S

R = H, NO_2, NH_2, halo, alkyl, aryl

38

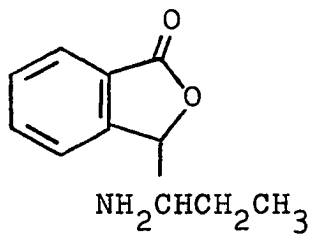


x = 5, 6, or 7

R = $(CH_3)_2CH$, $(CH_3)_3C$, or $(CH_3)_2CHCH_2$

39

β-adrenolytic activity, and are useful in the treatment of circulatory and heart diseases [54]. 1-Amino-1-phthalidylpropane, 40, is an analgesic [55], and 3-phenacylidenephthalide, 41, is a highly active inhibitor of root geotropism [51].



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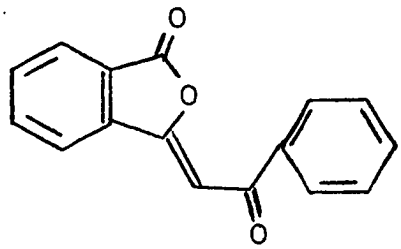
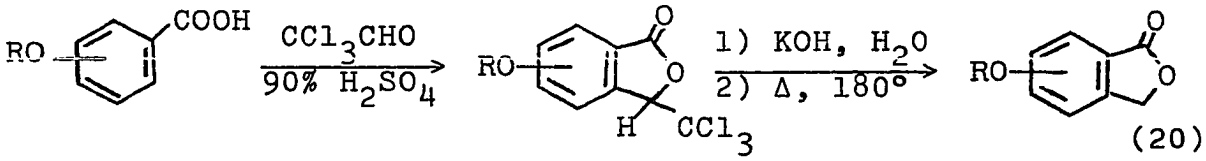


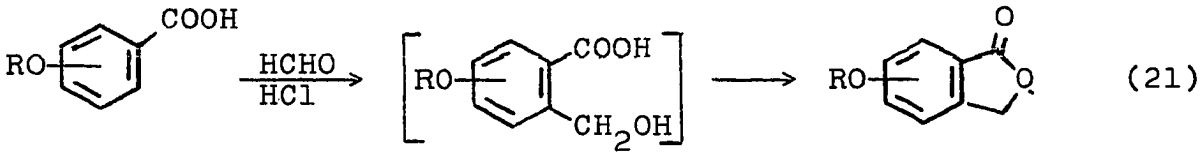
41

Until recently, most of the synthetic routes to phthalides involved condensation of aromatic acids with reagents that introduced a benzylic alcohol group ortho to the carboxylic acid, which then lactonized [55]. The oldest method employed chloral, which gave very poor yields (eq. 20)



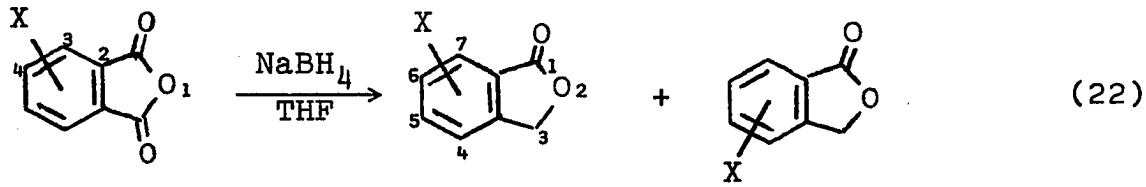
(20)

[48]. The more efficient Perkin method uses formaldehyde and hydrochloric acid (eq. 21) [56]. Unfortunately, this



(21)

requires electrophilic aromatic substitution on a deactivated aromatic ring; consequently, chloromethylation often occurs at positions other than the desired ortho position [57]. Another route to phthalides involves reduction of phthalic anhydrides [55], and recently McAlees et al. have obtained a variety of phthalides either by hydrogenation of substituted phthalic anhydrides over palladium [58] or by reduction with sodium borohydride (eq. 22) [59]. Hydro-

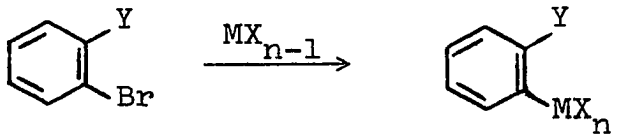


(22)

genation over palladium generally gives poor yields of phthalides, which usually are mixtures of isomers. Sodium borohydride reduction is better, affording phthalides in overall yields of 33-81%, with variable regioselectivity. For example, 3-nitrophthalic anhydride gives only 4-nitrophthalide, whereas 3-methylphthalic anhydride produces a 57:43 mixture of 4- and 7-methylphthalides. 4-Substituted anhydrides also exhibit such extremes of regioselectivity, depending on the substituent.

A number of papers have appeared in the past few years which attack the regioselectivity problem by directed metallations of appropriately substituted arenes. One approach

generates ortho-metallated aromatic compounds from ortho-haloaromatics (eq. 23), as in the facile palladium-catalyzed



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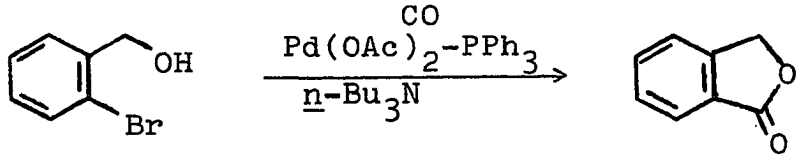
carbonylation of ortho-bromobenzyl alcohol very recently reported by Mori et al. [60] (eq. 24). A similar procedure



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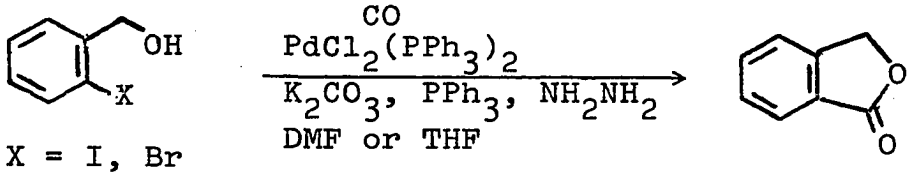
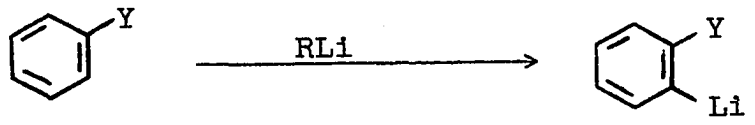
has been developed by Stille [61] (eq. 25). Unfortunately,



(25)

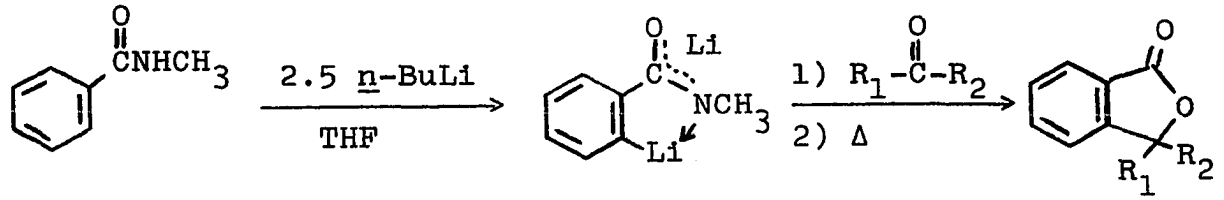
in order to obtain substituted phthalides, one first must prepare specific ortho-haloaromatic compounds, not always an easy task.

Another approach involves the directed metallation of aromatic substrates, in which a neighboring functional group promotes ortho-metallation and/or stabilizes the resulting aryl organometallic. Directed lithiation has been especially well studied, and is an increasingly important tool in organic syntheses (eq. 26) [62,63]. More than a dozen



(26)

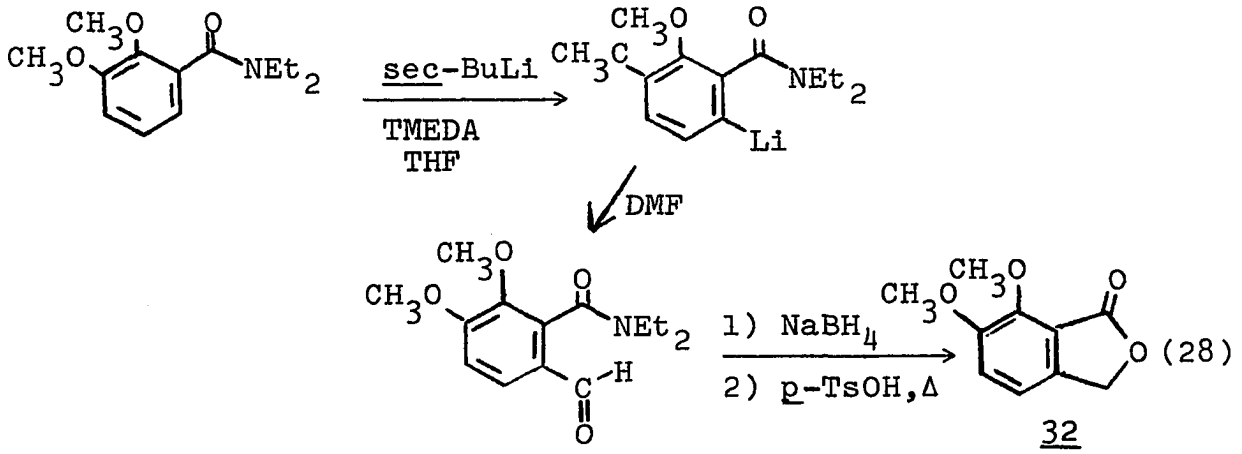
ortho-directing functional groups have been investigated, and the list continues to grow [64]. Directed lithiation has been used in a number of phthalide syntheses. The earliest procedure was developed by Puterbaugh and Hauser, who metallated N-methylbenzamide with excess n-butyllithium, condensed the lithio derivatives with a number of ketones, and cyclized the adducts (eq. 27) [65]. A number of 3,3-disubstituted



(27)

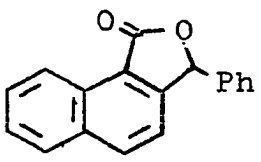
phthalides were thus prepared, some in very high yield. Later, Narasimhan and Bhide used the same procedure to synthesize such phthalides with alkoxy substituents on the ring [66]. Based on Beak and Brown's report of the ortho-lithiation of tertiary benzamides [67], de Silva et al. have prepared phthalides in high yields with one or two alkoxy substituents on the benzene ring, starting from the corresponding N,N-diethylbenzamides [68]. Lithiation is followed by formylation with DMF, and

subsequent reduction and cyclization (eq. 28). Meconin, 32, was obtained in a 90% overall yield in this fashion. Since



32

lithiation of m-anisamide occurs exclusively between the two ring substituents, and ortho to the amide function in p-anisamide, the regiospecificity of this reaction permits one to exert complete control over placement of the alkoxy substituents in the products [67]. Very recently, Watanabe and Snieckus have obtained some unusual polycyclic phthalides while attempting to prepare anthraquinones by their new concept of "tandem directed metallation" [64]. 1-N,N-Diethylnaphthamide and alkoxy-substituted benzamides gave mainly phthalide products, such as 42, 43, and 44, in high



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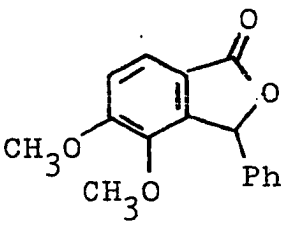

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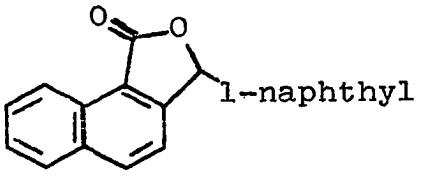
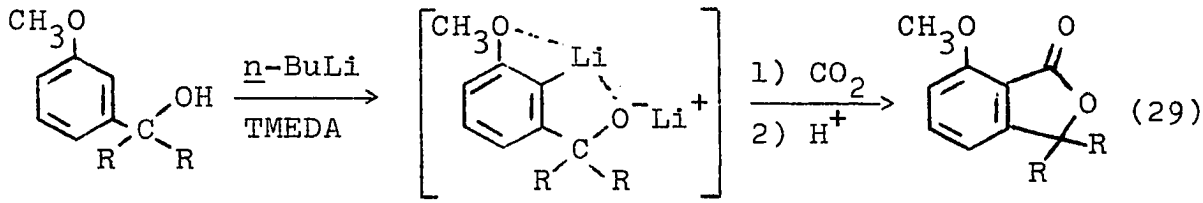


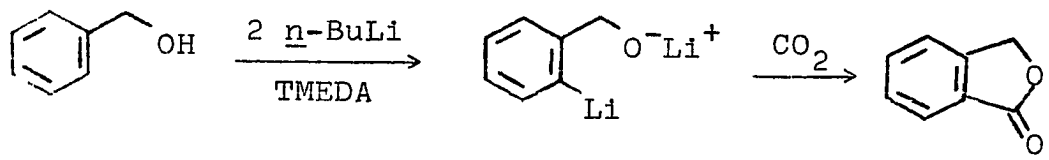
44

yields. However, one first must prepare the N,N-diethylbenzamide starting materials before beginning the reaction sequences described above. Uemura et al. have synthesized a number of 7-methoxyphthalides from 3-methoxybenzyl alcohols using a lithiation approach [69]. The position between the ring substituents undergoes preferential lithiation, and subsequent treatment with carbon dioxide and acid gives cyclized products (eq. 29). They found that starting



(29)

alcohols substituted with methyl group(s) at the benzylic position decreased the yield of phthalide due to steric hindrance at the 2-position on the ring, and that a rigid conformation of the benzylic hydroxyl group increases the amount of phthalide formed. Meyer and Seebach obtained a 50% overall yield of phthalide by the lithiation of benzyl alcohol, followed by treatment of the intermediate lithium ortho-lithiobenzyl alkoxide with carbon dioxide (eq. 30) [70].



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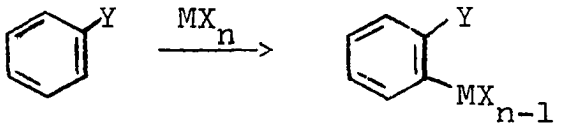
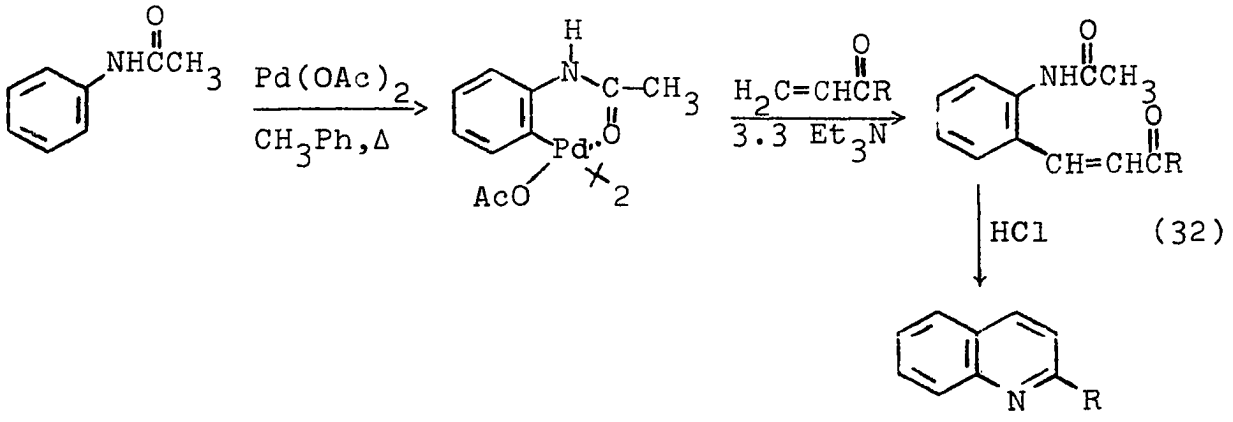
A third approach, direct electrophilic ortho-metallation of aromatic compounds with metals other than lithium, is well known (eq. 31) [71-73]. This method has not been as fully



(31)

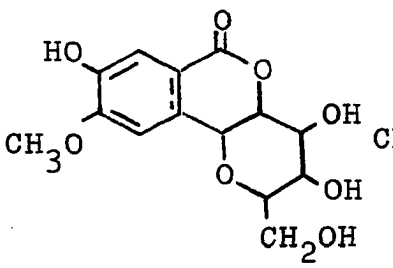
exploited as lithiation in planning overall synthetic routes. One excellent example was reported very recently by Horino and Inoue, in which direct cyclopalladation of acetanilides was followed by coupling with olefins, affording 2-substituted acetanilides (eq. 32) [74]. Intramolecular cyclizations gave



(32)

a variety of quinolines. Prior to our work, production of phthalides by this method was virtually unexplored.

3,4-Dihydroisocoumarins occur in many natural products [75]. Bergenin, 45, has been isolated from over two dozen plants. The Chinese antipyretic drug "Sheng ma," extracted from a plant, contains bergenin [76]. Compound 46 is



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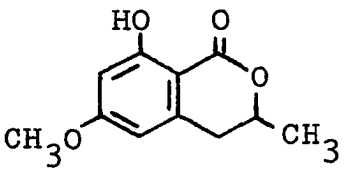

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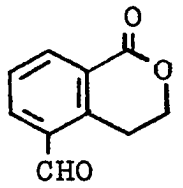
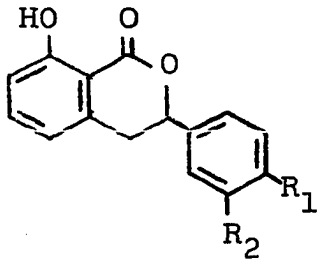


47

found in stored carrots [75]. It inhibits the germination and germ-tube growth of the fungus Thielaviopsia basicola, which causes root rot. Erythrocentaurin, 47, is obtained by hydrolysis of a bitter substance isolated from Swertia japonica. Other flavoring agents with this ring structure include hydrangenol (48; R_1=OCH_3, R_2=OH) and phyllodulcinol (48; R_1=OH, R_2=H), the sweet principles in Amacha (sweet tea) [75]. Mellein, 49, also known as ochracin, is produced



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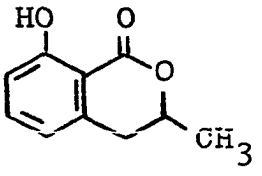

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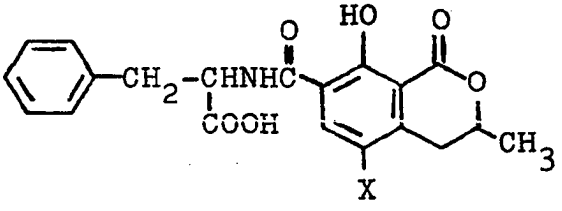
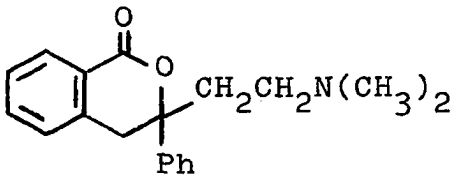


50

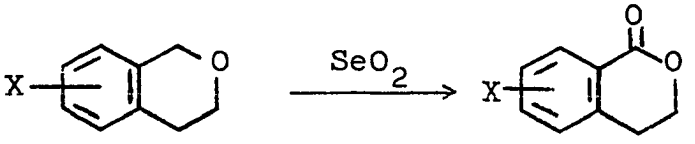
by Aspergillus melleus and A. ochraceus molds [75]. It bears quite a resemblance to compounds 50, the microbial toxins ochratoxin A (X=Cl) and B (X=H), which are the most widely studied 3,4-dihydroisocoumarins [77]. Synthetic compound 51



51

shows diuretic and hypotensive-antihypertensive activity [78].

Syntheses of 3,4-dihydroisocoumarins by classical methods usually involve condensations (Stobbe [79], Claisen or Perkin), cyclizations [80,81], and oxidations [75]. For example, high yields are obtained when isochromans are oxidized by selenium dioxide (eq. 33) [82]. The isochromans



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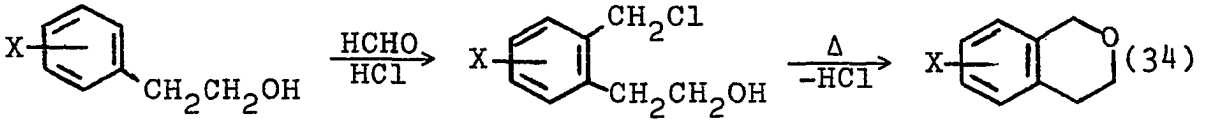
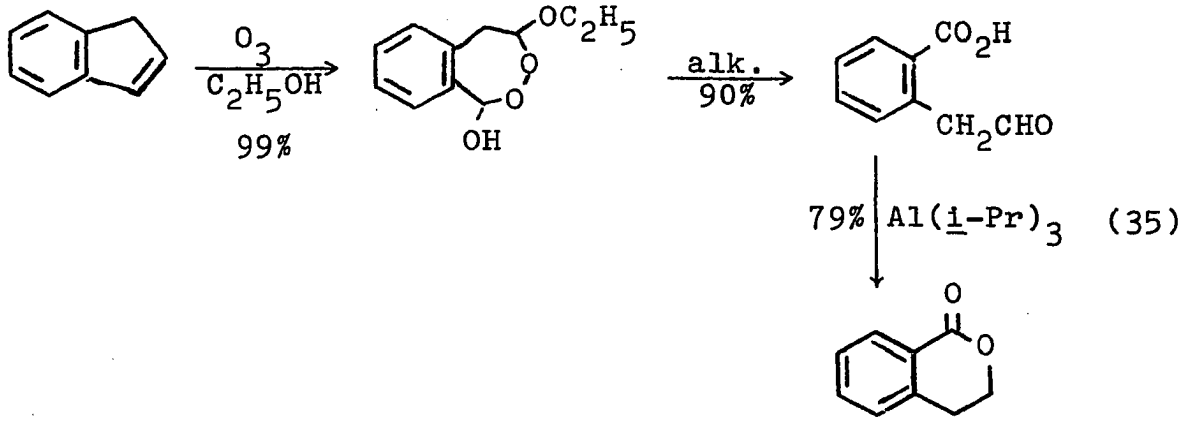
are prepared by chloromethylation of β-aryl ethyl alcohols, followed by cyclization (eq. 34) [82]. However, as was



(34)

mentioned earlier, the side chain cannot direct attack exclusively to the ortho position, and isomeric chloromethylated compounds are common side products. Another

method involves ozonization of indenes in ethyl alcohol, followed by decomposition of the intermediate cyclic perester and reduction (eq. 35) [83]. Unfortunately, the

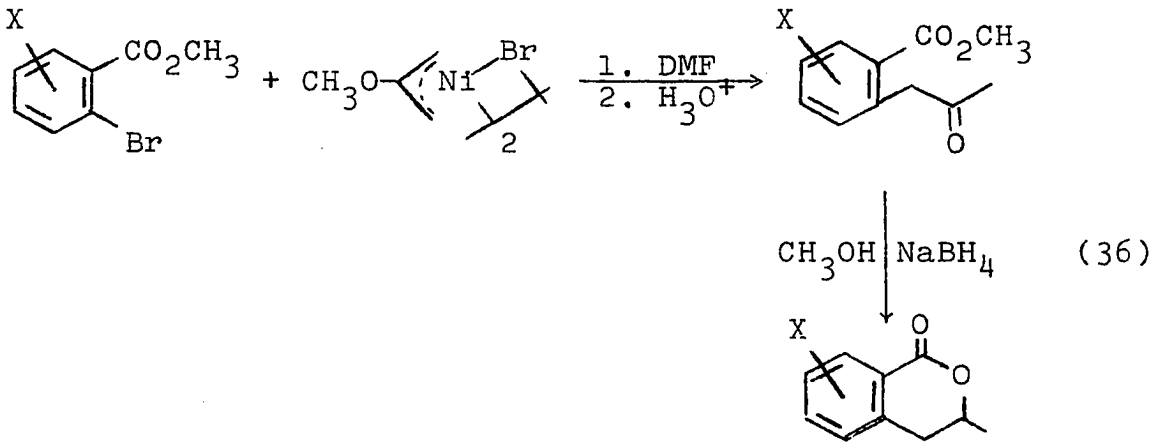


(35)

appropriately substituted indenes are not readily available. Few of the procedures listed above start with readily available materials or allow the introduction of a large variety of substituents.

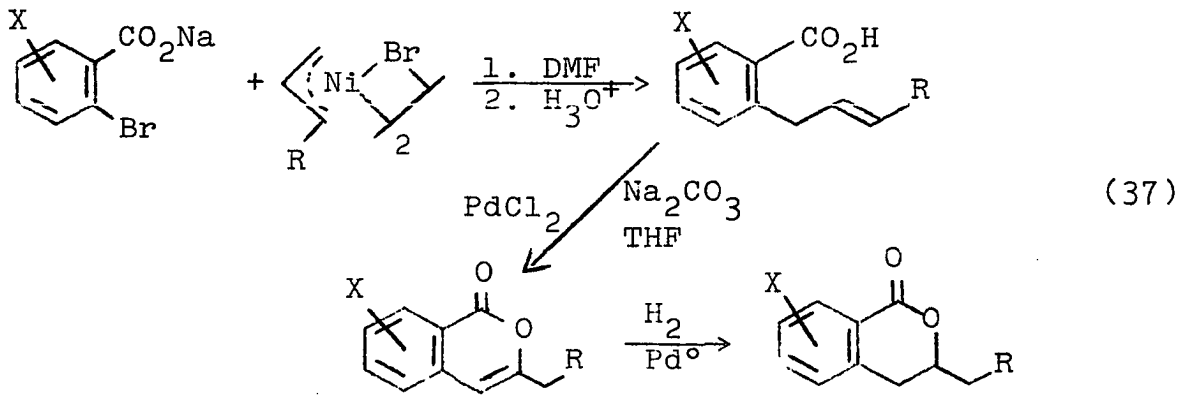
Directed metallation of arenes has provided an effective alternative route to 3,4-dihydroisocoumarins, as well as to phthalides. The use of ortho-haloaromatics to generate ortho-metallated species has been employed recently by Korte et al., who began with 2-bromoaromatic esters [84]. According to one scheme, π-allylnickel halide complexes are used to introduce an acetonyl group ortho to the ester function, and then sodium borohydride reduction of this

ketone effects cyclization, producing 3-methyl-3,4-dihydroisocoumarins (eq. 36). In another sequence, 2-alkenylbenzoic



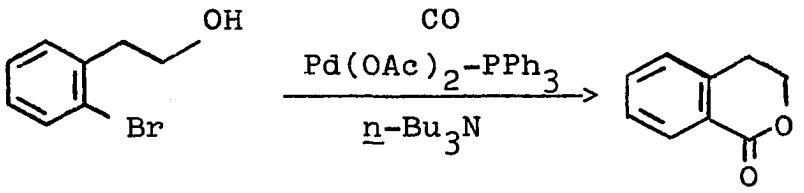
(36)

acids undergo palladium-assisted cyclization via nucleophilic attack of the carboxylate anion on the palladium-complexed olefin. Reduction with hydrogen gives the desired ring system (eq. 37). Mori et al. have prepared the parent



(37)

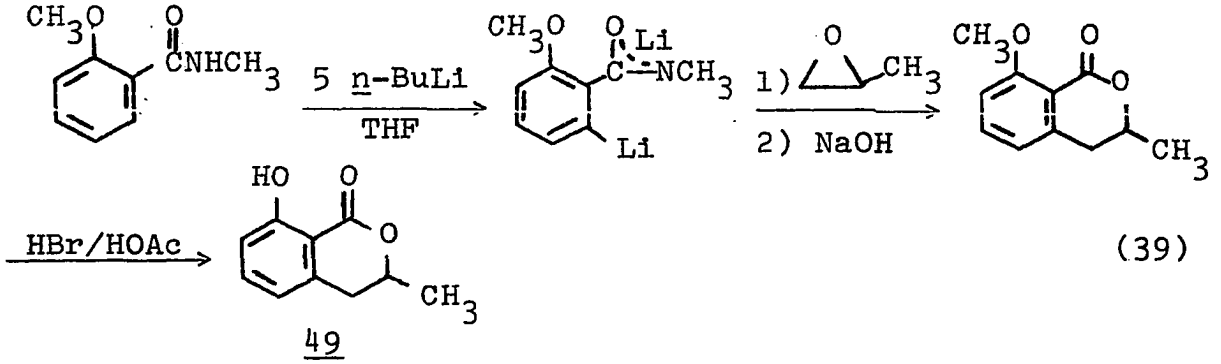
ring system by their direct palladium-catalyzed carbonylation of ortho-bromophenethyl alcohol (eq. 38) [60]. No other



(38)

examples were cited.

The direct lithiation of aromatic substrates, which has shown such promise in phthalide syntheses, has been used only rarely for 3,4-dihydroisocoumarins. Puterbaugh and Hauser reported only one attempt to form this ring system in their work with ortho-lithiated N-methylbenzamide, and the yield was very low [65]. Narasimhan and Bhide developed the procedure further, obtaining several methoxy-3,4-dihydroisocoumarins in 60-70% yields [66]. Mellein, 49, was synthesized in 59% overall yield (eq. 39).

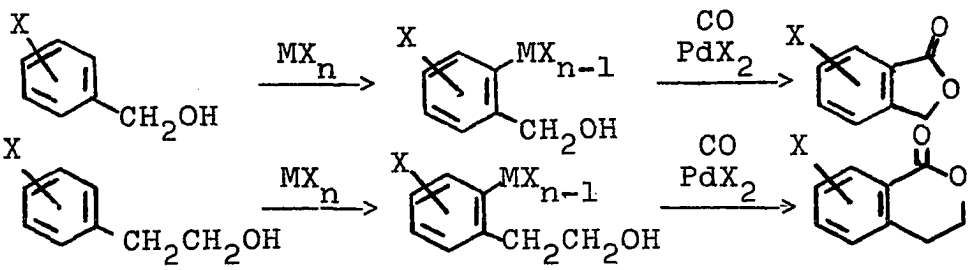


(39)

49

In the literature to date, there is no single synthetic strategy leading from easily available starting materials to both phthalides and 3,4-dihydroisocoumarins which also

accommodates a variety of substituents. Schemes involving directed metallations of aromatic substrates, such as those reported by Mori et al. [60] and Puterbaugh and Hauser [65], produced a limited number of examples of both ring systems. Unfortunately, both procedures have drawbacks. The method of Mori et al. requires prior preparation of appropriately substituted ortho-bromoaryl alcohols, which at once raises the question of regioselective ortho-bromination. Puterbaugh and Hauser's method, as elaborated by Narasimhan and Bhide [66], is highly regioselective, but one first must synthesize the necessary N-methylbenzamides. Our interest in the application of carbonylation reactions to the synthesis of biologically active lactones [37] encouraged us to look for a more effective route. The palladium-promoted carbonylation of ortho-metallated benzyl and β-phenethyl alcohols which were not derived from the corresponding ortho-haloaromatics looked promising (eqs. 40, 41). The rest of this chapter

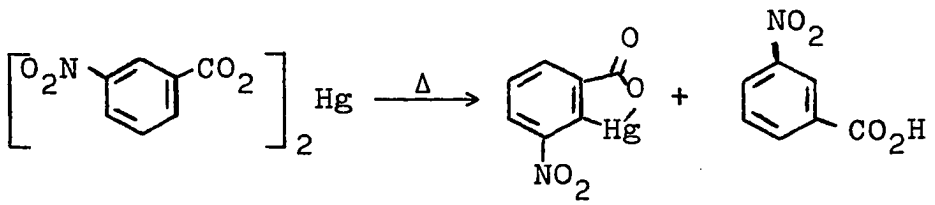


will report our full exploration of this synthetic strategy.

B. Results and Discussion

1. Preliminary studies

The first aspect of the problem that we considered was the preparation of isomerically pure ortho-substituted compounds. The use of mercury salts for this was first considered, as there have been literature reports of the generation of ortho-mercurated arenes in high yields. The thermal decomposition of mercuric m-nitrobenzoate affords anhydro-2-hydroxymercuri-3-nitrobenzoic acid (eq. 42) [85].



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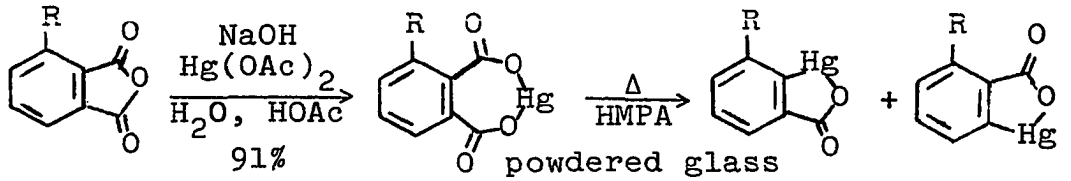
More recently, Newman and Vander Zwan have reported an improved procedure for the decarboxylation of mercuric salts of phthalic acids (eq. 43) [86]. Overall yields in this

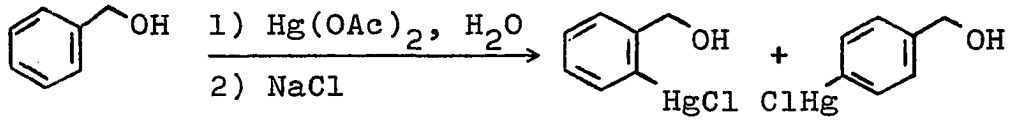


(43)

R = H, Cl, Br, NO_2, CO_2H, CH_3

scheme range from 85-94%, with ratios of 52 to 53 ranging from 10:0 (R=Cl) to 3:1 ($R=NO_2$). However, one must have the properly substituted phthalic anhydrides as starting

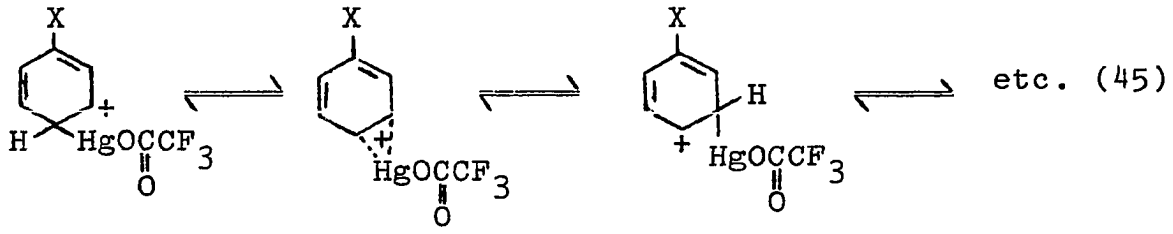
materials, and we were searching for simpler starting materials. Direct electrophilic mercuration of benzyl alcohol has been reported (eq. 44) [87]. The ortho mercurated benzyl



(44)

54 55

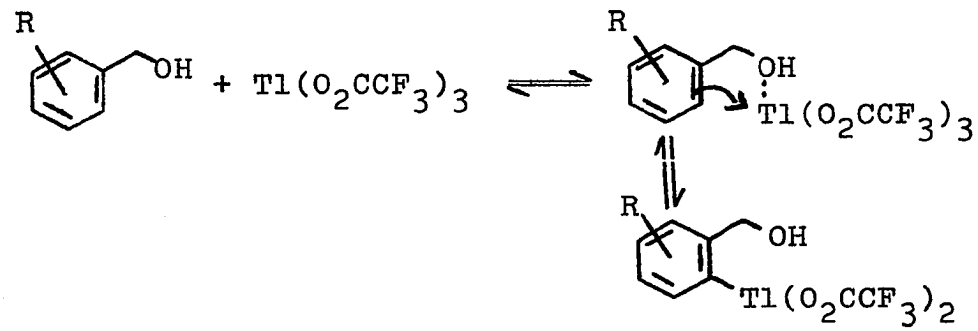
alcohol, 54, is produced in 56% yield, along with 14% of the para product, 55. The regioselectivity is not as high as we needed. Later, it was reported that polymercuration occurs very readily during aromatic electrophilic mercuration [88], and that facile mercury shifts in arene mercurinium ions can make regioselectivity difficult to control under these conditions (eq. 45) [89]. In addition, reported yields in



the palladium-promoted carbonylation of arylmercurials are low to moderate (10-56%) [90].

We next turned our attention to thallium, as the regioselectivity of electrophilic thallation of arenes by thallium(III) trifluoroacetate has been studied extensively

[91-95]. Unlike the mercuration process, thallation produces only monothallated aromatics [88], and transthallations (isomerizations) do not take place at lower temperatures [89]. Taylor et al. have published a thorough, systematic study of regioselectivity and orientation control in the electrophilic thallation of aromatic alcohols, acids, esters, and ethers [93]. These thallations were shown to be reversible substitution reactions, and, under conditions of kinetic control, ortho substitution predominates for benzyl and β-phenethyl alcohols and for benzoic acid, among others. The most probable intermediate here is a substrate-electrophile complex, in which the side-chain oxygen coordinates to the thallium, providing intramolecular delivery of thallium to the ortho position (eq. 46). The degree of ortho substitution

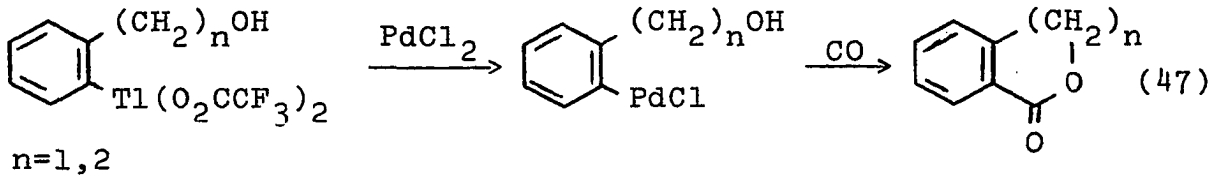


(46)

is dramatically affected by the ring size of the substrate-electrophile chelate, best results being obtained when five- and six-membered rings can be formed in the transition state. Increasing the size of the chelate ring causes ortho thallation to fall off sharply, as one can see from a

comparison of representative isomer distribution ratios. Thus, benzyl and β-phenethyl alcohols afford >99% and 83%, respectively, of the ortho-arylthallium compounds, whereas 3-phenyl-1-propanol produces 80% of the para-substituted isomer. Thallium, therefore, appeared to provide an excellent solution to the regioselectivity problem.

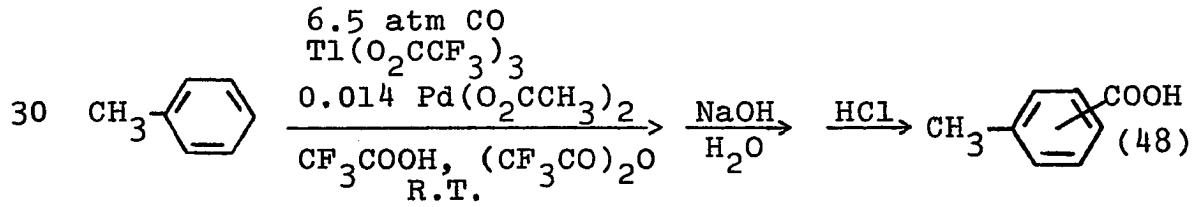
On the other hand, direct carbonylation of arylthallium compounds is difficult, requiring high temperatures and pressures [96]. In order to circumvent this, we decided to try transmetallation with palladium, as thallium-palladium exchange is a known reaction for certain organothallium compounds [88,97-100]. We anticipated that arylthallium trifluoroacetates would undergo transmetallation by palladium chloride, and after carbonylation and lactonization would provide the desired lactone ring systems (eq. 47).



n=1,2 (47)

Long after our investigations were well underway, a process for the oxycarbonylation of benzene or toluene employing thallium(III) trifluoroacetate and palladium(II) salts was patented by J. J. Van Venrooy [101]. His procedure involved combining the reagents in a mixture of solvents and stirring them under four to seven atmospheres of carbon

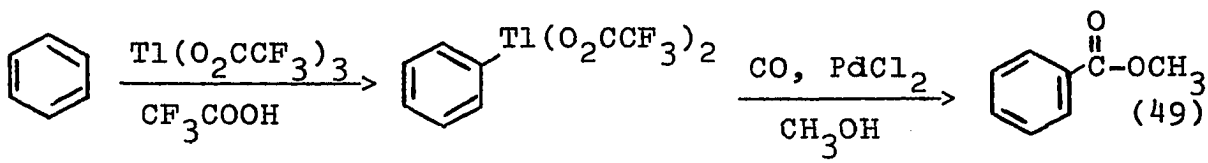
monoxide. Aqueous basic workup, followed by acidification, provided benzoic or toluic acids (eq. 48). Van Venrooy



(48)

normally used a large excess (two- to thirty-fold) of aromatic hydrocarbon, and based his yields (80-90%) on the amount of thallium reagent used. Unused benzene or toluene was recovered for later use. No other substrates were studied. In our experiments, one atmosphere of carbon monoxide was always used, and our yields were normally based on the amount of arene. Roughly stoichiometric amounts of thallium reagent and aromatic substrate were employed.

We studied the thallation-palladation-carbonylation sequence using benzene as a model system to determine conditions for optimum yields (eq. 49). Thallation of



(49)

benzene was run on a 15 mmol scale, and the phenylthallium bistrifluoroacetate was isolated and recrystallized from 1,2-dichloroethane. We obtained a 51% yield, consistent with the 48% reported by McKillop et al. [92]. Using this

intermediate, we made a systematic study of the carbonylation reaction by altering the following conditions: reaction temperature, addition of two equivalents of lithium chloride, and addition of one equivalent of magnesium oxide. Addition of lithium chloride presumably forms dilithium tetrachloropalladate, which has been used frequently for the palladation of arenes [71,102,103]. Previous experience with palladium-catalyzed carbonylations suggested that addition of an inorganic base might improve the yield [37]. Results are summarized in Table IV. The most significant result seen in

Table IV. Carbonylation of phenylthallium bistrifluoroacetate[a]

Entry	Equivalents of Added Salt(s)	% Yield of Methyl Benzoate (% Biphenyl)[b]		
		-78° → 25°	0°	25°
1	1 $PdCl_2$	28 (11)	53	13 (24)
2	1 $PdCl_2$, 2 LiCl	57	39 (3)	54
3	1 $PdCl_2$, 2 LiCl, 1 MgO	---	---	57
4	0.1 $PdCl_2$	---	---	13 (9)
5	0.1 $PdCl_2$, 2 LiCl	25 (7)	34 (6)	57
6	0.1 $PdCl_2$, 2 LiCl, 1 MgO	44 (7)	57	---

[a]One mmol $PhTl(O_2CCF_3)_2$ in CH_3OH.

[b]GLC analysis using tetradecane as an internal standard.

Table IV is that only catalytic amounts of palladium chloride are required, which vastly increases the potential synthetic utility of this reaction sequence. It is not necessary to add cupric chloride to reoxidize the palladium, as reported by Spencer and Thorpe for the palladium chloride-catalyzed olefination of arylthallium compounds [100]. Apparently, the thallium(III) salt generated upon transmetallation is a sufficiently strong oxidant that it continually reoxidizes the palladium metal formed upon carbonylation and lactonization (eqs. 50-53).

$$ArTlX_2 + PdX_4^{-2} \longrightarrow ArPdX_3^{-2} + TlX_3 \quad (50)$$

$$ArPdX_3^{-2} + CO \longrightarrow ArCOX + Pd + 2X^- \quad (51)$$

$$ArCOX + ROH \longrightarrow ArCO_2R + HX \quad (52)$$

$$Pd + TlX_3 \longrightarrow PdX_2 + TlX \quad (53)$$

For the most part, the carbonylations were quite clean, with only one side product, biphenyl, seen in a number of cases (Table IV). Undoubtedly, biphenyl arises from palladium-promoted coupling of phenylthallium bistrifluoroacetate. Uemura *et al.* previously reported a 44% yield of biphenyl from this substrate in the presence of palladium chloride [97]. Biphenyl was most frequently observed when our reaction was run at lower temperatures, no matter which salts were added. When the reaction was run at room

temperature, biphenyl was seen only when palladium chloride was the only salt added. Addition of lithium chloride and magnesium oxide appeared to suppress biphenyl formation at room temperature. Based on the results shown in entries 3, 5 and 6 of Table IV, which indicated that the highest yields of methyl benzoate could be obtained at room temperature in the presence of lithium chloride and magnesium oxide, subsequent carbonylation reactions were run using 0.1 equivalent of palladium chloride, two equivalents of lithium chloride, and one equivalent of magnesium oxide at room temperature.

The "direct" reaction was studied next, in which the phenylthallium intermediate was not isolated and recrystallized. Thallations were run in trifluoroacetic acid according to the published literature procedure [92]. Other solvents tried (methanol, THF, acetonitrile) gave no product at all. After thallation, excess trifluoroacetic acid was evaporated from the reaction, and the crude material subsequently was dissolved in methanol and added to a stirred mixture of palladium chloride, methanol, and the other salts under one atmosphere of carbon monoxide. Changing the proportions of benzene to thallic trifluoroacetate in the thallation reaction makes a big difference in overall yields, as shown in Table V. A nearly stoichiometric amount of the thallium reagent gives a 45-55% overall yield, whereas a large excess of thallic trifluoroacetate (entry 7) cuts the yield in half. A

Table V. Effect of stoichiometry on the thallation reaction

Entry	Benzene:$Tl(O_2CCF_3)_3$	% Yield a $PhCO_2CH_3$	Source of $Tl(O_2CCF_3)_3$
1	1:1	47	Aldrich
2	1:1.2	45	Aldrich
3	5:1	73[b]	Aldrich
4	1:0.9	44	---[c]
5	1:1	48	---[c]
6	1:1.2	55	---[c]
7	1:2	20	---[c]

[a]GLC yield based on 1 mmol benzene. Carbonylation conditions: 0.1 mmol $PdCl_2$, 2 mmol LiCl, 1 mmol MgO, 10 ml CH_3OH under 1 atmosphere CO at room temperature for 24 hr.

[b]GLC yield based on 1 mmol $Tl(O_2CCF_3)_3$.

[c]$Tl(O_2CCF_3)_3$ prepared by refluxing Tl_2O_3 purchased from Asarco in CF_3COOH.

five-fold excess of benzene afforded a much improved yield, based on one equivalent of $Tl(O_2CCF_3)_3$ (entry 3). Van Venrooy's procedure, described earlier, used a thirty-fold excess of benzene or toluene, and his yields of 80-90% were based on the amount of $Tl(O_2CCF_3)_3$ employed [101].

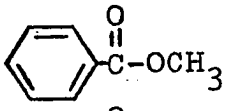
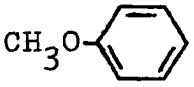
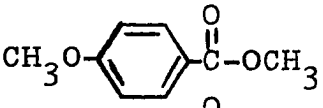
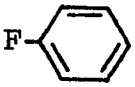
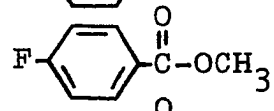
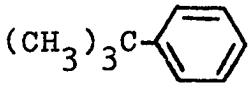
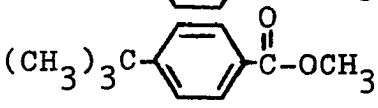
Another variable was the quality of the thallium reagent itself. At first, we purchased the reagent from Aldrich. It was a white powder, and appeared to be quite satisfactory in

all respects. When this supply was exhausted, we bought some from Alfa, since Aldrich was temporarily out of stock. However, the reagent from Alfa was a brownish, waxy material that gave lower yields than the Aldrich product. Finally, we prepared our own reagent by refluxing thallic oxide from Asarco (American Smelting and Refining Company) in trifluoroacetic acid [92]. This produced a white solid in nearly quantitative yield, which gave even better results in our reactions than the Aldrich reagent (compare entries 1 and 5, and 2 and 6 in Table V). This method is much more economical, too. Fifty grams of thallic trifluoroacetate from Aldrich costs $40, and we paid over $55 for the same quantity from Alfa. It cost us less than $9 to prepare the same amount of thallic trifluoroacetate from thallic oxide ourselves. We obtained a 2½-pound bottle of thallic oxide from Asarco, so we have more than enough for several years' work. All subsequent reactions employing thallic trifluoroacetate were run using our own reagent.

Several monosubstituted benzenes were esterified to study the effect of groups on the ring which would either activate or deactivate the ring towards aromatic electrophilic substitution.

Approximately equivalent amounts of arene and $Tl(O_2CCF_3)_3$ were used. The results are presented in Table VI. For comparison purposes, McKillop *et al.*'s yields of

Table VI. Synthesis of aryl esters *via* thallation-carbonylation

Entry	Arene	Product	% Yield[a]	Literature % Yield of p-ArI (Ref. 92)[b]
1			55	96(48)
2			62	70
3			42[c]	62(30)
4			80[d]	93

[a]GLC yield based on 1 mmol arene. Thallations performed according to procedures in Reference 92. Carbonylation conditions: 0.1 mmol $PdCl_2$, 2 mmol LiCl, 1 mmol MgO, 10 ml CH_3OH at room temperature for 24 hr.

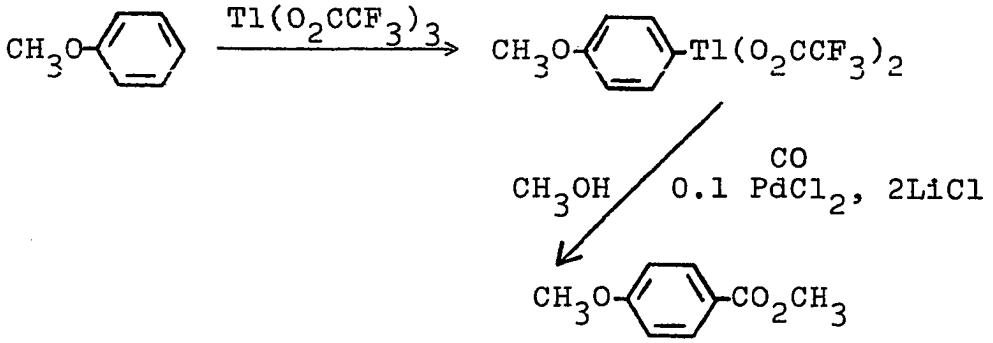
[b]GLC yield after thallation and treatment with aqueous potassium iodide (isolated yield of $ArTl(O_2CCF_3)_2$).

[c]Thallated for 48 hr.

[d]Carbonylated for 96 hr.

para aryl iodides, prepared from the same starting materials, are also shown [92]. Fluorine, a deactivating group (entry 3), does indeed decrease the yield, while a mildly activating alkyl group dramatically increases it (entry 4). It may seem surprising that the yield from anisole is lower than that from t-butylbenzene (entries 2 and 4, respectively) as the methoxy group more strongly activates the ring towards electrophilic substitution than alkyl groups. One plausible reason for the lowered yield is that alkoxybenzenes very easily undergo oxidative coupling in the presence of thallium(III) salts [104]. This side reaction will be discussed in more detail later.

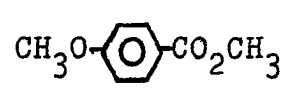
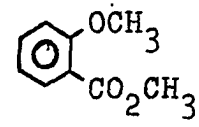
The effect of different thallation conditions on overall yields in the esterification of anisole was studied to determine which procedure was best (eq. 54). Results are



(54)

shown in Table VII. Of the conditions we tried, those reported by McKillop et al. (entry 1) [92] still give the best yield. GLC traces of the carbonylation reaction

Table VII. Esterification of anisole. Effect of thallation conditions[a,b]

Entry	Solvent(s)	Temperature, °C	Time	% Yield[c]	
					
1	TFA	-25	15 min	62	9
2	TFA	-25	30 min	48	8
3	TFA	25	15 min	32[d]	?
4	THF:TFA, 5:1	25	1 hr	46	4
5	THF:TFA, 5:1	25	2 hr	47	4
6	THF:TFA, 5:1	25	4 hr	54	4
7	THF:TFA, 5:1	0→25	1 day	44	2
8	THF:TFA, 5:1	0	2 days	33	2

[a]Equivalent amounts of anisole and $Tl(O_2CCF_3)_3$ (1 mmol) used in every case.

[b]Carbonylation conditions: 0.1 mmol $PdCl_2$, 2.0 mmol LiCl, 2.0 mmol MgO in 10 ml CH_3OH under 1 atmosphere CO at room temperature for 24 hr.

[c]GLC yield using methyl benzoate as an internal standard.

[d]Isolated, purified yield on a 5 mmol scale.

mixtures revealed that less than 1% of the starting material remained in every case, and that there was an impurity amounting to 2-9% of the product peak, which is most likely the ortho isomer. McKillop *et al.* reported a 7:93 ortho: para distribution for the thallation of anisole [92]. In the case of *t*-butylbenzene, only a trace of starting material remained, and less than 2% of the ortho isomer was observed. McKillop *et al.* reported 0% ortho thallation for this substrate [92].

Our results in these preliminary investigations demonstrated that the transmetallation of arylthallium compounds by palladium salts and subsequent carbonylation is potentially a very useful reaction sequence, and, as shown above, yields are good, especially when there is an activating group on the benzene ring. This encouraged us to explore the preparation of phthalides and other ring systems from appropriately substituted arenes by this method.

2. Phthalides

Phthalides were synthesized by thallation of benzyl alcohols with thallium(III) trifluoroacetate in trifluoroacetic acid [93], after which the arylthallium intermediates were carbonylated without further purification. The preparation of phthalide itself was somewhat disappointing, as shown in Table VIII. Although yields during carbonylation were

Table VIII. Synthesis of phthalide from benzyl alcohol

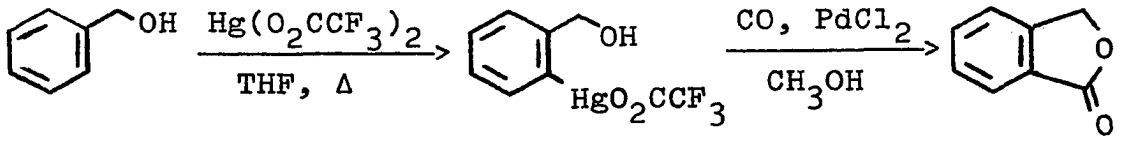
Thallation Conditions				Carbonylation Conditions		
Entry	$PhCH_2OH:Tl(O_2CCF_3)_3$	Temperature, °C	Time, Days	Solvent	Added Base[a]	% Yield[b]
1	1:1	0→25	1	THF	none	4
2	1:1	0→25	1	THF	MgO	19
3	1:1	0→25	1	THF	$NaOCH_3$	18
4	1:1	0→25	1	CH_3OH	MgO	22
5	1:1	0→25	1	CH_3OH	$NaOCH_3$	33
6	1:1	0→25	2	CH_3OH	MgO	28
7	1:1	0	1	CH_3OH	MgO	33
8	1:1	0	2	CH_3OH	none	15
9	1:1	0	2	CH_3OH	0.1 equiv. $NaOCH_3$	14
10	1:1	0	2	CH_3OH	MgO	20
11	1:1	0	2	THF	MgO	22
12	1:1	0	5	CH_3OH	MgO	20
13	1:2	0	2	CH_3OH	MgO	27
14	5:1	0	2	CH_3OH	$NaOCH_3$	53[c]
15	5:1	0	1	CH_3OH	MgO	43[c]

[a]One equivalent of base added.

[b]GLC analysis using an internal standard based on 1 mmol $PhCH_2OH$.

[c]GLC analysis using an internal standard based on 1 mmol $Tl(O_2CCF_3)_3$.

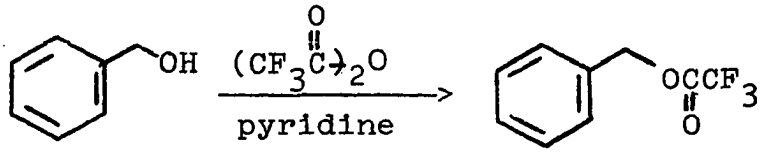
increased by adding an inorganic base, the best yield based on benzyl alcohol was never more than 33% (entries 5 and 7). One problem was incomplete thallation. GLC traces of all the carbonylation reaction mixtures showed that 25-35% of unreacted benzyl alcohol was still present. Longer exposure to the thallation medium was no help, as this decreased the yield (compare entries 7, 10, and 12). Using two equivalents of thallic trifluoroacetate also gave a poor yield (entry 13), as was true in our previous attempts to thallate benzene. A five-fold excess of benzyl alcohol gave a 53% yield (entry 14) based on one mmol thallic trifluoroacetate, but this negates the synthetic utility of this reaction. In the literature, previous attempts to metallate benzyl alcohol in the ortho position have also met with difficulty. Although Taylor et al. reported that benzyl alcohol is thallated in greater than 99% in the ortho position [93], no overall yield of thallated material was given, hinting that it was quite low. Mercuration of benzyl alcohol, as mentioned earlier, gave a 56% yield of the ortho arylmercurial and 14% of the para isomer [87]. We attempted such a mercuration using mercuric trifluoroacetate, analogous to the thallation reactions (eq. 55), but the maximum yield of phthalide was only 27%. We also observed 52% unreacted benzyl alcohol. When Meyer and Seebach



(55)

treated benzyl alcohol with n-butyllithium and then with carbon dioxide, their overall yield of phthalide was only 50%, as noted earlier [70]. Thus, the phenomenon of incomplete ortho metallation of benzyl alcohol appears to be a real problem, and is demonstrably not peculiar to thallium.

Besides incomplete thallation, another problem encountered was the formation of benzyl trifluoroacetate during the thallation step. An authentic sample was prepared (eq. 56). This ester has a sharp, distinctive odor, and this

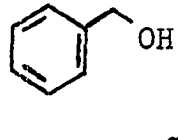
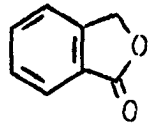
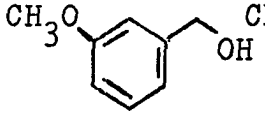
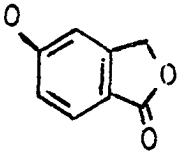
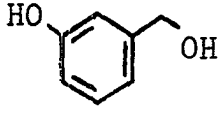
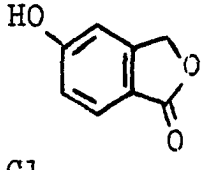
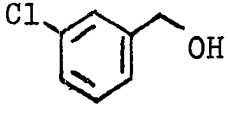
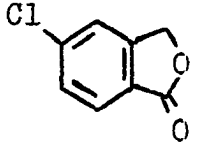
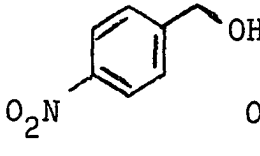
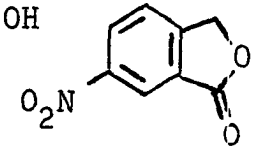


(56)

same odor was unmistakably present in the phthalide reaction mixtures. It was impossible to determine how much was there, as the GLC retention time of benzyl trifluoroacetate is the same as that of methanol, the solvent used in the carbonylation reaction.

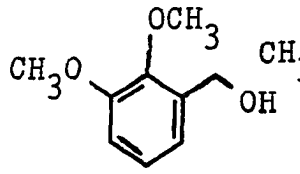
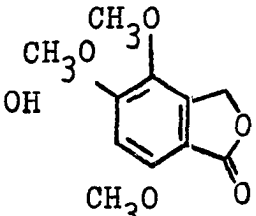
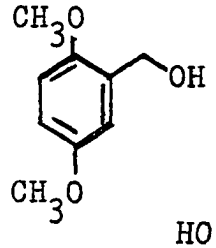
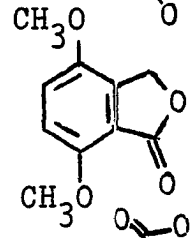
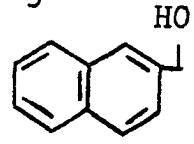
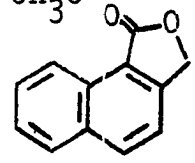
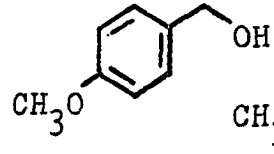
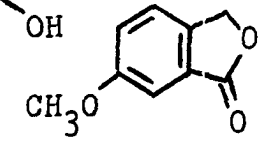
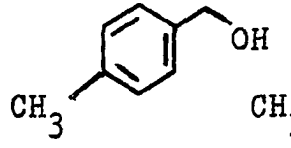
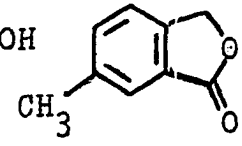
A series of substituted benzyl alcohols was studied next (Table IX). As predicted by our preliminary results with monosubstituted arenes, benzyl alcohols possessing groups that activate the ring towards electrophilic aromatic

Table IX. Phthalides from benzyl alcohols

Entry	Alcohol	Product	% Yield[a]	Purification	Mp, °C	Lit. mp, °C
1			33 (18)	Column chromatography on silica gel	68	73 [105]
2			89 (47)	Recrystallized from EtOAc	116-118	118 [106]
3			— (95)	None	223-224	222 [107] 223 [108]
4			45 (18)	Recrystallized from ether/hexane	154-155	154 [109]
5			0	---	---	143 [109]

[a]GLC analysis using an internal standard (isolated, purified yield).

Table IX. (Continued)

Entry	Alcohol	Product	% Yield[a]	Purification	Mp, °C	Lit. mp, °C
6			64 (54)	Recrystallized from hot water	122-123	123-124 [110]
7			— (31)	Recrystallized from hot water	162-165	168-170 [111]
8			– (4)	Preparative GLC	145	152-153 [112]
9			0	---	---	117-120 [58]
10			23 (22)	Recrystallized from ether/hexane	88	Unknown

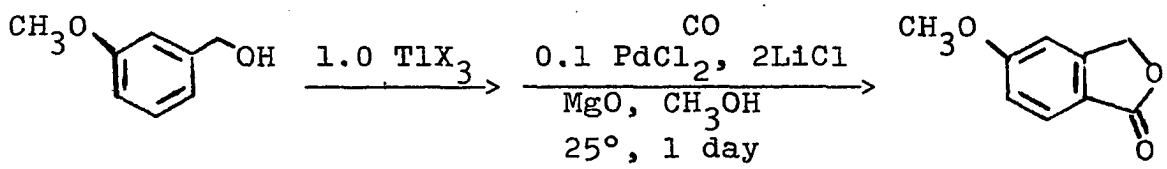
substitution gave much better results in our overall sequence. Alcohols with deactivating groups or with sterically crowded thallation sites gave poorer yields.

Since there were no reports in the literature concerning thallation of the substituted benzyl alcohols shown, our first task was to determine the best thallation conditions for the activated substrates. 3-Methoxybenzyl alcohol (entry 2 in Table IX) was studied first, as shown in Table X. The thallation conditions normally employed for benzyl alcohol proved to be too harsh (entry 1). We then tried a number of less severe conditions. Changing the solvent from trifluoroacetic acid to acetic acid did not help (entry 2).

However, using thallic acetate in a 5:1 mixture of acetic acid and trifluoroacetic acid afforded a 54% yield (entry 3). Thallic trifluoroacetate, which is a stronger thallating agent, gave an even better yield in the same solvent system (entry 4). The best yield of all was obtained with thallic trifluoroacetate in a 5:1 mixture of THF and trifluoroacetic acid (entry 6), whereas a smaller amount of trifluoroacetic acid gave a lower yield (entry 5).

We anticipated that 3-methoxybenzyl alcohol might thallate under conditions slightly more vigorous than those for anisole. Accordingly, we ran such reactions at room temperature instead of at -25° for short periods of time (entries 7-10). Thallation for 15 minutes afforded a 70%

Table X. Synthesis of 5-methoxyphthalide. Effect of thallation conditions[a]



Entry	Thallium Salt	Solvent(s) and Proportions, in ml	Temperature °C	Time	% Yield[b]
1	$Tl(O_2CCF_3)_3$	TFA	0 → 25	1 day	0[c]
2	$Tl(O_2CCF_3)_3$	HOAc	25	1 day	0[c]
3	$Tl(OAc)_3$	HOAc + TFA	25	1 day	54
4	$Tl(O_2CCF_3)_3$	HOAc + TFA 5:1	25	1 day	69
5	$Tl(O_2CCF_3)_3$	THF + TFA 5:0.5	25	1 day	38
6	$Tl(O_2CCF_3)_3$	THF + TFA 5:1	25	1 day	89
7	$Tl(O_2CCF_3)_3$	TFA	25	7 min	52
8	$Tl(O_2CCF_3)_3$	TFA	25	15 min	70
9	$Tl(O_2CCF_3)_3$	TFA	25	30 min	29
10	$Tl(O_2CCF_3)_3$	TFA	25	60 min	12

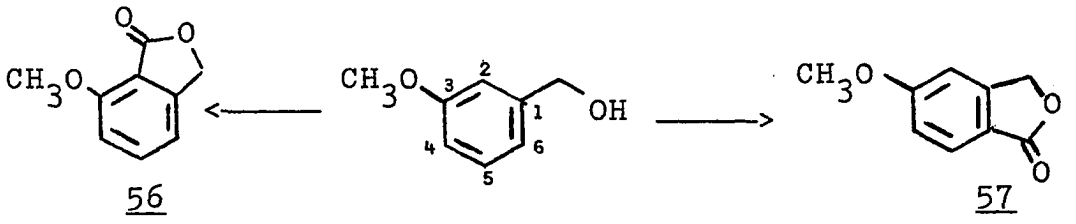
[a]Stoichiometric amounts of alcohol and thallium salt (1.0 mmol) used in all cases.

[b]GLC yield using diphenylmethane as an internal standard.

[c]Other products observed instead of desired product.

overall yield, which was better than any of the yields of methyl p-anisate shown in Table VII. However, since our best result came from thallation in a mixture of THF and trifluoroacetic acid (entry 6 in Table X), most subsequent thallations were performed using this diluted solvent medium. The reaction was run on a preparative scale several times using our best conditions from the GLC results. Crude isolated yields ranged from 73% to 100%, but yields of purified material (recrystallized from ethyl acetate or ether) never exceeded 47%.

The nearly exclusive production of 5-methoxyphthalide from 3-methoxybenzyl alcohol is an interesting point in itself. Due to the combined effects of the ortho delivery of thallium by the alcohol and the ortho, para directing capability of the methoxy group, both the 2- and 6-positions on 3-methoxybenzyl alcohol would be likely thallation sites (eq. 57). Therefore, we expected a mixture of 56 and 57,

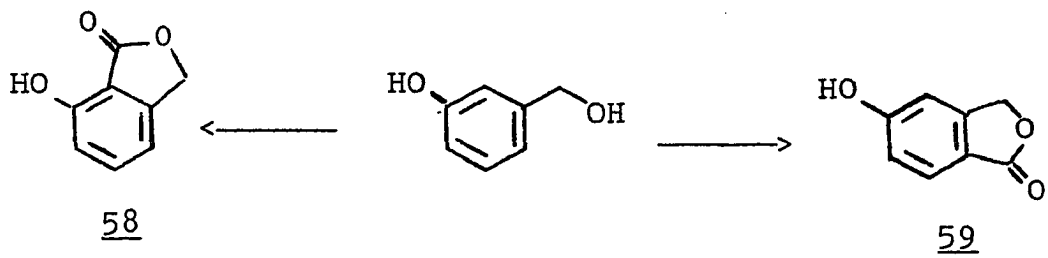


56 57 (57)

but, to our surprise, only a trace of 56 was observed by GLC in the crude carbonylated material, most of which was 57 (determined by coinjection of an authentic sample of 56).

Evidently, the 3-methoxy group renders the 2-position too crowded for the large thallium salt, so the relatively unhindered 6-position is thallated instead. Our method nicely complements the procedure of Uemura et al., in which the same starting material is lithiated in the 2-position, eventually affording only 56 (shown above in eq. 29 on page 36) [69].

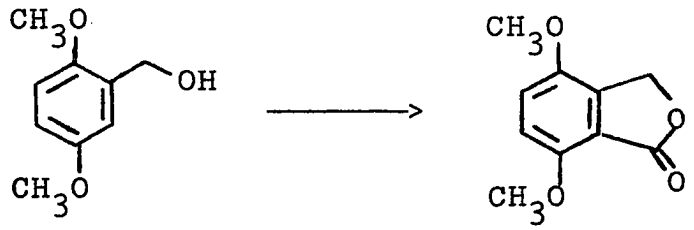
The thallation and carbonylation of 3-hydroxybenzyl alcohol (entry 3 in Table IX) produced even better results than in the case of 3-methoxybenzyl alcohol, as our reaction afforded a 95% isolated yield of 5-hydroxyphthalide. The fact that a hydroxy group is a stronger ortho, para directing group than methoxy in electrophilic aromatic substitution warranted milder thallation conditions than those developed for 3-methoxybenzyl alcohol. Thallation was performed in a more dilute acid system, with a 10:1 ratio of THF to trifluoroacetic acid. Again, it was conceivable that two products, 58 and 59, could be formed (eq. 58). Comparison by TLC of an



58 59 (58)

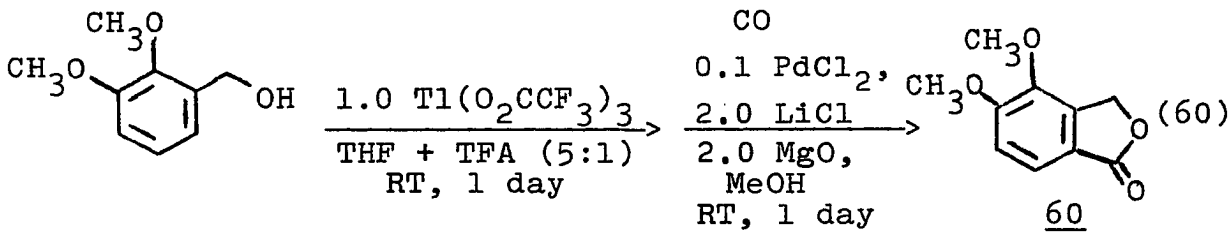
authentic sample of 58 and the crude reaction mixture after work-up showed that no 58 was present. In fact, the crude solid melted at 223-224°, whereas the reported melting point

of 59 is 222° [107] or 223° [108], and that of 58 is 135-136.5° [113]. Integration of the aromatic region in the ^1H NMR spectrum confirmed the structure to be that of 59. Thus, even a group as small as hydroxyl causes a steric barrier to thallation in the 2-position. These results help explain the low yield of 4,7-dimethoxyphthalide (entry 7 in Table IX), since the 6-position of 2,5-dimethoxybenzyl alcohol is also crowded (eq. 59).



(59)

Application of our reaction sequence to 2,3-dimethoxybenzyl alcohol (entry 6 in Table IX) gave a 64% yield of 4,5-dimethoxyphthalide, 60, which in the older literature is called pseudomeconin (eq. 60). After many attempts to find thallation conditions that would give an optimal overall



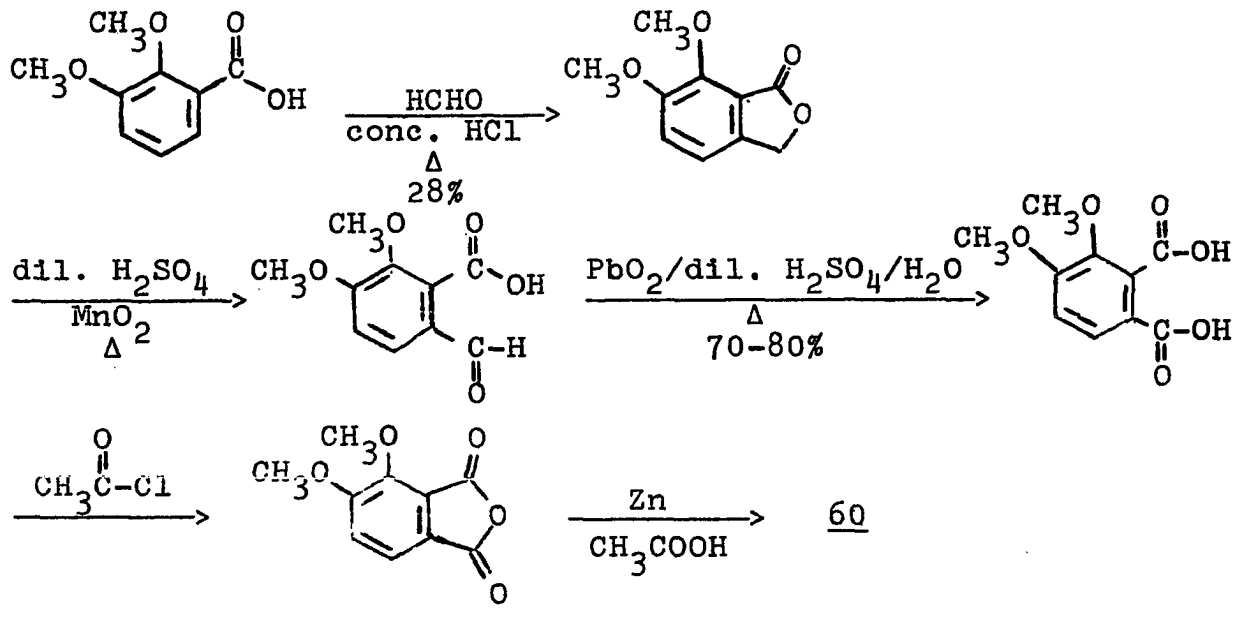
60

yield, we found two sets of conditions that seem to work equally well. Most thallations were run in the mixed solvent system used for 3-methoxybenzyl alcohol, as shown in eq. 59,

but thallation in undiluted trifluoroacetic acid for 15 minutes at -20° gave approximately the same results. Trace amounts of the trifluoroacetate ester of the starting alcohol were observed.

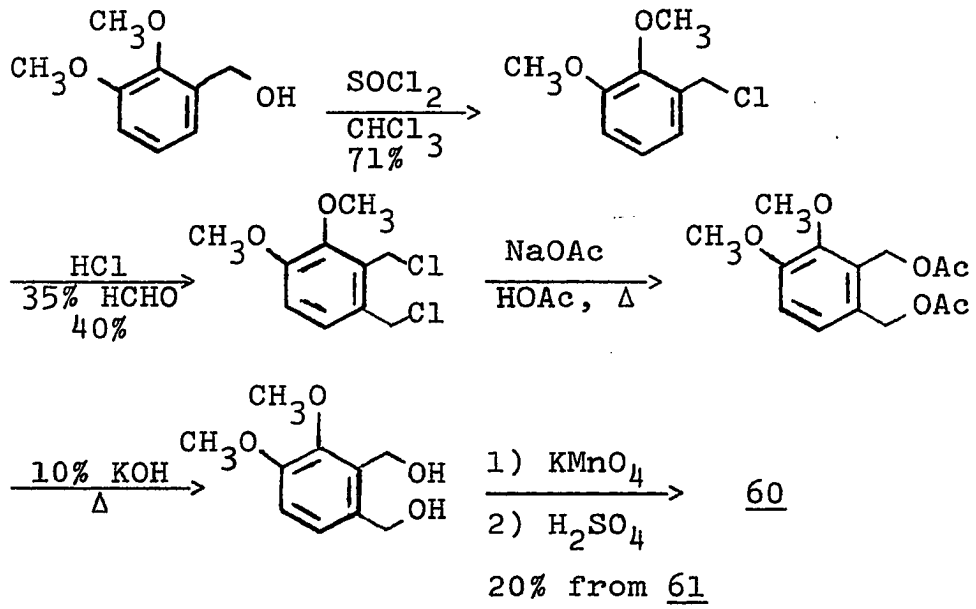
Our method affords a much higher overall yield of pseudomeconin in far fewer steps than the classical synthesis reported over five decades ago (Scheme II) [56]. Yields are

Scheme II

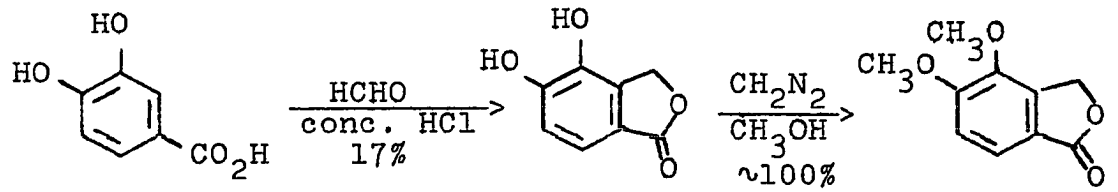


not given for many of these transformations, but, due to the poor yield of the chloromethylation step, the overall yield must be well below 20%. A second synthesis dating from 1950 also used chloromethylation, and the overall yield here was a meager 6% (Scheme III) [114]. Although the starting

Scheme III



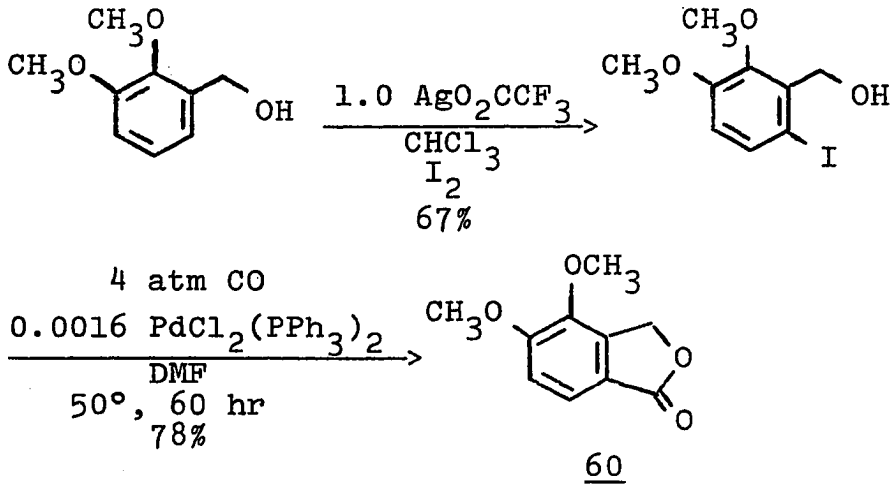
material is exactly the same as ours, it took five steps to accomplish what our method did in two steps. Syntheses of pseudomeconin have appeared only sporadically in the recent literature. One entailed the lithium borohydride reduction of 3,4-dimethoxyphthalic anhydride, which gave a mixture of isomers [115]. Another was achieved by the chloromethylation of 3,4-dihydroxybenzoic acid, followed by formation of the methyl ethers with diazomethane (eq. 61) [116].



(61)

60

Once again, chloromethylation gave a poor yield. Most of these previous syntheses demonstrate clearly the disadvantages of using chloromethylation to introduce a group into the ortho position of a substituted benzene ring. Directed ortho metallation conveniently avoids this, as we have shown. Very recently, Stille developed an approach very similar to ours, in which he generates an ortho metallated intermediate from 2,3-dimethoxy-6-iodobenzyl alcohol (eq. 62)



60 (62)

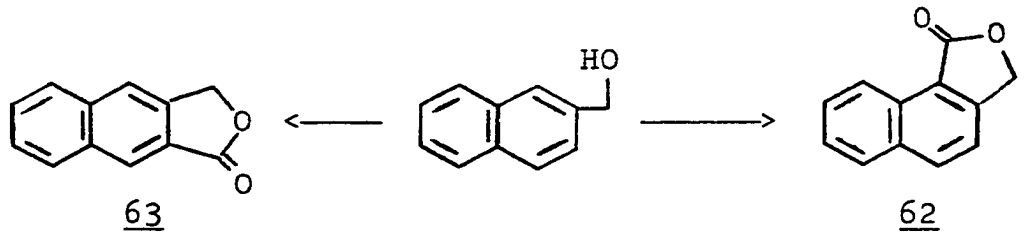
[61]. The overall yield of 60 is 52%, which compares favorably with our yield from the same starting material. However, a stoichiometric amount of silver trifluoroacetate, which is 2½ times as expensive as the corresponding commercial thallium reagent, is required to prepare the iodo compound.

Thallation and carbonylation of two benzyl alcohols with groups deactivating the ring towards electrophilic

aromatic substitution were also attempted for comparison purposes. Since a chloro group is a moderately deactivating ortho, para director, we hoped to obtain 5-chlorophthalide from 3-chlorobenzyl alcohol (entry 4 in Table IX). Indeed, this substrate required stronger thallation conditions than unsubstituted benzyl alcohol, which is stirred for one day at room temperature in trifluoroacetic acid; such conditions gave only 7% product, 31% unreacted starting material, and 44% 3-chlorobenzyl trifluoroacetate. Refluxing in trifluoroacetic acid for three hours afforded an optimized yield of 45%, although 28% starting material and 0.5% trifluoroacetate ester still were observed. The low isolated yield shown in Table IX was from an early attempt on a larger scale, when the thallation reaction mixture was refluxed only one hour. Subsequent higher GLC yields resulted from improved thallation conditions.

Using a more strongly deactivating group prevented the reaction completely. Because a nitro group is a meta director, we tried to prepare 6-nitrophthalide from 4-nitrobenzyl alcohol (entry 5 in Table IX). Thallating either at room temperature for nineteen days or at reflux for one day in trifluoroacetic acid gave no product whatsoever, and both times starting material was recovered nearly quantitatively. Attempts to prepare 6,7-benzophthalide (naphtho[1,2-*c*]furan-1(3*H*)-one) from 2-naphthalenemethanol

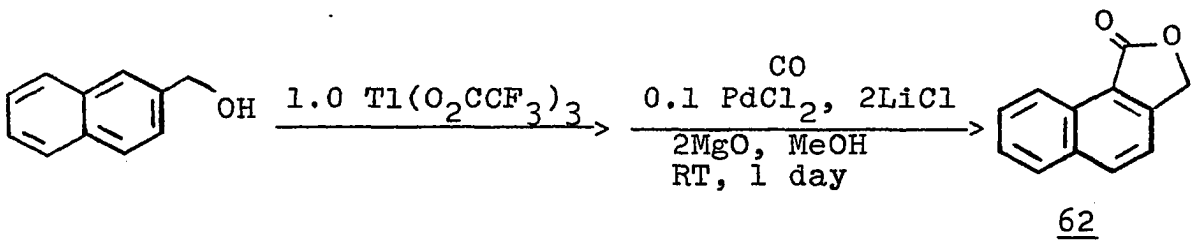
met with disaster (entry 8 in Table IX). Since electrophilic substitution in naphthalene occurs preferentially in the α-position, we expected that α-thallation should lead to 62 (eq. 63). Indeed, comparison of GLC traces of an authentic



63 62 (63)

sample of the isomeric linear 5,6-benzophthalide 63 and of our reaction mixtures showed that no 63 was formed, whereas a minute amount of 62 was isolated. Problems appeared to arise during thallation. Several different conditions were tried, as shown in Table XI. Using a diluted solvent system (entries 1 and 2) gave mostly unreacted starting material, indicating that stronger conditions were needed. However, thallations run in undiluted trifluoroacetic acid for short periods of time (entries 3 and 5) gave mixtures of starting material and tars. When we added a solution of thallic trifluoroacetate in trifluoroacetic acid to the starting alcohol, the mixture immediately became black. When we attempted this again, and diluted the reaction immediately with THF (entry 4), we were able to isolate a small amount of desired product after carbonylation by preparative GLC. Even though TLC showed that this isolated material was

Table XI. Thallation of 2-naphthalenemethanol



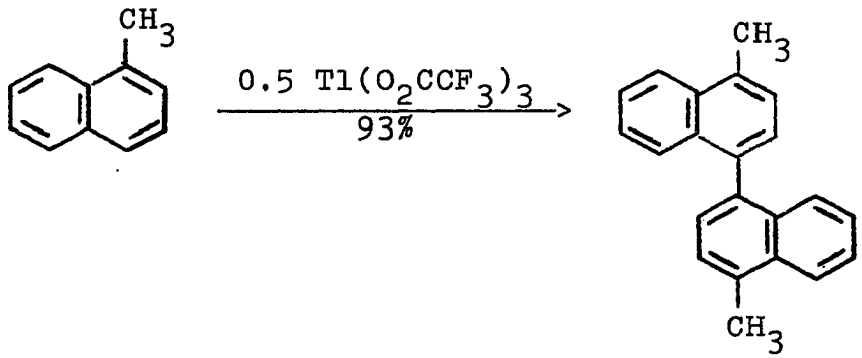
62

Entry	Solvent(s) and Proportions	Temperature, °C	Time	% Recovered Starting Material	% Yield[a] of 62
1	THF + TFA 5:1	25	1 day	87	0
2	THF + TFA 1:1	25	1 day	∿100	0
3	TFA	25	10 min	21	<5
4	TFA, then added THF 1:1	0→25	1 day	∿20	4
5	TFA	0	7 min	∿20	<5

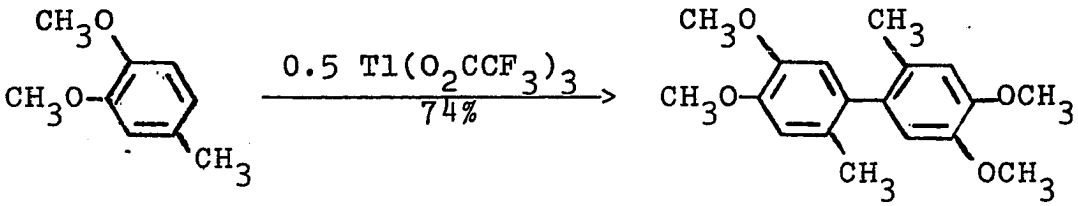
[a]Isolated yield.

contaminated with at least five other compounds, and the melting point was low, the NMR spectrum was consistent with structure 62.

One competing reaction which may be responsible for such low yields is thallium-promoted coupling. Recently, it was reported that aromatic compounds with lower oxidation potentials such as naphthalenes and polyalkoxybenzenes more readily undergo oxidative coupling than electrophilic aromatic substitution in the presence of thallic trifluoroacetate (eqs. 64, 65) [104, 117]. This is thought to involve

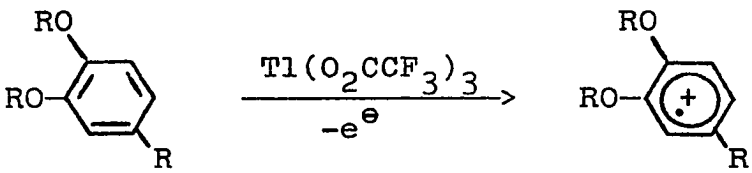


(64)



(65)

initial electron transfer from the aromatic substrate to Tl(III), which generates a radical cation (eq. 66). This

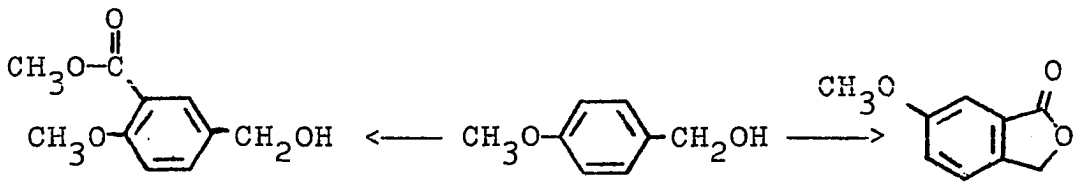


(66)

electrophile then reacts with another molecule of aromatic substrate, and the resulting intermediate is aromatized

oxidatively by Tl(III). In fact, in recent years there has been a growing number of reports concerning the utility of thallic trifluoroacetate-promoted oxidative coupling in organic synthesis as a method complementary to the Ullmann reaction [104, 117-121]. Most likely, this is the origin of the tars and other products observed in our reaction with 2-naphthalenemethanol. In the reactions with 2,3- and 2,5-dimethoxybenzyl alcohols described previously, it is highly probable that the dimethoxyaryl substrates also underwent similar coupling; the occurrence of this side reaction may be one reason for our moderate yields of the corresponding phthalides.

The next compound studied was p-anisyl alcohol (Table IX, entry 9). The object was to investigate which group exerted a stronger influence during thallation (eq. 67). If the



64 65 (67)

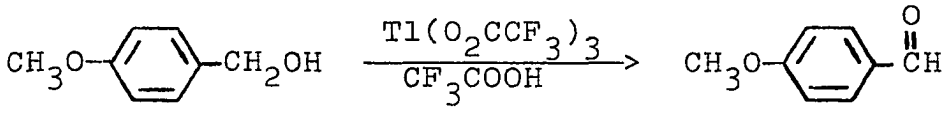
thallation were to proceed as usual, with the initial complexation of thallium salt with the alcohol and subsequent intramolecular ortho delivery of thallium, the product should be 65. If, however, the effect of the methoxy group, a moderately powerful ortho, para director in electrophilic

aromatic substitution, were stronger than complexation with the alcohol, then 64 should be formed (carbonylations are normally run in methanol, hence the methyl ester).

The thallation-carbonylation sequence was performed several times, with dismal results. Observation of the thallation reactions indicated that things were going wrong from the start. Normally, thallation reaction mixtures were clear, yellow to colorless solutions when the reagents were mixed, and some darkened gradually. When trifluoroacetic acid was the only solvent employed, the arylthallium compound usually precipitated out as a white solid after one day. Reactions diluted with THF remained clear and nearly colorless. However, when 4-methoxybenzyl alcohol was thallated in trifluoroacetic acid at -25° (the same conditions used for anisole), the mixture immediately became thick and dark red, and after 15 minutes it was a purplish-black goo. Subsequent carbonylation gave only an intractable tar. GLC analysis showed only a trace of starting material visible, whereas TLC showed a smear all the way up the plate.

Thallation in the diluted solvent system appeared to work better. The solution was clear and pale yellow, even after stirring one day at room temperature. Unfortunately, the mixture developed the color and consistency of grape jelly while the solvents were being removed. The material was carbonylated anyway. Analysis of the crude reaction

mixture by TLC showed some starting material present, plus four other fairly distinct spots. The mixture was chromatographed on a silica gel column to facilitate characterization. The first group of fractions eluted contained a single product, which NMR, IR, and MS indicated was p-anisaldehyde. This was confirmed by GLC upon co-injection with an authentic sample. The formation of this aldehyde was an unexpected development, as we had not observed it previously. Since the commercial substrate contained no aldehyde, we believe that it was formed during the thallation reaction (eq. 68).



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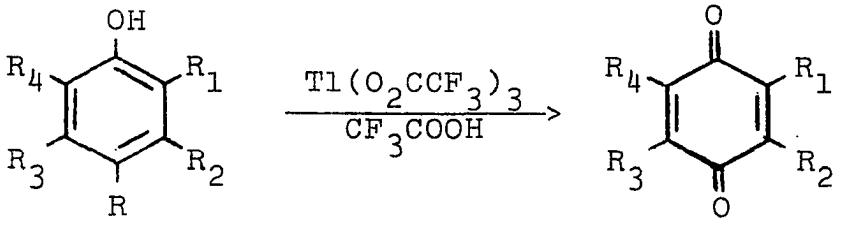
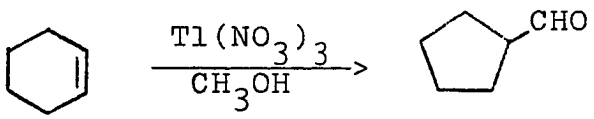
Thallic trifluoroacetate has been used as an oxidizing agent in the past, as in the synthesis of p-quinones from phenols (eq. 69) [122,123], and in the oxidative coupling reactions



(69)

mentioned above [104,117]. Other thallium(III) salts, such as thallic acetate, thallic nitrate, and thallic sulfate, are known to produce aldehydes during oxythallations of olefins (eqs. 70, 71) [95]. However, as far as we know, the



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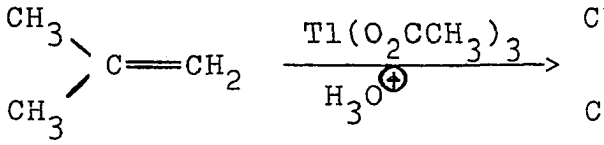


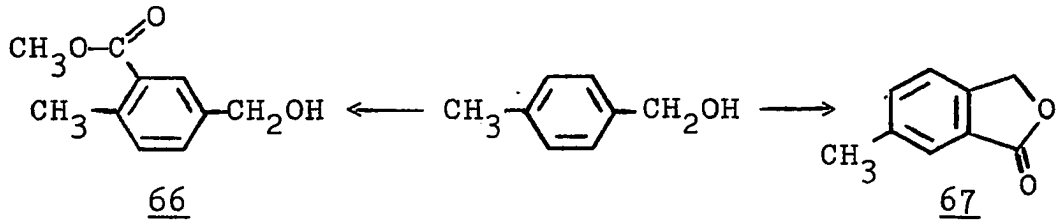
(71)

formation of aryl aldehydes from benzyl alcohols in the presence of thallic trifluoroacetate has not been reported. A possible mechanism for this transformation will be discussed in the mechanism section of this chapter.

The second group of fractions eluted contained a mixture of unreacted starting material and p-anisaldehyde. The total yield of aldehyde in this reaction was 12%, whereas 10% of the starting material was recovered.

The third group of fractions contained at least eight compounds, which, as shown by GC-MS, had molecular weights above 300. Although none was readily identifiable, the IR spectrum of this mixture showed a strong carbonyl absorption at 1730 cm^{-1}, a common absorption for esters of aryl acids. The NMR spectrum showed only aromatic-ring and methoxy protons. Presumably, these compounds are coupling products in various stages of oxidation, some of which may have thallated and carbonylated. There was no evidence whatsoever for either of the predicted products 64 or 65. This system was not investigated further.

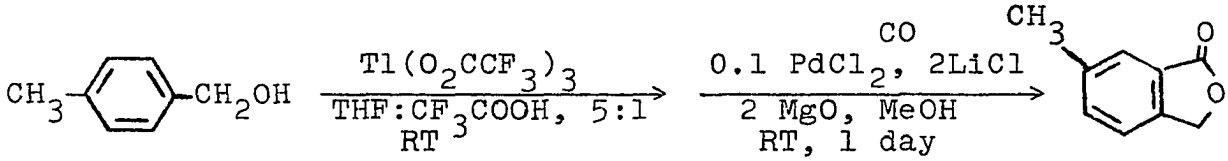
4-Methylbenzyl alcohol was studied next (entry 10 in Table IX). Since a methyl group is a less powerful ortho, para director than a methoxy group, we anticipated that it might not interfere with thallation ortho to the benzyl alcohol to such a large extent. Furthermore, alkylbenzenes have relatively high oxidation potentials, and more readily undergo electrophilic aromatic thallation than oxidative coupling [119]. The reverse is true for alkoxybenzenes, which have lower oxidation potentials and are more likely to couple. Once again, two products, 66 and 67, were possible (eq. 72). When the thallation reaction was run in neat



66 67 (72)

trifluoroacetic acid, the reaction sequence gave only tars. We finally had some success when we diluted the trifluoroacetic acid with a five-fold volume of THF, as for the methoxybenzyl alcohols. 6-Methylphthalide was isolated and characterized (see Experimental Section). This compound is apparently unknown in the literature. The best yield was obtained when the substrate was thallated for two days, as shown in Table XII. However, nearly half of the starting alcohol was recovered. Longer thallation did not improve

Table XII. Synthesis of 6-methylphthalide from 4-methylbenzyl alcohol



Thallation Time, Days	% Yield[a]		
	6-Methylphthalide	Starting Ar-CH_2-OH	Ar-CH_2-O(C=O)CF_3
1	8	51	trace
2	23	48	trace
3	20	39	∿2
5	∿2	36	trace

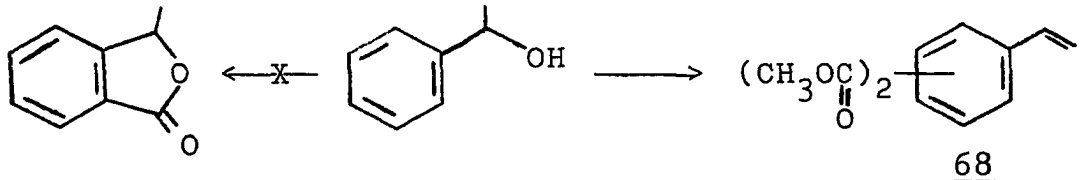
[a]GLC yield using phthalide as an internal standard.

the yield. Only a trace of p-methylbenzyl trifluoroacetate was seen.

Interestingly enough, some aldehyde was observed by IR and NMR in the crude reaction mixture, although not as much as in the reaction with 4-methoxybenzyl alcohol. The reaction sequence with benzyl alcohol was repeated to see whether any benzyldehyde would form. This indeed proved to be the case, as about 1% benzaldehyde was recovered by column

chromatography. Evidently, aldehyde formation is a common side reaction for these alcohols, albeit a minor one.

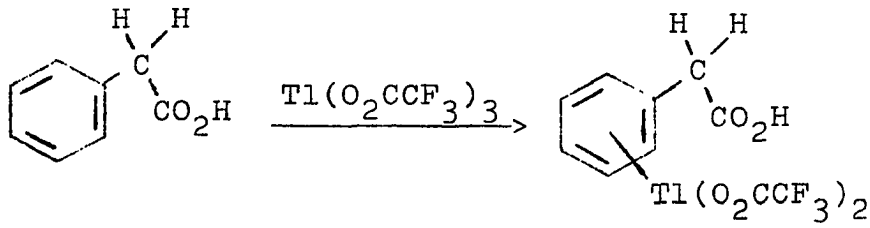
Benzyl alcohols substituted in the α-position failed to thallate in the ortho position. Reactions run with α-phenethyl alcohol gave none of the desired 3-methylphthalide (eq. 73). However, GLC analysis of the final reaction



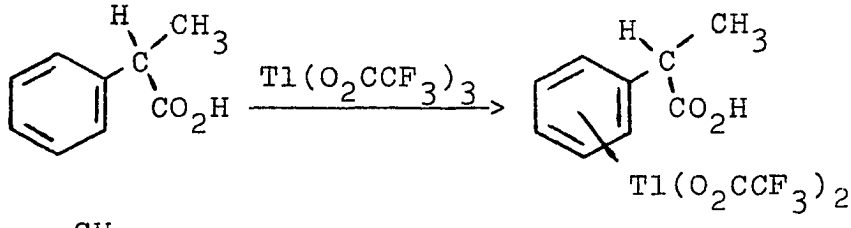
(73)

68

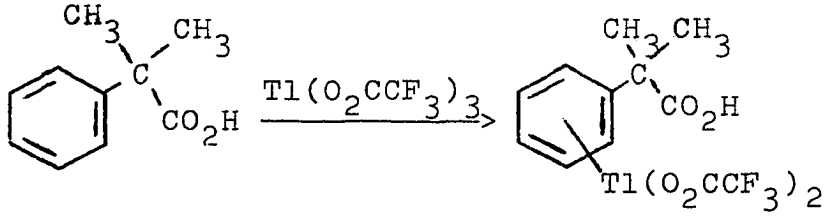
mixture revealed that much starting alcohol was present, along with at least two other products. One of these was isolated and identified as disubstituted styrene 68 by GC-MS, IR, and NMR spectra. Evidently the strongly acidic thallation conditions promote elimination in the secondary benzylic alcohol, leading to the styrene. Thallation occurs at other sites on the ring, which is followed by carbonylation and esterification with methanol. Had elimination not occurred, the yield of phthalide would undoubtedly have been modest at best, as ortho delivery of thallium is extremely sensitive to steric hindrance [93]. Such hindrance increases as the interfering group is moved closer to the complexation site. This was observed in the thallation of α-substituted phenylacetic acids (eqs. 74-76) [93]. One methyl group in



, o:m:p = 92:3:5 (74)



, o:m:p = 65:11:24(75)



, o:m:p = 0:37:63 (76)

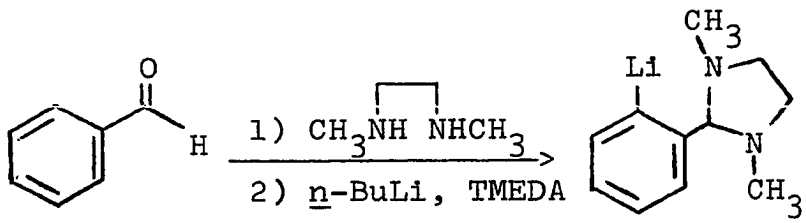
the α-position reduces significantly the proportion of ortho thallation, and two methyl groups prevent it entirely. In the case of α-phenethyl alcohol, the oxygen which should coordinate with the thallium is on a side chain one carbon atom shorter than in the phenylacetic acids, suggesting that the interfering α-methyl exerts a devastating steric effect. This is an unfortunate limitation of our reaction sequence, since 3-alkylphthalides are quite important, as discussed in the introduction to this chapter.

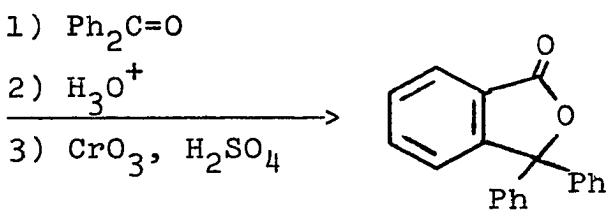
Triphenylcarbinol also gave no phthalide product, but this is hardly surprising in view of the tremendous steric barrier to ortho thallium delivery. Instead, a single compound

was isolated, which melted at 74-76°C. This was shown by NMR, IR, and MS to be methyl trityl ether (literature melting point, 82° [124]), obtained in 91% yield. Evidently, the triphenylmethyl carbonium ion forms as soon as triphenylcarbinol is exposed to trifluoroacetic acid, giving trityl trifluoroacetate, which, in turn, undergoes methanolysis in the second step of the reaction (eq. 77). The compound we

$$Ph_3C\text{-}OH \xrightarrow{CF_3COOH} Ph_3C\text{-}O\overset{O}{\overset{\|}{C}}CF_3 \xrightarrow{CH_3OH} Ph_3C\text{-}OCH_3 \qquad (77)$$

had hoped to prepare from triphenylcarbinol, 3,3-diphenylphthalide, 69, was synthesized very recently from benzaldehyde by Harris and Roth via directed ortho lithiation (eq. 78) [125]. Their overall yield was 48%.





(78)

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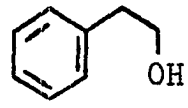
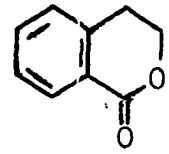
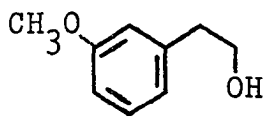
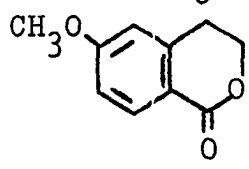
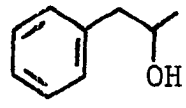
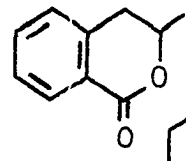
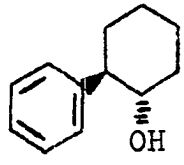
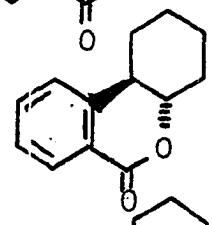
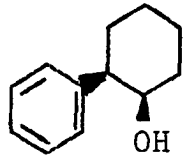
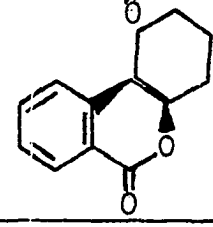
3. 3,4-Dihydroisocoumarins

3,4-Dihydroisocoumarins were prepared from β-phenethyl alcohols using our thallation-carbonylation sequence. Our results are summarized in Table XIII.

Preparation of the parent compound in this series (entry 1 in Table XIII) was more successful than in the case of phthalide. Yields were very sensitive to reaction conditions, as shown in Table XIV. The best set of conditions included thallation of β-phenethyl alcohol for one day, followed by carbonylation in methanol with two equivalents of magnesium oxide added (entry 1 in Table XIV). Thallating for two days instead of one significantly lowered the yield (entries 6 and 7). Using less magnesium oxide (one equivalent or none, entries 2 and 4) or using lithium carbonate (entry 3) during carbonylation decreased the yield somewhat, while changing the carbonylation solvent from methanol to THF drastically reduced the yield (compare entries 2 and 5). The reaction sequence was run again on a larger scale, using our best conditions, in order to examine the composition of the final reaction mixture more carefully. After work-up, a GLC trace of the mixture showed that the major component was the desired product, 3,4-dihydroisocoumarin. Starting β-phenethyl alcohol and its trifluoroacetate ester were also present; taken together, the amounts roughly equalled that of the product. In addition, a small peak having a longer

Table XIII. 3,4-Dihydroisocoumarins from β-phenethyl alcohols

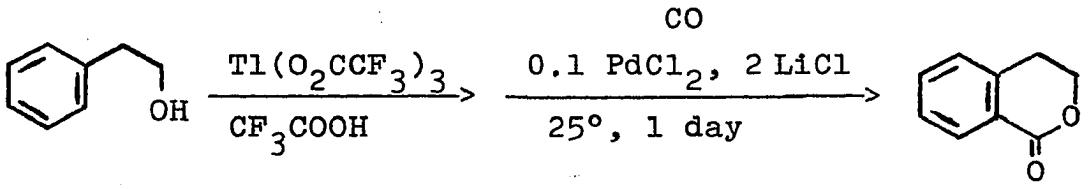
Entry	Alcohol	Product	% Yield[a]	Purification	Mp,°C	Lit. mp, °C
1			51(27)	Column Chromatography on Silica Gel	Oil	Oil[b]
2			58(45)	Column Chromatography on Silica Gel	60-62	68 [66, 126]; 71-72 [127]
3			75(58)	Preparative GLC	25-28	30 [128]; 53 [82]
4			77(43)	Recrystallized from EtOAc/ hexane	86-88	Unknown
5			88(9)[c]	Preparative GLC	80-84	Unknown

[a]GLC analysis using an internal standard (isolated, purified yield).

[b]Literature boiling point 176°/20 mm [82].

[c]Much product was lost during purification. Shortage of starting material prevented an optimized yield.

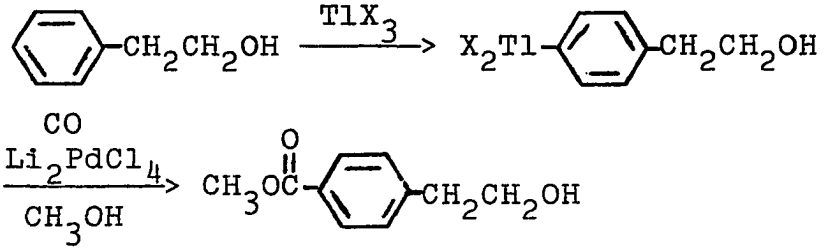
Table XIV. Synthesis of 3,4-dihydroisocoumarin from β-phenethyl alcohol



	Thallation Conditions		Carbonylation Conditions		
Entry	Temperature °C	Time, Days	Solvent	Equivalents of Added Base	% Yield[a]
1	0→25	1	CH_3OH	2 MgO	51
2	0→25	1	CH_3OH	1 MgO	48
3	0→25	1	CH_3OH	1 Li_2CO_3	42
4	0→25	1	CH_3OH	none	40
5	0→25	1	THF	1 MgO	14
6	0	2	CH_3OH	2 MgO	22
7	0	2	CH_3OH	1 MgO	18

[a]GLC analysis using an internal standard based on 1 mmol $PhCH_2CH_2OH$.

retention time than that of 3,4-dihydroisocoumarin was observed. The mixture was then chromatographed on a silica gel column. In all, 27% pure product was obtained, although other fractions contained product which was contaminated by starting material. The unknown material corresponding to the small peak seen in the GLC trace was isolated. NMR and IR spectra indicated that this was methyl 4-(2-hydroxyethyl)-benzoate, which was confirmed later by an exact mass spectrum. Most likely, this resulted from para thallation of β-phenethyl alcohol, followed by carbonylation and esterification (eq. 79). The isolated yield of this ester was 15%.



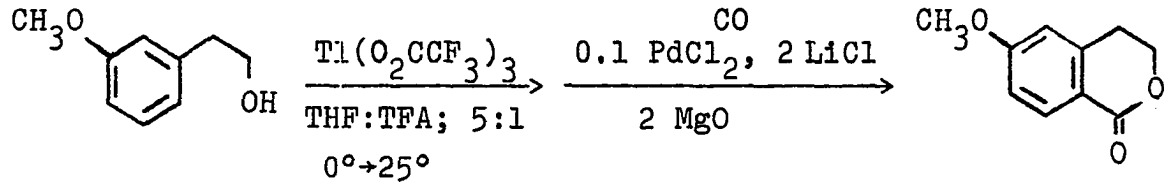
(79)

No product stemming from meta thallated substrate was isolated. Re-examination of the reaction run on a smaller scale for the optimized GLC yield showed that 15% of the para ester was indeed present. This relatively high percentage of para thallation was not too surprising, in view of the statistics reported by Taylor, et al. [93]. Thallation of β-phenethyl alcohol gave them an ortho:meta:para isomer distribution ratio of 83:6:11, with a 33% overall yield of

crude product. However, they stated that they made no attempt to optimize yields. It is possible that their isomer distribution is not completely correct, in view of their low overall yield. Our results lend support to their observation that the percent ortho thallation falls off when the size of the chelate ring during thallation is increased, and is very noticeable even when going from a five- to a six-membered ring. Oxidation of the starting alcohol to the corresponding aldehyde was not observed in this reaction.

Several substituted β-phenethyl alcohols were studied next. 3-Methoxy-β-phenethyl alcohol (entry 2 in Table XIII) was thallated in the diluted solvent system we developed for activated benzyl alcohols. The presence of an activating group on the ring did not result in as dramatic an improvement in yields as in the benzyl alcohol series; the yield of 6-methoxy-3,4-dihydroisocoumarin was only slightly better than the yield of the parent compound. When 3-methoxy-β-phenethyl alcohol was thallated for one day and then carbonylated, significant amounts of the starting alcohol and the trifluoroacetate ester of the starting alcohol were observed in the mixture after one day's carbonylation (entries 1 and 2, Table XV). Thallating the starting alcohol for longer periods of time had very little effect, as nearly the same yields of product were obtained as before, with approximately the same amounts of starting material

Table XV. Synthesis of 6-methoxy-3,4-dihydroioscoumarin



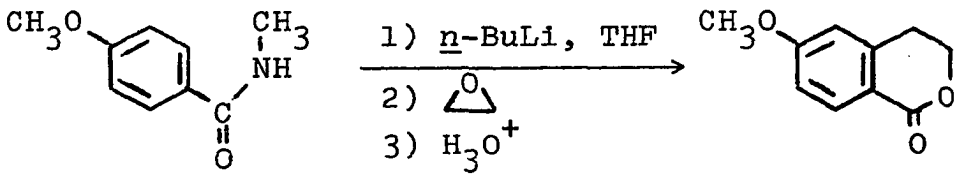
Entry	Thallation Time	Carbonylation Solvent	Carbonylation Time	% Yield[a]	% Residual Starting Alcohol[a]	% Trifluoroacetate Ester of Starting Alcohol[a]
1	1 day	THF	1 day	56	3	18
2	1 day	CH_3OH	1 day	41	27	0
3	2 days	THF	1 day	47	4	34
4	2 days	CH_3OH	1 day	45[b]	---[b]	---[b]
5	3 days	THF	1 day	58	6	14
6	3 days	THF	3 days	56	16	2

[a]GLC yield using phenyl benzoate as an internal standard.

[b]Isolated, purified yield. Rest of data not available.

still present (entries 3 and 5). Since thallation is a freely reversible reaction, even longer thallations very likely would not increase the yield. When the thallation of 3-methoxy-β-phenethyl alcohol was run in trifluoroacetic acid for 15 minutes at 25°C, an alternate set of conditions which also led to good yields of 5-methoxyphthalide from 3-methoxybenzyl alcohol, much tar was observed and less than 10% of 6-methoxy-3,4-dihydroisocoumarin was obtained.

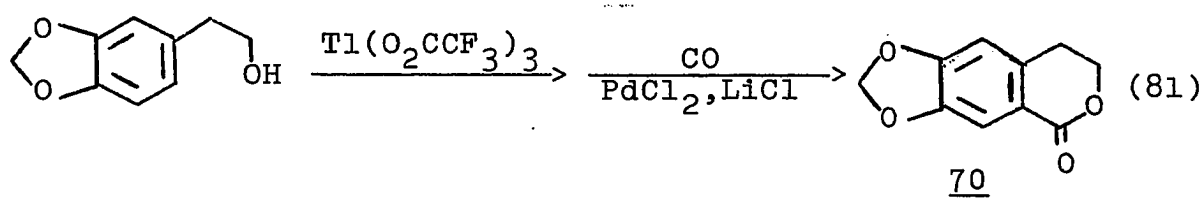
Carbonylating for longer periods of time had very little effect on the yield of product, as can be seen from entries 5 and 6. The proportion of starting alcohol to trifluoroacetate ester changed, but the combined amounts of these two compounds remained nearly constant. Yields of product were somewhat higher when THF rather than methanol was used as the carbonylation solvent. Our overall yield of 6-methoxy-3,4-dihydroisocoumarin is comparable to that reported by Narasimhan and Bhide, whose method was described earlier; they obtained a 50% yield starting from 4-methoxy-N-methylbenzamide (eq. 80) [66].



(80)

Another β-phenethyl alcohol with a moderately activating group on the ring was shown to give good results by some

Japanese workers who used our procedure based on our recent preliminary communication [129]. Irie obtained a 75% isolated yield of 3,4-dihydroisocoumarin 70 using our reaction sequence (eq. 81) [130]. This was a model system



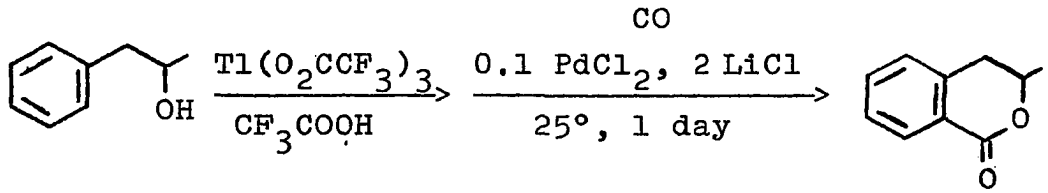
(81)

70

for part of a natural product synthesis to be mentioned later.

β-Phenethyl alcohols with alkyl substituents on the side chain gave us good results (entries 3, 4, and 5, Table XIII). Unlike α-phenethyl alcohol, in which the secondary benzylic alcohol preferentially underwent elimination, 1-phenyl-2-propanol gave 3-methyl-3,4-dihydroisocoumarin in fairly good yields (entry 3). This may be the case here because the hydroxyl group is not in the benzylic position, which would reduce the tendency to eliminate. Another contributing reason may be the fact that the side-chain methyl group is not α to the ring in this substrate, which lessens steric interference at the thallation site. Yields were optimized by adjusting certain reaction conditions, as shown in Table XVI. Changing the temperature or the duration of the thallation reaction appeared to have little effect (entries 1, 2, 3, 10, 11). Addition of bases to the carbonylation

Table XVI. Synthesis of 3-methyl-3,4-dihydroisocoumarin

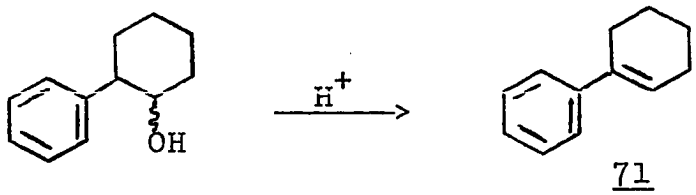


	Thallation Conditions		Carbonylation Conditions		
Entry	Temperature °C	Time, Days	Solvent	Equivalents Added Base	% Yield[a]
1	0	1	CH_3OH	1 MgO	63
2	0	5	CH_3OH	1 MgO	69
3	0	2	CH_3OH	1 MgO	58
4	0	2	CH_3OH	2 MgO	70
5	0	2	CH_3OH	1 Et_3N	56
6	0	2	CH_3OH	1 Li_2CO_3	56
7	0	2	CH_3OH	1 CaO	53
8	0	2	CH_3OH	1 K_2CO_3	23
9	0	2	CH_3OH	1 BaO	19
10	0→25	2	CH_3OH	1 MgO	61
11	0→25	1	CH_3OH	1 MgO	66
12	0→25	1	THF	1 MgO	66
13	0→25	1	CH_3OH	None	52
14	0→25	1	CH_3OH	1 Li_2CO_3	75
15	0→25	1	CH_3OH	1 K_2CO_3	20

[a]GLC yield using diphenylmethane as an internal standard.

mixture had a more noticeable impact (compare entries 13, 11, 14, and entries 3-9). Magnesium oxide or lithium carbonate improved yields significantly. Either methanol or THF appeared to be an equally good carbonylation solvent (entries 11 and 12). In all cases, less than 10% of the starting alcohol was seen on the GLC traces, while the trifluoroacetate ester peak was hidden under the methanol peak.

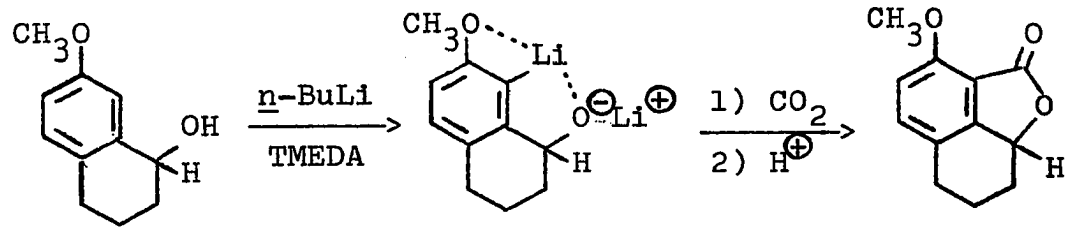
Both trans- and cis-2-phenyl-1-cyclohexanol (entries 4 and 5 in Table XIII), in which the thallation sites are more sterically hindered than in 1-phenyl-2-propanol, gave surprisingly high yields of the corresponding lactones. One would anticipate that the starting alcohol would undergo elimination to conjugated 1-phenylcyclohexene, 71, under the strongly acidic thallation conditions (eq. 82), but no



71 (82)

olefinic protons were observed in NMR spectra of the crude reaction mixtures. The unexpectedly high yield of lactone may be due in part to the somewhat rigid conformation of the alcohol. There is some precedent in the literature for this. In their lithiations of 3-methoxybenzyl alcohol derivatives, Uemura et al. reported that a rigidly held hydroxyl group

stabilized the intermediate lithio compound, giving a greater yield of phthalide than nonrigid systems upon carboxylation (eq. 83) (80% yield of the product shown in eq. 83, as

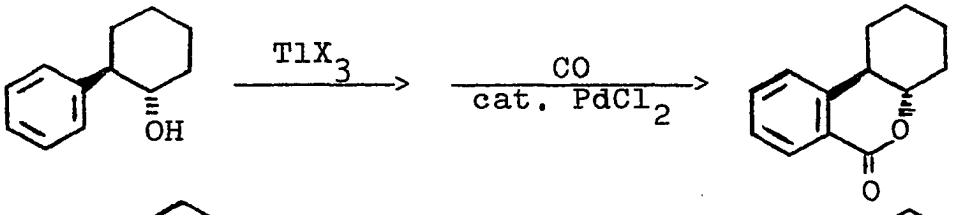


(83)

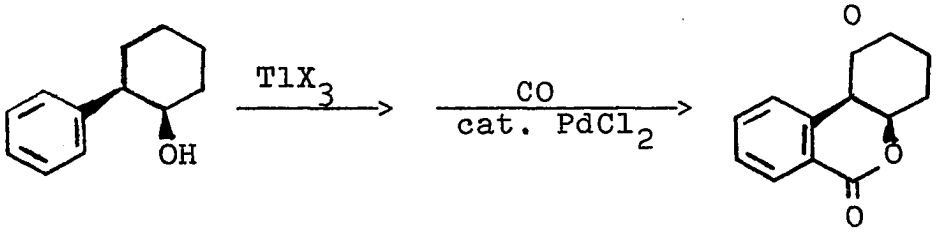
opposed to 53% yield of the parent compound, 7-methoxyphthalide) [69]. In the case of 2-phenyl-1-cyclohexanol, the most stable conformation of the molecule would occur when the rings are roughly at right angles to each other. This would limit severely the rotation around the carbon-carbon bond joining the two rings. The side chain on this molecule has far less rotational freedom than the side chains on β-phenethyl alcohol or 1-phenyl-2-propanol, and thus the hydroxyl group is held in proximity to the desired thallation site, resulting in higher yields. The preferred, nearly perpendicular conformation of the molecule also may be responsible for its resistance to elimination, as it would have to assume a planar conformation after elimination for the resulting olefin to be in conjugation with the adjacent phenyl ring. In our reactions with cis- and trans-2-phenyl-1-cyclohexanol, there was no evidence for elimination or epimerization. The only side products seen in GLC traces

were about 5% unreacted starting alcohol and about 10% trifluoroacetate ester of the starting alcohol.

Entries 4 and 5 in Table XIII demonstrate clearly that our reaction sequence is stereospecific as well as regiospecific, as the trans alcohol gave exclusively the trans fused lactone, whereas the cis alcohol gave only cis lactone (eqs. 84,85). The diastereomers were easily



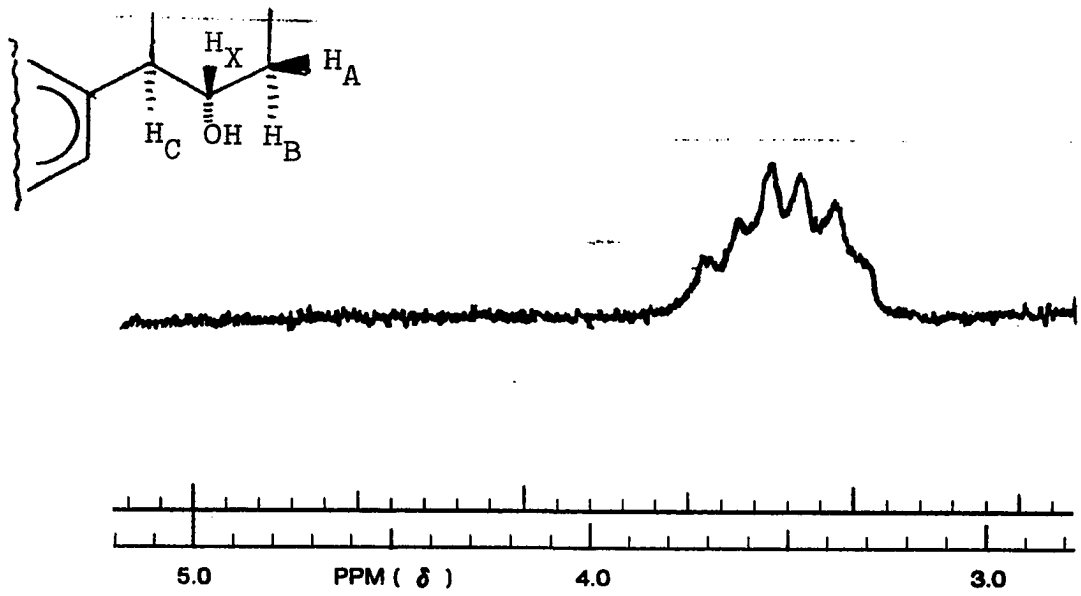
(84)



(85)

identified by NMR through the different chemical shifts and coupling constants for the proton on the carbon adjacent to the lactone oxygen as shown in Figures 1 and 2. The methine proton in question, labeled H_X in Figure 1, exhibits a very well-defined splitting pattern for both the trans alcohol and the trans lactone. According to a molecular model of the trans lactone, the protons labeled H_B, H_X, and H_C in Figure 1 are quite rigidly held in an axial orientation, while H_A is oriented equatorially. The axial-axial coupling constants for H_B-H_X and H_C-H_X are both 10 Hz, while the

Alcohol



Lactone

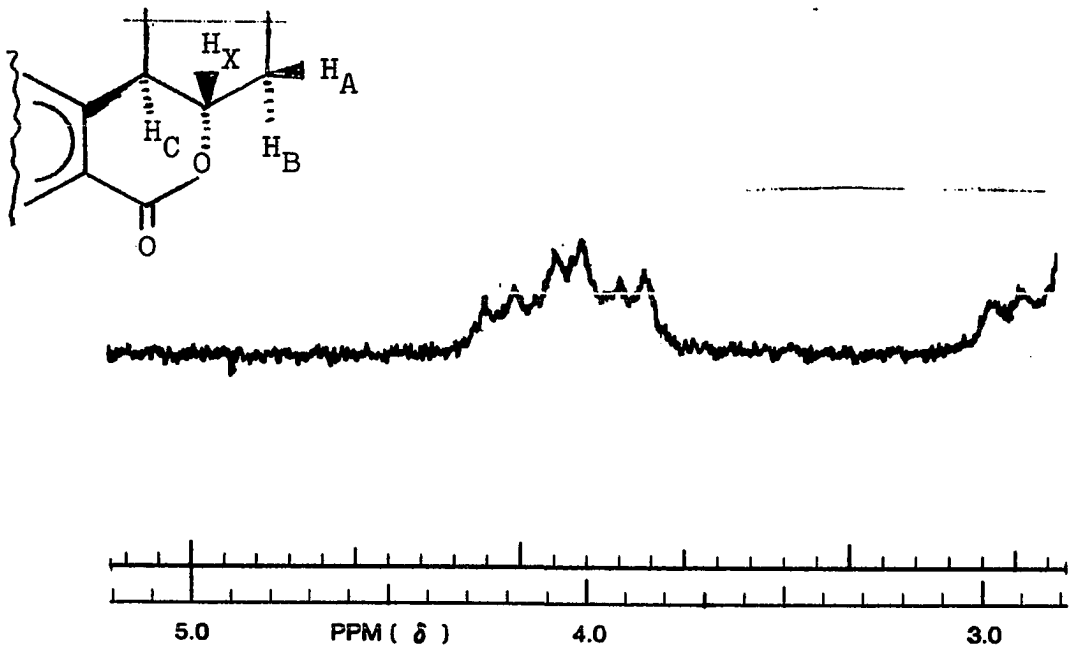
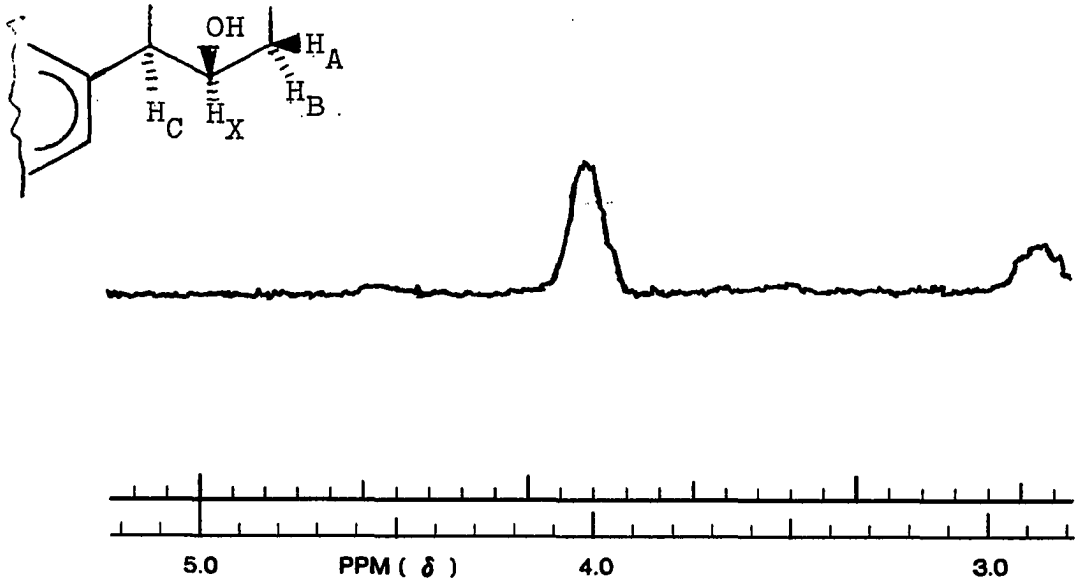


Figure 1. NMR spectra showing splitting of methine proton H_X in trans-2-phenyl-1-cyclohexanol and the trans fused lactone.

Alcohol



Lactone

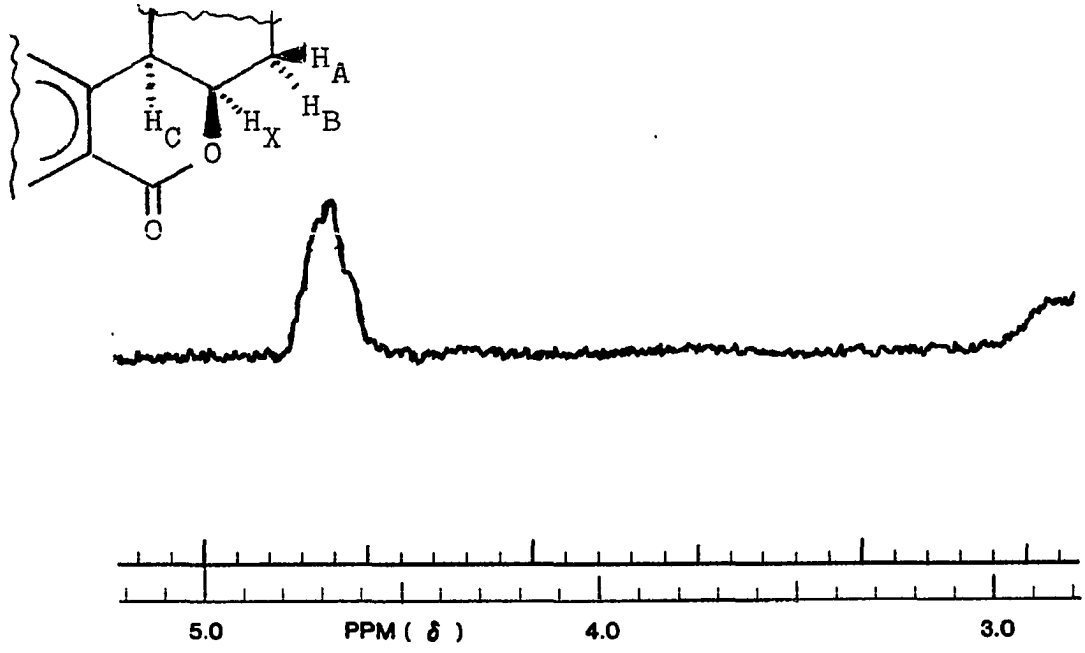
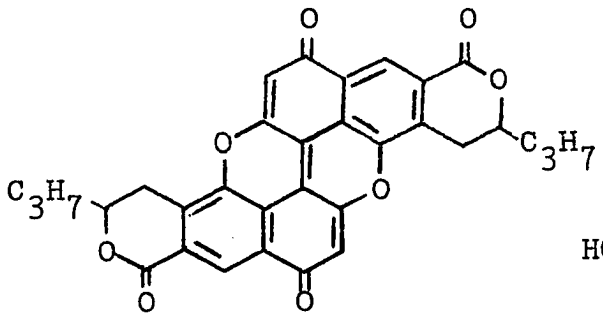


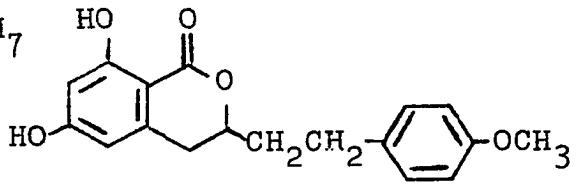
Figure 2. NMR spectra showing splitting of methine proton H_X in cis-2-phenyl-1-cyclohexanol and the cis fused lactone.

axial-equatorial coupling constant for H_A-H_X is 4 Hz. Although H_B and H_C are neither chemical shift equivalent nor magnetically equivalent, they have coincidentally the same coupling constant. In the case of the cis lactone shown in Figure 2, the methine proton H_X is now held in an equatorial orientation, thus precluding any axial-axial coupling. Consequently, the splitting pattern collapses to a broad singlet.

These syntheses of 3-substituted and polycyclic 3,4-dihydroisocoumarins are very encouraging, considering that a number of naturally occurring 3,4-dihydroisocoumarins and isocoumarins are structurally similar. Besides the several compounds mentioned in the introduction to this chapter, examples of such natural products include the green mold pigment xylidein, 72 [75]; agrimonolide, 73 [131-133],

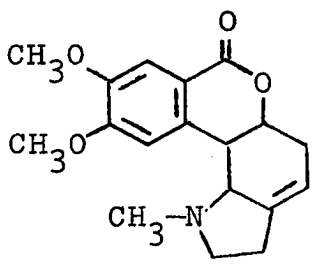


72

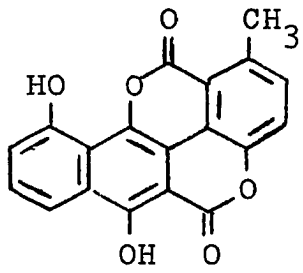


73

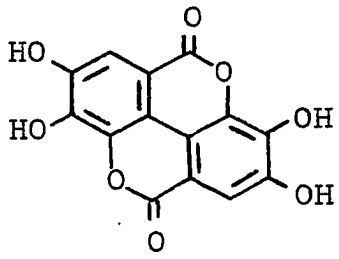
from the roots of Agrimona pilosa; the narcissus alkaloid homolycorine, 74 [134-136]; the aglycon of the antibiotic chartreusin, 75, recently synthesized by Kelly et al. [137]; and the yellow plant pigment ellagic acid, 76 [2]. One



74

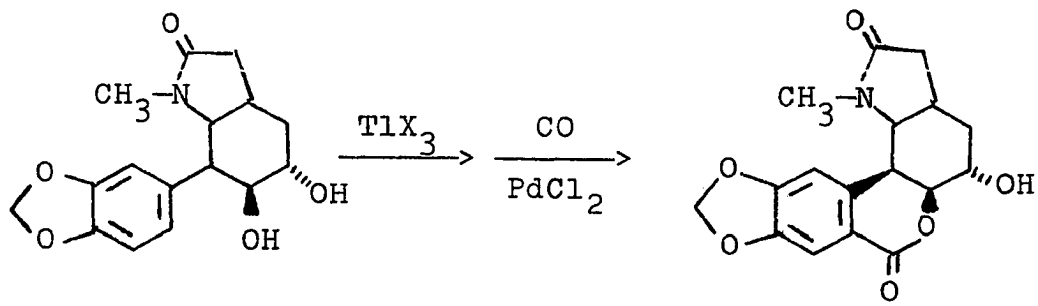


75



76

such natural product synthesis employing our procedure was attempted very recently. Irie prepared alkaloid 77 by thallation and palladium-promoted carbonylation of the appropriately substituted β-phenethyl alcohol (eq. 86) [130].



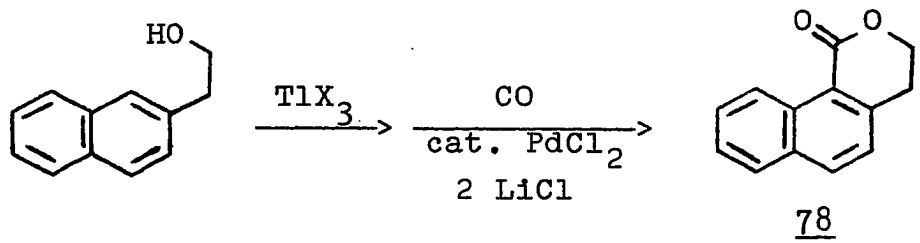
(86)

77

The model system, mentioned earlier, underwent thallation and carbonylation very well, but in this reaction, 77 was obtained in only 5% yield. We believe that the second

hydroxyl group, γ to the aromatic ring, may have been responsible for the poor yield by forming a Lewis acid-Lewis base chelate with thallium(III) trifluoroacetate, thus effectively preventing thallation on the ring. Appropriate blocking or masking of this second hydroxyl group may increase the yield considerably.

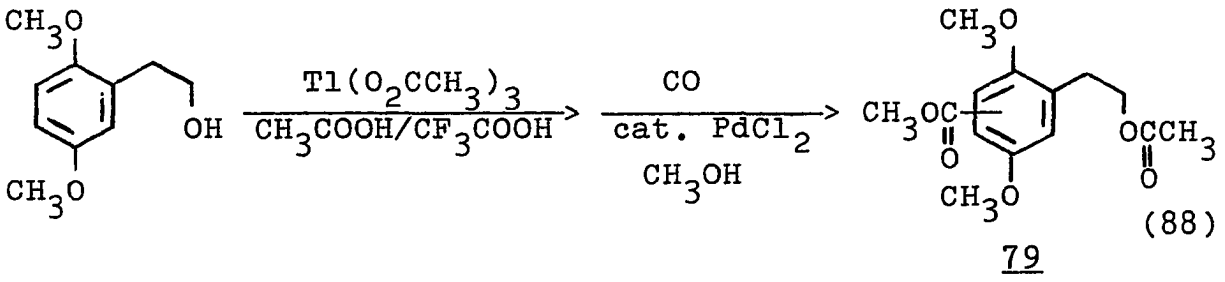
Two other β-phenethyl alcohols failed to give 3,4-dihydroisocoumarins under our reaction conditions. Application of our thallation-carbonylation sequence to 2-naphthaleneethanol (eq. 87) gave a mixture of unreacted



78 (87)

starting material and tars, but none of the desired product, 3,4-dihydro-7,8-benzoisocoumarin, 78, a known compound [138]. Undoubtedly, the naphthalene nuclei underwent thallium(III)-promoted oxidative coupling, as was the case in our nearly futile attempts to prepare the corresponding 6,7-benzophthalide from 2-naphthalenemethanol, as described earlier. 2,5-Dimethoxy-β-phenethyl alcohol was another uncooperative substrate. When thallation was attempted in the diluted trifluoroacetic acid-THF system developed for activated substrates, the final carbonylation mixture

contained mostly unreacted starting material, indicating that harsher conditions were required. Thallation in undiluted trifluoroacetic acid gave only black tar. Finally, thallation was performed with thallic acetate in acetic acid and trifluoroacetic acid (5:1 ratio). Carbonylation produced several compounds, none of which appeared to be the desired 5,8-dimethoxy-3,4-dihydroisocoumarin. The major component of this mixture was isolated by preparative GLC, and identified as 79 from its NMR, MS, and IR spectra (eq. 88). Evidently,



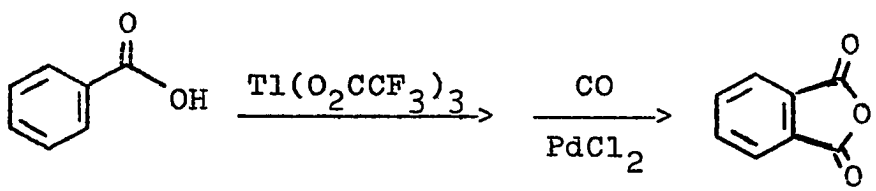
(88)

79

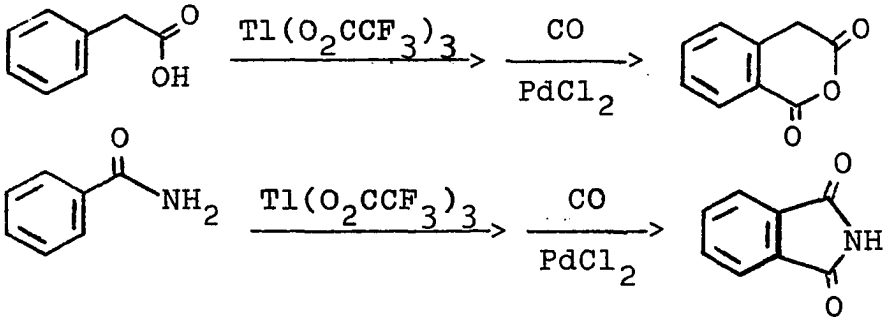
esterification of the starting alcohol occurred, followed by thallation somewhere on the ring; the exact site is unknown. Carbonylation and esterification gave the open-chain compound 79. The desired ortho thallation site in this substrate was sterically crowded, which prevented a high degree of ortho thallation, and the side chain bearing the hydroxyl group was free of constraints that would have forced it and the thallation site into propinquity. It is not surprising, therefore, that esterification of the alcohol occurred before any appreciable thallation in the ortho position could take place.

4. Other heterocycles

When Taylor et al. published their study of orientation control during electrophilic aromatic thallation of monosubstituted arenes, substituents on their substrates included alkyl groups, acids, esters, ethers, and alcohols [93]. We studied in depth the synthetic utility of benzyl and β-phenethyl alcohols which could be thallated selectively in the ortho position. As we have shown in the preceding sections of this chapter, ortho thallated aryl alcohols are indeed useful synthetic intermediates. which afford fairly easy access to the important phthalide and 3,4-dihydroisocoumarin ring systems. Since numerous aryl substrates containing functional groups other than alcohols can be ortho thallated, the palladium-assisted carbonylation of these compounds would extend greatly the versatility of our reaction sequence. In this fashion, one could anticipate the facile synthesis of cyclic anhydrides from acids, imides from amides, and other heterocycles from substrates bearing electron-rich functional groups which could form a five- or six-membered Lewis acid-Lewis base chelate with thallium(III) trifluoroacetate (eqs. 89-91).



(89)



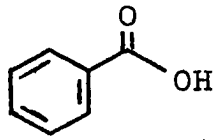
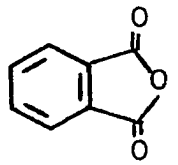
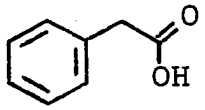
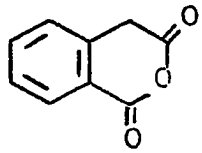
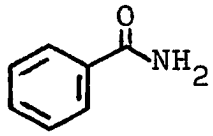
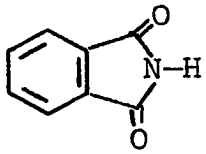
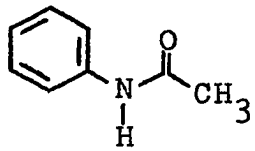
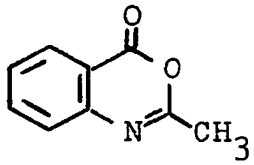
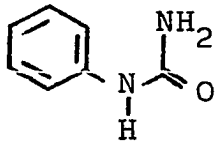
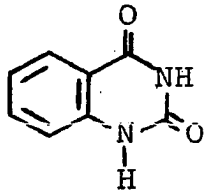
(90)

(91)

Literature data for aromatic acids were encouraging, as benzoic acid reportedly gives an isomer distribution of 95:5:0 for ortho:meta:para thallated material in 76% overall yield, even though an acid group deactivates the ring towards electrophilic aromatic substitution and is normally moderately meta directing [92]. For phenylacetic acid, the reported isomer distribution ratios were 92:3:5 for ortho:meta:para thallation, in overall yields up to 72% [93]. As far as we could ascertain, thallation of aryl amides has not been reported.

A number of aryl acids and amides underwent the reaction sequence to give the cyclocarbonylated products shown in Table XVII. Benzoic acid (entry 1) afforded a 44% GLC yield of phthalic anhydride. Thallation conditions were harsher than for aryl alcohols, because in this case electrophilic aromatic substitution had to occur on a deactivated aromatic ring. Accordingly, the mixture was refluxed overnight in trifluoroacetic acid [92]. Thallation at room temperature

Table XVII. Synthesis of other heterocycles via thallation-carbonylation

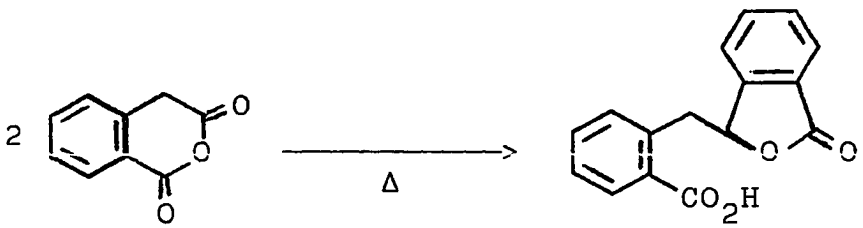
Entry	Starting Material	Product	Mp, °C	Lit. mp, °C	% Yield[a]
1			---	131-133 [139]	44(-)
2			137-139	140.5-141 [140]; 141-142 [141,142]	-(46)[b]
3			---	233-235 [143]	83(-)
4			---	79-80 [144-145]; 80-81 [146]	---[c]
5			---	353-354 [147]	---[c]

[a]GLC yield using an internal standard (isolated, purified yield).

[b]Purified by recrystallization from benzene.

[c]Not isolated as cyclic compound. See Table XVIII, page 109.

gave much lower yields. Even after five days' thallation at room temperature, only a 15% yield of phthalic anhydride was observed. Phenylacetic acid (entry 2) next was subjected to our reaction sequence. Unfortunately, it was impossible to obtain a GLC yield of the desired product, homophthalic anhydride, as all attempts to obtain consistent retention times and peak shapes on GLC traces of the commercial anhydride failed. Sometimes one broad peak was observed, and sometimes two peaks were seen. A search of the literature quickly gave the reason for this phenomenon: homophthalic anhydride is thermally unstable [140]. When heated to temperatures in the range of 210-230°C, the anhydride forms 3-(2-carboxybenzyl)-phthalide, 80 (eq. 92) [148]. The

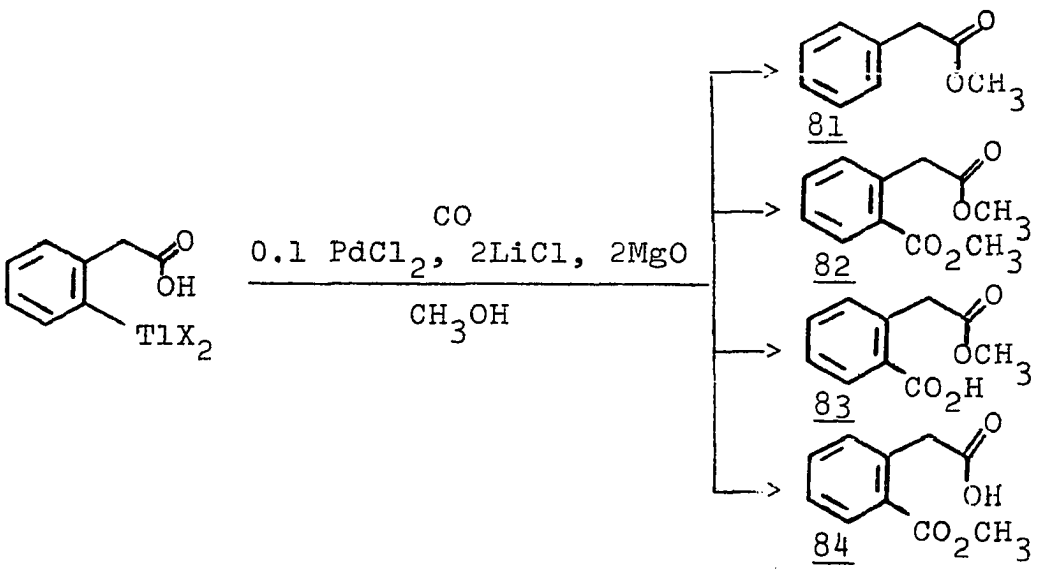


(92)

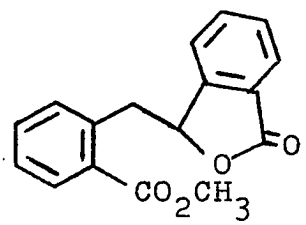
80

injection port on our GLC equipment was set at 250°C, so undoubtedly this was occurring. The possible determination of an isolated yield was considered next. The anhydride is easily soluble in chloroform [140], so it could be extracted away from some of the inorganic salts present in the

carbonylation reaction mixture. However, during work-up, the reaction mixture is usually washed with a saturated aqueous solution of ammonium chloride, and it was feared that the anhydride product might undergo hydrolysis. This would be highly undesirable, as the resulting homophthalic acid is completely insoluble in chloroform, and is only sparingly soluble in cold water [140], which would make isolation extremely difficult. An alternative procedure for obtaining an isolated yield involved using methanol as the carbonylation solvent in order to obtain the open-chain methyl ester, as this would serve as an effective measure of the extent of thallation and carbonylation of phenylacetic acid. Subsequent hydrolysis and heating of the homophthalic acid would give the anhydride [140]. Unfortunately, one could evision a multitude of possible products (eq. 93). Incomplete



esterification of the acid group already present on phenylacetic acid would result in a mixture of 82 and 84, while methanolysis of any anhydride formed could conceivably give rise to 83 and 84. Indeed, when the carbonylation reaction was run in methanol, a mixture of at least four products was observed on the GLC trace. GC-MS showed that the major peak in the final reaction mixture corresponded to 81, methyl phenylacetate, formed by esterification of unreacted starting material. The presence of 82, dimethyl homophthalate, was confirmed, and a compound of molecular weight 282 was observed. Very likely, this was 85, the methyl ester of 80,



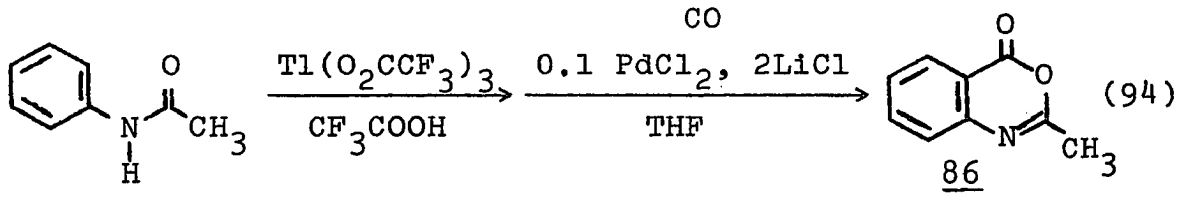
85

formed in the gas chromatograph. Compounds with molecular weights corresponding to 83 and 84 were not detected. In desperation, we tried to isolate the anhydride itself. The carbonylation reaction was run in THF, after which the mixture was diluted with chloroform and filtered. The residue left following evaporation of solvents was extracted repeatedly with chloroform; filtration and concentration of

this solution gave a creamy white solid. Recrystallization from benzene afforded a 46% yield of pure homophthalic anhydride, identical in all respects with authentic commercial material.

Thallation of benzamide (entry 3 in Table XVIII), heretofore unreported in the literature, was accomplished smoothly by using the same conditions as for benzoic acid. Carbonylation gave an 83% GLC yield of phthalimide. Two other aryl amides (entries 4 and 5) also underwent our reaction sequence, but the nature of the products (sensitivity to moisture or insolubility in organic solvents) prevented their isolation as the cyclocarbonylated materials. Instead, these were isolated as open-chain methyl esters (Table XVIII).

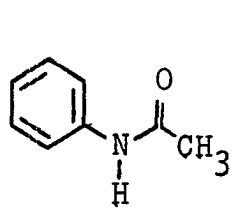
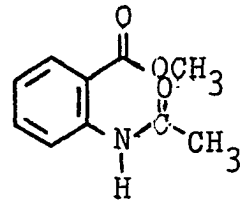
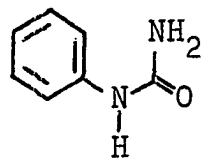
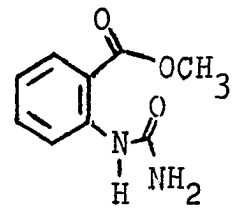
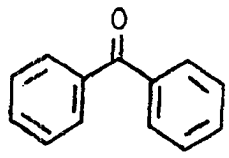
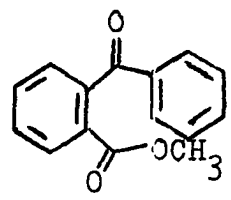
The thallation-carbonylation sequence was applied to acetanilide (entry 4 in Table XVII) in the hope of obtaining acetylanthranil, 86 (eq. 94). Such acylanthranils



86 (94)

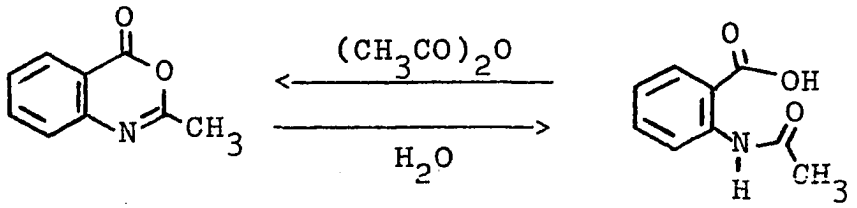
(benzoxazinones) can be regarded as cyclic mixed anhydrides which, when reacted with primary amines, produce physiologically active compounds, hence our interest in this ring system [152-153]. Thallation and carbonylation of

Table XVIII. Compounds isolated as open-chain methyl esters

Entry	Starting Material	Product	Purification Procedure	Mp, °C	Lit. mp, °C	% Yield[a]
1			Column Chromatography on Silica Gel	98	100-101 [149]	39
2			Crystallized from CH_3OH	175-176	177-177.5 [150]	17
3			Column Chromatography on Silica Gel	48-50	52 [151]	63

[a]Isolated, purified yield.

acetanilide would be a milder and, in some cases, a less laborious procedure for making 86 than existing methods [144-146, 154-156]. Thallation of acetanilide was effected by stirring with thallium(III) trifluoroacetate overnight in trifluoroacetic acid. More gentle thallation conditions were employed for acetanilide than for benzamide, because the acetamido group activates the ring moderately towards electrophilic aromatic substitution, and is an ortho, para director. The thallated substrate was then carbonylated in THF, but isolation and characterization were hampered by the sensitivity of acetylanthranil to water. In a moist atmosphere, 86 will hydrolyze to 87, but recrystallization from acetic anhydride reportedly regenerates 86 (eq. 95)

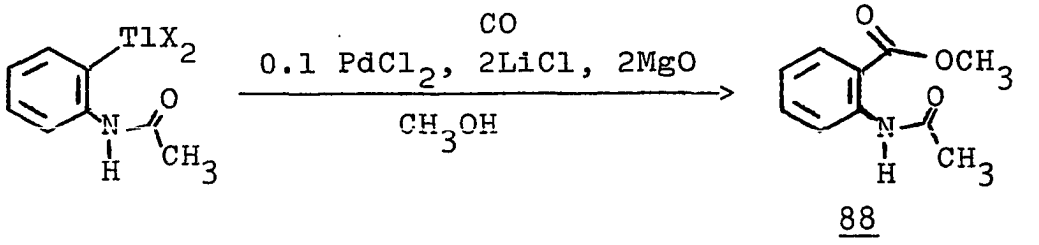


(95)

86 87

[154]. At first, isolation of acetylanthranil itself in a fashion similar to that used for the isolation of homophthalic anhydride was attempted. An IR spectrum of the sticky residue obtained after this work-up did not contain the characteristic bands at 1750, 1630, and 1600 cm^{-1} reported for acetylanthranil [156]. In spite of this, we

believed that some product had been present in the carbonylation mixture, because of the unmistakable odor detected during the first filtration. One of the early references concerning the preparation and properties of acetylanthranil mentions that it "smells like mouse excrement" [146]. This was the odor we noticed, and neither the starting material nor any of the other reagents used had such an odor. However, spectral data and other hard evidence were needed. Exposure of the reaction mixture to water during work-up in the hope of isolating 87 also failed to give any measurable results. Finally, it was decided to run the carbonylation reaction in methanol (entry 1 in Table XVIII) in order to isolate the methyl ester 88, which is not water-sensitive and is easily purified (eq. 96) [149]. This duly afforded a



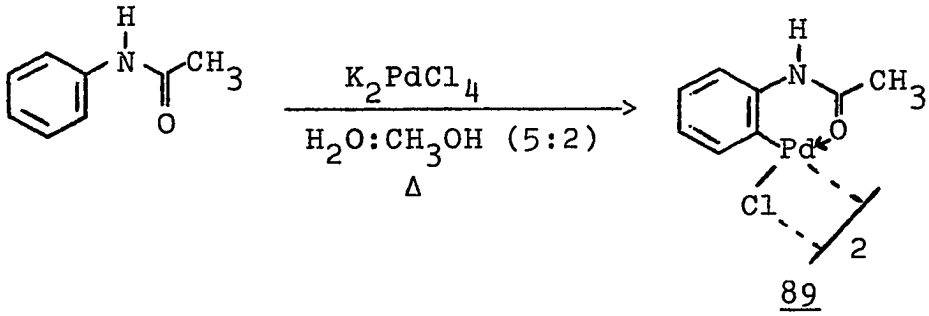
(96)

88

37% yield of pure 88, the methyl ester of N-acetylanthranilic acid. In this instance, when thallation was run for one day, about 28% of residual starting material was recovered from the final carbonylation mixture. A longer thallation time did not improve the yield, as thallation for two days gave

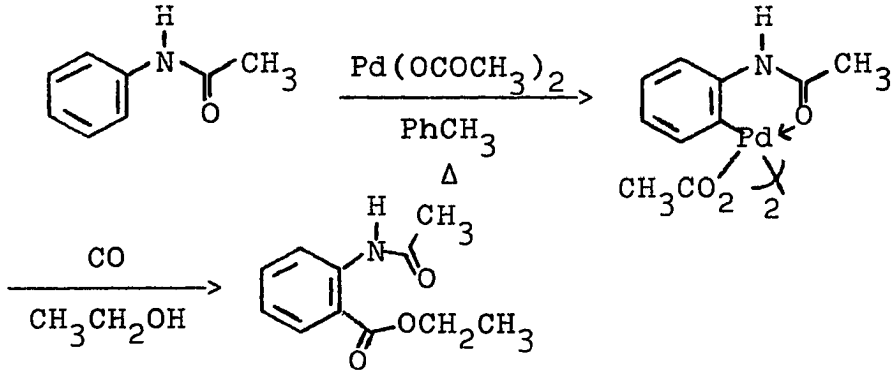
35% of the desired product and residual starting material in approximately the same proportion as observed before.

A search of the recent literature showed that acetanilide is known to undergo direct palladation in the ortho position. In 1975, Cameron and Kilner reported the formation of the six-membered metallocycle 89, but gave no proof of the structure (eq. 97) [157]. In 1979, Horino and Inoue



89 (97)

offered the first chemical evidence for the existence of ortho palladated acetanilide by carbonylating it in ethanol to give the ethyl ester of N-acetylanthranilic acid (eq. 98)

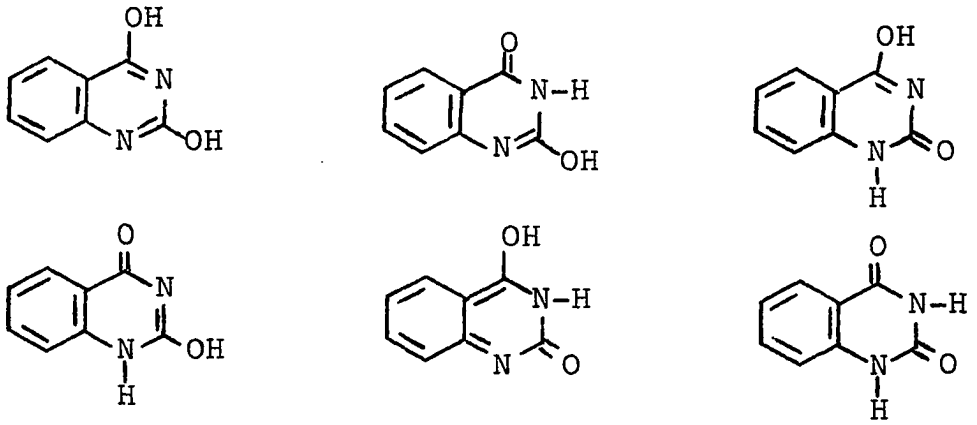


(98)

[74]. Their overall yields of ester from acetanilide ranged from 42% to 55%, somewhat higher than ours. However, their

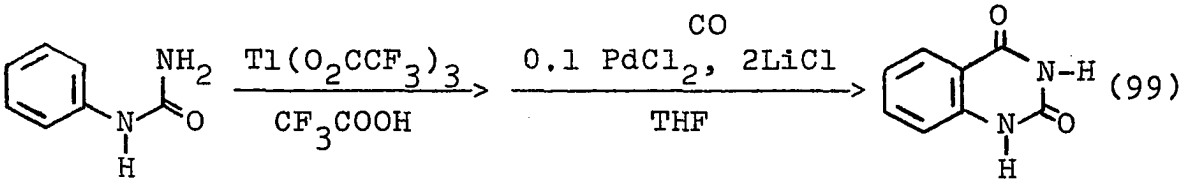
procedure consumes a stoichiometric amount of palladium acetate, whereas our method has the advantage of using only catalytic amounts of expensive palladium chloride.

2,4-(1H,3H)-Quinazolinedione can exist in six possible tautomeric forms, as shown below. Structure 90 is thought



90

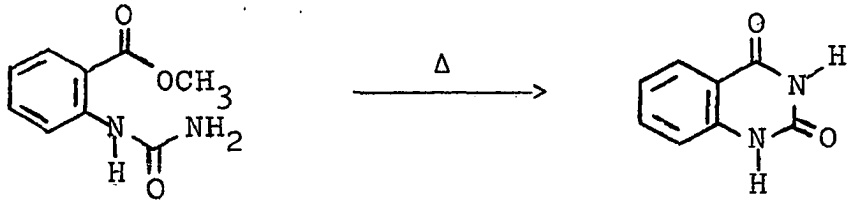
to predominate, due to the existence of two very strong carbonyl absorptions in the IR spectrum at 1720-1780 cm^{-1} and 1655-1712 cm^{-1} [158]. We attempted to prepare compound 90 from phenylurea (entry 5 in Table XVII) using our procedure (eq. 99). However, solubility data from the



(99)

90

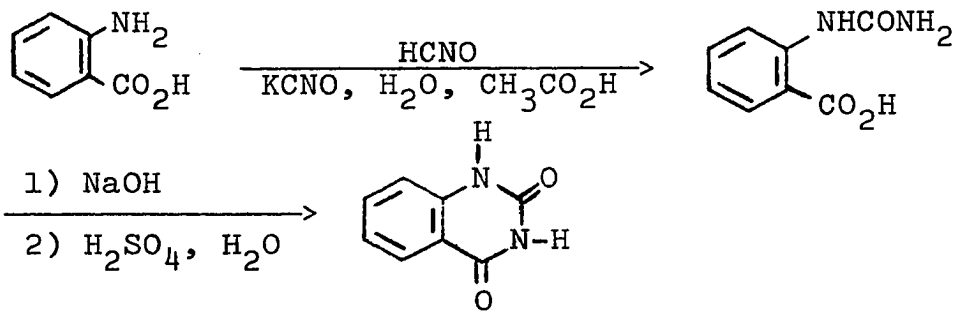
literature indicated that we would encounter much difficulty with the isolation of 90, as it is almost insoluble in most of the common organic solvents, but is somewhat soluble in cold water [147]. Water was added to the carbonylation mixture, which was then heated, filtered, and cooled. An IR spectrum of the solid which precipitated showed an intense absorption at 1665 cm^{-1}, but only a small shoulder at 1730-1750 cm^{-1}. The major carbonyl band from phenylurea, which originally appeared at 1650 cm^{-1}, was gone. We could not say definitely from this spectrum whether we had one or more of the tautomers of 90, or whether we had some other product. We thought it would be expedient to try to run the carbonylation in methanol, as the open-chain methyl ester was a known, more easily characterized compound (entry 2 in Table XVIII) [150]. This gave us a 17% yield of pure methyl 2-ureido-benzoate, which can be converted in a number of ways to the desired quinazolinedione, 90; such methods include boiling in water, treating with strong acid or strong base, or simply heating above its melting point (eq. 100) [150].



(100)

90

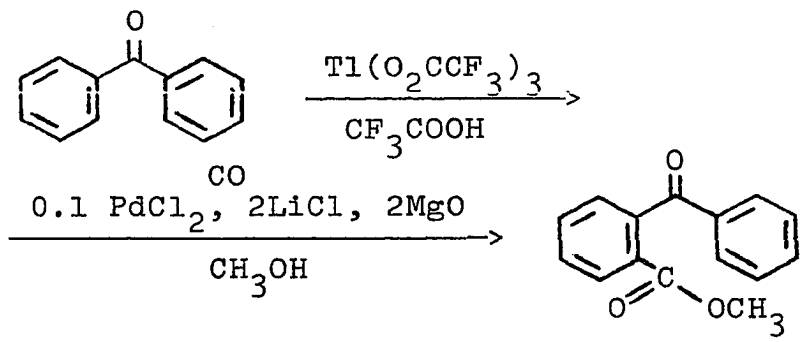
Although our successful preparation of methyl 2-ureido-benzoate demonstrates the versatility of our reaction sequence, it is of no economic advantage when compared with the high-yield synthesis published in 1943, which uses cheaper starting materials (eq. 101) [159].



(101)

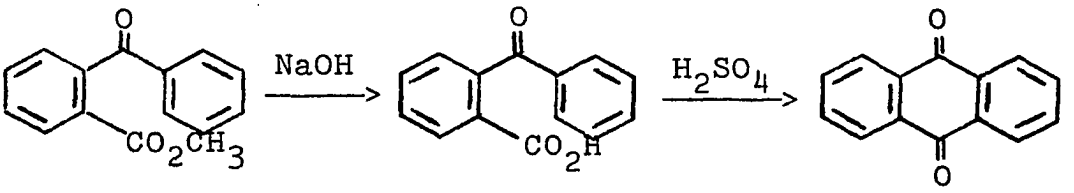
90

Benzophenone (entry 3 in Table XVIII) was thallated and then carbonylated cleanly in methanol to give methyl 2-benzoyl-benzoate (eq. 102). This compound was of interest



(102)

because hydrolysis and cyclization can be affected nearly quantitatively (eq. 103) [160-162], providing an entry into

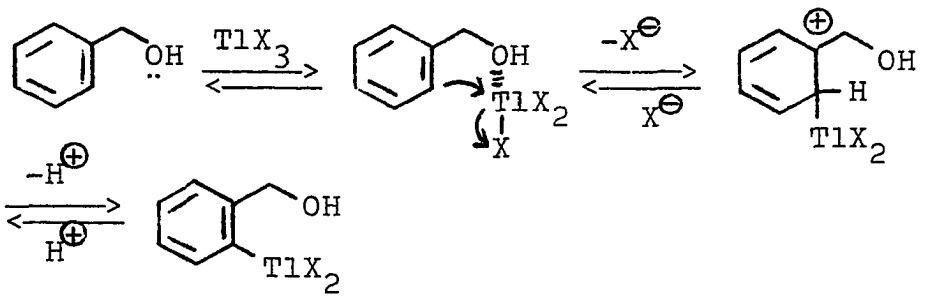


(103)

the valuable anthraquinone ring system. Thallation of benzophenone for two days, followed by carbonylation, afforded 58% of the desired product, but 38% of the starting material was recovered. A longer thallation time did not improve the yield very much, as thallation for four days gave 63% of the product, with 11% unreacted starting material observed.

5. Mechanism

It was shown in detail by McKillop et al. that the thallation of arenes by thallium(III) trifluoroacetate is an electrophilic aromatic substitution reaction, and it has been studied quite thoroughly [92]. Thallium is in Group IIIA of the Periodic Table, the same as boron and aluminum. Like these other elements, thallium tends to form electron-deficient compounds of the general formula TlX_3 in its higher oxidation state, which therefore can be classed as Lewis acids. The high degree of ortho thallation observed in the cases of benzyl and β-phenethyl alcohols, benzoic and phenylacetic acids, benzamide, and other substrates most likely results from the formation of a Lewis acid-Lewis base chelate, which holds the thallium salt in position for intramolecular delivery to the ortho position (eq. 104) [93].

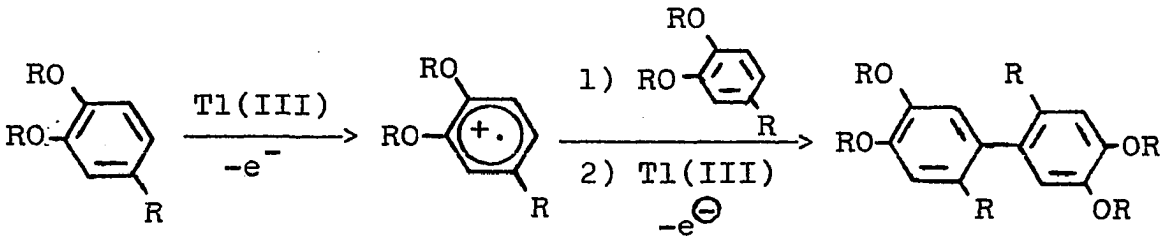


(104)

Electrophilic aromatic thallation is known to be a freely reversible reaction [93], which may explain why the relative proportions of unreacted starting material to product remained nearly unchanged in some of our reactions when thallation times were varied.

After the arylthallium intermediate has been formed, exposure to palladium chloride most likely results in transmetallation between thallium and palladium, similar to the transmetallation between mercury and palladium described in the mechanistic section of Chapter II, in which the oxidation state of neither metal changes. Insertion of carbon monoxide into the arylpalladium complex and subsequent esterification occur undoubtedly in the same fashion as described earlier in Chapter II, at which time the palladium(II) species is reduced to palladium(0). The palladium(0) is most likely re-oxidized by thallium(III) still present in solution, as described in the introduction to this chapter, thus completing the catalytic cycle.

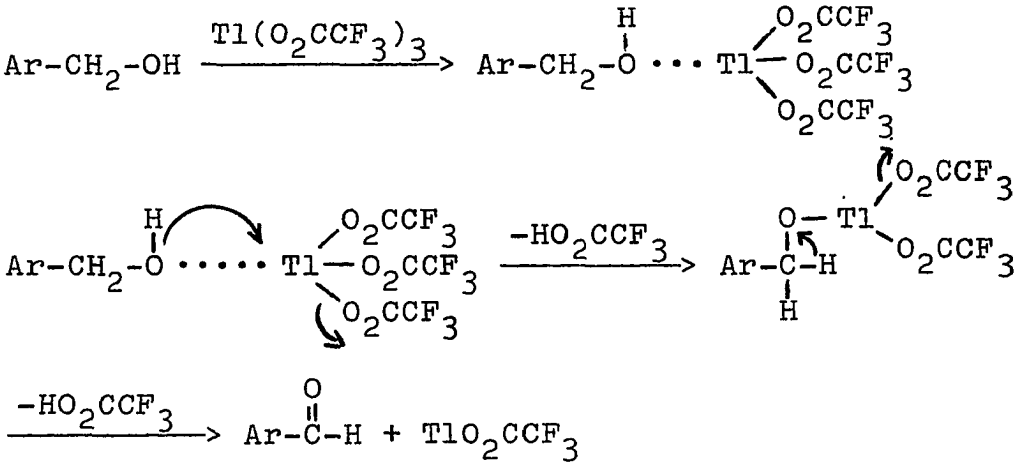
The tars and other high molecular weight products found in some of our reactions may result from thallium(III)-promoted coupling, as it is known that aromatic compounds having lower oxidation potentials, such as polyalkoxybenzenes, more readily undergo oxidative coupling than electrophilic aromatic substitution in the presence of thallium(III) trifluoroacetate [104,117]. This probably involves electron transfer from the arene to thallium(III), followed by attack of the radical cation thus formed on another molecule of arene, and subsequent oxidative aromatization (eq. 105) [117].



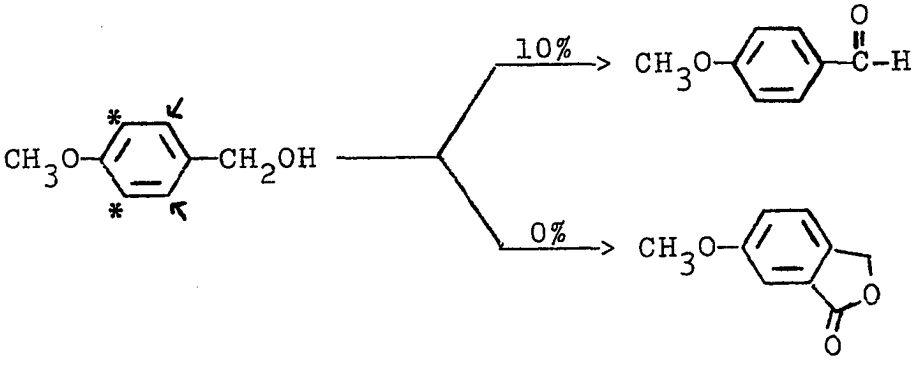
(105)

The isolation of small amounts of aryl aldehyde following the thallation-carbonylation of benzyl alcohols was an unexpected development. It is possible that these aldehydes were formed by oxidation of the benzyl alcohols by thallium(III) after formation of the Lewis acid-Lewis base complex (Scheme IV). This would be a favored process because of the thermodynamic ease of reduction of Tl(III) to Tl(I)

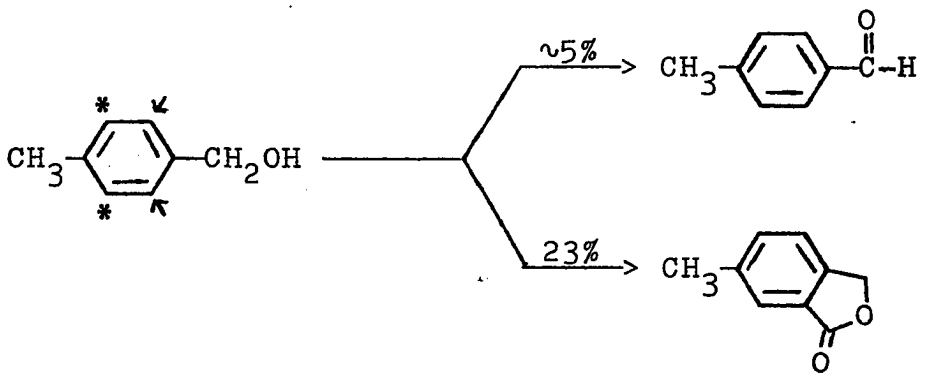
Scheme IV



[94]. Apparently, it occurred to a lesser extent than electrophilic aromatic thallation, because aldehydes were isolated only in small amounts (1 - 10%, based on starting alcohol). Evidently, the presence of a group which activated the ring towards electrophilic aromatic substitution suppressed aldehyde formation, as thallation of the ring was favored. Isolable quantities of aldehyde were formed only in the cases when the directive effect of the activating group (asterisks) was competing with ortho delivery of thallium by the side-chain alcohol (arrows) (eqs. 106,107),



(106)



(107)

or there was no activating group at all. We did not detect any aldehydes in our reactions with β-phenethyl alcohols, but most of these were secondary alcohols, which could not form aldehydes. The phenomenon of aldehyde formation was detected after most of our research was finished, so not all reactions with aryl alcohols were scrutinized carefully in order to see whether aldehydes had formed or not. Such oxidations of aryl alcohols to aldehydes or possibly to higher oxidation states may have contributed to the low yields observed in some of our reactions.

C. Conclusion

Benzyl and β-phenethyl alcohols, benzoic and phenylacetic acids, benzamide, acetanilide, phenylurea, and benzophenone were thallated selectively in the ortho position, and the resulting arylthallium compounds were carbonylated readily under mild conditions by stirring with a catalytic amount of palladium chloride and two equivalents

of lithium chloride under one atmosphere of carbon monoxide at room temperature in methanol or THF. The addition of two equivalents of magnesium oxide usually increased the yields of lactones (from the alcohols). The reaction sequence was shown to be highly regiospecific, especially in the case of 3-substituted benzyl alcohols, giving nearly exclusively the 5-substituted phthalides. It also was found to be highly stereospecific, as shown by the retention of stereochemistry in the thallation and carbonylation of cis- and trans-2-phenyl-1-cyclohexanols. Interfering side reactions included formation of trifluoroacetate esters or oxidation to aldehydes (of the starting alcohols), elimination of secondary benzyl alcohols to give styrenes, thallation in positions other than the ortho position and biaryl formation. Since thallium is so large, thallation is very sensitive to steric hindrance, and α-substitution in benzyl alcohols or 2,5-disubstitution in β-phenethyl alcohols substantially decreased the amount of ortho thallation

This reaction sequence provides a new, general route to the synthesis of phthalides, 3,4-dihydroisocoumarins, anhydrides, imides, and other heterocycles. It should prove useful in natural products synthesis, and already has found application in the laboratories of Professor Irie.

D. Experimental Section

1. Reagents

A word of caution is appropriate here. Thallium compounds are extremely toxic [91,93,163]. They must be handled with great care at all times. Heavy rubber gloves should be worn when working with them. Thallium compounds are cumulative poisons and may be fatal if inhaled, swallowed, or absorbed through the skin. It is essential that one's equipment and work area be kept scrupulously clean. In our work, all glassware that came in contact with thallium compounds was washed in a chromic acid-sulfuric acid bath. Thallium-containing residues were stored in a jar and then were buried away from water supplies by properly authorized personnel. Trifluoroacetic acid, which is corrosive, was used only in a well-ventilated hood.

All chemicals were used directly as obtained unless otherwise indicated. Benzyl alcohol, benzoic acid, benzene, and acetanilide were purchased from Fisher; β-phenethyl alcohol came from Matheson, Coleman, and Bell; benzophenone and anisole came from J. T. Baker; and 3-hydroxybenzyl alcohol came from Sigma. Reagents purchased from Aldrich include fluorobenzene, t-butylbenzene, 1-phenyl-2-propanol, α-phenethyl alcohol, 2,3-dimethoxybenzyl alcohol, 2-naphthaleneethanol, 2-naphthalenemethanol, 3-chlorobenzyl alcohol,

4-methoxybenzyl alcohol, 3-methoxybenzyl alcohol, 3-methoxyphenethyl alcohol, 2,5-dimethoxybenzyl alcohol, 4-methylbenzyl alcohol, trans-2-phenyl-1-cyclohexanol, 4-nitrobenzyl alcohol, phenylacetic acid, phenylurea, and benzamide. Reduction of 2-phenylcyclohexanone (Aldrich) with L-Selectride [164] gave cis-2-phenyl-1-cyclohexanol, and lithium aluminum hydride reduction of 2,5-dimethoxyphenylacetic acid (ICN Pharmaceuticals, Inc.) afforded 2,5-dimethoxyphenethyl alcohol. THF was distilled from calcium hydride before use, while trifluoroacetic acid was used directly as obtained from Aldrich. Methanol from Fisher was either stored over chemical sieves or used as is. Carbon monoxide was purchased from Matheson Gas Products. The palladium chloride was generously supplied by Johnson Matthey, Inc. and Engelhard Industries. Thallic oxide was obtained from Asarco (American Smelting and Refining Company).

The infrared and NMR spectra were recorded on a Beckman IR-4250 infrared spectrophotometer, and a Varian Associates A-60 NMR or a Hitachi Perkin-Elmer R-20B NMR spectrometer, respectively. The mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer, while the GC-mass spectra were recorded on a Finnegan 4023 GC-MS data system. GLC analyses were performed using a Varian Aerograph Model 920 gas chromatograph or a Varian 3700 gas chromatograph with an attached Varian CDS-111 chromatography data system.

Thin-layer chromatography was performed on Merck 60F 254 silica gel plates from Scientific Products. Silica gel for column chromatography (60-200 mesh) was purchased from Davison Chemical, and fractions were collected automatically by a Model FC-100 Micro Fractionator from Gilson Medical Electronics.

2. Preparation and use of thallium(III) trifluoroacetate

Our difficulties in obtaining commercially consistently high-quality thallium(III) trifluoroacetate were described in detail in the introduction to this chapter. We found it best to prepare our own by modifying slightly the procedure given by McKillop et al. [92]. Usually, thallium(III) oxide (25 g) was weighed into a 250 ml round bottom flask. Trifluoroacetic acid (100 ml) was then added and the mixture was stirred vigorously. A reflux condenser was attached, and water (12 ml) was added through the top of the condenser. The flask was wrapped with aluminum foil. and the mixture was refluxed overnight (12-19 hr). Filtration of the reaction mixture while still hot through a coarse sintered-glass Büchner funnel into a weighed 250 ml round bottom flask removed any residual brown or yellow solid. The colorless solution was concentrated as much as possible on a rotary evaporator. Usually, white solid could be observed in the flask at this stage. The last traces of solvent were removed

on a vacuum pump. The thallium(III) trifluoroacetate thus produced was a white solid scale around the sides of the flask. Yields ranged from 95-99%. The reagent was stored in the freezer in a stoppered round bottom flask wrapped in aluminum foil. Exposure to warm, moist air caused the white solid to become brown and sticky.

The reagent was weighed out (as quickly as possible, to avoid exposure to moisture) and dissolved in the appropriate amount of trifluoroacetic acid prior to each experiment. Early in our work, we tried keeping the thallium(III) trifluoroacetate in trifluoroacetic acid at a known concentration (usually one ml trifluoroacetic acid per mmol of thallium salt) and then measuring an appropriate volume of the solution, but we had poor results from this. Consequently, the thallium(III) trifluoroacetate was kept as a dry solid and used as needed.

3. Thallation of arenes

For the most part, thallations were carried out using literature procedures, which entailed stirring the substrates in a 1 M solution of thallium(III) trifluoroacetate in trifluoroacetic acid for a certain time period at a certain temperature, depending on the type of substrate [92,93]. Best results were obtained when 1.0-1.2 equivalents of thallium(III) trifluoroacetate were used per equivalent of

substrate. As in the literature [93], alcohols were cooled to 0°C, and then the freshly prepared thallium(III) trifluoroacetate solution was added. The resulting yellow, green, or brown mixture, protected from light, was stirred at 0°C for 3 hr, then allowed to warm up to room temperature and stirred overnight. Excess trifluoroacetic acid was co-evaporated with 1,2-dichloroethane. However, this procedure did not work for aryl alcohols with one or more activating groups (methoxy, hydroxy) on the ring, as these tended to polymerize under these conditions.

We found that diluting the solution with THF solved the problem. Thallation of 2,3-dimethoxybenzyl alcohol is representative of the technique used. One mmol of the alcohol was weighed into a 50 ml round bottom flask. One mmol of thallium(III) trifluoroacetate was dissolved in one ml trifluoroacetic acid, and then 5 ml of THF were added to this solution. This mixture was added to the alcohol slowly with stirring, producing a light yellow solution. The flask was then stoppered, wrapped with aluminum foil, and the solution was stirred overnight at room temperature. Solvents were removed on a rotary evaporator, and the residue was co-evaporated with 1,2-dichloroethane. The flask was evacuated at 1-3 mm Hg on a vacuum pump for 5-10 min to remove as much trifluoroacetic acid as possible, and then the material was carbonylated immediately without further

purification. Alternatively, either 2,3-dimethoxybenzyl alcohol or 3-methoxybenzyl alcohol was thallated by using a modification of the published procedure for the thallation of anisole [92]; instead of cooling the substrate to -20°C, the substrate was weighed into a 50 ml round bottom flask at room temperature, and the appropriate amount of 1 M thallium(III) trifluoroacetate solution in trifluoroacetic acid was added. The mixture was stirred at room temperature for 15 min, then excess solvent was removed as above, and the residue was then carbonylated.

Other procedural modifications had to be made depending on the nature of the substrate. The more strongly activated 3-hydroxybenzyl alcohol required milder thallation conditions than the methoxybenzyl alcohols, so twice as much THF was used to dilute the trifluoroacetic acid. Thallation of the deactivated 3-chlorobenzyl alcohol required harsher conditions, so the thallation mixture was refluxed for 3 hr. 4-Methylbenzyl alcohol underwent thallation best when the diluted solvent system (5:1 ratio of THF to trifluoroacetic acid) was used for two days. Thallation of benzoic acid was accomplished according to the literature procedure by refluxing the mixture overnight [92]. We found that this method also worked for benzamide. Phenylacetic acid was thallated in trifluoroacetic acid at room temperature for two days, as in the literature [93]. Acetanilide and

phenylurea were thallated by stirring with one equivalent of thallium(III) trifluoroacetate in trifluoroacetic acid at room temperature for one day, while benzophenone had to be stirred for two to four days.

4. Carbonylation of arylthallium intermediates

Methyl esters of substituted benzoic acids, phthalides, and 3,4-dihydroisocoumarins were prepared according to the following representative procedure. One mmol of appropriately substituted arene was thallated as described above, and was used without further purification. Palladium chloride (0.1 mmol, 0.0178 g), 2 mmol anhydrous lithium chloride (0.0844 g), and either 2 mmol magnesium oxide (0.0804 g) or 1 mmol lithium carbonate (0.0739 g) and 5 ml methanol were placed in a round bottom flask with a septum inlet. The system was flushed with carbon monoxide. The flask containing the arylthallium intermediate was removed from the vacuum pump, and the thallated substrate was dissolved in 5 ml methanol and added to the salts by disposable pipette against a small, constant carbon monoxide stream. The system was again flushed with carbon monoxide, and a balloon filled with carbon monoxide was connected to the top of the flask. The reaction was then stirred at room temperature overnight under 1 atm carbon monoxide. Anhydrides and phthalimide (from aryl acids and benzamide, respectively) were prepared

in nearly identical fashion, except that no inorganic base was used, and THF was employed as solvent. All yields determined by GLC analysis were run this way, with an internal standard added before analysis. Yields were calculated by using internal standard correction factors determined by using authentic product samples, either purchased or synthesized.

Isolated yields were determined using the above procedure on either a 5-mmol or a 10-mmol scale. A typical work-up of a 5-mmol scale carbonylation reaction, run in 50 ml methanol, was performed as follows. The reaction mixture (usually black) was diluted with 100 ml ether to precipitate as many inorganic salts as possible, and then vacuum filtered through Celite filter aid. The filtrate was concentrated on a rotary evaporator, and the residue was suspended in 150 ml fresh ether. This was washed with three 100 ml portions of saturated aqueous ammonium chloride solution, one 100 ml portion of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The crude product was either recrystallized as indicated in the various tables in the text, purified by preparative GLC, or purified by column chromatography on silica gel. The water-sensitive homophthalic anhydride was isolated by diluting the carbonylation solvent (THF) with chloroform, filtering, and evaporating the

solvents. The residue was extracted repeatedly with chloroform. The combined extracts were again concentrated, and the solid residue was recrystallized from benzene.

The compounds purified by column chromatography follow. Phthalide: R_f = .42; silica gel using ether:hexane (1:1) as eluent. 3,4-Dihydroisocoumarin: R_f = .41, silica gel using ethyl acetate:hexane (1:1), and then R_f = .60, silica gel using chloroform. Reaction mixture from 4-methoxybenzyl alcohol:silica gel using ether. 6-Methoxy-3,4-dihydroisocoumarin: R_f = .45, silica gel using ether. N-Acetylanthranilic acid, methyl ester: R_f = .68, silica gel using ether as eluent, followed by recrystallization from ethanol. 2-Benzoylbenzoic acid, methyl ester: R_f = .38, silica gel using ether:hexane (1:1).

The following new compounds were prepared and characterized. 6-Methylphthalide: ^{1}H NMR ($CDCl_3$) δ 2.47 (3H, s, CH_3), 5.28 (2H, s, $-CH_2-$), 7.20-7.75 (3H, m, aromatic); ir (max) ($CHCl_3$) 1765 (C=O), 1120-1160 (C-O) cm^{-1}; m/e 148.05241 (calcd for $C_9H_8O_2$, 148.05243). trans-1,2,3,-4,4a,10b-Hexahydro-6H-dibenzo[b,d]pyran-6-one: ^{1}H NMR ($CDCl_3$) δ 1.2-2.7 (8H, m, $\{CH_2\}_4$), 2.7-3.0 (1H, m, methine), 3.9-4.3 (1H, d of t, J_{ax-ax} = 10 Hz, J_{ax-eq} = 4 Hz, methine), 7.2-8.2 (4H, m, aromatic); ir (max) ($CHCl_3$) 1720 (C=O), 1280 (C-O), 1160 (C-O) cm^{-1}; m/e 202.09854 (calcd for

$C_{13}H_{14}O_2$, 202.09938). cis-1,2,3,4,4a,10b-Hexahydro-6H-dibenzo[b,d]pyran-6-one: ^{1}H NMR ($CDCl_3$) δ 1.3-2.3 (8H, m, $\{CH_2\}_4$), 2.6-3.0 (1H, br s, methine), 4.6-4.8 (1H, br s, methine), 7.2-8.3 (4H, m, aromatic); ir (max) ($CHCl_3$) 1710 (C=O), 1280 (C-O) cm^{-1}; m/e 202.10007 (calcd for $C_{13}H_{14}O_2$, 202.09938). cis-2-Phenylcyclohexyl trifluoroacetate: ^{1}H NMR ($CDCl_3$) δ 1.4-2.2 (8H, m, $\{CH_2\}_4$), 2.6-3.0 (1H, br s, methine), 3.9-4.1 (1H, br s, methine), 7.1-7.5 (5H, m, aromatic); ir (max) (thin film) 1780 (C=O), 1155 (C-O) cm^{-1}; m/e 272.1023 (calcd for $C_{14}H_{15}F_3O_2$, 272.1024). 2,3-Dimethoxybenzyl trifluoroacetate: ^{1}H NMR ($CDCl_3$) δ 3.8-4.4 (8H, br m, CH_3's; CH_2), 6.9-7.8 (3H, m, aromatic); ir (max) ($CHCl_3$) 1780 (C=O), 1488 (C-F), 1275 (C-O) cm^{-1}; m/e 264.0605 (calcd for $C_{11}H_{11}O_4F_3$, 264.0610).

Our spectral data for some of the less common known compounds that we prepared are as follows. 5-Methoxyphthalide: ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s, CH_3O), 5.1 (2H, br s, CH_2), 6.85-7.1 (2H, m, aromatic), 7.7-7.9 (1H, d, J = 8 Hz, aromatic next to carbonyl); ir (max) ($CHCl_3$) 1750 (C=O), 1602 (C=C), 1260-1190 (C-O) cm^{-1}; m/e 164 (parent, 32%), 163 (16%), 146 (46%), 135 (69%), 134 (14%), 119 (18%), 118 (base peak, 100%), 106 (18%), 105 (26%), 92 (21%), 91 (10%), 90 (15%), 78 (26%), 77 (56%), 76 (23%), 75 (11%), 65 (12%), 64 (11%), 63 (25%), 62 (10%). 51 (45%). 4,5-Dimethoxyphthalide: ^{1}H NMR ($CDCl_3$) δ 3.95 (6H, s,

CH_3O), 5.30 (2H, s, CH_2), 7.0-7.8 (2H, d of d, J = 8 Hz, aromatic); ir (max) ($CHCl_3$) 1760 (C=O); 1475 (CH_2O); 1270-1180 (C-O); d, 2940, 2815 (CH_3, CH_2); d, 1585, 1615 (C=C); m/e 194 (parent and base peak, 100%). 4,7-Dimethoxyphthalide: ^1H NMR ($CDCl_3$) δ 3.8 (3H, s, CH_3O), 3.9 (3H, s, CH_3O), 5.17 (2H, s, CH_2), 6.75-7.15 (2H, d of d, J = 14 Hz, aromatic); ir (max) ($CHCl_3$) 1750 (C=O); d, 2950, 2860 (CH_3, CH_2); 1470-1410 (CH_2-O); 1270-1150 (C-O); 1600 (C=C); m/e 194 (parent, 83%), 193 (30%), 180 (14%), 176 (13%), 166 (14%), 165 (59%), 151 (25%), 150 (11%), 149 (20%), 148 (50%), 135 (15%), 123 (12%), 122 (15%), 121 (24%), 120 (19%), 118 (base peak, 100%), 107 (16%), 93 (11%), 79 (13%), 77 (18%), 75 (10%), 65 (12%), 63 (14%), 53 (14%), 51 (15%). 5-Hydroxyphthalide: ^1H NMR (DMSO-d^6) δ 3.75 (1H, s, hydroxy), 5.29 (2H, s, CH_2), 6.9-7.1 (2H, m, aromatic), 7.6-7.75 (1H, d, J = 9 Hz, aromatic next to carbonyl); ir (max) (KBr) 1715 (C=O); 3260 (O-H); 1270 (C-O); 1463 (CH_2-O); d, 1600, 1615 (C=C); m/e 150 (parent, 34%), 149 (13%), 121 (base peak, 100%), 93 (21%), 92 (14%), 77 (12%), 65 (43%), 63 (28%), 55 (19%), 51 (17%), 44 (43%), 43 (22%), 41 (25%). Homophthalic anhydride: ^1H NMR ($CDCl_3$) δ 4.12 (2H, s, CH_2), 7.25-7.85 (3H, m, aromatic), 8.10-8.25 (1H, d with fine structure, J = 8 Hz, aromatic next to carbonyl); ir (max) ($CHCl_3$) d, 1803, 1754 (C=O); 1605 (C=C); 1280 (C-O) cm^{-1}; m/e 162.03168 (calcd for $C_9H_6O_3$, 162.03170).

N-Acetylanthranilic acid, methyl ester: ^{1}H NMR ($CDCl_3$) δ 2.01 (3H, s, CH_3-C(=O)-), 3.80 (3H, s, CH_3O-), 6.85-8.02 (3H, m, aromatic), 8.55-8.70 (1H, d with fine structure, J = 14 Hz, aromatic next to carbonyl), 11.95 (1H, br s, N-H); ir (max) ($CHCl_3$) d, 1705, 1685 (C=O); d, 1610, 1590 (C=C); 1265 (C-O); 3320 (N-H); m/e 193.07491 (calcd for $C_{10}H_{11}NO_3$, 193.07390). 2-Ureidobenzoic acid, methyl ester: ^{1}H NMR ($CDCl_3$ + DMSO-d^6) δ 2.88 (2H, s, NH_2), 3.90 (3H, s, CH_3), 5.75 (1H, br s, N-H), 6.95-8.05 (3H, m, aromatic), 8.40-8.54 (1H, d with fine structure, aromatic next to carbonyl); ir (max) (KBr) d, 1600, 1575 (C=C); 1260 (C-O); 3410 (N-H); d, 3270, 3210 (N-H); m/e 194.06912 (calcd for $C_9H_{10}N_2O_3$, 194.06915).

IV. SYNTHESIS OF ARYL OLEFINS, ISOCOUMARINS, AND OTHER HETEROCYCLES VIA THALLATION-OLEFINATION OF ARENES

A. Introduction

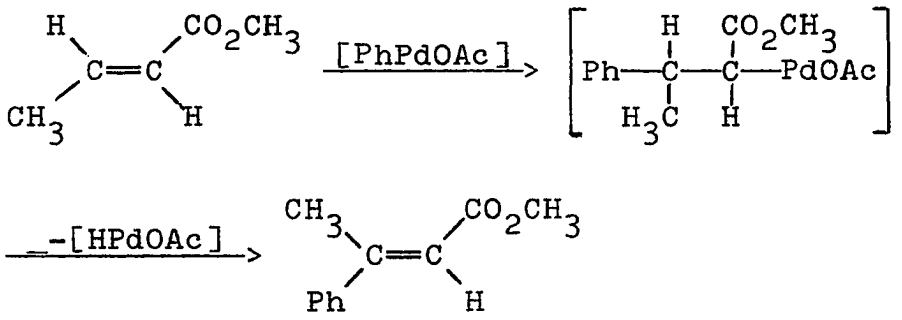
In the preceding chapter, we demonstrated one aspect of the synthetic utility of arylthallium compounds, in which palladium-promoted carbonylation led to a wide variety of compounds including esters, lactones, cyclic imides, and other heterocycles. In order to extend the synthetic applications of these organothallium intermediates, we undertook an exploration of the scope of palladium-promoted olefination of such compounds.

The study of palladium-catalyzed vinylic substitution is a large and well-trodden area of organic chemistry [165]. Heck has shown that an arylpalladium species, formed by the exchange reaction of an arylmercurial or main-group organometallic with a palladium(II) salt, adds across an olefin, and after subsequent loss of metal hydride affords the aryl-substituted olefin (eq. 108) [43]. Further investigation

$$\text{Ar-HgX} \xrightarrow{PdX_2} \text{Ar-PdX} \xrightarrow{H_2C=CHR} \text{Ar-}\overset{H}{\underset{H}{C}}\text{-}\overset{H}{\underset{R}{C}}\text{-PdX} \xrightarrow{-HPdX} \text{ArCH=CHR} \qquad (108)$$

revealed several important features of this reaction. With respect to the control of the direction of addition of organopalladium compounds to olefins, steric effects were found to predominate; the effectively larger organic group

of the organopalladium compound added to the least substituted carbon of the double bond, and the palladium group added to the more substituted carbon atom. Thus, in the addition of phenylpalladium chloride to 1-hexene, the phenyl group added to the 1-position of 1-hexene 80% of the time [166]. However, 20% internal addition is also observed. Electronic effects had lesser impact, but when applicable, the organic group tended to add to the more positive carbon of the double bond [166]. These reactions were found to be quite stereospecific, as internal olefins gave products consistent with a syn addition of the organopalladium reagent to the olefin, followed by cis elimination of a hydridopalladium species (eq. 109) [167,168].



(109)

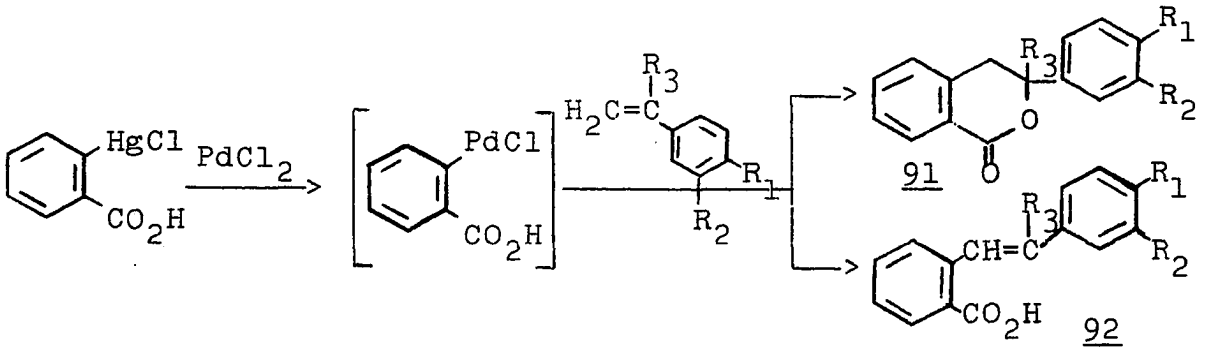
In two closely related reactions, arylpalladium or vinylpalladium species, again formed from aryl- or vinylmercurials, react with allylic halides, affording allylaromatic compounds [eq. 110) [169] or 1,4-dienes (eq. 111) [170].

$$ArHgX \xrightarrow{PdX_2} [ArPdX] \xrightarrow{CH_2=CH-CH_2X} ArCH_2CH=CH_2 + PdX_2 \quad (110)$$

$$R-CH=CH-HgX \xrightarrow{PdX_2} [RCH=CH-PdX]$$

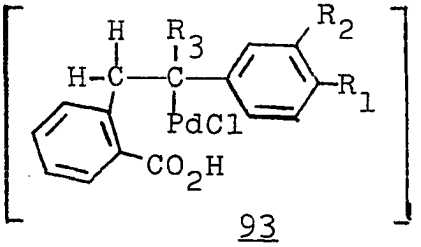
$$\xrightarrow{CH_2=CH-CH_2X} R-CH=CH-CH_2-CH=CH_2 + PdX_2 \quad (111)$$

Recently, Horino and Inoue applied the Heck reaction to the synthesis of 3,4-dihydroisocoumarins, starting with o carboxyphenylmercuric chloride and substituted styrenes (eq. 112) [171]. Cyclizations to 91 occur presumably via



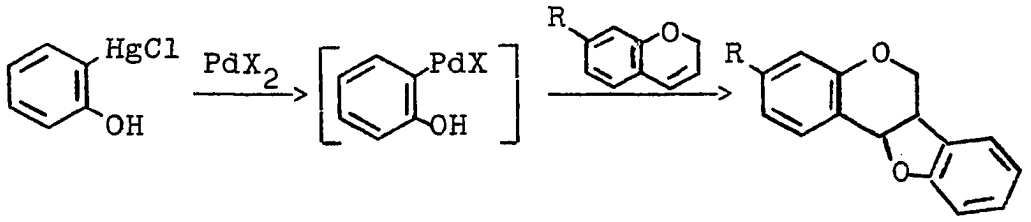
(112)

cleavage of the palladium-carbon bond in the intermediate complex 93 in the cases where R_1 was an electron-donating



93

group, capable of stabilizing the carbonium ion formed after cleavage of the carbon-palladium sigma bond. The carbonium ion then apparently reacts with the neighboring carboxyl group to give compound 91. In cases where R_1 was not an electron-donating group, stilbenes 92 were the major products. Earlier, Horino and Inoue had used the Heck arylation of 2H-chromens with o-chloromercuriphenol to synthesize chromanocoumarans (eq. 113) [172]. This

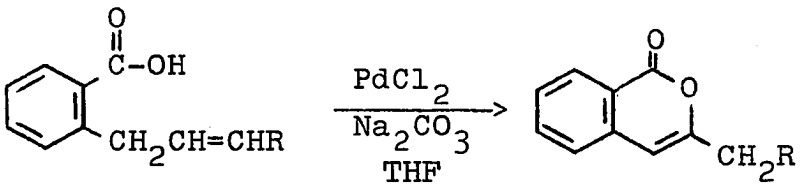


(113)

oxyphenylation was based on their previous observation that a phenyl group and the nucleophilic portion of a protic solvent added simultaneously to the double bond of benzocycloalkenes in the Heck arylation with phenylpalladium chloride in protic solvents.

Somewhat more cumbersome than Horino and Inoue's elegant use of the Heck reaction was the procedure reported by Korte et al. [84]. Instead of palladium-promoted olefination, π-allylnickel complexes were reacted with appropriately substituted aryl halides to give 2-alkenylbenzoic acids or 2-alkenylbenzamides. These were isolated,

and then cyclized by palladium(II) salts (eqs. 114,115) [84].



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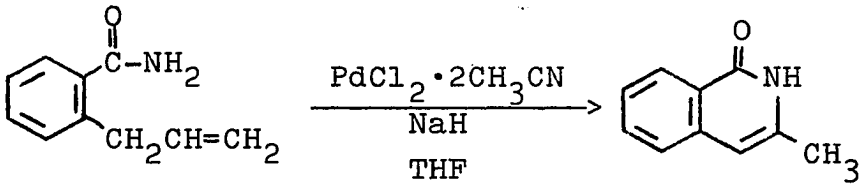
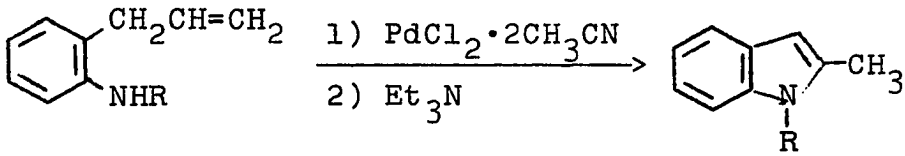


(115)

Other heterocycles have been prepared recently by the palladium-assisted cyclization of ortho substituted allylanilines [174], such as the synthesis of 2-methylindoles reported by Hegedus et al. (eq. 116) [175]. These methods

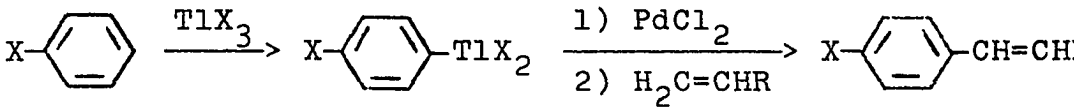


(116)

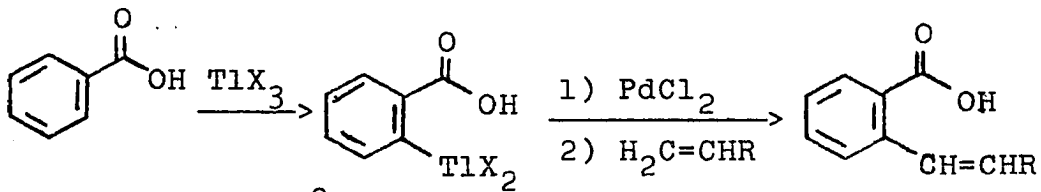
have the disadvantage, however, of requiring the prior preparation of appropriately substituted aryl halides, not always an easy task.

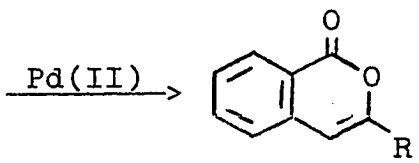
From the examples just cited, one can see that it would be very useful synthetically to devise a general, regiospecific method for the olefination of substituted arenes, as the facile palladium-catalyzed cyclization could lead to a variety of useful products, either various ring systems or

open-chain styrene derivatives. Unfortunately, the procedures reported by Korte et al. [84] and Hegedus et al. [174,175] require properly substituted aryl halides as starting materials, which are not always readily available. The halide is subsequently replaced by an allyl group using π-allylnickel halides, compounds very difficult to handle due to their extreme sensitivity to air and moisture. Horino and Inoue's procedures start with ortho substituted arylmercurials, which also have the drawback of not always being readily available. From our experience with the carbonylation of arylthallium compounds, we thought we might have a general method for preparing alkenyl arenes very regiospecifically. Trans-metallation of arylthallium intermediates by palladium(II) would give arylpalladium species, which then could undergo the Heck reaction with olefins. Depending on the type of substrate, one could choose whether or not one wanted cyclized products (eqs. 117-119). Ortho

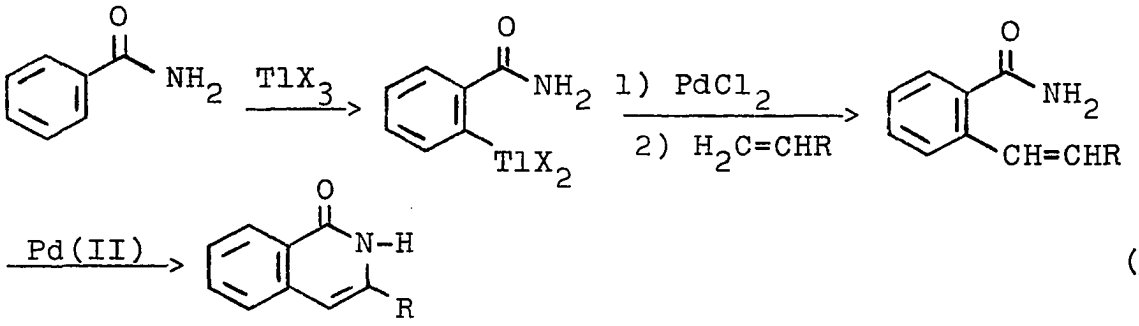


(117)



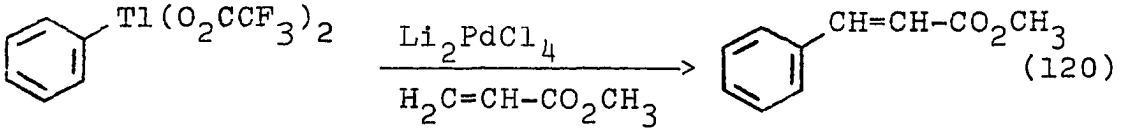


(118)



(119)

substitution of benzoic acids or benzamides conceivably could lead to isocoumarins or isocarbostyrils, respectively. The isocoumarin ring system is found in many natural products [2,75,176]. Isocarbostyrils have marked antidepressant, tranquilizing, analgesic, and sedative activity [177]. One could envision widespread use for such a reaction, especially if the palladium remaining after olefination would promote cyclization of the o-alkenylbenzoic acids or benzamides. We were encouraged by the fact that the reaction of organothallium compounds with olefins is known; Spencer and Thorpe obtained moderate-to-good yields of styrenes in this fashion (eq. 120) [100]. This led us to try similar reactions, as will be discussed next.



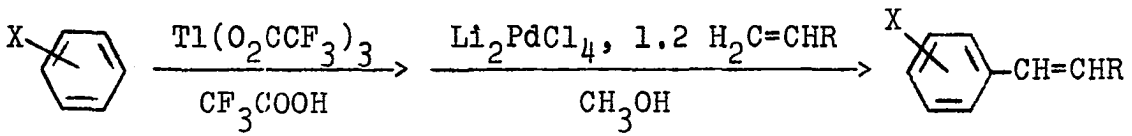
(120)

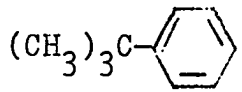
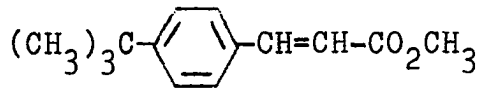
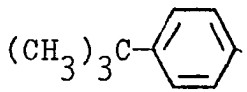
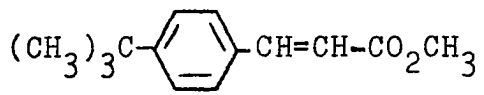
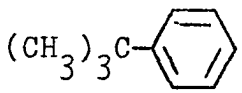
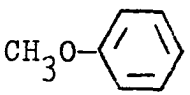
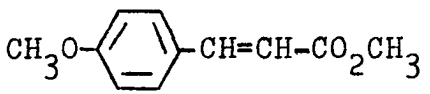
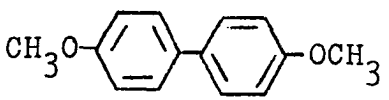
B. Results and Discussion

1. Preliminary studies

Our first efforts were directed towards the preparation of styrene derivatives by the method of Spencer and Thorpe [100], using different substrates, as shown in Table XIX. At first, things appeared to be proceeding well, as tert-butylbenzene and methyl acrylate afforded an 85% yield of methyl-p-tert-butyl-trans-cinnamate (entry 1) under our reaction conditions. The material was clean by NMR, with no cis isomer detected. The coupling constant for the trans olefinic protons was 17 Hz. Heck prepared the same compound starting from the same substrate, but he mercurated it instead of using thallium salts [178]. His overall yield was only 6%. Our hopes were raised even further when this reaction showed signs of being catalytic in palladium (entry 2), where we believed that the thallium(III) present in the reaction mixture re-oxidized the palladium, as in our carbonylation reactions. However, succeeding reactions did not work nearly so well. An attempt to add methyl crotonate, an internal olefin (entry 3), failed completely. A hard, granular, insoluble substance was isolated, which may have been polymerized olefin. Anisole (entries 4 and 5) gave very poor yields of desired products. The major isolated product in these reactions was the coupled biaryl, which most likely arose from palladium-promoted coupling of the arylthallium

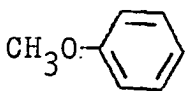
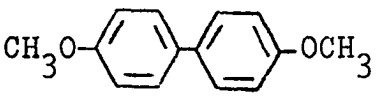
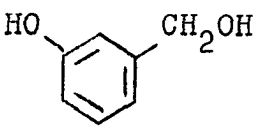
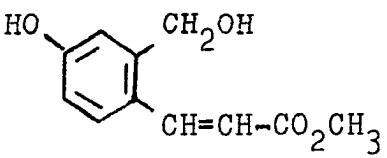
Table XIX. Synthesis of styrene derivatives



Entry	Substrate	Olefin	Product(s)	$PdCl_2$ Equivalents	% Yield[a]
1		$H_2C=CH-CO_2CH_3$		1.0	85
2		$H_2C=CH-CO_2CH_3$		0.1	80
3		$CH_3CH=CH-CO_2CH_3$	Polymer?	1.0	---
4		$H_2C=CH-CO_2CH_3$	 	1.0	4 8

[a]Isolated, purified yield.

Table XIX. (Continued)

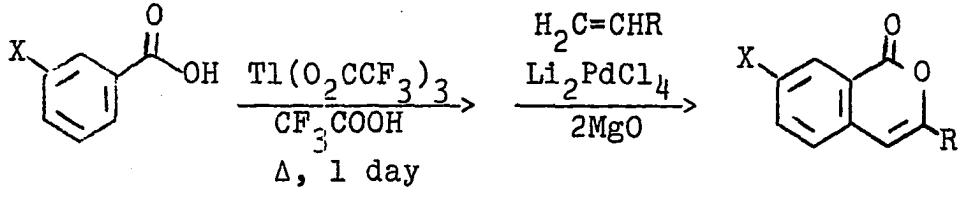
Entry	Substrate	Olefin	Product(s)	$PdCl_2$ Equivalents	% Yield[a]
5		$H_2C{=}CH{-}CO_2CH_3$		1.0	10
6		$H_2C{=}CH{-}CO_2CH_3$		1.0	19

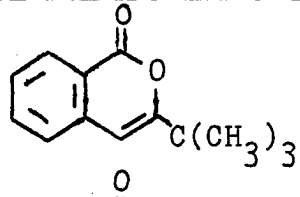
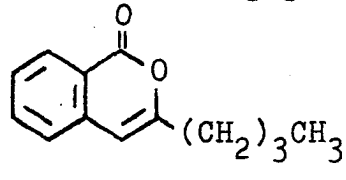
intermediate [97]. Lastly, a disubstituted substrate, 3-hydroxybenzyl alcohol, was subjected to the reaction sequence (entry 6). The adduct was isolated and characterized in 19% yield. The reaction was not at all clean, as TLC showed at least eight spots. The adduct shown in entry 6, Table XIX, was the major product seen. Evidently, there were many other unforeseen side reactions which complicated the picture far more than was the case in our carbonylation study. Somewhat disheartened, we nevertheless tried to prepare isocoumarins.

2. Isocoumarins

Benzoic acid was thallated and treated with a number of different olefins and allylic chlorides in the presence of a stoichiometric amount of palladium(II) chloride in order to prepare a variety of isocoumarins. Our results, presented in Table XX, were not encouraging, as yields ranged from only moderate to dismal. The reactions were not at all clean, and numerous products were observed on thin-layer chromatograms and in GLC traces of the final reaction mixtures. Extensive purification procedures, involving column chromatography on silica gel, repeated recrystallizations, sublimation, or combinations of the above, were necessary in every case. Even after purification procedures had been performed, some of the reaction products still were not clean. There were undoubtedly many side reactions which interfered, and some of these will be discussed in the section on mechanism. In

Table XX. Synthesis of isocoumarins by thallation-olefination of benzoic acids



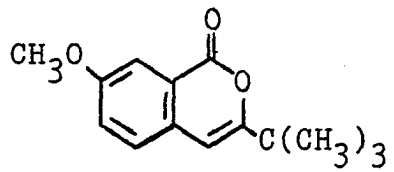
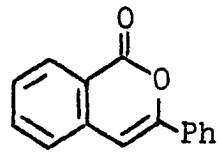
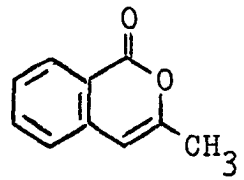
Entry	X	Olefin	Olefination Solvent	Product	Mp, °C (Lit. mp, °C)	% Yield[a]
1	H	2 $H_2C=CHC(CH_3)_3$	CH_3OH		60-61[b]	11
2	H	5 $H_2C=CH-(CH_2)_3CH_3$	CH_3OH		---[c] (45.5-46.5) [179]	<5

[a]Isolated, purified yield.

[b]This compound has not been reported in the literature.

[c]A sample clean enough to take a melting point could not be obtained.

Table XX. (Continued)

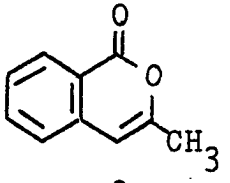
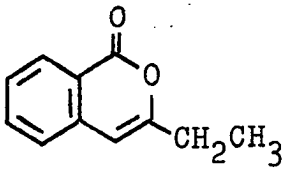
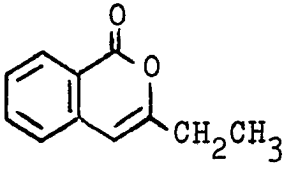
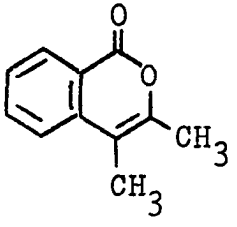
Entry	X	Olefin	Olefination Solvent	Product	Mp, °C (Lit. mp, °C)	% Yield[a]
3	CH_3O[d]	2 $H_2C{=}CH{-}C(CH_3)_3$	CH_3OH		112-125[b,e]	21
4	H	1.2 $H_2C{=}CH{-}Ph$	THF		76-78 (89-90) [180]	26[f]
5	H	2 $H_2C{=}CH{-}CH_2Cl$	CH_3OH		68-69 (71-72) [128,181]	39

[d]Thallated 1 hr.

[e]Although the material was clean according to GLC and TLC, the mp was not sharp.

[f]This may not be the right product. The NMR and IR data disagreed with those in the literature [180], but the exact mass was correct (222.06755; calcd for $C_{15}H_{10}O_2$, 222.06808).

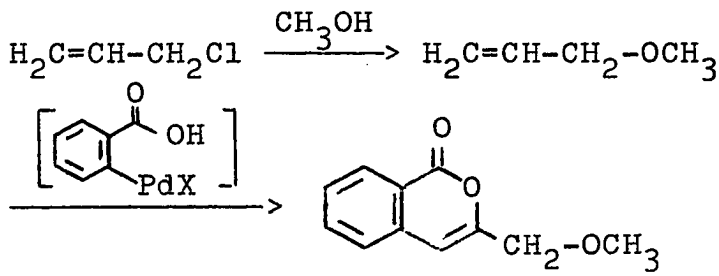
Table XX. (Continued)

Entry	X	Olefin	Olefination Solvent	Product	Mp, °C (Lit. mp, °C)	% Yield[a]
6	H	2 $H_2C{=}CHCH_2OCOCH_3$	CH_3OH			(24)[g]
7	H	5 $H_2C{=}CH{-}CH(CH_3)Cl$	CH_3OH		74-75 (76-77) [84]	28
8	H	5 $H_2C{=}CH{-}CH(CH_3)Cl$	THF			<5
9	H	5 $CH_3CH{=}CHCH_2Cl$	CH_3OH		--- (128-130) [182]	0[h]

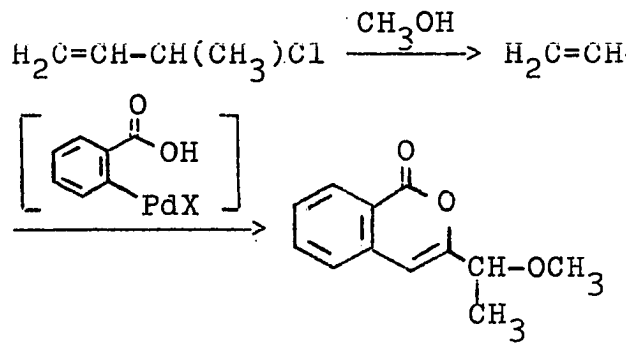
[g]GLC yield using an internal standard.

[h]The product isolated was 3-ethylisocoumarin (~5%).

the examples using allylic chlorides (entries 5 and 7), the methanol solvent itself was found to be responsible for a side reaction. In entries 5 and 7, although the major product isolated was the desired isocoumarin in both cases, the most common side product was an isocoumarin with a methyl ether on the side chain in the 3-position. This arose from addition of the organopalladium intermediate across the double bond of the allyl methyl ether resulting from a reaction between allyl chloride and methanol, and subsequent cyclization (eqs. 121, 122). However, even though the



(121)

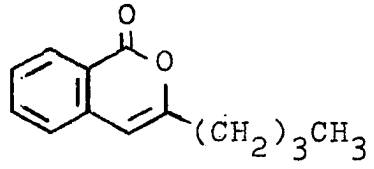


(122)

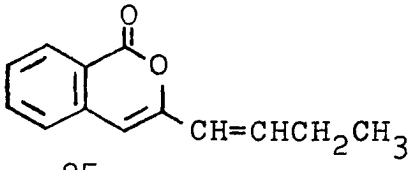
methanol caused a side reaction, it still gave better yields than THF (compare entries 7 and 8). The reaction with crotyl

chloride failed. Instead of the expected 3,4-dimethyl-isocoumarin, we isolated 3-ethylisocoumarin; there were many other components of the reaction mixture, but this was present in the largest amount as seen in the GLC traces and on TLC. Evidently, the palladium causes allylic rearrangement, because 3-ethylisocoumarin was the major product seen even when the crotyl chloride was distilled carefully before use to remove the 3-chloro-1-butene contaminant.

It is most unfortunate that these reactions did not give better yields or cleaner reactions, as several of the isocoumarins we isolated are structurally very similar to natural products. 3-n-Butylisocoumarin, 94, is structurally very close to artemidin, 95, which has been extracted from

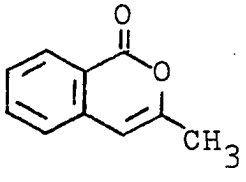


94

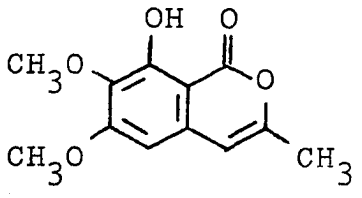


95

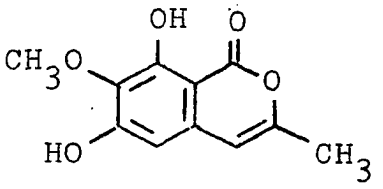
the above-ground portion of the tarragon plant [179,183]. 3-Methylisocoumarin, 96, resembles the metabolites, 97 and 98,



96

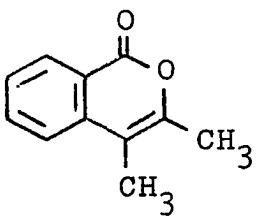


97

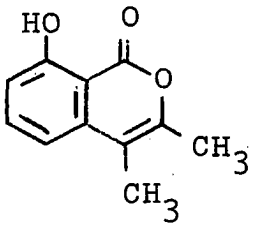


98

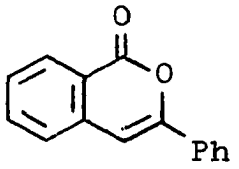
of natural insecticides extracted from the fungus Streptomyces mobaraensis [181]. 3,4-Dimethylisocoumarin, 99, is closely



99



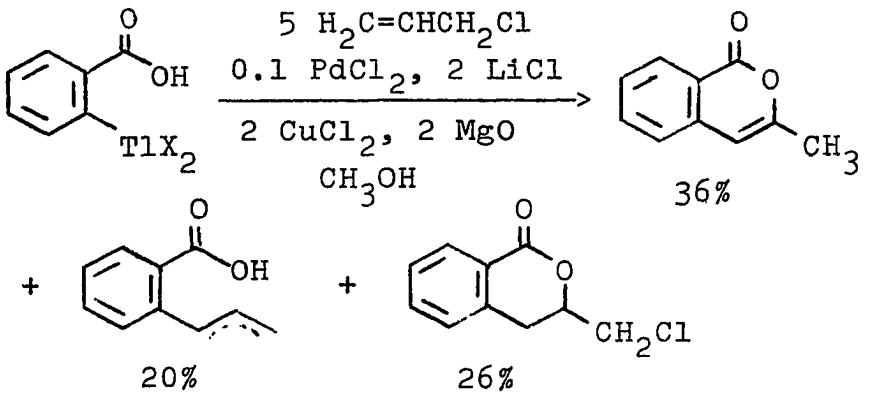
100



101

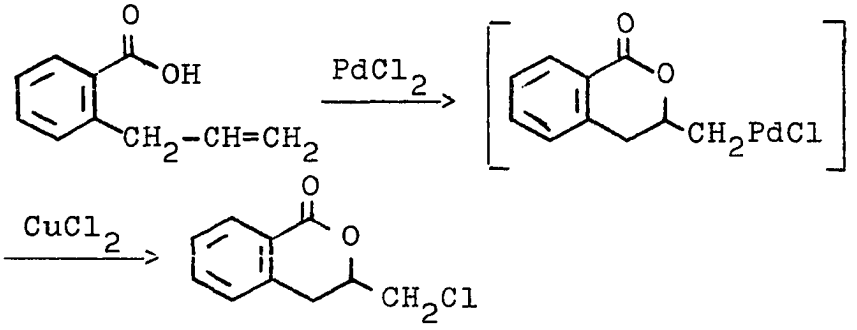
related to oospolactone, 100, a natural product isolated from the microorganism Oospora [182]. 3-Phenylisocoumarin, 101, has been isolated from the leaves of Homalium laurifolium J_{ACQ} [180].

Attempts to prepare isocoumarins using only a catalytic amount of palladium chloride generally met with disaster. No reoxidation of palladium was noted when the reactions corresponding to entries 5 and 6 in Table XX were run employing one-tenth equivalent of palladium chloride, as product yields were all lower than 10%. In these cases, no re-oxidant other than the thallium(III) present in the reaction mixture was added. Benzoquinone (used in a reaction corresponding to entry 5) also failed to re-oxidize palladium. Cupric chloride worked in only one case, but several different products were observed and identified by GC-MS (eq. 123). The chlorinated



(123)

product may have arisen from reaction of cupric chloride with the oxypalladated intermediate formed during ring closure (eq. 124). Running the reaction for a longer time did not



(124)

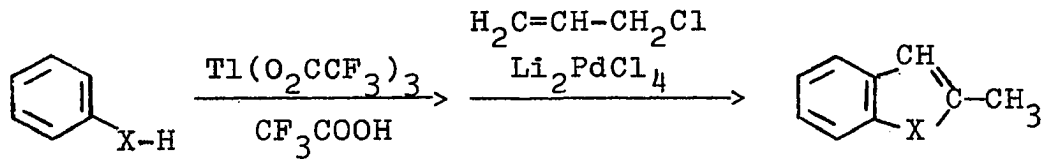
help, as the amount of desired product decreased drastically after two weeks. The noncyclized material was then the predominant product seen on GLC traces. The reaction was not catalytic when 3,3-dimethyl-1-butene was used instead of allyl chloride in the reaction shown in eq. 123. No isocoumarin was seen at all. It is possible that a chlorinated adduct may have been formed instead. The cyclizations of

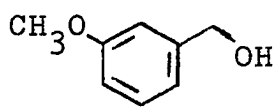
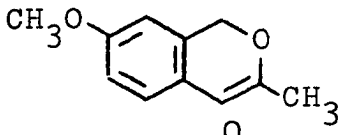
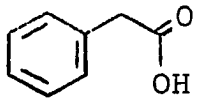
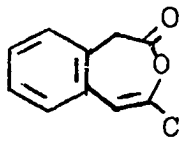
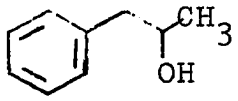
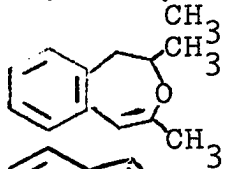
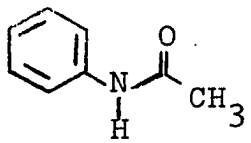
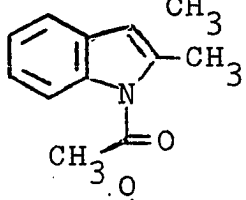
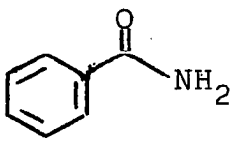
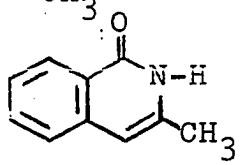
2-alkenylbenzoic acids reported by Korte et al. were run using a stoichiometric amount of palladium chloride, with only one exception [84]. They prepared 3-methylisocoumarin using a catalytic amount of palladium acetate and they employed cupric acetate as the reoxidant, with oxygen bubbled through the mixture. However, they had to reflux the reaction for five days, and obtained only a 41% yield of cyclized product. In all cases, a base, usually sodium carbonate, was used [84]. Our experience was similar in that 3-methylisocoumarin was the only cyclized product we could obtain with a catalytic amount of palladium chloride. We usually employed a base too, normally magnesium oxide.

3. Other heterocycles

Treating various other arylthallium intermediates with allyl chloride in the presence of palladium chloride gave even more dreary results than our isocoumarin yields, as shown in Table XXI. It is unfortunate that isocarbostyril (entry 5) was not formed, as this ring system is structurally similar to the valuable isoquinoline system. Perhaps using a more polar solvent than THF might solve the problem. It is also possible that the cyclopalladated intermediate 102 is very stable, and reluctant to undergo addition across an olefin.

Table XXI. Other heterocycles formed by thallation-olefination



Entry	Arene	Olefination Solvent	Expected Product	Lit. mp, °C	% Yield[a]
1		CH_3OH		---[b]	0[c]
2		THF		---[b]	0[c]
3		CH_3OH		---[b]	10
4		THF		39.5-41.5 [175]	14[d]
5		THF		210 [181]	0[e]

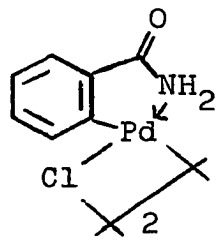
[a]Isolated, purified yield.

[b]This compound has not been reported in the literature.

[c]More than ten compounds observed in the GLC trace.

[d]Spectral data (NMR, ir, ms) identical with those in literature [175].

[e]Intractable tar formed. No product seen at the reported R_f value on a TLC plate when run in triethylamine [84].



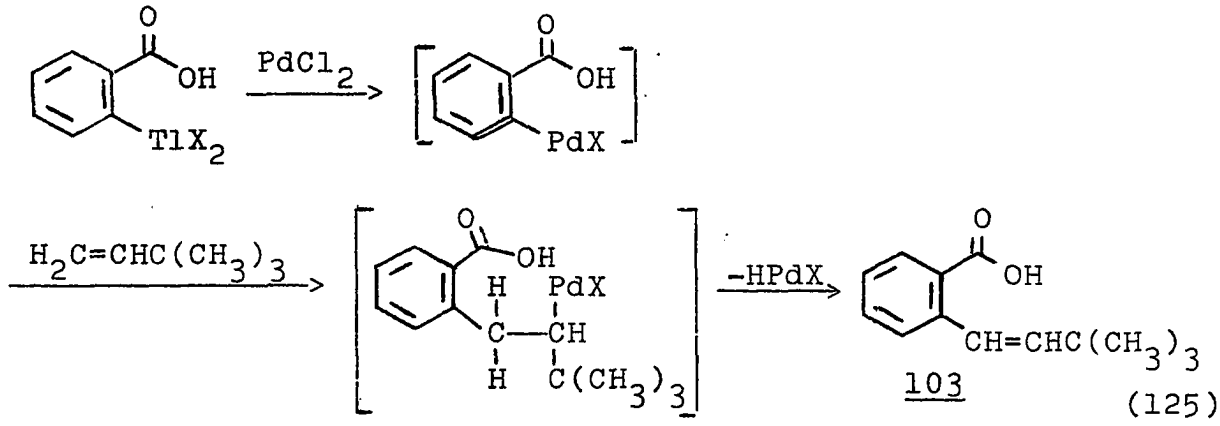
102

Our reactions were run using a stoichiometric amount of palladium chloride. Hegedus et al. were able to obtain good yields of nitrogen heterocycles when they cyclized 2-allylanilines with a catalytic amount of palladium chloride [175]. They found that cupric chloride or benzoquinone worked well as a re-oxidant, although the copper salts complicated the purification of indole products. Generally, they used triethylamine during these reactions [175]. We had no luck when we tried to run these reactions using only catalytic amounts of palladium chloride. For example, when we attempted to use cupric chlorides as the re-oxidant in the olefination of acetanilide (entry 4 in Table XXI), we obtained a 45% yield of 2-chloroacetanilide, and none of the desired indole. Running the reaction with a stoichiometric amount of palladium chloride finally gave us a small amount of the desired indole.

4. Mechanism

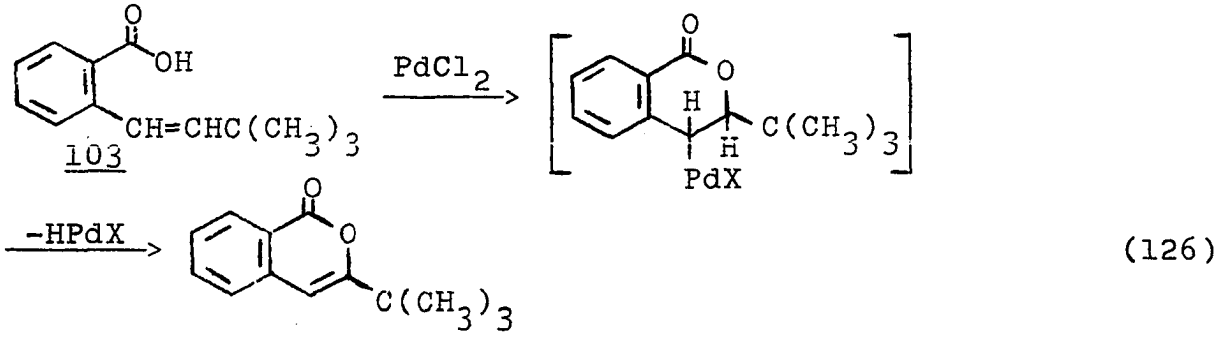
The mechanism of thallation was described in the section entitled mechanism in Chapter III, as was the mechanism of

transmetallation. The arylpalladium species most probably undergo a Heck reaction with the olefins used (eq. 125), as



(125)

discussed in the introduction to this chapter. The open-chain adduct 103 then undergoes cyclic oxypalladation and subsequent palladium-hydride elimination (eq. 126). This

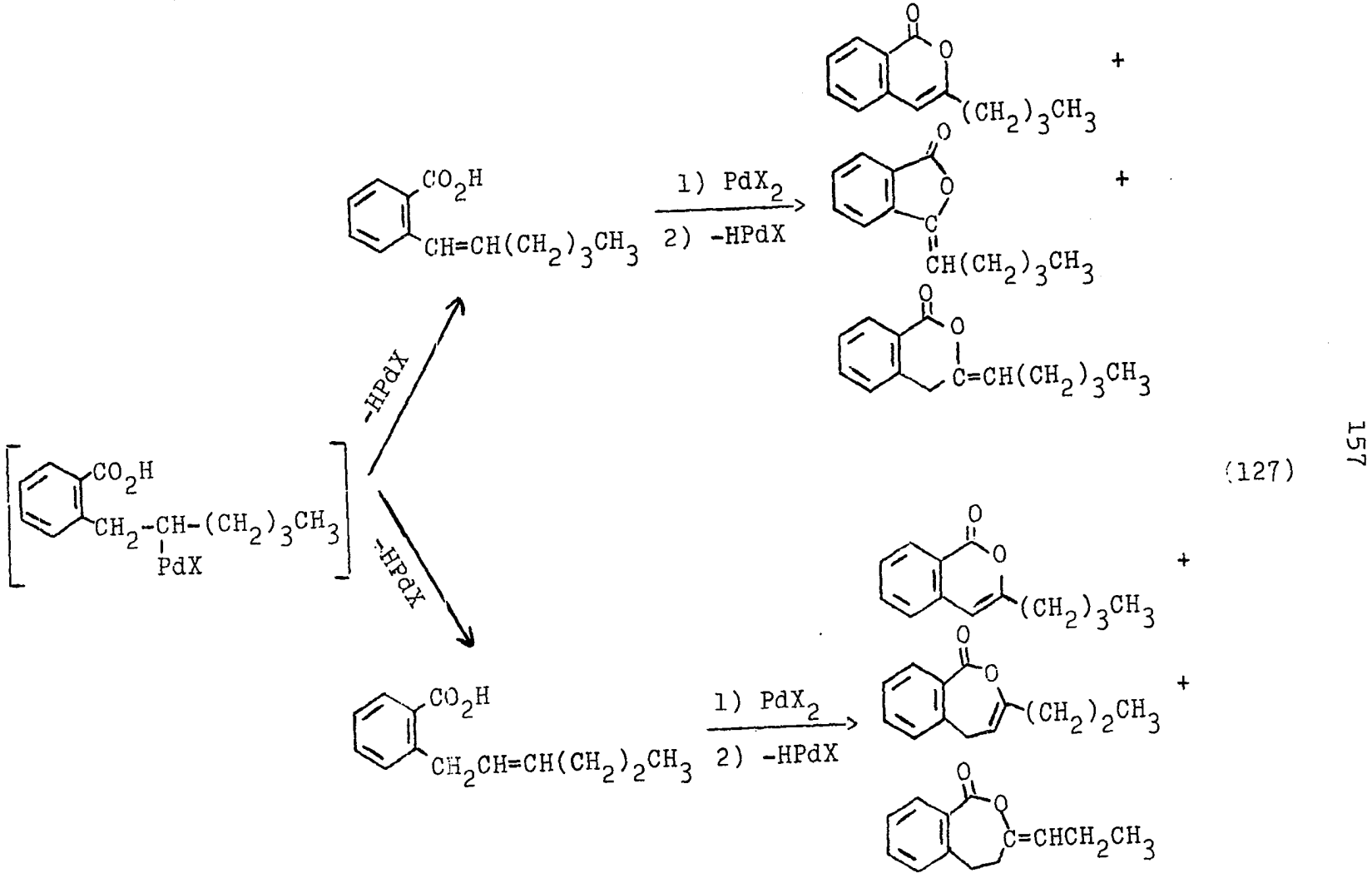


(126)

latter step probably causes trouble when β-hydride elimination is possible in more than one direction. We used 3,3-dimethyl-1-butene for most of our experiments with olefins in order to circumvent β-hydride elimination in the

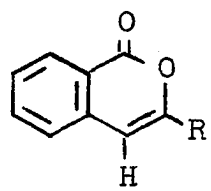
wrong direction. However, β-hydride elimination was possible in more than one direction in the case of 1-hexene. The initial addition undoubtedly gives the adduct shown at the beginning of eq. 127 (see page 157), as the addition of arenes to 1-hexene is known to occur principally at the terminus [166]. However, as noted earlier, significant amounts of internal addition can also occur, resulting in a number of additional products. From the alkylpalladium intermediate, one could envision a horrendous multiplicity of products. Cyclization could produce either a five- or six-membered ring in the top branch of eq. 127, and the steric factor which is so important in controlling the direction of the Heck reaction would not have much effect here, as both ends of the double bond are substituted. Indeed, NMR spectra of the crude reaction mixtures using 1-hexene indicated that both five- and six-membered rings were present, since many small peaks were seen between δ 5.0 and 7.0 ppm. As one can see from the following abbreviated table of known olefinic-proton chemical shifts, this undoubtedly meant that we had both ring systems present (Table XXII).

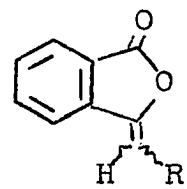
The reaction mechanism with allyl chlorides is quite similar to that for the olefins. Arylpalladium species add across the double bond as in the Heck reaction, but this time a palladium chloride species is eliminated, instead of a



(127)

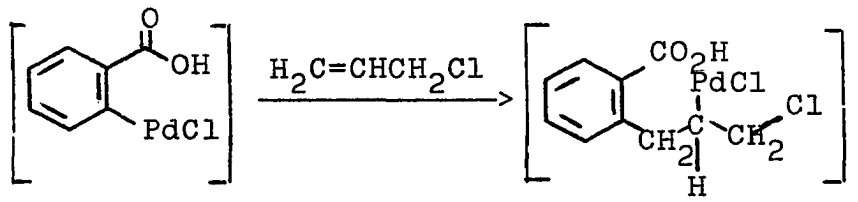
Table XXII. Chemical shifts of olefinic protons in isocoumarins and alkylidenephthalides

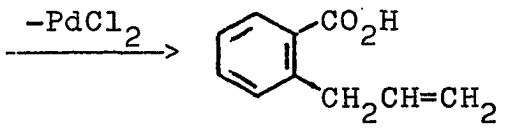




R	δ, Ppm	
	Isocoumarin	Alkylidenephthalide
$-CH_3$	6.10 [181]	---
$-CH_2CH_3$	6.32 [84]	E, 5.60 [51]
$-CH(CH_3)_2$	6.25 [84]	E, 5.48 [51], Z, 5.72 [51]
$-CH_2CH(CH_3)_2$	---	E, 5.63 [51], Z, 5.80 [51]
Ph	6.80 [180]	6.30 [184]

hydridopalladium species (eq. 128) [169,170]. Intermediate

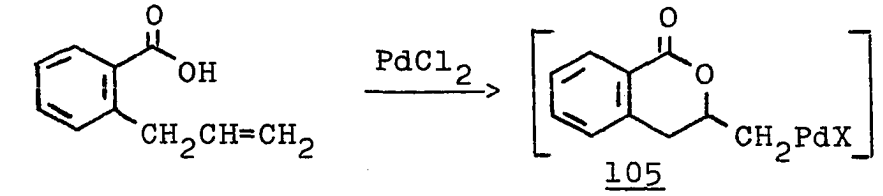


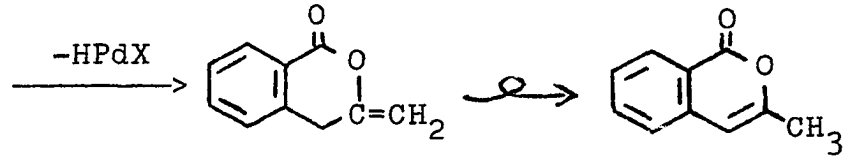


(128)

104

104 then undergoes cyclic oxypalladation, and rearrangement of the double bond gives the desired isocoumarin or other heterocycle (eq. 129). The origin of some of the side

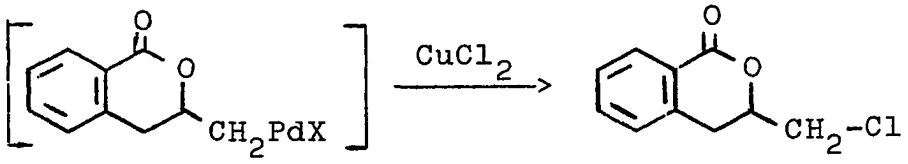




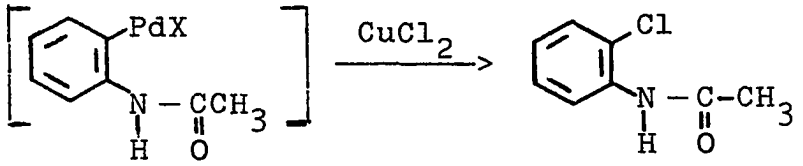
(129)

105

products mentioned in the discussion may have come from palladated intermediates such as 105. The chlorinated products seen when cupric chloride was used as a reoxidant are a good example (eqs. 130, 131). In our early work,



(130)



(131)

cyclizations were not observed when methyl acrylate was used as the olefin, presumably because the strong electron withdrawing carbomethoxy group prevents attack on the olefin by the electrophilic palladium salt.

C. Conclusion

The thallation-olefination reaction sequence did not work as well with arenes as we had hoped. Certain side reactions such as β-hydride elimination in more than one direction and ring closure to more than one ring size preclude good yields of a single product. It is possible that using a more polar solvent or treating the final reaction mixture with acid might increase the yields.

D. Experimental Section

1. Reagents

The reagents and equipment used for the work described in this chapter were discussed earlier in the Experimental Section of Chapter III. Some additional reagents were purchased, and used without further purification, unless otherwise noted. Allyl chloride (3-chloropropene), allyl acetate, 3-methoxybenzoic acid, and triethylamine were obtained from Eastman. 3,3-Dimethyl-1-butene, styrene, methyl acrylate, methyl vinyl ketone, 3-chloro-1-butene, and 1-chloro-2-butene (crotyl chloride) came from Aldrich. The crotyl chloride was distilled prior to use. 1=Hexene was purchased from Phillips Petroleum. Cupric chloride, which was dried in an oven overnight before use, and benzoquinone both came from Matheson, Coleman, and Bell.

2. Thallation of arenes

All thallations were performed as described in the Experimental Section of Chapter III.

3. General procedure for the olefination of arylthallium compounds

Arylthallium intermediates were prepared as described in Chapter III and used without further purification. On a 5 mmol scale, palladium chloride (5.0 mmol, 0.890 g), 10 mmol anhydrous lithium chloride (0.425 g), 10 mmol magnesium oxide

(0.402 g) and 25 ml solvent were placed in a 100-ml round bottom flask with septum inlet. The flask was flushed with argon. The arylthallium intermediate was dissolved in 25 ml solvent and added via disposable pipette against a backflush of argon. The olefin or allyl chloride (10-25 mmol) was added immediately by syringe. The reaction was stirred overnight under argon. The work-up procedures were identical to those described in the Experimental Section of Chapter III.

Purification of isolated compounds was usually performed by column chromatography on silica gel. Compounds purified by such chromatography include the following. 3-tert-Butylisocoumarin: R_f = .80; using benzene:ether (5:1). 3-Ethylisocoumarin: R_f = .63; using ethyl acetate:hexane (2:3). 3-tert-Butyl-7-methoxyisocoumarin: R_f = .50; using ethyl acetate:hexane (3:7). 3-Methylisocoumarin: R_f = .67; using ethyl acetate:hexane (2:3). N-Acetyl-2-methylindole: R_f = .68; using chloroform:acetone (10:1) [175]. 1,2-Dihydro-2,4-dimethyl-3-benzoxepin: R_f = .80· using ethyl acetate:hexane (1:1).

The following new compounds were prepared and characterized: 3-tert-Butylisocoumarin: mp 60-61°C (sublimed); ^{1}H NMR ($CDCl_3$) δ 1.31 (9H, s, $(CH_3)_3C$), 6.29 (1H, s, olefinic), 7.25-7.70 (3H, m, aromatic), 8.20-8.35 (1H, d with fine structure, J = 8Hz, aromatic next to carbonyl);

ir (max) (thin film) 1725 (C=O), 1640 (C=C) cm^{-1}; m/e 202.09834 (calcd for $C_{13}H_{14}O_2$, 202.09738). 3-tert-Butyl-7-methoxyisocoumarin: mp 112-125°C (chromatographed); ^1H NMR ($CDCl_3$) δ 1.31 (9H, s, $(CH_3)_3C$), 3.91 (3H, s, CH_3O), 6.65 (1H, s, olefinic), 6.95-7.89 (3H, m, aromatic); ir (max) ($CHCl_3$) 1720 (C=O), 1644 (C=C) cm^{-1}; m/e 232.10997 (calcd for $C_{14}H_{16}O_3$, 232.10995). Methyl(2-hydroxymethyl-4-hydroxy)-trans-cinnamate: mp 167-168°C (from ether-hexane); ^1H NMR (acetone-d^6) δ 3.00 (1H, br s, phenolic OH), 3.74 (3H, s, CH_3O), 4.28 (1H, br t, J = 5.5 Hz, CH_2-OH), 4.75 (1H, br d, J = 5.5 Hz, $-CH_2-$), 6.30 (1H, d, J = 16 Hz, trans-olefinic), 6.7-7.7 (3H, m, aromatic), 8.00 (1H, d, J = 16 Hz, trans-olefinic); ir (max) (thin film) 1735 (C=O), 1600 (C=C) cm^{-1}; m/e 208.07358 (calcd for $C_{11}H_{12}O_4$, 208.07356). 1,2-Dihydro-2,4-dimethyl-3-benzoxepin: (yellow oil); ^1H NMR ($CDCl_3$) δ 1.35 (3H, d, $CH_3-C(=O)H$), 1.94 (3H, s, CH_3-), 2.95 (2H, d, CH_2), 4.0-4.5 (1H, m, methine), 5 34 (1H, s, olefinic), 6.9-7.3 (4H, m, aromatic); ir (max) (thin film) 1650, 1605 (C=C) cm^{-1}; m/e 174.10457 (calcd for $C_{12}H_{14}O$, 174.10447).

V. CONCLUSION

In this work, we have investigated the preparation of a number of oxygen- and nitrogen-containing heterocycles, most of which belong to compound classes showing marked biological activity. These heterocycles, as well as several aryl esters and styrenes, were all made according to a unified synthetic strategy employing organopalladium intermediates. In Chapter II, the preparation of butenolides from propargylic alcohols via mercuration and palladium-assisted carbonylation was discussed. Although the intermediate mercurials were often isolated in low yields, the ease of preparing these vinylmercurials and the nearly quantitative yields of butenolides obtained from carbonylating them make this a worthwhile synthetic route to these valuable products. The procedure we developed uses only catalytic amounts of expensive palladium chloride, as cupric chloride serves as a re-oxidant. In Chapter III, the thallation and palladium-assisted carbonylation of arenes was shown to be a versatile synthetic pathway to a variety of compounds. Although it seemed at times that nature was not so simple, patterns emerged which could be explained rationally on the basis of steric effects or side reactions. Our reaction sequence can be quite useful, as long as one is aware of the limitations. For example, good yields of phthalides are obtained from benzyl alcohols when there is a group on the

ring activating it towards electrophilic aromatic substitution, and when the directive effect of this group is working in concert with the ortho delivery of thallium by the Lewis acid-Lewis base chelate formed by the alcohol and thallium(III) trifluoroacetate. Groups which deactivate the ring towards electrophilic aromatic substitution, substituents on the side chain α to the benzylic hydroxyl group, and activating groups on the ring which are positioned so that they compete with the ortho delivery of thallium all lower the yields of phthalides significantly. 3-Substituted benzyl alcohols will undergo thallation exclusively in the 6-position, on the side of the ring away from the substituent, due to the steric bulk of thallium. β-Phenethyl alcohols give good yields of 3,4-dihydroisocoumarins when there are side-chain substituents which hold the alcohol fairly rigidly. When the ring is substituted in the 2- and 5-positions, yields of cyclized product are lowered because of steric effects. Cyclic anhydrides, phthalimide. and nitrogen-containing heterocycles were obtained in moderate to good yields from aryl acids, benzamide, and N-aryl amides, respectively. Once again, expensive palladium chloride was used only in catalytic amounts, as the thallium(III) present in solution served as a re-oxidant. The results shown in Chapter IV were somewhat disappointing, for the thallation-olefination reaction sequence was not as

useful as had been hoped. Many reactions which were attempted failed altogether, and many of those that did give desired products gave low yields. With only one exception, these reactions required a stoichiometric amount of palladium chloride, and side products were observed in nearly every reaction tried. However, it is encouraging that some of the reactions succeeded, as this shows that the theory behind these reactions was sound. Perhaps a simple adjustment of reaction conditions, such as using a more polar, aprotic solvent like DMF, DMSO, or HMPA, will improve the yields significantly.

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