Regiospecific Alkenylation of Phenols by 1,1-Dimethylallene promoted by Platinum Catalysts

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1,1-Dimethylallene reacts with phenolic substrates in the presence of catalytic amounts of platinum(II) complexes. A regiospecific *C*-alkenylation takes place, affording *o*-isopentenylphenols and 2,2-dimethylchromans. Possible reaction mechanisms are also discussed.

The *o*-isopentenylphenols (1) and their cyclic derivatives, 2,2-dimethylchromans (2) and 2,2-dimethylchromens (3), are compounds whose skeleton is present in many natural substances.[1] Since they are useful model compounds for biogenetic studies [2] and have practical uses, there have been many efforts to synthesize them. The usual preparative procedures for (1) and (2) † are generally multi-step processes, with far from satisfactory yields.[4] The direct alkenylation of phenolic substrates with isoprene, which should be the most suitable method, leads to a mixture of products.[5] Only recently, with an acid catalyst [6] or under unusual Friedel–Crafts conditions,[7] has good regiochemical control of this reaction been attained, affording 2,2-dimethylchromans in high yields. Organometallic catalysts have also been used,[8] but mixtures of *ortho*- and *para*-alkenylated phenols were obtained.

During our studies [9] on the activation of co-ordinated double bonds towards nucleophilic addition, we found that 1,1-dimethylallene (DMA), a cumulated diene having the same skeleton as isoprene, can react with phenolic substrates, when co-ordinated to platinum(II). *ortho*-Alkenylation of the aromatic ring occurs in good yields. This reaction can be performed under catalytic conditions using several platinum(II) complexes as promoters.

In this paper we report the results of the reaction between DMA and phenols catalysed by the complex $[N(CH_2CH_2CH_3)_4][PtCl_3(C_2H_4)]$.

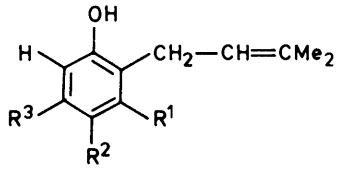
Results and Discussion

DMA co-ordinates to platinum(II) through the less substituted double bond, which thus becomes prone to nucleophilic addition. Stoicheiometric processes,[9d] using amines as nucleophiles, have been widely investigated, and in every case addition to the terminal carbon atom of the co-ordinated double bond was observed. Protolysis of the C–Pt bond of the addition product led to the isolation of isopentenyl derivatives, as shown in Scheme 1.

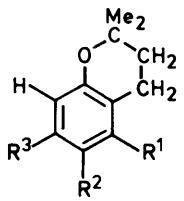
The extension of such studies to other potential reagents has shown that the aromatic ring of phenolic compounds can act by itself as a nucleophile towards co-ordinated DMA. In fact the reaction of the complex *cis*-$[PtCl_2(DMA)(PPh_3)]$ and phenol in a 1 : 1 ratio results in the formation of *o*-isopentenylphenol, according to equation (1). Small amounts of other

$$2\ cis\text{-}[PtCl_2(DMA)(PPh_3)] + 2\ C_6H_5OH = 2\ o\text{-}C_6H_4(CH_2{-}CH{=}CMe_2)OH + [PtCl_2(PPh_3)]_2 \quad (1)$$

organic products are also formed. It is worth emphasizing that the organic reaction products are not bound to the metal



(1)



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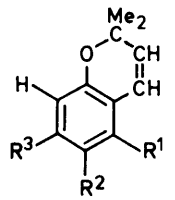

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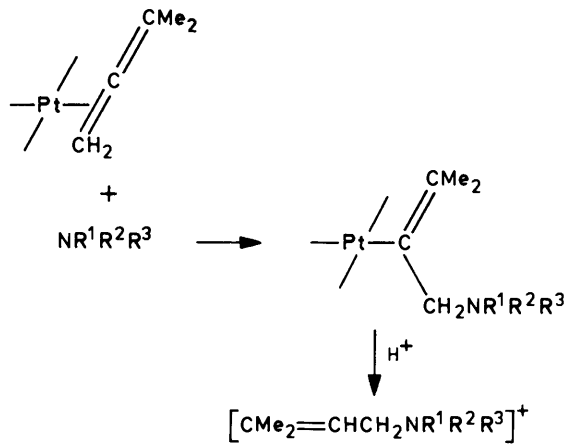


Scheme 1. R^i = H or alkyl

and the latter is recovered at the end of the reaction as a compound apt to restore the starting η^2-complex by co-ordination of free DMA.

On the basis of these findings we treated DMA and phenolic substrates in chloroform solution in the presence of catalytic amounts of platinum(II) complexes. Several were tested as catalysts including neutral species of the type *cis*- and *trans*-$[PtCl_2(C_2H_4)(ligand)]$ as well as anionic or cationic η^2-ethene complexes.‡ In all cases they were found to promote the catalytic reaction at least to some extent. Our results refer

† 2,2-Dimethylchromens (3) can be easily obtained from compounds (1) and (2) through dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[3]

‡ No differences were found by the use of olefinic rather than DMA complexes as catalysts, since a rapid exchange between the co-ordinated olefin and free DMA occurs in all cases.

Table 1. Reaction products of DMA with various phenols [a]

Phenol	T/°C	t/h	Conversion (%) [b]	Proportion of products (%) [b,c] A	B
Unsubstituted	60	6	93	48	13
3-Me	30	6	57	93 [d]	4
3-Me	30	24	78	58 [d]	25
3-Me	60	6	62	90 [d]	5
3-Me	60	24	83	55 [d]	32
3-MeO	30	6	63	92 [e]	2
3-MeO	30	24	82	61 [e]	24
3-MeO	60	6	70	95 [e]	3
3-MeO	60	24	88	58 [e]	30
4-Me	30	24	41	59	25
4-Me	60	24	45	56	28
4-MeO	30	24	38	35	52
4-MeO	60	24	43	4	83
2,6-$(MeO)_2$	60	24	8	5 [f]	

[a] 1 : 50 : 60 catalyst : phenol : DMA in chloroform solution. [b] Determined by g.l.c. analyses. [c] A = *o*-isopentenylphenol, B = 2,2-dimethylchroman; identification of the compounds was achieved by spectroscopic evidence by comparison with literature data. [d] Mixture of the two isomers 2-isopentenyl-5-methylphenol and 2-isopentenyl-3-methylphenol in approximate ratio of 92 : 8. [e] Mixture of the two isomers 2-isopentenyl-5-methoxy- and 2-isopentenyl-3-methoxy-phenol in *ca.* 95 : 5 ratio. [f] *O*-Isopentenyl phenol.

Table 2. ^{1}H N.m.r. spectra data (δ) for reaction products reported in Table 1

Product	Aromatic H	$ArCH_2$	CH=	$C(CH_3)_2$	$ArCH_3$ $ArOCH_3$	OH
(1; $R^1 = R^2 = R^3 = H$)	7.15—7.05 (2 H, m), 6.90—6.75 (2 H, m)	3.35 (d)	5.32 (t)	1.77 (s)		5.2br (s)
(1; $R^1 = R^2 = H$, $R^3 = CH_3$)	6.98 (1 H, d), 6.68 (1 H, d), 6.60 (1 H, s)	3.33 (d)	5.33 (t)	1.78 (s)	2.29 (s)	5.5br (s)
(1; $R^2 = R^3 = H$, $R^1 = CH_3$)	7.00 (1 H, t), 6.75 (1 H, d), 6.60 (1 H, d)	3.42 (d)	5.18 (t)	1.82 (s), 1.75 (s)	2.31 (s)	5.0br (s)
(1; $R^1 = R^2 = H$, $R^3 = OCH_3$)	6.98 (1 H, d), 6.44 (1 H, d), 6.42 (1 H, s)	3.30 (d)	5.31 (t)	1.78 (s)	3.77 (s)	5.15br(s)
(1; $R^2 = R^3 = H$, $R^1 = OCH_3$)	7.05 (1 H, t), 6.50 (1 H, s), 6.46 (1 H, s)	3.42 (d)	5.24 (t)	1.83 (s), 1.73 (s)	3.80 (s)	5.3br (s)
(1; $R^1 = R^3 = H$, $R^2 = CH_3$)	6.95 (1 H, s), 6.93 (1 H, d), 6.72 (1 H, d)	3.36 (d)	5.37 (t)	1.76 (s)	2.27 (s)	5.2br (s)
(1; $R^1 = R^3 = H$, $R^2 = OCH_3$)	6.85br (1 H, s), 6.79 (1 H, s), 6.56 (1 H, s)	3.32 (d)	5.31 (t)	1.75 (s)	3.75 (s)	5.1br (s)
(2; $R^1 = R^2 = R^3 = H$)	7.0—7.15 (2 H, m), 6.7—6.9 (2 H, m)	2.77 (t)	1.80 (t)	1.33 (s)		
(2; $R^1 = R^2 = H$, $R^3 = CH_3$)	7.01 (1 H, d), 6.71 (1 H, d), 6.70 (1 H, s)	2.82 (t)	1.76 (t)	1.38 (s)	2.34 (s)	
(2; $R^1 = R^2 = H$, $R^3 = OCH_3$)	6.98 (1 H, d), 6.45 (1 H, d), 6.39 (1 H, s)	2.74 (t)	1.80 (t)	1.35 (s)	3.78 (s)	
(2; $R^2 = CH_3$, $R^1 = R^3 = H$)	6.92 (1 H, d), 6.88 (1 H, s), 6.71 (1 H, d)	2.76 (t)	1.78 (t)	1.33 (s)	2.26 (s)	
(2; $R^2 = OCH_3$, $R^1 = R^3 = H$)	6.70 (2 H, m), 6.62br (1 H, s)	2.70 (t)	1.72 (t)	1.39 (s)	3.72 (s)	
2,6-$(CH_3O)_2C_6H_3OCH_2CH{=}CMe_2$	6.79 (1 ArH, t), 6.58 (2 ArH, d)	5.55 (=CH, t)	4.20 (OCH_2, d)	1.80, 1.72 [$C(CH_3)_2$, two s]	3.85 [$Ar(OCH_3)_2$, s]	

to the use of $[N(CH_2CH_2CH_3)_4][PtCl_3(C_2H_4)]$ as catalyst, since this complex has shown the best catalytic ability, relative to ease of preparation. Phenol, 3- and 4-methoxyphenol, 3- and 4-methylphenol, 2,6-dimethoxyphenol, and anisole were used as nucleophilic substrates. In all runs a 1 : 1.2 phenol : DMA ratio and a 50 : 1 phenol : catalyst ratio were adopted. The reactions were performed at two temperatures, 30 and 60 °C.

The experimental results are reported in Table 1, and some relevant ^{1}H n.m.r. data of the products are given in Table 2. By inspection of Table 1 it turns out that two main products are formed in all the reactions. These are an *o*-isopentenylphenol and a 2,2-dimethylchroman. The structure of the products gives evidence of effective regiochemical control. In fact, only one site of the aromatic ring is substantially involved in the metal-assisted *C*-alkenylation of the phenolic substrates. This should be compared with previous reports on similar processes promoted by Lewis acids; it was found [10] that the introduction of the isopentenyl group into phenolic rings occurs both *ortho* and *para* to the hydroxy-group, in a ratio depending on the experimental conditions. In our case the absence of *C*-alkenylation products for 2,6-dimethoxyphenol, the pattern of the aromatic protons in the ^{1}H n.m.r. spectrum of the addition product for unsubstituted phenol, and the easy cyclization to chromans and chromens of the isopentenyl derivatives from 3-methyl- and 3-methoxyphenol, point to the conclusion that addition to DMA is regiospecific. Only the *ortho* position is involved in the reaction of phenol. When 3-substituted phenols are treated only one product is isolated in good yield, corresponding to the addition to the less hindered *ortho*-position.*

The reaction mixture contains in all cases, beside the *o*-isopentenyl derivative, the corresponding cyclic 2,2-dimethylchroman. The amount varies widely depending on the temperature, the reaction time, and the phenolic substrate used. The highest yields of chroman were obtained by increasing the temperature and the reaction time. In one case, when 4-methoxyphenol was used as substrate, the chroman is the most abundant reaction product at 60 °C.

* Only a small amount of the other *ortho*-derivative was obtained (yield *ca.* 3% based on reacted phenol). We did not attempt to ascertain if any product of the addition involving the *para*-position was formed. The yield of such a product would not exceed 1%.

G.l.c. analyses of reaction mixtures at different reaction times have shown that the first reaction product is the *C*-alkenylated phenol. The chroman is subsequently formed and its percentage increases with time. Furthermore we have observed in a separate test that pure *o*-isopentenylphenol is slowly transformed into the corresponding chroman in the presence of catalytic amounts of $[N(CH_2CH_2CH_3)_4][PtCl_3(C_2H_4)]$. However, the data do not allow us to conclude that the chroman is exclusively formed from the *o*-isopentenylphenol through a metal-assisted cyclization. Different reaction paths, leading to the isopentenylphenol and to the chroman, may possibly involve the phenolic substrate and co-ordinated DMA.

Another reaction product, which is always present in a small amount, is isopentenyl phenyl ether. Indeed this is the only reaction product isolated in the addition of 2,6-dimethoxyphenol to DMA. Finally, minor amounts of high-boiling by-products, conceivably polyalkenylated derivatives, are also formed.

The runs at 30 and 60 °C do not show significant differences in the conversion rate of the phenolic substrates. The reaction temperature only affects the composition of the reaction mixture, as already mentioned.

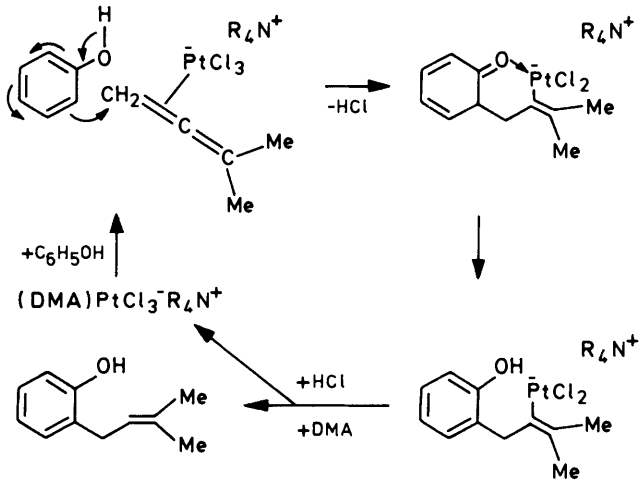
Runs at different reaction times were also carried out. We observed that the best results, comparing the degree of conversion of the phenolic substrate with the composition of the reaction products, were obtained within 6 h. After this period, the degree of conversion increases slowly, while the yields of the isopentenylphenol and of the chroman approach each other. For reaction times longer than 24 h, the previously mentioned high-boiling by-products become significant.

As far as the reactivity of the phenolic substrate is concerned, we have found that the phenols with a CH_3 or OCH_3 group *meta*, rather than *para* to the hydroxy-group, are distinctly more reactive, as expected from electronic effects.

It was found [11] that most of the studied processes involving the addition of a nucleophile to a transition metal co-ordinated double bond occur without activation of the nucleophile through preliminary co-ordination to the metallic centre. In fact, experimental evidence from stereochemical studies shows that the addition occurs with an *exo*-mechanism. Recently, this mechanism was also accepted [12] for a related catalytic reaction, *i.e.* hydroxy-addition in the Wacker process. As a matter of fact, an *exo*-addition should involve reaction on both the activated *ortho*- and *para*-positions of the phenyl ring, the latter being favoured on the basis of steric factors, at least for the unsubstituted phenol. Thus, the absence of measurable amounts of *para*-*C*-alkenylated phenols seems to suggest that an *exo*-mechanism is not valid when the aromatic ring acts as the nucleophile.

It is not possible, for the same reasons, to discard *exo*-addition for the reaction path leading to the *O*-isopentenyl phenolic by-products.

At this stage the simplest explanation of the experimental data assumes that the phenolic substrate is activated by co-ordination to the metallic centre through the oxygen atom. In this case, a five-co-ordinated species should be one of the reaction intermediates and the *ortho*-*C*-alkenylation would be the immediate consequence of the stereochemical features of this intermediate. It is worth noting that the metal-assisted alkylation of phenols by olefins in the presence of aluminium phenoxides involves *ortho*-substitution. For this reaction a close interaction of the phenol with the metal was claimed, followed by the addition of the hydrogen atom of the hydroxy-group, and of the *ortho*-carbon atom to the unsaturated carbons of the olefin in a six-membered concerted mechanism.[13] Scheme 2 shows a possible mechanism for the phenol



Scheme 2.

prenylation here reported. Two experimental observations agree with the proposed pathway. We found that the presence in the reaction medium of species having co-ordinating ability towards platinum(II), such as acetone or methyl cyanide, markedly decreased the reactivity of the substrate. Furthermore, we did not observe addition when the reaction between an ether, *i.e.* anisole, and DMA, in the presence of platinum compounds, was attempted under the above conditions.

Of course, more complicated reaction mechanisms could be proposed in order to explain the preponderant presence of *ortho*-substituted derivatives in the reaction products, including molecular rearrangement of a *C*-alkenyl phenol or a Claisen rearrangement. This latter process could involve isopentenyl phenyl ethers which were actually found in small amounts in the reaction products (see above). In this case, however, different regiochemistry should be observed for the formation of the *o*-alkenylphenols. These could be obtained by Claisen rearrangement of the alkenyl phenyl ethers arising after hydroxy-addition to the CMe_2 group of DMA. In fact, it must be pointed out that these ethers were not detected among the reaction products.

In conclusion, these experiments have shown that platinum(II) complexes are useful catalysts for the *C*-alkenylation of phenols with DMA, since they promote the regiospecific reaction between the diene and the aromatic ring.

Experimental

Chromatographic analyses were performed with a Perkin-Elmer Sigma 3B gas chromatograph using a 4 m column of SE-30 on Chromosorb W. Chromatographic separations were carried out with a Perkin-Elmer Series 2 liquid chromatograph using a silica A column and eluting with n-hexane–chloroform–methanol. ^1H N.m.r. spectra were recorded on a Bruker WH 270 spectrometer in $CDCl_3$ solution.

All solvents and reagents were of analytical grade. Phenols were distilled prior to use. *cis*-$[PtCl_2(DMA)(PPh_3)]$ was prepared by a known procedure.[9d] $[N(CH_2CH_2CH_3)_4][PtCl_3(C_2H_4)]$ was synthesized by mixing aqueous solutions of equimolar amounts of $K[PtCl_3(C_2H_4)]\cdot H_2O$ and $[N(CH_2CH_2CH_3)_4]Cl$. The solid precipitate was recrystallized from dichloromethane–methanol affording yellow-green crystals.

Stoicheiometric Reaction of Phenol with cis-$[PtCl_2(DMA)(PPh_3)]$.—To a chloroform solution of *cis*-$[PtCl_2(DMA)(PPh_3)]$ (0.6 g, 1 mmol), phenol (0.094 g, 1 mmol) was added.

The mixture was stirred at 45 °C for 4 h, and an orange solid formed. After this period, the solid was filtered off and identified as $[\{PtCl_2(PPh_3)\}_2]$ by standard procedures. The solution was concentrated and the residue extracted with diethyl ether. After evaporation of ether, a yellow oil (0.15 g) was obtained. This crude product was column-chromatographed on silica gel using n-hexane–ethyl acetate (92 : 8) as eluant. Three main fractions, 2,6-di-isopentenylphenol (a), 2-isopentenylphenol (b), and unchanged phenol were isolated and identified by ^{1}H n.m.r. spectra. Fraction (a) (0.035 g, 15%) showed δ_H 6.98 (2 H, d, ArH), 6.79 (1 H, t, ArH), 5.36 (1 H, s, OH), 5.33 (2 H, t, $ArCH_2$=C*H*), 3.35 (4 H, d, $ArCH_2$=CH), and 1.76 [12 H, s, $C(CH_3)_2$]. Fraction (b) (0.085 g, 52%) showed δ_H 7.15—7.05 (2 H, m, ArH), 6.90—6.75 (2 H, m, ArH), 5.32 (1 H, t, $ArCH_2$=C*H*), 5.19 (1 H, s, OH), 3.35 (2 H, d, $ArCH_2$=CH), and 1.77 [6 H, s, $C(CH_3)_2$].

ortho-Substitution in fraction (b) was demonstrated by the asymmetry of the aromatic proton multiplets in the ^{1}H n.m.r. spectrum and by the presence of an intense absorption band at 750 cm^{-1} in the i.r. spectrum, which is typical for 1,2-substituted aromatic rings.

Small amounts of other products, conceivably ethers, were also detected, but they were not identified.

General Procedure for Catalytic Runs.—The catalyst $[N(CH_2CH_2CH_3)_4][PtCl_3(C_2H_4)]$ (0.0052 g, 10^{-4} mol), DMA (0.41 g, 6×10^{-3} mol), and the appropriate amount of the phenol (5×10^{-3} mol) were dissolved in chloroform (2 ml). The mixture was heated at a fixed temperature (30 or 60 °C) for 6 or 24 h. The solvent was removed *in vacuo* and the residue extracted with diethyl ether. Quantitative analyses of the reaction mixture composition were carried out by g.l.c. techniques. The two major components, the *o*-isopentenylphenol and the corresponding 2,2-dimethylchroman, were isolated by h.p.l.c.

Cyclization to the Chroman of 5-Methyl-2-(3-methylbut-2-enyl)phenol.—The title phenol (0.088 g, 5×10^{-4} mol) and the platinum catalyst (0.0026 g, 0.5×10^{-4} mol) were dissolved in chloroform (1 ml) and heated at 60 °C for 24 h. G.l.c. analysis of the reaction mixture gave evidence of 20% formation of the corresponding chroman. No cyclization was observed in the absence of the platinum catalyst.

Cyclization to the Chromen[3] *of 5-Methyl-2-(3-methylbut-2-enyl)phenol.*—To a solution of the title phenol (0.176 g, 0.001 mol) in diethyl ether (10 ml), DDQ (0.250 g, 0.0011 mol) dissolved in the same solvent was added dropwise at room temperature. After 2 h stirring, the solvent was removed *in vacuo* and the residue purified by chromatography on silica gel eluting with 98 : 2 n-hexane–ethyl acetate. The chromen (0.105 g, 60%) was obtained as the first fraction, δ_H 6.87 (1 H, d, ArH), 6.65 (1 H, d, ArH), 6.62 (1 H, s, ArH), 6.30 (1 H, d, ArC*H*=CH), 5.55 (1 H, d, ArCH=C*H*), 2.29 (3 H, s, $ArCH_3$), and 1.43 [6 H, s, $C(CH_3)_2$].

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