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Palladium(II) Catalyzed Aromatic Acetoxylation

II. Nuclear Acetoxylation of Aromatic Compounds: A Reversal of the Usual Isomer Distribution Pattern in Aromatic Substitution

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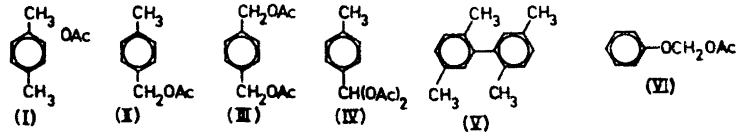
The reaction between monosubstituted aromatics and Pd(II) acetate in acetic acid in an oxygen atmosphere has been investigated. The monoacetoxylation products from compounds containing *o,p*-directing substituents were found to consist of predominantly *meta* isomer, whereas one compound with a *meta*-orienting substituent was found to give mainly *o,p*-acetoxylation. Thus the isomer distributions observed are reversed with respect to ordinary electrophilic aromatic substitutions. Polymethylsubstituted benzenes were found to give side-chain acetoxylation products.

The first paper in this series [1] reported a study of the oxidation of *p*-xylene with Pd(II) acetate in acetic acid. The objective of this study was to optimize the reaction parameters for formation of the *nuclear* acetoxylation product, 2,4-dimethylphenyl acetate (I), in competition with primarily the α acetates II–IV and other compounds, such as biaryl V.



The best relative yields of I were realized when the oxidation was carried out in the presence of oxygen at reflux temperature with only Pd(II) acetate present. Addition of alkali metal acetates strongly favors side-chain acetoxylation. Under these conditions a I/II ratio of 70:30 was obtained, and the reaction was catalytic in the Pd(II) species, although it had the disadvantage

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of being very slow. Nevertheless, we felt it would be of considerable interest to elucidate the characteristics of this direct nuclear acetoxylation process. This paper is a report [2] of the Pd(II) acetate oxidation of a series of aromatic compounds with the goal of determining the isomer distribution of the monoacetoxy derivatives. The results obtained reveal an unusual and interesting effect, in that predominant *meta* substitution is observed in the acetoxylation of compounds with substituents which behave as *ortho,para*-directing in normal electrophilic aromatic substitutions.

RESULTS

The compounds listed in Table 1 were chosen so as to make only nuclear substitution possible, and were oxidized with Pd(II) acetate in glacial acetic acid at 115° in an oxygen atmosphere. Product distributions were determined at low conversion, the [Pd(II)]/[substrate] ratio being kept at about 0.1 in order to favor the acetoxylation process. Lower ratios tend to produce more of the biaryl products (see below).

Table 1. Isomer distributions in Pd(II) acetate acetoxylation,[a] anodic acetoxylation,[b] and diisopropyl peroxydicarbonate-cupric chloride oxygenation[c] of aromatic compounds.

Compound	Pd(II) acetate acetoxylation			Anodic acetoxylation			$(i\text{-PrOCO}_2)_2$-$CuCl_2$ oxygenation[d]		
	o(α)	*m*(β)	*p*	*o*(α)	*m*(β)	*p*	*o*(α)	*m*(β)	*p*
t-Butylbenzene	–	95	5	35	22	43			
Anisole	1	97	2	67	4	29	63	1	36
Biphenyl	2	98	–	31	1	68	47	4	49
Chlorobenzene	3	88	9	37	6	58	54	13	33
Bromobenzene	5	81	14	30	3	67			
Iodobenzene	25	69	6	17	4	79			
Methyl benzoate	44	35	21	No reaction					
Toluene[e]	19	62	19	43	11	46	57	15	28
Naphthalene	56	44		94	4		92	8	

[a] [Pd(II)]/[substrate]≈0.1, temp. 115°, oxygen atmosphere, reaction period 4 h. [b] In HOAc/0.5 M NaOAc at 25°, Pt anode. [c] For experimental conditions, see Ref. 4. [d] Aryl isopropyl carbonates are formed. [e] Henry [5] reported this distribution under conditions differing from those employed here; potassium dichromate was present as a co-oxidant in a strongly acidic medium (CH_3SO_3H in HOAc).

Table 1 shows the isomer distributions of the acetates formed. A strong preponderance of *meta* substitution is observed for compounds with *o,p*-directing substituents. In line with this behavior, the proportion of β isomer from naphthalene is unusually high, although it is not the major product. If a *meta*-orienting substituent is present, as in methyl benzoate, the isomer distribution is in favor of the *ortho* and *para* isomers, again a reversal of the normal substitution pattern in aromatic substitution. For comparison, isomer distributions from two other direct aromatic oxygenation reactions, anodic

acetoxylation [3] and oxygenation with diisopropyl peroxydicarbonate-cupric chloride,[4] are included in Table 1. Both of these processes show isomer distributions characteristic of electrophilic aromatic substitutions. For certain substrates, side-reactions occurred with formation of products other than acetoxy derivatives. From naphthalene, two binaphthyls (ratio of 1,1′- to 1,2′-binaphthyl 22 : 78) were detectable in a yield corresponding to 1 % of the two acetoxynaphthalenes. In the *t*-butylbenzene reaction, small amounts of toluene and phenol were observed. In the oxidation of anisole, the nuclear acetates were not the main products. Instead, cleavage of the CH_3-O bond to give phenol and attack on the methyl group to give acetoxymethyl phenyl ether (VI) are important side-reactions, the distribution of phenol, VI, and nuclear acetates being 63, 17, and 17 %. In addition, 1 % of dimethoxybiphenyls (three isomers) was detected together with small amounts of three unidentified products.

Chloro- and bromobenzene gave in addition to the acetates traces of phenol and phenyl acetate. Iodobenzene gave only 12 % iodophenyl acetates, the remaining part of the product mixture consisting of phenyl acetate (23 %), biphenyl (31 %), and two isomers of diiodobenzene (together 34 %).

Phenyl acetate did not undergo acetoxylation under the conditions specified,[5] phenol and diacetoxybiphenyls (at least four isomers) being the only products found.

For three substrates, naphthalene, *t*-butylbenzene, and methyl benzoate, we also studied the influence of adding aluminium chloride (a Lewis acid), triphenylphosphine (a Lewis base) and tetrabutylammonium acetate (TBA). The possible mode of action of these additives was described in Part I.[1] The results are shown in Tables 2 (naphthalene) and 3 (*t*-butylbenzene). For methyl benzoate it suffices to say that all three additives completely suppressed the acetoxylation process, biaryl coupling being the favored process in the presence of aluminium chloride and triphenylphosphine.

Table 2. Effect of additives on the Pd(II) acetate acetoxylation of naphthalene in acetic acid at 115° in an oxygen atmosphere; reaction period 4 h; [Pd(II)]/[naphthalene] = 0.1.

[Additive]/[Pd(II)]	Nuclear acetoxylation		Binaphthyls			Ratio acetoxy/biaryl
	α	β	1,1′	1,2′	2,2′	
– –	56	44	22	78	–	100
$[AlCl_3]/[Pd(II)] = 1$	89	11	15	67	18	1
$[PPh_3]/[Pd(II)] = 1$	58	42	18	72	–	100
[TBA]/[Pd(II)] = 10	73	27	26	74	–	100

In the naphthalene experiments (Table 2) aluminium chloride changed the isomer distribution for acetoxylation toward a more normal 89 : 11 ratio between α and β isomer, whereas triphenylphosphine left it unchanged. TBA had a small effect toward increasing the amount of α isomer. As in the case of *p*-xylene,[1] aluminium chloride strongly increased the proportion of biaryl

Table 3. Effect of additives on the Pd(II) acetate acetoxylation of *t*-butylbenzene in acetic acid at 115° in an oxygen atmosphere; reaction period 4 h; [Pd(II)]/[*t*-butylbenzene] = 0.1.

[Additive]/[Pd(II)]	Nuclear acetoxylation			Biaryl coupling products
	o	*m*	*p*	
–	–	95	5	–
$[AlCl_3]/[Pd(II)] = 1$	–	–	–	Main product
$[PPh_3]/[Pd(II)] = 1$	–	92	8	Traces
[TBA]/[Pd(II)] = 10	–	95	15	Traces

product. The results with *t*-butylbenzene (Table 3) were similar to those with naphthalene: Aluminium chloride strongly favored biaryl coupling, triphenylphosphine had little effect, and TBA changed the isomer distribution of acetoxy derivatives toward a more "normal" one.

A number of different polymethylbenzenes were also oxidized under identical conditions in order to study the competition between nuclear and side-chain acetoxylation. As demonstrated in Table 4, only *p*-xylene gave a nuclear

Table 4. Product distributions in the Pd(II) acetate acetoxylation of methylsubstituted aromatic hydrocarbons in acetic acid at 115° in an oxygen atmosphere; reaction period 4 h; [Pd(II)]/[substrate] = 0.1.

Ar in Ar–CH_3	ArCHO	$Ar'(CHO)_2$[a]	$ArCH_2OH$	$ArCH_2OAc$	Ar'' < CH_2OH[b] / CH_2OAc	Nuclear acetate
4-$CH_3C_6H_4$	56			7		37
3,5-$(CH_3)_2C_6H_3$	82		7	11		–
2,4,5-$(CH_3)_3C_6H_2$	63	8	7	21		–
3,4,5-$(CH_3)_3C_6H_2$	48[c]	11		10	30[d]	–
2,3,4,5-$(CH_3)_4C_6H$	18[e]	3[f]		28[g]	50[i]	–
				trace[h]		

[a] No attempt was made to establish the exact structure of the dialdehydes. [b] Denotes a compound derived from the substrate by substitution with one hydroxy and one acetoxy group. No attempt was made to establish the exact structure of these compounds; mass spectral data indicate that both substituents appear in the methyl groups. [c] Three isomers in the proportions 20 : 36 : 44. [d] Four isomers (1 : 2 : 19 : 78). [e] Three isomers (8 : 14 : 78). [f] Four isomers (6 : 7 : 29 : 58). [g] 2,3,5,6-Isomer. [h] 2,3,4,5-Isomer. [i] Two isomers (9 : 91).

acetate, whereas the higher polymethylbenzenes studied gave side-chain acetates. At very low conversion, mesitylene also gives a trace of nuclear acetate. In most cases a large proportion of aldehyde and dialdehyde(s) was present in the product mixture, which is characteristic for reactions carried out under oxygen.[1] From isodurene and pentamethylbenzene, products derived from substitution by one hydroxyl and one acetoxy group were obtained in relatively large amounts.

The acetoxylation of one heteroaromatic compound, thiophene, was attempted, but failed consistently. Incidentally, anodic acetoxylation also fails in this case.[6] Only bithienyls were formed under the conditions employed (see Table 5).

Table 5. Isomer distribution in the biaryl coupling of thiophene in acetic acid.

Reaction conditions	Bithienyls 2,2′	2,3′	3,3′
$PdCl_2$/NaOAc, reflux	56	44	Traces
$Pd(OAc)_2/O_2$/111° (3 h)	93	7	–
$Pd(OAc)_2$/Ar/NaOAc (3 h)	83	15	–

Some preparative experiments were run with naphthalene as substrate, and were conducted under conditions known to make the process catalytic in Pd(II) species: Pd(II) acetate in acetic acid, reflux temperature, oxygen bubbling, no additive, [Pd(II)]/[substrate]≈0.01). Table 6 summarizes the

Table 6. Yields and product distribution in the oxidation of naphthalene (3.3 M) with Pd(II) acetate (0.03 M) in acetic acid at reflux temperature after 400 h.

	Naphthyl acetates α+β	Binaphthyls 1,1′	1,2′	2,2′	Oligomers[a]
Yield, g	0.75	15.3	17.8	3.9	33.8
Yield, mmol	4.03	60.2	70.8	15.2	89.0[b]
Yield, %	45	670	790	170	1490[b]

[a] Mixture of trimer (15 %), tetramer (65 %), pentamer (19 %), and hexamer (1 %). [b] Calculated on the basis that the whole mixture consists of trimer.

distribution and yields of products after a reaction period of 400 h; at the low [Pd(II)]/[substrate] ratio employed, the biaryl coupling process is seen to be strongly favored, binaphthyls and higher oligomers being by far the major products. Apparently the successful application of the acetoxylation reaction among other things demands conditions at which [Pd(II)]/[substrate] can be kept at a much higher value, *e.g.*, by continuously adding the substrate as the reaction progresses. The conclusion arrived at in Part I[1] with regard to preparative applications still appears to be valid: Nuclear acetoxylation mediated by Pd(II) acetate is an impractically slow process. It is, however, synthetically interesting due to its unusual tendency toward *meta* substitution. We are at present working on the problem of speeding up the reaction while retaining the anomalous features with respect to orientation.

The discussion of the results will be deferred to Part III[7] of this series.

EXPERIMENTAL PART

Materials. Substrates and other chemicals used were purchased in the highest quality available and further purified by recrystallization, distillation, or preparative gas chromatography, if deemed necessary. Reference compounds (acetoxy compounds,[3] aldehydes, biaryls, *etc.*) were synthesized according to well known procedures. The identity and purity of all compounds were checked by mass, IR, and NMR spectral analysis as well as by gas chromatography. Retention times (Perkin-Elmer Model 880 gas chromatograph, equipped with an electronic integrator) for nuclear acetates are given in Table 7.

Table 7. Retention times[a] for nuclear acetates.

Substrate	Retention times, nuclear acetates			Column temperature
	o(α)	*m*(β)	*p*	
Naphthalene	44	49		200
t-Butylbenzene	39.0	41.3	50.5	155
Anisole	25.3	34.4	37.2	155
Phenyl acetate	27.6	38.5	40.0	170
Biphenyl	13.9	31.8	35.1	200
Chlorobenzene	25.1	30.8	31.9	150
Bromobenzene	35.7	45.5	47.5	155
Iodobenzene	34.2	44.2	46.5	180
Methyl benzoate	13.8	29.8	41.6	190

[a] Analyses were performed on a 4 m × 0.3 cm 10 % Apiezon L on Chromosorb W column, except for the biphenyl products, where a 3 m × 0.3 cm 5 % neopentylglycol succinate on Chromosorb W column was used.

For side-chain acetates the following values were found on a 3 m × 0.3 cm 5 % neopentylglycol succinate on Chromosorb W column (temperature of column and retention time in min given in parentheses): 2,4,6-trimethylphenyl (165°, 9.5), 2,4-dimethylbenzyl (165°, 12.0), 2,3,5,6-tetramethylphenyl (165°, 19.6), 2,4,5-trimethylbenzyl (165°, 22.3), 2,4,6-trimethylbenzyl (165°, 19.5), 2,3,5,6-tetramethylbenzyl (180°, 26.7), 2,3,4,6-tetramethylbenzyl (180°, 27.4), and 2,3,4,5-tetramethylbenzyl acetate (180°, 32.9).

Oxidation experiments were performed according to either of the two methods described in Part I.[1] Identification of compounds was based on mass spectral analysis alone, or mass spectral/gas chromatographic comparison with authentic samples (LKB 9000 system).

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