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Palladium(II) Catalyzed Aromatic Acetoxylation. V. Mixed Amine Acetatonitratopalladium(II) Complexes as Catalysts in the Acetoxylation of Chlorobenzene

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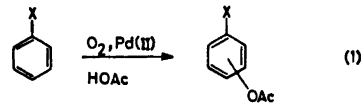
The palladium(II) acetate catalyzed acetoxylation of aromatic compounds has been further investigated, using chlorobenzene as the substrate. Addition of cooxidants, such as dichromate or nitrate, speeds up the reaction by a factor of about 50 but decreases the *meta* selectivity somewhat. In the presence of nitrate (or nitric acid or nitrogen dioxide) Pd metal never precipitates during the reaction. The nitrate catalyzed reaction could be run with a high degree of *meta* selectivity (up to 65 % of the product mixture) if an amine was added in an amount equivalent to the formation of a bisaminepalladium(II) complex. When 2,2′-bipyridine was used for complexation, the compound acetato(2,2′-bipyridine)nitratopalladium(II) monohydrate could be isolated from the reaction mixture. This complex, synthesized separately, possessed good catalytic activity for acetoxylation of chlorobenzene.

Previous work in this series [1,2] and by others [3–14] has established that direct acetoxylation of aromatics — in the ring and/or in the α position of an alkylsubstituted aromatic compound — can be achieved *via* a palladium acetate catalyzed process in boiling acetic acid in an oxygen atmosphere, as shown for nuclear acetoxylation of a monosubstituted benzene derivative in eqn. 1. The isomer distribution turned out to be anomalous under these or similar conditions,[2,10,14] the *meta* acetoxy derivative being the predominant isomer from a number of monosubstituted benzenes with otherwise *ortho*, *para*-directing substituents (*i.e.* in electrophilic substitution). These findings were rationalized in terms of an addition-elimination mechanism, in which electrophilic attack by a palladium(II) species is the initial step.[15]



(1)

Under the conditions described above, the reaction is, however, too slow to be of any practical value,[1] and we have therefore continued our studies of Pd(II) catalyzed aromatic acetoxylation with the aim of finding ways of speeding up the process while retaining the *meta* selectivity. This latter feature is of obvious interest from the synthetic point of view, since it gives a one-step route to phenol derivatives that are otherwise only accessible by multi-step procedures.

Some clues — apart from the well known effect of adding strong acid [3,6] — as to which directions one should look for additional catalytic effects in aromatic acetoxylation were to be found in the literature. Thus, Henry [10] had shown that the addition of a co-oxidant, such as potassium dichromate, to the $Pd(OAc)_2$/HOAc system favors nuclear acetoxylation in a substrate (toluene) that otherwise would give predominantly α acetoxylation.[7–9] Also here a selectivity for *meta* substitution was noticeable (*ortho*:*meta*:*para* equal to 19:62:19 in the presence of methanesulfonic acid). In the analogous vapor phase reaction, acetoxylation over a palladium based catalyst,[16] a similar facilitation of nuclear acetoxylation, coupled to a certain degree of *meta* selectivity, was

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noticed when the catalyst contained a co-oxidant. Moreover, Henry [10] as well as other investigators [6,12,14] has found that the addition of nitrate ion, nitric acid, or oxides of nitrogen has an accelerating effect upon aromatic acetoxylation, yet that nitration then becomes a significant side reaction.

We have applied these and similar ideas to the Pd(II) catalyzed nuclear acetoxylation of chlorobenzene, a substrate that after some preliminary experimentation was found to be a good model compound, since both nitration and biaryl coupling were only minor side reactions. The results indicate that it is indeed possible to speed up the reaction by a factor of about 50 while still retaining the *meta* selectivity to a high degree. Mixed amine acetatonitratopalladium(II) complexes were found to be best in this respect. The 2,2′-bipyridine-acetatonitratopalladium complex was isolated and characterized and found to possess good catalytic activity.

RESULT

A first approach to increase the rate of a reaction is to change the solvent. Since DMF has turned out to be a superior solvent for the palladium acetate catalyzed oxidation of terminal alkenes to ketones,[17] we first tried a mixture of acetic acid and DMF (1:1 v/v) as a solvent for the acetoxylation of chlorobenzene under oxygen. However, DMF acted as a reductant for Pd(II) acetate at the temperature employed and hence this solvent cannot be used. The main product from this reaction was, somewhat curiously, *N*,*N*-dimethylacetamide.

N,*N*-Dimethylacetamide in a mixture with acetic acid was then tried but with similar negative results; at 90 °C Pd(II) is reduced by the solvent mixture and acetoxylation runs with chlorobenzene at 65 and 85 °C did not yield any acetoxylation products. Dimethyl sulfoxide as a co-solvent also underwent oxidation by Pd(II), giving the corresponding sulfone. Thus, none of the dipolar aprotic solvents tried is inert towards Pd(II).

Next we added a strong acid to the reaction mixture (Table 1, experiments 2 and 3). As expected, this changed the reaction path from acetoxylation to predominant biaryl coupling, a mixture of dichlorobiphenyls (at least five of the six possible ones) being obtained. With methanesulfonic acid this process was essentially instantaneous and should be of pre-

Table 1. Acetoxylation of chlorobenzene by $Pd(OAc)_2$ in acetic acid after 4 h at 115 °C[a].

Experiment No.	Atmosphere	Added component	Acetoxychlorobenzenes Yield,[b] %	Isomer distribution *o*	*m*	*p*
1	O_2	None[c]	2.9	3	71	26
2	O_2	CF_3COOH (5 ml)	2.0	16		84[d,e]
3	O_2	CH_3SO_3H (2 ml)	Trace[e]			
4	O_2	$K_2Cr_2O_7$ (15 mmol)	56	15	45	39
5	N_2	$K_2Cr_2O_7$ (15 mmol)	56	15	46	38
6	O_2	$K_2Cr_2O_7$ (15 mmol), CF_3COOH (5 ml)	146	40	32	28
7	O_2	$K_2Cr_2O_7$ (15 mmol), CH_3SO_3H (2 ml)	22	59	19	22
8	O_2	$K_2Cr_2O_7$ (15 mmol), CCl_3COOH (7 ml)	16	70	14	16
9	O_2	$Cu(OAc)_2.H_2O$ (1 mmol)	Trace[f]			
10	O_2	$Sn(OAc)_2$ (1 mmol)	None			
11	O_2	$K_2S_2O_8$ (1 mmol)	9	8	56	36
12	O_2	$(NH_4)_2S_2O_8$ (1 mmol)	3.6	18	46	36
13	O_2	H_2O_2 (12 mmol)	Trace[g]			
14	O_2	NO_2 (10 mmol)	61	27	33	40

[a] All experiments were performed with 1.0 mmol of $Pd(OAc)_2$ and 9.9 mmol of chlorobenzene. The total amount of acetic acid and added liquid component was 50 ml. [b] Based on $Pd(OAc)_2$. [c] Reported [2] *o*:*m*:*p* = 3:88:9. [d] Difficult to analyze due to the small amount formed. [e] The main product was a mixture of isomeric dichlorobiphenyls. [f] Traces of phenyl acetate were detected. [g] H_2O_2 decomposed as soon as Pd(0) precipitated.

parative interest if the isomer distribution can be controlled. Trifluoroacetic acid also caused the formation of predominantly biaryl products, although a low yield of acetoxychlorobenzenes was secured.

Following Henry's observations,[10] we performed experiments in which potassium dichromate was added as a co-oxidant (Table 1, experiments 4 and 5). Both reactions, which differed from each other by being run under oxygen and nitrogen, respectively, gave acetoxylation products in a reasonably fast process (about 20 times faster than in the absence of potassium dichromate), showing that the finding that toluene is predominantly acetoxylated in the ring under these conditions is due to a rate increase of the nuclear substitution reaction. The reaction became even faster when trifluoroacetic acid was present together with potassium dichromate (146 % yield after 4 h), whereas under otherwise identical conditions methanesulfonic acid and trichloroacetic acid decreased the rate (Table 1, experiments 6 – 8). However, these rate increases are accompanied by changes in the isomer distribution, so that the desired *meta* selectivity has disappeared. Instead, the *ortho* isomer is slightly favored. No coupling was noticed in the experiments with dichromate present.

Some other oxidants were tried (experiments 9 – 13 in Table 1) but with no apparent success with respect to the aims of this investigation. In these cases acetoxylation did occur, but the reactions were either too slow or complicated by side reactions. Moreover, these reactions as well as all mentioned above suffered from the disadvantage of Pd metal precipitation with a concomitant sluggishness of the reoxidation of Pd(0) to Pd(II). Apart from this practical drawback, Pd(0) can catalyze unwanted reactions.

However, the last experiment (No. 14 in Table 1) gave very promising results from several points of view. Addition of NO_2 to the reaction solution caused a fairly rapid acetoxylation process to occur while at the same time the solution remained homogeneous during the run. Only a trace of chloronitrobenzenes was formed as a by-product, and the isomer distribution, although not directly in favor of the *meta* isomer, was only little affected.

A number of runs (Table 2) in which NO_2 was used as a co-oxidant were performed. Since water is formed during the reaction it was

Table 2. Acetoxylation of chlorobenzene in acetic acid after 4 h at 115 °C in the presence of NO_2.[a]

Experiment No.	Added component	Acetoxychlorobenzenes Yield,[b] %	Isomer distribution *o*	*m*	*p*	Nitration, %[b]
14	None	61	27	33	40	Trace
15	H_2O (2 mmol)	59	26	34	40	Trace[c]
16	CF_3COOH (5 ml)	49	17	49	34	20
17	CF_3COOH (10 ml)[d]	11	5	51	44	Trace[e]
18	NaOAc (10 mmol)	29	24	42	34	5
19	HNO_3 (0.2 ml)	92	25	34	41	Trace[f]
20	HNO_3 (1.0 ml)	110	26	33	41	Trace[f]
21	Pyridine (1.0 mmol)	75	13	57	30	5
22	Pyridine (1.3 mmol)	88	6	61	33	4
23	Pyridine (2.0 mmol)	45	6	61	33	5
24	Pyridine (4.0 mmol)	3.6	3	68	29	Trace
25	2,2′-Bipyridine (1.0 mmol)	79	5	48	47	2
26	2,2′-Bipyridine (1.0 mmol), HNO_3 (1.0 ml)	0				
27	2,2′-Bipyridine (1.0 mmol)	0[g]				

[a] All experiments were performed with 1.0 mmol of $Pd(OAc)_2$, 10.0 mmol of NO_2, and 9.9 mmol of chlorobenzene in an oxygen atmosphere. The total amount of acetic acid and added liquid component was 50 ml. [b] Based on $Pd(OAc)_2$. [c] The reaction was followed to 140 % yield; at this stage the solution was still catalytically active. [d] At 80 °C. [e] Chlorophenols (5 %) were also formed. [f] Bisacetoxylation (4 %) also occurred. [g] No NO_2 added.

Table 3. Acetoxylation of chlorobenzene by $Pd(OAc)_2$ in the presence of complexing agents and NO_2 in acetic acid at 115 °C [a].

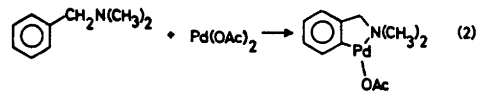
Experiment No.	Complexing agent	Reaction period, h	Acetoxychlorobenzenes Yield,[b] %	Isomer distrib. *o*	*m*	*p*	Nitration, %[b]
23	Pyridine (2 mmol)	4	45	6	61	33	5
25	2,2′-Bipyridine (1 mmol)	4	79	5	48	47	Trace
26	Isoquinoline (2 mmol)	4	88	6	65	30	Trace
27	Ethylenediamine (1 mmol)	4	81[c]	15	40	45	Trace
28	1,4-Diazabicyclo[2,2,2]octane (1 mmol)	1	20	21	44	45	1
29	Benzalaniline (1 mmol)	1	Trace				
30	*N*,*N*-Dimethylbenzylamine (2 mmol)	1	34	11	47	42	Trace
31	Acetylacetone (1 mmol)	4	65	23	37	40	Trace
32	EDTA (1 mmol)	1	18	20	45	35	1

[a] All experiments were performed with 1.0 mmol of $Pd(OAc)_2$, 10.0 mmol of NO_2, and 9.9 mmol of chlorobenzene in an oxygen atmosphere. The total amount of acetic acid and added liquid component was 50 ml. [b] Based on $Pd(OAc)_2$. [c] Yield after 1 h 52 %.

first established that small amounts of water had no effect on the yield and product distribution (nor had acetic anhydride), and that additives like trifluoroacetic acid, sodium acetate, or nitric acid did not have any deleterious effect upon the yield but on the other hand did not increase the *meta* selectivity to the desired level. Complexing bases of the pyridine type (Tables 2 and 3) were better in this respect and did not decrease the rate if not added in excessive amounts (*cf.* Table 2, experiments 23 and 24). All factors considered, isoquinoline appears to be the best complexing base hitherto found (experiment 26), the percentage of the *meta* isomer being 61 %, the yield 88 % after 4 h, and the occurrence of nitration almost negligible.

In the experiment (No. 15) with water present, the reaction was run for 27 h, after which time the yield was 250 %, based on the Pd(II) acetate used. The reaction mixture was still catalytically active and no Pd metal had precipitated. The isomer distribution changed slightly with time, being 17:37:46 at the discontinuation of the experiment, presumably due to different reactivity of the three isomers toward further acetoxylation. A second acetoxylation process does take place, as shown by the detection of at least three isomers of diacetoxychlorobenzene (22 % yield). Bisacetoxylation was noticed in two other cases as well (experiments 19 and 20).

Ethylenediamine was the most strongly rate accelerating base tried, the yield after 1 h being 52 % and after 4 h 71 %. A similar high initial rate was noticed with benzyldimethylamine (34 % after 1 h) but this reaction later slowed down appreciably (7 % during the second hour). In both cases the reaction mixture turned dark, probably due to oxidative degradation of the amine; it is also possible that benzyldimethylamine is removed in a palladation reaction, such as that depicted in eqn. 2:



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This type of compound is known from the literature.[18]

When NO_2 in excess was added to a solution of palladium acetate and 2,2′-bipyridine in acetic acid, a yellow precipitate was formed. The same precipitate was also produced when the reaction mixture from experiment No. 25 was allowed to cool. A solution of the filtered and dried complex in acetic acid has the same catalytical effect as the initial solution, without any extra NO_2 being added. Elemental analyses and spectral data (IR, NMR) showed that the salt must be acetato(2,2′-bipyridine)nitratopalladium(II) monohydrate. This complex reacted

Table 4. Acetoxylation of different substrates by some catalysts in acetic acid at 115 °C.[a]

Exp. No.	Substrate	Reaction period, h	Catalyst	Acetoxy derivatives Yield[b]	Isomer distribution *o*	*m*	*p*
33	Anisole	2	2,2′-Bipy Pd(OAc) (NO_3)	Low[c]	10	41	49
34	Phenyl acetate	2	2,2′-Bipy Pd(OAc) (NO_3)	Low	20	60	20
35	Chlorobenzene	4	2,2′-Bipy Pd(OAc) (NO_3)	70	2	60	38
36	Benzene	4	(Isoquin)$_2$Pd(OAc)$_2$+NO_2[e]	610[d]			
37	Methyl benzoate	4	(Isoquin)$_2$Pd(OAc)$_2$+NO_2[e]	0			

[a] All experiments were performed with 1 mmol of the complex, 9.9 mmol of the substrate, and 50 ml of HOAc in an O_2 atmosphere. [b] Based on the amount of complex. [c] A mixture of nitroanisoles was the main product. [d] Yield of nitrobenzene, 305 %. [e] 5.5 mmol.

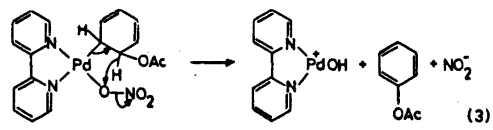
with excess nitric acid in HOAc and gave a solution of (2,2′-bipyridine)dinitratopalladium(II), which was catalytically inactive.

The mixed acetatonitrate complex was then used as a catalyst for the acetoxylation of a number of substrates (Table 4). Chlorobenzene (experiment 35) gave a higher *meta* selectivity than and almost the same yield of acetoxychlorobenzenes as in experiment 25 (Table 3) in which the complex was generated in solution. Compounds with activating groups gave acetoxylation products but in low yield; as expected, nitration is the major process in the case of anisole (experiment 33) and, in spite of much experimentation, it has not yet been possible to suppress this reaction. Even benzene is nitrated to a fairly high degree (experiment 36) under similar conditions. Methyl benzoate did not react at all. Phenyl acetate gave a mixture of diacetoxybenzenes as the main product but at a surprisingly low rate, which might explain why earlier attempts to acetoxylate phenyl acetate under slightly different conditions have failed.[10]

DISCUSSION

The primary aim of this investigation has been to increase the rate of the Pd(II) catalyzed nuclear acetoxylation of aromatic compounds while retaining the anomalous *meta* selectivity noticed earlier. At the same time it was desirable to find a better method of reoxidizing the Pd(0) state, so that no Pd metal would precipitate. Otherwise, there is a risk that the heterogeneous reoxidation reaction will be rate-limiting and/or that Pd metal might cause unwanted reactions.

The system palladium(II) acetate/NO_2 or HNO_3 in combination with oxygen represents a first step toward the realization of these goals, even if the *meta* selectivity is not so pronounced in these cases and in some cases published in the patent literature[14] (toluene, *o*:*m*:*p* = 16:41:43; isopropylbenzene, *o*:*m*:*p* = 0:59:41, *t*-butylbenzene, *o*:*m*:*p* = 0:43:57). However, modification of the acetatonitrato catalyst by adding a pyridine base increases the *meta* selectivity, 2,2′-bipyridine and isoquinoline being the best ligands so far studied. The isolation of a defined complex with good catalytic activity indicates that it is essential that palladium has both nitrate and acetate as a ligand (the corresponding complexes with two nitrate or acetate groups, respectively, were catalytically inactive). This is in accordance with the mechanism discussed earlier,[15] in which the first step is the reversible formation of a π complex between the palladium species, PdL_4, and the aromatic compound which then undergoes attack by a nucleophile (in acetoxylation, acetate ion) to form an adduct. Loss of $PdHL_3$ completes the reaction sequence.



(3)

It is the last step that is affected favorably by the addition of a co-oxidant, nitrate ion being especially effective since it can be present within

the coordination sphere of the adduct (eqn. 3) and regenerate a Pd(II) species directly.

The improvements of the acetoxylation process described in this paper have made the reaction feasible from the practical point of view, at least for laboratory use. A remaining drawback is the nitration reaction which becomes especially pronounced in compounds with activating substituents. Attempts to find other oxidants with properties similar to those of nitrate ion have so far failed.

EXPERIMENTAL

Materials. All chemicals used were purchased in the highest commercial quality available or prepared according to literature methods (see also Parts I and II of this series [1,2]). Solutions of nitrogen dioxide were prepared by heating a known amount of lead nitrate and dissolving it in glacial acetic acid. Identification of compounds was based on mass spectral/gas chromatographic (LKB 9000 system) comparison with authentic samples. Analyses [1,2] were performed with a Varian 1700 gas chromatograph in conjunction with a disc integrator. Biphenyl was used as an internal standard.

Analytical oxidation experiments. These were performed according to method B in Part I [1] with the modifications described in the tables.

Preparation of acetato(2,2'-bipyridine)nitratopalladium(II) monohydrate. 2,2'-Bipyridinepalladium(II) acetate [19] was dissolved in acetic acid and an excess of nitrogen dioxide was dissolved in the solution. The yellow-red precipitate was collected and recrystallized from acetic acid or DMF, m.p. 202 °C (dec.). IR (KBr): 3600 – 2950 (broad); 1600(w); 1385(s) cm^{-1}. NMR (DMSO-d_6): δ 2.10(s, 3); 3.35(s, 2); 7.7 – 8.6(m,8). (Found: C 35.8; H 3.24; N 10.2. Calc. for $C_{12}H_{13}N_3O_6Pd$: C 35.8; H 3.24; N 10.5).

Diacetoxychlorobenzenes. The retention times of the three isomers were 12, 13, and 14 min, respectively, on a 2 m × 0.3 cm 5 % neopentylglycol succinate on Chromosorb W column (120 – 200 °C at 10 °C/min). The mass spectra of the three isomers were very similar with a small parent peak at *m/e* 228 (2 – 3 %) and major peaks at *m/e* 186 (15 – 17), 146 (20 – 30), and 144 (100).

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