

Palladium(II) Catalyzed Aromatic Acetoxylation. VII.*

Preparative Scale Acetoxylation by Potassium Peroxydisulfate with Palladium(II) as a Catalyst

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The palladium(II) catalyzed acetoxylation of aromatic substrates can be achieved by using potassium peroxydisulfate as the oxidant. Preparative runs on a number of substrates show that the reaction is remarkably clean and that monosubstituted arenes with normally *ortho,para*-directing substituents give *meta* acetoxy isomer to a high extent. Side-chain acetoxylation can be favored for suitable substrates by adding excess acetate ion. The reaction appears to be subject to autoinhibition by the aryl acetates formed.

Previous work on the palladium(II) catalyzed acetoxylation of aromatic substrates has shown that nuclear acetoxylation is favored by the presence of a co-oxidant, such as dichromate,¹ nitrate,^{2,3} or peroxydisulfate.⁴ Moreover, nuclear acetoxylation of simple benzene derivatives displays a certain degree of selectivity for *meta* substitution,³⁻⁵ in some cases as high as 80–90 %. The *meta* selectivity is most pronounced when oxygen itself serves as the co-oxidant,^{5,6} but can be retained also with others if a complexing amine of suitable steric requirements is added.⁴ 2,2'-Bipyridine has been found to function well in this respect.^{3,4}

Semi-micro scale experiments with the system potassium peroxydisulfate/acetic acid in the presence of catalytic amounts of 2,2'-bipyridine-palladium(II) complex have shown⁴ that aromatic substrates can be acetylated in the ring as well as the α position in a remarkably

clean reaction. We now present additional results for this reaction, mainly with the aim of demonstrating its synthetic scope and utility.

RESULTS

The synthetic runs were performed on a 0.25 mol scale with palladium(II) acetate and 2,2'-bipyridine added in catalytic amounts. Potassium peroxydisulfate was employed in slight excess relative to substrate. The heterogeneous reaction mixture was stirred vigorously for 4 h at reflux temperature, after which period the peroxydisulfate had been consumed. Inadequate stirring caused palladium metal to precipitate and thus the catalytic effect to cease rapidly. Control experiments without any catalyst added gave no product at all. In the absence of peroxydisulfate the reaction was very slow, as noted previously,^{5,6} only traces of product being obtained after 4 h.

Table 1 shows typical results for a number of aromatic compounds which undergo exclusively or predominantly nuclear acetoxylation, whereas Table 2 gives results for substrates which are acetylated to some extent, predominantly or only in the α position of the side-chain. The α substitution reaction is favored by the addition of sodium acetate, as has been found previously,^{6,7} and hence the reactions in Table 2 have been run with 0.1 M sodium acetate present.

Inspection of the tables shows that the reaction is indeed catalytic in palladium(II) (yield

* Part VI, see Ref. 4.

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Table 1. Acetoxylation of aromatic compounds by potassium peroxydisulfate with Pd(II) as a catalyst.^a

Compound (Exp. No.)	Acetoxy derivatives Yield, ^b %				Isomer distribution			Other products (Yield, ^c %)
	A	B	C	D	<i>ortho</i> ^d	<i>meta</i> ^e	<i>para</i>	
Benzene (1)	700	28	18	—	—	—	—	Unknowns (3)
Fluorobenzene (2) ^f	400	16	12	—	20	42	38	
Chlorobenzene (3)	940	38	26	82	7	51	42	Dichlorobenzene (trace)
Bromobenzene (4)	860	34	20	—	8	55	37	Dibromobenzene (trace)
Benzotrifluoride (5) ^g	138	6	3	—	Trace	73	27	Unknowns (5)
Acetophenone (6)	400	16	11	81	1	77	22	
Phenyl acetate (7)	605	24	14	—	25	42	33	
Anisole (8) ^h	640	26	15	—	2	58	40	Phenol (2)
Methyl benzoate (9)	575	23	12	—	4	62	34	
Diphenylmethane (10) ⁱ	748	30	25	68	3	60	37	
<i>t</i> -Butylbenzene (11)	550	22	15	—	Trace	56	44	
Biphenyl (12)	775	31	24	—	3	52	45	
2,2-Dimethylindan (13) ^j	750	30	22	—	—	—	—	2,2-Dimethylind- anone (1)
Indan (14)	190	8	0 ^k	—	34	66	—	
Naphthalene (15)	395	16	9	—	22	78	—	
Thiophene (16)	—	—	—	—	—	—	—	Polymer only
Toluene (17)	630	25	30	65	6	59	36	See also Table 2

^a Reaction conditions, see text. ^b A: GLC yield based on the amount of Pd(II) used; B: GLC yield based on initial amount of substrate; C: Isolated yield based on initial amount of substrate; D: Yield based on substrate consumed. ^c Yield according to B. ^d α isomer in exp. 15 and 4- in exp. 14. ^e β isomer in exp. 15 and 5- in exp. 14. ^f Reaction period 6 h. ^g Reaction period 8 h. ^h Nuclear acetate 76, phenyl acetoxy-methyl ether 24 %. ⁱ Nuclear acetate 69, α isomer 31 %. ^j [NaOAc] 0.1 M; acetoxy derivatives: 1-acetoxy-2,2-dimethylindan, nuclear acetate (trace). ^k Could not be isolated.

Table 2. Acetoxylation of some methylbenzenes by potassium peroxydisulfate with Pd(II) as a catalyst.^a

Compound (Exp. No.)	Acetoxy derivatives Yield, ^b %				Isomer distribution		Other products (Yield, ^c %)
	A	B	C	D	α	Nuclear	
Toluene (17) ^d	630	25	20	65	10	90 ^e	Benzaldehyde
<i>o</i> -Xylene (18) ^d	580	23	15	74	39	61 ^f	1,2,4-Trimethylbenzene (+) 3,4-dimethylbenzyl acetate (2)
<i>p</i> -Xylene (19)	470	19	11	—	86	14	Trimethylbenzenes (5) <i>p</i> -Methylbenzaldehyde (5)
Mesitylene (20)	406	16	11	—	99	Trace	3,5-Dimethylbenzal- dehyde (2)
Durene (21)	775	31	19	—	100	—	Hexamethylbenzene (trace)
Hexamethylbenzene (22)	890	36	29	—	100	—	

^a Reaction conditions, see text, [NaOAc] 0.1 M. ^b A: GLC yield based on Pd(II); B: GLC yield based on initial amount of substrate; C: Isolated yield based on initial amount of substrate; D: Yield based on substrate consumed. ^c Yield according to B. ^d No sodium acetate present. ^e Isomer distribution: *ortho* 8, *meta* 59, *para* 36. ^f 3,4-Dimethylphenyl acetate.

A) but that the degree of conversion "in one pass", to borrow a phrase from heterogeneous catalysis terminology (yields B and C), is fairly low. On the other hand, yields based on the amount of substrate consumed (D) are high, between 60 and 80 %. We made several attempts to increase the degree of conversion by increasing the peroxydisulfate to substrate ratio but it turned out that the reaction ceased after 4 h, independently of the ratio employed. A control experiment in which a mixture of chlorophenyl acetates was added from the beginning of a reaction aiming at the acetoxylation of chlorobenzene, demonstrated that very little additional chlorophenyl acetate had been formed during the usual reaction period of 4 h. Hence it can be concluded that the reaction is gradually inhibited by the products formed.

DISCUSSION

The acetoxylation of aromatic compounds can be achieved by various oxidative substitution processes, where the oxidant is either the anode⁸ or a suitable metal ion,⁹ such as Pb(IV), Mn(III), Co(III), Ce(IV), Pd(II), and Ag(II).¹⁰ Of the metal ion promoted reactions, only the two last-mentioned combine the desirable features of being catalytic, giving a reasonably clean reaction, and being selective for ring positions in the presence of C-H bonds in the α position. The palladium(II) reaction has the additional bonus of giving a highly unusual ring substitution pattern, with the *meta* acetoxy compounds as the predominant isomer (Table 1). From the synthetic point of view, this reaction therefore commands great interest as a possibility of modifying substitution patterns in aromatic substitution, e.g., by changing the nature of the amine ligand. We are presently working on this and other aspects of Pd(II) catalyzed acetoxylation.

EXPERIMENTAL

Materials. See Refs. 3-6, 11, and 12.

Acetoxylation procedure. A mixture of substrate (0.25 mol), potassium peroxydisulfate (0.30 mol), palladium(II) acetate (0.01 mol) and 2,2'-bipyridine (0.005 mol) in glacial acetic acid (1000 ml) was stirred vigorously for 4 h at reflux temperature (in expts. 2 and 5, 6 and 8 h, respectively). The reaction mixture was

worked up by addition of water (500 ml) and extraction by dichloromethane (500 ml). The water/acetic acid layer was extracted with two additional portions of dichloromethane of 150 ml each. The combined extracts were washed with water (2 x 500 ml), and sodium bicarbonate solution (100 ml) and finally dried with magnesium sulfate. After filtration and evaporation the residue was distilled in a Claisen flask. In some cases where GLC analysis indicated the presence of by-products, the crude product was distilled in a concentric tube column (Fischer Spaltrohr-System) of ca. 40 theoretical plates. In experiment 22 the crude product mixture, containing hexamethylbenzene and pentamethylbenzyl acetate, was washed with ligroin (b.p. 40-60 °C) to remove hexamethylbenzene, whereafter the acetate was recrystallized from ethanol.

Analyses. Unless otherwise noted, yields and isomer distributions were determined using a Varian 1400 gas chromatograph, equipped with a disc integrator (2 m x 3 mm neopentylglycol succinate, 5 % on Chromosorb W or 2 m x 3 mm Apiezon L, 10 % on Chromosorb W column). The yields were calculated using an internal standard calibrated against authentic samples. Used standards: In exp. 1, phenol; expts. 2-11, 13, 14, 15, 17, biphenyl; exp. 12, β -naphthyl acetate; expts. 18, 20, 22, 2,4,5-trimethylbenzyl acetate; exp. 19, *m-t*-butylphenyl acetate; exp. 21, 3,5-dimethylbenzyl acetate. The identification of products was based on GLC/MS comparison (LKB 9000 system) with authentic samples.

1-Acetoxy-2,2-dimethylindan was identified by its ¹H NMR spectrum: δ 1.12 [6 H, s, C(CH₃)₂], 2.06 (3 H, s, OCOCH₃), 2.7-2.9 (2 H, m, methylene protons), 5.8 (1 H, s, methine proton), 7.1-7.4 (4 H, m, aromatic protons). The products in exp. 2 (fluorophenyl acetates) and 17 (cresyl acetates and benzyl acetate) were analyzed as the corresponding hydroxy compounds. The *meta/para* ratio in exp. 9 was determined by ¹H NMR spectroscopy using a lanthanide shift technique.

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