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THE PALLADIUM-CATALYSED ARYLATION OF ACTIVATED ALKENES WITH AROYL CHLORIDES

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Summary

Aroyl chlorides react with activated alkenes in presence of a tertiary amine and a catalytic amount of palladium acetate to give arylated alkenes, specifically cinnamic acid derivatives and stilbenes. The reaction involves a highly efficient decarbonylation of the aroyl chloride. High yields can be obtained at low catalyst concentration by choice of an appropriate base. The reaction is not particularly sensitive to substituents in the aroyl chloride, although strongly electron-donating groups are advantagenous (yields up to 98%). With monosubstituted alkenes *E*-isomers are formed with almost complete specificity. A mechanism for the reaction is proposed.

Introduction

The palladium-catalysed arylation of alkenes using aryl iodides and bromides has been reported by Mizoroki [1] and by Heck [2]. The reaction has been investigated in considerable detail by Heck and reviews have appeared [3,4]. Matsuda [5] has reported the use of arenediazonium salts in this reaction.

We have found that similar palladium-catalysed arylations can be carried out using aroyl halides instead of aryl halides [6]. This is advantageous in that a wide range of aroyl chlorides is readily available and that aroyl chlorides are generally cheaper than the corresponding aryl bromides. The reaction involves a highly efficient decarbonylation of the aroyl halide.

During the course of our work Chiusoli [7] reported that triphenylphosphine-palladium complexes catalyse the formation of methyl 3-benzoylacrylate and methyl cinnamate from benzoyl chloride and methyl acrylate. This reaction is very much slower than those reported here, owing to the inhibitory effect of triphenylphosphine.

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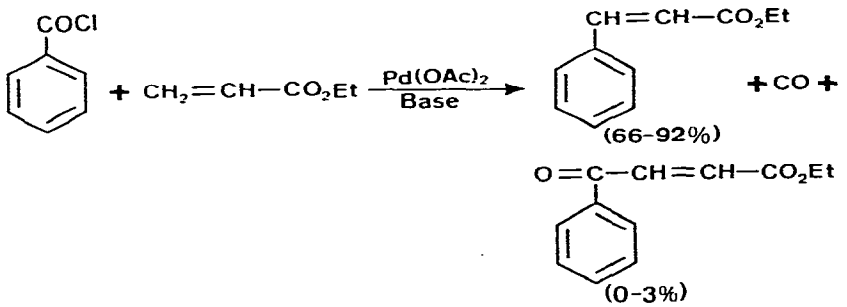
Results

The reaction of benzoyl chloride and ethyl acrylate was chosen as model system for the initial work.



In all cases, ethyl cinnamate was the major product of the reaction. The yield of ethyl 3-benzoylacrylate was generally less than 3%, and was often zero. A base is needed to neutralise the hydrogen chloride formed. The reaction was carried out in an inert atmosphere (argon) to exclude moisture and to prevent catalytic oxidation.

General conditions

Poor results were obtained when no solvent was used for the reaction. Aromatic hydrocarbons gave the best results, and *p*-xylene was preferred. Toluene may be used but its boiling point is too low for best results. Ethers, esters, nitriles and ketones have also been used successfully.

Initial studies were carried out at 100°C, but better results were subsequently obtained at 120 or 130°C, the latter being now generally used.

Palladium acetate was used as catalyst. Several other palladium(0) or palladium(II) species were tried, including $Pd(DBA)_2$ (DBA = dibenzylideneacetone), $PdCl_2$, $Pd(acac)_2$, $PdCl_2(NCC_6H_5)_2$, and $Pd(OAc)_2$(bipy), but they showed no advantage over palladium acetate. It was found, however, that the presence of two moles of triphenylphosphine per mole of palladium was enough to inhibit the reaction almost completely. Thus yields of only a few per cent after several hours reaction were obtained under conditions where in absence of phosphine ligands high yields were achieved in less than one hour.

Base

Best results have been obtained with tertiary amines having p*K*-values in the range 7.5 to 11. Weaker bases lead to a slower reaction and stronger ones tend to react directly with the aroyl chloride in side reactions. Inorganic bases, such as lithium acetate can also be used, but often lead to precipitation of some of the palladium as metal during the reaction. This does not occur with the organic bases.

Table 1 lists the results obtained with a number of tertiary amines. There is clearly little to choose between them from the point of view of yield, and tri-n-butylamine was used for much of the initial work. During this we observed that

TABLE 1

BASE DEPENDENCE OF THE FORMATION OF ETHYL CINNAMATE FROM BENZOYL CHLORIDE AND ETHYL ACRYLATE [a]

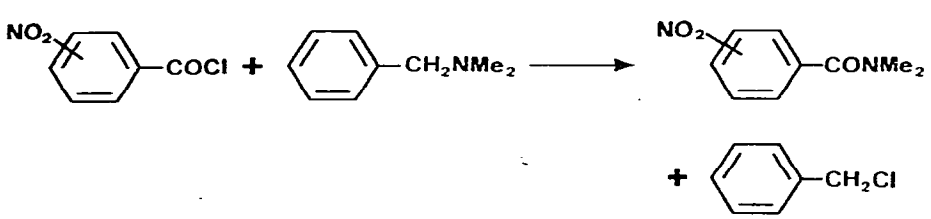
Base	Ethyl cinnamate (%)
Tri-n-butylamine	66
Tri-n-octylamine	67
Ethyldiisopropylamine	66
Ethyldicyclohexylamine	63
1,2,2,6,6-Pentamethylpiperidine	55

[a] Benzoyl chloride 25 mmol, ethyl acrylate 31.25 mmol, amine 31.25 mmol, palladium acetate 0.25 mmol, toluene 50 ml, 100°C, 4 h.

the competing reaction of this base with benzoyl chloride was a significant problem in some cases. This reaction gave several products and was not investigated further. We therefore investigated amines of lower pK-values, the results being given in Table 2. N-Benzyldimethylamine gave the best results both as regards yield and reaction rate. This was particularly apparent in reactions at low palladium concentration (below), where tri-n-butylamine is of less value.

In subsequent studies it was found that the best results with N-benzyldimethylamine were achieved at 130°C. This enabled high yields of ethyl cinnamate to be obtained even at a catalyst concentration of 0.01 mol% in relatively short reaction times (Table 3). The efficiency of the reaction is demonstrated by the attainment of a turnover number of 7600 at an initial activity of 135 min^{-1}. The observed reduction in yield on proceeding to 0.005 mol% catalyst may well be caused by the impurities present, which at this concentration are in excess over palladium. In view of the marked effect of the pK of the amine on the reaction, N-3-chlorobenzyldimethylamine (pK = 8.67) and N-benzyldiethylamine (pK = 9.62) were compared with N-benzyldimethylamine (pK = 9.03) under like conditions (0.1 mol% catalyst). Both gave slightly poorer results than N-benzyldimethylamine. The use of this amine is limited however, by the presence of strongly electron-withdrawing groups in the aroyl chloride, when cleavage can occur. Thus when a nitro substituent is present, the following reaction competes with the arylation.

In such cases N-ethylmorpholine can often be advantageously used. Although this base leads to a much slower catalytic reaction than N-benzyldimethylamine or even tri-n-butylamine, it does not appear to react with aroyl chlorides



at all. Even at low palladium concentrations (0.01—0.03 mol%) good yields could be achieved, though reaction times of 12—24 hours can be necessary.

TABLE 2

EFFECT OF THE pK OF THE BASE ON THE FORMATION OF ETHYL CINNAMATE [a]

Base	pK [b]	Ethyl cinnamate (%)
N-Ethylmorpholine	7.80	45
N-Benzyldimethylamine	9.03	84
Tri-n-butylamine	10.89	46

[a] Benzoyl chloride 25 mmol, ethyl acrylate 31.25 mmol, amine 31.25 mmol, palladium acetate 0.25 mmol, toluene 50 ml, 100°C, 2 h. [b] From reference 8.

TABLE 3

EFFECT OF CATALYST CONCENTRATION ON THE FORMATION OF ETHYL CINNAMATE [a]

Palladium (mol%) [b]	Time (h)	Yield (%)	Turnover No.	Initial activity (min^{-1})
0.05	1.5	80	1600	60
0.02	2	76	3800	68
0.01	4	76	7600	135
0.005	6	53	10600	57

[a] Benzoyl chloride 50 mmol, ethyl acrylate 50 mmol, *N*-benzyldimethylamine 50 mmol, *p*-xylene 100 ml, 130°C. [b] Relative to benzoyl chloride. (Palladium acetate used).

Acid halides

The reaction readily tolerates substituents which do not react with aroyl chlorides (Table 4). It can be seen that the position of substitution has little effect on the reaction. Substituents in the 2-position which are bulky or can coordinate to the palladium would be expected to show a larger effect. In general strongly electron-donating groups favour the reaction and strongly electron-withdrawing groups hinder it. This again appears to be an effect on the competing reaction of the aroyl chloride with the amine. Poly-substituted

TABLE 4

ARYLATION OF ETHYL ACRYLATE WITH MONOSUBSTITUTED AROYL CHLORIDES [a]

Substituent	Time (h)	Yield (%)
2-Cl	1.5	74
3-Cl	2	75
4-Cl	2	79
2-Me	1.5	78
3-Me	2	72
4-Me	3	64
3-MeO	2	98
4-Br	2	79
4-F	1.5	63
4-NO_2	1	55
2-MeCO	0.8	57
4-C_6H_5	1.5	64

[a] Aroyl chloride 50 mmol, ethyl acrylate 62.5 mmol, tri-n-butylamine 62.5 mmol, palladium acetate 0.5 mmol, *p*-xylene 100 ml, 120°C.

TABLE 5

ARYLATION OF ETHYL ACRYLATE WITH POLYSUBSTITUTED AROYL CHLORIDES [a]

Substituent	Time (h)	Yield (%)
3,4-$(Me)_2$	2	62
3,4-$(Cl)_2$	2	34
2-Me, 3-NO_2	1.5	55
3,5-$(MeO)_2$	2	84
3,4,5-$(MeO)_3$	2	44
2,3,4,5,6-$(F)_5$	6	59 [b]

[a] Aroyl chloride 100 mmol, ethyl acrylate 125 mmol, tri-n-butylamine 100 mmol, palladium acetate 1 mmol, *p*-xylene 200 ml, 120°C. [b] *N*-Ethylmorpholine as base.

TABLE 6

ARYLATION OF ACTIVATED ALKENES (CH_2=CH-X) WITH BENZOYL CHLORIDE [a]

X	Time (h)	Yield (%)
CO_2Et	2.5	84 [b]
C_6H_5	2	77
p-ClC_6H_4	5	93
$CONEt_2$	2	70
CN	3	54
COMe	2	48 [c]

[a] Benzoyl chloride 50 mmol, alkene 62.5 mmol, tri-n-butylamine 50 mmol, palladium acetate 0.5 mmol, *p*-xylene 100 ml, 120°C. [b] With *N*-benzyldimethylamine at 130°C, 92% in 0.5 h. [c] With *N*-benzyldimethylamine.

aroly chlorides can also be used (Table 5), but the cumulative effect of electron-withdrawing substituents is quite significant as can be seen for 3,4-dichlorobenzoyl chloride.

Aliphatic and simple vinylic acid chlorides such as acroylyl and crotonoyl chlorides do not give the reaction. Cinnamoyl chloride reacted with ethyl acrylate to give ethyl 5-phenyl-2,4-pentadieneoate in 69% yield using *N*-benzyldimethylamine as base at 130°C. The less readily available aroyl bromides and iodides show no advantages over aroyl chlorides.

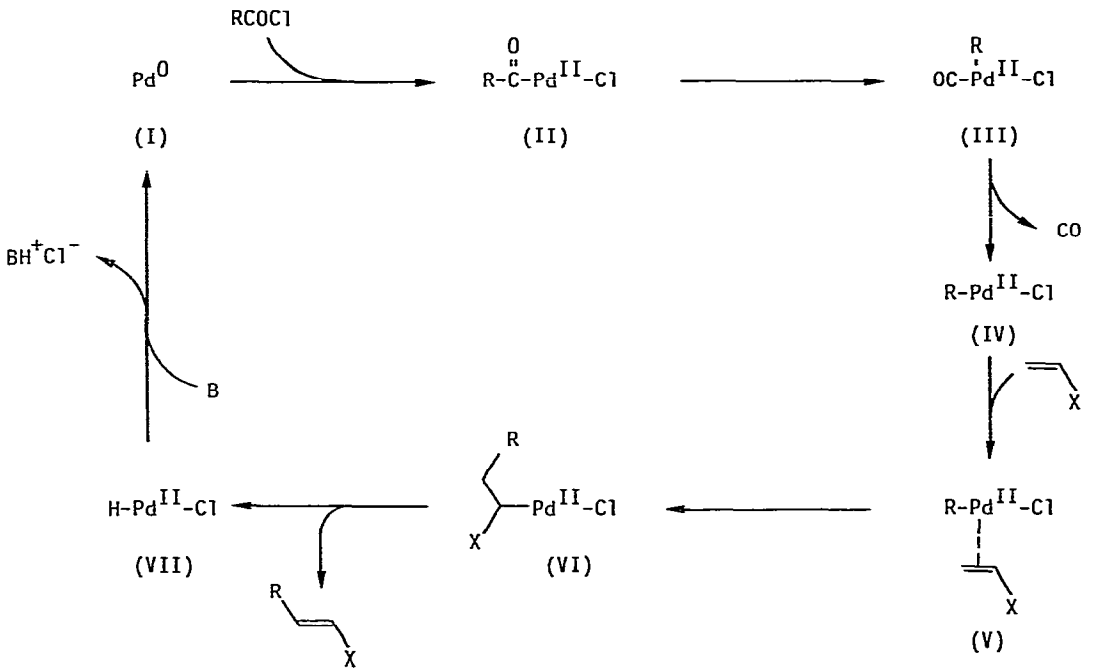
Alkenes

The reaction is also fairly general for activated alkenes (Table 6). The cinnamonitrile formed is 92% *E*- and 8% *Z*-isomer. In other cases, only the *E*-isomer is formed. No arylation was observed with vinyl-*p*-tolyl sulphone, vinyl-n-butyl ether or allyl acetate. Vinyl acetate lead to the formation of stilbene in low yield. An analogous reaction has previously been observed by Heck in palladium-catalysed arylation with arylmercury salts [9]. More complex alkenes lead to extensive formation of isomers. Non-activated alkenes react poorly or not at all, with the exception of ethylene. These reactions will be reported separately.

Discussion

Our proposed mechanism for the reaction is given in Scheme 1. It is based on the expected mechanism for the decarbonylation of acid chlorides [10] and for

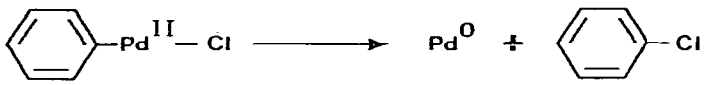
SCHEME 1. Proposed mechanism for the arylation of alkenes with aroyl chlorides. (R = aryl, X = activating group, B = base. Non-reacting ligands omitted).



alkene arylation with aryl halides [3,4]. Only reacting groups are shown as nothing is known about the ligands occupying the vacant coordination sites; these are probably filled by alkene, chloride ion or possibly the amine. The preliminary stoichiometric reduction of palladium acetate to a palladium(0) species would be affected by alkene and base. Oxidative addition of the aroyl chloride would lead to II. In the absence of any strongly-bound ligands occupying the other coordination sites, the aryl migration to the metal to give III should be a facile process. The release of carbon monoxide is to be expected in absence of any ligands that could stabilise a palladium(II) carbonyl at these temperatures. Alkene coordination is depicted as the next step though it is probable that the alkene is present as a ligand throughout the catalytic cycle. The alkene insertion, product elimination and regeneration of palladium(0) could then follow as proposed by Heck [3,4].

A feature of the reaction is that the decarbonylation takes place with great rapidity at temperatures 80—100°C below those previously reported for the very slow palladium-catalysed decarbonylation of benzoyl chloride [10]. Although in the previous work palladium metal was used as catalyst, it was reported that this was partly dissolved during the reaction and it is therefore not possible to say whether the reaction was homogeneously or heterogeneously catalysed. We have found that negligible decarbonylation of benzoyl chloride occurs in two hours at 190°C in presence of 1 mol% of palladium acetate. If in the arylation reaction the alkene is omitted, no decarbonylation occurs in two hours at 130°C. It has very recently been reported that a temperature of 360°C is required for an efficient palladium-catalysed decarbonylation of benzoyl

chloride [11], the reaction occurring in the gas phase. The principal difference between the two reactions is that the alkene arylation provides a simple mechanism for the reduction of palladium(II) by converting it to VII. This suggests that the slow nature of the direct decarbonylation [10] may be due to the difficulty of the reductive elimination:



but ligand effects cannot be completely discounted. We attribute the inhibition of the reaction by triphenylphosphine to the blocking of the coordination sites in II needed for the phenyl migration. It is here of interest to note that the palladium-catalysed reactions of aroyl chlorides with alkynes, in which triphenylphosphine is used as ligand, proceed without decarbonylation [12], giving 1-alkynyl ketones.

A further point of interest is the almost complete specificity of the reaction for the formation of *E*-isomers with monosubstituted alkenes. As sterically bulky ligands are absent this must be attributed to electronic factors.

The mechanism proposed in Scheme 1 does not readily explain the dependence of the reaction on the choice of base. One possibility is that the amine functions as a ligand. It is also conceivable that VI undergoes a base-catalysed elimination giving the product, palladium(0) and the amine salt in one step. However, since transition metal alkyls having a hydrogen on the β-carbon atom quite generally undergo rapid alkene elimination [13], we prefer the two-step mechanism VI → VII → I.

Experimental

Palladium acetate was purchased from Engelhard. Other chemicals were from Fluka, Merck and Aldrich. Alkenes were used without prior removal of the polymerisation inhibitor. Gas chromatography was carried out using a Varian 3700 together with a Shimadzu Chromatopac E1A integrator. IR and NMR spectra were recorded using Perkin—Elmer 157 and Varian XL-100 instruments. Elemental analyses were performed by the Microanalytical Laboratory at Ciba—Geigy. Ethyl cinnamate was determined by gas chromatography using n-octadecane as standard. Other products were isolated and characterised by elemental analysis and IR and NMR spectroscopy.

Alkene arylation

The following procedure was generally used for the reaction. To *p*-xylene (100 ml) were added under argon palladium acetate (0.1122 g, 0.5 mmol), aroyl chloride (50 mmol), alkene (62.5 mmol), amine (62.5 mmol) and if used, n-octadecane (2 g). The mixture was then stirred at the required temperature (see text) for the appropriate time. A reflux condensor was used to prevent loss of alkene, and was equipped with an argon bubbler. The reaction mixture was then extracted with 2 *N* HCl (50 and 25 ml), 2 *N* NaOH (25 ml) and water (25 ml), and dried for 15 min with magnesium sulphate (5 g). After removal of

the solvent under reduced pressure, the product was isolated by distillation or recrystallisation.

If *N*-benzyldimethylamine is used the hydrochloride salt can generally be filtered off after the reaction in high yield.

Aroyl chlorides

Benzoyl chloride from Fluka was distilled before use. Other aroyl chlorides were prepared from the free acids using a 20—50% excess of thionyl chloride in toluene in presence of a few drops of DMF, at 60—70°C. They were purified by distillation and/or recrystallisation and characterised as above.

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