Journal of Organometallic Chemistry, 270 (1984) 115–120
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

HOMOGENEOUS PALLADIUM-CATALYSED ARYLATION OF ACTIVATED ALKENES WITH ARYL CHLORIDES

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(Received March 21st, 1984)

Summary

A study has been made of arylation of activated alkenes with aryl chlorides homogeneously catalysed by palladium acetate in the presence of triphenylphosphine or tri-*p*-tolylphosphine. Electron-withdrawing substituents in the aryl chloride favour the reaction. Only moderate yields could be obtained, and the maximum turnover number was 51, mainly because of precipitation of palladium metal. The probable mechanism of the reaction is discussed.

Introduction

The palladium-catalysed arylation of activated alkenes with aryl bromides and iodides has been reported by Mizoroki [1] and Heck [2]. The reaction has been studied in detail by Heck, who reported that aryl chlorides do not normally react catalytically [3,4], although stoichiometric reactions were possible [5]. A heterogeneously catalysed arylation of styrene derivatives by chlorobenzene has been described [6], but the yields were poor and other alkenes scarcely reacted.

We recently reported a very significantly improved version of the homogeneous palladium-catalysed arylation of activated alkenes with aryl bromides and iodides which makes possible the attainment of turnover numbers of more than 100'000 in some cases [7,8]. Using this method, we were able to arylate a variety of activated alkenes with aryl chlorides using palladium acetate plus triphenylphosphine as catalyst [9], and we now describe this work in detail. Since our studies, the homogeneously catalysed arylation of styrene with chlorobenzene, giving stilbene, has been reported [10]; other aryl chlorides or alkenes were not mentioned.

Results

On the basis of our experience of the arylation of activated alkenes with aryl bromides [7,8], the reaction of 4-chlorobenzaldehyde with acrylonitrile using sodium acetate as base in DMF was used to study the effect of variation of temperature,

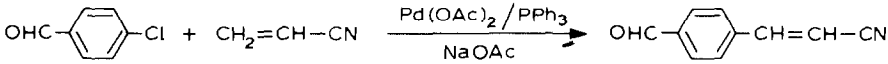
0022-328X/84/$03.00

TABLE 1
EFFECT OF PHOSPHORUS LIGANDS ON THE PALLADIUM-CATALYSED ARYLATION OF ACRYLONITRILE WITH 4-CHLOROBENZALDEHYDE[a]

Phosphorus ligand	4-Formylcinnamonitrile	
	Yield (%)	*E*/*Z*
PPh_2Bu^t	12	78/22
$P(p\text{-}MeOC_6H_4)_3$	8	68/32
$P(p\text{-}Tol)_3$	34	72/28
$P(o\text{-}Tol)_3$	4	65/35
PPh_3	28	70/30
$P(p\text{-}FC_6H_4)_3$	17	63/37
$Ph_2P(CH_2)_2PPh_2$	22	71/29
$Ph_2P(CH_2)_3PPh_2$	8	69/31
$Ph_2P(CH_2)_4PPh_2$	7	67/33

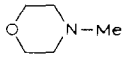
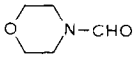
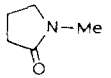
[a] 4-Chlorobenzaldehyde 10 mmol, acrylonitrile 10 mmol, sodium acetate 10 mmol, palladium acetate 0.1 mmol, DMF 10 ml, 150 °C, 6 h, P/Pd = 4 for all ligands

reaction time, triphenylphosphine/palladium acetate ratio and total and relative concentration of the reactants on the yield of 4-formylcinnamonitrile.



Both *E* and *Z* isomers are formed, with the former predominating. At 1 mol%

TABLE 2
EFFECT OF BASE AND SOLVENT ON THE PALLADIUM-CATALYSED ARYLATION OF ACRYLONITRILE WITH 4-CHLOROBENZALDEHYDE[a]

Solvent	Base	4-Formylcinnamonitrile	
		Yield (%)	*E*/*Z*
DMF	NaOAc	28	70/30
DMF	$Bu^n{}_3N$	11	67/33
DMF	$C_6H_5CH_2NMe_2$	20	69/31
DMF		19	74/26
DMF	K_2CO_3	0	–
DMA	NaOAc	25	65/35
	NaOAc	28	79/21
	NaOAc	29	70/30
EtCN	Et_3N	15	58/42
p-Xylene	$C_6H_5CH_2NMe_2$	0	–

[a] 4-Chlorobenzaldehyde 10 mmol, acrylonitrile 10 mmol, base 10 mmol, palladium acetate 0.1 mmol, triphenylphosphine 0.4 mmol, solvent 10 ml, 150 °C, 6 h.

TABLE 3
PALLADIUM-CATALYSED ARYLATION OF ACTIVATED ALKENES WITH 4-CHLOROBENZALDEHYDE[a]

Alkene	Yield (%)
CH_2=CH-CO_2Et	39
CH_2=CH-$CONEt_2$	45
CH_2=CH-CN	23
CH_2=CH-C_6H_5	37

[a] 4-Chlorobenzaldehyde 50 mmol, alkene 50 mmol, sodium acetate 50 mmol, palladium acetate 0.5 mmol, triphenylphosphine 2 mmol, DMF 20 ml, 150 °C, 6 h.

palladium acetate and 4 mol% triphenylphosphine this lead to a best yield of only 28%. Precipitation of palladium metal occurs but only towards the end of the reaction. The optimum temperature was 150 °C compared with 130 °C for the aryl bromides.

A series of mono- and di-phosphine ligands were then studied under similar conditions (Table 1). In all cases the phosphorus/palladium ratio was maintained at 4. Tri-*p*-tolylphosphine gave the best result, followed by triphenylphosphine and 1,2-bis(diphenylphosphino)ethane. Tri-*o*-tolylphosphine, which Heck has shown to be of great value in arylation with aryl bromides [3], was much less effective.

Variation of solvent and base (Table 2) showed that sodium acetate in a polar solvent gave the best yields. However, this effect is far less marked than in the case of the aryl bromides [8]. The isomer ratio shows no obvious dependence on the solvent-base combination or on the phosphorus ligand.

Table 3 shows the behaviour of different alkenes in the reaction. The concentration was changed from 1 to 2.5 *M* here. With acrylonitrile significant amounts of the *Z* isomers were always formed (Tables 1 and 2). The other alkenes gave only the *E* products. Similar behaviour was observed in arylation with aryl bromides [8]. Using ethyl acrylate, a number of *para*-substituted chlorobenzene derivatives were studied (Table 4). Electron-withdrawing substituents were found to favour the reaction. Whereas aryl bromides generally reacted better the more strongly electron-withdrawing the substituent [8], methyl 4-chlorobenzoate gave the best result here, a turnover number of 51 being achieved.

TABLE 4
PALLADIUM-CATALYSED ARYLATION OF ETHYL ACRYLATE WITH SUBSTITUTED ARYL CHLORIDES[a]

Substituent	Yield (%)
4-NO_2	21
4-CN	32
4-COMe	26
4-CHO	39
4-CO_2Me	51
H	4

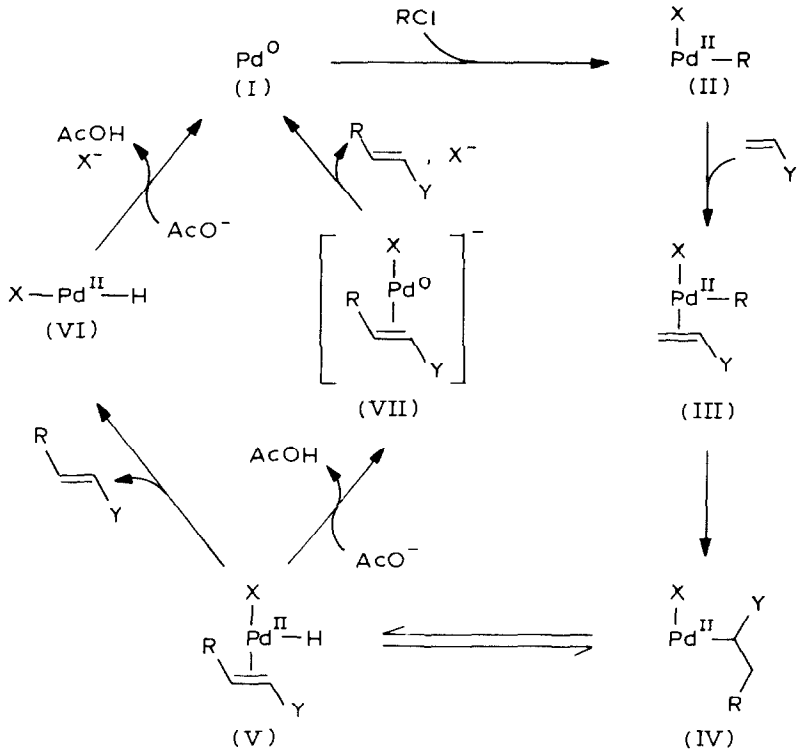
[a] Aryl chloride 50 mmol, ethyl acrylate 50 mmol, sodium acetate 50 mmol, palladium acetate 0.5 mmol, triphenylphosphine 2 mmol, DMF 20 ml, 150 °C, 6 h.

Discussion

We expect that the mechanism of arylation of activated alkenes with aryl chlorides (Scheme 1) will be similar to that suggested by Heck for aryl bromides and iodides [3]. After the initial reduction of the added palladium(II) to palladium(0) by the alkene, oxidative addition of the aryl chloride occurs followed by alkene coordination and its insertion into the aryl–palladium bond. β-Elimination gives the product and a palladium(II) hydride, which with the base regenerates palladium(0).

Notwithstanding the relatively high palladium concentration of 1 mol%, the yields obtained are moderate to poor. This is often due to precipitation of palladium metal and cessation of the reaction. Attempts to prevent formation of metal by addition of more phosphine ligand or by using chelating diphosphines were unsuccesful.

The group X (Scheme 1) in the intermediates II–VI may well be acetate, since this group is always in excess over chloride in view of the low conversions. In aryl bromide arylations, acetate is in excess at least until late in the reaction. Further, acetate as a ligand is as good as or perhaps even better than the halides. Thus the difference between the mechanisms of arylation of alkenes with aryl chlorides and bromides would be reduced to the oxidative addition and its immediate product.



(R = aryl ; X = Cl⁻, AcO⁻; Y = activating group)

SCHEME 1. Probable mechanism of the arylation of activated alkenes with aryl chlorides (PPh_3 ligands omitted) (R = aryl; X = Cl^-, AcO^-; Y = activating group)

before halide–acetate exchange. The significantly lower rate of the oxidative addition of aryl chlorides relative to bromides and iodides [11] must therefore be the reason for the vastly inferior performance of the aryl chlorides in these reactions and would lead to a higher proportion of the palladium accumulating as palladium(0), with the concomitant increase in the risk of precipitation of the metal.

The very poor performance of tri-*o*-tolylphosphine, which is the preferred ligand for aryl bromides [3,8], in these reactions (see Table 2 and compare the *p*-tolyl analogue) supports this view. The steric hindrance to coordination provided by the methyl groups would further reduce the rate of oxidative addition and enhance the palladium(0) concentration.

The step IV–V is probably reversible in view of the ready β-elimination reaction of metal alkyls [12]. Heck's mechanism then involves the route V–VI–I. An alternative route which we have proposed to explain the stereochemistry of related arylations with aroyl chlorides [13] would involve the sequence V–VII–I, in which the equilibrium IV $\rightleftharpoons$ V persists until the base destroys the hydride to give VII. The anionic palladium(0) complex VII could be expected to have only transient existence and would rapidly dissociate the ligand X and coordinate triphenylphosphine. Further comment on the two alternative routes is not possible in view of the absence of reliable information on the relative rates of the reactions V $\rightarrow$ VI, V $\rightarrow$ VII and V $\rightarrow$ IV.

Experimental

Palladium acetate was obtained from Engelhard. Tri-*o*-tolylphosphine was prepared by the literature method [14]. Other phosphorus ligands were from Fluka or Strem. Anhydrous sodium acetate was from Merck and other chemicals were from Fluka. ^{1}H NMR spectra were recorded on a Varian XL-100, IR spectra on a Perkin–Elmer 157 and mass spectra on Varian CH5 and CH7 instruments. Elemental analyses were performed by the Microanalytical Laboratory at Ciba-Geigy. All products were fully characterised. Yields given were determined by gas chromatography using a Varian 3700 instrument fitted with OV 101 and OV 225 columns and a Shimadzu Chromatopac E1A integrator.

General procedure

Reactions were carried out in 50 or 100 ml glass pressure tubes which could be closed with spring loaded glass caps having a Teflon seal. All reactions were carried out under argon. The following procedure is typical.

Ethyl 4-cyanocinnamate. In a 100 ml pressure tube containing a small magnetic stirring bar were placed 4-chlorobenzonitrile (6.88 g, 50 mmol), anhydrous sodium acetate (4.1 g, 50 mmol) and DMF (20 ml). Argon was passed with stirring for 5 min and then palladium acetate (0.1122 g, 0.5 mmol), triphenylphosphine (0.524 g, 2 mmol) and ethyl acrylate (5.24 ml, 50 mmol) were added. The alkene was added last because of the possible loss by evaporation, especially with acrylonitrile. The tube was sealed and stirred in an oil bath at 150 °C for 6 h. After cooling, the solvent was removed and dichloromethane (50 ml) was added. The solution was filtered to remove sodium salts and palladium metal. The material on the filter was washed with dichloromethane (5–10 ml), and a small portion of the filtrate (ca. 0.3 ml) was removed for the gas chromatographic determination of the yield. The filtrate was

removed and the residue distilled to give ethyl 4-cyanocinnamate at 125–138°C/0.3 mmHg. This was redistilled in a Kugelrohr apparatus to give the pure product, which crystallised. 3.06 g (30%). (Yield by gas chromatography 32%). White crystals, M.p. 69.5°C. Anal. Found: C, 71.62; H, 5.54; N, 7.16; O, 15.92. $C_{12}H_{11}NO_2$ calcd.: C, 71.63; H, 5.51; N, 6.96; O, 15.90%.

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