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PALLADIUM CATALYZED SYNTHESIS OF ARYL, HETEROCYCLIC AND VINYLIC ACETYLENE DERIVATIVES

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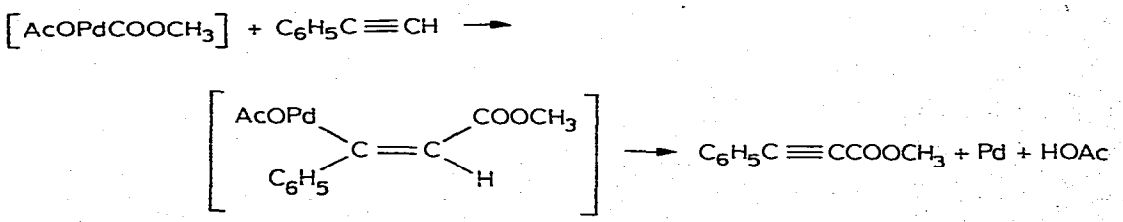
Summary

Monosubstituted acetylenes are converted into disubstituted acetylenes by reaction with aryl, heterocyclic or vinylic bromides or iodides at 100°C in the presence of a basic amine and diacetatobis(triphenylphosphine)palladium(II) catalyst.

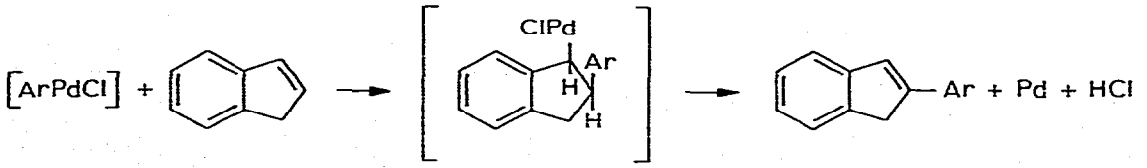
Introduction

Previously we reported that phenyl, methyl, and carbomethoxyl groups could be substituted for the acetylenic hydrogen in phenylacetylene by reaction of the compound at 0°-25°C with phenyl-, methyl-, and carbomethoxy-palladium acetates, respectively. The organopalladium acetates were prepared in situ from the corresponding organomercuric acetates and palladium acetate [1]. The reaction with carbomethoxypalladium acetate was not improved by the addition of tri-n-butylamine [1]. The reaction was believed to proceed according to the following mechanism, based on better understood similar reactions which occurred with olefins [2,3].



The *trans* elimination of the hydridopalladium acetate was unusual, particularly since it did not appear to be base catalyzed. However, there was a precedent in olefin chemistry. When the preferred *cis*-hydride elimination cannot occur for steric reasons, a *trans* elimination can occur, at least in the reactions

of 4-methoxy-3-nitrophenyl- [4] or phenyl- [5] palladium chlorides with indene. The *cis* addition of the arylpalladium group places the palladium on the benzylic carbon with no *cis*-β-hydrogens available for the subsequent elimination. The *trans*-β-hydrogen is apparently then lost since the 2-arylindenes are one of the products formed.



More recently we have found it much more practical to generate organopalladium complexes by oxidative addition reactions from organic halides and palladium(0)phosphine complexes rather than from mercurials, for use in olefinic substitution reactions [6]. We thought it possible that substituted acetylenes might be prepared more practically also by use of the oxidative addition reaction. This paper reports experiments showing that this can be done very readily, but that the mechanism of the reaction may be different from that believed to operate in the above examples.

Results and discussion

A variety of organic halides and acetylenes were reacted at 100°C with basic amines and catalytic amounts of $Pd(OAc)_2[P(C_6H_5)_3]_2$. These conditions were generally about the same as those used previously in the palladium catalyzed olefin substitution reactions [6] except that a much larger excess of the amine was used as solvent. Successful reactions producing disubstituted acetylenes are summarized in Table 1. Four aryl halides (iodobenzene, bromobenzene, 4-bromobenzaldehyde and 4-bromonitrobenzene); four vinylic halides (*E*- and *Z*-2-bromostyrene, 2-bromopropene, and methyl *E*-3-bromo-2-methylpropenoate) and one heterocyclic halide (2-bromothiophene) were employed. These halides were reacted with one or more of the following four acetylenes: phenylacetylene, 1-hexyne, 2-methyl-1-buten-3-yne and t-butylacetylene. Reactions were carried out at 100°C for 0.5 to 2.5 h and yields of products varied from 53 to 88%. When $Pd(OAc)_2$ without a phosphine was used as catalyst no diphenylacetylene was obtained from the reaction of phenylacetylene with bromobenzene, in the presence of triethylamine, and only a 40% yield was obtained with iodobenzene.

It is clear that the reacting acetylenes were partly being used up in reactions other than those forming the disubstituted acetylene, since increasing the amount of the acetylene relative to the halide present generally led to a higher yield of disubstituted acetylene product. Diluting the reaction mixture with a large excess of amine also decreased the amount of side reaction, presumably polymerization, relative to the substitution.

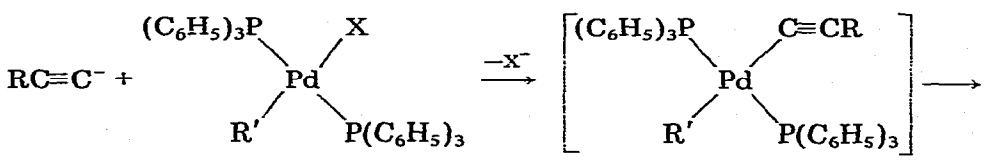
The yields of products were influenced by the structure of the organic halide; the more reactive the halide was in the oxidative addition, the better the reaction generally proceeded. Thus, iodobenzene gave higher yields than bromo-

benzene, with phenylacetylene and triethylamine it gave 73% diphenylacetylene in 1.5 h, while bromobenzene in 2.5 h (with a larger excess of phenylacetylene) produced only 51% of that product. Electron-withdrawing substituents in the halide also generally improved the reactions. *p*-Bromobenzaldehyde and phenylacetylene with triethylamine gave 66% of 4-phenylethynylbenzaldehyde in 1 h compared with bromobenzene which required 2.5 h to react to form only 51% diphenylacetylene.

The alkylacetylenes were less reactive than phenylacetylene. With triethylamine as the base only the more reactive halides will add to alkylacetylenes in significant yield. Iodobenzene, for example, does not react with 1-hexyne or t-butylacetylene under these conditions. The alkylacetylenes, however, became more reactive when more basic secondary amines were employed rather than triethylamine. Thus, with piperidine as the base, 1-hexyne and iodobenzene reacted readily forming 1-phenyl-1-hexyne in 62% yield. The data suggest that under the new reaction conditions, either the palladium hydride elimination from the reaction intermediate becomes base catalyzed or another mechanism is operating. A possible alternative mechanism could involve an attack of an incipient acetylide anion on the organopalladium intermediate followed by reductive elimination of the disubstituted acetylene. The effect of the base then would be to assist in removing the acetylenic proton and since monoalkylacetylenes are less acidic than monoarylacetylenes, the more basic amine would be required in the reactions of the monoalkylacetylenes, particularly when they were being reacted with the less reactive halides. Cassar has demonstrated the reductive elimination reaction with presumably analogous arylnickel complexes [7]. If the acetylide intermediate was not formed rapidly then acetylene polymerization would probably occur instead by a multiple insertion mechanism. The initial reduction of the catalyst presumably is caused by the acetylene perhaps by forming a diacetylene. Triethylamine does not reduce the catalyst at 100°C.

$$(Pd[P(C_6H_5)_3]_2(OAc)_2 + 2\ RC{\equiv}C^- \rightarrow Pd[P(C_6H_5)_3]_2 + RC{\equiv}C{-}C{\equiv}CR + 2\ OAc^-)$$

$$Pd[P(C_6H_5)_3]_2 + R'X \rightarrow R'Pd(X)[P(C_6H_5)_3]_2$$



$$\rightarrow R'C{\equiv}CR + Pd[P(C_6H_5)_3]_2$$

Thus, the major limitation of this disubstituted acetylene and enyne preparation is that halides with strongly electron-donating substituents, or halides which are otherwise made relatively unreactive in the oxidative reaction with the palladium(0) catalyst, do not react well. Otherwise, the reaction appears widely applicable and it will provide a convenient new method for obtaining a variety of acetylene derivatives.

TABLE 1. ACETYLENIC SUBSTITUTION REACTIONS (REACTION TEMP. = 100°C)

Organic halide (mmol)	Acetylenic reactant (mmol)	Amine (ml)	Catalyst[a]	Reaction time (h)	Product (yield %)	B.p. or m.p. (reported) °C	Mol. wt. found (calcd.)	NMR spectrum (τ)
Iodobenzene (10)	Phenylacetylene (12.5)	Triethylamine (20)	A	1.5	Diphenylacetylene (57, 73[b])	59.5-61 (60-61)[c]		
Bromobenzene (10)	Phenylacetylene (20)	Triethylamine (20)	A	2.5	Diphenylacetylene (51)[b]			
Bromobenzene (10)	Phenylacetylene (20)	Piperidine (20)	A	2.5	Diphenylacetylene (64)[b]			
Iodobenzene (5)	1-Hexyne (10)	Piperidine (10)	B	1	1-Phenyl-1-hexyne (62)[b]			
E-2-Bromostyrene (10)	Phenylacetylene (20)	Triethylamine (50)	A	1	*E*-1,4-Diphenyl-1-buten-3-yne[d] (70)[b]			
Z-2-Bromostyrene (20)	Phenylacetylene (40)	Triethylamine (50)	C	1	*Z*-1,4-Diphenyl-1-buten-3-yne[d] (66.9)			Identical to that previously reported[d]
Iodobenzene (100)	2-Methyl-1-buten-3-yne (200)	Triethylamine (200)	C		2-Methyl-4-phenyl-1-buten-3-yne (71)	42-43/ 0.35 Torr	142.079 (142.078)	(Neat) 2.34-2.85m (5H), 4.55m (1H), 4.74m (1H), 8.07s(br) (3H)
2-Bromopropene (10)	Phenylacetylene (12.5)	Triethylamine (20)	C	1	2-Methyl-4-phenyl-1-buten-3-yne (88)[b]			
4-Bromobenzaldehyde (50)	Phenylacetylene (75)	Triethylamine (100)	C	1	4-(Phenylethynyl)-benzaldehyde (66.0)	98-98.5	206.069 (206.073)	[$(CD_3)_2SO$] 0.08s (1H), 2.00d (2H), 2.20d (2H) J = 8 Hz, 2.20-2.70m (5H)
2-Bromothiophene (10)	Phenylacetylene (20)	Piperidine (20)	B	0.5	2-Phenylethynylthiophene (53.0)	48-49 (48.5-49.5)[e]	^{32}S 184.035 ^{33}S (184.035) 185.040 ^{34}S (185.034) 186.034 (186.030)	(CCl_4) 2.32-2.86m (7H), 3.00, 3.06, 3.09, 3.14m (1H)
4-Bromonitrobenzene (20)	t-Butylacetylene (30)	Triethylamine (40)	B	0.5	4-(t-Butylethynyl)nitrobenzene (88.4)	103-104	203.091 (203.095)	($CDCl_3$) 2.01d (2H), 2.65d (2H) J = 9 Hz, 8.67s (9H)
Methyl *E*-3-bromo-2-methylpropenoate (20)	t-Butylacetylene (30)	Triethylamine (40)	C	2.25	Methyl *E*-2,6,6-trimethylhept-2-en-4-ynoate (58.6)	47-48/ 0.45 Torr	180.115 (180.115)	(Neat) 3.41q (1H), 8.02d (3H) J < 2 Hz, 6.30s (3H), 8.73s (9H)

[a] A = 1 mol % $Pd(OAc)_2$, 2 mol % Ph_3P; B = 2 mol % $(Ph_3P)_2Pd(OAc)_2$; C = 1 mol % $(Ph_3P)_2Pd(OAc)_2$. [b] Yield determined by VPC. [c] Ref. 10. [d] Ref. 11. [e] Ref. 12.

Experimental

Methyl E-3-bromo-2-methylpropenoate

This material was prepared by the method of Canbere [8].

Z-2-Bromostyrene

This was prepared by the method of Cristol and Norris [9].

General method for acetylenic substitution reactions

The indicated quantities of organic halide, acetylenic reactant, amine, and catalyst were placed in a heavy-walled Pyrex reaction bottle which was then flushed with argon and capped with a self-sealing rubber-lined cap. The mixture was stirred magnetically and heated on a steam bath.

In reactions where yield was determined by VPC analysis, an internal standard was added initially and the reactions were run until the yields of products no longer increased.

In cases where products were isolated, the reactions were run until VPC analysis showed that all of the starting halide had reacted. The bottles were then cooled and opened. The reaction mixtures were diluted with ether, filtered, and the filtrates were washed several times with ether. Volatile materials were removed under reduced pressure and the residues were then either distilled or sublimed. Sublimed materials were subsequently recrystallized. *Z*-1,4-Diphenyl-1-buten-3-yne was isolated by chromatography of the residue, eluting with hexane.

4-(t-Butylethynyl)nitrobenzene

4-Bromonitrobenzene (4.04 g, 20 mmol), t-butylacetylene (2.46 g, 30 mmol) and 40 ml triethylamine were placed in a heavy-walled Pyrex reaction bottle containing a magnetic stirring bar. $(Ph_3P)_2Pd(OAc)_2$ (0.298 g, 0.4 mmol) was added and the bottle was flushed with argon and capped with a self-sealing rubber-lined cap. The mixture was then heated with stirring on a steam bath. After 30 min, VPC analysis showed that essentially all of the starting bromide had reacted. The reaction mixture was diluted with 100 ml ether and filtered and the residue on the filter was washed several times with ether. The ether and other volatile materials in the filtrate were removed under reduced pressure leaving a brown solid which was sublimed at 100°C/0.2 Torr. Recrystallization of the sublimate from hexane afforded 3.59 g (88.4%) of 4-(t-butylethynyl)-nitrobenzene, m.p. 103-104°C.

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