Tetrahedron Letters,Vol.29,No.34,pp 4325-4328,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

PALLADIUM CATALYSED TANDEM CYCLISATION-ANION CAPTURE PROCESSES. HYDRIDE ION CAPTURE BY VINYLPALLADIUM SPECIES.

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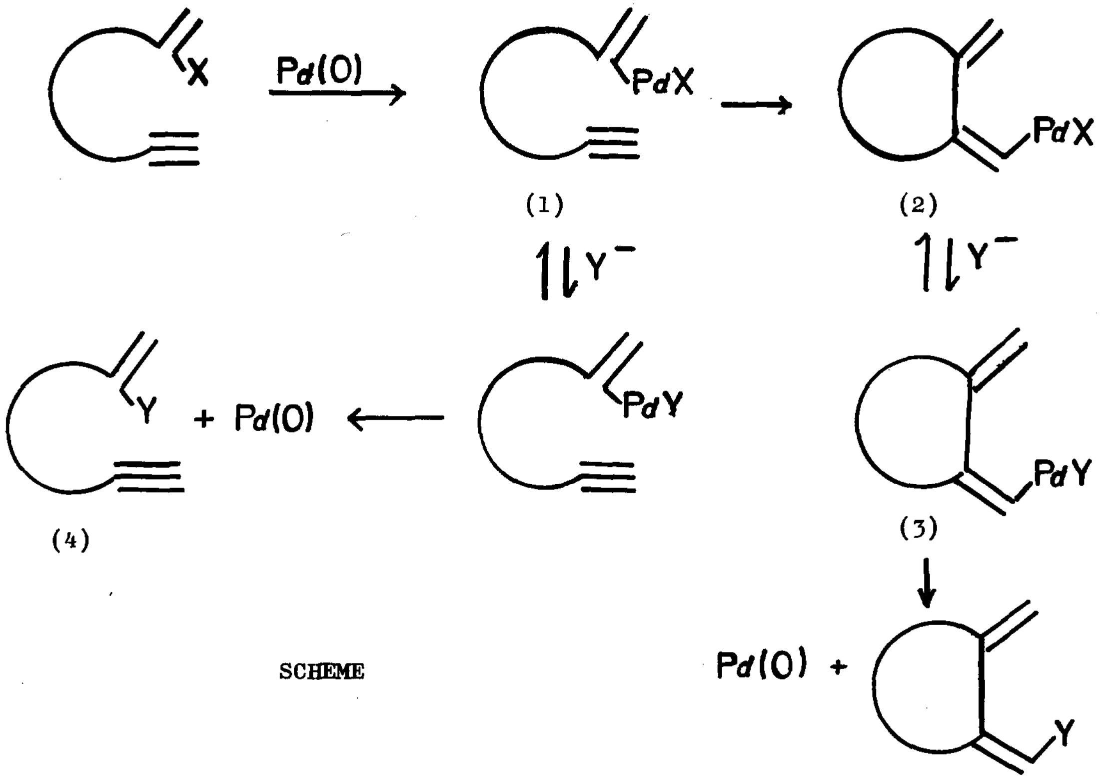
Abstract. A new palladium catalysed-anion capture process is proposed, Examples are provided involving cyclisation of o-(ω-acetylenic)-aryl iodides and 2-bromo-1,6-enynes to heterocyclic- and carbocyclic-vinylpalladium species followed by hydride ion capture.

The Heck reaction[1] involves the palladium-catalysed vinylation of aryl, heteroaryl, vinyl or benzyl halides and has proved a valuable method for carbon-carbon formation in the appropriate synthetic context. It has been extensively studied for the synthesis of heterocyclic compounds, notably by Hegedus[2] and Ban[3].

The synthetic utility of the Heck reaction was recently further enhanced by the observation[4] that the addition of tetrabutylammonium chloride permitted Heck reactions to be carried out in DMF at, or near, room temperature in good yield,[5,6] and by extension of the reaction to the construction of bridged-rings, spirocyclic systems and tetrasubstituted carbon centres.[7,8]

Similar palladium catalysed cyclisation reactions of 2-bromo- or 2-iodo-1,ω-enynes (Scheme) cannot occur because of lack of a β-hydride elimination pathway for the intermediate (2, X=Br or I). However, if an anion exchange process, Y for X (Scheme), could be incorporated such that reductive elimination of Pd(0) occurs from (3) (Scheme), then a new tandem cyclisation-anion capture process would result. The use of the word "anion" in this context is meant to embrace both ionic and covalent sources of Y and is felt to be more appropriate than the term cross-coupling.

We now have results to hand that confirm the feasibility of the Scheme and which suggest it will be widely applicable.[9,10] We have utilised a catalyst system comprising 10 mol% palladium acetate and 20 mol% triphenylphosphine in acetonitrile with the addition of piperidine (4 mol) and formic acid (3 mol) to provide a base and a hydride ion source. Using this system at 60°C the aryl iodides (5a-c) cyclise regio- and stereo-specifically via a 5-exo-dig process to (6a-c) over 12h. in 40-60% yield.[11] Similarly (7a) and (7b) cyclise regiospecifically to (8a) and (8b) respectively in 60-70% yield via a 6-exo-dig process. The latter cyclisation occurs stereospecifically.[11]

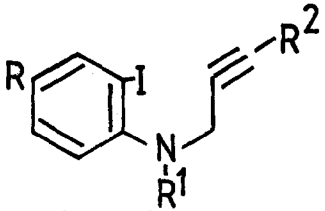


SCHEME

The Mannich bases (5d) and (7c) react under analogous conditions, but with no added piperidine and only one mol. of formic acid, to give (9) (30%) and (10) (33%) respectively. These products presumably arise from (6d) and (8c) respectively by elimination of piperidine. Diene (10) undergoes the Diels-Alder reaction with N-methylmaleimide to give (11) (80%).

The reaction is not restricted to aryl iodides. Thus (12a) is cyclised by the palladium catalyst over 43h at 30°C to (13a) (38%). At 80°C the cyclisation produces a 4.3:1 mixture (40%) of (13a) and (13b). The trimethylsilyl derivative (12b) cyclised under similar conditions to give (13b) (47%) using benzene as solvent. Use of acetonitrile as solvent at 80°C, together with variation of the amounts of piperidine and formic acid, leads to increased yields (up to 75%) but produces various mixtures of (13a), (13b), (13c), and (14a) in which (13b) usually predominates. Enyne (12c) cyclises at 80°C using the palladium catalyst system to give (13c) in poor yield (~10%).

Finally, the diyne (15) is cyclised by the standard catalyst system at 60°C, but with only 2 mol. of piperidine and formic acid, to give a ca. 2.4:1 mixture of (13a) and (14a). In contrast 5 mol% of Wilkinson's catalyst, $(Ph_3P)_3RhCl$, under the same conditions, but at 80°C, gives a

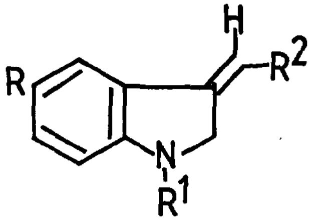


(5) a. R=R^2=H, R^1=Ac

b. R=CO$_2$Et,R^1=Ac,R^2=H

c. R=H, R^1=Ac,R^2=Me

d. R=H, R^1=Ac,R^2=CH$_2$N

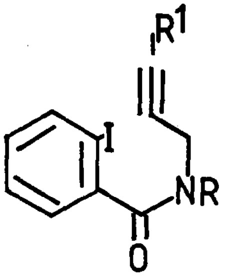


(6) a. R=R^2=H, R^1=Ac

b. R=CO$_2$Et,R^1=Ac,R^2=H

c. R=H, R^1=Ac, R^2=Me

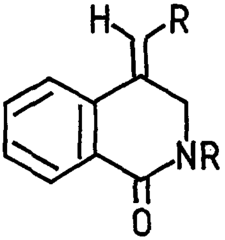
d. R=H,R^1=Ac,R^2=CH$_2$N



(7) a. R=Me, R^1=H

b. R=CH$_2$Ph, R^1=Me

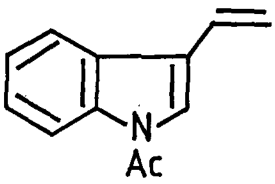
c. R=Me,R^1=CH$_2$N



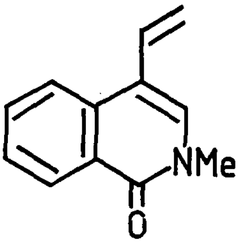
(8) a. R=Me, R^1=H

b. R=CH$_2$Ph, R^1=Me

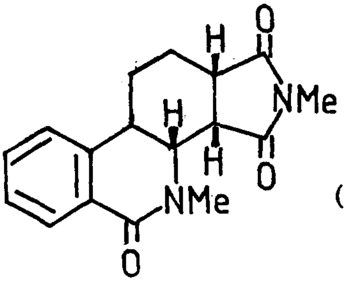
c. R=Me, R^1=CH$_2$N



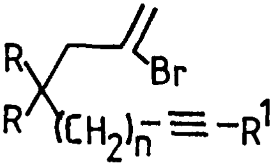
(9)



(10)



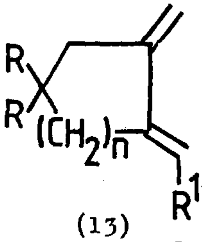
(11)



(12) a. R=CO$_2$Et,R^1=H,n=1

b. R=CO$_2$Et,R^1=SiMe$_3$,n=1

c. R=CO$_2$Et,R^1=H,n=2

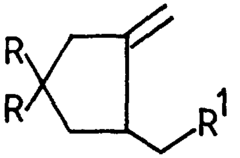


(13)

a. R=CO$_2$Et,R^1=H, n=1

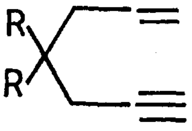
b. R=CO$_2$Et,R^1=SiMe$_3$,n=1

c. R=CO$_2$Et,R^1=H, n=2

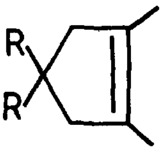


(14) a. R=CO$_2$Et, R^1=H

b. R=CO$_2$Et, R^1=SiMe



(15) R=CO$_2$Et



(16) R=CO$_2$Et

2.9:1:1 mixture (75%) of (16), (13a) and (14a).

Thus for cases where the anion Y is hydride the relative rates of cyclisation (1) $\longrightarrow$ (2) and "anion" exchange (2) $\longrightarrow$ (3) are frequently favourable. Little, if any, anion exchange of (1) followed by reductive elimination to give (4) is observed. Alkyl- and π-alkyl-palladium species arising from 5-exo-trig cyclisations, onto proximate alkenes and dienes respectively, can also be intercepted by appropriate hydride ion sources.[10]

We thank Pfizer Ltd., SERC and Queen's University for support.

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11. The stereochemistry of the products reported herein was established by n.O.e. studies.

(Received in UK 8 June 1988)