PALLADIUM HOMOGENEOUS AND SUPPORTED CATALYSIS: SYNTHESIS OF FUNCTIONAL ACETYLENICS AND CYCLISATION TO HETEROCYCLES

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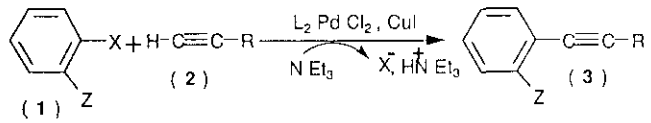
Abstract - Homogeneous and supported palladium catalysis is a good way to synthesize functional ortho-phenylacetylenes from acetylenes and ortho-halogenated aromatics. Functional ortho-phenylacetylenes are cyclised into various benzoheterocyclic compounds.

The catalysis with palladium complex has taken an increasing significance as a synthetic tool in organic chemistry. The synthesis of phenylacetylenes catalyzed by palladium and copper was first described by Hagihara et al. [1] . Our interest is to develop this smooth reaction [2]. This resent paper is concerned with the synthesis of functional ortho-phenylacetylenes (3) and cyclisation into benzoheterocycles [3]. Some functional ortho-phenylacetylenes were reported as precursor of benzoheterocyclic compounds [3-8]. This approach was not widely used due to the difficulty to obtain functional ortho-phenylacetylenes (3).

The synthesis of functional ortho-phenylacetylenes, described by Castro et al. [6] is still used [7], but requires drastic conditions and hazardous copper (I) acetylides.

Synthesis of ortho-functional phenylacetylenes (3):

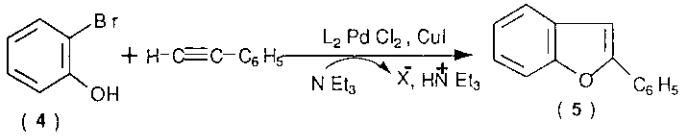
Palladium and copper allow smooth and efficient synthesis of (3) at room temperature, contrary to the literature we test the reaction with unprotected functional group. We report here that no protection is need with amine group as at the synthesis described during our work [4].



(1) (2) (3)

X= I,Br L=$P(C_6H_5)_3$ Z= NH_2 ; R= C_6H_5(a), $Si(CH_3)_3$ (b), CH_2OH (c)
R= C_6H_5 Z= $NHCOCH_3$(d), CH_2OH (e), $COOCH_3$(f), COOH (g)

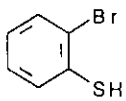
With 2-bromophenol (4), the formation of carbon-carbon bond and the cyclisation occurs spontaneously in the reaction conditions.



(4) (5)

Dedicated to Professor Sir Derek Barton on the occasion of his 70th Birthday.

With 2-iodobenzoic acid, the mixture becomes heterogeneous and no reaction is observed. A homogeneous mixture can be obtained with dichloromethane as a cosolvent, but no reaction takes place. With the methyl ester (**1f**), the reaction runs readily (85%).
2-Bromothiophenol (**6**), or its disulfide (**7**), forms insoluble and inactive complexes with palladium catalyst, and, the reaction is inhibited.



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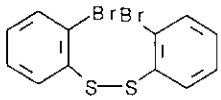
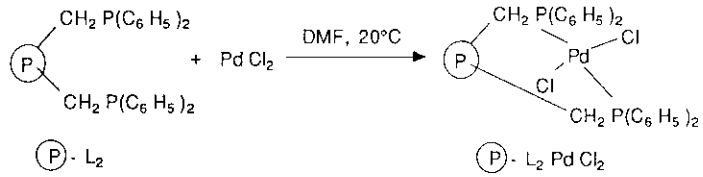


(7)

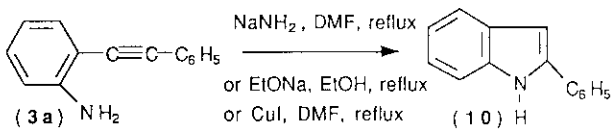
Palladium complex (P-L_2 $PdCl_2$) (**9**) bound to polystyrene can be used in these reactions, and, the catalyst recovered by filtration can be reused with a slight loss of activity (80% of initial activity of (**9**)).



(**8**) (**9**)

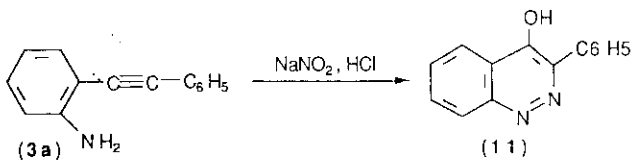
Cyclisation of benzoheterocycles

Recently cyclisation of desactivated aminophenylacetylene (carbamate,sulfonamide) into indoles was described under basic conditions. The 2-aminodiphenylacetylene (**3a**) is easily cyclised into 2-phenylindole (**10**) with sodium amide (2 eq.) in DMF (yield 85%) or sodium ethoxide(2 eq.) in ethanol (yield 70%). The best result is obtained by heating (**3a**) in DMF with copper(I) iodide as catalyst under argon (yield 99%). Palladium chloride in acetonitrile recently described [9] or copper(I) iodide in pyridine, gave poorer result (yield 80% and 82% of (**10**) respectively).



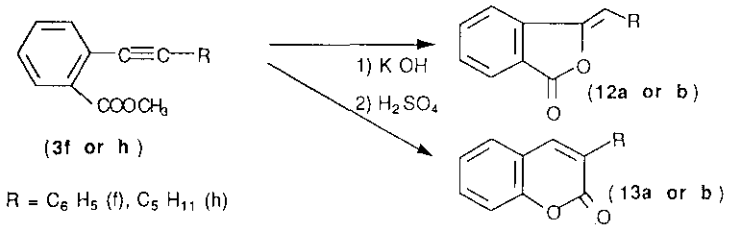
(**3a**) (**10**)

The 2-aminodiphenylacetylene(**3a**) treated by nitrous acid give the 4-hydroxy-3-phenylcinnoline (**11**).



(**3a**) (**11**)

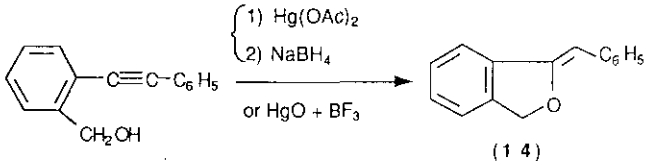
Saponification of ester of 2-carboxydiphenylacetylene (**3f**) followed by acidification with acetic acid gives a mixture of 2-diphenylacetylenecarboxylic acid (**3g**) and 3-benzylidene-phthalide(**12a**). With a strong acid only 3-benzylidenephthalide (**12a**) is obtained, trace of phenyl-3-isocoumarine (**13a**) was not formed (ir, tlc). These results contrast with those obtained by cyclisation of corresponding amide (H_2SO_4+$HgSO_4$)[10]. Saponification and acidification of methyl 2-heptynylbenzoate (**3h**) gave exclusively the isocoumarin (**13b**).



(**3f** or **h**)

R = C_6H_5 (f), C_5H_{11} (h)

The 2-hydroxymethyldiphenylacetylene (**3e**) is transformed into 1-benzylidene-dihydroisobenzofuran (**14**) by treatment with mercuric acetate followed by in situ reduction with sodium borohydride (yield 82%). We found that catalytic cyclisation with mercuric oxide and boron trifluoride produced a cleaner product with a better yield than stoichiometric mercuration.



(**3e**) (**14**)

In conclusion homogeneous and supported palladium catalysis allows a smooth and efficient synthesis of ortho-functional phenylacetylenes precursors of many benzoheterocyclic compounds.

EXPERIMENTAL

Bis(triphenylphosphine)palladium dichloride:

Bis(triphenylphosphine)palladium dichloride was prepared according a modified process of the literature [11] as follow : Palladium chloride (1.336g, 8 mmol) and triphenylphosphine (4.2g, 16 mmol) were dissolved in DMF(120 ml) at room temperature under argon. After 24 h the yellow solid formed was filtered, washed with water (30 ml), ethanol,ether and dry, yield (95%).

Synthesis of ortho-functional phenylacetylenes(**3**):

A typical procedure:

2-Aminodiphenylacetylene (3a)

Copper(I) iodide(16 mg, 1 mmol), bis(triphenylphosphine)palladium dichloride (70 mg, 1 mmol), 2-iodoaniline (2.2g, 10 mmol) were stirred under argon in triethylamine (60 ml). We added phenylacetylene (1.02g, 10 mmol), a precipitate was formed. After 18 h of stirring at room temperature, the solvent is evaporated under vacuo. Ether (200 ml) is added, the solution was filtered on celite and the solution is washed with water (30 ml). The organic phase was dried on magnesium sulfate and evaporated in vacuo. The product was crystallized from cyclohexane.Yield 90% ,mp 92°C (cyclohexane) [lit.[12] mp 89-90°C (petroleum ether)]; C_{14} H_{11} N : Calcd C, 87.01; H, 5.74, Found C, 86.80; H, 5.83 ; ir (KBr): 3650 and 3500(νNH_2), 2250($\nu C\equiv C$), 1620($\nu C=C$arom.) ; nmr($CDCl_3$): δ 7.80-7.00 and 6.90-6.40 (m,9H,Harom), 4.30(broad s, 2H,NH_2).

2-Trimethylsilylethynylaniline (3b)

Prepared from 2-iodoaniline and trimethylsilylacetylene; yield 96%; liq. maroon, purified by chromatography on silica gel with dichloromethane as solvent; C_{11} H_{15} N Si: Calcd. C,69.79; H ,7.98. Found C ,69.51; H, 8.09 ; nmr ($CDCl_3$) : δ 7.80-6.40(m,4H,C_6H_4), 4.25(s broad,2H,NH_2), 0.22(s,9H,CH_3).

2'-Aminophenyl-3-propyn-1-ol (3c)

Prepared from 2-iodoaniline and 2-propyn-1-ol; yield 87% ; liq. maroon, purified by chromatography on silica gel with acetonitrile as solvent; C_9 H_9 N O: Calcd C, 73.43; H, 6.17. Found C,73.10; H 6.02 ; nmr ($CDCl_3$+ DMSO-d_6) : δ 7.80-6.40(m,4H,C_6H_4), 4.60(broad s,2H,NH_2), 4.20(s,2H,CH_2), 3.30 (s,1H,OH).

2-Acetamino-2-diphenylacetylene (3d)

Prepared from 2-iodoacetanilide and phenylacetylene; yield 92%; white solid, purified by chromatography on silica gel with acetonitrile as solvent; mp 122°C; C_{16} H_{13} N O : Calcd. C 81.68; H 5.57. Found C 82.01; H 5.46; ir(nujol) 3270(νNH_2), 1680($\nu C=O$).

2-Hydroxymethyldiphenylacetylene (3e)

Prepared from 2-bromobenzyl alcohol and phenylacetylene; yield 94%; white solid, purified by chromatography on silica gel with acetonitrile as solvent; mp 71°C (cyclohexane) [lit. [6] mp 69-71°C (petroleum ether)]; C_{15} H_{12} O : Calcd C, 86.51; H, 5.81. Found C, 86.31; H, 5.87; ir (nujol): 3280(νOH), 2200($\nu C\equiv C$), 1590(C=Carom.), 1190(C-O); nmr ($CDCl_3$) : δ 7.20(m, 9H,Harom), 4.95(s,2H,CH_2), 2.35(s,1H,OH).

Methyl Diphenylacetylene-2-carboxylate (3f)

Prepared by the reaction of 1-heptyne with methyl 2-iodobenzoate; yield 94%; yellow liq., purified by chromatography on silica gel with a mixture of cyclohexane / ethyl acetate (1/1) as solvent; C_{16} H_{12} O_2 : Calcd C,81.33; H, 5.12. Found C, 81.09; H,5.04 ; ir (film) 2210($\nu C\equiv C$), 1720 ($\nu C=O$); nmr ($CDCl_3$) : δ 8.10-7.20 (m, 9H, Haro.), 3.90(s,3H,CH3).

Diphenylacetylene-2-carboxylic acid (3g)

Methyl diphenylacetylene-2-carboxylate (1.18g, 5 mmol) was saponified by reflux for 4 h with an. aqueous solution of sodium hydroxide (30%, 20 ml). After acidification with acetic acid (pH=5) the mixture was extracted with ether (3X200 ml). The organic phase was dried on magnesium sulfate and evaporated in vacuo to a waxy solid. This solid was a mixture of (**3g**) and (**12a**). By preparative chromatography on silica gel (40/60: ethyl acetate / cyclohexane) we obtained the acid as the more polar product. The acid (**3g**) was crystalized in a mixture of cyclohexane- acetic acid; yield 50%; white solid, mp 126 °C [lit.[13] mp 126-127.5 °C

(heptane-acetic acid)]; $C_{15}H_{10}O_2$: Calcd C, 81.07; H, 4.54 . Found C, 80.78; H, 4.61; ir(KBr) : 3200-2600(vOH), 2210(vC≡C), 1690(vC=O acid).

Methyl 2-Heptynylphenylbenzoate (3h)

Prepared by the reaction of 1-heptyne with methyl 2-iodobenzoate; yield 85%; yellow oil, purified by chromatography on silica gel.with a mixture of cyclohexane / ethyl acetate (1/1) as solvent ; $C_{15}H_{18}O_2$: Calcd C, 78.22; H, 7.88 . Found C, 78.13; H, 7.25; ir (film): 2215(vC≡C), 1735 (vC=O),1250 ; nmr($CDCl_3$) : δ 8.20-7.00 (m,4H, Harom.), 3.90(s, 3H, CH_3O), 2.70(t,J=7Hz,2H,CH_2-C≡), 1.75-1.30(m,6H,CH_2), 0.99(t, J=7Hz,3H,CH_3).

Bis(bromo2phenyl)disulphide (6)

It was obtained by iodine oxidation (508 mg, 2 mmol) of commercial available 2-bromothiophenol (756 mg, 4 mmol) in triethylamine (100 ml) at room temperature. After evaporation of solvent in vacuo, ether (150 ml) is added .The organic layer was washed with sodium hydroxide (10%, 30 ml),with hydrochloric acid (10%, 30 ml) and water (2X30 ml). After drying on magnesium sulfate evaporation of ether yielded a white solid ; yield 95%; mass spectra (70ev): 376(M^+); 216; 108.

Polymers support:

Macroporous Merrifield resin 20%(containing about 3.6 mmol of CH_2Cl /g of resin) was transformed into phosphinated resin by treatment with lithium diphenylphosphine in dry THF under argon, according the procedure described [8,14].

These phosphinated resin **(8)** (5 g)was shaken with a solution of palladium chloride(668 mg) in DMF(100 ml) for 24 h. The polymer was recovered by filtration and washed with with DMF (100 ml) and CH_2Cl_2(100 ml). It was then extracted with CH_2Cl_2 for 24 h in a Soxhlet-apparatus. The resin **(9)** contained about 1.4 mmol palladium complex/g from microanalysis data.

Cyclisation of benzoheterocycles

2-Phenylbenzofuran (5)

It was obtained from 2-bromophenol and phenylacetylene; yield 79%.The solid was crystallized from cyclohexane; white solid; mp 120°C (subli.) [lit. [15], mp 120-121°C (petroleum ether)]; $C_{14}H_{10}O$: Calcd C, 86.57; H, 5.19 . Found C, 86.48; H, 5.17.

2-Phenylindole (10)

With sodium amide : **(3a)** (1.93g,10 mmol) and sodium amide (0.925g, 25 mmol) were refluxed in DMF (200 ml) under argon for 2 h. After addition of water (200 ml) the mixture was extracted with ether (800X3ml), washed with water (4X20 ml) and dried on magnesium sulfate. Evaporation of ether gave a white solid ; yield 85%. The solid was crystallized from methanol.

With copper iodide : **(3a)** (1.93g,10 mmol) in DMF (40 ml) was reflux under argon during 4 h with copper (I) iodide (11 mg, 0.58 mmol). The solvent was evaporated in vacuo and the residue was dissolved in ether, insoluble copper salts were removed by filtration. Evaporation of ether gave white solid ; yield 99%. The solid was crystallized from methanol.

White plate; mp 188°C (methanol) [lit.[6] mp 189°C]; tlc(cyclohexane/ethylacetate, UV); 2-phenylindole (Rf 0.68), 2-aminodiphenylacetylene (Rf 0.23); $C_{14}H_{11}N$: Calcd C, 87.01; H, 5.74; Found C 87.09; H, 5.81.

4-Hydroxy-3-phenylcinnoline (11)

An aqueous sodium nitrite solution (2%, 3 ml) was added at O°C to a mixture of 2-aminodiphenylacetylene (120 mg, 0.62 mmol) in hydrochloric acid (37%, 4 ml). After 2 h the mixture was reflux for 1 h and after cooling at room temperature the precipitate was filtered and crystallized from ethanol; yield 82%; white solid; mp 259-260°C [lit.[12] mp 260-261°C (ethanol)]; $C_{14}H_{10}N_2O$: Calcd C, 76.66; H, 4.54 . Found C 76.82,H. 4.48.

3-Benzylidenephthalide (12a)

By use of sulfuric acid instead of acetic acid (pH=1) and with a similar work up described for (**3g**) we obtained pure 3-benzylidenephthalide(**12a**); yield 90%; white solid after recrystallization from tetrahydrofuran; mp 97-99°C [lit.[13] mp 99-100°C]; $C_{15}H_{10}O_2$: Calcd. C, 81.06; H, 4.54; Found C, 81.20; H, 4.56;ir (nujol):1720(νC=O), no band at 1745[(3-phenylisocoumarine (**13a**)].

3-Pentylisocoumarin (13b)

Methyl 2-heptynylphenylbenzoate (**3h**) (921mg, 4 mmol) was saponified by reflux for 4 h with an aqueous solution of sodium hydroxide (30%, 18 ml). After acidification with sulfuric acid (pH=1) the mixture was extracted with ether (3X200 ml). The organic phase was dried on magnesium sulfate and evaporated in vacuo The residue dissolved in benzene (20 ml) was filtered through a short column of alumina to yield a yellow oil; yield 71%; $C_{14}H_{16}O_2$: Calcd C, 77.75; H, 7.46 . Found C, 77.25; H, 7.54 ; ir (CCl_4):1745(CO),1660(C=C) ; nmr ($CDCl_3$): δ 8.35-7.00(m,4H,H arom.), 6.27(s, 1H,CH=), 2.50(t,J= 7Hz,2H,CH_2-C=), 1.75-1.30(m,6H,CH_2), 0.99(t,J= 7Hz,3H,CH_3).

1-Benzylidenedihydroisobenzofuran (14)

Cyclisation by mercuration:

2-Hydroxymethyldiphenylacetylene(832 mg, 4mmol) was stirred at room temperature overnight with a solution of mercuric acetate (1.28 g, 4 mmol) in a mixture of water (30 ml) and ether (50 ml). A mixture of sodium hydroxide (0.42g, 10.5 mmol) and sodium borohydride (0.2g, 5.26 mmol) in water (20 ml) was added. Mercury was removed by filtration on celite. After ether addition (200 ml) the organic phase was washed with water (3X30 ml), dried on magnesium sulfate and evaporated in vacuo. The product was crystallized from cyclohexane; yield 82%.

Catalytic cyclisation :

2-Hydroxymethyldiphenylacetylene(698 mg, 3.35 mmol) in ether (30 ml) was stirred at room temperature with mercury(II) oxide (22 mg, 0.1mmol) and boron trifluoride etherate (0.2 ml) during 12 h. Ether (200 ml) and then water (30 ml) was added. The organic phase was washed with a sodium hydroxide solution (5%, 40 ml), dried on magnesium sulfate and evaporated in vacuo. The product was crystallized from cyclohexane; yield 98%;.orange crystal, mp 98-100°C (cyclohexane) [lit.[6] mp 100°C (petroleum ether)]; $C_{15}H_{12}O$: Calcd C, 86.51; H, 5.81. Found C,86.41; H, 5.90; ir(nujol): 1650(νC=C),1270(νC-O),1060,700; nmr ($CDCl_3$): δ 7.30 (m, 9H, Harom), 5.95(m,1H,CH=), 5.50(s,2H,CH_2).

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