# PALLADIUM-ASSISTED ORGANIC REACTIONS-I

# APPLICATION OF THE HECK REACTION TO THE PREPARATION OF 4-STYRYLISOQUINOLINE DERIVATIVES

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Abstract— Treatment of a number of N-methylisocarbostyrils with mercuric acetate gives rise to the 4mercurated derivatives, which undergo insertion reactions with methyl acrylate and with styrenes in the presence of palladium acetate.

Benzo [c]phenanthridine alkaloids<sup>1,2</sup> have attracted some attention recently because fagaronine  $(1)^3$ has a high activity against the P388 test system. A number of synthetic routes to the ring-system has been devised,<sup>1.2,4</sup> among them<sup>5</sup> the photochemical ring-closure of 4-styrylisoquinoline derivatives (4) which, themselves, are prepared by the condensation of arylglyoxals with 1.2-dihydroisoquinolines (Scheme 1). Although in principle this is a short route to benzo[c]phenanthridines from readily available starting materials, the main disadvantages are (a) difficulty in preparing and purifying the required arylglyoxals and (b) the condensation of these with secondary 1,2-dihydroisoquinolines of the type 2 favours the N-substituted isoquinolinium salt (5) over the required 4-substituted derivative 3.

Heck<sup>6,7</sup> has shown that transient arylpalladium complexes, generated either from arylmercuriacetates or chlorides, or by oxidative addition of aryl iodides or bromides, in the presence of palladium acetate or Li<sub>2</sub>PdCl<sub>4</sub>, undergo useful insertion reactions into a wide range of alkenes to yield arylalkenes (Scheme 2). Insertion occurs predominantly at the least hindered end of the double bond, and the trans product usually is formed. Thus, the reaction of phenylmercuric acetate with methyl acrylate or with styrenc in the presence of palladium acetate or Li<sub>2</sub>PdCl<sub>4</sub> gave high yields of trans methyl cinnamate and trans-stilbene, respectively. An early application to heterocyclic chemistry, and one of relevance to our work involved\* the treatment of 5chloromercuriuridine (6a) with ethene in the presence







of  $Li_2PdCl_4$  to yield **6b**, which was then reduced to 5-ethyluridine (**6c**).



Repetition of the reaction with o- and *p*-chlorostyrenes gave the expected products 7f and 7g, respectively, in



As N-methylisocarbostyril (7a) undergoes<sup>9,10</sup> electrophilic substitution at  $C_4$ , then if 7a could also be mercurated at  $C_4$ , it might be possible to apply the Heck reaction to the preparation of 4-styrylisoquinoline derivatives. When 7a was added to a solution of mercuric acetate, the mercurated derivative 7b was formed as a white crystalline solid, which was isolated in 70  $^{\circ}_{o}$  yield. Substitution had occured at C<sub>4</sub> as indicated by the <sup>1</sup>H NMR spectrum which exhibited a one hydrogen singlet 7.2 $\delta$  (C<sub>3</sub> H) and no absorption between 6 and 7 $\delta$ , characteristic of C<sub>4</sub>-H. The mercuriacetate derivative (7b) reacted with methyl acrylate, in the presence of a stoichimetric amount of palladium acetate, to yield the trans compound 7c in 78°, yield. This product was identical with the compound prepared<sup>11</sup> from N-methylisocarbostyryl-4-aldehyde (7d), thus confirming the structure of 7b.

The reaction of **7b** with styrene under similar conditions gave the *trans*-azastilbene (**7e**) in  $57^{\circ}_{o}$  yield.

reasonable yield However, when 7b was reacted with 3.4-dimethoxystyrene, the required product (8) could be isolated in only 1-2°, yield. No other component of the complex mixture could be characterised. Although Heck states that yields of products dropped when the arylmercuriacetate or chloride contains electrondonating substituents, very little work has been reported using styrenes so substituted, and nothing with 3,4-dimethoxystyrene. When phenylmercuric acetate was reacted with styrene under our conditions, trans-stilbene was isolated in 67% yield, whereas 3,4dimethoxystyrene reacted to give only 3 ", of 3,4dimethoxystilbene. With p-methoxyphenylmercuric acetate and styrene the corresponding stilbene was obtained in 65°, yield, whereas 3,4,4'-trimethoxystilbene could not be detected in the complex mixture formed when p-methoxyphenylmercuric acetate and 3.4-dimethoxystyrene were reacted in MeCN solution in the presence of palladium acetate. This aspect of the Heck reaction will be reported in detail subsequently.



It was interesting to find that both 7h and 9a could be mercurated at  $C_4$ , despite the presence of the electron-rich 3.4-dimethoxybenzene ring in each. The position of mercuration was established from the <sup>1</sup>H NMR spectra of the products. However, 5-nitro-2methylisocarbostyril could not be mercurated. The mercuriacetate derivative (9b) reacted with methyl acrylate in MeCN solution in the presence of a stoichimetric amount of palladium acetate to provide a good yield of 9c. which offers an alternative photochemical route to the benzo [c]phenanthridine nucleus. Further work on the scope of these reactions is in progress.

#### **EXPERIMENTAL**

IR spectra were recorded on Perkin Elmer 237 instrument. <sup>1</sup>H NMR spectra were obtained with Varian EM360 or Jeol PS100 spectrometers and chemical shifts are expressed in parts per million ( $\delta$ ) downfield from TMS as an internal standard. Mass spectra were recorded with AEI MS12 instrument. All m.ps are uncorrected.

2-Methylisocarbostyr)1-4-mercuriacetate (7b). 2-Methylisocarbostyril (10g; 0.0063 mol) was added all at once to a stirred soln of mercuric acetate (2.13g; 0.0063 mol) in AcOH (100ml), and after 16hr at room temp the soln was evaporated to dryness in *vacuo* The white powdery residue was crystallised from EtOH to give white needles of 7b (1.5 g; 70° a), m.p. 220 222°. <sup>1</sup>H NMR (d<sub>6</sub> DMSO): 2.0s [3] (MeCO); 3.6s [3] (N-Mei); 7.2s [1° (C<sub>3</sub>-H); 7.4-84 m [4]; (Ar-H). [Found: C, 34.3; H, 2.7; N, 3.2 C<sub>1.2</sub>H<sub>11</sub>NO<sub>3</sub> requires: C, 34.5; H, 2.6; N, 3.55° a]

6.7-Dimethoxy-2-methylisocarhostyryl-4-mercuriacetate (7i) was prepared similarly, and obtained in  $34^{\circ}_{0}$  yield as white needles, m.p. 250 251° from EtOH, <sup>-1</sup>H NMR (d<sub>6</sub>DMSO): 1.76s [3] (MeCO); 3.5s [3] (N-Me): 3.86s and 3.88s [6] (2 × OMe); 71s [1] (C<sub>3</sub>-H): 7.35s [1] and 7.56s [1] (C<sub>5</sub> H + C<sub>8</sub> H). [Found: C, 35.0; H, 3.0; N, 2.9. C<sub>14</sub>H<sub>15</sub>HgNO<sub>5</sub> requires: C, 35.2; H, 3.1; N, 2.9°<sub>0</sub>].

3-(3,4-Dimethoxyphenyl)-2-methylisocarbostyryl-4-mercurracetate (9b) was prepared similarly to the above Hg derivatives and was obtained as white crystalline powder in 47°, yield, m.p. 250–252. <sup>1</sup>H NMR (d<sub>6</sub>DMSO): 2.05 s [3] (MeCO): 3.35 s [3] (N-Me), 3.9 s [3] and 3.95 s [3] (2 × OMe): 7.8 7.9 m [3] (Ar-H), 7.4-7.6 m [3] (C<sub>5</sub>-H + C<sub>6</sub>-H + C<sub>7</sub> H): 8.4 m [1] (C<sub>8</sub>-H). [Found: C, 42.8; H, 3.7; N, 2.0, C<sub>20</sub>H<sub>19</sub>HgNO<sub>5</sub> requires: C, 43.35; H, 34; N, 25%].

trans-Stilbene. A mixture of phenylmercuriacetate<sup>12</sup> (1.78 g, 5 mmol), styrene (2.0 ml) and palladium acetate

(1.13g, 5 mmole) in MeCN (10 ml) was stirred overnight at room temp. Pd metal was deposited as a mirror, the homogeneous mixture was poured into water (100 ml) and extracted into CHCl<sub>3</sub> ( $2 \times 50$  ml). The combined CHCl<sub>3</sub> solns were washed ( $2 \times 50$  ml H<sub>2</sub>O), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to leave a clear gum. Crystallisation from MeOH gave *trans*-stilbene (600 mg, 67 °<sub>a</sub>) m p. 122–124 (lit.<sup>13</sup> m.p. 122–124 ).

4-Methoxy-trans-stilbene was prepared similarly in  $65^{\circ}$ , yield, m.p. 115- 117 from MeOH.

3.4-Dimethoxy-trans-stilbene was similarly propared in 3 ", yield and obtained as small colourless prisms from MeOH. [Found C, 80.2, H, 6.4. Cale, for  $C_{16}H_{16}O_2$ ; C, 80.0; H, 6.6 ",].

Methyl trans-3(4(2-methylisocarbostyryl)propenate (7c)) A mixture of powdered **7b** (5 mmol) and palladium acetate (5 mmol) in MeCN (10 ml) was sturred at r.t. for 10 min, then methyl acrylate (2 ml) was added and stirring was continued overnight. The soln was filtered through keiselguhr, which was then extracted with CHCl<sub>3</sub>. This extract and the original eluate were separately centrifuged, decanted from Pd metal and evaporated to dryness to yield a gum (2.05 g) from the MeCN soln and a solid (0.8 g) from the CHCl<sub>3</sub>. The gum and the solid were combined and crystallised from MeOH (charcoal) to give long white needles (0.675 g: 56 "a) of 7c, m.p. 170–171 (lit.<sup>1+</sup> m.p. 170–171.)

2-Methyl-4-trans-styrylisocarbostyril (73). A mixture of powdered 7b (2.09 g; 5 mmol) and palladium acetate (1.13 g; 5 mmol) in McCN (10 ml) was stirred at r.t. 10 min then styrene (2 ml) was added. After stirring overnight at r.t. the mixture was poured into water (100 ml) and extracted with CHCl<sub>3</sub> (3 × 50 ml). The combined CHCl<sub>3</sub> extracts were washed with water (100 ml) dried (MgSO<sub>2</sub>) and evaporated to leave a gum (2.0 g). Trituration with ether gave a solid which was crystallised from MeOH to give pale yellow prisms of 7e (0.74 g; 54 °<sub>0</sub>). m.p. 148–150. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.44–8.56 m. [1] (C<sub>8</sub>-H); 7.2–7.8 m [10] (C<sub>3</sub>H + C<sub>8</sub> + C<sub>6</sub>H<sub>8</sub> + -CH=), 6.9 d [1] J = 16 Hz (CH=), 3.6 s [3] (NCH<sub>3</sub>). [Found: C, 82.75; H, 5.7; N, 5.4, C<sub>18</sub>H<sub>1</sub>×NO requires: C. 82.6; H, 5.7; N, 5.4, °<sub>10</sub>.

2-Methyl-4-trans- $(2^{\circ}-chloro)$ styrylisocarbostyril (7f) This was prepared similarly to 7e and was obtained in 73  $^{\circ}_{0}$  yield as white needles from EtOH, m.p. 176–178° [Found C, 73.0; H, 4.7; 4.5; C<sub>18</sub>H<sub>14</sub>CINO requires: C, 73.1; H, 4.7; N, 4.7 $^{\circ}_{0.2}$ ]

2-Methyl-4-trans-(4'-chloro)styrylisocarbostyril (7g) was similarly prepared in  $41^{\circ}_{\circ}$  yield, was obtained as white needles, m.p. 155–157 from MeOH [Found: C, 72.9; H, 4.3; N, 4.6; C<sub>18</sub>H<sub>14</sub>CINO requires: C, 73.1, H, 4.7; N, 4.7°<sub>0</sub>,

Methyl trans-3- [4-]2-methyl-3-(3,4-dimethoxyphenyl)isocarbostyryl]propenate (9c). A mixture of 9b (350 mg, 0.00063 mole), palladium acetate (1.13 g; 0.00063 mole) and methyl acrylate (1.0 ml) in MeCN (5.0 ml) was stirred at r.t. overnight. After filtration through keiselguhr the solid was extracted with hot CHCl<sub>3</sub>, the soln dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness to leave a gum which was boiled with MeOH and charcoal, filtered and crystallised to give white needles (50 mg; 20° a) of 9c m.p. 134–135<sup>-1</sup> H NMR (CICl<sub>3</sub>): 8.5-8.6m [1] (C<sub>8</sub>-H), 6.8 × 2m [7] (Ar H's); 6.1d J = 16 Hz [1] (=CH<sup>-1</sup>); 3.95 s and 4.0 s [6] (2 × OCH<sub>3</sub>); 3.75 s [3] (CH<sub>3</sub>O); 3.35 s [3] (NCH<sub>3</sub>). [Found, C, 69.5; H, 5.2; N, 3.2, C<sub>22</sub>H<sub>21</sub>NO<sub>4</sub> requires; C, 69.7, H, 5.5; N, 3.7° a].

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