# Palladium-Catalyzed Coupling Reaction of 3-Bromo Benzo[*b*]furan, -thiophene and -selenophene 2-Carboxaldehyde. Preparation of Tetracyclic Heteroaromatic Derivatives*

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3-Oxo-2,3-dihydrobenzo[*b*]furans, -thiophenes and -selenophenes **1a – c** afforded the bromo-aldehydes **2** under Vilsmeier-Haack-Arnold conditions. Palladium-catalysed aryl-aryl coupling of **2** with *o*-formyl-phenylboronic acid allowed the formation of dialdehydes **3** which underwent McMurry cyclisation or pinacol condensation to yield polycyclic aromatic derivatives **4** or the dihydroxylated compounds **5**.

*Key words:* Vilsmeier-Haack-Arnold Reaction, Suzuki Coupling, McMurry Reaction, Polycyclic Heteroaromatic Derivatives

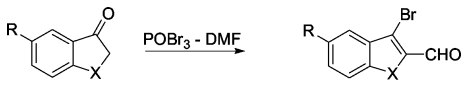
## Introduction

The construction of the $\beta$-haloacrolein moiety *via* the Vilsmeier-Haack-Arnold reaction followed by palladium-catalysed coupling reactions gives access to different types of structures [1 – 6]. Certain tetracyclic heteroaromatic compounds show interesting biological activities, for example as antitumour agents [7]. Using a sequence of Vilsmeier-Haack-Arnold reaction, Suzuki coupling and McMurry cyclisation, we were able to prepare new tetracyclic compounds.

## Results and Discussion

3-Oxo-2,3-dihydro-benzo[*b*]furans, thiophenes and selenophenes **1a – d** are easily available starting materials which underwent the Vilsmeier-Haack-Arnold bromoformylation when treated with $POBr_3$/DMF. 3-Bromo-2-carboxaldehyde derivatives **2a – d** (Scheme 1) were obtained in good yields (80 – 93%). The same reaction can also be run with $POCl_3$ affording the chloro-derivative but the following coupling reaction worked in better yields with the bromo-derivative.

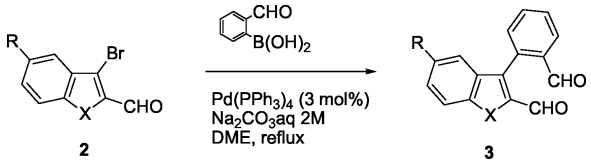
In a second step, the bromo derivatives **2** were coupled with *o*-formyl-phenylboronic acid using




a: X = O R = $OCH_3$
b: X = O R = $SCH_3$
c: X = S R = H
d: X = Se R = H

Scheme 1.

Gronowitz modified Suzuki coupling conditions [8] to give dialdehydes **3** (Scheme 2). When the classical Suzuki conditions were used (toluene, 2M $Na_2CO_3$, 3% $Pd(PPh_3)_4$), degradation of the catalyst occurred shown by the apparition of black palladium. Employing Gronowitz's conditions (DME, 2M $Na_2CO_3$, 3% $Pd(PPh_3)_4$) allows the catalyst to stay stable besides increasing the yields and diminishing the reaction time (about half the time).




**2** **3**

Scheme 2.

Cyclisation of compounds **3a – d** to form the tetracyclic derivatives **4** was performed using the method of McMurry [9, 10]. When the dialdehydes **3a – d** were refluxed in THF in the presence of $TiCl_4$/Zn

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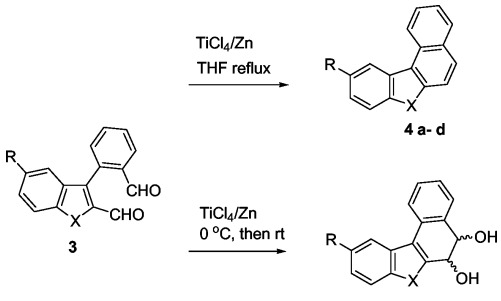
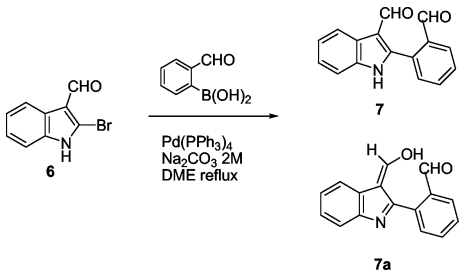



Scheme 3.




Scheme 4.

(Scheme 3), the fully aromatic compounds **4a – d** were obtained in good yields (63 – 93%). When the reaction was started at 0 °C and then continued at room temperature (Scheme 3), the dihydroxylated derivatives **5b – d** were isolated in good yields (66 – 87%).

In the case of indole derivatives, bromoformylation was run on oxindole and gave compound **6** in 74% yield (Scheme 4). Suzuki coupling with *o*-formylphenylboronic acid was achieved in the conditions used above and gave compound **7** in 83% yield. Compound **7** showed a structurally interesting feature as it exists in the indolenine form **7a** which is not suitable for McMurry cyclisation.

In conclusion, the Vilsmeier-Haack-Arnold reaction proves to be very helpful for building interesting polycyclic aromatic frameworks, because it provides an access to difunctionalized derivatives from cyclic ketones.

## Experimental Section

The following spectroscopic and analytical instruments were used: NMR: Bruker AC 250 (solvent $CDCl_3$ or $CDCl_3$/[$D_6$]-DMSO); $\delta$ values in ppm, coupling constants $J$ in Hz). IR: Perkin Elmer 881, $\nu$ in $cm^{-1}$. Elemental analysis were made on a Carlo Erba elemental analyzer Model 1106.

*Synthesis of compounds* **2a** – **d***: General procedure*

To a solution of phosphorus oxybromide (4.3 g, 15 mmol) in chloroform (5 ml) was added DMF (1.1 ml, 15 mmol). The mixture was stirred for 30 min at 0 °C and brought to 20 °C. Then, a solution of **1a – d** (10 mmol) in 15 ml of DMF was added dropwise. The reaction mixture was then heated for 6 h at 70 °C. After cooling, the reaction mixture was poured onto ice-water and neutralized to pH 4 – 5 by addition of sodium acetate. The precipitate was filtered, washed with water and recristallyzed from ethanol-water.

**2a**: 94%, orange solid; m. p. 161 °C. – $^1$H NMR ($CDCl_3$): $\delta$ = 3.89 (s, 3H, OC$H_3$), 7.02 (d, 4-H, $J$ = 2.6), 7.19 (dd, 6-H, $J$ = 2.58 and 9.09), 7.47 (d, 7-H, $J$ = 9.08), 9.94 (CHO). – $C_{10}H_7O_3Br$ (255.06): calcd. C 47.09, H 2.77; found C 47.15, H 2.70.

**2b**: 80%, orange solid; m. p. 117 °C. – $^1$H NMR ($CDCl_3$): $\delta$ = 2.57 (s, SC$H_3$), 7.49 (m, 3H), 9.97 (s, CHO). – $C_{10}H_7O_2BrS$ (271.13): calcd. C 44.30, H 2.60; found C 44.40, H 2.65.

**2c**: 93%, pink solid; m. p. 115 °C. – $^1$H NMR ($CDCl_3$): $\delta$ = 7.53 (m, 5-H, 6-H), 7.93 (dd, 4-H, $J$ = 2.06 and 8.55), 8.11 (dd, 7-H, $J$ = 2.21 and 8.97), 10.21 (s, CHO). – $C_9H_5OBrS$ (241.11): calcd. C 44.83, H 2.09; found C 44.75, H 1.99.

**2d**: 84%, beige solid; m. p. 104 °C. – $^1$H NMR ($CDCl_3$): $\delta$ = 7.51 (m,5-H, 6-H), 7.91 (dd, 4-H, $J$ = 2.05 and 7.59), 8.11 (dd, 7-H, $J$ = 2.26 and 8.10), 10.19 (s,CHO). – $C_9H_5OBrSe$ (288): calcd. C 37.53, H 1.75 ; found C 37.40, H 1.80.

**6**: 74%, beige solid; m. p. 230 °C. – $^1$H NMR ($CDCl_3$/[$D_6$]-DMSO): $\delta$ = 7.03 (m, 5-H, 6-H), 7.19 (dd, 4-H), 8.00 (dd, 7-H), 9.77 (s, CHO), 12.16 (s,NH). – $C_9H_6NOBr$ (224.05): calcd. C 48.25, H 2.70, N 6.25; found C 48.15, H 2.60, N 6.32.

*Preparation of compounds* **3a** – **d***: General procedure*

In a three-necked round bottom flask, 6.95 mmol of **1**, 249 mg of $Pd(PPh_3)_4$ (0.03 eqiv) and 100 ml of DMF were introduced. The solution was degassed for 10 min with argon. Then, *o*-formyl-phenylboronic acid (9.03 mmol) dissolved in a minimum of ethanol and 7 ml of an aqueous solution of 2M $Na_2CO_3$ were added. The reaction mixture was heated at 80 °C until disappearance of the starting material (TLC). At room temperature, the reaction mixture was filtered and 50 ml of brine and 100 ml of ethyl acetate were added to the filtrate. The organic phase was washed with water and 10% sodium hydroxide solution. The solid obtained was purified by recrystallisation or column chromatography on silica gel.

**3a**: 87%, yellow solid; m. p. 112 °C ($CH_2Cl_2$). – IR (KBr): $\nu$ = 1596, 1669. – $^1$H NMR ($CDCl_3$): $\delta$ = 3.77 (s, $OCH_3$), 6.75 (d, 4-H, $J$ = 2.39), 7.22 (dd,6-H, $J$ = 2.45 and 8.87), 7.56 (d, 6'-H, $J$ = 7.20), 7.58 (d, 7-H, $J$ = 8.85), 7.72 (m, 1H), 7.78 (m, 1H), 8.17 (d,3'-H, $J$ = 7.49), 9.73 (s, CHO), 9.98 (s, CHO). – $^{13}$C NMR ($CDCl_3$): $\delta$ = 190.04, 172.12 (CHO),157.54, 150.23, 149.25, 134.98, 131.92, 128.89 (C); 134.25, 132.51, 129.90, 129.02, 121.06, 113.52, 102.09

(CH), 55.69 ($OCH_3$). – $C_{17}H_{12}O_4$ (280.37): calcd. C 72.85, H 4.08; found C 72.60, H 3.90.

**3b**: 89%, yellow solid; m. p. 93 °C ($CH_2Cl_2$). – IR (KBr): $\nu$ = 1674, 1694. – $^1$H NMR ($CDCl_3$) $\delta$ = 2.46 (s, $SCH_3$), 7.28 (d, 4-H, $J$ = 1.77), 7.52 (m, 1H), 7.54 (dd, 6-H, $J$ = 1.83 and 8.87), 7.61 (d, 7-H, $J$ = 8.68), 7.71 (m, 1H), 7.81 (m, 1H), 8.16 (dd, 3'-H, $J$ = 1.27 and 8.06), 9.74 (s, CHO), 9.97 (s, CHO). – $^{13}$C NMR ($CDCl_3$): $\delta$ = 190.31, 179.26 (CHO), 153.43, 148.95, 135.41, 134.99, 131.11, 129.19, 128.20 (C); 134.13, 132.08, 130.25, 129.99, 119.84, 113.29 (CH); 17.17 ($SCH_3$). – $C_{17}H_{12}O_3$ S (296.37): calcd. C 68.90, H 4.08; found C 68.80, H 3.95.

**3c**: 72%, orange solid; m. p. 97 °C ($CH_2Cl_2$). – IR (KBr): $\nu$ = 1648, 1702. – $^1$H NMR ($CDCl_3$): $\delta$ = 7.38 (m, 2H), 7.46 (d, 6'-H, $J$ = 8.19), 7.52 (dd, 4-H, $J$ = 8.04), 7.74 (m, 2H), 8.01 (d, 7-H, $J$ = 7.98), 8.17 (dd, 3'-H, $J$ = 1.31 and 8.06), 9.66 (s, C*H*O), 9.76 (s, CHO). – $^{13}$C NMR ($CDCl_3$): $\delta$ = 190.3, 185.7 (CHO), 146.6, 144.5, 142.9, 142.8, 136.9, 135.6 (C); 134.0, 131.9, 129.8, 128.6, 127.1, 126.5, 125.9 (CH). – $C_{16}H_{10}O_2S$ (266.32): calcd. C 72.16, H 3.78; found C 71.98, H 3.85.

**3d**: 80%, red solid; m. p. 97 °C ($CH_2Cl_2$). – IR (KBr): $\nu$ = 1659, 1701. – $^1$H NMR ($CDCl_3$): $\delta$ = 7.40 (m, 2H), 7.50 (m, 2H), 7.72 (d, 6'-H, $J$ = 7.91), 7.77 (d, 4-H, $J$ = 7.95), 8.01 (d, 7-H, $J$ = 7.70), 8.17 (d, 3'-H, $J$ = 7.31), 9.66 (s, CHO), 9.76 (s, CHO). – $C_{16}H_{10}O_2Se$ (313.98): calcd. C 61.36, H 3.22; found 61.23, H 3.15.

**7a**: 83%; beige solid; m. p. 187 °C ($CH_2Cl_2$/MeOH). – $^1$H NMR ($CDCl_3$/[$D_6$]-DMSO): $\delta$ = 6.85 (s, OH), 6.41 (s, 1H, =CH), 7.14 (m, 2H), 7.35 (m, 2H), 8.02 (m, 4-H – 7-H), 10.33 (s, CHO). – $C_{16}H_{11}NO_2$ (249.26): calcd. C 77.10, H 4.45, N 5.62; found C 77.20, H 4.30, N 5.50.

*Synthesis of compounds* **4a** – **d***: General procedure*

To a suspension of zinc powder (7.48 mmol, 485 mg) in anhydrous THF (5 ml) was added slowly at −10 °C 0.35 ml (3.17 mmol) of $TiCl_4$. The solution was then refluxed and compounds **3a – d** (0.569 mmol) dissolved in THF (20 ml) were added. Reflux was maintained until disappearance of **3** (TLC). After cooling, the reaction mixture was poured into an aqueous solution of $NaHCO_3$ (10%) and extracted with ether. Compounds **4a – d** were purified by column chromatography.

**4a**: 87%, orange solid; m. p. 159 °C ($CH_2Cl_2$/$C_6H_6$). – $^1$H NMR ($CDCl_3$): $\delta$ = 3.98 (s, $OCH_3$), 6.98 (dd, 9-H, $J$ = 2.46 and 8.98), 7.11 (d, 11-H, $J$ = 2.39), 7.51 (d, 8-H, $J$ = 8.95), 7.53 (m, 2H), 7.73 (m, 2H), 8.36 (d, 5-H, $J$ = 8.39), 8.47 (d, 6-H, $J$ = 8.36). – $^{13}$C NMR ($CDCl_3$): $\delta$ = 156.24, 155.49, '152.31, 150.61, 129.47, 125.74, 122.09 (C); 127.93, 123.23, 123.12, 111.89, 111.65, 105.11, 96.27 (CH); 52.26 ($OCH_3$). – $C_{17}H_{12}O_2$ (248.28): calcd. C 82.24, H 4.87; found C 82.32, H 4.80.

**4b**: 93%, yellow solid, m. p. 162 °C ($CH_2Cl_2$/$C_6H_6$). – $^1$H NMR ($CDCl_3$): $\delta$ = 2.65 (s, SC*H*$_3$). 7.51 (dd, 9-H, $J$ = 1.87 and 8.57), 7.56 (td, 3-H), 7.63 (d, 5-H, $J$ = 8.75), 7.73 (td, 2-H), 7.74 (d, 6-H, $J$ = 8.82), 7.94 (d, 4-H, $J$ = 8.90), 8.03 (d, 8-H, $J$ = 8.40), 8.36 (d, 11-H, $J$ = 1.77), 8.58 (d, 1-H, $J$ = 8.17). – $^{13}$C NMR ($CDCl_3$): $\delta$ = 154.8, 154.5, 132.3, 130.5, 129.9, 125.7, 116.7 (C); 129.2, 128.9, 127.7, 127.3, 124.5, 123.6, 123.3, 112.6, 112.2 (CH), 18.4 ($SCH_3$). – $C_{17}H_{12}OS$ (264.34): calcd. C 77.24, H 4.58; found C 77.30, H 4.65.

**4c**: 67%, colourless solid; m. p. 112 °C ($CH_2Cl_2$/$C_6H_6$). – $^1$H NMR ($CDCl_3$): $\delta$ = 7.44 (m, 9-H), 7.58 (m, 3-H – 10-H), 7.71 (m, 12-H), 7.82 (d, 5-H, $J$ = 8.46), 7.96 (d, 6-H, $J$ = 8.58), 8.01 (d, 4-H, $J$ = 8.03), 8.06 (d, 8-H, $J$ = 7.31), 8.91 (d, 4-H, $J$ = 8.03), 8.06 (d, 8-H, $J$ = 7.31), 8.91 (d, 11-H, $J$ = 8.30), 9.03 (d,1-H, $J$ = 8.46). – $^{13}$C NMR ($CDCl_3$): $\delta$ = 129.48, 127.61, 126.96, 126.49, 126.41, 125.31, 125.06, 124.84, 123.82, 123.21 (CH). – $C_{16}H_{10}S$ (234.05): calcd. C 82.01, H 4.30; found C 81.92, H 4.25.

**4d**: 78%, beige solid; m. p. 141 – 144 °C ($CH_2Cl_2$/$C_6H_6$). – $^1$H NMR ($CDCl_3$): $\delta$ = 7.43 (m, 9-H), 7.57 (m, 3-H – 10-H), 7.72 (m, 2-H), 7.82 (d, 5-H, $J$ = 8.55), 7.95 (d, 6-H, $J$ = 8.59), 8.01 (d, 4-H, $J$ = 7.81), 8.04 (d, 8-H, $J$ = 7.72), 8.91 (d,1-H, $J$ = 7.81), 9.05 (d, 11-H, $J$ = 8.45). – $C_{16}H_{10}$ Se (281.21): calcd. C 68.34, H 3.58; found C 68.12, H 3.49.

*Synthesis of compounds* **5b** – **d***: General procedure*

To a suspension of zinc powder (7.48 mmol, 485 mg) in anhydrous THF (5 ml) was added slowly at −10 °C 0.35 ml (3.17 mmol) of $TiCl_4$. Compounds **3b – d** (0.569 mmol) dissolved in 20 ml of THF were added at −10 °C. The reaction mixture was stirred at room temperature until disappearance of compound **3** (TLC). The reaction mixture was poured into an aqueous solution of $NaHCO_3$ and extracted with ether. After drying and evaporating the solvent, the diols **5** were precipitated in petroleum ether.

**5b**: yellow oil, purified by column chromatography with $CH_2Cl_2$ as eluent. – IR (KBr): $\nu$ = 3320. – $^1$H NMR ($CDCl_3$/[$D_6$]-DMSO): $\delta$ = 2.65 (s, SC*H*$_3$), 2.72 (m,OH), 4.10 (m, 6-H), 5.70 (m, OH), 7.35 (d, 9-H, $J$ = 1.72 and 8.52), 7.51 (d, 4-H), 7.54 (m, 2-H), 7.71 (m, 3-H), 8.23 (d, 11-H, $J$ = 1.72), 8.37 (d, 1-H, $J$ = 8.15), 8.44 (d, 8-H, $J$ = 8.53). – $C_{17}H_{14}O_3S$ (282.29): calcd. C 68.44, H 4.73; found C 68.32, H 4.65.

**5c**: 82%, colourless solid; m. p. 206 °C (pet. ether). – IR (KBr): $\nu$ = 3316. – $^1$H NMR ($CDCl_3$/[$D_6$]-DMSO): $\delta$ = 4.59 (m, 5-H, 6-H), 4.83 (m, OH), 5.26 (m ,OH); 7.14 (m, 4H), 7.62 (d, 8-H, $J$ = 7.12), 7.75 (d, 4-H – 11-H), 8.09 (d, 1-H, $J$ = 8.01). – $^{13}$C NMR ($CDCl_3$/[$D_6$]-DMSO): $\delta$ = 148.24, 141.31, 139.05, 137.50, 131.15, 129.70 (C); 126.80, 126.22, 125.83, 125.01, 124.30, 123.84, 122.62 (CH); 74.31,

74.03 (CH). – $C_{16}H_{12}O_2S$ (268.33) calcd. C 71.62, H 4.51; found C 71.50, H 4.40.

**5d**: 87%, colourless solid; m. p. 209 °C (pet. ether). – IR (KBr): $\nu = 3326$. – $^1$H NMR ($CDCl_3$/[$D_6$]-DMSO): $\delta = 4.67$ (m, 5-H, 6-H), 4.80 (d, OH, $J = 4.20$), 5.22 (d, OH, $J = 4.20$), 7.16 (m, 4H), 7.59 (d, 11-H, $J = 7.15$), 7.74 (m, 2H), 8.09 (d,1-H, $J = 8.01$). – $^{13}$C NMR ($CDCl_3$/[$D_6$]-DMSO): $\delta = 148.20$, 141.42, 140.6, 139.04, 137.53, 131.25 (C); 126.9, 126.3, 125.0, 124.4, 123.9, 123.5, 122.7 (CH); 74.42, 74.20 (CH). – $C_{16}H_{12}O_2Se$ (315.23): calcd. C 60.96, H 3.84; found C 60.82, H 3.75.

[1] S. Deprets, G. Kirsch, Heterocyclic Commun. **5**, 275 (1999).
[2] S. Deprets, G. Kirsch, Eur. J. Org. Chem. 1353 (2000).
[3] S. Deprets, G. Kirsch, Heterocyclic Commun. **7**, 421 (2001).
[4] S. Hesse, G. Kirsch, Tetrahedron Lett. **43**, 1213 (2002).
[5] S. Deprets, G. Kirsch, Arkivoc i 40 – 48 (2002).
[6] S. Hesse, G. Kirsch, Synthesis 717 (2003).
[7] G. Kirsch, Curr. Org. Chem. **5**, 507 (2001).
[8] S. Gronovitz, V. Bolosik, S. Lavitz, Chem. Scr. **23**, 120 (1984).
[9] J. E. McMurry, Chem. Rev. **89**, 1513 (1989).
[10] D. Lenoir, Synthesis 553 (1977).