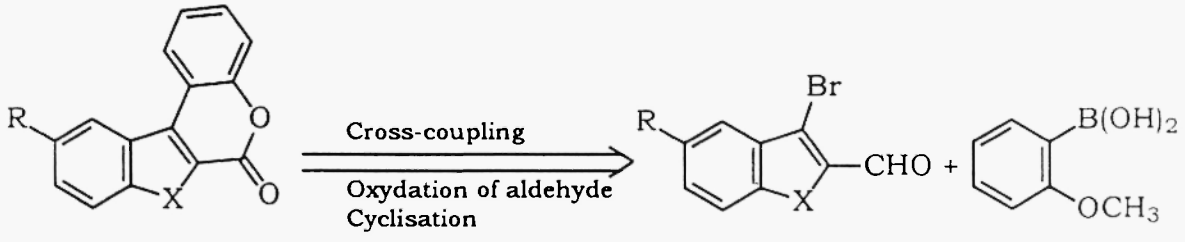
SYNTHESIS OF NEW HETEROCYCLIC ANALOGUES OF ISOCOUMESTANE

S. Deprets, G. Kirsch*
Groupe de Synthèse Organique et Hétérocyclique
Laboratoire de Chimie Organique, Université de Metz, Ile du Saulcy
F-57012 METZ Cedex 01

Abstract : The synthesis of substituted Isocoumestan and heterocyclic analogues, obtained by replacing ring B by thiophene and selenophene, is reported.

Introduction :

Condensed polycyclic derivatives containing the coumarin ring system are of interest due to their biological effects (1). One such compound, Coumestrol (3,9-dihydroxybenzofuro[3,2-c][1]benzopyran-6(H)-one), a natural product obtained from *Ladino clover* and *alfalfa*, has been reported to possess estrogenic activity (2). There are many reports in literature for the synthesis of Isocoumestan (3). In this paper, we present a novel approach to the preparation of substituted Isocoumestan 1 and new analogues of this compound 2 involving a cross-coupling strategy (Scheme 1).

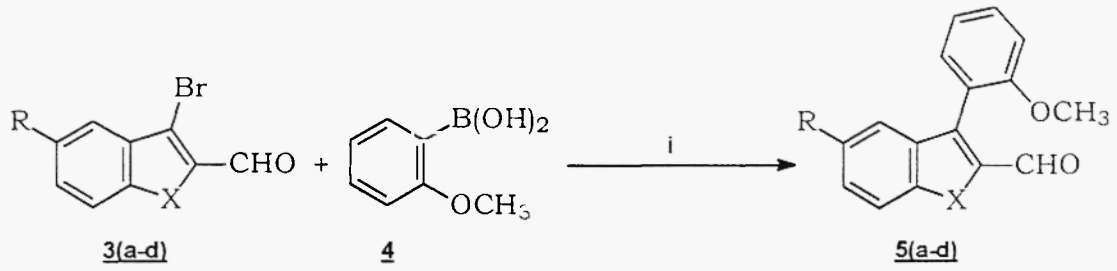


X = O R = -OCH_3 1
X = S, Se R = H 2

Scheme 1

Results and discussion :

Palladium-catalysed cross-coupling between diversely substituted 3-bromo-2-formylbenzo[b]furanes, -thiophene and -selenophene **3(a-d)** (4) and 2-methoxyphenyl boronic acid **4** using a modification of Suzuki's procedure (5) afforded the biaryls **5(a-d)** in high yields (Scheme 2, Table I).



3(a-d) 4 5(a-d)

Reagents and conditions : **i** : $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 2N (2 éq.), DME, reflux

Scheme 2

Table I : Suzuki's cross-coupling reaction

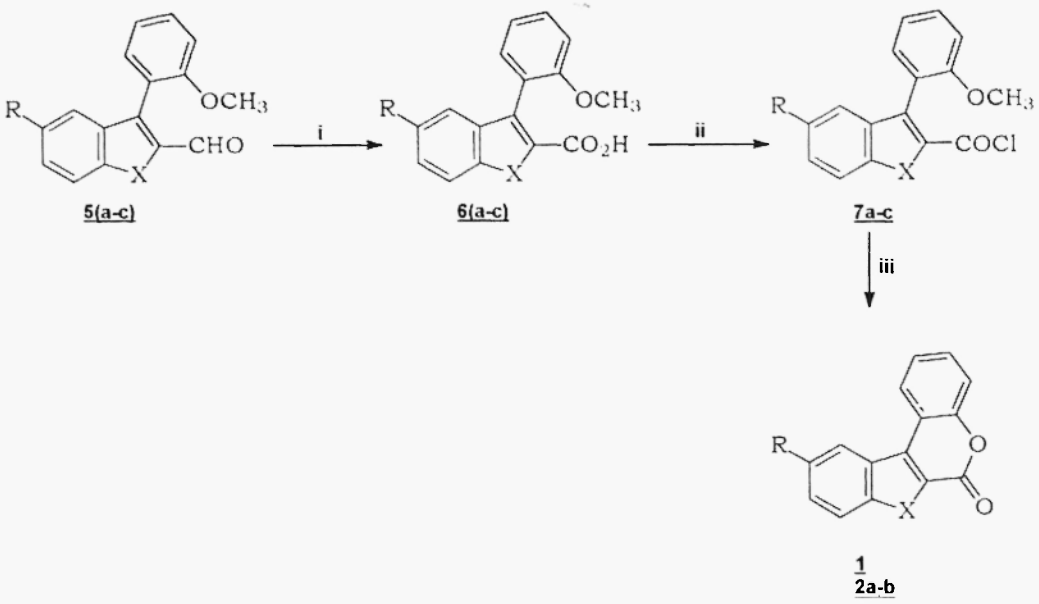
R	X	Product	Yield (%)
OCH_3	O	**5a**	97
H	S	**5b**	91
H	Se	**5c**	60

Oxidation of aldehydes **5a-c** with sodium chlorite (6) in the presence of 30% H_2O_2 in acetonitrile at room temperature allowed the formation of acids **6a-c** (Table II).

Table II : Oxidation of aldehydes 5(a-c)

R	X	Product	Yield (%)
OCH_3	O	**6a**	88
H	S	**6b**	81
H	Se	**6c**	94

Conversion of the acids **6(a-c)** to substituted Isocoumestan **i** and their heterocyclic analogues **2** was best achieved by treating the corresponding acyl chlorides **7(a-c)** with aluminium chloride in dichloromethane at room temperature (Scheme 3, Table III). This method gave better yields than the others previously used for the synthesis of Isocoumestan : HBr / AcOH (3a), Py / HCl (3b).



Reagents and conditions : **i** : $NaClO_2$, H_2O_2 30%, CH_3CN, r.t. ; **ii** : $SOCl_2$, CH_2Cl_2, reflux ; **iii** : $AlCl_3$, CH_2Cl_2, r.t.

Scheme 3

Table III : Cyclisation of acyl chlorides 7(a-c)

R	X	Product	Yield (%)
OCH_3	O	**1**	97
H	S	**2a**	83
H	Se	**2b**	94

Experimental section :

General : Melting points were determined on a KOFLER bench and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 250 MHz instrument. Infrared spectra (IR) were measured on a PERKIN-ELMER 881 spectrometer and are reported in wavenumbers (cm^{-1}). Compounds **3(a-c)** were prepared as described in reference (4). CH_3CN was distilled over potassium carbonate. DME was distilled over lithium aluminium hydride.

General procedure for the Suzuki's cross-coupling reaction :

Bromo derivatives **3a-c** (1g, 1 eq.) were dissolved in DME (50 ml) and purged with N_2. $Pd(PPh_3)_4$ (3 mol %) was added, and the mixture stirred (15 minutes), and treated with sodium carbonate 2M (2eq.), at which time the solution became cloudy. 2-Methoxyphenyl boronic acid (1.1 eq.) was added as a solid. The solution was heated under reflux until **3a-c** had disappeared (TLC). The solvent was removed under vacuum and the residue extracted with ether. The organic layer was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give **5a-c**.

5-Methoxy-3-(2-methoxyphenyl)benzo[b]furane-2-carbaldehyde **5a** :

Yield : 97% ; m.p. 118°C ; ^1H NMR ($CDCl_3$) : δH : 3.80 (s, 3H, OCH_3) ; 6.95 (d, 1H, Ar, J = 2.47 Hz) ; 7.11 (m, 2H, Ar) ; 7.17 (dd, 1H, J = 2.51 Hz, 8.50 Hz) ; 7.45 (d, 1H, J = 2.47 Hz) ; 7.11 (m, 2H, Ar) ; 7.17 (dd, 1H, Ar, J = 2.51 Hz, 8.50 Hz) ; 7.45 (d, 1H, Ar, J = 8.48 Hz) , 7.52 (d, 2H, Ar, J = 8.75 Hz) ; 9.72 (s, 1H, CHO) ; ^{13}C NMR ($CDCl_3$) : δC : 55.5 ; 55.9 ; 103.7 ; 111.5 ; 113.3 ; 119.3 ; 119.4 ; 120.9 ; 128.1 ; 130.1 ; 130.8 ; 132.0 ; 148.6 ; 150.6 ; 156.2 ; 157.0 ; IR (KBr) : 1670 (CO) cm^{-1}.

3-(2-Methoxyphenyl)benzo[b]thiophene-2-carbaldehyde **5b** :

Yield : 91% ; ^1H NMR ($CDCl_3$) : δH : 3.77 (s, 3H, OCH_3) ; 7.08 (m, 1H, Ar) ; 7.11 (m, 1H, Ar) ; 7.33 (d, 1H, Ar, J = 7.21 Hz) ; 7.36 (d, 1H, Ar, J = 7.32 Hz) ; 7.43 (m, 2H, Ar) ; 7.56 (d, 1H, Ar , J = 8.21 Hz) ; 7.95 (d, 1H, Ar, J =) 7.84 Hz) ; 9.71 (s, 1H, CHO) ; ^{13}C NMR ($CDCl_3$) : δC : 55.6 ; 111.4 ; 120.6 ; 122.6 ; 125.0 ; 126.2 ; 127.5 ; 127.9 ; 130.6 ; 132.0 ; 142.2 ; 142.9 ; 143.0 ; 147.4 , 157.3 ; 187.2 ; IR (KBr) : 1673 (CO) cm^{-1}.

3-(2-Methoxyphenyl)benzo[b]selenophene-2-carbaldehyde **5c** :

Yield : 60% ; m.p. 119°C ; ^1H NMR : δH : 3.75 (s, 3H, OCH_3) ; 7.10 (m, 2H, Ar) , 7.43 (m, 5H, Ar) ; 7.95 (d, 1H, Ar, J = 7.77 Hz) ; 9.70 (s, 1H, CHO) ; ^{13}C NMR ($CDCl_3$) : δC : 55.6 ; 111.4 ; 120.6 ; 122.6 ; 126.2 ; 127.5 ; 127.9 ; 130.6 ; 131.9 ; 136.8 ; 142.2 ; 142.9 ; 147.4 ; 157.3 , 164.5 ; 187.2 ; IR (KBr) : 1654 (CO) cm^{-1}.

General oxidation procedure with $NaClO_2$:

A solution of 245 mg (2.22 mmoles, 1.4 eq.) of $NaClO_2$ in 2.3 ml of water was added dropwise to a stirred mixture of aldehyde **5a-c** (1.59 mmole, 1 eq.) in 7 ml of acetonitrile, 70 mg (0.477 mmole, 0.3 eq.) of NaH_2PO_4 in 0.65 ml of water and 0.79 ml (7.95 mmoles, 5 eq.) of 30% H_2O_2, keeping

the temperature at 10°C. Oxygen evolved from the solution was monitored until the end of the reaction (about 2 hours). A small amount of Na_2SO_3 was added to destroy the unreacted HOCl and H_2O_2. After acidification with 10% aqueous HCl, the precipitated acids **6a-c** were collected and recrystallized from water.

5-Methoxy-3-(2-methoxyphenyl)benzo[b]furane-2-carboxylic acid **6a** :

Yield : 88% ; m.p. 179°C ; ^{1}H NMR ($CDCl_3$-DMSO) : δH : 3.77 (2s, 6H, OCH_3) ; 6.82 (d, 1H, Ar, J = 2.25 Hz) ; 7.07 (m, 3H, Ar) ; 7.45 (m, 3H, Ar) ; ^{13}C NMR ($CDCl_3$-DMSO) : δC : 55.5 ; 55.9 ; 103.2 ; 111.5 ; 112.9 ; 118.4 ; 119.6 ; 120.5 ; 127.0 ; 128.9 ; 130.1 ; 131.3 ; 150.0 ; 156.5 ; 156.6 ; 157.0; 163.4.

3-(2-Methoxyphenyl)benzo[b]thiophene-2-carboxylic acid **6b** :

Yield : 72% ; m.p. 229°C ; ^{1}H NMR ($CDCl_3$-DMSO) : δH : 3.58 (s, 3H, OCH_3) ; 6.88 (d, 1H, Ar, J = 8.38 Hz) ; 6.94 (d, 1H, Ar, J = 7.54 Hz) ; 7.09 (dd, 1H, Ar, J = 1.68 Hz, 7.33 Hz) ; 7.24 (m, 4H, Ar) ; 7.79 (d, 1H, Ar, J = 7.53 Hz) ; IR (KBr) : 2841 (OH) ; 1661 (CO) cm-1.

3-(2-Methoxyphenyl)benzo[b]selenophene-2-carboxylic acid **6c** :

Yield : 94% ; m.p. 223°C ; ^{1}H NMR : δH : 3.53 (s, 3H, OCH_3) ; 6.86 (m, 2H, Ar) ; 7.02 (dd, 1H, Ar, J = 1.63 Hz, 7.50 Hz) ; 7.20 (m, 4H, Ar) ; 7.74 (d, 1H, Ar, J = 7.75 Hz).

General Procedure for Synthesis of 2H-Benzoheteraryl[2,3-c][1]benzopyran-6-ones **1** and **2a-b** :

To a solution of acids **6a-c** (0.3 mmole, 1 eq.) in anhydrous methylene chloride (5 ml) was added thionyl chloride (0.45 mmole, 1.5 eq.). The mixture was then refluxed over 1 hour and concentrated in vacuo to afford the acyl chloride quantitatively. To a suspension of aluminium chloride (0.9 mmole, 3 eq.) in anhydrous methylene chloride (3 ml) was added dropwise, at 0°C, a solution of the acyl chloride (0.3 mmole, 1 eq.) in anhydrous methylene chloride (2 ml). The mixture was allowed to stir at room temperature for 10 hours and then hydrolysed with 10 ml of hydrochloric acid 0.1 N. The aqueous layer was extracted with methylene chloride (3× 5ml). The organic phase was dried over sodium sulfate and concentrated under reduce pressure. The residue was then purified by column chromatography on silica gel (eluent : methylene chloride / Petroleum ether (1/1)).

10-Methoxy-2H-benzofuro[2,3-c][1]benzopyran-6-one **1** :

Yield : 97% ; m.p. 209°C ; ^{1}H NMR ($CDCl_3$) : δH : 3.98 (s, 3H, OCH_3) ; 7.27 (dd, 1H, Ar, J = 2.49 Hz, 9.11 Hz) ; 7.49 (m, 3H, Ar) ; 7.58 (d, 1H, Ar, J = 2.45 Hz) ; 7.66 (d, 1H, Ar, J = 9.20 Hz) , 8.13 (dd, 1H, Ar, J = 8.18 Hz) ; ^{13}C NMR ($CDCl_3$) : δC : 56.1 ; 104.5 ; 113.6 , 114.0 ; 117.1 ; 117.7 ;

119.2 , 123.0 , 123.9 ; 124.9 ; 127.3 ; 129.6 ; 139.3 ; 152.1 ; 152.5 ; 157.3 ; IR (KBr) : 1724 (CO) cm^{-1}.

2H-Benzothieno[2,3-c][1]benzopyran-6-one **2a** :

Yield : 83% ; m.p. 192°C ; ^1H NMR ($CDCl_3$) : δH : 7.55 (m, 5H, Ar) ; 8.06 (d, 1H, Ar, J = 1.56 Hz, J = 8.25 Hz) ; 8.56 (d, 1H, Ar, J = 8.26 Hz) ; 8.73 (dd, 1H, Ar, J = 1.35 Hz, 8.15 Hz) ; ^{13}C NMR ($CDCl_3$) : δC : 118.2 ; 119.1 ; 123.3 ; 124.6 ; 126.0 ; 127.0 ; 127.5 ; 128.1 ; 129.2 ; 129.9 ; 137.7 ; 141.8 ; 145.2 ; 153.0 ; 158.9 ; IR (KBr) : 1730 (CO)cm^{-1}.

2H-Benzoseleno[2,3-c][1]benzopyran-6-one **2b** :

Yield : 94% ; m.p. 198°C ; ^1H NMR ($CDCl_3$) : δH : 7.46 (m, 1H, Ar) ; 7.60 (m, 3H, Ar) ; 7.64 (dd, 1H, Ar, J = 1.85 Hz, 8.04 Hz) ; 8.10 (d, 1H, Ar, J = 7.29 Hz) ; 8.58 (d, 1H, Ar, J = 7.83 Hz) ; 8.75 (d, 1H, Ar, J = 7.75 Hz) ; ^{13}C NMR ($CDCl_3$) : δC : 118.3 ; 119.3 ; 123.4 ; 124.7 ; 126.1 ; 127.1 ; 127.6 ; 128.2 ; 129.4 ; 130.0 ; 137.9 ; 141.9 ; 145.3 ; 153.2 ; 159.5 ; IR (KBr) : 1718 (CO) cm^{-1}.

References :

(1) D. Lednicer, S.C. Lysler, G.W. Duncan, J. Med.Chem., **8**, 725, (1965)

(2) E.M. Bickoff, A.L. Livington, A.N. Booth, Arch.Biochem.Biophys., **88**, 262, (1960)

(3) **a)** J.N. Chatterjea, K. Achari, N.C. Jain, J. Indian Chem.Soc., **47**, 590 (1970) ;

b) U.K. Joshi, R.M. Kelkar, M.V. Paradkar, Indian J.Chem., **23B**, 456, (1984)

c) H.I. King, R.H. Holland, F.P. Reed, A. Robertson, J.Chem.Soc. 1672, (1948)

d) V.K. Mahesh, M. Maheshwari, R.S. Sharma, Indian J.Chem. **19B**, 129 (1980)

e) N. Someshwari, K. Shrihari, V. Sundaramurthy, Synthesis, **9** , 605 (1977)

(4) Z. Arnold, J. Zemlicka, Collect. Czech. Chem. Comm., **24**, 2385, (1959)

(5) **a)** For a review see : N. Miyaura, A. Suzuki, Chem. Rev. **95**, 2457, (1995)

b) S. Gronowitz, K. Lavitz, Chem.Scr. **24** , 5, (1984)

c) S. Gronowitz, V. Bobosik, K. Lavitz, Chem. Scr. **23** , 120, (1984)

(6) F. Montanari, J. Org. Chem. **51** , 567, (1986).

Received on April 24, 1999