A first synthesis of isothiocoumestan and heterocyclic analogues

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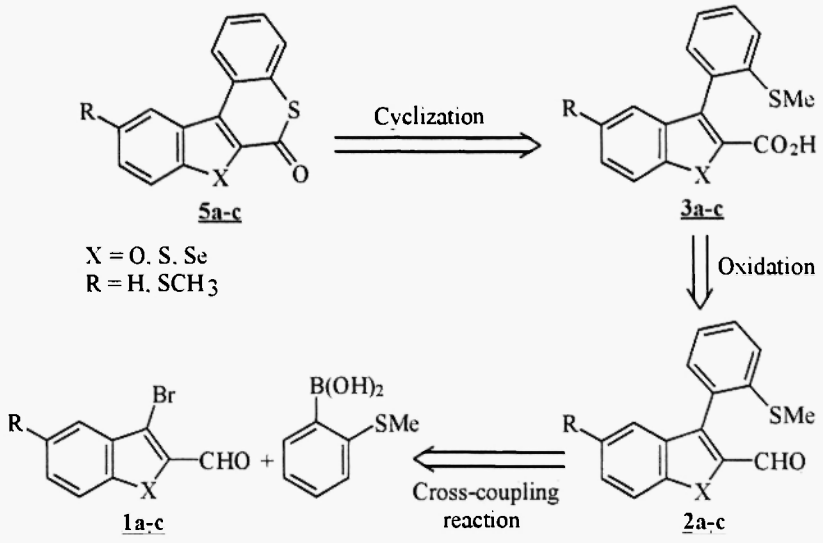
Abstract : Substituted isothiocoumestan **5a** and heterocyclic analogues **5b-c**, obtained by replacing ring B by different heterocycles like thiophene and selenophene, were prepared.

Introduction :

Though there are many reports in literature for the synthesis of isocoumestans (1-6) , none are available for the synthesis of isothiocoumestans. In this paper, we present a method, based on a cross-coupling strategy applied to haloformylheterocycles to access to isothiocoumestans and analogues. Thus 2H-benzofuro[2,3-c][1]benzothiopyran-6-one, 2H-benzothieno[2,3-c][1]benzothiopyran-6-one and 2H-benzoseleno[2, 3-c][1]benzothiopyran-6-one were prepared.

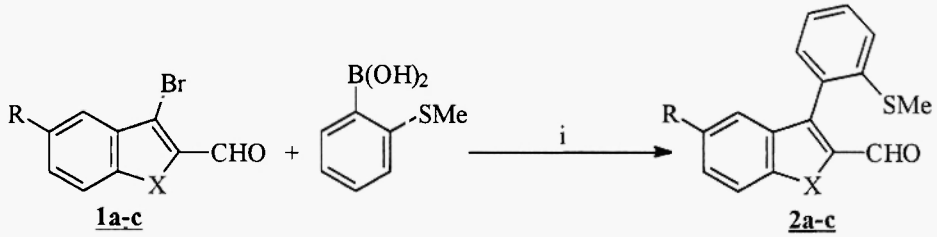
Results and discussion :

2H-benzoheteroaryl[2, 3-c][1]benzothiopyran-6-one **5** were prepared by intramolecular cyclization of acids **3** obtained from aldehydes **2** (Scheme 1).



Scheme 1

3-[2-Methylthiophenyl]-benzo[b]furane(-thiophene or -selenophene)-2-carboxaldehydes **2a-c**, key compounds in this strategy, were prepared by palladium-catalysed cross-coupling reaction of the appropriate 3-bromo-benzo[b]furane (-thiophene or -selenophene)-2-carboxaldehydes **1a-c** (7) with 2-methylthiophenyl boronic acid under Suzuki cross-coupling conditions (8) (Scheme 2).

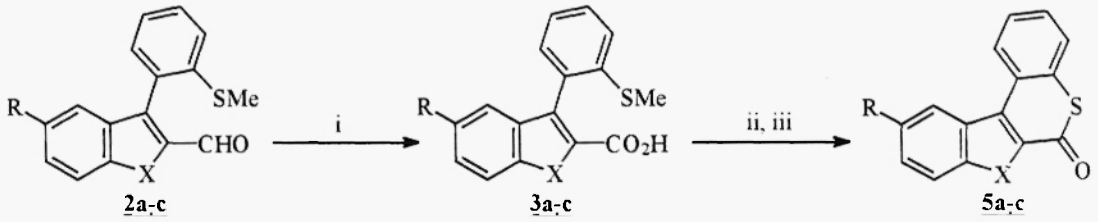


Reagents and conditions : **i** : $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 2N (2 eq.), DME, reflux (**2a** : X=O, R=-SMe, 81% ; **2b** : X=S, R=-H, 69% ; **2c** : X=Se, R=H, 79%)

Scheme2

Oxidation of aldehydes **2a-c** with sodium chlorite in the presence of 30% H_2O_2 in acetonitrile (9) at room temperature led to the oxidation of both the formyl and the methylthio group. Oxidation of the aldehyde only was successful using silver oxide in a mixture of water and dimethyl sulfoxide (Scheme 3 ; Table 2).

Conversion of acids **3(a-c)** to substituted isothiocoumestans and heterocyclic analogues was best achieved by treating the corresponding acyl chlorides **4(a-c)** with aluminium chloride in dichloromethane at room temperature (Scheme 3 ; Table II).



2a-c **3a-c** **5a-c**

Reagents and conditions : **i** : $AgNO_3$, NaOH, H_2O, DMSO, r.t. ; **ii** : $SOCl_2$, CH_2Cl_2, reflux ; **iii** : $AlCl_3$ (3 eq.), CH_2Cl_2, 0°C to r.t.

Scheme 3

Table II. Oxidation of aldehydes 2a-d and cyclization of acyl chlorides 4a-d

R	X	Yield of oxidation (%)	Product	Yield of cyclization (%)	Product
$-SCH_3$	O	88	**3a**	83	**5a**
-H	S	91	**3b**	81	**5b**
-H	Se	78	**3c**	67	**5c**

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 **1(a-c)** were prepared as described in reference (7). CH_3CN was distilled over potassium hydroxyde. DME was distilled over lithium aluminium hydride.

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

Bromo derivatives **1a-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 was stirred (15 minutes), and treated with sodium carbonate 2M (2eq.). 2-Methylthiophenyl boronic acid (1.1 eq.) was added as a solid. The solution was heated to reflux until **1a-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 **2a-c**.

5-Methylthio-3-(2-methylthiophenyl)benzo[b]furane-2-carbaldehyde 2a :

Yield : 81% ; m.p. 88°C ; ^{1}H NMR ($CDCl_3$) : δH : 2.41 (s, 3H, SCH_3) ; 2.48 (s, 3H, SCH3) ; 7.34 (m, 2H, ArH) ; 7.38 (m, 2H, ArH) ; 7.50 (m, 2H, ArH) ; 7.57 (d, 1H, ArH) ; 9.67 (s, 1H, CHO) ; ^{13}C NMR ($CDCl_3$) : δC : 15.8 ; 17.4 ; 113.2 ; 121.1 ; 125.0 , 125.8 , 130.0 , 130.1 ; 131.3 ; 127.2 ; 128.2 ; 131.2 ; 134.2 ; 139.4 ; 148.6 ; 153.9 ; 175.4 ; IR (KBr) : 1677 (CO) cm^{-1}.

3-(2-Methylthiophenyl)benzo[b]thiophene-2-carbaldehyde 2b :

Yield : 69% ; m.p. 89°C ; ^{1}H NMR ($CDCl_3$) : δH : 2.35 (s, 3H, SCH_3) ; 7.29(m, 2H, ArH) ; 7.36 (d, 2H, ArH, J = 7.77 Hz) ; 7.45 (m, 2H, ArH) ; 7.48 (d, 1H, ArH, J = 7.49 Hz) ; 7.97 (d, 1H, ArH, J = 7.70 Hz) ; 9.63 (s, 1H, CHO) ; ^{13}C NMR ($CDCl_3$) : δC : 15.8 ; 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) : 1648 (CO) cm^{-1}.

3-(2-Methylthiophenyl)benzo[b]selenophene-2-carbaldehyde 2c :

Yield : 79% , m.p. 94°C ; ^{1}H NMR : δH : 2.35 (s, 3H, SCH_3) ; 7.30 (m, 2H, Ar) ; 7.36 (d, 2H, ArH, J = 7.69Hz) ; 7.45 (m, 1H, ArH) ; 7.48 (d, 1H, ArH, J = 7.74 Hz) ; 7.50 (m, 1H, ArH) ; 7.97 (d, 1H, ArH, J = 7.46 Hz) ; 10.21 (s, 1H, CHO) ; ^{13}C NMR ($CDCl_3$) : δC :15.6 , 124.6 ; 125.2 ; 125.3 ; 126.3 ; 127.2 ; 128.2 ; 129.6 ; 130.7 ; 132.3 ; 139.4 ; 141.7 ; 143.2 ; 142.6 ; 148.8 , 186.6 ; IR (KBr) : 1677 (CO) cm^{-1}.

General oxidation procedure with Ag_2O :

A solution of $AgNO_3$ (17.05 mmol, 4.1 eq.) in 3 ml of distilled water was added dropwise to a stirred mixture of NaOH (8.71 mmol, 2.1 eq.) in 3ml of distilled water. Aldehyde **2a-c** (4.15 mmol, 1 eq.) in DMSO was added to the solution of Ag_2O in water. The solution was stirred at room temperature until **2a-c** had

disappeared (TLC). Acidification with 10% aqueous HCl and the precipitated acids **3a-c** were collected and recrystallized in water.

5-Methylthio-3-(2-methylthiophenyl)benzo[b]furane-2-carboxylic acid 3a :

Yield : 88% ; m.p. 184°C ; ^{1}H NMR ($CDCl_3$-DMSO) : δH : 2.37 (2s, 6H, SCH_3) ; 6.82 (d, 1H, Ar, J = 2.25 Hz) ; 7.07 (m, 3H, ArH) ; 7.45 (m, 3H, ArH) ; ^{13}C NMR ($CDCl_3$-DMSO) : δC : 15.9 ; 17.6 ; 55.87 ; 103.21 ; 111.54 ; 112.95 ; 118.36 ; 119.59 ; 120.48 ; 126.96 ; 128.95 ; 130.1 ; 131.29 , 149.99 ; 156.48 ; 156.56 ; 157.03 ; 163.36 ; IR (KBr) : 2742 (OH) ; 1682 (CO) cm^{-1}.

3-(2-methylthiophenyl)benzo[b]thiophene-2-carboxylic acid 3b :

Yield : 91% ; m.p. 207°C ; ^{1}H NMR ($CDCl_3$-DMSO) : δH : 2.32 (s, 3H, SCH_3) ; 7.15 (dd, 1H, ArH, J = 1.06, 8.36 Hz) ; 7.27 (m, 2H, ArH) ; 7.30 (d, 1H, ArH, J = 7.82 Hz) ; 7.35 (d, 1H, ArH, J = 8.02 Hz) ; 7.42 (m, 2H, ArH) ; 7.93 (d, 1H, ArH, J = 7.92 Hz) ; IR (KBr) : 2799 (OH) ; 1652 (CO) cm^{-1}.

3-(2-methylthiophenyl)benzo[b]selenophene-2-carboxylic acid 3c :

Yield : 78% ; m.p. 209°C ; ^{1}H NMR ($CDCl_3$-DMSO) : δH : 2.33 (s, 3H, SCH_3) ; 7.15 (dd, 1H, ArH, J = 0.93, 8.18 Hz) ; 7.26 (m, 1H, ArH) ; 7.28 (m, 1H, ArH) ; 7.34 (d, 1H, ArH, J = 8.32 Hz) ; 7.37 (m, 2H, ArH) ; 7.43 (d, 1H, ArH, J = 7.32 Hz) ; 7.94 (d, 1H, ArH, J = 8.27 Hz) ; ^{13}C NMR ($CDCl_3$-DMSO) : δC : 15.16 ; 123.4 ; 125.3 ; 126.0 ; 126.2 ; 127.2 ; 129.5 ; 129.7 ; 130.7 ; 133.3 , 136.1 ; 139.3 ; 142.5 ; 142.8 , 143.9 ; 164.0.

General Procedure for Synthesis of 2H-Benzoheteraryl[2,3-c][1]benzothiopyran-6-ones **5a-c** :

To a solution of acids **3a-c** (0.3 mmol, 1 eq.) in anhydrous methylene chloride (5 ml) was added thionyl chloride (0.45 mmol, 1.5 eq.). The mixture was then refluxed over 1 hour and concentrated in vacuo to afford the acyl chloride **4a-c** quantitatively. To a suspension of aluminium chloride (0.9 mmol, 3 eq.) in 3 ml of anhydrous methylene chloride was added dropwise, at 0°C, a solution of the acyl chloride (0.3 mmol, 1 eq.) in 2 ml of anhydrous methylene chloride. The mixture was stirred at room temperature for 10 hours and hydrolysed with 10 ml of hydrochloric acid 0.1 N. The aqueous layer was extracted with methylene chloride (3×5ml), dried over sodium sulfate and evaporated under reduced pressure. The residue was then purified on silica gel (eluent : methylene chloride / petroleum ether (1/1)).

10-Methylthio-2H-benzofuro[2,3-c][1]benzothiopyran-6-one 5a :

Yield : 83% ; m.p. 225°C ; ^{1}H NMR ($CDCl_3$) : δH : 2.63 (s, 3H, SCH_3) ; 7.61 (m, 4H, ArH) ; 7.67 (d, 1H, ArH, J = 8.77 Hz) ; 8.28 (s, 1H, ArH) ; 8.46 (dd, 1H, ArH, J = 8.38 Hz) ; ^{13}C NMR ($CDCl_3$) : δC : 17.94 ; 113.79 , 122.04 ; 124.81 ; 125.40 ; 126.26 ; 127.05 ; 127.59 ; 128.21 ; 130.17 ; 134.84 ; 135.04 ; 144.77 ; 154.37 ; IR (KBr) : 1718 (CO) cm^{-1}.

2H-Benzothieno[2,3-c][1]benzothiopyran-6-one 5b :

Yield : 81% ; m.p. 181°C ; ^{1}H NMR ($CDCl_3$) : δH : 7.54 (m,4H, ArH) ;7.65 (dd, 1H, ArH, J = 2.38, 8.04 Hz) ; 8.06 (dd, 1H, ArH, J = 1.82, 8.29 Hz) ; 8.73 (d, 2H, ArH, J = 7.68 Hz) ; ^{13}C NMR ($CDCl_3$) : δC : 125.54 , 126.55 ; 126.90 ; 126.86 ; 126.97 ; 127.11 ; 127.83 ; 127.87 ; 128.27 ; 134.19 , 135.36 ; 139.63 ; 142.34 ; 144.03 ; 161.10 ; IR (KBr) : 1708 (CO)cm^{-1}.

2H-Benzoseleno[2,3-c][1]benzothiopyran-6-one 5c :

Yield : 67% ; m.p. 182°C , ^{1}H NMR ($CDCl_3$) : δH : 7.59 (m, 4H, ArH) ; 7.66 (dd, 1H, ArH, J = 7.72 Hz) ; 8.05 (dd, 1H, ArH, J = 7.73 Hz) , 8.72 (d, 2H, J = 7.07 Hz) ; ^{13}C NMR ($CDCl_3$) : δC : 118.29 ; 119.27 ; 123.44 ; 124.67 ; 126.09 ; 127.11 ; 127.61 ; 128.20 ; 129.42 ; 129.97 ; 137.92 ; 141.91 ; 145.35 ; 153.22 ; 159.50 ; IR (KBr) : 1701(CO) cm^{-1}.

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