Synthesis of 5-Methylbenzo[*b*]thieno[2,3-*c*]isoquinolines and 5-Methylbenzo[*b*]seleno[2,3-*c*]isoquinolines

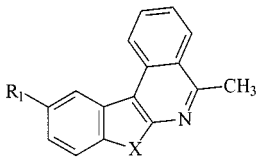
Stéphanie Deprets[a] and Gilbert Kirsch*[a]

Keywords: Heterocycles / Rearrangements / Stille coupling / Suzuki coupling / Bischler–Napieralski cyclization / Isoquinolines

5-Methylbenzo[*b*]thieno[2,3-*c*]isoquinolines and 5-methylbenzo[*b*]seleno[2,3-*c*]isoquinolines **11b**,**c** have been prepared by Bischler–Napieralski cyclization of 2-acetamido-3-phenylbenzo[*b*]heteroarenes.

Introduction

Though there are many reports in the literature concerning the synthesis of 6-methylbenzo[*b*]heteroaryl[2,3-*c*]quinolines,[1] none of these methods are applicable to the synthesis of annelated isoquinoline derivatives **11**. In this paper, we describe the synthesis of 5-methylbenzo[*b*]thieno[2,3-*c*]isoquinolines and 5-methylbenzo[*b*]seleno[2,3-*c*]-isoquinolines **11b**,**c**, as well as an attempt to synthesize the 5-methylbenzo[*b*]furo[2,3-*c*]isoquinolines **11a**. Our strategy is based on a cross-coupling starting from 2-acetyl-3-bromo (or trifluoromethanesulfonyl)benzo[*b*]heterocycles **2a**,**b** and **3b**,**c** or from 2-carbaldehyde-3-bromobenzo[*b*]heterocycles **7a–c**.

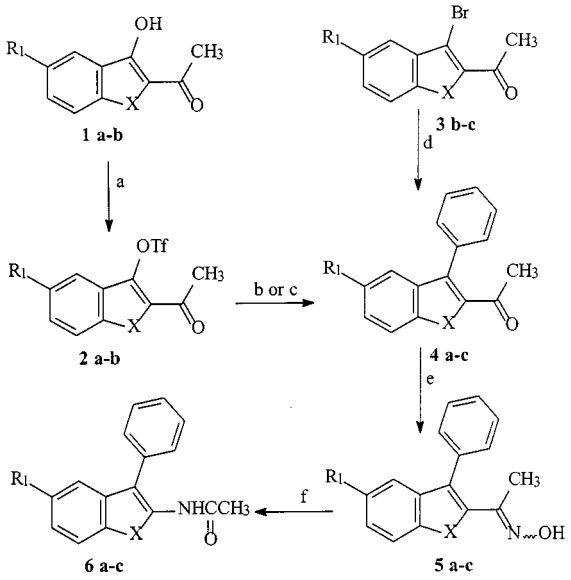


X = O,S,Se
R^1 = H,SCH_3
11

The synthesis of the acetamido derivatives **6a–c**, which are central to our strategy, was achieved starting from either the triflates **2a**,**b**, the bromo derivatives **3b**,**c** (Scheme 1), or the 2-carbaldehyde-3-bromobenzo[*b*]heterocycles **7a–c** (Scheme 2).

Results and Discussion

Treatment of the triflates **2a**,**b** (obtained from **1a**,**b**) with phenyltributylstannane in the presence of catalytic amounts of Pd^0 and 3 equivalents of LiCl in dioxane under reflux[2] afforded the corresponding products **4a**,**b** in high yields (Scheme 1). The use of LiCl prevented prior decomposition of the catalyst. Compounds **4a–c** were also prepared by heating the 2-acetyl-3-bromobenzo[*b*]heterocycles **3b**,**c** with phenylboronic acid in the presence of 3 mol-% $Pd(PPh_3)_4$ in dimethoxyethane.[3] Aqueous sodium carbonate solution (2 equivalents) was added to facilitate the reaction (Scheme 1). The results of these Pd-catalysed cross-coupling reactions are summarized in Table 1.



Scheme 1. Synthesis of the acetamido derivatives **6a–c** by Beckmann rearrangement of the oximes **5a–c**; reagents and conditions: (a) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (b) $PhSnBu_3$ (1.5 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), LiCl (3 equiv.), $CuBr_2$ (0.05 equiv.), dioxane, reflux (Method A); (c) $PhB(OH)_2$ (3 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), Na_2CO_3 (7 equiv.), CuI (1.1 equiv.), toluene, reflux (Method B); (d) $PhB(OH)_2$ (1.5 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), 2 N aq. Na_2CO_3 (2 equiv.), DME, reflux (Method C); (e) NH_2OH, HCl (1.5 equiv.), AcONa (1.5 equiv.), EtOH, reflux; (f) PPA (10 equiv.), toluene, reflux

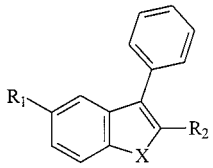
The oximes **5a–c** were prepared in high yields by reacting the ketones **4a–c** with hydroxylamine hydrochloride in the presence of sodium acetate in ethanol.

In order to achieve Beckmann rearrangement of the oximes **5a–c**,[4] the use of 10 equivalents of polyphosphoric acid in refluxing toluene was found to be necessary; all attempts to carry out the reaction under milder conditions were unsuccessful. With X = S or Se, the acetamido derivatives **6b**,**c** were isolated in yields of 73% or higher (Table 2, Scheme 1). However, with X = O, only degradation of thestarting material took place. Therefore, we chose to invest-

[a] Groupe de Synthèse Organique et Hétérocyclique, Laboratoire de Chimie Organique, Université de Metz,
Ile du Saulcy, 57012 Metz Cedex 01, France

  1434–193X/00/0407–1353 $ 17.50+.50/0

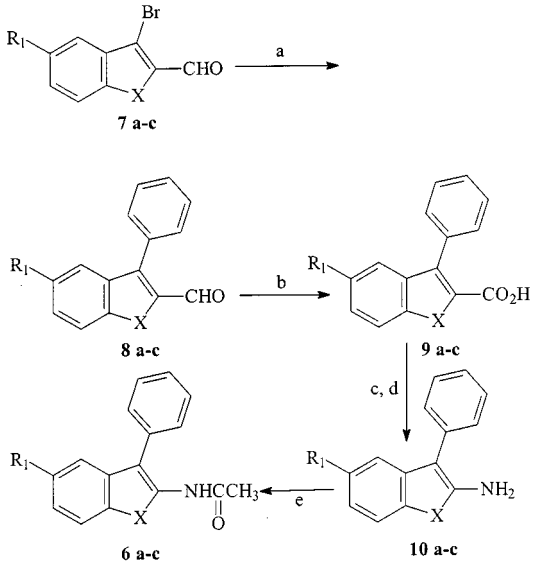
Table 1. Palladium-catalysed cross-coupling products **4a–c**, **8a–c**



Compound	R_1	R_2	X	Method	Yield (%)
4a	SCH_3	$COCH_3$	O	B	92
4b	H	$COCH_3$	S	A	76
4b	H	$COCH_3$	S	B	84
4c	H	$COCH_3$	Se	A	94
8a	SCH_3	CHO	O	A	91
8a	SCH_3	CHO	O	C	84
8b	H	CHO	S	A	82
8b	H	CHO	S	C	92
8c	H	CHO	Se	A	81
8c	H	CHO	Se	C	81

Table 2. Beckmann rearrangement of oximes **5**

Compound	R^1	X	Yield (%)
6a	SCH_3	O	degradation
6b	H	S	83
6c	H	Se	73



Scheme 2. Synthesis of the acetamido derivatives **6a–c** by acetylation of the amines **10a–c**; reagents and conditions: (a) $PhSnBu_3$ (1.5 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), LiCl (3 equiv.), $CuBr_2$ (0.05 equiv.), dioxane, reflux (Method A) or $PhB(OH)_2$ (1.5 equiv.), 2 N aq. Na_2CO_3 (2 equiv.), DME, reflux (Method C); (b) $NaClO_2$ (1.4 equiv.), 30% H_2O_2 (5 equiv.), NaH_2PO_4, H_2O, CH_3CN or MeOH; (c) $SOCl_2$ (1.5 equiv.), CH_2Cl_2, reflux, then NaN_3 (3.7 equiv.), acetone/water, 0 °C to room temp.; (d) DMF, reflux; (e) Ac_2O, pyridine, room temp.

igate an alternative synthetic route involving milder conditions (Scheme 2).

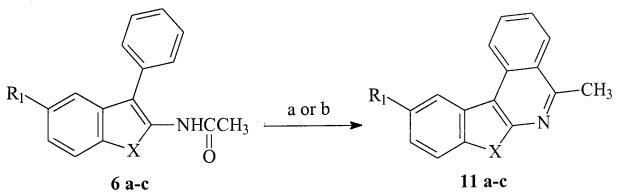
The carbaldehydes **8a–c**, obtained by Stille or Suzuki cross-coupling reactions of the bromo derivatives **7a–c** (Table 1, Scheme 2), were oxidized to the corresponding carboxylic acids **9a–c**. Treatment of the carboxaldehydes **8b**,**c** with sodium chlorite in the presence of hydrogen peroxide in acetonitrile[5] or methanol gave the carboxylic acids **9b**,**c**. Reaction of compound **8a** (R_1 = SCH_3) under these conditions resulted in oxidation of both the formyl and methylthio groups. In this case, we used silver oxide, which is a fairly specific oxidizing agent for the formyl group. The reaction was carried out in aqueous DMSO.

Acyl azides were prepared in high yields by reaction of acyl chlorides with sodium azide in aqueous acetone at 0 °C. Hydrolysis of the isocyanates formed by Curtius rearrangement[6] of the acyl azides led to the amines **10a–c**. Finally, compounds **6a–c** were obtained by acetylation of **10a–c** using acetic anhydride in pyridine. This synthetic route allowed us to synthesize the acetamido derivatives **6a–c** in good overall yields, even with X = O (Table 3, Scheme 2).

Bischler–Napieralski cyclization[7] of the acetamido derivatives **6a–c** required the use of 20 equivalents of $POCl_3$ or a mixture of 20 equivalents of $POCl_3$ and 10 equivalents of P_2O_5 in refluxing toluene. With X = S or Se, moderate

Table 3. Amino derivatives **10** and acetamido derivatives **6**

Compound	R^1	X	Yield (%)
10a	SCH_3	O	72 (from **9a**)
10b	H	S	73 (from **9b**)
10c	H	Se	83 (from **9c**)
6a	SCH_3	O	71
6b	H	S	87
6c	H	Se	79



Scheme 3. Bischler–Napieralski cyclization of the acetamido derivatives **6a–c**; reagents and conditions: (a) $POCl_3$ (20 equiv.), toluene, reflux; (b) $POCl_3$ (20 equiv.), P_2O_5 (10 equiv.), toluene, reflux

Table 4. Bischler–Napieralski cyclization

Compound	R_1	X	Yield (%) $POCl_3$	Yield (%) $POCl_3/P_2O_5$
11a	SCH_3	O	degradation	degradation
11b	H	S	35	54
11c	H	Se	39	44

yields of compounds **11b**,**c** were obtained. Unfortunately,-with X = O, only degradation took place (Scheme 3, Table 4).

Experimental Section

General: Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. – ^{1}H- and ^{13}C-NMR spectra were recorded with a BRUKER AC 250-MHz instrument. – Infrared (IR) spectra were recorded with a Perkin–Elmer 881 spectrometer and are reported in wavenumbers (cm^{-1}). Compounds **7a–c** were prepared as described in ref.[8] CH_3CN was distilled from potassium hydroxide. DME was distilled from $LiAlH_4$.

General Procedure for the Stille Cross-Coupling Reaction. – Method A: The triflate derivative **2a**,**b** (0.775 mmol, 1 equiv.) was dissolved in dioxane (4 mL) and the resulting solution was purged with argon. $Pd(PPh_3)_4$ (3 mol-%) was added, the mixture was stirred for 15 min, and then lithium chloride (2.32 mmol, 3 equiv.) and $CuBr_2$ (0.05 equiv.) were added, followed by phenyltributylstannane (1.04 equiv.). The resulting mixture was heated under reflux until **2a**,**b** had been consumed (TLC). The solvent was then removed in vacuo and the residue was extracted with ethyl acetate. The organic phase was washed with saturated brine and dried with sodium sulfate. Removal of the solvent under reduced pressure left a residue, which was purified by column chromatography on silica gel (CH_2Cl_2).

General Procedure for the Suzuki Cross-Coupling Reaction. – Method B: The triflate derivative **2a**,**b** (1.62 mmol, 1 equiv.) was dissolved in toluene (40 mL) and the resulting solution was purged with argon. $Pd(PPh_3)_4$ (4 mol-%) was added, the mixture was stirred for 15 min, and then powdered sodium carbonate (11.34 mmol, 7 equiv.) and CuI (1.78 mmol, 1.1 equiv.) were added, followed by solid phenylboronic acid (4.86 mmol, 3 equiv.). The resulting mixture was heated under reflux until **2a**,**b** had been consumed (TLC). The solvent was then removed in vacuo and the residue was extracted with ethyl acetate. The organic phase was washed with saturated brine and dried with sodium sulfate. Removal of the solvent under reduced pressure left a residue, which was purified by column chromatography on silica gel (CH_2Cl_2).

Method C: The appropriate bromo derivative **3b**,**c** or **7a–c** (1.0 g, 1 equiv.) was dissolved in DME (50 mL) and the resulting solution was purged with argon. $Pd(PPh_3)_4$ (3 mol-%) was added, the mixture was stirred for 15 min, and then 2 N sodium carbonate solution (2 equiv.) was added, which resulted in some cloudiness of the solution. Phenylboronic acid (1.1 equiv.) was then added as a solid. The resulting mixture was heated under reflux until **3b**,**c** or **7a–c** had been consumed (TLC). The solvent was then removed in vacuo and the residue was extracted with diethyl ether. The organic phase was worked-up by column chromatography on silica gel eluting with CH_2Cl_2 to give **4b**,**c** or **8a–c**.

5-(Methylthio)-3-phenylbenzo[*b*]furan-2-carbaldehyde (8a): Yield: 91% (Method A); 84% (Method C); yellow solid, m.p. 88 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.52 (s, 3 H, SCH_3), 7.53 (dd, 1 H, *J* = 1.70 Hz, 8.02 Hz, ArH), 7.60 (m, 7 H, ArH), 9.86 (s, 1 H, CHO). – ^{13}C NMR ($CDCl_3$): δ = 17.5 (SCH_3), 113.2, 120.8, 129.2, 129.5, 129.9, 130.1 (CH), 127.8, 128.9, 133.5, 134.3, 148.1, 153.8 (C), 179.8 (CHO). – IR (KBr): $\tilde{\nu}$ = 1669 cm^{-1} (CO). – $C_{16}H_{12}O_2S$ (268.26): calcd. C 71.64, H 4.51; found C 71.82, H 4.66.

3-Phenylbenzo[*b*]thiophene-2-carbaldehyde (8b): Yield: 82% (Method A); 92% (Method C); yellow solid, m.p. 85 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.39 (m, 1 H, ArH), 7.52 (m, 6 H, ArH), 7.72 (dd, 1 H, *J* = 1.23 Hz, 8.05 Hz, ArH), 7.97 (d, 1 H, *J* = 7.93 Hz, ArH), 9.78 (s, 1 H, CHO). – ^{13}C NMR ($CDCl_3$): δ = 123.26, 125.19, 125.45, 128.39, 128.79, 129.07, 130.49 (CH), 132.33, 138.87, 139.26, 141.93, 145.68 (C), 186.03 (CHO). – IR (KBr): $\tilde{\nu}$ = 1654 cm^{-1} (CO). – $C_{15}H_{10}OS$ (238.23): calcd. C 75.62, H 4.23; found C 75.73, H 4.29.

3-Phenylbenzo[*b*]selenophene-2-carbaldehyde (8c): Yield: 81% (Method A); 81% (method C); yellow solid, m.p. 76 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.39 (m, 1 H, ArH), 7.50 (m, 2 H, ArH), 7.73 (dd, 1 H, *J* = 1.20 Hz, 7.75 Hz, ArH), 7.98 (d, 1 H, *J* = 7.52 Hz), 9.78 (s, 1 H, CHO). – ^{13}C NMR ($CDCl_3$): δ = 125.3, 126.5, 127.6, 128.2, 128.7, 129.1, 130.4 (CH), 133.9, 142.1, 143.1, 143.3, 151.1 (C), 187.1 (CHO). – IR (KBr): $\tilde{\nu}$ = 1657 cm^{-1} (CO). – $C_{15}H_{10}OSe$ (285.19): calcd. C 63.17, H 3.53; found C 63.31, H 3.58.

2-Acetyl-5-methylthio-3-phenylbenzo[*b*]furan (4a): Yield: 92% (Method B); yellow solid, m.p. 88 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 2.55 (s, 3 H, SCH_3), 7.31 (m, 1 H, ArH), 7.52 (m, 6 H, ArH), 7.61 (d, 1 H, *J* = 8.02 Hz, ArH). – ^{13}C NMR ($CDCl_3$): δ = 17.6 (SCH_3), 28.31 (CH_3), 112.22, 122.55, 123.79, 127.95, 128.56, 128.67, 130.74, 147.13, 154.12, 189.59 (CO). – IR (KBr): $\tilde{\nu}$ = 1678 cm^{-1} (CO). – $C_{17}H_{14}O_2S$ (282.28): calcd. C 72.33, H 5.00; found C 72.47, H 5.17.

2-Acetyl-3-phenylbenzo[*b*]thiophene (4b): Yield: 76% (Method A); 84% (Method B); white solid, m.p. 70 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.10 (s, 3 H, CH_3), 7.38 (m, 3 H, ArH), 7.45 (d, 1 H, *J* = 8.42 Hz, ArH), 7.53 (m, 3 H, ArH), 7.89 (d, 1 H, *J* = 8.26 Hz, ArH). – ^{13}C NMR ($CDCl_3$): δ = 29.72 (CH_3), 122.56, 124.79, 125.67, 127.49, 128.70, 128.79, 129.65 (CH), 134.22, 140.83, 140.91, 141.00, 142.10 (C), 193.77 (CO). – IR (KBr): $\tilde{\nu}$ = 1682 cm^{-1} (CO). – $C_{16}H_{12}OS$ (252.26): calcd. C 76.18, H 4.79; found C 76.35, H 4.93.

2-Acetyl-3-phenylbenzo[*b*]selenophene (4c): Yield: 94% (Method A); yellow solid, m.p. 92 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.01 (s, 3 H, CH_3), 7.35 (m, 5 H, ArH), 7.52 (m, 2 H, ArH), 7.54 (d, 1 H, *J* = 7.59 Hz, ArH), 7.93 (d, 1 H, *J* = 7.86 Hz, ArH). – ^{13}C NMR ($CDCl_3$): δ = 29.34 (CH_3), 124.90, 125.67, 127.41, 128.02, 128.67, 128.84, 129.49 (CH), 136.51, 142.08, 144.02, 145.13, 145.73 (C), 194.8 (CO). – IR (KBr): $\tilde{\nu}$ = 1677 cm^{-1} (CO). – $C_{16}H_{12}OSe$ (297.20): calcd. C 64.22, H 4.04; found C 64.33, H 4.23.

General Procedure for the Beckmann Rearrangement: To a solution of the appropriate oxime **5a–c** (0.32 mmol, 1 equiv.) in toluene (7 mL) was added 1 g of polyphosphoric acid. The reaction mixture was heated under reflux until the oxime had been consumed (TLC). The solution was then poured into aqueous sodium hydroxide solution (20%) and the resulting mixture was extracted with ethyl acetate. The combined organic phases were washed with saturated brine and dried with sodium sulfate. Removal of the solvent under reduced pressure left a residue, which was used without further purification.

***N*-(5-Methylthio-3-phenylbenzo[*b*]furan-2-yl)acetamide (6a):** Yellow solid, m.p. 218 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 2.51 (s, 3 H, SCH_3), 7.45 (m, 7 H, ArH), 7.63 (d, 1 H, *J* = 1.76 Hz, ArH). – ^{13}C NMR ($CDCl_3$): δ = 17.96 (SCH_3), 25.65 (CH_3), 112.23, 118.83, 120.26, 126.64, 127.90, 128.19 (CH), 128.49, 129.35, 129.75, 133.27, 143.29, 151.13 (C), 172.19 (CO). – IR (KBr): $\tilde{\nu}$ = 3223 (NH), 1662 cm^{-1} (CO). – $C_{17}H_{15}NO_2S$ (297.30): calcd. C 68.68, H 5.08, N 4.71; found C 68.83, H 5.14, N 4.59.

***N*-(3-Phenylbenzo[*b*]thiophen-2-yl)acetamide (6b):** Yellow solid, m.p. 218 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 3 H, CH_3), 7.28 (dd, 1

H, J = 1.11 Hz, 8.16 Hz), 7.31 (m, 1 H, ArH), 7.46 (m, 4 H, ArH), 7.56 (d, 2 H, J = 8.23 Hz, ArH), 7.81 (dd, 1 H, J = 1.98 Hz, 8.66 Hz, ArH), 7.90 (s, 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 23.6 (CH_3), 121.0, 123.5, 124.5, 128.1, 128.2, 129.6, 129.7 (CH), 119.29, 133.5, 134.6, 135.2, 136.7 (C), 166.8 (CO). – IR (KBr): $\tilde{\nu}$ = 3358 (NH), 1651 cm^{-1} (CO). – $C_{16}H_{13}NOS$ (267.27): calcd. C 71.90, H 4.90, N 5.24; found C 72.04, H 5.06, N 5.15.

***N*-(3-Phenylbenzo[*b*]selenophen-2-yl)acetamide (6c):** Yellow solid, m.p. 225 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 3 H, CH_3), 7.26 (m, 2 H, ArH), 7.41 (m, 3 H, ArH), 7.50 (dd, 2 H, J = 7.60 Hz, ArH), 7.59 (d, 1 H, J = 8.30 Hz, ArH), 7.86 (dd, 1 H, J = 8.57 Hz, ArH), 7.98 (s, 1 H, NH). – IR (KBr): $\tilde{\nu}$ = 3286 (NH), 1656 cm^{-1} (CO). – $C_{16}H_{13}NOSe$ (314.23): calcd. C 61.15, H 4.17, N 4.46; found C 61.27, H 4.23, N 4.49.

General Procedure for Oxidation with $NaClO_2$: A solution of $NaClO_2$ (245 mg, 2.22 mmol, 1.4 equiv.) in water (2.3 mL) was added dropwise to a stirred solution of carbaldehyde **8b**,**c** (1.59 mmol, 1 equiv.) in acetonitrile (7 mL), to which NaH_2PO_4 (70 mg, 0.477 mmol, 0.3 equiv.) in water (0.65 mL) and 30% H_2O_2 (0.79 mL, 7.95 mmol, 5 equiv.) had been added. The temperature of the mixture was maintained at 10 °C and oxygen evolution was monitored until the reaction was complete. A small amount of Na_2SO_3 was subsequently added to destroy the remaining HOCl and H_2O_2. Acidification with 10% aqueous HCl afforded the acid **9b** or **9c** as a solid, which was collected by filtration.

General Procedure for Oxidation with Ag_2O: A solution of $AgNO_3$ (8.71 mmol, 2.1 equiv.) in distilled water (3 mL) was added to a solution of NaOH (4.1 equiv.) in distilled water (3 mL). A solution of compound **8a** (4.15 mmol, 1 equiv.) in DMSO (2 mL) was then added dropwise and the heterogeneous mixture was stirred a further 2 h. The precipitated silver salts were then filtered off in vacuo, washed with a small volume of water, and the basic filtrate was washed several times with CH_2Cl_2. The solution was then acidified to pH = 3–4 with concentrated HCl and extracted with CH_2Cl_2. The combined extracts were dried with sodium sulfate and the solvent was evaporated in vacuo to afford purified **9a**.

5-Methylthio-3-phenylbenzo[*b*]furan-2-carboxylic Acid (9a): Yield: 81%; white solid, m.p. 240 °C. – ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3 H, SCH_3), 3.20 (s, 1 H, OH), 7.25 (m, 4 H, ArH), 7.38 (m, 3 H, ArH). – IR (KBr): $\tilde{\nu}$ = 2568 (OH), 1687 cm^{-1} (CO). – $C_{16}H_{12}O_3S$ (284.26): calcd. C 67.60, H 4.26; found C 67.27, H 4.23.

3-Phenylbenzo[*b*]thiophene-2-carboxylic Acid (9b): Yield: 95%; white solid, m.p. 229 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.38 (m, 1 H, ArH), 7.42 (dd, 2 H, J = 2.01 Hz, J = 7.55 Hz, ArH), 7.54 (m, 5 H, ArH), 7.92 (d, 1 H, J = 8.06 Hz). – $C_{15}H_{10}O_2S$ (254.23): calcd. C 70.86, H 3.96; found C 71.17, H 4.13.

3-Phenylbenzo[*b*]selenophene-2-carboxylic Acid (9c): Yield: 91%; orange solid, m.p. 218 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.34 (m, 3 H, ArH), 7.42 (m, 2 H, ArH), 7.48 (m, 3 H, ArH), 7.93 (d, 1 H, J = 8.88 Hz, ArH). – IR (KBr): $\tilde{\nu}$ = 2799 (OH), 1652 cm^{-1} (CO). – $C_{15}H_{10}O_2Se$ (301.19): calcd. C 59.81, H 3.34; found C 60.27, H 3.23.

Preparation of Amines 10a–c from Carboxylic Acids 9a–c: A solution of the appropriate carboxylic acid **9a–c** (1 equiv., 1.86 mmol) in dry CH_2Cl_2 (5 mL) was treated with thionyl chloride (1.5 equiv., 2.79 mmol). The reaction mixture was heated under reflux until gas evolution had ceased (about 1 h). The excess thionyl chloride and CH_2Cl_2 were then evaporated under reduced pressure. A solution of the acyl chloride (1.86 mmol) in acetone (10 mL) was then added dropwise to a solution of sodium azide (3.7 equiv., 6.81 mmol) in water (1.5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 20 min and then water (20 mL) and hexane (20 mL) were added. The organic layer was washed with saturated brine and dried with sodium sulfate. Removal of the solvent under reduced pressure left a residue, which was used without further purification. A solution of the acyl azide (1.50 mmol) in DMF (3 mL) was heated at 110 °C for 2 h. After cooling to room temperature, water (20 mL) and ethyl acetate (20 mL) were added. The organic layer was washed with saturated brine and dried with sodium sulfate. Removal of the solvent under reduced pressure left a residue, which was purified by column chromatography on silica gel (CH_2Cl_2).

3-Phenyl-5-methylthiobenzo[*b*]furan-2-ylamine (10a): Yield: 89%; orange oil. – ^{1}H NMR ($CDCl_3$): δ = 2.49 (s, 3 H, SCH_3), 4.37 (s, 2 H, NH_2), 7.08 (dd, 1 H, J = 1.84 Hz, J = 8.47 Hz, ArH), 7.22 (d, 1 H, J = 8.39 Hz), 7.29 (m, 1 H, ArH), 7.51 (m, 5 H, ArH). – IR (KBr): $\tilde{\nu}$ = 3378 cm^{-1} (NH_2). – $C_{15}H_{13}NOS$ (255.26): calcd. C 70.58, H 5.13, N 5.49; found C 70.73, H 5.19, N 5.34.

3-Phenylbenzo[*b*]thiophen-2-ylamine (10b): Yield: 82%; orange oil. – ^{1}H NMR ($CDCl_3$): δ = 4.23 (s, 2 H, NH_2), 7.08 (dd, 1 H, J = 1.84 Hz, J = 8.47 Hz, ArH), 7.22 (d, 1 H, J = 8.39 Hz, ArH), 7.29 (m, 2 H, ArH), 7.51 (m, 5 H, ArH). – IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1} (NH_2). – $C_{14}H_{11}NS$ (225.24): calcd. C 74.65, H 4.92, N 6.22; found C 74.73, H 5.01, N 6.14.

3-Phenylbenzo[*b*]selenophen-2-ylamine (10c): Yield: 86%; yellow oil. – ^{1}H NMR ($CDCl_3$): δ = 4.22 (s, 2 H, NH_2), 7.05 (m, 1 H, ArH), 7.23 (m, 2 H, ArH), 7.47 (d, 5 H, J = 8.17 Hz, ArH), 7.65 (d, 1 H, J = 7.80 Hz, ArH). – IR (KBr): $\tilde{\nu}$ = 3380 cm^{-1} (NH_2). – $C_{14}H_{11}NSe$ (272.20): calcd. C 61.78, H 4.07, N 5.15; found C 61.93, H 4.21, N 5.09.

General Procedure for the Bischler–Napieralski Cyclization: $POCl_3$ (20 equiv.) was slowly added to a mixture of the appropriate amide **6a–c** (1 equiv.) and P_2O_5 (10 equiv.) in toluene. The resulting mixture was heated under reflux until **6a–c** had been consumed (TLC). The solution was then poured into water and extracted with ethyl acetate. The combined organic extracts were washed with saturated brine and dried with sodium sulfate. Removal of the solvent under reduced pressure left a residue, which was purified by column chromatography on silica gel (CH_2Cl_2).

5-Methylbenzo[*b*]thieno[2,3-*c*]isoquinoline (11b): Yield: 54%; yellow solid, m.p. 151 °C. – ^{1}H NMR ($CDCl_3$): δ = 3.00 (s, 3 H, CH_3), 7.44 (m, 1 H, ArH), 7.52 (m, 1 H, ArH), 7.60 (m, 1 H, ArH), 7.91 (m, 1 H, ArH), 7.92 (d, 1 H, J = 7.80 Hz, ArH), 8.24 (d, 1 H, J = 8.44 Hz, ArH), 8.63 (d, 1 H, J = 8.16 Hz, ArH), 8.81 (d, 1 H, J = 8.52 Hz, ArH). – $C_{16}H_{11}NS$ (249.26): calcd. C 77.09, H 4.45, N 5.62; found C 77.32, H 4.58, N 5.49.

5-Methylbenzo[*b*]seleno[2,3-*c*]isoquinoline (11c): Yield: 44%; yellow solid, m.p. 134 °C. – ^{1}H NMR ($CDCl_3$): δ = 3.09 (s, 3 H, CH_3), 7.44 (m, 1 H, ArH), 7.59 (t, 1 H, ArH), 7.68 (t, 1 H, ArH), 7.90 (t, 1 H, ArH), 8.03 (d, 1 H, J = 8.10 Hz, ArH), 8.30 (d, 1 H, J = 8.38 Hz, ArH), 8.76 (d, 1 H, J = 8.19 Hz, ArH), 8.95 (d, 1 H, J = 8.62 Hz, ArH). – $C_{16}H_{11}NSe$ (296.22): calcd. C 64.87, H 3.74, N 4.73; found C 64.98, H 3.87, N 4.64.

[1] S. Yamaguchi, Y. Ohhira, M. Yamada, H. Michitani, Y. Kawase, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 952–954.
[2] [2a] W. J. Scott, J. K. Stille, *J. Am. Chem. Soc*. **1986**, *108*, 3033–3040. – [2b] A. M. Echavarren, J. K. Stille, *J. Am. Chem. Soc*. **1987**, *109*, 5478–5486.

[3] [3a] For a review, see: N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483. – [3b] S. Gronowitz, K. Lavitz, *Chem. Scr.* **1984**, *24*, 5–10. – [3c] S. Gronowitz, V. Bobosik, K. Lavitz, *Chem. Scr.* **1984**, *23*, 120–123.
[4] L. G. Donaruma, W. Z. Heldt, *The Beckmann Rearrangement*, in *Org. React*. **1960**, *11*, 5–14, Wiley, New York.
[5] F. Montanari, *J. Org. Chem*. **1986**, *51*, 567–569.
[6] J. R. Pfister, W. E. Wymann, *Synthesis* **1983**, 38–40.
[7] [7a] A. Nefzi, J. M. Ostrich, R. A. Haugten, *Chem. Rev.* **1997**, *97*, 449–472. – [7b] S. Doï, N. Shirai, Y. Sato, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2217–2221.
[8] Z. Arnold, J. Zemlicka, *Coll. Czech. Chem. Commun.* **1959**, *24*, 2385–2389.

Received May 19, 1999
[O99287]