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Synthesis of new thieno[3,2-*b*]pyridine derivatives by palladium-catalyzed couplings and intramolecular cyclizations

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ABSTRACT

Two methyl 3-aminothieno[3,2-*b*]pyridine-2-carboxylates were prepared from 3-fluoro or 3-nitropicolinonitriles and methyl thioglycolate in DMF/KOH(aq). From the unsubstituted precursor in the pyridine ring, di(hetero)arylamines were obtained by C–N Buchwald–Hartwig coupling with bromonitrobenzenes and with 2-bromopyridine. In the latter case a tetracyclic compound was formed by intramolecular cyclization. Using a brominated derivative in the pyridine ring as a coupling component, it was possible to synthesize C–C (Suzuki and Sonogashira) and C–N (Buchwald–Hartwig) coupling products and a tetracyclic compound obtained by bifunctionalization of the thienopyridine system.

Thienopyridine derivatives have shown interesting biological activities. Namely diheteroarylamine derivatives of the thieno[3,2-*b*]pyridine skeleton,[1] substituted thieno[3,2-*b*]pyridine ureas,[2] and thieno[3,2-*c*]pyridine ureas[3] were shown to be inhibitors of the vascular endothelial growth factor receptor (VEGFR-2) mediator of the biological function of the vascular endothelial growth factor (VEGF), related to angiogenesis and metastasis.

Two derivatives of the thieno[3,2-*c*]pyridine moiety, the (+)-(*S*)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetate, clopidogrel[4,5] (Plavix®) and the 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine, ticlopidine[5] (Ticlid®), are being used in the clinic as antiplatelet agents to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease.

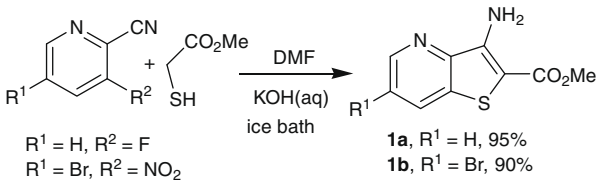
Among the methods used to prepare the thieno[3,2-*b*]pyridine moiety, Fort et al. reported an efficient method by using a three-step process allowing the construction of the thiophene ring. The key step was the regioselective lithiation–bromination of the 3-methylthiopyridine followed by Sonogashira coupling and halogenocyclization producing the fused heterocycles.[6]

Here we present the synthesis of two thieno[3,2-*b*]pyridines **1a** and **1b** as components for palladium-catalyzed couplings by reaction either on the pyridine or on the thiophene ring. Compounds **1** were prepared in excellent yield, reacting the 3-fluoropicolinonitrile (for **1a**) or the 5-bromo-3-nitropicolinonitrile (for **1b**) with methyl thioglycolate in DMF using an excess of KOH(aq) (Scheme 1), following a known procedure.[7] Compound **1a** was already prepared by Dunn and Norrie in only 35% yield from 3-chloropicolinonitrile and thioglycolate in DMF, using sodium methoxide as the base.[8]

The di(hetero)arylamines **2a,b** were obtained in high yields by C–N Buchwald–Hartwig coupling,[10] of compound **1a** with bromonitrobenzenes using xantphos (4,5-bis(diphenylphosphane)-9,9-dimethylxanthene) as the ligand, (Scheme 2, i). The use of this ligand promotes the C–N coupling of deactivated amines.[7]

Compounds **2a,b** were reduced in very high yields, to the corresponding amino compounds **3a,b** even without the purification of the nitro precursors (Scheme 2, ii).[11] In the reduction of compound **2a** to compound **3a**, the formation of the corresponding lactam did not occur. The use of iron and acetic acid at 115 °C[12] did not reduce the nitro compounds. Compounds **3** can be further functionalized by several types of reactions.

From compound **1a** we were also able to synthesize the tetracyclic compound **4** by a tandem C–N coupling with 2-bromopyridine followed by intramolecular cyclization involving the nucleophilic attack of the pyridine nitrogen on the carbonyl of the ester group



Scheme 1. Synthesis of methyl 3-aminothieno[3,2-*b*]pyridine-2-carboxylates **1a**[8] and **1b**.[9]

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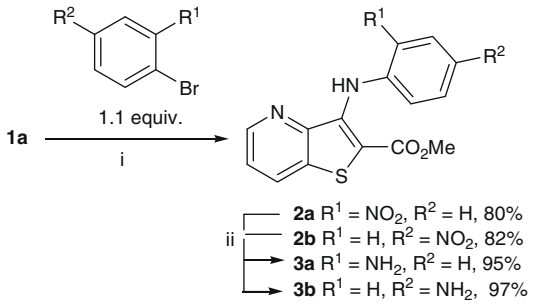
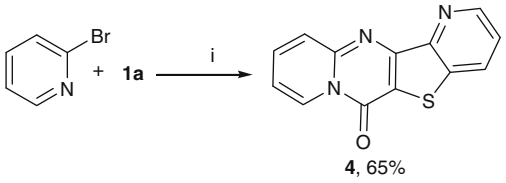


Scheme 2. Synthesis of di(hetero)arylamines **2a,b** by C–N coupling of **1a** with bromonitrobenzenes and reduction to the amino compounds **3a,b**. Reagents and conditions: (i) $Pd(OAc)_2$ 15 mol %, xantphos 18 mol %, 2 equiv Cs_2CO_3, dry dioxane, 2 h, 120 °C; (ii) 1 equiv NH_4Cl, 8 equiv Fe, EtOH/THF/H_2O (3:1:0.5), 80 °C, 2 h.

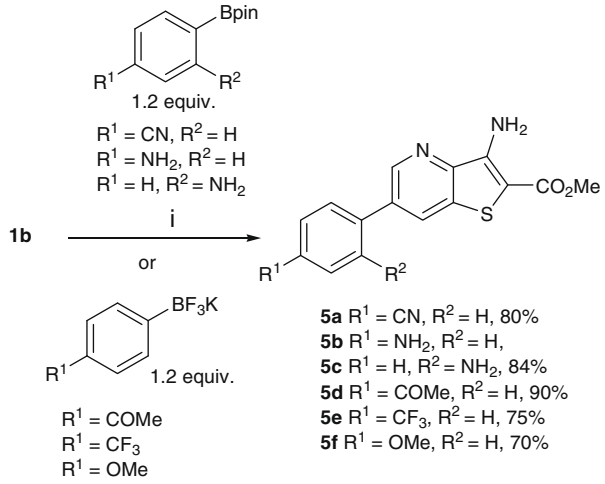


Scheme 3. Synthesis of the tetracyclic compound **4** from 2-bromopyridine and compound **1a**. Reagents and condition: (i) $Pd(OAc)_2$ 15 mol %, xantphos 18 mol %, 2 equiv Cs_2CO_3, dry dioxane, overnight, 120 °C.

with loss of MeOH (Scheme 3). This type of reaction was already performed by us in the benzo[*b*]thiophene series.[7]

Using compound **1b** as a coupling component we have obtained C–C Suzuki coupling[13] products **5**, using arylpinacolborates[14] or potassium aryltrifluoroborate salts,[15] in high to excellent yields (70–90%) (Scheme 4). The corresponding boronic acids under the same conditions did not react to afford the Suzuki products.

From compound **1b** and arylacetylenes we have obtained the C–C Sonogashira[16] products **6** in high to excellent yields (70–90%)

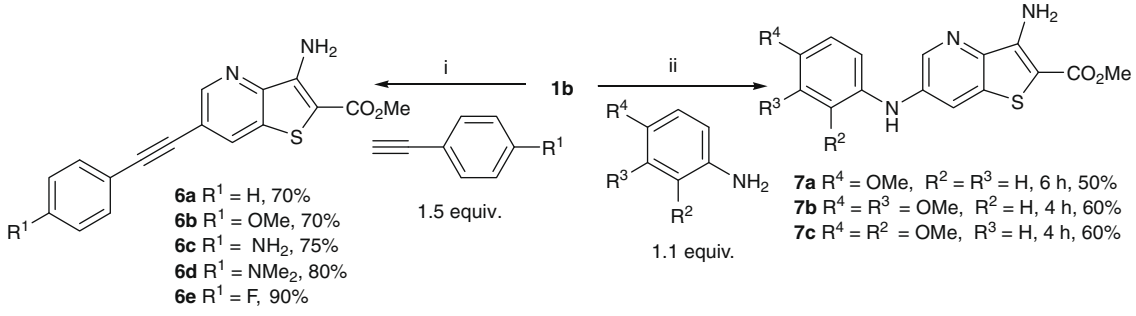


Scheme 4. Synthesis of Suzuki coupling products **5** from compound **1b** and arylpinacolborates or potassium aryltrifluoroborate salts. Reagents and conditions: (i) $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1) 2 mol %, 6 equiv K_2CO_3, DME/H_2O (3:1), 1–3 h, 90 °C.

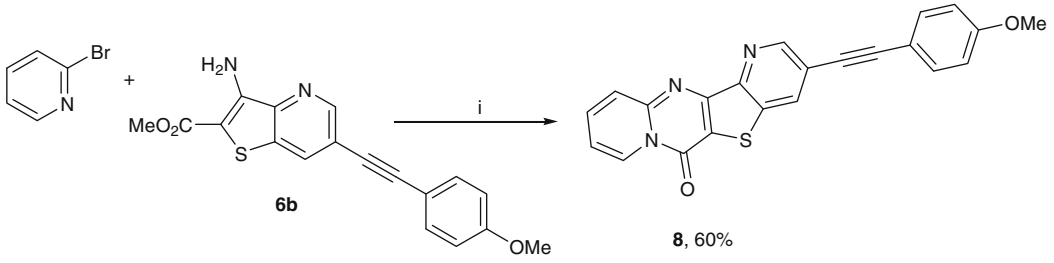
(Scheme 5, i). In the synthesis of the di(hetero)arylamines (50–60%) by C–N coupling from **1b** and arylamines, *rac*-BINAP (*rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) which is a more general ligand was used (Scheme 5, ii). The use of xantphos as a ligand gave as minor products bifunctionalized di(hetero)arylamines resulting from other C–N coupling involving the bromine of compound **1b** and the free amino group of the di(hetero)arylamines formed.

The bifunctionalization of compound **6b** by C–N coupling with 2-bromopyridine gave the tetracyclic compound **8** (Scheme 6). Other reactions on the amino group of the system are also possible.

In summary we were able to obtain a wide variety of new thieno[3,2-*b*]pyridine derivatives from two functionalized starting materials, using C–C and C–N palladium-catalyzed couplings and



Scheme 5. Synthesis of Sonogashira products **6** and C–N Buchwald–Hartwig coupling products **7** from **1b**. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$ 5 mol %, CuI 3 mol %, 3 equiv NEt_3 , dry DMF, Ar, 100 °C, 1.5 h; (ii) $Pd(OAc)_2$ 16 mol %, *rac*-BINAP 18 mol %, 1.8 equiv Cs_2CO_3, toluene, 100 °C, Ar.



Scheme 6. Synthesis of a tetracyclic compound **8**[17] from reaction of compound **6b** with 2-bromopyridine. Reagents and conditions: (i) $Pd(OAc)_2$ 15 mol %, xantphos 18 mol %, 2 equiv Cs_2CO_3, dry dioxane, overnight, 120 °C.

intramolecular cyclizations when 2-bromopyridine was used as a C–N coupling component. The fluorescence of the tetracyclic compounds obtained in this work will be studied and compared with earlier results on a benzothienopyridopyrimidone prepared by us from a benzo[*b*]thiophene derivative.[18] The ability to bifunctionalize **1b** makes it a key compound in this series.

The biological activity of the compounds obtained will be studied in collaboration with other research groups.

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9. *Methyl 3-amino-6-bromothieno[3,2-b]pyridine-2-carboxylate* (**1b**): From 5-bromo-3-nitropicolinonitrile (1.00 g, 4.40 mmol) in DMF (15 mL), methylthioglycolate (560 mg, 5.28 mmol) and KOH (475 mg, 13.2 mmol)/H_2O (3.4 mL) at 0 °C (ice bath) were added. The mixture was left to stir for 2 h at 0 °C. A precipitate came out and the reaction mixture was poured into crushed ice with stirring. The precipitate was filtered, dried in the oven at 50 °C, and a yellow solid was obtained (1.10 g, 90%), mp 157–159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.92 (3H, s, OMe), 6.19 (2H, br s, NH_2), 8.21 (1H, d, J = 2.1 Hz, HetAr-H), 8.65 (1H, d, J = 2.1 Hz, HetAr-H) ppm. ^{13}C NMR ($CDCl_3$,75.4 MHz): δ 51.77 (OMe), 119.34 (C), 133.17 (CH), 135.30 (C), 144.99 (C), 147.12 (C), 147.68 (CH), 165.10 (C=O) ppm. MS (EI): *m/z* (%) 288 ($M^{+\,81}$Br, 74), 286 (M^{+79}Br, 76), 256 (M^{+81}Br−OMe, 89), 254 (M^{+79}Br−OMe, 100). HRMS M^+ calcd for $C_9H_7{}^{79}BrN_2O_2S$ 285.9412, found 285.9406. M^+ calcd for $C_9H_7{}^{81}BrN_2O_2S$ 287.9391, found 287.9389.
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17. *Tetracyclic compound* **8**: The reaction was performed in a dried Schlenk tube under argon, using 2-bromopyridine (0.0400 mL, 0.360 mmol), $Pd(OAc)_2$ (10 mg, 0.045 mmol), xantphos (32 mg, 0.054 mmol), Cs_2CO_3 (195 mg, 0.600 mmol), and the Sonogashira product **6b** (100 mg, 0.300 mmol) in dry dioxane (2 mL) and the mixture was heated overnight at 120 °C. After cooling, AcOEt (5 mL) and H_2O (5 mL) were added and the phases were separated. The organic phase was dried ($MgSO_4$), filtered, and removal of the solvent gave a brown oil which was submitted to column chromatography using a solvent gradient from 50% diethyl ether/petroleum ether 40–60 °C till neat diethyl ether. Compound **8** was isolated as a yellow solid (70 mg, 60%) mp 289–291 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (3H, s, OMe), 6.93 (2H, d, J = 8.8 Hz, Ar-H), 7.18–7.22 (1H, m, HetAr-H), 7.55 (2H, d, J = 8.8 Hz, Ar-H), 7.75–7.80 (1H, m, HetAr-H), 8.00–8.03 (1H, m, HetAr-H), 8.40 (1H, d, J = 2 Hz, HetAr-H), 9.03 (1H, d, J = 2 Hz, HetAr-H), 9.13–9.16 (1H, m, HetAr-H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 55.37 (OMe), 84.91 (C), 95.08 (C), 114.18 (C), 114.23 (2 × CH), 115.00 (CH), 116.60 (C), 120.71 (C), 126.45 (CH), 127.14 (CH), 133.33 (CH), 133.42 (2 × CH), 135.01 (CH), 136.87 (C), 147.81 (C), 150.05 (C), 150.79 (CH), 152.30 (C), 154.88 (C), 160.37 (C=O). MS (EI): *m/z* (%) 383 (M^+, 100), 368 (M^+, −15, 27). HRMS M^+ calcd for $C_{22}H_{13}N_3O_2S$ 383.0728, found 383.0729.
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