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Reactivity of several deactivated 3-aminobenzo[*b*]thiophenes in the Buchwald–Hartwig C–N coupling. Scope and limitations

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Abstract—Di(hetero)arylamines were prepared in moderate to high yields by Buchwald–Hartwig C–N coupling of bromobenzenes bearing electron-withdrawing groups and of a bromobiphenyl with several methyl 3-aminobenzo[*b*]thiophene-2-carboxylates, using the coupling conditions for heteroaromatic amines [$Pd(OAc)_2$, Xantphos, Cs_2CO_3 in dioxane, 120 °C]. The use of these aminobenzo[*b*]thiophenes as coupling components avoids the step of changing the amino group into a bromine atom, like we have done before to perform C–N couplings using the corresponding 3-bromobenzo[*b*]thiophenes. Nevertheless, the couplings using the methyl 3-aminobenzo[*b*]thiophene-2-carboxylates were only successful with bromobenzenes bearing electron-withdrawing groups and a bromobiphenyl or with electron deficient rings such us as bromopyridines. Using the latter compounds, different substituted 6*H*-benzothieno[3,2-*d*]pyrido[1,2-*a*]pyrimid-6-ones were obtained by C–N coupling followed by an intramolecular cyclization. These tetracyclic compounds may have interesting biological activity like it was already demonstrated by us for the non substituted derivative.

1. Introduction

The diarylamine skeleton is commonly found in several compounds with biological activity,[1] in materials with interesting electronic properties[2] and in ligands for transition metals.[3]

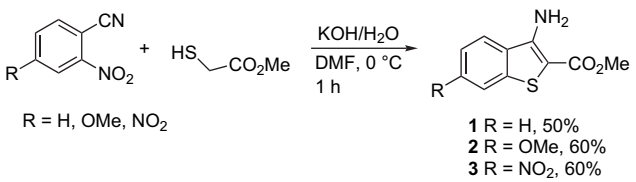
For some years now, we have been interested in the synthesis of diaryl and diheteroarylamines by Buchwald–Hartwig C–N coupling[4] of substituted 3-bromobenzo[*b*]thiophenes with anilines and aminopyridines,[5,6] and of substituted bromothiophenes with aliphatic amines or anilines,[7] and with aminopyridines.[8] Recently, we were also able to react substituted aminothiophenes with bromopyridines but the former did not react with bromobenzenes.[9]

Here we report the C–N coupling of bromobenzenes bearing electron-withdrawing groups and 2-bromopyridines with several methyl 3-aminobenzo[*b*]thiophene-2-carboxylates using the coupling conditions for heteroaromatic amines.[10] When 2-bromopyridines were used as coupling components, the corresponding benzothienopyridopyrimidones were obtained. This was already observed by us in an earlier work using the ethyl 3-bromobenzo[*b*]thiophene-2-carboxylate and 2-aminopyridine as coupling components.[6] The 6*H*-benzothieno[3,2-*d*]pyrido[1,2-*a*]pyrimid-6-one thus obtained was shown to induce cellular apoptosis in tumoral cell lines after photoactivation, in very low concentrations.[11]

2. Results and discussion

2.1. Synthesis of 3-aminobenzo[*b*]thiophene-2-carboxylates 1–3

The aminated coupling components **1–3** are already known[12,13] and were prepared here in good yields from 2-nitrobenzonitriles, methyl thioglycolate, and aqueous KOH in DMF at 0 °C (Scheme 1).[12]



Scheme 1. Synthesis of 3-aminobenzo[*b*]thiophene-2-carboxylates **1–3**.

Compound **2** was first prepared in a very low overall yield (14%) from 2,4-difluorobenzonitrile. The latter gave a mixture of 2-fluoro-4-methoxybenzonitrile and 4-fluoro-

Keywords: Buchwald–Hartwig coupling; Palladium; Di(hetero)arylamines; Methyl 3-aminobenzo[*b*]thiophene-2-carboxylates; Pyridines; Benzothienopyridopyrimidones.
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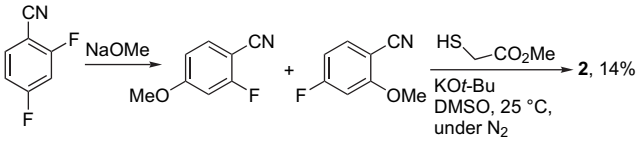
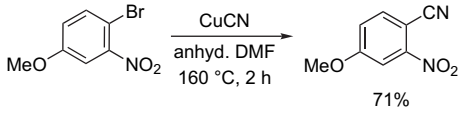
2-methoxybenzonitrile by treatment with sodium methoxide, which was used without purification to obtain compound **2** (Scheme 2).[13]



Scheme 2. Earlier synthesis of 3-aminobenzo[*b*]thiophene **2**.[13]

In the present work we have prepared in good yield the 4-methoxy-2-nitrobenzonitrile as precursor of compound **2**, by reacting 3-nitro-4-bromoanisole with CuCN in DMF (Scheme 3). This method had already been used by some of us in the synthesis of 4-cyano-2,5-dimethylacetanilide from the corresponding brominated compound.[14]



Scheme 3. Synthesis of 4-methoxy-2-nitrobenzonitrile from 3-nitro-4-bromoanisole.

The 3-amino-6-nitrobenzo[*b*]thiophene **3** was prepared earlier by others in moderate yield from 2-fluoro-4-nitrobenzonitrile using NEt_3 in MeCN.[13]

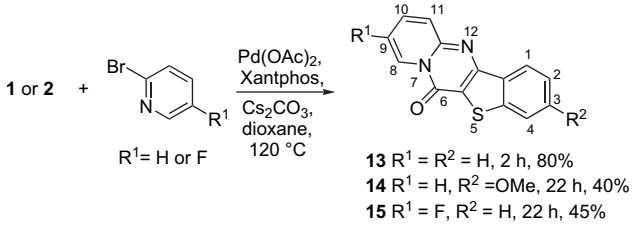
2.2. Synthesis of arylheteroarylamines by Buchwald–Hartwig coupling of bromobenzenes bearing electron-withdrawing groups with compounds 1–3

The methyl 3-aminobenzo[*b*]thiophene-2-carboxylates **1**–**3**, which are precursors by substitutive deamination of the 3-bromobenzo[*b*]thiophenes used earlier by us,[6] were coupled with several bromobenzenes bearing electron-withdrawing groups (CN, CHO, NO_2) and with bromobiphenyl under C–N coupling conditions used for heteroaromatic amines (Table 1).[6,10] The corresponding arylheteroarylamines **4**–**12** were obtained in moderate to good yields. In the synthesis of **6a** from amine **1** and 4-nitrobromobenzene, triarylamine **6b** was also isolated in a very low yield (Table 1). This may be due to the high reactivity of this bromobenzene as Buchwald–Hartwig coupling component, which reacts also with the diarylamine **6a**.

Attempts to perform the C–N couplings with bromobenzenes bearing methoxy groups even in the *meta* position were unsuccessful. This constitutes a limitation for the use of the amino compounds **1**–**3** as coupling components and it may be due to the deactivation of the amine by the methyl carboxylate of position 2.

2.3. Synthesis of tetracyclic compounds by Buchwald–Hartwig coupling of 2-bromopyridines with methyl 3-aminobenzo[*b*]thiophene-2-carboxylates 1 and 2 followed by intramolecular cyclization

The aminobenzo[*b*]thiophenes **1** and **2** reacted with 2-bromopyridines, using the same C–N coupling conditions presented in Table 1, giving compounds **13**–**15** after intramolecular cyclization (Scheme 4). This was already observed by us in the synthesis of compound **13** from the ethyl 3-bromobenzo[*b*]thiophene-2-carboxylate and 2-aminopyridine.[6]



Scheme 4. Synthesis of benzothieno[3,2-*d*]pyrido[1,2-*a*]pyrimid-6-ones by C–N coupling and intramolecular cyclization.

Compound **13** was obtained in an excellent yield after a short time of heating and its purification was easier using the actual starting materials. As this compound had already shown biological activity,[11] the substituted compounds obtained for the first time in the present work, **14** and **15**, will also be tested.

3. Conclusions

We were able to prepare several arylheteroarylamines and benzothieno[3,2-*d*]pyrido[1,2-*a*]pyrimid-6-ones from methyl 3-aminobenzo[*b*]thiophene-2-carboxylates by Buchwald–Hartwig C–N coupling followed in the latter case by an intramolecular cyclization. The method has a wide application to bromobenzenes bearing electron-withdrawing groups and electron deficient rings like bromopyridines. Nevertheless using these conditions, reaction with bromobenzenes bearing electron-donating groups did not occur.

The reactions presented here occur with the amino precursors of the corresponding brominated benzo[*b*]thiophenes, obtained by substitutive deamination, that we used before in this type of couplings thus avoiding one step.

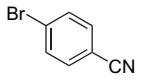
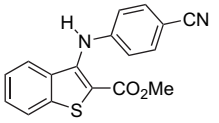
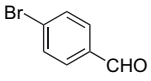
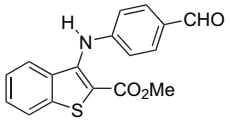
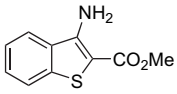
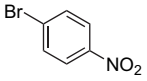
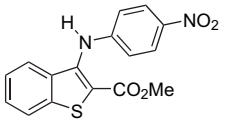
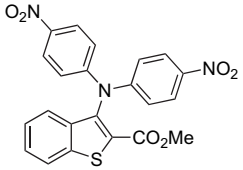
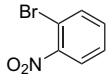
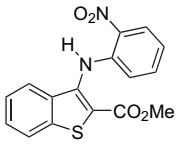
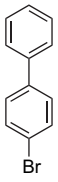
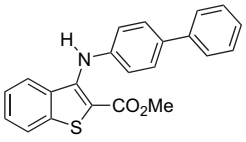
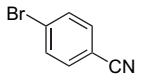
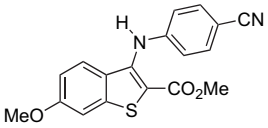
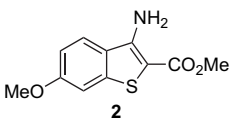
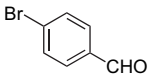
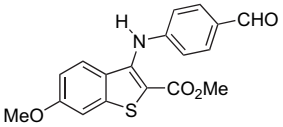
4. Experimental

4.1. Materials and methods

Melting points (°C) were determined in a Stuart SMP3 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus (300 and 75.4 MHz, respectively). ^{1}H–^{1}H spin–spin decoupling, DEPT θ 45° and bidimensional heterocorrelation ^{1}H–^{13}C techniques (HMQC and HMBC) were used to attribute some signals. Chemical shifts are given in parts per million and coupling constants in hertz. The mass spectra were obtained by electronic impact unless stated in the mass spectrometry external service of the University of Vigo (Spain). Elemental analysis was performed on a LECO CHNS 932 elemental analyzer.

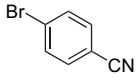
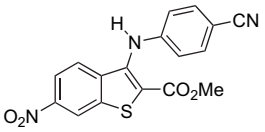
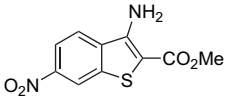
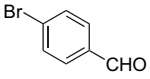
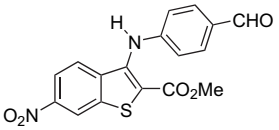
The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed on Macherey-Nagel silica gel 230–400 mesh. Preparative thin layer chromatography (PLC) was performed in 20×20 cm

Table 1. Buchwald–Hartwig coupling components and arylheteroarylamines products **4–12**

Amino compound	Bromobenzene	Time (h)	Arylheteroarylamine (%)
		3	 **4**, 65%
		2	 **5**, 70%
 **1**		3	 **6a**, 61% +  **6b**, 3%
		1	 **7**, 83%
		3	 **8**, 63%
		1	 **9**, 30%
 **2**		3	 **10**, 30%

(*continued*)

Table 1. (*continued*)

Amino compound	Bromobenzene	Time (h)	Arylheteroarylamine (%)
		5	 **11**, 35%
 **3**		3	 **12**, 76%

(i) $Pd(OAc)_2$ (10 mol %), Xantphos (12 mol %), Cs_2CO_3 (2.8 equiv), dry dioxane, 120 °C (silicone bath), 1–5 h.

plates Macherey-Nagel, Layer 2 mm SIL G-200 UV_{254}. Petroleum ether refers to the boiling range 40–60 °C. Ether refers to diethylether. When solvent gradient was used, the increase of polarity was made gradually from petroleum ether to mixtures of ether/petroleum ether increasing 10% of ether until the isolation of the product.

Xantphos refers to 4,5-bis(diphenylphosphane)-9,9-dimethylxanthene.

2-Nitrobenzonitrile and 2,4-dinitrobenzonitrile were purchased from Sigma–Aldrich.

4.1.1. 4-Methoxy-2-nitrobenzonitrile. 3-Nitro-4-bromoanisole (2.50 g, 0.0110 mol) was dissolved in anhyd DMF and CuCN (1.5 equiv) was added. The mixture was heated at 160 °C for 2 h. After cooling it was poured into crushed ice and a precipitate was formed, which was filtered and dried under vacuum. The greenish solid obtained was dissolved in $CHCl_3$ and the solution was filtered. The solvent removal of the filtrate gave a yellow solid (1.36 g, 71%), mp 129–131 °C. ^{1}H NMR ($CDCl_3$): 3.99 (3H, s, OMe), 7.28 (1H, dd, J=9 and 2.4 Hz, 5-H), 7.79–7.84 (2H, m, 3 and 6-H) ppm. ^{13}C NMR ($CDCl_3$): 56.52 (OCH_3), 99.40 (C), 111.06 (CH), 115.24 (C), 119.94 (CH), 136.59 (CH), 150.09 (C), 163.18 (C) ppm.

4.2. General procedure for the C–N coupling

In a dry Schlenk tube, dry dioxane (3–5 mL), the arylhalide (1.1 equiv), $Pd(OAc)_2$ (10 mol %), Xantphos (12 mol %), Cs_2CO_3 (2.8 equiv), and the methyl 3-aminobenzo[*b*]thiophene-2-carboxylates **1**–**3** were added under argon and the mixture was heated with stirring at 120 °C (silicone bath) for some hours (following the reaction by TLC). After cooling, ethyl acetate was added and the mixture was filtered under vacuum. The filtrate was evaporated under reduced pressure to give a residue, which was submitted to column chromatography (silica 230–400 mesh) using solvent gradient from neat petroleum ether to mixtures of diethyl ether/petroleum ether, increasing 10% of ether till the isolation of the product, unless stated otherwise.

4.2.1. Methyl 3-(4-cyanophenylamino)benzo[*b*]thiophene-2-carboxylate (4). 4-Bromobenzonitrile (145 mg, 0.796 mmol), amine **1** (150 mg, 0.724 mmol), heating for 3 h. Compound **4** was isolated by column chromatography using solvent gradient till 20% ether/petroleum ether as a white solid (145 mg, 65%), mp 139–141 °C, after some washes with petroleum ether. ^{1}H NMR ($CDCl_3$): 3.94 (3H, s, OMe), 7.00 (2H, d, J=8.7 Hz, 2′ and 6′-H), 7.27–7.33 (1H, m, Ar–H), 7.47–7.54 (4H, m, Ar–H), 7.81–7.85 (1H, m, ArH), 8.59 (1H, br s, N–H) ppm. ^{13}C NMR ($CDCl_3$): 52.23 (OCH_3), 104.37 (C), 112.41 (C), 118.63 (2′ and 6′-CH), 119.31 (C), 123.47 (CH), 124.11 (CH), 124.99 (CH), 127.95 (CH), 132.09 (C), 133.31 (3′ and 5′-CH), 139.67 (C), 142.43 (C), 146.74 (C), 165.08 (C=O) ppm. Anal. Calcd for $C_{17}H_{12}N_2O_2S$: C 66.22, H 3.92, N 9.08, S 10.40; found: C 66.29, H 4.07, N 9.15, S 10.01.

4.2.2. Methyl 3-(4-formylphenylamino)benzo[*b*]thiophene-2-carboxylate (5). 4-Bromobenzaldehyde (147 mg, 0.796 mmol), amine **1** (150 mg, 0.724 mmol), heating for 2 h. Compound **5** was isolated using column chromatography and 50% ether/petroleum ether as a yellow solid (158 mg, 70%), mp 139–140 °C, after some washes with petroleum ether. ^{1}H NMR ($CDCl_3$): 3.94 (3H, s, OMe), 7.06 (2H, d, J=8.4 Hz, 2′ and 6′-H), 7.25–7.32 (1H, m, Ar–H), 7.46–7.56 (2H, m, Ar–H), 7.77–7.85 (3H, m, ArH), 8.63 (1H, br s, N–H), 9.89 (1H, s, CHO) ppm. ^{13}C NMR ($CDCl_3$): 52.22 (OCH_3), 112.20 (C), 118.35 (2′ and 6′-CH), 123.42 (CH), 124.06 (CH), 125.20 (CH), 127.93 (CH), 130.45 (C), 131.38 (3′ and 5′-CH), 132.25 (C), 139.69 (C), 142.66 (C), 148.38 (C), 165.13 (C=O), 190.69 (CHO) ppm. Anal. Calcd for $C_{17}H_{13}NO_3S$: C 65.68, H 4.21, N 4.50, S 10.30; found: C 65.85, H 4.35, N 4.69, S 9.94.

4.2.3. Methyl 3-(4-nitrophenylamino)benzo[*b*]thiophene-2-carboxylate (6a) and methyl 3-(bis(4-nitrophenyl)-amino)benzo[*b*]thiophene-2-carboxylate (6b). 1-Bromo-4-nitrobenzene (161 mg, 0.796 mmol), amine **1** (150 mg, 0.724 mmol), heating for 3 h. Compound **6b** was isolated by column chromatography using solvent gradient till 20% ether/petroleum ether as a yellow solid (17.0 mg, 3%), mp 201–203 °C, after some washes with petroleum ether. ^{1}H NMR ($CDCl_3$): 3.76 (3H, s, OMe), 7.17 (4H, d, J=9.3 Hz, 2′,6′,2″ and 6″-H), 7.34–7.46 (2H, m, Ar–H), 7.54–7.60 (1H, m, Ar–H), 7.95 (1H, d, J=9 Hz, Ar–H), 8.16 (4H, d, J=9.3 Hz, 3′,5′,3″ and 5″-H) ppm. ^{13}C NMR ($CDCl_3$):

52.62 (OCH_3), 120.88 (4×CH), 123.12 (CH), 123.64 (CH), 125.50 (4×CH), 126.03 (CH), 128.44 (CH), 128.48 (C), 135.41 (C), 139.49 (C), 140.04 (C), 142.96 (C), 150.49 (C), 160.60 (C=O) ppm. MS (EI): *m/z* (%) 449.07 (M^+, 6), 389.12 (M^+-CO_2Me, 100). HRMS [M^+] calcd for $C_{22}H_{15}N_3O_6S$ 449.0682, found 449.0683.

Compound **6a** was isolated as the major product using 15% ether/petroleum ether as a yellow solid (143 mg, 61%), mp 133–135 °C, after some washes with petrol. ^1H NMR ($CDCl_3$): 3.95 (3H, s, OMe), 6.99 (2H, d, *J*=9 Hz, 2′ and 6′-H), 7.27–7.35 (1H, m, Ar–H), 7.49–7.55 (2H, m, Ar–H), 7.85 (1H, d, *J*=8.7 Hz, ArH), 8.15 (2H, d, *J*=9.3 Hz, 3′ and 5′-H), 8.66 (1H, br s, N–H) ppm. ^{13}C NMR ($CDCl_3$): 52.34 (OCH_3), 113.50 (C), 117.50 (2′ and 6′-CH), 123.54 (CH), 124.30 (CH), 124.93 (CH), 125.47 (3′ and 5′-CH), 128.06 (CH), 132.14 (C), 139.67 (C), 141.73 (C), 141.84 (C), 148.72 (C), 164.98 (C=O) ppm. MS (EI): *m/z* (%) 328.05 (M^+, 5), 298.08 (M^+-30, 31), 266.04 (100). HRMS [M^+] calcd for $C_{16}H_{12}N_2O_4S$ 328.0518, found 328.0527.

4.2.4. Methyl 3-(2-nitrophenylamino)benzo[*b*]thiophene-2-carboxylate (7). 1-Bromo-2-nitrobenzene (166 mg, 0.800 mmol), amine **1** (170 mg, 0.800 mmol), heating for 1 h. Compound **7** was isolated as a yellow solid (218 mg, 83%), mp 207–209 °C, after some washes with ether. ^1H NMR ($CDCl_3$): 3.96 (3H, s, OMe), 6.85–6.98 (2H, m, ArH), 7.29–7.38 (2H, m, ArH), 7.48–7.54 (2H, m, ArH), 7.85–7.88 (1H, m, ArH), 8.24 (1H, dd, *J*=8.4 and 1.5 Hz, ArH), 10.33 (1H, br s, NH) ppm. ^{13}C NMR ($CDCl_3$): 52.46 (OCH_3), 118.33 (C), 118.70 (CH), 119.48 (CH), 123.46 (CH), 124.46 (CH), 124.59 (CH), 126.41 (CH), 127.80 (CH), 133.27 (C), 134.83 (CH), 135.63 (C), 138.86 (C), 139.45 (C), 140.26 (C), 163.59 (C=O) ppm. MS (EI): *m/z* (%) 328.05 (M^+, 7), 298.08 (M^+-30, 7), 266.01 (100). HRMS [M^+] calcd for $C_{16}H_{12}N_2O_4S$ 328.0518, found 328.0524.

4.2.5. Methyl 3-(biphenyl-4-ylamino)benzo[*b*]thiophene-2-carboxylate (8). 4-Bromobiphenyl (169 mg, 0.724 mmol), amine **1** (150 mg, 0.724 mmol), heating for 3 h. Compound **8** was isolated by column chromatography using solvent gradient till 5% ether/petroleum ether as a yellow solid (163 mg, 63%), mp 158–159 °C, after some washes with petroleum ether. ^1H NMR ($CDCl_3$): 3.94 (3H, s, OMe), 7.12–7.22 (3H, m, ArH), 7.31–7.37 (1H, m, ArH), 7.40–7.57 (6H, m, ArH), 7.59–7.64 (2H, m, ArH), 7.79 (1H, m, ArH), 8.79 (1H, br s, NH) ppm. ^{13}C NMR ($CDCl_3$): 51.92 (OCH_3), 106.99 (C), 121.62 (2×CH), 123.26 (CH), 123.49 (CH), 125.71 (CH), 126.70 (2×CH), 126.94 (CH), 127.64 (2×CH), 127.69 (CH), 128.78 (2×CH), 131.97 (C), 136.12 (C), 140.04 (C), 140.52 (C), 141.61 (C), 145.86 (C), 165.76 (C=O) ppm. MS (EI): *m/z* (%) 359.10 (M^+, 41), 327.07 (100). HRMS [M^+] calcd for $C_{22}H_{17}NO_2S$ 359.0980, found 359.0973.

4.2.6. Methyl 3-(4-cyanophenylamino)-6-methoxybenzo[*b*]thiophene-2-carboxylate (9). 4-Bromobenzonitrile (98.0 mg, 0.500 mmol), amine **2** (120 mg, 0.500 mmol), heating for 1 h. Compound **9** was isolated by column chromatography using solvent gradient till 30% ether/petroleum ether as a yellow solid (51.0 mg, 30%), mp 205–207 °C, after washes with petrol. ^1H NMR ($CDCl_3$): 3.91 (3H, s, OMe), 3.92 (3H, s, OMe), 6.90 (1H, dd, *J*=9.0 and 2.4 Hz, 5-H), 7.00 (2H, d, *J*=8.7 Hz, 2′ and 6′-H), 7.23 (1H, d, *J*=2.4 Hz, 7-H), 7.36 (1H, d, *J*=9.0 Hz, 4-H), 7.52 (2H, d, *J*=8.7 Hz, 3′ and 5′-H), 8.62 (1H, br s, N–H) ppm. ^{13}C NMR ($CDCl_3$): 52.05 (OCH_3), 55.64 (OCH_3), 104.39 (C), 104.85 (7-CH), 109.52 (C), 114.94 (5-CH), 118.75 (2′ and 6′-CH), 119.32 (C), 125.77 (C), 125.86 (4-CH), 133.32 (3′ and 5′-CH), 141.93 (C), 142.61 (C), 146.72 (C), 160.08 (C), 165.12 (C=O) ppm. MS (EI): *m/z* (%) 338.07 (M^+, 40), 306.05 (M^+-OMe, 100). HRMS [M^+] calcd for $C_{18}H_{14}N_2O_3S$ 338.0725, found 338.0736.

4.2.7. Methyl 3-(4-formylphenylamino)-6-methoxybenzo[*b*]thiophene-2-carboxylate (10). 4-Bromobenzaldehyde (122 mg, 0.660 mmol), amine **2** (120 mg, 0.500 mmol), heating for 3 h. Compound **10** was isolated by column chromatography using solvent gradient till 30% ether/petroleum ether as a yellow solid (55.0 mg, 30%), mp 169–171 °C, after washes with petroleum ether. ^1H NMR ($CDCl_3$): 3.91 (3H, s, OMe), 3.92 (3H, s, OMe), 6.89 (1H, dd, *J*=9.0 and 2.4 Hz, 5-H), 7.06 (2H, d, *J*=8.7 Hz, 2′ and 6′H), 7.23 (1H, d, *J*=2.4 Hz, 7-H), 7.41 (1H, d, *J*=9.0 Hz, 4-H), 7.78 (2H, d, *J*=8.7 Hz, 3′ and 5′H), 8.68 (1H, br s, N–H), 9.88 (1H, s, CHO) ppm. ^{13}C NMR ($CDCl_3$): 52.04 (OCH_3), 55.62 (OCH_3), 104.73 (CH), 109.27 (C), 114.87 (CH), 118.42 (2′ and 6′-CH), 125.89 (C), 126.05 (CH), 130.41 (C), 131.37 (3′ and 5′-CH), 141.90 (C), 142.79 (C), 148.30 (C), 160.03 (C), 165.13 (C=O), 190.71 (CHO) ppm. MS (EI): *m/z* (%) 341 (M^+, 65), 281 (M^+-CO_2Me, 100). HRMS [M^+] calcd for $C_{18}H_{15}NO_4S$ 341.0722, found 341.0722.

4.2.8. Methyl 3-(4-cyanophenylamino)-6-nitrobenzo[*b*]-thiophene-2-carboxylate (11). 4-Bromobenzonitrile (107 mg, 0.590 mmol), amine **3** (150 mg, 0.590 mmol), heating for 5 h. The crude was submitted to a dry flash column using silica (150–230 mesh)/ether and compound **11** was isolated as a red solid (81.0 mg, 35%), mp 194–196 °C, after some washes with petrol. ^1H NMR ($CDCl_3$): 3.98 (3H, s, OMe), 6.99 (2H, d, *J*=8.4 Hz, 2′ and 6′-H), 7.53–7.63 (3H, m, ArH), 8.11 (1H, dd, *J*=9.0 and 2.1 Hz, 5-H), 8.59 (1H, br s, N–H), 8.76 (1H, d, *J*=2.1 Hz, 7-H) ppm. ^{13}C NMR ($CDCl_3$): 52.72 (OCH_3), 105.48 (C), 117.41 (C), 118.90 (5-CH), 118.95 (2′ and 6′-CH), 119.78 (7-CH), 125.62 (4-CH), 133.38 (C), 133.57 (3′ and 5′-CH), 136.04 (C), 139.28 (C), 141.64 (C), 146.08 (C), 146.92 (C), 164.22 (C=O) ppm. MS (FAB): *m/z* (%) 354 (M^++H, 54), 353 (M^+, 70). HRMS [M^++H] calcd for $C_{17}H_{12}N_3O_4S$ 354.0549, found 354.0551.

4.2.9. Methyl 3-(4-formylphenylamino)-6-nitrobenzo[*b*]-thiophene-2-carboxylate (12). 4-Bromobenzaldehyde (48.0 mg, 0.260 mmol), amine **3** (66.0 mg, 0.260 mmol), heating for 3 h. Compound **12** was isolated washing the crude with ether as a yellow solid (70.0 mg, 76%), mp 180–182 °C, after some washes with petroleum ether. ^1H NMR ($CDCl_3$): 3.99 (3H, s, OMe), 7.05 (2H, d, *J*=8.7 Hz, 2′ and 6′-H), 7.64 (1H, d, *J*=9.0 Hz, 4-H), 7.82 (2H, d, *J*=8.7 Hz, 3′ and 5′-H), 8.10 (1H, dd, *J*=9.0 and 2.1 Hz, 5-H), 8.66 (1H, br s, N–H), 8.76 (1H, d, *J*=2.1 Hz, 7-H), 9.91 (1H, s, CHO) ppm. ^{13}C NMR ($CDCl_3$): 52.68 (OCH_3), 118.70 (2′ and 6′-CH), 118.79 (5-CH), 119.73 (7-CH), 125.83 (4-CH), 128.24 (C), 131.17 (4′-C), 131.50 (3′ and 5′-CH), 136.21 (C), 139.28 (C), 141.91 (C), 146.90 (C), 147.60 (1′-C), 164.25 (C=O), 190.53 (CHO) ppm.

MS (FAB): *m/z* (%) 357 (M^++H, 100). HRMS [M^++H] calcd for $C_{17}H_{13}N_2O_5S$ 357.0545, found 357.0550.

4.3. Synthesis of 6*H*-benzothieno[3,2-*d*]pyrido-[1,2-*a*]pyrimid-6-ones

The same procedure as described above (Section 4.2) was used.

4.3.1. 6*H*-Benzothieno[3,2-*d*]pyrido[1,2-*a*]pyrimid-6-one (13). Amine **1** (100 mg, 0.483 mmol), 2-bromopyridine (76.2 mg, 0.483 mmol), heating for 2 h. The crude was submitted to a dry flash column using silica (150–230 mesh)/ether and compound **13** was isolated as a light yellow solid (98 mg, 80%), ^1H and ^{13}C spectra confer with the ones presented in our earlier work.[6]

4.3.2. 6*H*-3-Methoxybenzothieno[3,2-*d*]pyrido[1,2-*a*]pyrimid-6-one (14). 2-Bromopyridine (54.0 mg, 0.340 mmol), amine **2** (75.0 mg, 0.340 mmol), heating for 22 h. Compound **14** was isolated using preparative thin layer chromatography (PLC)/$CHCl_3$ as light yellow solid (43.0 mg, 40%), mp 284–286 °C. ^1H NMR (DMSO-d_6, T=70 °C): 3.92 (3H, s, OMe), 7.20 (1H, dd, J=8.7 and 2.4 Hz, 2-H), 7.28–7.34 (1H, m, ArH), 7.69 (1H, d, J=2.4 Hz 4-H), 7.78 (1H, d, J=8.7 Hz, ArH), 7.86–7.93 (1H, m, ArH), 8.25 (1H, d, J=8.7 Hz, 1-H), 9.00 (1H, br d, J=8 Hz, ArH) ppm. ^{13}C NMR (DMSO-d_6, T=70 °C): 55.60 (OCH_3), 106.51 (CH), 111.25 (C), 114.76 (CH), 114.85 (CH), 124.38 (CH), 125.43 (CH), 125.95 (CH), 127.05 (C), 135.44 (CH), 143.34 (C), 149.14 (C), 153.21 (C), 153.30 (C), 161.14 (C) ppm. MS (EI): *m/z* (%) 282 (M^+, 100). HRMS [M^+] calcd for $C_{15}H_{10}N_2O_2S$ 282.0463, found 282.0460.

4.3.3. 6*H*-9-Fluoro-benzothieno[3,2-*d*]pyrido[1,2-*a*]pyrimid-6-one (15). 2-Bromo-5-fluoropyridine (131 mg, 0.724 mmol), amine **1** (150 mg, 0.724 mmol), heating for 22 h. The crude was submitted to column chromatography from neat petroleum ether till 20% ethyl acetate/petroleum ether and compound **15** was isolated as a light yellow solid (79.0 mg, 45%), mp 277–279 °C, after some washes with petroleum ether. ^1H NMR (DMSO-d_6, T=60 °C): 7.60–7.66 (1H, m, ArH), 7.69–7.75 (1H, m, ArH), 7.88–7.94 (1H, m, ArH), 7.99–8.06 (1H, m, ArH), 8.16 (1H, d, J=8.1 Hz, ArH), 8.38 (1H, br d, J=7.8 Hz, ArH), 8.94–8.97 (1H, m, ArH) ppm. ^{13}C NMR (DMSO-d_6, T=60 °C): 109.02 (C), 111.95 (d, J=42 Hz, CH), 123.49 (CH), 123.69 (CH), 125.29 (CH), 127.88 (d, J=11.46 Hz, CH), 128.11 (d, J=6.64 Hz, CH), 129.81 (CH), 133.59 (C), 140.92 (C), 147.23 (C), 153.24 (d, 241.58 Hz, C–F), 152.88 (C), 153.33 (C) ppm. MS (EI): *m/z* (%) 270 (M^+, 100). HRMS [M^+] calcd for $C_{14}H_7FN_2OS$ 270.0263, found 270.0262.

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