Novel synthetic routes to thienocarbazoles *via* palladium or copper catalyzed amination or amidation of arylhalides and intramolecular cyclization

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Abstract – Palladium or copper catalyzed aminations or amidations were performed to obtain diarylamines and diarylacetamides precursors of thienocarbazoles. The fact that an *ortho*-bromodiarylamine didn't cyclize to the corresponding thienocarbazole under conditions known for carbazoles from *ortho*-halodiphenylamines, conducted us to a highgly efficient method of palladium-catalyzed intramolecular cyclisation with *N*-deprotection of *ortho*-halodiarylacetamides to thienocarbazoles. Other method of intramolecular cyclization of diarylamines based on the reoxidation of the Pd(0) formed by $Cu(OAc)_2$, avoiding the use of stoichiometric amounts of $Pd(OAc)_2$, gave thienocarbazoles in a moderate yield, including a ring A methoxylated compound. An attempt to combine palladium and copper catalyses in a "one pot" reaction of amination and intramolecular cyclization gave as major product a *N*-benzo[*b*]thiophene substituted carbazole and the required thienocarbazole in low yield.

1. Introduction

Due to their interesting biological activities carbazole alkaloids constitute an important class of natural compounds.[1] Their isolation from different sources (terrestrial plants, marine sources and streptomycetes) induced the development of novel strategies of synthesis of structurally unprecedent carbazole derivatives.[2] Heteroannellated carbazoles are often of potential biological interest, mostly based on their special affinity to DNA. Therefore this type of compounds play a crucial role as potential leads for the discovery of antitumor active drugs.[3]

One of the standard methodologies that the medicinal chemist can use as a rational approach to lead optimisation is the bioisosteric replacement.[4,5] Bioisosteres are substituents or groups, that do not necessarily have the same size or volume, but have a similarity in chemical or physical properties which could produce broadly similar biological properties but being expected significant changes in selectivity, toxicity and metabolic stability. However there are many examples where bioisosteric replacements have resulted in marked increases in potency as well as efficacy. The use of classical

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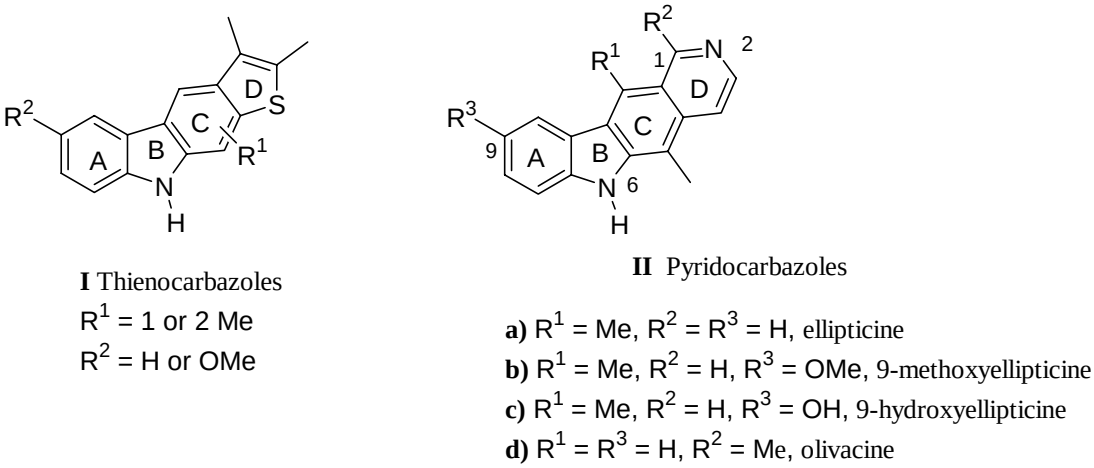
isosteres as benzene, thiophene and pyridine resulted in analogues with biological activity retention among different series of pharmacological agents.[5] Thus thienocarbazoles **I** are bioisosteric analogues of the known natural antitumoral pyridocarbazoles, ellipticines **IIa-c** and olivacine **IId**, by substitution of the pyridine ring by a thiophene and are being prepared to evaluate their biological activity either as DNA intercalating compounds, interacting or not with Topoisomerase II, or as radical scavengers compounds.[6] The achievement of less toxic compounds than pyridocarbazoles is also a very important goal.



I Thienocarbazoles
R^1 = 1 or 2 Me
R^2 = H or OMe

II Pyridocarbazoles

a) R^1 = Me, R^2 = R^3 = H, ellipticine
b) R^1 = Me, R^2 = H, R^3 = OMe, 9-methoxyellipticine
c) R^1 = Me, R^2 = H, R^3 = OH, 9-hydroxyellipticine
d) R^1 = R^3 = H, R^2 = Me, olivacine

Figure 1. Structure of thienocarbazoles **I** and pyridocarbazoles **II**

The sulfur atom can provide interesting properties to this type of molecules like the establishement of additional long distance hydrogen bonds with the DNA chains or even confer to the molecule interesting photochemical properties for use as markers or in phototherapy applications.[7, 8] Some preliminary studies of fluorescence of our new molecules have already begun.

The methyl groups and their position on the bioactive pyridocarbazoles showed to be important for the antitumor activity.[9] Ring A substitution had also proven to be very important for the activity being 9-methoxy and 9-hydroxyellipticines **IIb** and **c** much more active than ellipticine **IIa**.[10]

In recent years we have been interested in finding a ring B method for the synthesis of substituted linear and angular thienocarbazoles, in order to evaluate their structure-activity relationship. The angularity or the linearity of the molecules, the position of the methyl groups, together with the introduction of ring A substituents, namely groups that increase water solubility and/or activity, are important features for biological devices.

Some convergent ring B methods have already been envisaged by us for the synthesis of several methylated thienocarbazoles but the yields were either too low from diarylamines [11,12] or fair to moderate from nitrodiaryl compounds.[13]

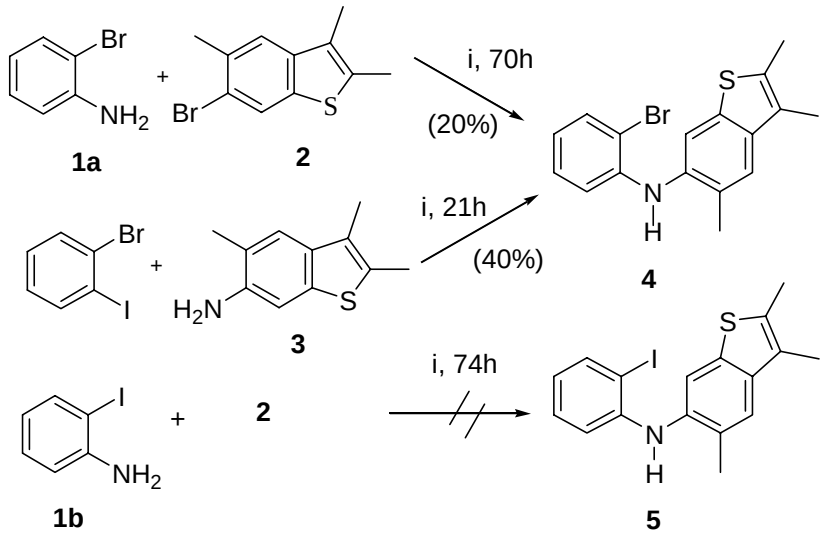
In this paper we report a high efficient palladium-catalyzed cyclization with deprotection of *ortho*-halodiarylamides, prepared by copper-catalyzed Goldberg coupling, [11] to the corresponding novel thieno[3,2-*c*]carbazole. This method enables the synthesis of differently substituted hiherto linear and angular thienocarbazoles from appropriated precursors.

Other method of cyclization based in the reoxidation of Pd(0) by $Cu(OAc)_2$[14], avoiding the use of a stoichiometric amount of Pd $(OAc)_2$ in the oxidative cyclization of diarylamines gave also rise to the corresponding thieno[3,2-*c*]carbazoles, including a ring A methoxylated, in a moderate yield. The diarylamines were prepared either by hydrolysis of diarylacetamides or by palladium catalyzed amination of aryl halides under Buchwald's conditions.[15] An *ortho*-bromodiarylamine obtained using the latter conditions, didn't cyclise to the corresponding thienocarbazole under the Sakamoto's cyclisation conditions.[16]

2.Results and discussion

2.1. Synthesis of an *ortho*-bromodiarylamine under Buchwald's conditions and attempted intramolecular cyclisation

First it was decided to couple *ortho*-haloanilines **1a** and **1b** with 6-bromobenzo[*b*]thiophene **2** [17] or 2-bromo-iodobenzene with 6-aminobenzo[*b*]thiophene **3** under Buchwald's conditions [15] to obtain *ortho*-halodiarylamines. Some modifications such as the use of higher amounts of $Pd(OAc)_2$ (3 mol%) and BINAP (4 mol%) comparing to those used in literature [15] were needed in our case, may be due to some complexation of the palladium by the sulfur atom. Bromobenzo[*b*]thiophene **2** gave 20% yield of *o*-bromodiarylamine **4** in the coupling with *o*-bromoaniline (Scheme 1). When *o*-bromo-iodobenzene was reacted with aminobenzothiophene **3**, the yield was increased to 40% in one third of the reaction time. The reactions were followed by TLC and stopped when the formation of the product seemed not to increase. In both cases the starting materials were recovered. Under the same conditions no iodo diarylamine **5** could be prepared from compounds **1b** and **2**, occurring decomposition of the aniline.

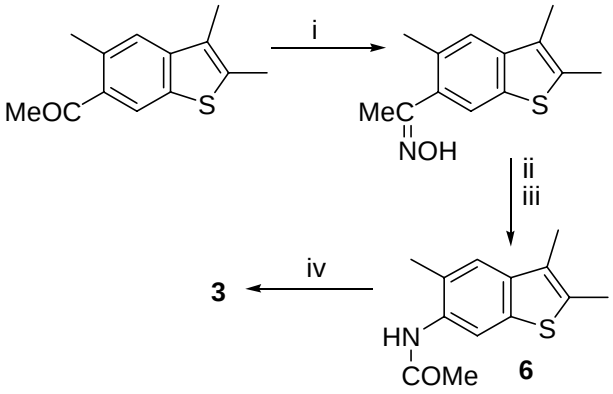


i) $Pd(OAc)_2$ (3mol%), BINAP(4mol%), *t*BuONa (1.4 equiv.), toluene 90 ^oC, under Ar

Scheme 1. Synthesis of *o*-bromodiarylamine **4** by palladium catalyzed amination of arylhalides

The use of $Pd_2(dba)_3$ and DPPF, as described for the preparation of *ortho*-halodiphenylamines precursors of carbazole,[16] was not effective in our case.

The amine **3** was obtained under drastic basic conditions [18] from the corresponding steric hindered acetamide **6** which was prepared by Beckmann rearrangement of the oxime of 6-acetylated compound [19] (Scheme 2).



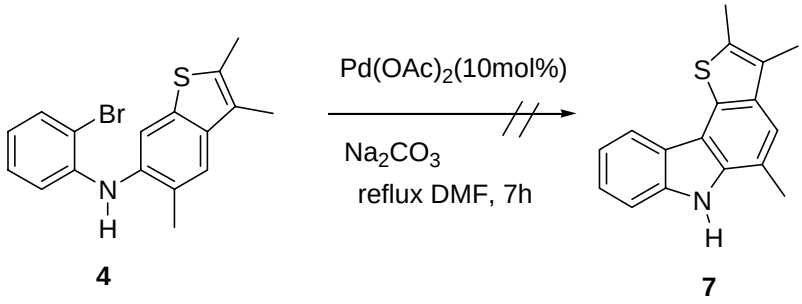
i) $NH_2OH.HCl$, NaOH, H_2O/EtOH, 1h30min reflux ; ii) dry ether, PCl_5
iii) removal of ether, H_2O, 1h reflux; iv) 10equiv. NaOH, ethyleneglycol 1h reflux

Scheme 2. Synthesis of amide **6** and amine **3**

Attempts to perform the C-N coupling using the acetamide **6** under Buchwald's conditions were unsuccessfull.

When the *ortho*-bromodiarylamine **4** was submitted to Sakamoto's intramolecular cyclization conditions, that have worked to obtain carbazoles from *ortho*-bromodiphenylamine,[16]

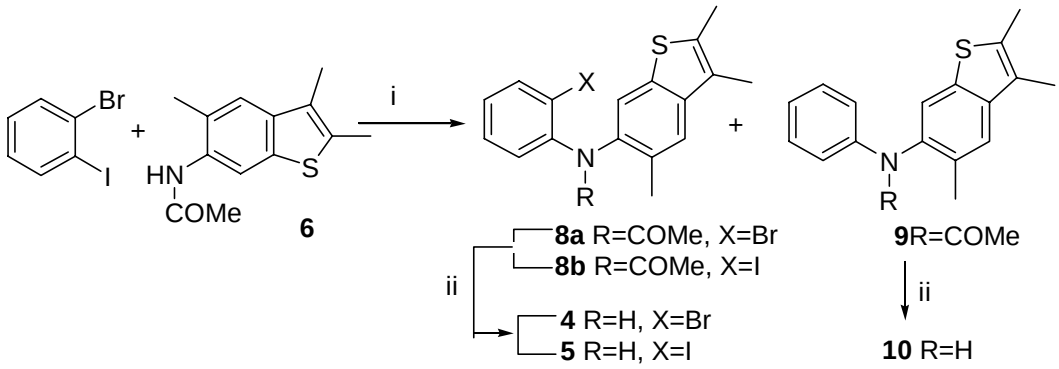
thienocarbazole **7** did not form (Scheme 3). Changing the base to NEt_3 no thienocarbazole was obtained either.



Scheme 3. Attempted intramolecular cyclization by Sakamoto's conditions

2.2. Synthesis of *ortho*-halodiarylamides by Goldberg coupling and intramolecular cyclisation

The latter unsuccessful result led us to try our Goldberg coupling conditions,[11] reacting acetamide **6** with 2-bromo-iodobenzene using 30 mol% of Cu_2O, K_2CO_3, heating without solvent at 180 ^oC. A mixture of acetamides **8a** and **8b** (~ 40% yield) was obtained and it was impossible to separate the compounds by chromatography, being characterized by mass spectrometry. Along with amides **8a** and **8b** the dehalogenated amide **9** was isolated in 8% yield (Scheme 4). The use of a stoichiometric amount of Cu_2O didn't increase significatively the yield for amides **8a,b** and the yield for amide **9**, as a by-product was not altered.

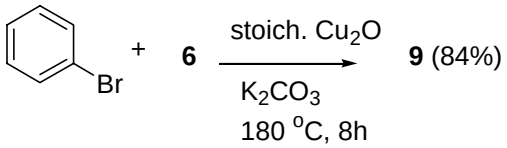


Scheme 4. Synthesis and deprotection of diarylamides **8** and **9**

Due to the hindered rotation around the amide bond in **8**, ^{1}H-NMR spectra of these compounds reveal several sets of signals and could not be used for structure assignment. Thus, the amides **8** were converted to amines **4** and **5,** obtained also as a mixture (~ 75% yield), using drastic basic conditions[17] in gently refluxing ethylene glycol (silicone bath at 200 ^oC) (Scheme 4). Iododiarylamine **5** was characterized by ^{1}H-NMR excluding the proton signals of amine **4** already

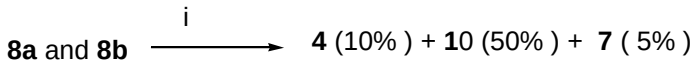
prepared by palladium catalysis (Scheme 1). The structure of amine **5** was also confirmed deprotecting the amide **8b** independently obtained (30% yield) from Goldberg coupling (soich. Cu_2O) of 1,2-di-iodobenzene and amide **6**. The same reaction was also performed using the much less expensive 1,2-dibromobenzene and **6** to give amide **8a** (30% yield) which was submitted to Sakamoto's cyclization conditions to afford thienocarbazole **7** in high yield..

Amide **9** showed also hindered rotation in the ^{1}H-NMR spectrum giving after deprotection, in the same conditions, the corresponding amine **10** (Scheme 4). Amide **9** was independently synthesized in high yield using the Goldberg coupling reaction and a stoichiometric amount of Cu_2O as outlined in Scheme 5.



Scheme 5. Golbberg coupling to obtain amide **9**

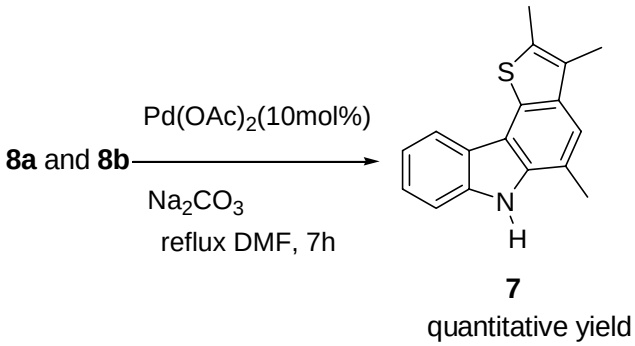
Deprotection of **8a** and **8b** with NaOH in a vigourous refluxing ethylene glycol (silicone bath at 220 ^{o}C), resulted in the formation of **10** in 50% yield, together with the *ortho*-bromodiarylamine **4** in 10% yield and the thienocarbazole **7** in 5% yield (Scheme 6). In another experiment increasing the time of reflux in these conditions, the proportions of the three products did not change. The formation of thienocarbazole **7** in these conditions indicates that a strong basic medium submitted to a high temperature induces in a small extent the cyclization reaction, possibly through a benzyne intermediate.



i) NaOH (10equiv.), ethylene glycol, 1h vigorous reflux

Scheme 6. Drastic basic conditions in ethylene glycol vigorous refluxing

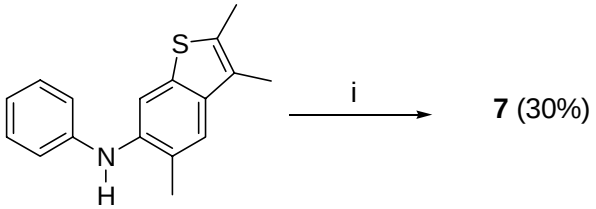
While Sakamoto's cyclization conditions have only been used with *o*-halodiarylamines, we decided to use them with the mixture of *o*-haloacetamides **8a** and **8b**. Surprisly the thienocarbazole **7** was obtained with *N*-deprotection, in quantitative yield (Scheme 7). A control experiment performed in the same conditions without the palladium catalyst, did not provide the thienocarbazole **7**.



Scheme 7. High efficient synthesis of thienocarbazole **7**

2.3. Intramolecular cyclisation of diarylamines using $Pd(OAc)_2$ and $Cu(OAc)_2$

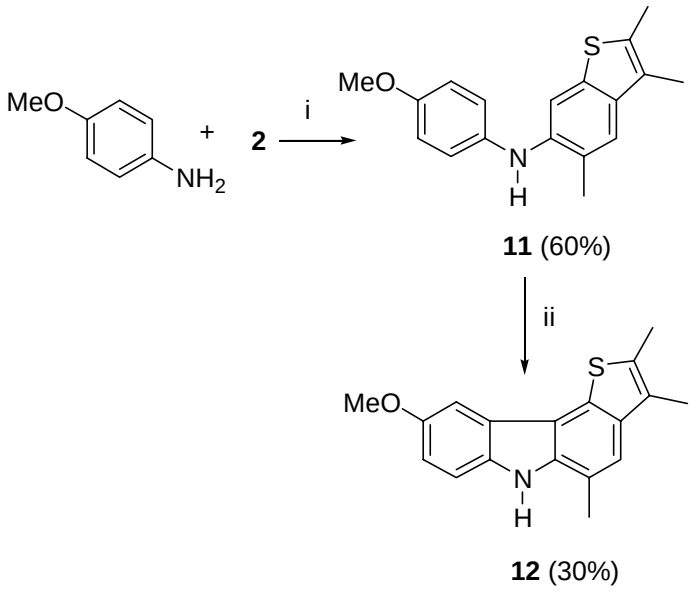
Cyclization of the dehalogenated acetamide **9** to thienocarbazole **7** didn't occur when the same conditions were used, but the corresponding amine **10** gave the thienocarbazole **7** in 30% yield when treated with palladium acetate (50mol%) and copper acetate (3equiv.) in acetic acid at 120 ^{o}C, (Scheme 8). The role of $Cu(OAc)_2$ is the reoxidation of the Pd(0) formed after electrophilic attack of $Pd(OAc)_2$ on the aromatic rings, avoiding the use of a stoichiometric amount of this reagent.[14]



i) $Pd(OAc)_2$ (50mol%), $Cu(OAc)_2$ (3equiv.), acetic.acid 120 ^{o}C, 7h

Scheme 8.Cyclization of diarylamine **10** to thienocarbazole **7**

This also constitutes a valuable method for the synthesis of thienocarbazoles that will be applied to diarylamines prepared either by *N*-deprotection of diarylacetamides or by palladium catalysed amination of arylhalides. As an example, the methoxydiarylamine **11** was prepared in 60 % yield, coupling the arylhalide **2** with 4-methoxyaniline under Buchwald's conditions and then cyclized to the corresponding methoxylated thieno[3,2-*c*]carbazole **12** in 30% yield in the same oxidative conditions (Scheme 9).

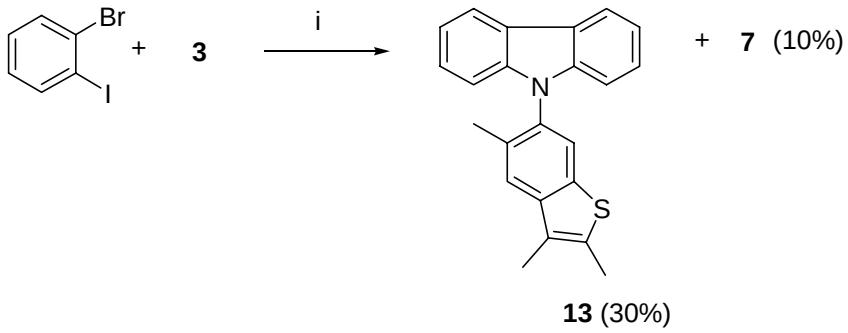


i) $Pd(OAc)_2$ (3mol%), BINAP(4mol%), 1.4 equiv. *t*BuONa, toluene 90 ^oC, 24h, under Ar
ii) $Pd(OAc)_2$ (50mol%), $Cu(OAc)_2$ (3equiv.), acetic.acid 120 ^oC, 7h

Scheme 9. Synthesis of diarylamine **11** by Buchwald coupling and cyclization to thienocarbazole **12**

2.4. "One pot" procedure of C-N coupling and intramolecular cyclisation combining copper and palladium catalyses

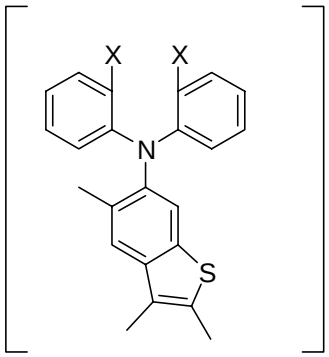
A "one pot" procedure attempt to obtain the thienocarbazole **7**, combining copper and palladium catalyses, reacting amine **3** with 2-bromo-iodobenzene in reflux of DMF for 10 h, gave the *N*-benzo[*b*]thiophene substituted carbazole **13** (M^+ 341) as major product in 30% yield and the thienocarbazole **7** only in 10% yield (Scheme 11). Lowering the time of heating the two products were obtained in the same proportion.



i) Cu_2O (20mol%), $Pd(OAc)_2$ (10mol%), K_2CO_3, DMF, 10h reflux

Scheme 10. "One pot" procedure to carbazole **13** and thienocarbazole **7**

The formation of a dihalogenated intermediate **14** before cyclization to carbazole **13**, is in agreement with the synthesis of *N*-methylsulfonylcarbazole from *N*-methylsulfonyl-*o,o´*-dibromodiphenylamine.[16]



14

X=Br or I

The same "one pot" conditions were not successful when applied to acetamide **6** and 2-bromo-iodobenzene, resulting in extensive decomposition.

3.Conclusion

Novel synthetic routes to thienocarbazoles based on the combination of metal assisted C-N coupling and intramolecular cyclisations were described. The target compounds could act as DNA-binding agents which may be used as biological or medical relevant probes or drugs. These methods will be applied to the preparation of linear and angular methylated thienocarbazoles substituted in ring A by electron donating or withdrawing groups, for evaluation of their biological activity and structure activity relationship.

4.Experimental

4.1. Materials and methods

Melting points (^{o}C) were determined in a Gallenkamp apparatus and are uncorrected. IR spectra were recorded as nujol mulls on a Perkin-Elmer 1600-FTIR spectrophotometer and wavenumbers are given in cm^{-1}. ^{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 and DEPT θ 45º were used. Chemical shifts are given in ppm and coupling constants in Hz. The mass spectra were obtained on a Unicam GC/MS 120 spectrometer or on a Micromass Autospec 3F by an electronic impact (70eV) direct injection method. Elemental analysis was performed on a LECO CHNS 932 elemental analyser.

The reactions were monitered by thin layer chromatography (TLC). Column chromatography was performed on Macherey-Nagel silica gel 230-400 mesh. Preparative Layer Chromatography (PLC)

was performed in 20x20cm plates Macherey-Nagel, Layer 2mm SIL G-200 UV_{254}. Petroleum ether refers to the boiling range 40-60 ^{o}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.

4.2. Synthesis of 6-Acetamido-2,3,5-trimethylbenzo[*b*]thiophene (6): To hydroxylamine hydrochloride (8.30 g, 119 mmol) in 13 ml of water, a solution of NaOH (3.50 g, 87.5 mmol) in 12 ml of water was added with external cooling. 6-Acetyl-2,3,5-trimethylbenzo[*b*]thiophene [19] (12.5 g, 57.0 mmol) was then added in a sufficient amount of ethanol to promote a homogeneous solution, which was heated at reflux for 1 h 30 min. After cooling the precipitate formed was filtered and dried at 60 ^{o}C. The colourless solid obtained showed to be the corresponding oxime (10.6 g, 80%) m.p. 191-193 (lit[19] 191, from petroleum ether). ^{1}H NMR: ($CDCl_3$): 2.26 (3H, s, Me), 2.28 (3H, s, Me), 2.46 (3H, s, Me), 2.50 (3H, s, Me), 7.41 (1H, s, H-7), 7.60 (1H, s, H-4). MS: 233 (100, M^+) 218 (78) 201 (82). To the oxime (6.00 g, 25.7 mmol) in dry ether (150 ml) PCl_5 (6.00 g, 28.6 mmol) was added and the mixture was left stirring for 30 min. The ether was removed and water was added. The aqueous mixture was heated at reflux for 1h 30min and after cooling the colourless precipitate formed was filtered, dried and showed to be the amide **6** (4.00 g, 67%), m.p. 188-190. IR: 3237 (N-H), 1651 (C=O). ^{1}H NMR: ([D_6]DMSO) 2.08 (3H, s, Me), 2.23 (3H, s, Me), 2.31 (3H, s, Me), 2.43 (3H, s, Me), 7.47 (1H, s, H-4), 7.85 (1H, s, H-7), 9.33 (1H, s, N-H).^{13}C NMR: ([D_6]DMSO) 11.10 (CH_3), 13.49 (CH_3), 18.19 (CH_3), 23.31 (NCO*C*H_3), 117.92, 122.06, 126.28 (C), 128.32 (C), 132.88 (C), 133.06 (C), 134.65 (C), 138.07 (C), 168.35 (C). MS: 233 (73, M^+), 191 (100), 190 (53), 176 (41). Anal. calcd for $C_{13}H_{15}NOS$:. C 66.92, H 6.48, N 6.00, S 13.74 %; found: C 66.79, H 6.23, N 5.94, S 13.72.

4.3. General procedure for the synthesis of diarylamines 4 and 11 under Buchwald's conditions: A dry Schlenk tube was charged under Ar with dry toluene (3-4 ml), the arylhalide, the arylamine, *t*-BuONa (1.4 equiv.), $Pd(OAc)_2$ (3 mol%), racemic BINAP (4 mol%) and the mixture was heated at 90 ^{o}C for several hours. The reaction was followed by TLC. After cooling water and ether were added. The organic phase was separated, dried ($MgSO_4$) and solvent removed to give an oil which was submitted to chromatographic purification to give the product and starting materials.

4.3.1. 6-(2-Bromophenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (4): From arylhalide **2** [17] (0.510 g, 2.00 mmol) and bromoaniline **1a** (0.430 g, 2.50 mmol) heating for 70 h and column chromagraphy using petroleum ether, the arylhalide **2** was recovered in 57% yield as the less polar product, compound **4** was obtained in 20% yield as a white solid, m.p.126-128. IR: 3377 (N-H). ^{1}H NMR: ($CDCl_3$) 2.29 (3H, s, Me), 2.37 (3H, s, Me), 2.47 (3H, s, Me), 5.96 (1H, s, N-H), 6.69 (1H,

oct, *J* = 7.93, 7 and 1.5, H-4'), 6.81 (1H, dd, *J* = 8.24 and 1.5, H-6'), 7.11 (1H, sept, *J* = 8.24, 7 and 1.5, H-5'), 7.46 (1H, s, H-7), 7.52 (1H, dd, *J* = 7.93 and 1.5, H-3'), 7.61 (1H, s, H-4). ^{13}C NMR: ($CDCl_3$) 11.37 (CH_3), 13.76 (CH_3), 18.33 (CH_3), 110.94 (C), 114.70, 116.45, 119.75, 122.84, 126.44, 128.19, 128.99 (C), 132.69, 133.02 (C), 136.11 (C), 136.38 (C), 138.31 (C), 142.90 (C). Anal. calcd for $C_{17}H_{16}BrNS$: C 58.97, H 4.66, N 4.04, S 9.26; found: C 58.71, H 4.77, N 3.91, S 9.31.

From 2-bromo-iodobenzene (0.185 g, 0.650 mmol) and arylamine **3** (0.100 g, 0.500 mmol) heating for 21 h, compound **4** was obtained in 40% yield after column chromatography.

4.3.2. 6-(4-Methoxyphenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (11): From arylhalide **2** (0.240 g, 2.00 mmol) and 4-methoxyaniline (0.500 g, 2.00 mmol), heating for 24 h, and using solvent gradient from petroleum ether to 30% ether/petroleum ether in the chromatographic purification, compound **11** was obtained as a white solid (0.350 g, 60%), m.p. 127-129, which after crystallization from ether/petroleum ether gave white crystals m.p. 130-132. IR: 3394 (N-H). ^{1}H NMR: ([D_6]DMSO) 2.19 (3H, s, Me), 2.29 (3H, s, Me), 2.36 (3H, s, Me), 3.70 (3H, s, OMe), 6.84 (2H, d, *J* = 9, H-3' and 5'), 6.94 (2H, d, *J* = 9, H-2' and 6'), 7.03 (1H, s, H-7), 7.28 (1H, s, H-4), 7.38 (1H, s, N-H). ^{13}C NMR: ([D_6]DMSO) 11.12 (CH_3), 13.31 (CH_3), 18.39 (CH_3), 55.19 (OCH_3), 108.52, 114.53, 120.18, 122.66, 125.01 (C), 126.15 (C), 129.59 (C), 134.54 (C), 135.83 (C), 137.62 (C), 140.73 (C), 153.54 (C). Anal. calcd for $C_{18}H_{19}NOS$: C 72.70, H 6.44, N 4.71, S 10.78; found: C 73.00, H 6.27, N 4.78, S 10.70.

4.4. Goldberg coupling

4.4.1 6-(2-Bromophenyl)acetamido-2,3,5-trimethylbenzo[*b*]thiophene (8a), 6-(2-iodophenyl)acetamido-2,3,5-trimethylbenzo[*b*]thiophene (8b) and 6-(phenyl)acetamido-2,3,5-trimethylbenzo[*b*]thiophene (9): A mixture of the acetamide **6** (1.00 g, 4.30 mmol), 2-bromo-iodobenzene (1.80 g, 6.40 mmol), K_2CO_3 (0.600 g, 4.30 mmol), Cu_2O (0.190 g, 1.33 mmol) was heated at 180 ^{o}C for 12 h. After cooling chloroform was added and the mixture was filtered. The filtrate was evaporated to give a brown oil which was submitted to column chromatography using solvent gradient from petroleum ether to 50% ether/petroleum ether. As the less polar product, the dehalogenated amide **9** was obtained as a white solid (0.100 g, 8%), m.p. 212-214. IR: 1675 (C=O). ^{1}H NMR spectra in $CDCl_3$ or in [D_6]DMSO at several temperatures showed hindered rotation, being this compound identified by the ^{1}H NMR spectrum of the corresponding amine **10** (see below). MS: 312 (8, M^++2), 311 (20, M^++1,), 310 (100, M^+). Anal. calcd for $C_{19}H_{19}NOS$: C 73.75, H 6.19, N 4.53, S 10.36; found: C 73.45, H 6.37, N 4.74, S 10.34.

Another fraction was isolated as a yellow light solid and showed to be a mixture of **8a** and **8b** (0.650 g, ~ 40%), m.p. 148-150. ^{1}H NMR spectra in $CDCl_3$ or in [D_6]DMSO at several temperatures showed hindered rotation, being the characterization done by the obtention of the corresponding amines **4** and **5** (see below). MS: 436 (100, M^+ of **8b**, 100), 390 (30, M^+ ^{81}Br of **8a**), 388 (30, M^+ ^{79}Br of **8a**).

4.4.2. 6-(phenyl)acetamido-2,3,5-trimethylbenzo[*b*]thiophene (9): A mixture of the acetamide **6** (0.215 g, 0.920 mmol), 2-bromobenzene (0.174 g, 1.10 mmol), K_2CO_3 (0.320 g, 2.30 mmol), Cu_2O (0.130 g, 0.920 mmol) was heated at 180 ^{o}C for 8 h. After cooling chloroform was added and the mixture was filtered. The filtrate was evaporated to give a brown oil which was submitted to column chromatography using solvent gradient from petroleum ether to 10% ether/petroleum ether to give amide **9** as a white solid (0.240 g, 84%) with identical properties to those presented above.

4.5. General procedure of deprotection of acetamides 6, 8a,b and 9: A solution of the acetamide and sodium hydroxide (10 equiv.) in ethylene glycol was heated at reflux (silicone bath at 200 ^{o}C). After cooling, the mixture was poured into iced water and after stirring, extracted with ether. The organic phase was dried ($MgSO_4$), filtered and the solvent removed to give an oil which was submitted to chromatographic purification or to crystallization.

4.5.1. 6-Amino-2,3,5-trimethylbenzo[*b*]thiophene (3): Acetamide **6** (0.700 g, 3.00 mmol), NaOH (1.20 g, 30.0 mmol) in ethylene glycol (5 ml) were heated for 3 h. Chromatographic column using solvent gradient from petroleum ether to 50% ether/petroleum ether, gave the amine **3** as a colourless solid (0.357 g, 51%), m.p. 96-98. IR: 3423 (N-H). ^{1}H NMR: ($CDCl_3$) 2.22 (3H, s, Me), 2.30 (3H, s, Me), 2.41 (3H, s, Me), 3.60 (1H, s, N-H), 7.04 (1H, s, H-7), 7.26 (1H, s, H-4).^{13}C NMR: ($CDCl_3$) 11.37 (CH_3), 13.54 (CH_3), 17.90 (CH_3), 106.99, 120.70 (C), 122.35, 126.25 (C), 129.12 (C), 134.16 (C), 137.03 (C), 141.60 (C). Anal. calcd for $C_{11}H_{13}NS$: C 69.07, H 6.85, N 7,32, S 16.76; found: C 68.96, H 6.89, N 7.25, S 16.57.

4.5.2. 6-(2-Bromophenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (4) and 6-(2-iodophenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (5): A mixture of acetamides **8a** and **8b** (0.200 g, ~ 0.460 mmol)) and sodium hydroxide (0.184 g, 4.60 mmol)) in ethylene glycol (5 ml) was refluxed for 1 h. After column chromatography using solvent gradient from petroleum ether to 30% ether/ petroleum ether, a white solid was obtained (~ 75%) which ^{1}H NMR spectrum showed to be a mixture of amines **4** and **5** being **5** in a slightly excess. ^{1}H NMR: ($CDCl_3$) 2.29 (2x3H, s, 2xMe of **4** and **5**), 2.37 (2x3H, s, 2xMe of **4** and **5**), 2.47 (2x3H, s, 2xMe of **4** and **5**), 5.82 (1H, s,

N-H of **5**), 5.96 (1H, s, N-H of **4**), 6.57 (1H, oct, *J* = 7.93, 7 and 1.5, H-4' of **5**), 6.69 (1H, oct, *J* = 7.93, 7 and 1.5, H-4' of **4**), 6.77 (1H, dd, *J* = 8.24 and 1.5, H-6' of **5**), 6.81 (1H, dd, *J* = 8.24 and 1.5, H-6' of **4**), 7.11 (1H, sept partially obscured, *J* = 8.24, 7 and 1.5, H-5' of **4**), 7.14 (1H, sept partially obscured, *J* = 8.24, 7 and 1.5, H-5' of **5**) 7.46 (2x1H, s, 2x H-7 of **4** and **5**), 7.52 (1H, dd, *J* = 7.93 and 1.5, H-3' of **4**), 7.60 (1H, s, 2x H-4 of **4** and **5**), 7.77 (1H, dd, *J* = 7.93 and 1.5, H-3' of **5**).

The signals of compound **4** were later confirmed from the deprotection of amide **8b**, independently obtained from the Goldberg coupling of 1,2-di-iodobenzene and amide **6** (see section 2.2).

4.5.3. 6-(Phenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (10): A mixture of amide **9** (0.100 g, 0.323 mmol) and sodium hydroxide (0.130 g, 3.20 mmol) in ethylene glycol (5 ml) was refluxed for 1 h. The oil obtained was crystallized from ether/petroleum ether to give colourless crystals (70.0 mg, 75%), m.p. 138-140. IR: 3384 (N-H). ^{1}H NMR: ($CDCl_3$) 2.27 (3H, s, Me), 2.37 (3H, s, Me), 2.45 (3H, s, Me), 5.45 (1H, s, N-H), 6.93 (2H, m, Ar-H), 7.26 (2H, m, Ar-H), 7.41 (1H, s, H-7), 7.60 (1H, s, H-4). ^{13}C NMR: ($CDCl_3$) δ 11.37 (CH_3), 13.70 (CH_3), 18.40 (CH_3), 112.69, 116.90, 120.13, 122.72, 126.37 (C), 126.55 (C), 129.34, 131.79 (C), 136.54 (C), 136.79 (C), 137.87 (C), 144.62 (C). Anal. calcd for $C_{17}H_{17}NS$: C 76.36, H 6.41, N 5.24, S 11.99; found: C 76.55, H 6.21, N 4.91, S 11.71.

4.6. Palladium-catalyzed cyclization with deprotection of acetamides 8a,b

4.6.1. 2,3,5-Trimethyl-*6H*-thieno-[3,2-*c*]carbazole (7): The mixture of amides **8a** and **8b** (0.150 g, ~ 0.350 mmol), Na_2CO_3 (57.0 mg, 0.540 mmol) and $Pd(OAc)_2$ (10 mol%) in refluxing DMF (5 ml) were heated for 7 h. After cooling, ethyl acetate (20 ml) and water (30 ml) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 10 ml). The organic phase was dried and filtered. Removal of the solvent left a brown residue (0.130 g) which was submitted to PLC (50% ether/petroleum ether) to afford the product as a white solid (83.0 mg, quantitative yield), m.p. 215-217. IR: 3411 (N-H). ^{1}H NMR: ($CDCl_3$) 2.40 (3H, s, Me), 2.59 (3H, s, Me), 2.69 (3H, s, Me), 7.35 (1H, td, *J* = 8 and 1.2, H-9), 7.46 (1H, td, *J* = 8 and 1.2, H-8), 7.48 (1H, s, H-4), 7.55 (1H, broad d, *J* = 8, H-7), 8.14 (1H, s, N-H), 8.16 (1H, broad d, *J* = 8, H-10). ^{13}C NMR: ($CDCl_3$) 11.74 (CH_3), 13.75 (CH_3), 17.16 (CH_3), 110.66, 116.05 (C), 117.07 (C), 119.57 (C), 119.78, 121.56, 122.91 (C), 125.00, 126.98 (C), 128.54 (C), 129.72 (C), 135.02 (C), 136.50 (C), 138.97 (C). Anal. calcd for $C_{17}H_{15}NS$: C 76.94, H 5.70, N 5.30, S 12.08; found: C 76.69, H 5.45, N 5.16, S 12.01.

4.7. General procedure for intramolecular cyclization of non *ortho*-halogenated amines 10 and 11: A mixture of the diarylamine, $Pd(OAc)_2$ (0.5 equiv), $Cu(OAc)_2$ (3 equiv) and glacial acetic acid was heated at 120 ºC for 7 h. After cooling, ether (15 ml) and water (10 ml) were added. The phases were separated and the organic phase was washed with water, dried ($MgSO_4$) and filtered. Solvent removal gave an oil which was submitted to P.L.C 50% ether/petroleum ether to afford the product. Starting material was recovered.

4.7.1. Thienocarbazole (7): From amine **10** (0.170 g, 0.640 mmol), in glacial acetic acid (4 ml), thienocarbazole **7** was obtained as a white solid (50.0 mg, 30%), which showed identical properties to those presented above.

4.7.2. 9-Methoxy-2,3,5-trimethyl-*6H*-thieno[3,2-*c*]carbazole (12): From amine **11** (0.140 mg, 0.470 mmol) in glacial acetic acid (5 ml), thienocarbazole **12** was obtained as a light yellow solid (40.0 mg, 30%), giving colourless crystals from ether/petroleum ether cristalization m.p. 201-203. IR: 3378 (N-H). ^{1}H NMR: ($CDCl_3$) 2.40 (3H, s, Me), 2.59 (3H, s, Me), 2.67 (3H, s, Me), 4.01 (3H, s, OMe), 7.10 (1H, dd, *J* = 8.7 and 2.4, H-8), 7.44 (2H, broad d, *J* = 8.7, H-7 and H-4 obscured), 7.62 (d, 1H, *J* = 2.4, H-10), 8.01 (1H, s, N-H). ^{13}C NMR: ($CDCl_3$) 11.78 (CH_3), 13.76 (CH_3), 17.19 (CH_3), 56.06 (OCH_3), 104.14, 111.38, 114.30, 116.06 (C), 117.26 (C), 119.52, 123.27 (C), 127.03 (C), 128.42 (C), 129.44 (C), 133.88 (C), 134.65 (C), 137.31 (C), 154.13 (C). MS: 295 (100, M^+), 280 (37, M^+-15). HRMS $C_{18}H_{17}NOS$: caldt. M^+ 295.10307; found 295.10339.

4.8 Synthesis of *N*-[6-(2,3,5-trimethylbenzo[*b*]thiophene)]carbazole (13): Amine **3** (0.270 g, 1.40 mmol), 2-bromo-iodobenzene (0.410 g, 1.40 mmol), $Pd(OAc)_2$ (10 mol%), Cu_2O (20 mol%), K_2CO_3 (2.5 equiv) in dimethylformamide (10 ml) were heated at reflux for 10 h 30 min. After cooling, water and ether were added and the organic phase was separated, washed with water, dried ($MgSO_4$) and filtered. Removal of solvent left a brown solid (0.240 g) which was submitted to P.L.C., 50% ether/petroleum ether giving as the less polar product the *N*-substituted carbazole **13** as a light yellow solid (0.140 g, 30%), m.p. 187-189. ^{1}H NMR: ($CDCl_3$) 2.05 (3H, s, Me), 2.40 (3H, s, Me), 2.56 (3H, s, Me), 7.06 (broad 2H, d, *J* = 8, H-1 and 8), 7.30 (2H, td, *J* = 8 and 1.2, H-3 and 6), 7.40 (2H, td, *J* = 8 and 1.2, H-2 and 7), 7.67 (1H, s, H-7'), 7.76 (1H, s, H-4'), 8.19 (2H, broad d, *J* = 8, H-4 and 5).^{13}C NMR: ($CDCl_3$) 11.50 (CH_3), 13.99 (CH_3), 17.82 (CH_3), 109.80, 119.46, 120.28, 122.69, 122.94 (C), 123.14, 123.27, 125.86, 126.67 (C), 127.20, 132.15 (C), 133.14 (C), 135.67 (C), 136.27 (C), 141.50 (C), 141.56 (C). MS: 341 (100, M^+). HRMS $C_{23}H_{19}NS$: caldt. M^+ 341.123822, found 341.123963.

The thienocarbazole **7** was isolated as a white solid (30.0 mg, 10%) with identical properties to those presented above.

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