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

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Received 10 April 2002; revised 4 July 2002; accepted 23 July 2002

Abstract—Palladium or copper catalyzed aminations or amidations were performed to obtain diarylamines and diarylacetamides precursors of thienocarbazoles. The fact that an ortho-bromodiarylamine did not cyclize to the corresponding thienocarbazole under conditions known for carbazoles from ortho-halodiphenylamines, conducted us to a highly efficient method of palladium-catalyzed intramolecular cyclization 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.

Keywords: C–N coupling; copper; palladium; cyclization–deprotection; thienocarbazoles.

1. Introduction

Due to their interesting biological activities carbazole alkaloids constitute an important class of natural compounds. Their isolation from different sources (terrestrial plants, marine sources and streptomycetes) induced the development of novel strategies of synthesis of structurally unprecedented carbazole derivatives. 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.

One of the standard methodologies that the medicinal chemist can use as a rational approach to lead optimisation is the bioisosteric replacement. 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 potencies as well as efficacy. The use of classical isosteres as benzene, thiophene and pyridine resulted in analogues with biological activity retention among different series of pharmacological agents. 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. The achievement of less toxic compounds than pyridocarbazoles is also a very important goal (Fig. 1).

The sulfur atom can provide interesting properties to this type of molecules like the establishment 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. 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. Ring A substitution had also proven to be very important for the activity being 9-methoxy and 9-hydroxy-ellipticines IIb and c much more active than ellipticine IIa.

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\textsuperscript{11,12} or fair to moderate from nitrodiaryl compounds.\textsuperscript{13}

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

Other method of cyclization based in the reoxidation of Pd(0) by Cu(OAc)\textsubscript{2},\textsuperscript{14} avoiding the use of a stoichiometric amount of Pd(OAc)\textsubscript{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.\textsuperscript{15} An ortho-bromodiarylamidine obtained using the latter conditions, did not cyclize to the corresponding thienocarbazole under the Sakamoto’s cyclization conditions.\textsuperscript{16}

2. Results and discussion

2.1. Synthesis of an ortho-bromodiarylamine under Buchwald’s conditions and attempted intramolecular cyclization

First it was decided to couple ortho-haloanilines 1\textsubscript{a} and 1\textsubscript{b} with 6-bromobenzo[b]thiophene 2\textsuperscript{17} or 2-bromo-iodobenzene with 6-aminobenzo[b]thiophene 3 under Buchwald’s conditions\textsuperscript{15} to obtain ortho-halodiarylamines. Some modifications such as the use of higher amounts of Pd(OAc)\textsubscript{2} (3 mol\%) and BINAP (4 mol\%) comparing to those used in literature\textsuperscript{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-bromodiarylamidine 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 1\textsubscript{b} and 2, occurring decomposition of the aniline.

The use of Pd\textsubscript{2}(dba)\textsubscript{3} and DPPF, as described for the preparation of ortho-halodiphenylamines precursors of carbazole,\textsuperscript{16} was not effective in our case.

The amine 3 was obtained under drastic basic conditions\textsuperscript{18} from the corresponding sterically hindered acetamide 6 which was prepared by Beckmann rearrangement of the oxime of 6-acetylated compound\textsuperscript{19} (Scheme 2).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{structure.png}
\caption{Structure of thienocarbazoles I and pyridocarbazoles II.}
\end{figure}
Attempts to perform the C–N coupling using the acetamide under Buchwald’s conditions were unsuccessful.

When the ortho-bromodiarylamine 4 was submitted to Sakamoto’s intramolecular cyclization conditions, that have worked to obtain carbazoles from ortho-bromodiphenylamine, thienocarbazole 7 did not form (Scheme 3). Changing the base to NEt₃ no thienocarbazole was obtained either.

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

The latter unsuccessful result led us to try our Goldberg coupling conditions, reacting acetamide 6 with 2-bromoiodobenzene using 30 mol% of Cu₂O, K₂CO₃, heating without solvent at 180°C. 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 Cu₂O did not increase significantly the yield for amides 8a, b and the yield for amide 9, as a by-product was not altered.

Due to the hindered rotation around the amide bond in 8, ¹H 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 by refluxing gently ethylene glycol (silicone bath at 200°C) (Scheme 4).

Iododiarylamine 5 was characterized by ¹H 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 (stoich. Cu₂O) 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 ¹H 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 Cu₂O as outlined in Scheme 5.

Deprotection of 8a and 8b with NaOH in a vigorous refluxing ethylene glycol (silicone bath at 220°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.

2.3. Intramolecular cyclization of diarylamines using Pd(OAc)₂ and Cu(OAc)₂

Cyclization of the dehalogenated acetamide 9 to thienocarbazole 7 did not occur when the same conditions were
used, but the corresponding amine 10 gave the thienocarbazole 7 in 30% yield when treated with palladium acetate (50 mol%) and copper acetate (3 equiv.) in acetic acid at 120°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.

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).

2.4. ‘One pot’ procedure of C–N coupling and intramolecular cyclization 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$_{r}$ 341) as major product in 30% yield and the thienocarbazole 7 only in 10% yield (Scheme 10). Lowering the time of heating the two products were obtained in the same proportion.

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.

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 cyclizations 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. General

Melting points (°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. ¹H and ¹³C NMR spectra were recorded on a Varian Unity Plus (300 and 75.4 MHz respectively). ¹H–¹H spin–spin decoupling and DEPT spectra were used. Chemical shifts are given in ppm and coupling constants in Hz. The mass spectra were obtained on a Micromass Autospec 3F by an electron impact (70 eV) direct injection method. Elemental analysis was performed on a LECO CHNS 932 elemental analyser.

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% methanol to promote a homogeneous solution, and 10% water and ether were added. Petroleum ether refers to the boiling range 40–60°C. Ether refers to diethyl ether. When solvent gradient was used, the increase of polarity was made gradually from 100% petroleum ether to mixtures of ether/petroleum ether 24 h, and using solvent gradient from petroleum ether to 40% ether/petroleum ether in the chromatographic purification.

4.1.1. 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 35% HCl (8.30 g, 119 mmol) in 13 ml of water, a solution of NaOH and 35% HCl (8.30 g, 119 mmol) in 13 ml of water. The precipitate formed was filtered and dried at 60°C. From arylhalide (3.50 g, 87.5 mmol) in 12 ml of water was added with (8.30 g, 119 mmol) in 13 ml of water, a solution of NaOH and 35% HCl (8.30 g, 119 mmol) in 13 ml of water, a solution of NaOH and 35% HCl (8.30 g, 119 mmol) in 13 ml of water. The precipitate formed was filtered, dried and showed to be the corresponding compound.

4.2. 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, 1.4 equiv. Pd(OAc)₂ (3 mol%), racemic BINAP (4 mol%) and the mixture was heated at 90°C for several hours. The reaction was followed by TLC. After cooling water and ether were added. The organic phase was separated, dried (MgSO₄) and solvent removed to give an oil which was submitted to chromatographic purification to give the product and starting materials.

4.2.1. 6-(2-Bromophenyl)amino-2,3,5-trimethylbenzo[b]thiophene (6). From arylhalide 2 (0.510 g, 2.00 mmol) and bromoaniline 1a (0.430 g, 2.50 mmol) heating for 70 h and column chromatography 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, mp 126–128. IR: 3377 (N–H). ¹H NMR: (CDCl₃) 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, 7.15 Hz, H–4'), 6.81 (1H, dd, J = 8.24, 1.5 Hz, H–6'), 7.11 (1H, sept, J = 8.24, 7.15 Hz, H–5'), 7.46 (1H, s, H–7), 7.52 (1H, dd, J = 7.93, 1.5 Hz, H–3'), 7.61 (1H, s, H–4). ¹³C NMR: (CDCl₃) 11.37 (CH₃), 13.76 (CH₃), 18.33 (CH₃), 110.94 (C), 114.70, 116.45, 119.75, 122.84, 124.44, 128.19, 128.99 (C), 132.66, 133.02 (C), 136.11 (C), 136.38 (C), 138.31 (C), 142.90 (C). Anal. calcd for C₁₇H₁₆BrNS: C 72.70, H 6.44, N 4.71, S 10.78; found: C 72.75, H 6.40, N 4.75, S 10.72.

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

4.2.2. 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 50% ether/petroleum ether in the chromatographic purification, compound 11 was obtained as a white solid (0.350 g, 60%), mp 127–129 (from chloroform and petroleum ether). When crystallization from ether/petroleum ether gave white crystals mp 130–132. IR: 1539 (N–H). ¹H NMR: (CD₂DMSO) 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 Hz, H–3' and 5'), 6.94 (2H, d, J = 9 Hz, H–2' and 6'), 7.03 (1H, s, H–7), 7.28 (1H, s, H–4), 7.38 (1H, s, N–H). ¹³C NMR: (CD₂DMSO) 11.12 (CH₃), 13.31 (CH₃), 18.39 (CH₃), 55.19 (OCH₃), 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 C₁₇H₁₆O₃N: C 72.70, H 6.44, N 4.71, S 10.72; found: C 73.00, H 6.27, N 4.78, S 10.70.

4.3. Goldberg coupling

4.3.1. 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), K₂CO₃ (0.600 g, 4.30 mmol), CuO (0.190 g, 1.33 mmol) was heated at 180°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 amine 9 was obtained as a white solid (0.100 g, 8%), mp 212–214. IR: 1675 (C=O). 1H NMR spectra in CDCl3 or in [D6]DMSO at several temperatures showed hindered rotation, being this compound identified by the 1H NMR spectrum of the corresponding amine 10 (see below). MS: 312 (8, M+2), 311 (20, M+1), 310 (100, M+). Anal. calcd for C10H9NO: C 79.48, H 6.91, N 7.30; found: C 79.48, H 6.87, N 7.30.

Another fraction was isolated as a yellow light solid and showed to be a mixture of 8a and 8b (0.650 g, ~40%), mp 148–150. 1H NMR spectra in CDCl3 or in [D6]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+), 310 (100, M+). Anal. calcd for C17H17NO: C 76.36, H 6.41, N 5.24; found: C 76.36, H 6.41, N 5.22.

Another fraction was isolated as a yellow light solid and showed to be a mixture of 8a and 8b (0.650 g, ~40%), mp 148–150. 1H NMR spectra in CDCl3 or in [D6]DMSO at several temperatures showed hindered rotation, being this compound identified by the 1H NMR spectrum of the corresponding amine 10 (see below). MS: 312 (8, M+2), 311 (20, M+1), 310 (100, M+). Anal. calcd for C10H9NO: C 79.48, H 6.91, N 7.30; found: C 79.48, H 6.87, N 7.30.

Another fraction was isolated as a yellow light solid and showed to be a mixture of 8a and 8b (0.650 g, ~40%), mp 148–150. 1H NMR spectra in CDCl3 or in [D6]DMSO at several temperatures showed hindered rotation, being this compound identified by the 1H NMR spectrum of the corresponding amine 10 (see below). MS: 312 (8, M+2), 311 (20, M+1), 310 (100, M+). Anal. calcd for C10H9NO: C 79.48, H 6.91, N 7.30; found: C 79.48, H 6.87, N 7.30.

4.4.1. 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.

4.4.2. 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 1H NMR spectrum showed to be a mixture of amines 4 and 5 being 5 in a slightly excess. 1H NMR: (CDCl3) 2.92 (2H, s, 2Me of 4 and 5), 2.37 (2H, s, 2Me of 4 and 5), 2.47 (2H, s, 2Me 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, 7.15 Hz, H-4 of 4), 6.69 (1H, oct, J=7.93, 7.15 Hz, H-4 of 5), 6.77 (1H, dd, J=8.24, 1.5 Hz, H-6 of 5), 7.11 (1H, sept partially obscured, J=8.24, 1.5 Hz, H-5 of 4), 7.14 (1H, sept partially obscured, J=8.24, 1.5 Hz, H-5 of 5), 7.46 (2H, s, 2H-7 of 4 and 5), 7.52 (1H, dd, J=7.93, 1.5 Hz, H-3 of 4), 7.60 (1H, s, 2H-4 of 4 and 5), 7.77 (1H, dd, J=7.93, 1.5 Hz, H-3 of 5).

The signals of compound 5 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. Palladium-catalyzed cyclization with deprotection of acetamides 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°C). After cooling, the mixture was poured into iced water and after stirring, extracted with ether. The organic phase was dried (MgSO4), filtered and the solvent removed to give an oil which was submitted to chromatographic purification or to crystallization.

4.4.3. 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, 2.00 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%), mp 138–140. IR: 3384 (N–H). 1H NMR: (CDCl3) 2.27 (3H, s, Me), 2.37 (3H, s, Me), 2.45 (3H, s, Me), 5.45 (1H, s, N–H of 10), 6.93 (2H, m, Ar-H), 7.26 (2H, m, Ar-H), 7.41 (1H, s, H-7), 7.60 (1H, s, H-4).

13C NMR: (CDCl3) 11.37 (CH3), 13.70 (CH3), 18.40 (CH3), 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 C17H13NO: C 78.86, H 5.33, N 5.24; found: C 78.86, H 5.33, N 5.22.

4.6. General procedure for intramolecular cyclization of non ortho-halogenated amines 10 and 11

A mixture of the diarylamine, Pd(OAc)2 (0.5 equiv.), Na2O (0.350 mmol), Na2CO3 (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 (20 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, 75%), mp 138–140. IR: 3384 (N–H). 1H NMR: (CDCl3) 2.27 (3H, s, Me), 2.37 (3H, s, Me), 2.45 (3H, s, Me), 5.45 (1H, s, N–H of 10), 6.93 (2H, m, Ar-H), 7.26 (2H, m, Ar-H), 7.41 (1H, s, H-7), 7.60 (1H, s, H-4).

13C NMR: (CDCl3) 11.37 (CH3), 13.70 (CH3), 18.40 (CH3), 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 C17H13NO: C 78.86, H 5.33, N 5.24; found: C 78.86, H 5.33, N 5.22.
Cu(OAc)$_2$ (3 equiv.) and glacial acetic acid was heated at 120°C 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 PLC 50% ether/petroleum ether to afford the product. Starting material was recovered.

4.6.1. 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.

4.6.2. 9-Methoxy-2,3,5-trimethyl-6-[[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 crystallization mp 201–203. IR: 3378 (N–H). 1H 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, ¼ 8, 1.2 Hz, H-3 and 6), 7.40 (2H, td, ¼ 8 Hz, H-4 and 5). 13C 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: 295 (100, M$^+$), 280 (37, M$^+$ – 15). HRMS C$_{18}$H$_{17}$NOS: calcd. M$^+$ 295.10307; found 295.10339.

Acknowledgements

Thanks are due to Foundation for the Science and Technology-IBQF-Univ. Minho (Portugal) for financial support, to the Research Incitement Programme of the Calouste Gulbenkian Foundation (Portugal) and to Escola Superior Agrária-Instituto Politécnico de Bragança for supporting in part Isabel C. F. R. Ferreira PhD.

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