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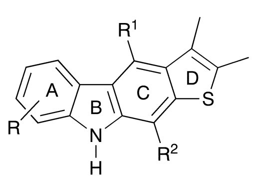
Synthesis of Precursors of Linear Thienocarbazole Analogues of Ellipticine and Olivacine

Fernanda M. C. Peixoto,[a] Maria-João R. P. Queiroz*[a] and Gilbert Kirsch[b]

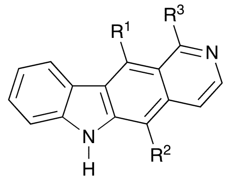
[a] *Departamento de Química, Universidade do Minho, Campus de Gualtar, 4710 Braga, Portugal*
[b] *Laboratoire de Chimie Organique, Groupe de Synthèse Organique et Hétérocyclique, Université de Metz Ile du Saulcy, 57045 Metz, France*

Amides from Goldberg coupling in the benzo[*b*]thiophene series have been prepared as precursors of linear thienocarbazoles by ring B convergent methods of synthesis.

With the aim of synthesizing thienocarbazoles **I**, analogues of the anti-tumour alkaloids ellipticine **II** and olivacine **III**, by a ring B convergent method of synthesis (chemical or photochemical), we have prepared a series of substituted benzo[*b*]thiophene derivatives *via* a Goldberg coupling[3] reaction. The anilino derivatives of the benzo[*b*]thiophenes were prepared by reacting the corresponding bromobenzo[*b*]thiophenes with different acetanilides or the acetamido-benzo[*b*]thiophenes with different aryl bromides.

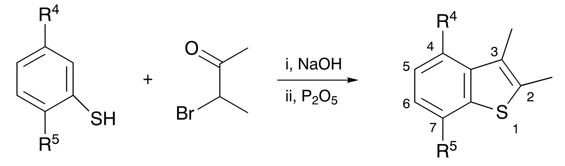


Thieno[2,3-*b*]carbazoles **I**
R = H, 1- or 2-OMe



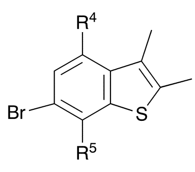
Pyrido[4,3-*b*]carbazoles
$R^1 = R^2 = Me, R^3 = H$ Ellipticine **II**
$R^1 = H, R^2 = R^3 = Me$ Olivacine **III**

The preparation of the benzo[*b*]thiophenes was achieved in several steps. The tri- or tetra-methylbenzo[*b*]thiophenes **1** were prepared according to Werner's method.[4] Condensation of the *o*-thiocresol or *p*-xylenethiol in alkaline medium with 3-bromobutan-2-one gave the corresponding ketones which were readily cyclised, using phosphorus pentaoxide, to the benzo[*b*]thiophenes **1**. Bromination[5] of compounds **1** led to the bromo derivatives **2** in good yields (56–78%). The acetamido derivatives **3** were prepared by Beckmann rearrangement on the oximes obtained from the corresponding acetyl derivatives **4**.[6]



$R^4 = H, R^5 = Me$
$R^4 = R^5 = Me$

1



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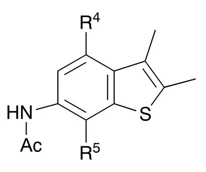

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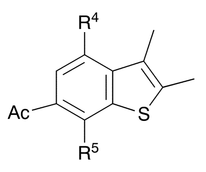
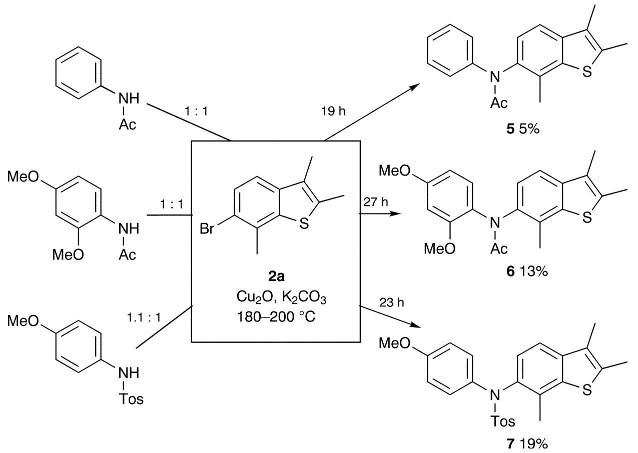


4

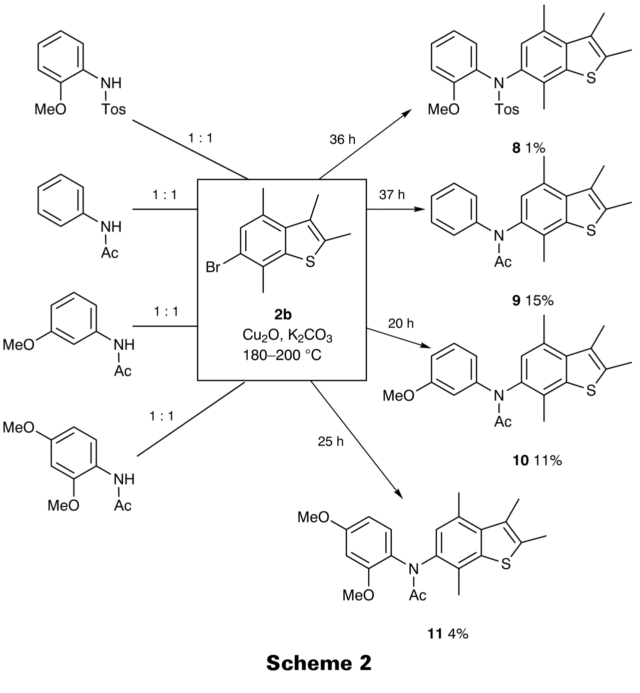
a $R^4 = H, R^5 = Me$
b $R^4 = R^5 = Me$



Scheme 1

The first Goldberg couplings were made with the bromobenzo[*b*]thiophenes and acetanilides (or tosylanilides) (Schemes 1 and 2) under the classical Goldberg conditions[3] (Cu_2O, K_2CO_3, 180–200 °C, no solvent). The yields of isolated products were generally low, and the starting materials were not completely recovered due to the harsh conditions of the reaction.

Another attempt at synthesizing **5** was made by condensing bromobenzene with the acetamido-benzo[*b*]thiophene **3a** (Scheme 3) when the yield went up to 35%.



Scheme 2

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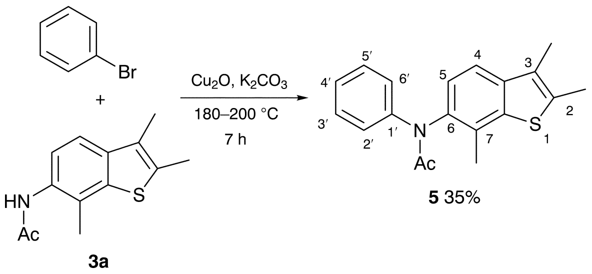
*To receive any correspondence.



Scheme 3

Reacting the bromobenzene derivatives with the acetamido-benzo[*b*]thiophenes seemed to be the right method to conduct this coupling and, in fact, in all the condensations the yields were greatly improved (Scheme 4) and the products were isolated in fair to good yields. Use of this method allowed us also to lower the reaction time (to 9–10 h from 20–37 h).

Characterization of the obtained compounds by ^{1}H NMR showed hindered rotation around the amide bond (broad and doubled signals for the methoxy and methyl groups). Spectra in different solvents and at different temperatures were run. The spin–spin decoupling technique was also very useful in the attribution of the proton signals. A discussion of the ^{1}H NMR spectra is presented together with the experimental work.

Cyclisation of these amides or the corresponding amines by photochemical or chemical methods has been undertaken and some preliminary results have already been presented.[9]

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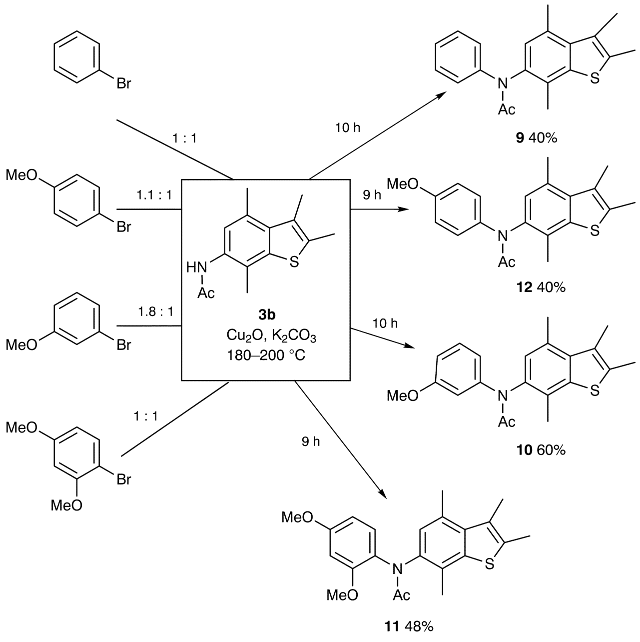
Techniques used: ^{1}H NMR spectroscopy using spin–spin decoupling, IR and UV spectroscopy, mass spectrometry, elemental analysis

References: 9

Schemes: 4



Scheme 4

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