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Synthesis of new 3-arylindole-2-carboxylates using β,β-diaryldehydroamino acids as building blocks. Fluorescence studies

Maria-João R. P. Queiroz,[a,*] Ana S. Abreu,[a,b] Elisabete M. S. Castanheira[b] and Paula M. T. Ferreira[a]

[a]*Centro de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal*
[b]*Centro de Física, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal*

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Abstract—Several new methyl 3-arylindole-2-carboxylates were synthesized in high yields using a metal assisted [$Pd(OAc)_2/Cu(OAc)_2$, DMF, 130 °C] intramolecular C–N cyclization of β,β-diaryldehydroamino acids, developed by us, thus extending the scope of this reaction. The latter were obtained by a bis-Suzuki coupling of a β,β-dibromodehydroalanine with arylboronic acids bearing either electron-donating groups (EDGs) or electron-withdrawing groups (EWGs). We were able to establish general conditions for this coupling reaction [$PdCl_2dppf\cdot CH_2Cl_2$ 1:1 (20 mol %), boronic acid (5 equiv), Cs_2CO_3 (1.4 equiv), THF/H_2O 1:1, 80 °C]. This strategy constitutes a novel, general and unprecedented approach to the synthesis of 3-arylindole-2-carboxylates. The fluorescence of the differently substituted indoles prepared was studied in several polar and non-polar solvents. In general the new indoles exhibit a solvent sensitive emission. The indoles with EDGs (OCH_3 and SCH_3) have reasonable fluorescence quantum yields in all solvents except in water. The indole with the cyano groups shows high fluorescent quantum yields in all solvents studied, despite the lower solvent sensitivity of its emission. The indole with the acetyl groups only exhibits reasonable fluorescence quantum yields in protic solvents. These studies show that the new 3-arylindole-2-carboxylates are good candidates to be used as fluorescent probes.

1. Introduction

The substituted indole nucleus is found in numerous natural products, being very important in medicinal chemistry and its synthesis continues to attract much interest.

A variety of well-established classical methods for the synthesis and functionalization of indoles are now available. The accessibility of the starting materials and their compatibility with the reaction conditions generally dictate the method of choice for synthesizing a target indole. More recently palladium-catalyzed reactions have been used to synthesize indole derivatives since they are generally tolerant to a wide range of functionalities.[1] Some of these reactions are based on an intramolecular C–N cyclization of *o*-allylanilines,[2] *o*-alkynylanilines,[3–5] or dehydrophenylalanine derivatives bearing an iodine atom in the phenyl ring.[6,7]

There are only a few reports available for the synthesis of 3-arylindole-2-carboxylates. Nakamura and Ukita synthesized ethyl 3-arylindole-2-carboxylates from α-diazophosponates and 2-aminobenzophenones using a rhodium catalyst and DBU in a two step or in a one-pot procedure.[8] Recently, Takamura et al. prepared 3-substituted indole-2-carboxylates using Fisher indole synthesis of arylhydrazones obtained from α-diazoesters and aryllithium reagents.[9]

In our laboratories, we have developed a metal assisted (palladium/copper) intramolecular C–N cyclization reaction of β,β-bis(benzo[*b*]thienyl)dehydroalanines or β-(benzo[*b*]thienyl)dehydrophenylalanines, also prepared by us, to thienoindoles, benzo[*b*]thienopyrroles or 3-(benzo[*b*]thienyl)indoles.[10,11]

Here we describe general conditions for the synthesis of β,β-diaryldehydroamino acids in high yields by a bis-Suzuki cross-coupling of a β,β-dibromodehydroalanine[10a] with several boronic acids bearing either electron-withdrawing groups (EWGs) or electron-donating groups (EDGs). The coupling products were submitted to our intramolecular C–N cyclization conditions, giving new 3-arylindole-2-carboxylates in excellent yields, thus extending the scope of this reaction.

Keywords: β,β-Diaryldehydroamino acids; Bis-Suzuki coupling; Metal assisted C–N cyclization; 3-Arylindole-2-carboxylates; Fluorescent probes.

* Corresponding author. Tel.: +351253604378; fax: +351253678983; e-mail: mjrpq@quimica.uminho.pt

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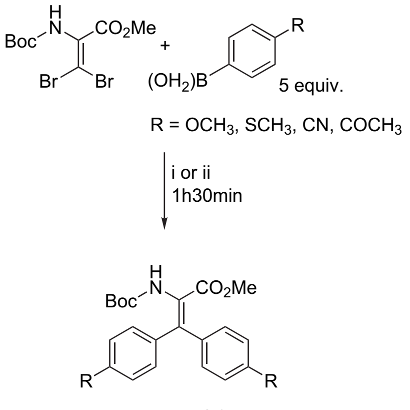
The fluorescence properties of indoles have been widely studied, mainly due to the biological relevance of these compounds and also to the utility of the indole chromophore as an intrinsic probe of the structure and function of proteins and enzymes.[12] In this work, the fluorescence properties of the synthesized new indoles were studied in several polar and non-polar solvents, showing that they may be used as solvatochromic fluorescent probes. This type of probes has found extensive applications, namely as probes for proteins,[13–15] micelles and microemulsions[16–20] and lipid membranes.[21–23] Owing to their solvent sensitive emission, the 3-arylindole-2-carboxylates prepared may be useful to probe microenvironment changes in biological media.

2. Results and discussion

2.1. Synthesis

Several β,β-diaryldehydroalanines **1a–d** were synthesized by Suzuki coupling[24] of a β,β-dibromodehydroalanine, previously prepared by us,[10a] with differently substituted phenylboronic acids (Scheme 1). Applying the conditions used earlier by us in the synthesis of β,β-bis(benzo[*b*]thienyl)dehydroalanines[10b] (Scheme 1, Conditions i) some of the coupling products were only obtained in low to moderate yields (Table 1). By changing the conditions (Scheme 1, Conditions ii) it was possible to obtain all the coupling products **1a–d** in good to high yields (Table 1), thus establishing general conditions for this bis-Suzuki coupling.



1a R = OCH_3
1b R = SCH_3
1c R = CN
1d R = $COCH_3$

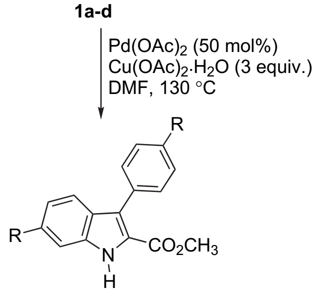
Scheme 1. (i) $PdCl_2(PPh_3)_2$ (20 mol %), Na_2CO_3 (4 equiv), DME/H_2O (10:1), 90 °C and (ii) $PdCl_2dppf\cdot CH_2Cl_2$ 1:1 (20 mol %), Cs_2CO_3 (1.4 equiv), THF/H_2O(1:1), 80 °C.

Table 1. Results obtained in the synthesis of β,β-diaryldehydroalanines

Compound	Yields/%	
	Conditions i	Conditions ii
1a	80	85
1b	34	74
1c	15	90
1d	41	75

In all cases, small amounts of the corresponding C–C dimers of the boronic acids and *p*-hydroxylated compounds were also isolated.

The β,β-diaryldehydroalanines **1a–d** were used as building blocks for the synthesis of new 3-arylindole-2-carboxylates **2a–d** using our metal assisted C–N intramolecular cyclization in high yields (Scheme 2). We have already studied the best reaction conditions in terms of amounts of $Pd(OAc)_2$[10b] and reaction temperature and we have proposed a mechanism involving the formation of a palladacycle followed by extrusion of Pd(0), which may be reoxidized to Pd(II) by $Cu(OAc)_2$. The cleavage of the *tert*-butoxycarbonyl group (Boc) follows the cyclization and is probably due to the acetic acid formed.[11]



2a R = OCH_3, 99%
2b R = SCH_3, 99%
2c R = CN, 83%
2d R = $COCH_3$, 84%

Scheme 2. Synthesis of methyl 3-arylindole-2-carboxylates by a C–N intramolecular metal assisted cyclization.

The results show that the cyclization is not highly affected by the presence of EDGs or EWGs in the phenyl rings, despite the almost quantitative yields obtained for indoles **2a** and **2b**. Thus we have established a new and effective method for the synthesis of 3-arylindole-2-carboxylates from β,β-diaryldehydroamino acids as building blocks.

2.2. Fluorescence studies

The absorption and the fluorescence properties of indoles **2a–d** were studied in several solvents (Table 2). As an example, the absorption and emission spectra of compounds **2a–d** in dichloromethane are displayed in Figure 1.

The absorption maxima wavelengths of **2a–d** in several solvents are shown in Table 2. The molar extinction coefficients, ε, at λ_{max} are typical of $\pi\rightarrow\pi^*$ transitions, varying in the range 1.1×10^4–3×10^4 $M^{-1}\,cm^{-1}$ (Table 2). As these compounds have a heterocyclic nitrogen atom, transitions involving the non-bonding nitrogen electrons have similar properties to those of $\pi\rightarrow\pi^*$ transitions,[25,26] as the n orbital generally overlaps the π orbital of adjacent carbon atoms. In fact, the near-ultraviolet absorption of indole and their derivatives is generally attributed to two strongly overlapping $\pi\rightarrow\pi^*$ transitions,[27–29] with an average ε value for unsubstituted indole of 5550 $M^{-1}\,cm^{-1}$,[25] which also justifies its relatively high fluorescence quantum yield.[30]

All the indole derivatives prepared have a carboxylate group and it is known that many carbonyl compounds exhibit low