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Synthesis of new aminoporphyrins via palladium-catalysed cross-coupling reactions

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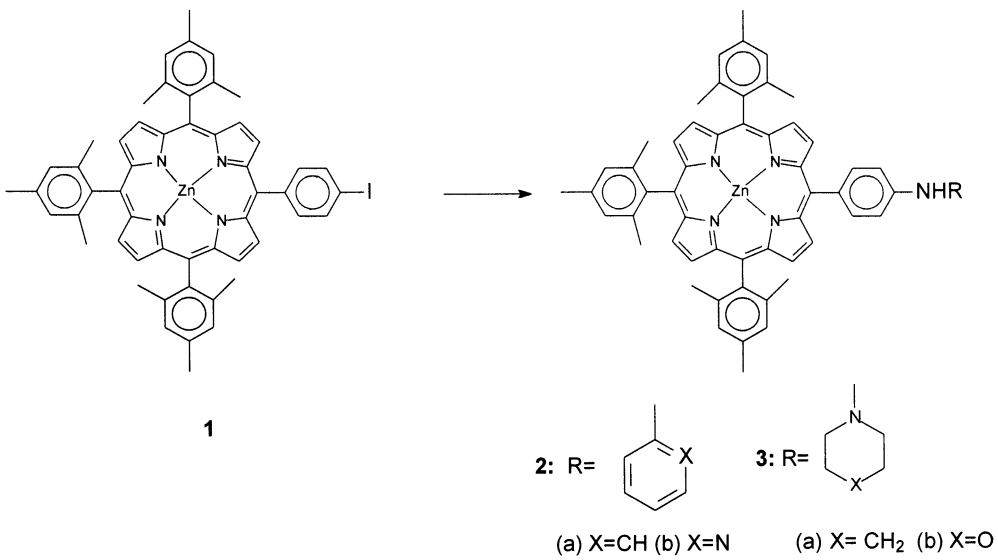
Abstract—A convenient method for the preparation of a variety of amino substituted zinc porphyrins using palladium-catalysed intermolecular carbon–nitrogen coupling reactions between haloporphyrins and a series of amino derivatives is reported.

Some porphyrins and related tetrapyrrolic compounds tend to accumulate in malignant tumours to higher concentrations than in adjacent normal tissues, thus providing a tool for the detection and treatment of a variety of cancers.[1] Although the actual mechanism of tumour retention remains elusive, it is well established that tumour uptake of such derivatives varies according to their overall chemical structure, physical properties and tendency to aggregate. Although a number of porphyrin-based drugs have been approved for clinical trials, tumour specificity of these photodynamic agents is limited.[2] Cationic porphyrin complexes containing a tertiary amine are of particular interest since they exert good affinity for nucleic acids and are efficient catalysts for DNA cleavage.[3] Most published procedures to prepare such positively charged porphyrins involve mixed condensation of selected precursors, requiring a separate synthesis for each desired complex. Accordingly, there exists a continuing need for more efficient methods to obtain such complexes, preferably using a single porphyrin precursor.



Scheme 1.

Keywords: porphyrin; palladium catalyst; coupling reaction; amino derivatives.

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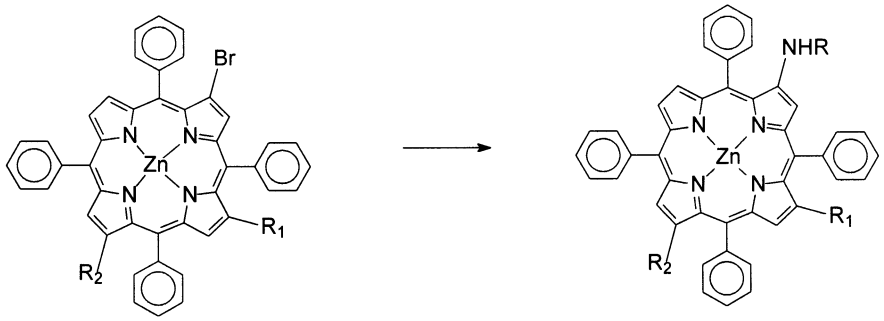
As a continuation of our earlier work on the use of palladium in porphyrin[4] and phthalocyanine synthesis,[5,6] we investigated the use of palladium-catalysed cross-coupling reactions to prepare cationic porphyrins. Palladium catalysis has emerged as a versatile and efficient synthetic technique for carbon–nitrogen bond formation through cross-coupling reactions of aryl halides with amines.[7,8] In this paper, we describe for the first time a general procedure of the palladium-catalysed intermolecular C–N bond formation of halogenated porphyrins and a series of amino derivatives.

The procedure to prepare the novel unsymmetrical aminoporphyrins is shown in Schemes 1 and 2. The iodoporphyrin[9] **1** was used as the starting material for the coupling reaction. Initially, we tried to couple **1** with various amino derivatives at room temperature under the Buchwald condition[10] in the presence of 18-crown-6. However, the reaction did not proceed, even after stirring over an extended period of time. Instead, we adapted the following procedure. Compound **1** and the selected amino derivative, together with 1,1′-bis(diphenylphosphino)ferrocene (DPPF), (DPPF)$PdCl_2$ as catalyst, and sodium-*t*-butoxide as base, were heated for 4–6 hours in dry THF under N_2 using the Hartwig condition[11] to yield compounds **2a**, **3a** and **3b**. Cross coupling of **1** with 2-aminopyridine to afford compound **2b** was only effective upon changing the catalyst and ligand to tris(dibenzylideneacetone) dipalladium(0) [$(Pd_2(dba)_3$], and 2,2′-bis(diphenylphosphino)-1,1-binaphthyl (BINAP), respectively, using the Buchwald condition[12] (Scheme 1).

The ready availability of the aminoporphyrins led us to explore their reactivity for coupling with aryl halides. A number of new porphyrin derivatives were synthesised in this manner. Although the reactivity of the aminoporphyrins is comparable to that of the haloporphyrins the use of the latter can be advantageous since they react with aliphatic, aryl, as well as mono- and disubstituted, amino derivatives. In contrast, the aminoporphyrins can only be coupled with arylhalides. Similarly, when the *cis*- and *trans*-diaminoporphyrins were treated with arylhalide, porphyrins with corresponding diamino substituents were obtained in low to moderate yields. All compounds were purified by silica gel column chromatography and identified by their characteristic UV–Vis spectral properties and molecular ion in LRMS and HRMS-FAB.

Using this approach, the synthesis of β-substituted aminoporphyrins was also investigated. The readily available tetraphenylporphyrin (TPPZn) bearing a halogen at a β-position,[13] i.e. 2-bromoTPPZn (**4**) and 2,7(12)-dibromoTPPZn (**5**), were coupled with a series of aliphatic and aromatic amino derivatives. As expected, the reactivity of the bromoporphyrins is less than that of the iodoporphyrins. This methodology[14] was also applied to couple **4** with ε-caprolactam using DPPF/(DPPF)$PdCl_2$ and sodium-*t*-butoxide, which afforded a porphyrin coupled to a lactam **14** in moderate yield. The bis(amino) derivatives were also obtained from their corresponding dibromoporphyrin analogue. Thus, the treatment of **5** with various amino derivatives gave **7**, **9**, **11** and **13**.

All coupling products gave the expected HRMS molecular ion for the assigned molecular composition. The ^1H NMR spectra of all compounds gave characteristic signals of the β-proton at the carbon atom adjacent to the amino substituent, downfield from the remaining β-protons. This method greatly simplifies the fabrica-



4 R_1=H; R_2=H
5 R_1=H; R_2=Br
R_1=Br; R_2=H

6 R=C_6H_{13}; R_1=H; R_2=H
7 R= n-C_6H_{13}; R_1=H; R_2=$C_6H_{13}NH$
R= C_6H_{13}; R_1=$C_6H_{13}NH$; R_2=H
8 R=C_6H_{11}; R_1=H; R_2=H
9 R= n-C_6H_{11}; R_1=H; R_2=$C_6H_{11}NH$
R= C_6H_{11}; R_1=$C_6H_{11}NH$; R_2=H
10 R= C_6H_5; R_1=H; R_2=H
11 R= C_6H_5; R_1=H; R_2=C_6H_5NH
R= C_6H_5; R_1=C_6H_5NH; R_2=H
12 R= 2-C_5H_4N; R_1=H; R_2=H
13 R= 2-C_5H_4; R_1=H; R_2=2-NHC_5H_4NH
R= 2-C_5H_4; R_1=C_5H_4NH; R_2=H
14 R= ε-caprolactam; R_1=H; R_2=H

Scheme 2.

tion of cationic porphyrins and dramatically amplifies the number of complexes that can be obtained, including many analogues that are not readily accessible via conventional routes.

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