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Synthesis of Monofunctionalised Phthalocyanines using Palladium Catalysed Cross-coupling Reactions

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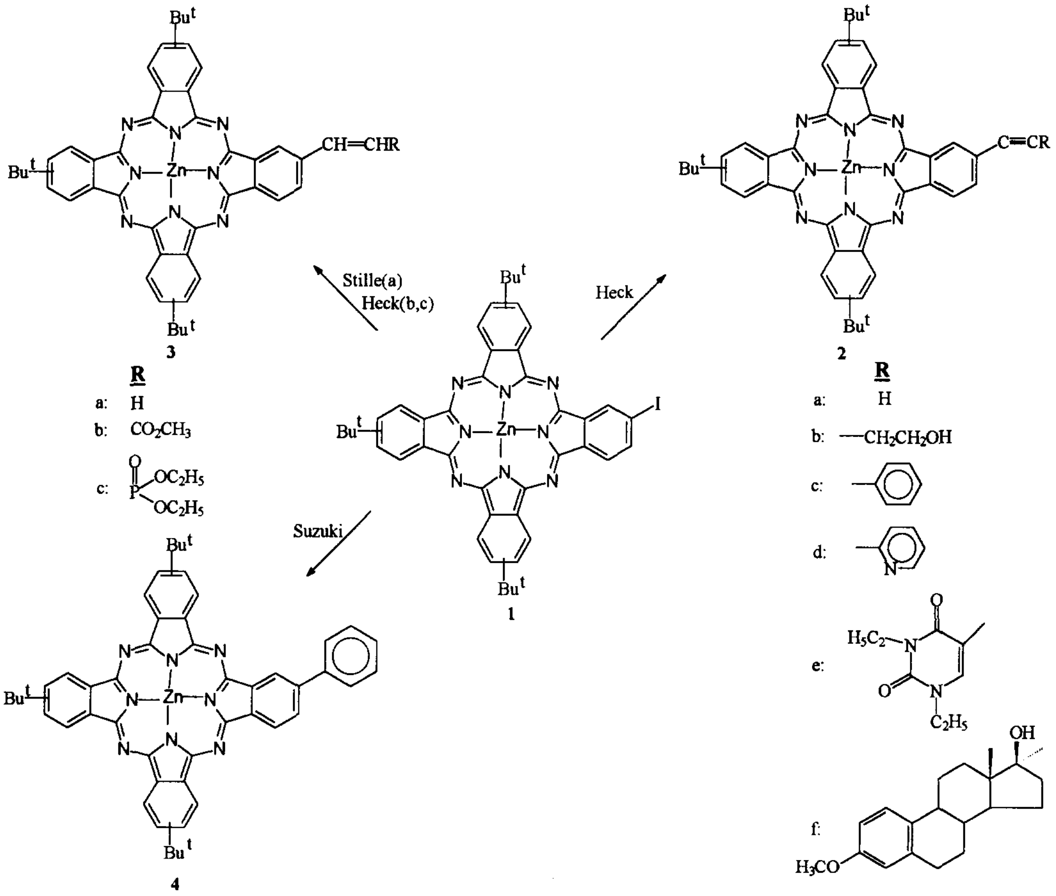
Abstract: The preparation of unsymmetrical monofunctionalised zinc phthalocyanines, using a palladium catalysed coupling reaction between zinc(II) tri(*t*-butyl)-4-iodophthalocyanine and a series of terminally substituted acetylenic derivatives, diethylvinyl phosphonate, methylacrylate (Heck Reactions), vinyltin derivatives (Stille reaction) and aryl boronated acids (Suzuki reaction), is described. © 1997, Elsevier Science Ltd. All rights reserved.

Recently much attention has been focused[1] on the synthesis and characterisation of new phthalocyanine (Pc) derivatives with interesting optical, electrical and catalytic properties through structural modifications in the periphery and/or substitutions about the central metal ion. Introduction of these minor changes in the nature and position of the side group permits the fine tuning of the properties of Pcs. Our interest in the synthesis of new Pc derivatives results from their potential medical applications as photodynamic agents in cancer therapy[2] (PDT) and as antiviral agents for blood sterilisation.[3] Synthetic routes to symmetrical Pcs are relatively straightforward,[1] starting from the appropriately substituted phthalonitrile. However, unsymmetrical Pcs containing different substituents in the benzo rings are more difficult to obtain. Published routes for preparing unsymmetric phthalocyanines mostly involve *in situ* syntheses of the phthalocyanine macrocycle by condensation of two differently substituted phthalonitrile precursors in appropriate stoichiometric ratios to yield mono- through tetrasubstituted Pcs.[4-6] Other more specific methods to prepare unsymmetrical Pcs have also been reported including polymer support methods,[7,8] stepwise synthetic procedures,[9] the condensation of two different phthalyl precursors[10] and the use of Meerwein reaction conditions.[11] More recently the synthesis via a ring enlargement reaction of subphthalocyanines through a condensation reaction with 1,3-diiminoisoindolenine has received much attention.[12] Applications of the latter method are, however, limited since isoindolenine derivatives featuring substituents sensitive to the particular reaction conditions cannot be used. Thus there exists a continuing need for more efficient methods to synthesize unsymmetrical functionalised Pcs.

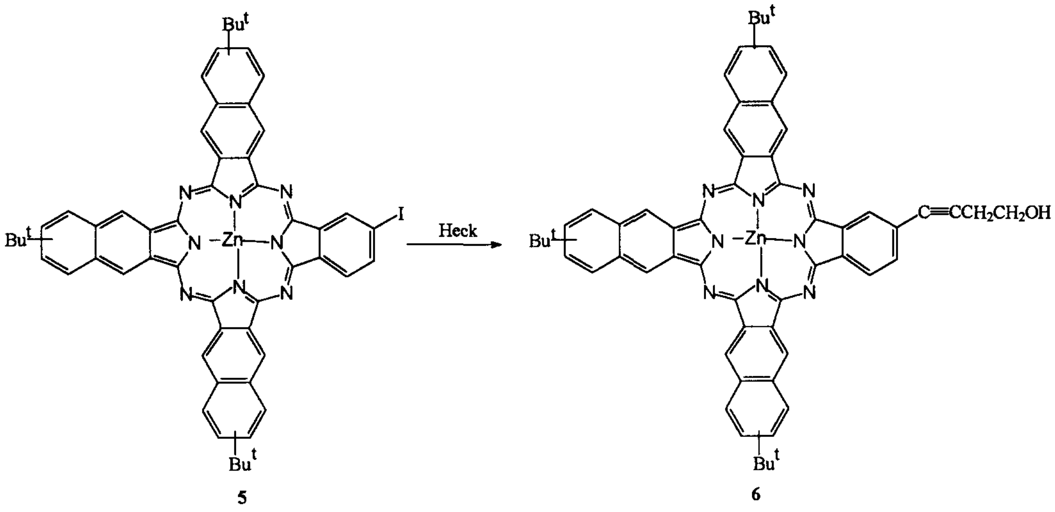
Transition-metal catalysed coupling reactions are of great current interest and palladium is the most widely used metal for such processes.[13] We previously applied this reaction for the synthesis of various substituted porphyrins.[14] We now report for the first time the use of the palladium catalyst for the preparation of unsymmetrically substituted Pcs via a monoiodo Pc intermediates. A large variety of monofunctionalised derivatives were obtained, including many analogues which are not readily accessible via conventional routes.

Zinc(II) tri(*t*-butyl)-4-iodophthalocyanine (**1**), the starting material for the coupling reaction, was prepared via the Sandmeyer reaction from the corresponding monoamino precursor.[11] The latter was obtained via the condensation of the 4-nitrophthalonitrile and 4-*t*-butylphthalonitrile with zinc acetate, which gave a mixture of mono- through tetranitro Pc, and reduction of the nitro group to an amino group using $Na_2S.9H_2O$ followed by chromatographic purification to yield the pure 4-amino-tri-(*t*-butyl)ZnPc. Recently, synthesis of monoamino Pc in high yield via subPcs have also been reported.[15] In a typical reaction, the monoiodo Pc (**1**) was dissolved in toluene containing triethylamine as a base and treated at room temperature for 2-4 h with trimethylsilylacetylene in the presence of a catalytic amount of *bis*(triphenylphosphine)palladium(II) chloride and copper(I) iodide (Heck reaction).[13] The acetylene derivative **2a** was obtained after removing the trimethylsilyl group by treatment with 0.05M aqueous sodium hydroxide in methanol. This ethynyl derivative can be used as starting material for the preparation of a dimeric Pc either via coupling to another iodoPc or via the oxidative homocoupling of ethynes.[17]



Scheme 1

Other substituted alkynes which were reacted with **1** include 3-butyn-1-ol (**2b**), phenyl (**2c**), pyridine (**2d**), purine (**2e**) and estrogenic groups (**2f**) yielding a wide variety of Pc substituted through a common acetylenic linkage at the 4-position (Scheme 1). In the same manner, 3-substituted isomers of **2**, **3** and **4** were obtained using the 3-iodo analogue of **1** as precursor. All alkynes reacted smoothly to give the corresponding pure zinc(II) alkyne-substituted Pc, after column chromatography over silica, in 50-85% yield. Similar products were obtained from the Heck reaction of monoiodobenzonaphthoporphyrazine (**5**) with alkynes. For example, an excess of 3-butyn-1-ol reacted with **5** to yield the corresponding coupling product **6** (Scheme 2). The characteristic absorption maxima of **6** at 764 nm and 733 nm, of almost equal intensity, render such compounds of particular interest for photodynamic applications in medicine.[16]



Scheme 2

Using alkenes instead of alkynes, Heck reaction conditions allowed the coupling of the monoiodo Pc **1** and diethylvinyl phosphonate to afford the Pc-ethenephosphonate **3c**. Similarly, **1** was coupled with methyl acrylate in the presence of the palladium(II) acetate catalyst to yield Pc-carboxylic acids **3b**. It should be noted that very few alternative methods are available to prepare such derivatives.[18] The Stille coupling reaction of organotin reagents such as vinyltributyltin with **1** offers yet another procedure to prepare Pc-styrene derivatives (**3a**). The reaction was conducted under neutral conditions using tetrakis(triphenylphosphine)palladium(0) and yields were high. Compound **1** also underwent smooth Suzuki cross-coupling reaction with phenylboronic acid to give the phenyl-Pc **4** in high yield (Scheme 1). The reaction was carried out at 80-90 °C for 4 h in dioxane containing Pd(0) and tribasic potassium phosphate. The reaction conditions are sufficiently mild so that a variety of functionalised boronic acid groups can be used. Elemental analysis and the spectral data (MS, ^{1}H NMR, UV-Vis) for new products were consistent with assigned formulations. The FAB mass spectrum in *m*-nitrobenzyl alcohol or thioglycosol as matrix, revealed a molecular ion corresponding to the selected coupling product and a cluster of molecular peaks corresponding to the various isotope abundances of the natural metal ion present in the centre of the Pc. The electronic spectra gave Soret and Q absorbance bands characteristic of Pc molecules.

In summary, application of the palladium catalysed coupling methodology greatly simplifies the preparation of unsymmetrical Pcs and substantially enlarges the spectrum of analogues which can be obtained.

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