

Synthesis and utilisation of 2,7'-diindolymethanes and a 2-(2-indolyl)pyrrolylmethane as macrocyclic precursors

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Abstract—Treatment of 3-(4-chlorophenyl)-7-hydroxymethyl-4,6-dimethoxyindole with 3-(4-chlorophenyl)-4,6-dimethoxyindole results in the generation of two geometrically isomeric diindolymethanes in addition to a novel triindolyl oligomer, which has been structurally characterised. The 2,7'-diindolymethanes were found to be unstable under Vilsmeier formylation conditions, thus hampering macrocycle precursor construction. In an alternate approach, the 3-(4-chlorophenyl)-4,6-dimethoxyindole-7-carbaldehyde was converted into the indolyl-pyrrolyl macrocycle precursor 5-(3-(4-chlorophenyl)-4,6-dimethoxyindole-2-ylmethyl)-4-ethyl-3-methylpyrrole-2,7-dicarbaldehyde, which was used to generate an unsymmetrical pentaaza macrocycle.

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1. Introduction

We have been interested in the non-template synthesis of indole-containing ligands for some time,^{1–4} and have recently reported our latest results.⁵ We now report some results relating to the generation of precursors of macrocyclic imines based on the 2,7'-diindolymethane and 2-(2-indolyl)pyrrole structures. Such diarylmethanes are usually constructed by the reaction of electron-rich arenes with formaldehyde, or by the acid-catalysed addition of an arene to a benzylic alcohol, the latter being the initial intermediate in the addition of an arene to formaldehyde. The most effective route to the indolymethanols proceeds via the reduction of indole-carbaldehydes.

2. Results and discussion

2.1. Diindolymethane ligand systems

The first strategy has already been used to generate the symmetrical 2,2'-diindolymethane system.⁶ The construction of an unsymmetrical diindolymethane would permit the development of a series of macrocycles that would no longer have a symmetrical coordination field. This would

further allow the investigation of the chemical and physical properties of metal complexes incorporating the indole unit.

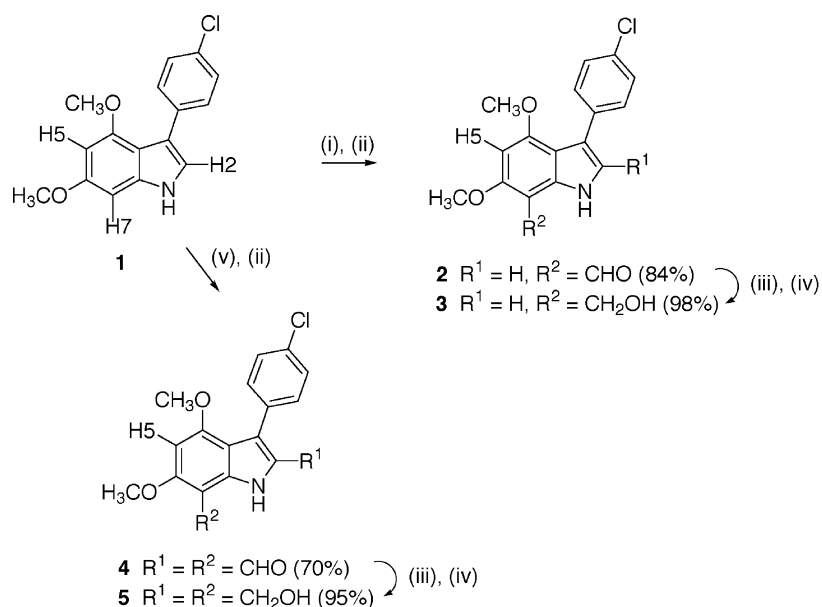
It has been shown previously⁷ that reduction of the 7-carbaldehyde functionality to the corresponding methyl alcohol, followed by treatment with acid, promotes the nucleophilic attack of existing unsubstituted indole sites on the carbocation so generated. Such a procedure may also give rise to trimeric cyclic and tetrameric oligomeric species if self-condensation occurs.⁷

It has been observed that the nucleophilic attack of a 3-(4-halophenyl)-4,6-dimethoxyindole on an indolyl-7-methanol occurs primarily via position 2-to produce a 2,7'-linked diindolymethane.⁷ A second isomer, the 7,7'-linked diindolymethane, was also observed, although in much lower yield. The latter would generate an eight-membered bisanionic coordination sphere on coordination and was thus, eliminated from this study.

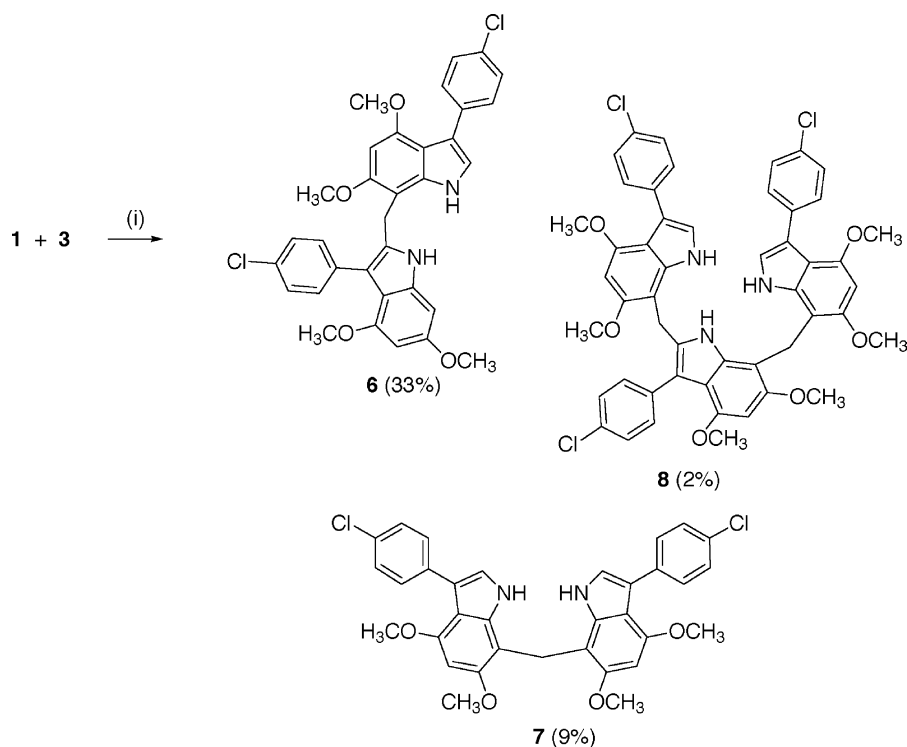
Treatment of the aldehyde **2**, derived from highly substituted indole **1**,⁵ with an excess of sodium borohydride in tetrahydrofuran affords the corresponding 7-methanol **3** (Scheme 1). This alcohol was found to be particularly sensitive to acidic environments, presumably due to the promotion of self-condensation reactions. Similarly, the reaction of indole **1** with an excess of Vilsmeier reagent at elevated temperature followed by basic work-up afforded a good yield of the diformyl species **4**, which can be converted to **5** in the same manner (Scheme 1).

Keywords: Indole; Diindolymethane; Vilsmeier; Macrocycle.

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Scheme 1. Reagents and conditions: (i) $POCl_3$, DMF, $0^\circ C$; (ii) NaOH, H_2O ; (iii) $NaBH_4$, THF, Δ ; (iv) H_2O ; (v) $POCl_3$, DMF, $50^\circ C$.



Scheme 2. Reagents and conditions: (i) HOAc, Δ .

Reaction of **1** with **3** (Scheme 2) in boiling glacial acetic acid gave three products: unsymmetrical 2,7'-diindolylmethane **6** (separated from co-incident **1** after extensive chromatography) and the 7,7'-diindolylmethane **7**. The third product gave a mass spectral base peak that indicated the presence of three chlorine atoms at m/z 885–891 and 1H NMR data indicated a trimeric oligomer with two inequivalent methylene groups, containing both 2,7- and 7,7'-indolyl linkages. X-ray quality crystals of oligomer **8** were obtained such that an unambiguous structural assignment could be made.

The trimer (Fig. 1) crystallises in the monoclinic space group $P2_1/c$ and is a 2,7-disubstituted indole, where the substituent indoles are pendant from the central indole via the two methylene linkages. There are two distinct trimers (A and B) within the unit cell with slightly differing structural parameters, as indicated in Table 1. The tetrahedral nature of the linkages enables the molecule to adopt a partial box configuration (Fig. 2). An edge-to-face arene–arene interaction⁸ is apparent within the lattice between the edge of a chlorophenyl moiety of the central indole of one molecule and the face of a terminal 7,7'-linked indole of the adjacent molecule (median distance

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