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Synthesis of symmetrical and unsymmetrical diindolylmethanes via acid-catalysed electrophilic substitution reactions

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ABSTRACT

A range of activated indole-2-carboxylate derivatives was prepared via the Hemetsberger indole synthesis. Vilsmeier formylation was explored to establish regioselectivity and to prepare a range of new indole carbaldehydes. The indole aldehydes were reduced to the corresponding hydroxymethylindoles in good yields by the use of sodium borohydride in THF. Symmetrical 4,4′-, 6,6′- and 7,7′-diindolylmethanes were prepared via the acid-catalysed reaction of the corresponding hydroxymethylindoles. Furthermore, the treatment of methyl 4-hydroxymethyl-5,6-dimethoxyindole-2-carboxylate and a range of methyl indole esters with acetic acid led to the formation of unsymmetrical 4,6′- and 4,7′-dindolylmethanes.

1. Introduction

Indole heterocyclic systems are biologically valuable scaffolds that occur in many natural products and considerable effort has been devoted to the synthesis of complex and pharmacologically active indole alkaloids. There has been significant interest in heterocyclic aromatic systems derived from dimethoxyindoles as well as dimethoxyindole-containing heterocyclic compounds due to their possible biological and pharmacological activities.[1,2] It is well established that in indoles, C3 is the most nucleophilic position for electrophilic substitution reactions.[3–5] As part of an ongoing study, we have investigated and compared the nucleophilic reactivity of various dimethoxyindole derivatives, which differed in the location of the methoxy groups in the benzene ring. The Vilsmeier formylation reaction was utilised for an exploratory investigation into the reactivity of these systems. The reduction of activated indole carbaldehydes affords the related hydroxymethylindoles, which can generate interesting macrocycles and fascinating oligomers in good yields.[6,7] The chemoselective reduction using sodium borohydride is valuable to illustrate that the ester functions are typically not affected by sodium borohydride.[8] Our group has previously reported a range of symmetrical and unsymmetrical diindolylmethanes.[9] 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.[10]

2. Results and discussion

2.1. Preparation of methyl dimethoxyindole-2-carboxylates

According to the literature, numerous methods can be applied to the preparation of activated indole scaffolds.[11,12] The Hemetsberger reaction[13,14] is potentially one of the most important methods for the synthesis of indoles. It was used to afford a range of methyl dimethoxyindole-2-carboxylate derivatives via vinyl azides **5**–**8**, which are generated by the condensation of the corresponding dimethoxybenzaldehydes **1**–**4** with methyl azidoacetate in methanolic sodium methoxide (Scheme 1). The thermal decomposition of vinyl azides **5**–**8** followed by intramolecular cyclisation gave the indoles **9**–**12**.[13–24] The literature is very mixed on the details for the azides and the indoles, with regard to melting points, yields and NMR spectroscopic data, so our data are recorded in the Experimental section for ease of access and comparison.

2.2. Formylation of methyl dimethoxyindole-2-carboxylates

It was thought that Vilsmeier formylation is not only an excellent indicator for the identification of reactivity and regioselectivity,

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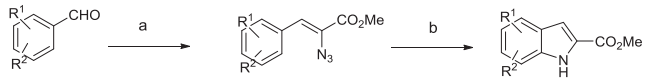
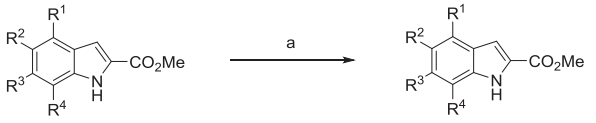


Num.	Benzaldehyde	Num.	2-Azido ester	Num.	Indole
1	R^1= 2-OMe R^2= 3-OMe	5	3-(2,3-dimethoxyphenyl)	9	4,5-dimethoxy
2	R^1= 3-OMe R^2= 4-OMe	6	3-(3,4-dimethoxyphenyl)	10	5,6-dimethoxy
3	R^1= 2-OMe R^2= 5-OMe	7	3-(2,5-dimethoxyphenyl)	11	4,7-dimethoxy
4	R^1= 2-OMe R^2= 4-OMe	8	3-(2,4-dimethoxyphenyl)	12	4,6-dimethoxy

Scheme 1. Reagents and conditions: (a) $N_3CH_2CO_2Me$, NaOMe, anhydrous MeOH, <10 °C, 4 h, 75–81%; (b) xylene, 2 h, reflux, 82–95%.

but also delivers an aldehyde, which can be used for further useful synthetic transformations. Our group has reported that Vilsmeier formylation of methyl 5,7-dimethoxyindole-2-carboxylate has occurred selectively at C4.[25] This could be explained by the electron donating effect of the methoxy groups on the benzenoid ring and deactivation at C3 due to the electron-withdrawing ester group located at C2. It was anticipated that a methyl ester group at C2 would deactivate the C3 position in all dimethoxyindole-2-carboxylates and also the location of methoxy groups on the benzenoid ring would affect the site of reactivity of dimethoxyindole-2-carboxylate systems.

In the current work, new dimethoxyindole carbaldehydes **13**–**16** were synthesised using Vilsmeier formylation from indoles **9**–**12**, respectively (Scheme 2).



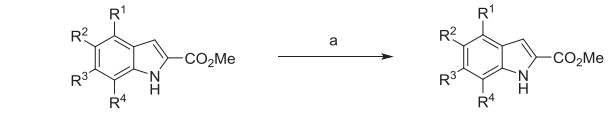
	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
9	OMe	OMe	H	H	13	OMe	OMe	H	CHO
10	H	OMe	OMe	H	14	CHO	OMe	OMe	H
11	OMe	H	H	OMe	15	OMe	H	CHO	OMe
12	OMe	H	OMe	H	16	OMe	H	OMe	CHO

Scheme 2. Reagents and conditions: (a) i: $POCl_3$, DMF, −10 °C, 20 min; ii: overnight, rt, 86–95%.

The methyl 4,5- and 4,6-dimethoxyindole-2-carboxylates, **9** and **12**, would be expected to show similar activation to formylation at C7. The designated products **13** and **16** were, respectively, synthesised by treatment of the corresponding methyl indole esters with the Vilsmeier reagent at low temperature. In the ^{1}H NMR spectrum of methyl 4,5-dimethoxy-7-formylindole-2-carboxylate **13**, the indole NH proton was shifted downfield to 10.48 ppm due to hydrogen bonding between the carbonyl oxygen and indole NH proton. The appearance of H3 as a doublet resonating at δ 7.40 ppm and the H6 proton as a singlet at δ 7.19 ppm indicated that the formylation occurred at C7. The same peak pattern was observed for the methyl 4,6-dimethoxy-7-formylindole-2-carboxylate **16**. The indole NH proton was found at 10.61 ppm and the H3 proton appeared as a doublet at δ 7.20 ppm. Furthermore, the H5 peak, which resonated as a doublet signal in the ^{1}H NMR spectrum of starting material **12**, became a singlet at 6.04 ppm due to the disappearance of the meta coupling between H5 and H7. In the case of methyl 4,7-dimethoxyindole-2-carboxylate **11**, the most preferable position for electrophilic substitution would probably be C6 due to the effect of delocalisation of the lone pair of electrons on the indole nitrogen atom. The reaction of methyl 4,7-dimethoxyindole-2-carboxylate **11** with the Vilsmeier reagent gave the expected product **15** (Scheme 2). The ^{1}H NMR spectrum of compound **15** confirmed that the formylation occurred on the benzene ring. The signal for H3 appeared as a doublet at δ 7.39 ppm while only one singlet was observed at δ 7.05 ppm corresponding to the chemical shift of the H5. The methyl 5,6-dimethoxyindole-2-carboxylate **10** can be selectively brominated at the 3-position by the use of *N*-bromosuccinimide in dichloromethane.[26] However, the methyl 5,6-dimethoxyindole-2-carboxylate **10** would be expected to undergo formylation at C4 to give compound **14**, which was indeed obtained as a crystalline solid by the treatment of the methyl indole ester with Vilsmeier reagent (Scheme 2). The most significant feature in the ^{1}H NMR spectrum of the 4-formylindole ester **14** was the characteristic H3 proton, which appeared as a doublet due to the coupling with the indole NH proton. While the singlet at δ 6.78 ppm in the spectrum of the starting material **10** was assigned to H7, the same proton signal was shifted downfield to δ 7.80 ppm in the case of the compound **14**. Clearly, the electron donating methoxy groups located at C5 and C6 activate the benzene ring for formylation at C4 rather than C3. Another reason for the C4 substitution is the electron-withdrawing C2-ester group, which deactivates the 3-position of the indole **10**.

2.3. Chemoselective reduction of formyl-dimethoxyindole-2-carboxylates

Reduction of formylindoles to the corresponding hydroxymethylindoles is a well-known reaction and some of the products have been used in the construction of indole macrocycles or diindolylmethane systems.[6,10,27] Sodium borohydride is a common reducing agent for this reaction and gives the hydroxymethylindoles in high yield.[6,7] In the current work, formylindole-esters **13**–**16** were initially treated with sodium borohydride in a variety of solvents, such as methanol, ethanol, isopropanol and tetrahydrofuran, to optimise the reaction yields of the products **17**–**20**. It was found that when the reactions were conducted in tetrahydrofuran at room temperature, more than 85% yields of the products were obtained (Scheme 3).



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
13	OMe	OMe	H	CHO	17	OMe	OMe	H	CH_2OH
14	CHO	OMe	OMe	H	18	CH_2OH	OMe	OMe	H
15	OMe	H	CHO	OMe	19	OMe	H	CH_2OH	OMe
16	OMe	H	OMe	CHO	20	OMe	H	OMe	CH_2OH

Scheme 3. Reagents and conditions: (a) $NaBH_4$, THF, rt, 2 h, >85%.

2.4. Acid-catalysed reaction of hydroxymethyl-dimethoxyindole-2-carboxylates

It was envisaged that the acid-catalysed reaction of a range of hydroxymethyl-dimethoxyindole-2-carboxylate derivatives **17**–**20** would allow the construction of useful diindolylmethanes via a mechanism involving the expulsion of formaldehyde. Our group has previously shown that the reaction of 3-(4-chlorophenyl)-4,6-dimethoxyindole **21** with 3-(4-chlorophenyl)-7-hydroxymethyl-4,6-dimethoxyindole **22** in boiling acetic acid led to the unsymmetrically linked 2,7′-**23** and symmetrically linked 7,7′-diindolylmethanes **24** (Scheme 4).[10] The nucleophilic attack of the indole onto the indolyl-7-methanol gave the 2,7′-diindolylmethane **23** as the major product, and 7,7′-diindolylmethane **24** was formed in much lower yield.[10]