# Augmented indoles

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**Abstract**

The indole ring presents a good platform for synthesis because of its nucleophilic capacity at C3, to a lesser extent at C2, and also through the indole anion at N1. The development of new indoles with strategically placed methoxy groups at C4 and C6, or C5 and C7, provides even better platforms not only through increased general activation, but also through specific activation at C7 and C4 respectively. As a result of this multi-faceted activity, it is possible to generate a variety of additional rings fused to the indole platform. This rather general strategy of molecular augmentation leads to new types of indole structures, some of which bear resemblance to natural indole alkaloids. A selection of examples is presented.

**Keywords:** Indoles, benzofurans, quinolines, isoquinolines, benzpyrazoles

## Contents

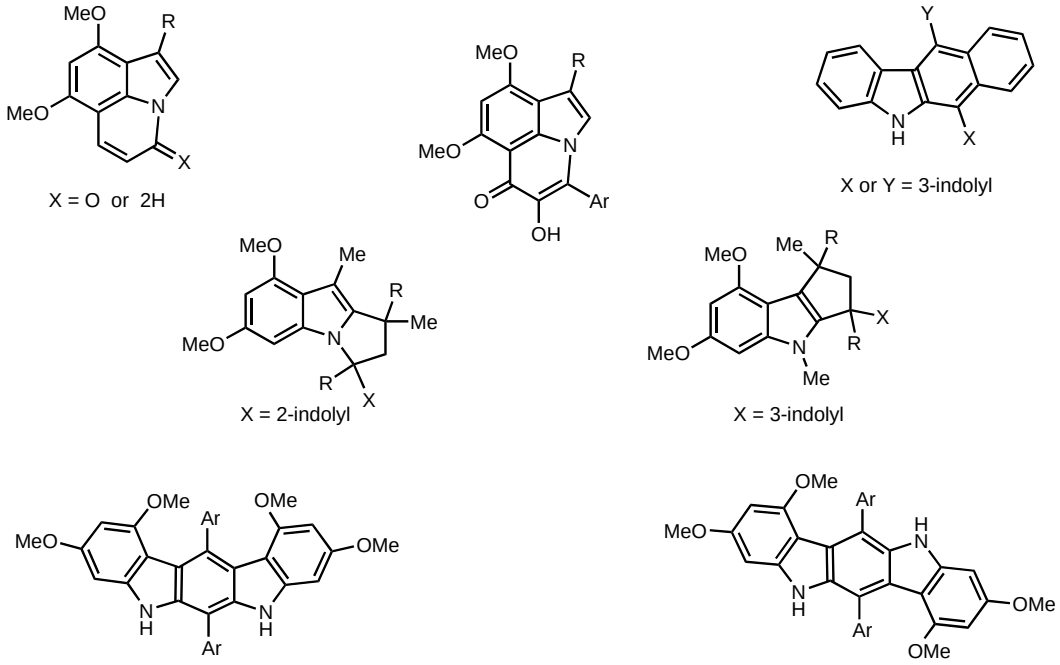
# 1. Introduction

Indoles undergo ready electrophilic addition and substitution reactions at C3, and if this position is substituted, attack is diverted to C2. The introduction of electron-donating methoxy groups on the benzene ring direct activity to other positions, depending on the substitution pattern. So 4,6-dimethoxy substitution directs reactivity to C7, and 5,7-dimethoxy substitution directs it to C4. So far we have made use of the first of these substitution patterns to build a variety of augmented indoles, ie. indoles containing additional rings as the result of their ambident nucleophilic properties (Scheme 1).[1-5] We now present further examples of this strategy, together with some examples employing the second substitution pattern.

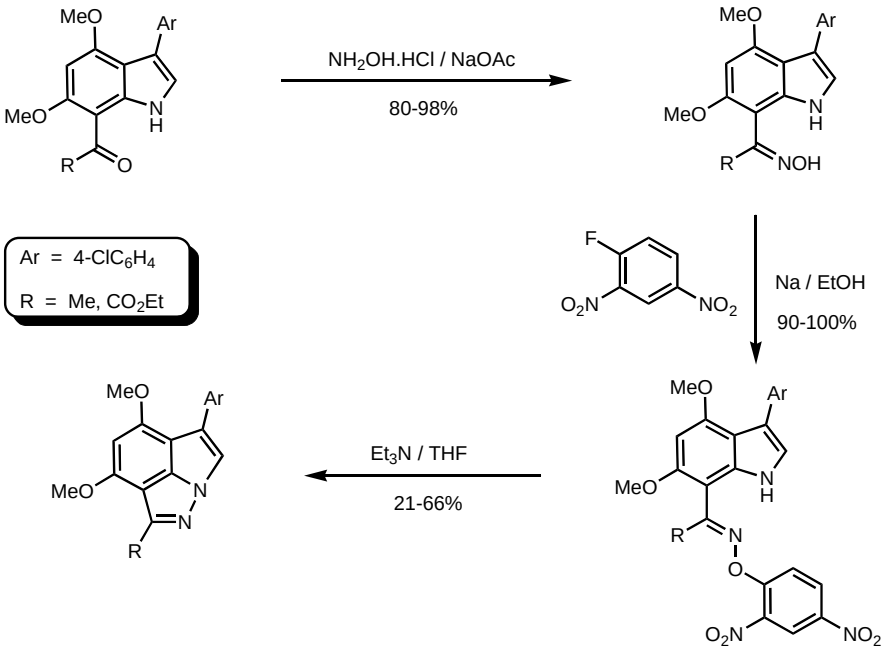
# 2. Results and Discussion

## 2.1. Reactions of some indole-7-oximes

3-Aryl-4,6-dimethoxyindoles can be formylated and acylated at C7, using Vilsmeier or Friedel-Crafts reactions.[6] The resulting carbonyl compounds can be converted to the related oximes, then combined with fluoro-2,4-dinitrobenzene under basic conditions to yield the corresponding oxime ethers. On treatment of these with triethylamine or sodium hydride, those of the aldehydes give 7-cyano-indoles,[7] whereas those derived from ketones generate pyrazoloindoles, as the result of cyclisation between the indole and oxime nitrogen atoms (Scheme 2).



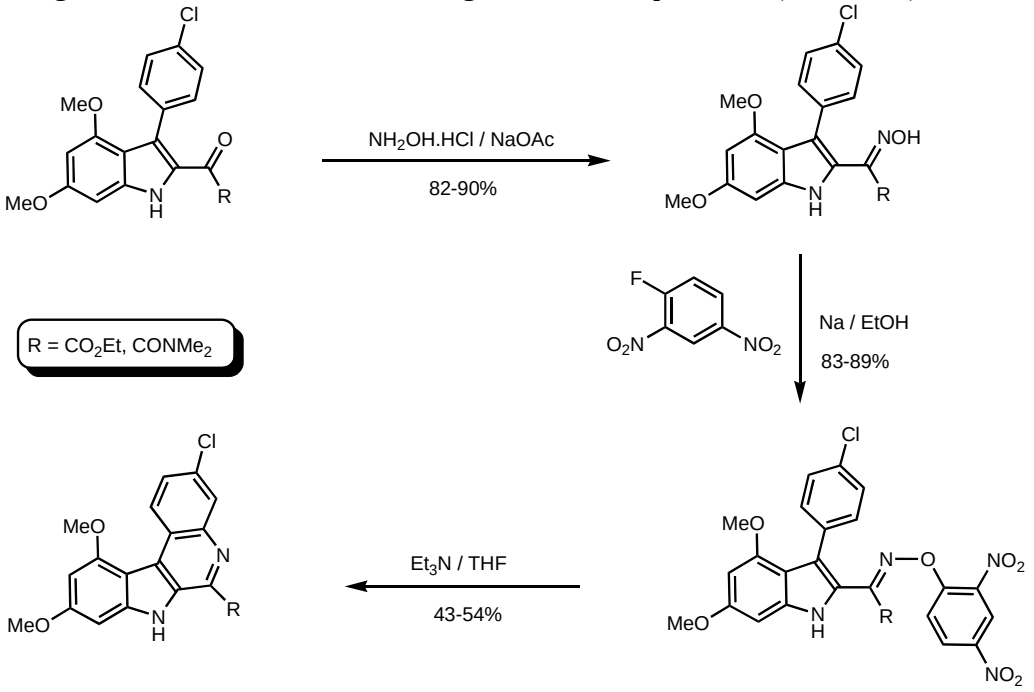

**Scheme 1**




**Scheme 2**

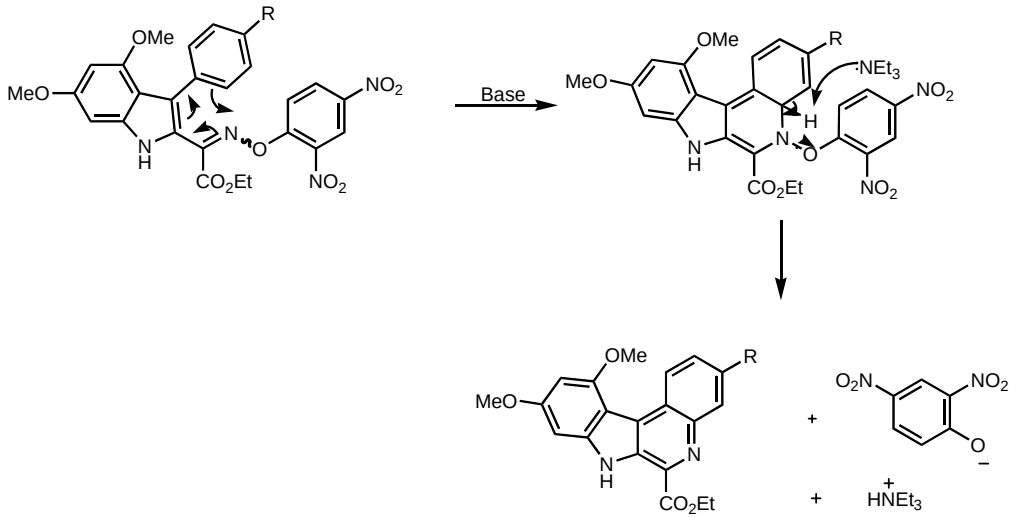
## 2.2. Reactions of some indole-2-oximes

The same kind of reaction sequence can be effected with the related 2-acylated-3-aryl-4,6-dimethoxyindoles. In this case, cyclisation occurs between the *ortho*-carbon of the 3-aryl group and the nitrogen atom of the oxime ether, to give an indoloquinoline (Scheme 3).




**Scheme 3**

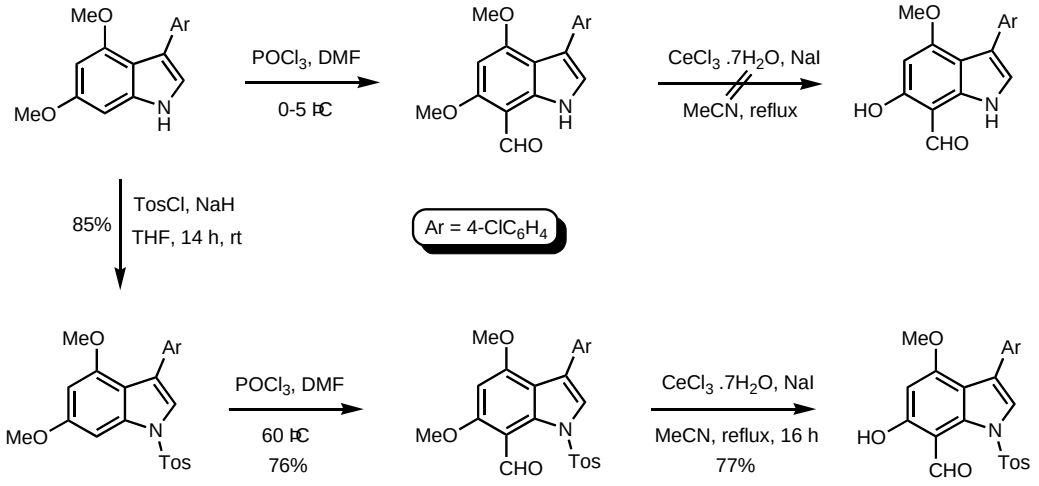
Kinetic and other mechanistic studies of this reaction favour an electrocyclic process to generate an intermediate from which 2,4-dinitrophenol is eliminated (Scheme 4).




**Scheme 4**

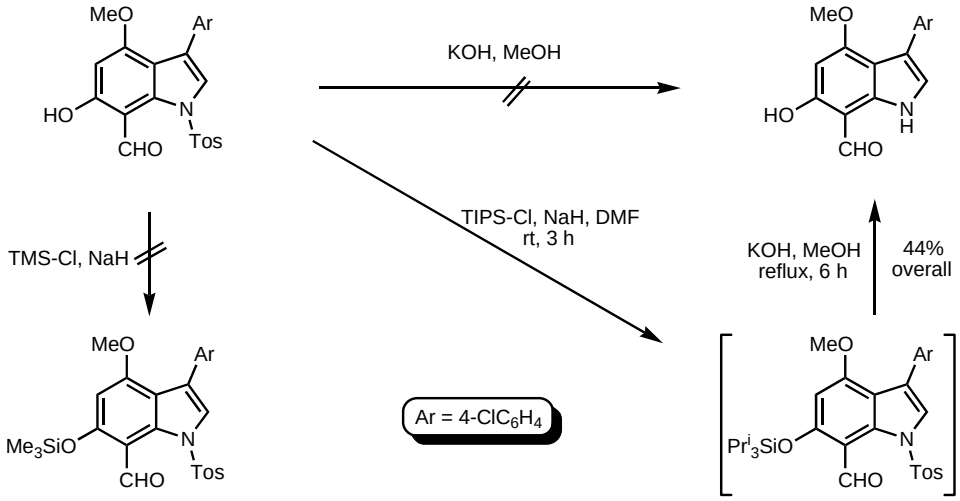
## 2.3. Cyclisation between C7 and C6 on the indole ring

A second aspect of our work relates to cyclisation between C7 and C6. In order to achieve this, the 6-methoxy group must undergo demethylation to give a reactive phenolic group. Selective demethylation at C6 proved to be quite a challenge, as we relied on the use of sodium iodide in conjunction with cerium (III) chloride, and chelation of cerium between the two oxygen atoms of the 6-methoxy and the 7-formyl groups. For this to occur, the indole nitrogen atom needed to be protected as the tosylate (Scheme 5).



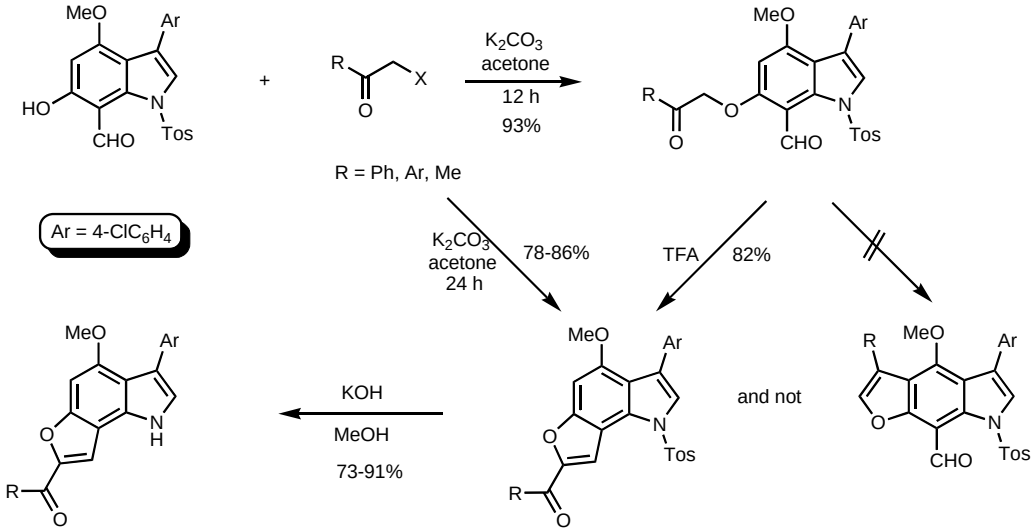

**Scheme 5**

Removal of the tosylate then required protection of the phenolic group as a TIPS derivative (Scheme 6).




**Scheme 6**

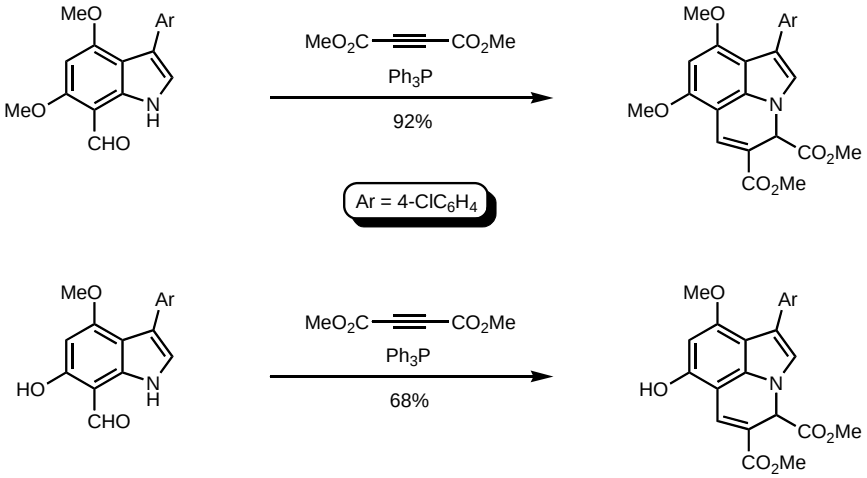
With the 6-hydroxy-7-formylindole in hand, it was converted by reaction with α-haloketones into furoindoles, as the result of cyclisation between the acylmethyl ether on to the 7-formyl group. No cyclisation occurred on to the C5 position of the indole (Scheme 7).




**Scheme 7**

## 2.4. Cyclisation between C7 and N1 on the indole ring

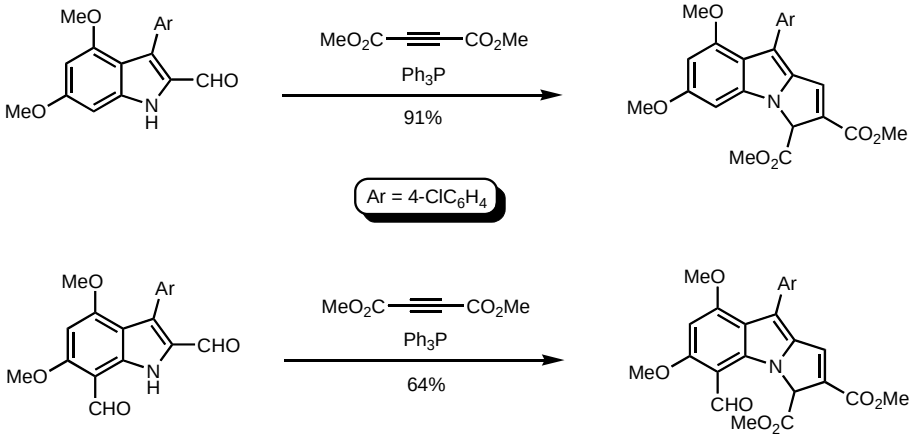
Salicylaldehydes have been shown to react with dimethyl acetylenedicarboxylate and triphenylphosphine to give cyclised products resulting from an intramolecular Wittig reaction.[8-10] Similar reactions can be achieved from indole-7-carbaldehydes, and a six-membered ring is fused between C7 and N1, to give pyrroloquinolines. In the case of a 6-hydroxy-7-formylindole, there is a choice of reaction between the indole nitrogen and the phenolic oxygen atoms. In the event, the reaction is completely selective for the nitrogen atom (Scheme 8).




**Scheme 8**

## 2.5. Cyclisation between N1 and C2 on the indole ring

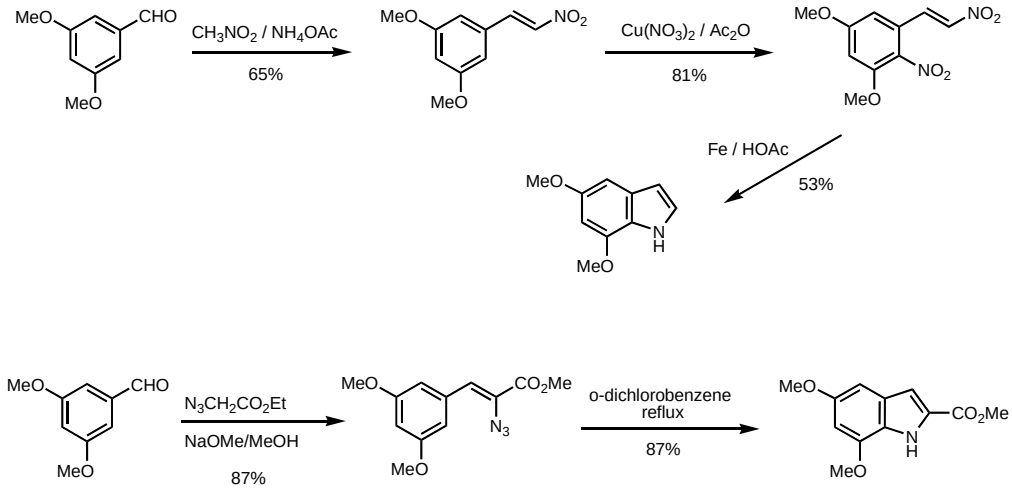
Reaction of the related indole-2-carbaldehydes under the same conditions gives pyrroloindoles, as the result of cyclisation between N1 and C2. It is notable that reaction of a 2,7-dicarbaldehyde is completely selective for the 2-position, and again a pyrroloindole is formed in preference to a pyrroloquinoline (Scheme 9).




**Scheme 9**

## 2.6. Formation of 5,7-dimethoxyindoles

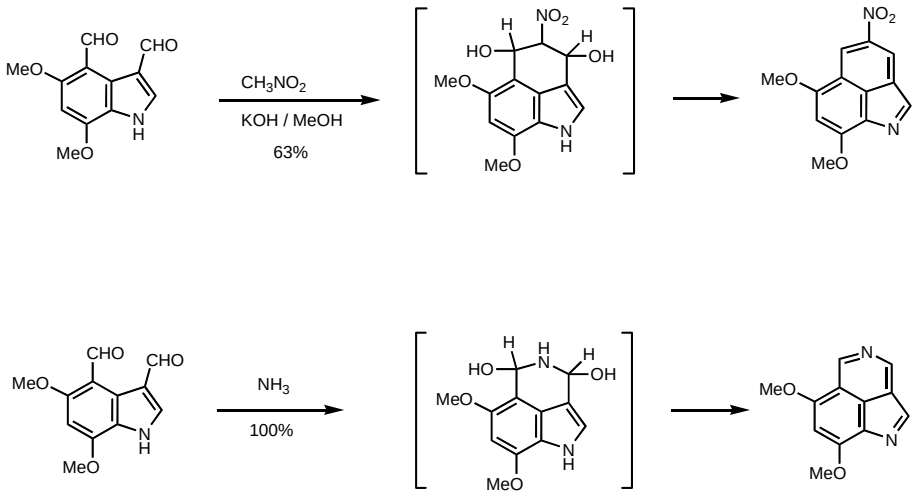
Finally, we present some examples of reactions involving 5,7-dimethoxyindoles. These examples use 5,7-dimethoxyindole and methyl 5,7-dimethoxyindole-2-carboxylate as the starting materials. [11-13] Their modified synthetic routes are straightforward and effective (Scheme 10).




**Scheme 10**

## 2.7. Cyclisation between C3 and C4 on the indole ring

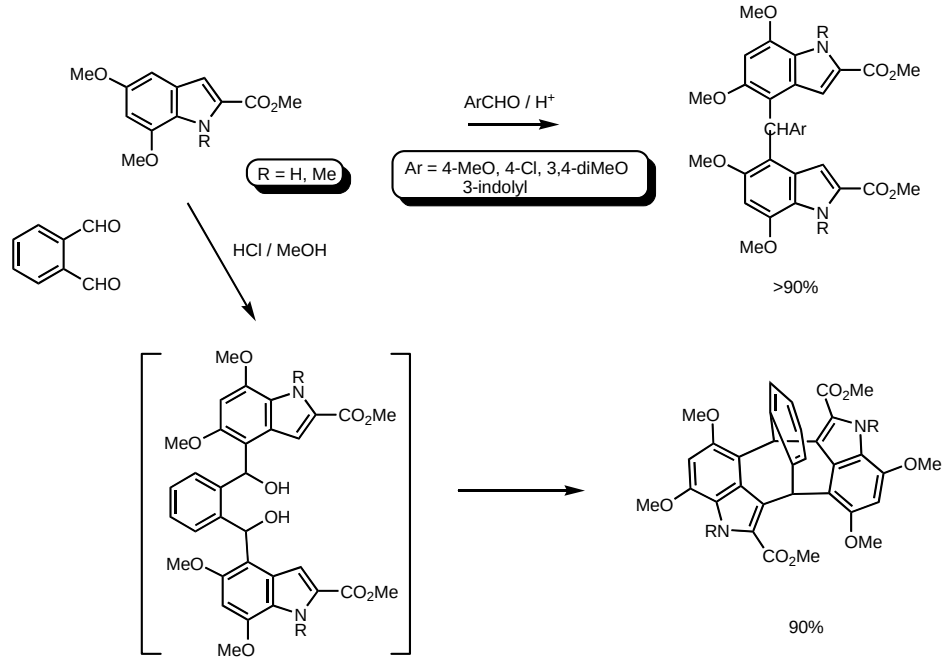
Formylation of 5,7-dimethoxyindole gives a mixture of the 3- and 4-carbaldehydes, but ways have been found to achieve selective reaction.[14] However, the 3,4-dicarbaldehyde can be formed easily using excess Vilsmeier reagent, and reacts readily with nitromethane or ammonia, to give augmented indoles with a fused benzene or pyridine ring respectively (Scheme 11).[14]




**Scheme 11**

### 2.8. Regioselective reactions of 5,7-dimethoxyindoles with aldehydes

Methyl 5,7-dimethoxyindole-2-carboxylate undergoes completely selective formylation at C4. Furthermore, it reacts readily with aryl aldehydes, again selectively at C4, to give 4,4'-diindolylmethanes. However reaction with *o*-phthaldialdehyde results in the formation of a new ring between C3 and C4 and the formation of a trypticene analog in high yield. It is likely that initial reaction takes place at C4, followed by cyclisation onto the less nucleophilic C3 positions (Scheme 12).




**Scheme 12**

This interesting Y-shaped structure could serve as a useful platform for further elaboration.

## 3. Conclusions

Activated indoles such as 4,6-dimethoxyindoles and 5,7-dimethoxyindoles are capable of reaction in two positions, so as to encourage the formation of new rings. Thus the indole framework can be augmented in a variety of ways to afford new polycyclic structural types.

## 4. Acknowledgements

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## 5. References

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