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Expedient routes to valuable bromo-5,6-dimethoxyindole building blocks

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ABSTRACT

The synthesis of 3-, 4-, 7-bromo and 4,7-dibrominated 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) derivatives is reported. Hemetsberger and Bartoli indole syntheses were investigated and expedient routes to the desired compounds were developed. These indoles are valuable substrates for elaboration using transition metal-mediated cross-coupling chemistry.

Indoles are heterocyclic structures of unquestionable importance. It is well recognised that the indole moiety is a privileged structural motif found in numerous natural products and various synthetic compounds.[1] Moreover, a large number of indole-containing compounds show potential as therapeutic agents.[2] Thus, development of methods which allow rapid access to functionalised indolic 'building blocks' is considered a crucial aspect of drug development endeavours. In this vein, 5,6-dihydroxyindole (DHI) **1** and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) **2** are examples of naturally occurring indole building blocks found in interesting natural products and biopolymers.[3,4] As such, derivatives of DHI and DHICA, which are suitably functionalised for further elaboration, conceptually exemplify useful synthetic intermediates with potential application in a drug discovery setting. Herein, we describe the development of expedient routes to a small library of high value bromo DHI and DHICA derivatives **3–9** (Fig. 1).

We began our study with a three-step synthesis of **6** from commercially available veratraldehyde (**10**) (Scheme 1) using a Hemetsberger–Knittel approach as previously reported.[5] Veratraldehyde (**10**) was condensed with methyl azidoacetate to afford the azidocinnamate **11**. When **11** was heated at 140 °C in xylene, nitrogen was evolved with concomitant formation of indoles **12** and **13**. The reaction occurs via a transient nitrene intermediate which inserts onto the aromatic ring. Under these conditions, this cyclisation has been reported to occur with varying degrees of regioselectivity[5,6] and in our hands **12** (54% isolated yield) was formed along with **13** in a ratio of approximately 10:1. Indole **12** can be selectively brominated at the 3-position with pyridinium tribromide in pyridine,[5] however, we found that the use of *N*-bromosuccinimide in dichloromethane was more convenient and afforded **6** as desired.

It was envisaged that a similar Hemetsberger–Knittel protocol could be applied to the synthesis of the hitherto unreported DHICA

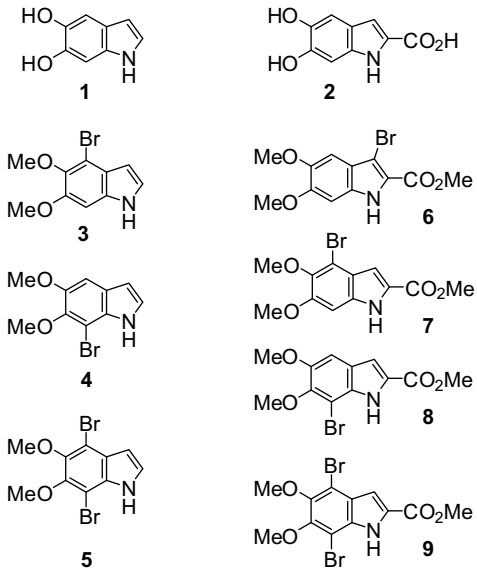
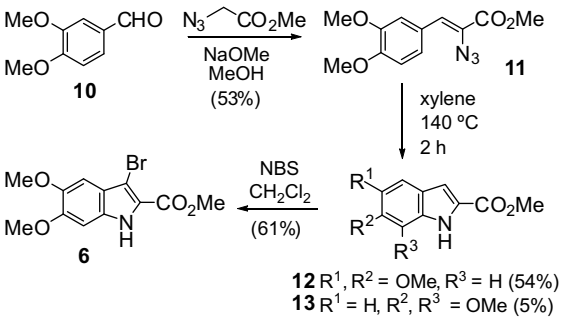


Figure 1.



Scheme 1.

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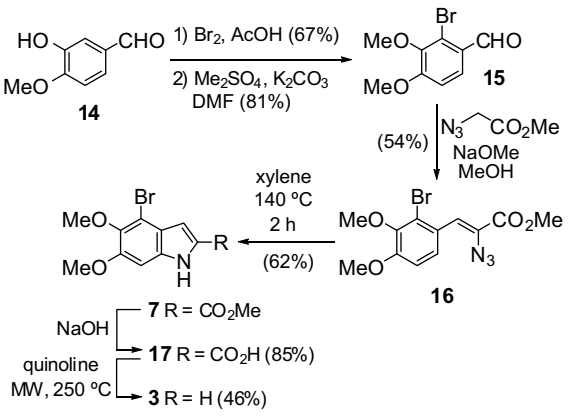
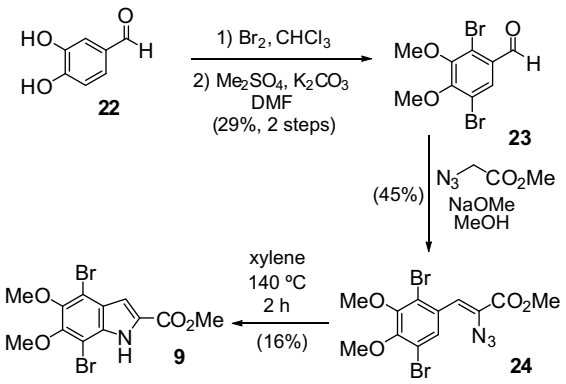


Scheme 2.

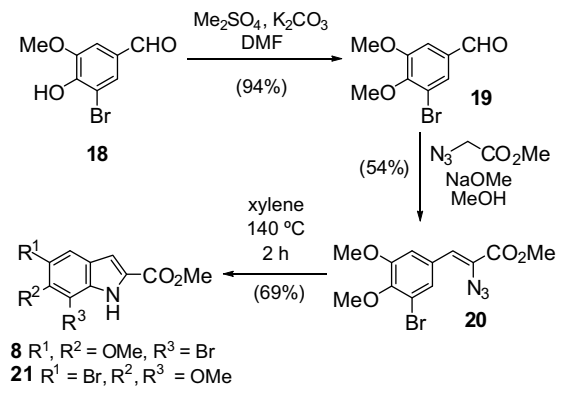


Scheme 4.

derivatives **7**–**9** and we initiated our investigation with the synthesis of the 4-bromo derivative **7** (Scheme 2). Isovanillin (**14**) was brominated and subsequently methylated using standard conditions to afford 2-bromoveratraldehyde (**15**). Knoevenagel condensation of **15** with methyl azidoacetate afforded bromo azidocinnamate **16** which was then converted to the desired DHICA derivative **7** as outlined above. DHICA derivatives can provide access to DHI derivatives by a two-step deletion of the ester group at the 2-position. This decarboxylation protocol was applied to **7** to afford the corresponding DHI derivative **3**. Saponification of the methyl ester proceeded smoothly to yield the acid **17** which underwent microwave mediated, thermal decarboxylation in quinoline to give **3** in a modest yield over 2 steps.[7]

Conceptually, an analogous route to the 7-bromo DHICA derivative **8** (Scheme 3) is similarly expedient. However, with two positions available for the singlet nitrene insertion, the synthetic route is clearly complicated by a potential lack of regioselectivity in the key cyclisation step. Commercially available 5-bromovanillin (**18**) was first methylated using standard conditions to give 5-bromoveratraldehyde (**19**) which was subsequently converted to the requisite azidocinnamate **20**. Somewhat unexpectedly, thermally induced cyclisation then afforded a 1:1 mixture of indole products **8** and **21** in moderate yield. Nonetheless, careful chromatography or recrystallisation of the product mixture allowed for the isolation of gram quantities of the desired DHICA derivative **8**.

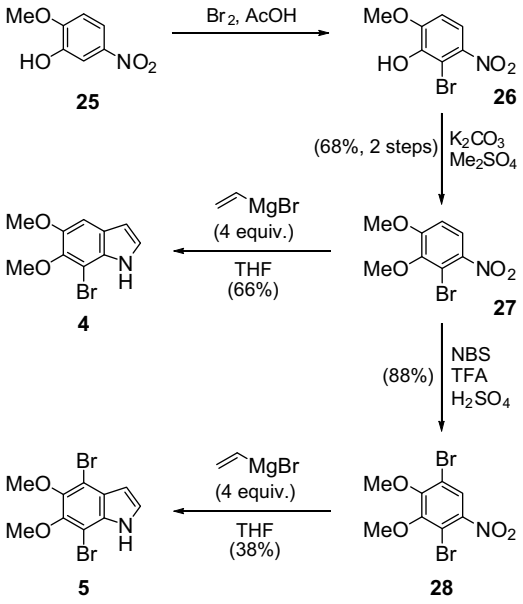
Attention was then turned to the synthesis of the final DHICA derivative, dibromoindole **9** (Scheme 4). Dihydroxybenzaldehyde **22** was sequentially brominated and methylated to afford the known 2,5-dibromoveratraldehyde **23**.[8] This synthesis of **23** is complicated by the formation of significant quantities of side products, 5-bromoveratraldehyde **19** (26%) and 5,6-dibromoveratraldehyde (13%). Formation of **19** indicates that the initial dibromination step was incomplete while formation of 5,6-dibromoveratraldehyde highlights the inherent unselective nature of the dibromination reaction. Alternative conditions for the dibromination and a step-wise bromination protocol were investigated but they did not lead to a more efficient synthesis of **23**. Compound **23** was then condensed with methyl azidoacetate following the protocol outlined previously to give the desired dibromoazidocinnamate **24**. Unlike the observed unselective cyclisation of **20**, cyclisation of azidocinnamate **24** was expected to afford a single product as there is no possibility for the formation of regioisomeric indoles in this case. However, when compound **24** was heated in xylene at 140 °C for 2 h a mixture of products was formed. The desired indole **9** was isolated in low yield along with separable side-products. It is worth noting that the formation of non-indolic products in cyclisations of this type is not without precedent. The intermediate vinyl nitrene is known to react in a substrate, temperature and solvent dependant manner.[9,10] Thus, in addition to aromatic C–H insertion to afford indoles, vinyl nitrenes can, in certain cases, undergo intramolecular electrocyclisation or dimerisation to give isolable 2*H*-azirines or dihydropyrazines, respectively.[10] Despite current complications, efforts to optimise conditions for the conversion of **24** to **9** are ongoing in our laboratories.



Scheme 3.

Decarboxylation of DHICA derivatives **8** and **9** would lead to the final desired DHI derivatives **4** and **5**, respectively. However, in view of the inefficiencies associated with the syntheses of **8** and **9** (e.g., regio and chemoselectivity problems) an alternative, expedient and more efficient route to target compounds **4** and **5** was sought. The Bartoli indole synthesis is unprecedented in its brevity. Moreover, this reaction works best with *ortho*-substituted nitrobenzenes to afford 7-substituted indoles.[11] As a result, this protocol appeared well suited to the synthesis of DHI derivatives **4** and **5** and its practical application is outlined in Scheme 5. Commercially available 5-nitroguaiacol (**25**) was brominated selectively between the hydroxyl and nitro groups and subsequently methylated to afford the key synthetic intermediate **27**. Treatment of **27** with 4 equiv of vinylmagnesium bromide according to the Bartoli protocol afforded the desired indole **4** in moderate yield.

We then turned our attention to the synthesis of the 4,7-dibromo DHI derivative **5** from precursor **28**. It was envisaged that **28** could be accessed via selective bromination of **27** at the 5-position. This selective bromination was a feasible proposition because of the directing effects of the nitro and methoxy groups, however, we found that the deactivating effects of the nitro and bromo substituents curtailed efforts to brominate the substrate under standard conditions (e.g., Br_2 in acetic acid). Recent reports have shown that in an acidic TFA/H_2SO_4 mixed solvent system,



Scheme 5.

N-bromosuccinimide is a powerful brominating agent and effectively brominates deactivated aromatic systems.[12] Gratifyingly, when these conditions were employed, the conversion of **27** to the dibromo intermediate **28** proceeded smoothly and in very good yield. Finally, treatment of **28** with vinylmagnesium bromide as previously outlined yielded the desired indole **5** in modest yield.

In summary, the syntheses of 3-, 4-, 7-bromo and 4,7-dibrominated 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) derivatives **3**–**9** have been described. The syntheses are highlighted by their expediency and have led to the rapid preparation of gram quantities of each of the target compounds **3**–**9**. The bromoindoles described herein are being utilised in our laboratories for the preparation of a variety of novel DHI and DHICA derivatives. The results of these studies will be reported in due course.

Acknowledgement

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