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N-Arylation of a hindered indoline as a route to 2-(2-methyl-1-(4-oxo-3,4-dihydrophthalazin-1-yl)-1*H*-indol-3-yl)acetic acid derivatives

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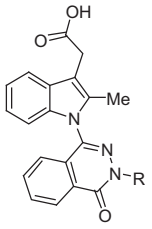
ABSTRACT

A convenient synthesis of 2-(2-methyl-1-(4-oxo-3,4-dihydrophthalazin-1-yl)-1*H*-indol-3-yl)acetic acid derivatives is described using a microwave-promoted multi-step S_NAr reaction. The desired products were found to exhibit atropisomerism.

Prostaglandin D_2 (PGD_2) is involved in a wide variety of inflammatory conditions. Two receptors have been identified for PGD_2, DP_1, and more recently DP_2 (CRTh2).[1–3] The recent discovery of CRTh2 has prompted an enormous effort both in industry as well as in academia for the identification of CRTh2 antagonists.[4] Indole acetic acids have found great prominence in this area of research.[5] Our efforts in this particular area have led us to investigate structural motifs like 1 (Fig. 1) as antagonists for CRTh2.

Our initial retrosynthetic analysis of **1** led to the obvious disconnection between the two biaryl rings. We envisaged constructing this bond using a metal mediated coupling of an appropriately functionalized substrate or a base promoted S_NAr reaction.[6] Preliminary experiments showed that 3,6-dichloropyridazine **5** could be coupled to the desired indole **4**, suggesting that 1,4-dichlorophthalazine **2** could also be a suitable coupling partner as well (Scheme 2). Additionally, phthalazinones **3** could be used in the event that 1,4-dichlorophthalazine failed to couple to **4**. Strategy **A** (Scheme 1) was preferred as structural diversity may be installed at a later stage in the synthesis. Unfortunately, extensive efforts to achieve this bond construction using both **2** as well as a variety of



1a= Bn
1b= CH_2CF_3

Figure 1. Compounds with the indole acetic acid scaffold.

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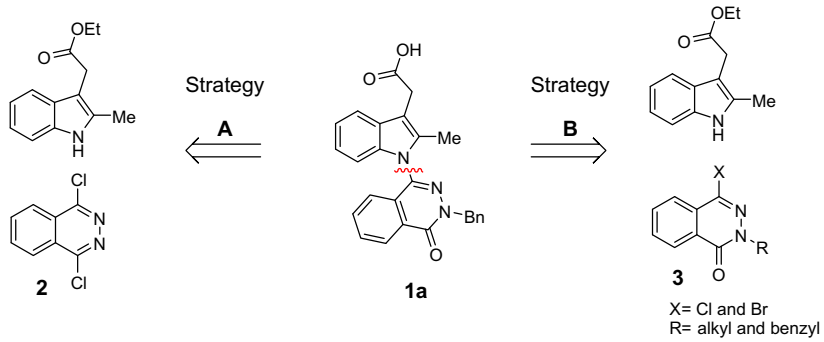
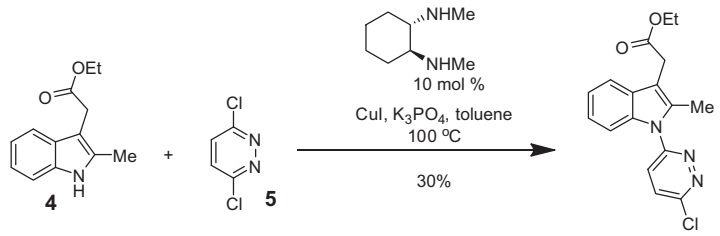
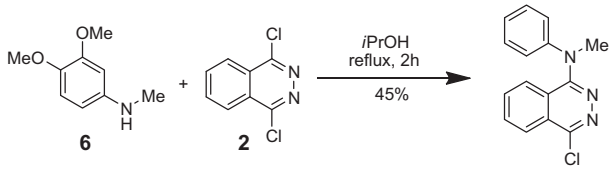


Scheme 1. Initial synthetic strategy for the construction of indole acetic acids.



Scheme 2. Precedent for Buchwald coupling of **4**.



Scheme 3. Precedent for the synthetic strategy.

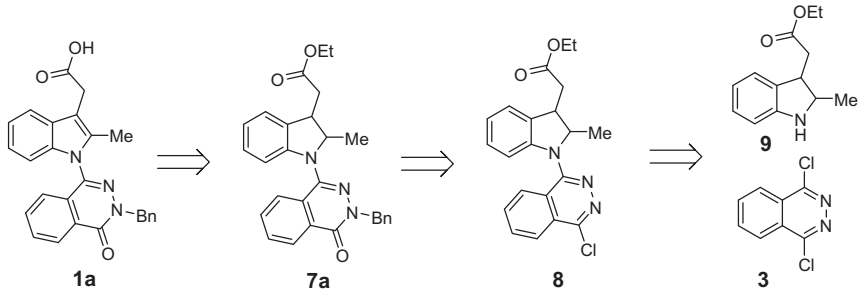
functionalized phthalazinones **3** were unsuccessful. This required us to reevaluate our approach.

We surmised that both the substitution at the 2-position of the indole as well as the electron withdrawing nature of the ester served to decrease the nucleophilicity of the indole nitrogen. Dearomatization of the indole should, in principle, increase the nucleophilicity of the nitrogen while retaining the desired molecular framework. Indeed, such a strategy has been previously utilized.[7] However, details regarding the yields and efficiency of these reactions were not disclosed. Additionally, indoline intermediates could be valuable compounds in our medicinal chemistry endeavor. Since we had a large amount of intermediate **4** available and literature precedent for using indolines, this strategy was determined to be a worthy pursuit.[8]

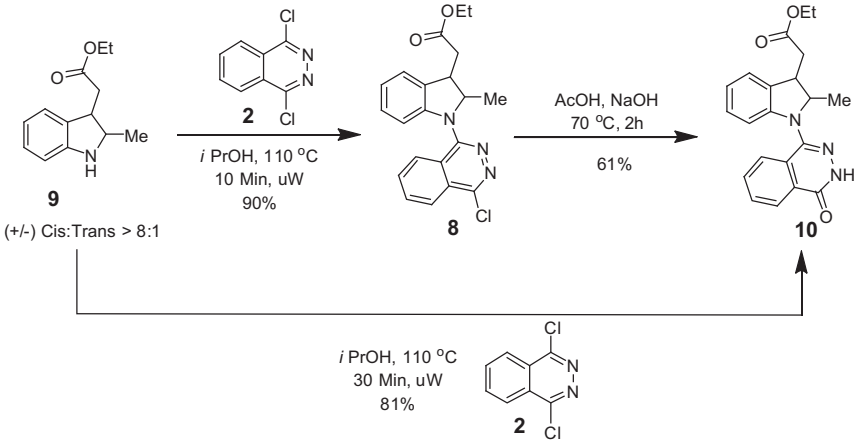
We envisaged the desired product arising from an oxidation followed by ester hydrolysis. N-Arylated indoline **7** would come from hydrolysis of **8** followed by N-alkylation. The functionalized indoline **8** would be constructed from an S_NAr reaction and the indoline starting material **9** would be derived from reduction of the parent indole **4** (Scheme 4).

The synthesis commenced with the known reduction of commercially available ethyl 2-(2-methyl-1*H*-indol-3-yl)acetate **4** using a mixture of Et_3SiH and TFA. The reduction proceeded as reported to afforded indoline 9 as an 8:1 cis:trans mixture.[9] With indoline **9** in hand, we were curious to try the S_NAr reaction. We selected a modified version of the conditions for the coupling of aniline **7** with 1,4-dichlorophthalazine (Scheme 3). As a starting point, we decided to use microwave heating as these conditions would allow for rapid evaluation of the reaction at a larger range of temperatures. To our delight, the initial experiment revealed that microwave heating of indoline 9 along with 1,4-dichlorophthalazine **2** in *i*PrOH at 110 °C produced the desired functionalized product 8 in 90% yield. Treatment of 8 with NaOH in AcOH at 70 °C for 2 h afforded **10** in 61% yield (Scheme 5).

Upon evaluating the by-products of the microwave promoted S_NAr reaction, we found a small amount of **10** present in the crude reaction mixture. We pondered whether this finding could be exploited to drive the reaction directly to **10** obviating the need



Scheme 4. Retrosynthetic analysis of **1a**.



Scheme 5. Microwave promoted coupling.

for the moderately yielding hydrolysis step. By simply extending the microwave heating times from 10 min to 30 min, we were able to drive the reaction to **10** with an isolated yield of 81% (Scheme 5). At this stage, we chose to functionalize **10** because it provided the best opportunity to introduce the greatest structural diversity into the desired compounds. This also gave us the opportunity to investigate the indoline acetic acids for activity against CRTh2 by simply converting the indoline esters to acids.

Treatment of **10** with benzyl bromide in the presence of K_2CO_3 and DMF at 70 °C, led to the desired indoline 7a as a mixture of cis and trans isomers. A variety of electrophiles may be used in this step. Isolation and stereochemical assignment of each of the isomers was straight-forward at this point. Treatment of the indoline 7 with DDQ in toluene at 110 °C (**11**) followed by saponification with LiOH afforded the desired compound **1** (Scheme 6).

With the desired compounds in hand, we wanted to determine if these compounds exhibited atropisomerism. Similar but more sterically congested compounds have been reported to have restricted rotation about the axial bond. Indeed, ^{13}C NMR experiments utilizing liquid crystal alignment media showed that **1a** exists in two conformations at ambient temperature (Fig. 2). To further investigate the atropisomeric nature of these molecules, **1a** was separated using chiral LC chromatography. The absolute stereochemistry was not determined for each enantiomer. Racemization of **1** was observed to be slow and by definition, **1a** is a class 2 atropisomeric compound.[10] More specifically, a solution of **ent-1a** racemized to 90% ee, at ambient temperature after 20 h. The racemization half-life was calculated to be 19 days at 25 °C. Interestingly, appropriate modifications to **1** may lead to axially chiral ligands for asymmetric catalysis.

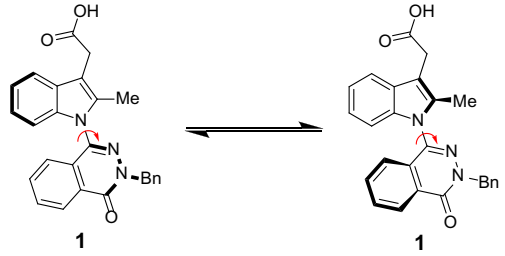
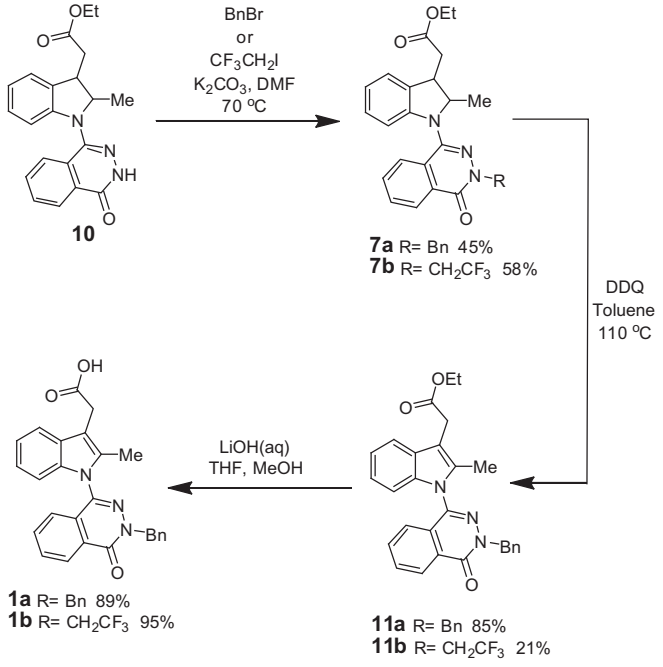


Figure 2. Atropisomerism of **1**.



Scheme 6. DDQ mediated oxidation.

In summary, we report for the first time, the synthesis of 2-(2-methyl-1-(4-oxo-3,4-dihydrophthalazin-1-yl)-1*H*-indol-3-yl)acetic acid derivatives. The key features are the utilization of an indoline as a masked indole, a microwave promoted, multi-step S_NAr reaction and late-stage oxidation to the desired compounds. Moreover, **1** was found to be a class 2 atropisomeric compound.

Acknowledgments

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