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Schwartz's Reagent-Mediated Regiospecific Synthesis of 2,3-Disubstituted Indoles from Isatins

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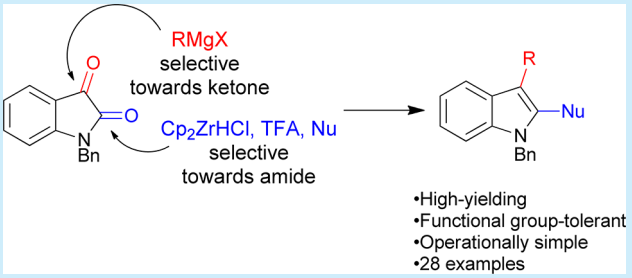
Supporting Information

ABSTRACT: An expeditious, functional group-tolerant synthesis of indoles from isatins is described. Isatins are treated with Grignard reagents to yield oxindoles. These, in turn, are reduced with Schwartz's reagent and subjected to nucleophile addition and dehydration to yield 2,3-disubstituted indoles regiospecifically. This represents a divergent approach to the synthesis of these medicinally and synthetically important compounds.



Indoles are one of the most enduring motifs in organic chemistry. They form the core of a myriad of natural products and occur in a number of medicinally relevant compounds.[1] Their importance is expressed in the wealth of methods for their synthesis developed over the years.[2] One of the most commonly used methods is the classic Fisher indole synthesis.[3] More recently, a number of transition-metal-mediated methods have appeared, the most well-known of which is the Larock indole synthesis.[4]

Despite the rich methodology available for their synthesis, the chemistry of indoles is not free of challenges. Among them, especially pronounced is the question of regioselectivity in the synthesis of 2,3-disubstituted indoles.

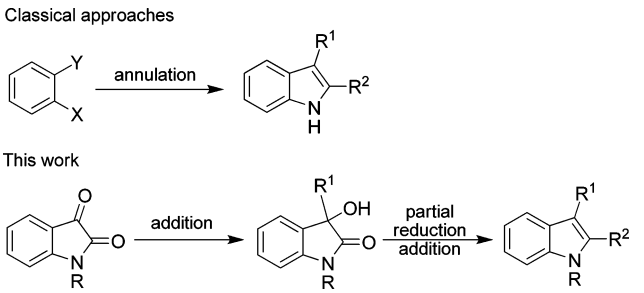
The majority of known methods are most suitable for the synthesis of 2- or 3-monosubstituted indoles. This is problematic, as 2,3-disubstituted indoles are compounds of marked importance.[5]

As most known strategies for the synthesis of indoles involve the annulation of the azacycle to an existing aromatic ring (Scheme 1), a possibility of differently annulated regioisomers arises. Addressing this issue is a priority in modern methods of indole synthesis.

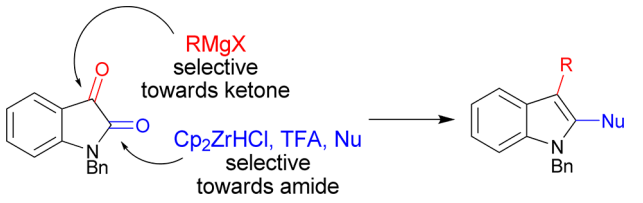
We envisioned an alternative approach to the regioselective synthesis of 2,3-disubstituted indoles that involved the differential activation of the two carbonyl groups present in the isatin molecule (Scheme 2). Isatins are an ideal substrate for the synthesis of indoles owing to their ready availability.[6,7] We expected that the ketone group would undergo ready substitution by a number of nucleophiles, leaving the amide carbonyl to be manipulated in the next step.

The unique chemistry of Schwartz's reagent, allowing for the selective activation of amide carbonyls,[8] prompted us to employ this reagent in the second step of the synthesis to form a reactive iminium moiety which would allow the addition of a range of nucleophiles not available in previous work.[7] We expected the partial reduction and addition to proceed in a one-pot manner,

Scheme 1. Different Approaches to the Synthesis of Indoles



Scheme 2. Selective Activation of Isatin Carbonyls



with subsequent dehydration to the indole proceeding spontaneously under the acidic conditions employed. The anticipated reaction pathway is shown in Scheme 3. The amide carbonyl group undergoes reduction with Schwartz's reagent. The resulting zirconium complex is decomposed by the action of added TFA. The addition of the nucleophile yields a hydroxyamine, which is then dehydrated in the acidic conditions employed.

To test our hypothesis, we synthesized a series of oxindoles containing different functional groups from *N*-benzylisatin (Scheme 4). We employed modified literature conditions[9] and

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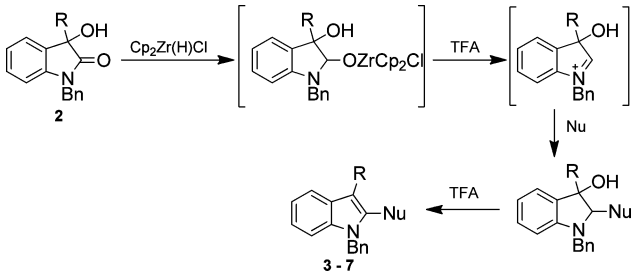
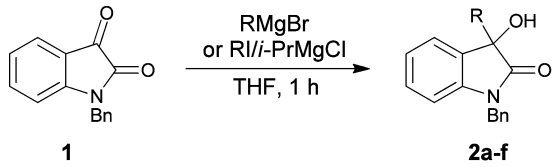
Scheme 3. Anticipated Reaction Pathway



Scheme 4. Synthesis of Oxindoles from *N*-Benzylisatin



2a R = Me
2b R = Ph
2c R = 4-$MeOC_6H_4$
2d R = 4-$EtO_2CC_6H_4$
2e R = 4-CNC_6H_4
2f R = 4-$NO_2C_6H_4$

used magnesium–iodine exchange[10] to obtain the Grignard reagents necessary. The 3-substituted oxindoles were produced in good yields.

We then subjected the synthesized oxindoles to reduction with Schwartz's reagent using a modified literature procedure.[8c] As it turned out, using more than 1 equiv of the reductant did not improve the yield. We discovered that cooling the reaction mixture prior to the addition of Schwartz's reagent avoided over-reduction of the sensitive functionalities. Preformed Schwartz's reagent was employed as using a reagent generated in situ led to over-reduction to 2-unsubstituted indoles.

Next, we subjected the reduced substrates to the addition of the nucleophile in the same pot. The addition of allyltributylstannane, acetophenone enol TMS ether, and indole proceeded smoothly. In the case of thiophenol it was necessary to use only 1 equiv of the nucleophile. Otherwise, extensive over-reduction to a 3-monosubstituted indole occurred. Amines were unreactive; neither pyrrolidine nor *p*-anisidine gave the expected product. We are currently working on addressing this issue. The reaction with dimethyl malonate did not proceed under the standard conditions, but we were able to obtain the expected effect by the addition of an excess of TMSOTf. We suspect that this is due to the additional activation of the nucleophile by the formation of a ketene acetal in situ. Contrary to our expectations, we normally isolated a mixture of the target indole and the product of addition which did not dehydrate spontaneously. We found that simple treatment of the crude reaction mixture with excess TFA in CH_2Cl_2 effected dehydration, converting the mixture into the desired indole only (Scheme 5). The product was normally obtained in good to excellent yield (Table 1).

Only when the nitro-substituted oxindole was subjected to the reaction with thiophenol did we isolate low amounts of the desired indole, probably due to over-reduction of the nitro group by the thiol reagent. In the case of other functional groups the yields stayed uniformly high. We also did not observe the desired product in the reactions of dimethyl malonate with the arylnitro-

Scheme 5. Synthesis of Indoles from Oxindoles

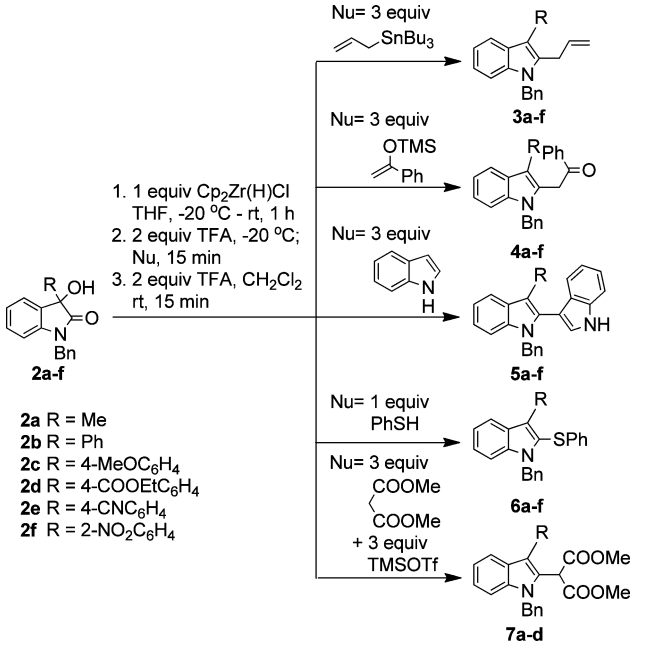


Table 1. Yields of Indoles

substrate	product yield (%)				
2a	**3a**, 99	**4a**, 82	**5a**, 80	**6a**, 49	**7a**, 51
2b	**3b**, 99	**4b**, 82	**5b**, 70	**6b**, 84	**7b**, 55
2c	**3c**, 75	**4c**, 78	**5c**, 73	**6c**, 67	**7c**, 35[a]
2d	**3d**, 84	**4d**, 57	**5d**, 69	**6d**, 41	**7d**, 59
2e	**3e**, 75	**4e**, 73	**5e**, 49	**6e**, 67	*b*
2f	**3f**, 65	**4f**, 67	**5f**, 49	**6f**, 12[a]	*b*

[a]These products could not be isolated in pure form; yield is estimated from NMR. [b]No expected product was isolated.

and -cyano-substituted substrates. This is probably due to the more forcing conditions required in the reactions with this nucleophile. The same probably accounts for the poor yield when employing the electrophile bearing the acid-sensitive methoxy group. We believe that these limitations might be overcome by careful optimization of the reaction conditions. In the case where TMSCN was employed as the nucleophile, we observed quite a different reaction outcome. Instead of obtaining the desired indole, we isolated a compound to which we ascribe the tetrahydroquinoline structure **8**. We suspect that this is due to the decomposition of zirconocene by cyanide anion with the release of cyclopentadiene, which reacts with the nascent iminium salt in the manner of a Povarov reaction[11]–fragmentation cascade (Scheme 6). We believe that the observed unusual *anti* stereochemistry stems from the minimization of steric hindrance in the bicyclic intermediate. This represents a new approach to the diastereoselective synthesis of highly substituted tetrahydroquinolines.[12] We are currently in the process of investigating the scope of this transformation.

The results show that the method employed is regiospecific in contrast to classical methods that rely on constructing the five-membered azacycle from scratch. The excellent functional group tolerance of this method allows the introduction of varied substituents to the product structure, allaying the limitations of previous methods, i.e., especially the work of Lu et al.[7] In comparison to that methodology, the present method allows for sensitive functionalities to be introduced in the addition step

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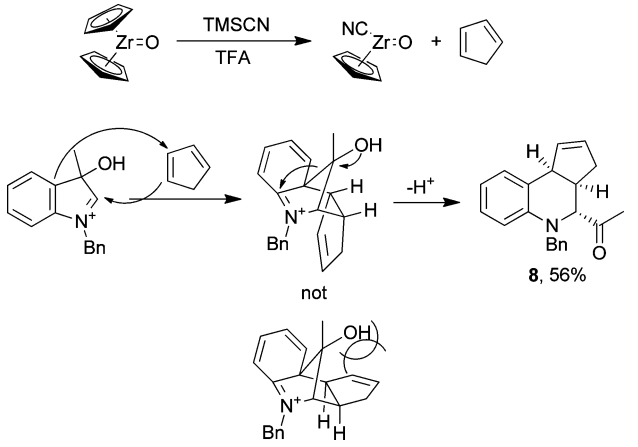
Scheme 6. Mechanism of Rearrangement to Tetrahydroquinoline



(Scheme 4) while preserving them in the next synthetic steps. This represents a marked departure from the previous work, where mainly hydrocarbon-substituted indoles could be obtained. The intermediacy of an iminium cation enables the use of a wider array of nucleophiles than only Grignard reagents, which have been used under rather forcing conditions.[7] The method described is carried out in a straightforward and rapid fashion, permitting the synthesis of large libraries of compounds in a timely manner. A diverse set of nucleophiles can be employed, including C- and S-nucleophiles, which leads to greater diversification of the products.

In summary, we have developed an expeditious method of synthesizing 2,3-disubstituted indoles from commercially available isatins regiospecifically. The methodology is characterized by high functional group tolerance and employs the readily available Schwartz's reagent as the reducing agent. It opens up an attractive route to a variety of 2,3-disubstituted indoles and has the potential to aid in the synthesis of pharmacologically and synthetically relevant indole derivatives. We have also described a new diastereoselective synthesis of highly substituted tetrahydroquinolines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03449.

Detailed synthetic procedures, characterization, and ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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