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Synthesis of 3,3-disubstituted oxindoles

Kevin G. Liu* and Albert J. Robichaud

Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, United States

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Abstract—A novel and efficient two-step synthetic sequence for the preparation of 3,3-disubstituted oxindoles was developed starting from arylhydrazines and α-branched aldehydes via Fischer indole type synthesis followed by imine oxidation.
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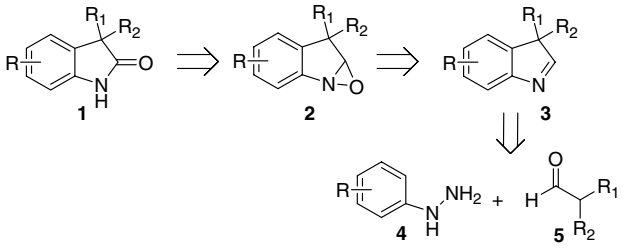
3,3-Disubstituted oxindoles (**1**, Scheme 1) represent important structural elements of indole alkaloids. There are examples of their use as synthetic intermediates and they have been shown to be important components of bio-active compounds.[1] Traditional syntheses of 3,3-disubstituted oxindoles typically involve alkylation of 3-unsubstituted oxindoles with or without a protecting group on the nitrogen and are limited only to aliphatic substitution. When the disubstituents are not identical, this approach must introduce the di-substitution stepwise and has proven to be very challenging in controlling the monoalkylation. More recently, considerable progresss has been made in developing new synthetic methods in the preparation of 3,3-disubstituted oxindoles via intramolecular reactions. These include intramolecular Heck reaction,[2] intramolecular amide α-arylation,[3] intramolecular radical type reaction,[4,5] Claisen rearrangement,[6–8] Pummerer reaction,[9] and Black-type C-acylation.[10] Intermolecular cycloadditions have also been reported for the synthesis of spirooxindoles.[11–15] Herein we report a general and efficient synthesis of 3,3-disubstituted oxindoles based on Fischer indole chemistry.



Scheme 1.

In our quest for a general entry to these valuable intermediates, we envisioned that 3,3-disubstituted oxindoles **1** could be synthesized from oxaziridines **2** (Scheme 1) via a simple rearrangement. The rearrangement of oxaziridines to give amides under thermal or photochemical conditions is well documented.[16,17] The preparation of oxaziridines **2** could be obtained through the oxidation of indolenines **3** which could be readily prepared via Fischer indole synthesis.

Classical Fischer indole syntheses involve the reaction between an aldehyde and an arylhydrazine with a catalyst, such as a Lewis acid or transition metal, to provide the indole product directly.[18] When α-branched aldehydes are used in the Fischer indole synthesis, 3,3-disubstituted indolenines **3** are typically formed as the products as reported previously.[19–21] During the course of our studies we reinvestigated this reaction with a variety of arylhydrazines and α-branched aldehydes and found that under mildly acidic conditions at 60 °C, indolenines **3** were formed in good yields (0.5–3 h). While monitoring the reaction closely by LCMS it was found that elevated reaction temperature led to significant side products. Isolation of the main component of these side products showed that rearrangement of the 3,3-disubstituted indolenine to the 2,3-substituted indole was occurring under these more severe conditions. Details of this interesting finding, albeit precedented,[19,21] will be reported separately. Without purification, crude indolenines **3** were subjected to oxidation with *m*CPBA. Although the presumed intermediate oxaziridines **2** could not be isolated, the final product

* Corresponding author. Tel.: +1 732 274 4415; fax: +1 732 274 4505; e-mail: liuk1@wyeth.com

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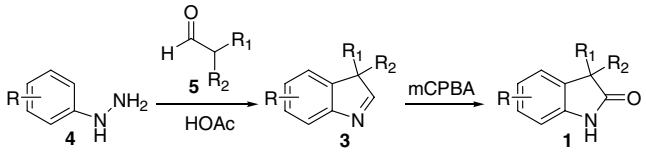
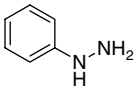
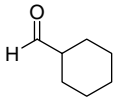
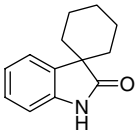
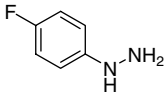
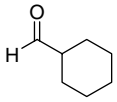
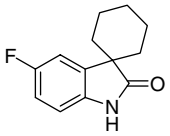
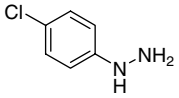
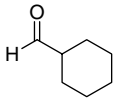
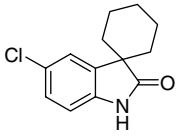
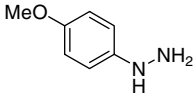
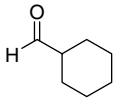
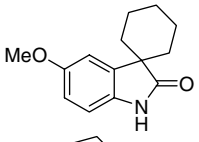
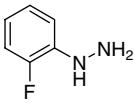
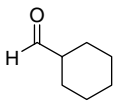
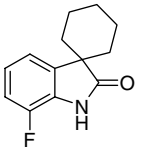
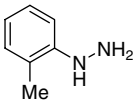
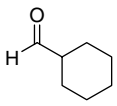
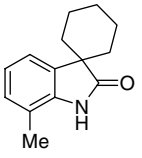
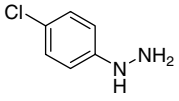
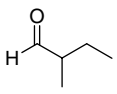
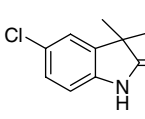
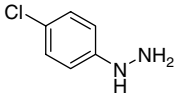
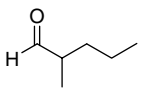
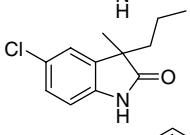
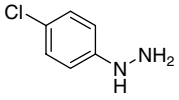
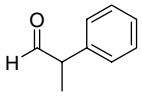
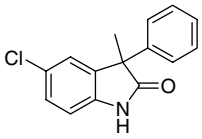
Table 1. Synthesis of 3,3-disubstituted oxindoles



Entry	Hydrazine **4**[a]	Aldehyde **5**	Product **1**	Yield[b] (%)
1a				40
1b				41
1c				46
1d				53
1e				57
1f				35
1g				40
1h				34
1i				32

[a] All arylhydrazines are HCl salts except entry **1a**.
[b] Overall yields from arylhydrazines and aldehydes.

oxindoles **1** were obtained in modest to good yields. The inability to isolate the reactive oxaziridine **2** is not too surprising as it most likely undergoes rapid rearrangement due to the reduced basicity of the aniline nitrogen.[16,17] Noteworthy is that several other oxidizing agents, for example, DMSO/HCl, phosphoric acid, oxone, hydrogen and *t*-butyl peroxides, were also explored, but failed to provide desired products in satisfactory yields or purity.

To demonstrate the generality of this methodology, a broad range of arylhydrazines and α-branched aldehydes were chosen to explore the scope of this approach. The results are summarized in Table 1. In general, modest to good overall yields were obtained for all substrates investigated.

General procedure: To a solution of aldehyde **5** (0.80 mmol) in AcOH (8 mL) was added arylhydrazine

4 (0.80 mmol). The mixture was heated at 60 °C for 30 min to 2 h (monitored by LC–MS), cooled, and concentrated to dryness using a rotavapor. The residue was redissolved in CH_2Cl_2 and washed with Na_2CO_3 solution. The organic layer was dried over Na_2SO_4, and concentrated in vacuo to provide indolenine **3**. Crude indolenine **3** was dissolved in CH_2Cl_2 (9 mL), and *m*CPBA (179 mg, 0.80 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1 h and concentrated. The residue was redissolved in EtOAc, washed with sodium bisulfite, Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4, concentrated, and purified by chromatography with EtOAc in CH_2Cl_2 to provide the oxindole product.

In summary, we have developed a novel and efficient two-step synthetic sequence for the preparation of 3,3-disubstituted oxindoles starting from arylhydrazines and α-branched aldehydes. The asymmetric version of this methodology is currently under investigation and progress will be reported in due course.

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