Category

Synthesis of Heterocycles

Key words

spirocycles

oxindoles

Ullmann coupling

Claisen rearrangement

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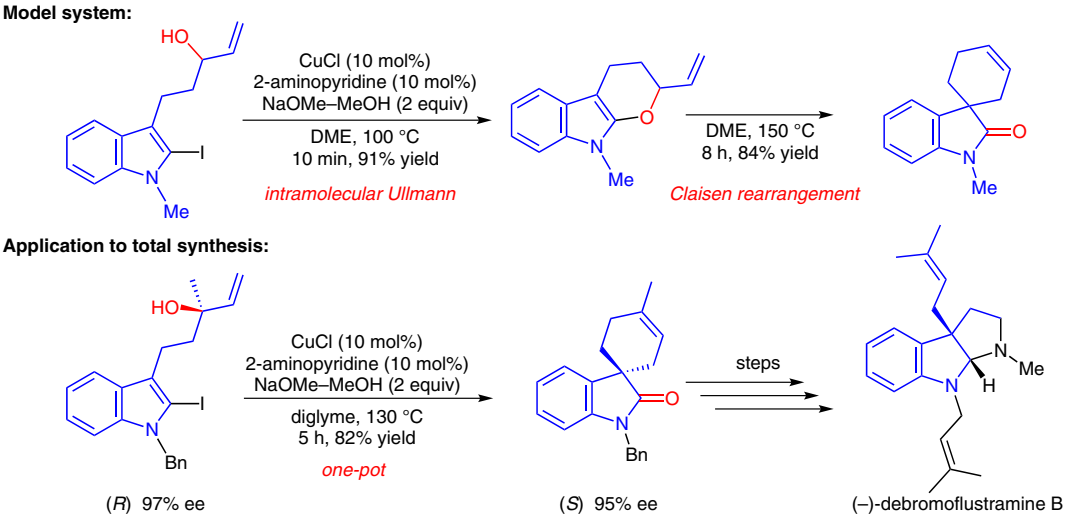
Stereoselective Synthesis of Spirocyclic Oxindoles Based on a One-Pot Ullmann Coupling/Claisen Rearrangement and its Application to the Synthesis of a Hexahydropyrrolo[2,3-*b*]indole Alkaloid

Tetrahedron **2013**, *69*, 9481–9493.

Construction of Spirocyclic Oxindoles for Indole Alkaloid Synthesis



Significance: Oxindoles bearing a quaternary stereogenic center at C3 represent attractive synthetic targets due to both their biological activity and their utility as synthetic intermediates. Kobayashi and co-workers have previously reported a stereoselective Claisen rearrangement of bicyclic dihydropyrans to provide multifunctionalized spiro[4.5]decanes (see Review below). The current study extends this methodology to the rearrangement of pyranoindoles, which are accessed from readily synthesized 2-haloindoles through an intramolecular Ullmann condensation (IUC), to yield spirocyclic oxindoles in a stereoselective manner. Oxidative cleavage of the olefin moiety of the products leads to stereochemically defined oxindoles, which can be readily elaborated into members of the hexahydropyrrolo[2,3-*b*]indole family of alkaloids, as demonstrated by the synthesis of (–)-debromoflustramine B.

Review: A. Nakazakia, S. Kobayashi *Synlett* **2012**, *23*, 1427–1445.

Comment: Optimization studies demonstrated that the IUC proceeded best under modified Hauptman coupling conditions (CuCl, 2-aminopyridine, NaOMe). The Claisen rearrangement occurred simply by heating the intermediate pyranoindoles. Due to issues with the stability of the intermediates, a one-pot sequence was developed in which, on completion of the IUC, the temperature was raised to effect the rearrangement. Indoles incorporating *trans* substituents on the allylic alcohol afforded the oxindole as single diastereomers (NOE, X-ray analyses), the stereochemistry of which indicated that the rearrangement proceeds through a boat-like transition state. The *cis* isomers did not give the desired products, and attempts to form furanoindoles also failed. A range of *N*-indole protecting groups were tolerated. A remarkable rate enhancement was observed running the reaction in glyme solvents, which avoided the use of a sealed tube. Subjecting enantiopure secondary alcohols to the reaction led to a slight erosion in enantiomeric excess (10–15% ee), whereas the ee of chiral tertiary alcohols was maintained.

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Synfacts 2014, 10(1), 0026 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340424; **Reg-No.:** V15513SF