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### Stereoselectivities of the Intramolecular Diels-Alder Reaction in the Azanona- and Azaditriene Series Preparation of Some Polyhydro-Isoindoles, Polyhydroisoquinolines, Decahydropyrido[2,1-*A*]Isoindo-Les and Decahydro-2H[-Pyrido[1,2-*B*]Isoquinolines

Anders Tsirk; Salo Gronowitz; Anna-Britta Hörnfeldt

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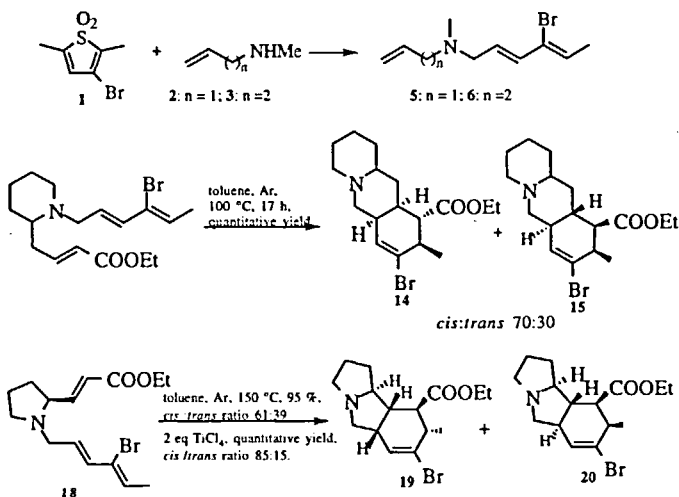
# Stereoselectivities of the Intramolecular Diels-Alder Reaction in the Azanona- and Azaditriene Series, Preparation of Some Polyhydro-Isoindoles, Polyhydroisoquinolines, Decahydropyrido[2,1-*A*]Isoindo-Les and Decahydro-2*H*[-Pyrido[1,2-*B*]Isoquinolines

ANDERS TSIRK, SALO GRONOWITZ and  
 ANNA-BRITTA HÖRNFELDT

*Organic Chemistry 1, Chemical Center, Lund University, P. O. Box 124,  
 S-221 00 Lund, Sweden*

Substituted polyhydroisoindoles and polyhydroisoquinolines were prepared through ring-opening of 3-bromo-2,5-dimethylthiophene-1,1-dioxide (**1**) with amines **2** and **3** giving trienes **5** and **6**, which could be cyclized in an intramolecular Diels-Alder reaction (IMDA). As examples the stereoselective preparation (92–99%) of decahydropyrido[2,1-*a*]isoindoles (**14** and **15**) an decahydro-2*H*-pyrido[1,2-*b*]isoquinolines (**19** and **20**) in 60–63% via a  $\text{TiCl}_4$  catalyzed IMDA reaction is shown.

**Keywords:** thiophene-1,1-dioxides; ring-opening; IMDA



The ring-opening was faster with functionalized pyrrolidines and piperidines and with optically active prolinol asymmetric induction was achieved in the IMDA reaction. The rate of the IMDA reaction was increased by transforming the hydroxymethyl group, via Swern oxidation and Wittig reactions, to compounds such as **18**.<sup>1-3</sup>

Multivariate optimization of the reaction was carried out in order to obtain better yields, using 3-bromo-2,5-dimethylthiophene-1,1-dioxide and 2-(2-hydroxyethyl)piperidine as model reagents. Solvent type, temperature and molar ratio between amine and dioxide and dilution were variables included in the optimization. The yield was increased, but still only 43 % was obtained. We realized that in order to increase the yield of the desired product blocking or suppressing of the reaction from the 2-position of the dioxide should be helpful, so we turned to the reaction of 3-bromo-2-isopropyl-5-methyl-2-thiophene-1,1-dioxide and 2-(2-hydroxyethyl)piperidine and now very high yields were obtained.

It was found that the steric demand of the isopropyl group is steering the diastereomer production. In both the 656 and 666 systems, the *trans* isomers are selectively formed.<sup>4</sup> The asymmetric induction in the ring-opening of 3-bromo-5-ethyl-2-isopropylthiophene-1,1-dioxide with prolinol was studied and asymmetric induction at C (2) in the ring-opened product was observed to some extent and was explained by the preferential formation of E- tautomers over Z-tautomers.<sup>5</sup>

The rate determining step of the ring-opening reaction is the amine-mediated tautomerization of double bonds and this step was studied in more detail applying kinetic isotope effects, using 5-trideuteriomethyl-3-bromo-2-isopropylthiophene and 2-(2-hydroxyethyl)piperidine. In another experiment the undeuterated compound was used in combination with N,O-dideuterio-2-piperidyl-1-ethanol.<sup>4</sup> Small isotope effects of 1.49 and 1.39 were observed, probably depending upon internal return. The results suggest that the tautomerization can be described in terms of a concerted four mechanism analogous to the amine mediated tautomerization of the indene system described by Cram and by Bergson.

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