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Stereocontrolled Construction of the 3,4-Dihydrothiacarbazol-2(9*H*)-one Skeleton by Using Bifunctional Squaramide-Catalyzed Cascade Reactions

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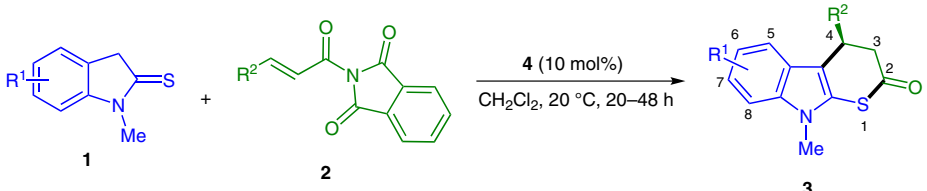
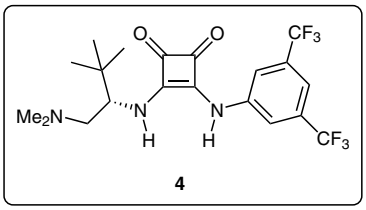
Enantioselective Synthesis of 3,4-Dihydrothiacarbazol-2(9*H*)-ones



R^1 = H, 5-Cl, 6-Me, 6-F, 6-Cl, 6-Br, 7-Cl

R^2 = Me, Ph, 2-furyl, 2-thienyl, 2-BrC_6H_4, 2-ClC_6H_4, 3-$MeOC_6H_4$, 3-$O_2NC_6H_4$, 3-$F_3CC_6H_4$, 3-BrC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-BrC_6H_4 4-ClC_6H_4, 4-FC_6H_4, (*E*)-styryl

24 examples
37–92% yield
54–98% ee



Significance: Reported is the enantioselective synthesis of 3,4-dihydrothiacarbazol-2(9*H*)-ones **3** by reaction of indoline-2-thiones **1** with *N*-alkenoylphthalimides **2** catalyzed by the chiral squaramide **4**. Screening of organocatalysts with double hydrogen-bond donor ability led to squaramide **4** derived from L-*tert*-leucine as the best catalyst for this transformation affording high enantioselectivity. The reaction conditions were optimized in terms of solvent, temperature, and catalyst loadings. Lower temperatures (0 °C) culminated in lengthy reaction time and lower yield but equivalent ee, while higher temperatures (40 °C) provided equivalent reaction yields but loss of stereocontrol. The study of the reaction scope showed that the presence of different substituents on both **1** and **2** were tolerated, but in some cases loss of stereocontrol without following a pattern was observed.

Comment: The indole skeleton is an important class of heterocycles present in many natural products with broad biological activities, and can be synthesized by many well-described methodologies (see Review below). The thiopyran indole **3** was obtained by an activation process promoted by two hydrogen-bonding interactions of **2** with the squaramide organocatalyst, followed by a Michael addition step and a thiolysis reaction. The starting materials **1** and **2** are readily available. Although a mild process, the reported approach has long reaction times and the study of the reaction scope is narrow.

Review: G. R. Humphrey, J. T. Kuethe *Chem. Rev.* **2006**, *106*, 2875–2911.

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