REATION OF CYCLIC THIOIMIDATES WITH METHYL 3-OXO-4-PENTENOATE (NAZAROV'S REAGENT). TOTAL SYNTHESIS OF (+)-EPÍ-LUPININE

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Abstract - Annulation of cyclic thioimidates with Nazarov's reagent in the presence of mercuric chloride gave indolizidine and quinolizidine derivatives. Stereospecific transformation of the quinolizidine to (+)-epí-lupinine is described.

Cyclic thioimidates are important building blocks for synthesis of N-heterocycles such as alkaloids. In connection with our research on the utilization of cyclic thioimidates in a heterocyclic synthesis, we studied the annulation of cyclic thioimidates with methyl 3-oxo-4-pentenoate (Nazarov's reagent). In this communication, we describe an efficient and stereospecific synthesis of (+)-epí-lupinine from the annulated product.

Robinson annulation using Nazarov's reagent is an important route to functionalized 6-membered ring compounds. Reaction of cyclic thioimidates (1 and 2) with Nazarov's reagent (3) in the presence of mercuric chloride (HgCl₂) in methanol at room temperature gave indolizidine (4) and quinolizidine (5) in 59% and 62% yields, respectively, together with methyl 5-methylthio-3-oxo-pentenoate (6).

![Scheme 1](image-url)
Transformation of $\sim$ into (+)-epi-lupinine is shown in Scheme 2. Reduction of $\sim$ with diisobutylaluminum hydride (DIBAL-H) in the presence of triethylamine (NEt$_3$) in tetrahydrofuran (THF) stereospecifically gave 8-ketoester quinolizidine ($\sim$) in 55% yield. Thio-ketalization of $\sim$ with 1,2-ethanedithiol in the presence of boron trifluoride etherate (BF$_3$·OEt$_2$) in trifluoroacetic acid (CF$_3$COOH) afforded the corresponding thio-ketalized compound ($\sim$) in 81% yield, which was converted to ester quinolizidine (9)(51%) by desulfurization with Raney Ni (W-2). Finally, $\sim$ underwent reduction with lithium aluminum hydride (LiALH$_4$) to give (+)-epi-lupinine (10) (75%) which had spectra identical to that of authentic material.$^{3a}$

Next, hydrolysis of $\sim$ with aq. potassium hydroxide solution followed by dicarboxylation with aq. hydrochloric acid gave enaminoketone (11) (85%) which was served as the key intermediate for (+)-elaeokanine synthesis.$^{10}$

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REFERENCES AND NOTES


6. In the absence of HgCl₂, yields of 4 and 5 decreased and that of 6 increased.

7. All new compounds were fully characterized spectroscopically (IR, 1H NMR, MS spectral) and by combustion and/or high resolution mass spectral analyses.


9. (+)- (5S,6S)-1-Aza-5-carbomethoxybicyclo[4.4.0]decan-4-one (2). 1H NMR (200 MHz, CDCl₃) δ 3.24 (1H, d, J=11 Hz, C₄-H), 3.73 (3H, s, COOMe).


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