REACTION OF CYCLIC THIOIMIDATES WITH METHYL 3-OXO-4-PENTENOATE (NAZAROV'S REAGENT). TOTAL SYNTHESIS OF (±)-EPI-LUPININE

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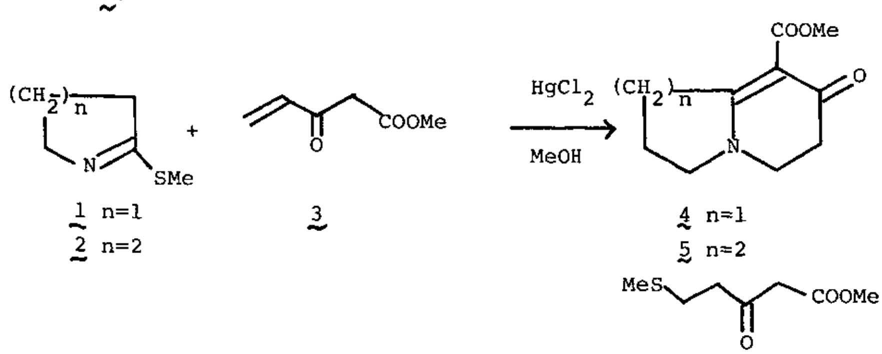
Abstract - Annulation of cyclic thioimidates with Nazarov's reagent in the presence of mercuric chloride gave indolizidine and quinolizidine derivatives. Stereospecific transformation of the quinolizidine to (±)-*epi*-lupinine is described.

Cyclic thioimidates are important building blocks for synthesis of N-heterocycles such as alkaloids.[1] In connection with our research on the utilization of cyclic thioimidates in a heterocyclic synthesis,[2] 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 (±)-*epi*-lupinine[3] from the annulated product.

Robinson annulation using Nazarov's reagent is an important route to functionalized 6-membered ring compounds.[4] Reaction of cyclic thioimidates (1 and 2) with Nazarov's reagent (3)[5] in the presence of mercuric chloride ($HgCl_2$)[6] (1 eq.) in methanol at room temperature gave indolizidine (4)[7] and quinolizidine (5)[7] in 59% and 62% yields, respectively, together with methyl 5-methylthio-3-oxo-pentenoate (6).

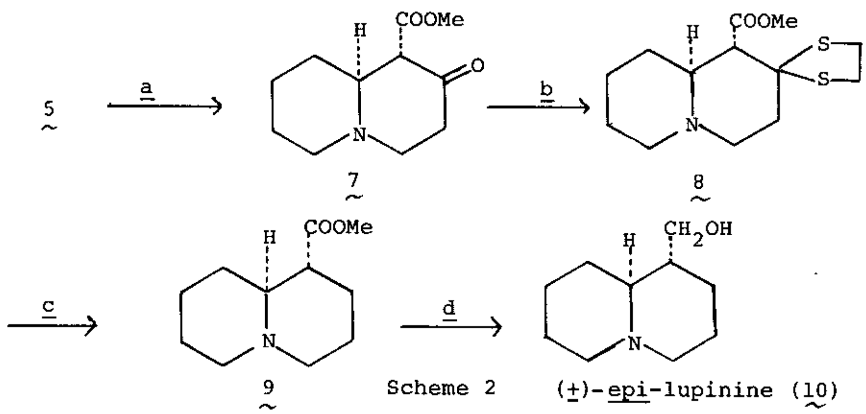


1 n=1
2 n=2
3
4 n=1
5 n=2
6

Scheme 1

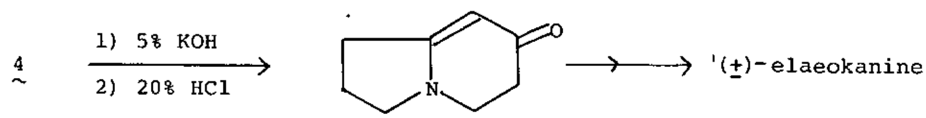
Transformation of 5 into (±)-epi-lupinine is shown in Scheme 2. Reduction of 5 with diisobutylaluminum hydride (DIBAL-H) in the presence of triethylamine (NEt_3) in tetrahydrofuran (THF)[8] stereospecifically gave β-ketoester quinolizidine (7)[7,9] in 55% yield. Thioketalization of 7 with 1,2-ethanedithiol in the presence of boron trifluoride etherate ($BF_3.OEt_2$) in trifluoroacetic acid (CF_3COOH) afforded the corresponding thioketalized compound (8) in 81% yield, which was converted to ester quinolizidine (9)[7] (51%) by desulfurization with Raney Ni (W-2). Finally, 9 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 4 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]



Scheme 2

a: DIBAL-H, NEt_3, THF, -50°C, 5 h. b: $HS(CH_2)_2SH$, $BF_3.OEt_2$, CF_3COOH, r. t., 15 h.
c: Raney Ni (W-2), EtOH, reflux, 3 h. d: $LiALH_4$, THF, reflux, 1 h.



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Scheme 3

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6. In the absence of $HgCl_2$, yields of **4** and **5** decreased and that of **6** increased.

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

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9. (±)- (5S,6S)-1-Aza-5-carbomethoxybicyclo[4.4.0]decan-4-one (**7**). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.24 (1H, d, J=11 Hz, C_4-H), 3.73 (3H, s, COOMe).

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