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Synthesis of Hexahydroindol-6-ones by Cycloacylation of Vinylogous Urethanes

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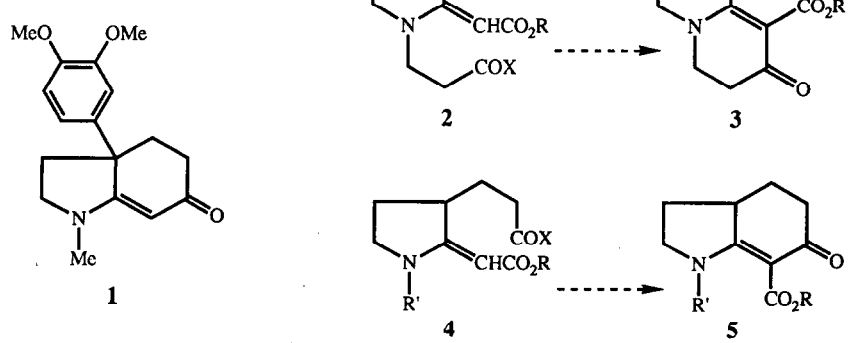
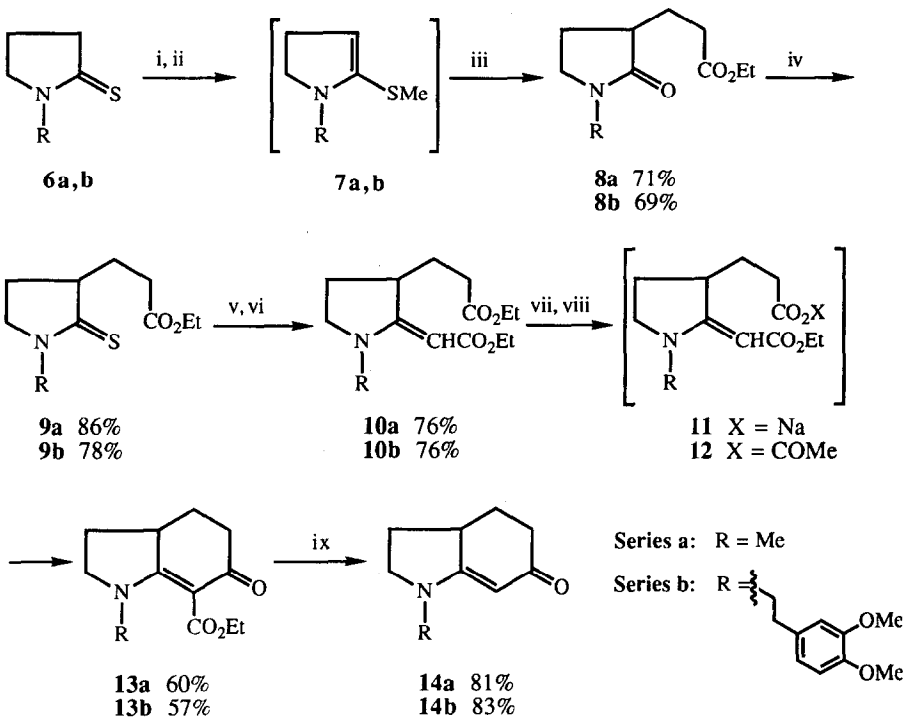
Key words: thiolactam; vinylogous urethane; sulphide contraction; hexahydroindol-6-one; Robinson annulation

Abstract: The title compounds were prepared by variations of a route in which the principal stages include conversion of N-substituted pyrrolidine-2-thiones **6** into vinylogous urethanes **10**, which undergo subsequent cycloacylation. A related approach that uses a Robinson annulation was also partly successful.

The partially or fully saturated indole nucleus, a common structural component of alkaloids isolated from the genera *Sceletium*[1] and *Erythrina*[2], is also well represented amongst the metabolites produced by members of the Amaryllidaceae[3]. The methodology we previously devised[4] for making the alkaloid Δ^7-mesembrenone **1** has not lent itself to the construction of 1,2,3,3a,4,5-hexahydro-6*H*-indol-6-ones in general, so we continued to seek new methods for making this azabicyclic system. The approach we now describe develops a theme that we first introduced in a synthesis of several indolizidine alkaloids[5]: formation of the bicyclic system by intramolecular cycloacylation of vinylogous urethanes, as exemplified by the conversion of **2** into **3**. Making the parent hexahydroindol-6-one nucleus **5** by a similar approach entails an analogous cyclisation of substrates **4** bearing the substituted propanoate chain on C-3 of the heterocycle rather than on N. The alkoxycarbonylmethylene substituent at C-2 is most conveniently introduced by the Eschenmoser sulphide contraction[6], which can either precede or follow the manipulations necessary at C-3. Thus in approaching the target systems **5**, we have a measure of flexibility in the order in which the two appropriately functionalised carbon chains of **4** may be introduced.

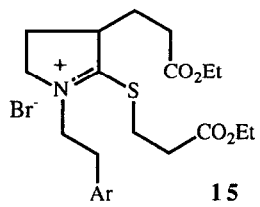


One successful realisation of this strategy is shown in Scheme 1. This route exploits the efficient conjugate addition of an enamine to an α,β-unsaturated ester for the introduction of the alkyl chain at C-3. The salts formed from the reaction of pyrrolidine-2-thiones **6** and iodomethane, on treatment with *n*-butyllithium under carefully controlled conditions at -50°C, gave the ketene S,N-acetals **7**. These reacted *in situ* with ethyl acrylate to produce lactams **8** after hydrolytic work-up. Regeneration of the thione group in **9** was easily achieved with Lawesson's reagent[7]. Salt formation with ethyl bromoacetate followed by sulphide contraction yielded **10**, thereby setting the stage for the crucial cycloacylation. As we had previously discovered with indolizidines, cyclisation of these compounds could not be accomplished directly. However, heating **10** with aqueous sodium hydroxide brought about hydrolysis of only the saturated ester group. The sodium salts **11** were isolated, dried thoroughly, and then treated with acetic anhydride in acetonitrile to give the bicyclic systems **13**, presumably *via* mixed anhydrides **12**. The yields of cyclised products were moderate **13a**, 60%; **13b**, 57%); though alternative products were not isolated, it should be noted that competing acylation of the vinylogous urethane with acetic anhydride, a process that we have observed in other circumstances, is probable. Basic hydrolysis and decarboxylation of **13** afforded the target systems **14a** and **14b** in overall yields of 22.6% and 19.4% respectively based on **6**[8]. Compound **14b** has been prepared twice before by substantially different routes[9].



Scheme 1. Reagents: (i) MeI, THF, 0°C to r.t.; (ii) *n*-BuLi, THF, -50°C to r.t.; (iii) $H_2C{=}CHCO_2Et$, THF, r.t.; (iv) Lawesson's reagent, toluene, reflux; (v) $BrCH_2CO_2Et$, MeCN, r.t.; (vi) PPh_3, NEt_3, MeCN, r.t.; (vii) 0.2M NaOH, H_2O, reflux, then drying at 60°C/1 mm Hg/24 h; (viii) Ac_2O, MeCN, r.t.; (ix) 2M NaOH, H_2O, reflux

Several variations of the above reaction scheme were investigated. Deprotonation of pyrrolidine-2-thiones **6** with *n*-butyllithium in THF yielded anions that could be alkylated to give compounds **9** directly. Reaction with ethyl acrylate was poor because of competing polymerisation, and isolated yields of **9** were *ca.* 11% at best. Improved results were obtained with ethyl 3-bromopropionate at -78°C, though competing elimination and subsequent polymerisation also affected the outcome. The highest yields obtained were 59% for **9a**, and 20% for **9b**. In the latter case, cation exchange with tetrabutylammonium fluoride prior to the addition of the alkylating agent improved the yield to 63%. With excess ethyl 3-bromopropionate, the anion of **6b** produced the isolable salt **15** (60%); equilibration with ethyl bromoacetate followed by standard sulphide contraction conditions thereafter gave **10b** in 54% yield. None of these variations constitutes a major improvement in yield over the route shown in Scheme 1, although they do reduce the number of steps.



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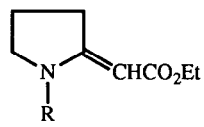
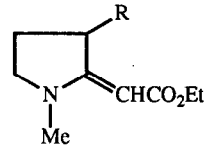


16a,b



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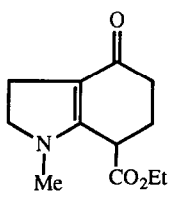
The sulphide contraction on thiones **6** can also be performed before introducing the functionalised chain at C-3. Vinylogous urethanes **16a** and **16b**, prepared from appropriate precursors in 89% and 76% yields respectively, were readily deprotonated at C-3 in THF solution on treatment with *n*-butyllithium. The resulting anion of **16a**, though alkylated efficiently by simple alkyl halides such as iodomethane or allyl bromide to give the expected products **17** (R = Me, 83%; R =allyl, 92%), once again failed to react cleanly with ethyl acrylate, and gave a poor yield of **10a** with ethyl 3-bromopropionate (14%). However, alkylation of the anion of **16b** with ethyl 3-bromopropionate produced **10b** in an acceptable yield of 52% as long as the initial temperature was kept at *ca.* -80°C.

Yet another potential loop in the synthetic sequence involves acylating compounds **16** at the enamine's β-carbon position with a suitable bifunctional electrophilic reagent *before* creating the 3a,4-bond of the indol-6-one targets. For this purpose we examined the reaction of **16a** with acryloyl chloride. In boiling benzene or acetonitrile solution at high dilution, the sole product isolated (70% and 42% respectively) was the hexahydroindol-4-one **18**. This surprising result has a precedent in the literature[10]: several acyclic vinylogous urethanes have been shown to give analogous products with acryloyl chloride (but not crotonoyl or cinnamoyl chlorides) by a pathway involving initial acylation on the carbonyl oxygen followed by a [3,3]-sigmatropic rearrangement on to the enamine carbon and cyclisation of the resulting ketene intermediate. We showed that crotonoyl and cinnamoyl chlorides reacted with **16a** to yield the expected products **19** of enamine acylation (R = Me, 21%; R = Ph, 46%; uncertain stereochemistry), but that there was no subsequent cyclisation. Furthermore, a fairly concentrated solution of acryloyl chloride and **16a** in boiling acetonitrile produced a mixture of the isomers of **20** (83%), formed by acylation with, and conjugate addition to, the acryloyl system.



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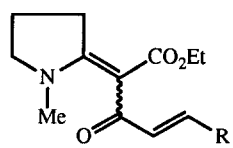

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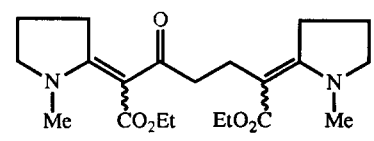

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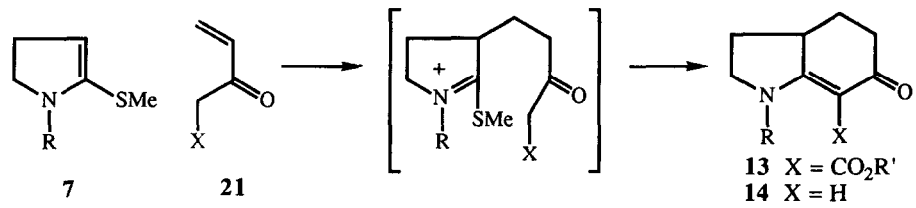
In principle, the shortest approach to the target hexahydroindol-6-ones **14** would be by Robinson ring annulation (Scheme 2). Reaction of the ketene S,N-acetals **7** with methyl vinyl ketone rather than acrylate should, under conditions of thermodynamic control, yield the bicyclic targets directly. Indeed, in the case of **7a**, formed *in situ* as described above, treatment with methyl vinyl ketone **21** (X = H) did give the desired compound **14a**, but only in 21% yield (not optimised) because of competing polymerisation. Efforts to produce the ester-substituted bicyclic system **13a** by a similar reaction with Nazarov reagents[11] (alkyl 3-oxopent-4-enoates **21**, X = CO_2R') also gave low yields (*ca.* 20%) despite a promising precedent based on the use of alkylthioamidates[12]. Part of the problem stems from the sensitivity of the enones to traces of base, and we expect improvements if the ketene S,N-acetals are isolated and purified prior to use (*e.g.*, as has been described for **7a**[13]). Extensions along these lines are now being investigated, as is the application of the new methodology to the synthesis of appropriate alkaloids.



7 **21** **13** X = CO_2R' **14** X = H

Scheme 2

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