



Synthesis of pyrrolidin-3-ones from dihydropyran precursors via spiro-*N,O*-acetals

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ABSTRACT

2,2-Disubstituted pyrrolidin-3-ones are prepared in three steps from simple dihydropyran derivatives; the key spiro-*N,O*-acetal intermediate is a useful *N*-sulfonylketoinimium ion precursor. This route represents a formal synthesis of the indolizidine alkaloid core, with potential application to pyrrolizidines and quinolizidines.

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The structures of at least 400 pyrrolizidine alkaloids have been reported and many total syntheses and innumerable synthetic approaches are now documented.¹ In a previous contribution to the area we described an unusual construction of the five-membered ring by C–C bond formation at the α -amino position, exemplified by the synthesis of heliotridane and a dihydroxylated analogue.² More recently, we required a short route to pyrrolizidine ketone derivatives **6** ($n, m = 1$), Scheme 1, bearing either H, OH, or alkyl bridgehead substituents, which we considered might be obtained from a common ketoinimium intermediate **4**. Our overall plan was to effect a sequence of ring-interchanges from readily-available dihydrofurans to the pyrrolizidine core via a spirocyclic *N,O*-acetal as shown. An advantage of this general approach lies in its equal applicability to indolizidines (**6**; $n, m = 1$ or 2) and quinolizidines (**6**; $n, m = 2$). We now report proof-of-principle results that establish the viability of this ring-interchange route to -izidine alkaloids.

The spirocyclisation of an α -(ω -sulfonylamidoalkyl)enol ether (cf. **2**→**3**) does not appear to have precedent; however, the intermolecular *N*-sulfonylamidation of oxonium ions derived from enol ethers is well known.³ In addition, within their synthesis of the EFGH-ring system of azaspiracid-1, Oikawa et al. reported a closely related process in which *N*-spirocyclisation onto an oxonium ion derived from an acetal was achieved under carefully controlled Lewis acidic conditions.⁴ The azaspiracid literature contains a number of similar examples of spirocyclisation of carbamates,⁵ and the condensation of both *N*- and *O*-nucleophiles with ketones can also be used to produce spiro-*N,O*-acetals.⁶

Precedent for the second key step (cf. **3**→**5**) is much more limited and, to the best of our knowledge, *N*-tosylketoinimiums of general structure **4** are so far not described.⁷ Nevertheless, *N*-sulfonyliminium species lacking the conjugating carbonyl have been

widely used in C–C bond-forming processes and we expected those proposed in Scheme 1 to behave similarly.⁸

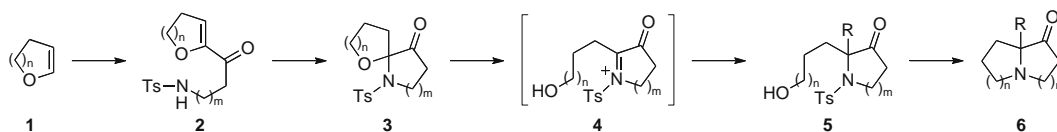
During the development of routes to substrates of the form **2** we discovered that 2-acyldihydrofurans are prone to oxidative rearrangement,⁹ therefore we focused on the more tractable derivatives of dihydropyran and carried the oxygen functionality through as the alcohol rather than the ketone. A first substrate (**10**, Scheme 2) was prepared from 2-formyldihydropyran (**7**)¹⁰ in three steps: addition of lithioacetonitrile,¹¹ nitrile reduction and sulfonylation. Spirocyclisation followed precedent well-established in the spiroacetal literature¹² and exposure of sulfonamide **10** to PPTS afforded two separable diastereomers, **11** and **12**, of the desired spirocycle (3:1 ratio, 63% isolated yield).

Unambiguous stereochemical assignment of these isomers could not be secured by NOE experiments, but X-ray-quality crystals were grown of the major isomer (**11**) which was then shown to have the hydroxy group *cis*-to the tetrahydropyranyl oxygen, Figure 1.¹³ The diastereomeric ratio is assumed to represent the equilibrium value. The calculated lowest energy conformations of both **11** and **12** are very similar to that in the crystal, and isomer **11** is more stable under a variety of basis sets.¹⁴ In the crystal, the C–NTs bond is situated equatorially—the steric bulk of this group overriding any electronic axial preference¹⁵—and NOE experiments also support this as the preferred conformation in solution [the *CH(OH)* protons both correlate with just the axial *CH₂O* proton].

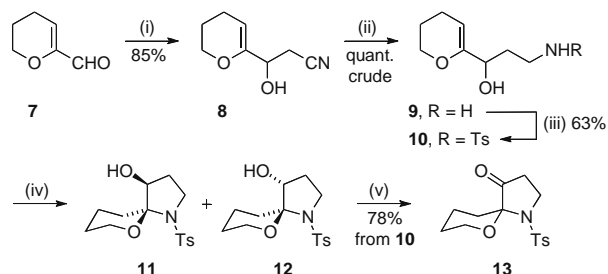
We were concerned in this initial work that hydride migration would terminate the intended iminium ion chemistry prematurely¹⁶ therefore, the spirocyclic alcohols were oxidised to ketone **13** which was then treated with allyltrimethylsilane in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 3) according to Somfai's procedure.^{8b} The reaction progressed very slowly at -78°C , and in order to achieve complete consumption of the spirocycle, it was necessary to allow the mixture to reach room temperature which resulted in a moderate yield of the allylated compound **15** along with minor products **16** and **17** originating from secondary reactions of the

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Scheme 1. General route to pyrrolizidine, indolizidine and quinolizidine ketones from cyclic enol ethers via spiro-*N,O*-acetals ($n, m = 1, 2$; $R = H, OH, Me$).



Scheme 2. Reagents: (i) LiCH_2CN , THF; (ii) LiAlH_4 , THF; (iii) TsCl , K_2CO_3 , aq THF; (iv) PPTS (6%), CH_2Cl_2 ; (v) Dess–Martin periodinane, CH_2Cl_2 .

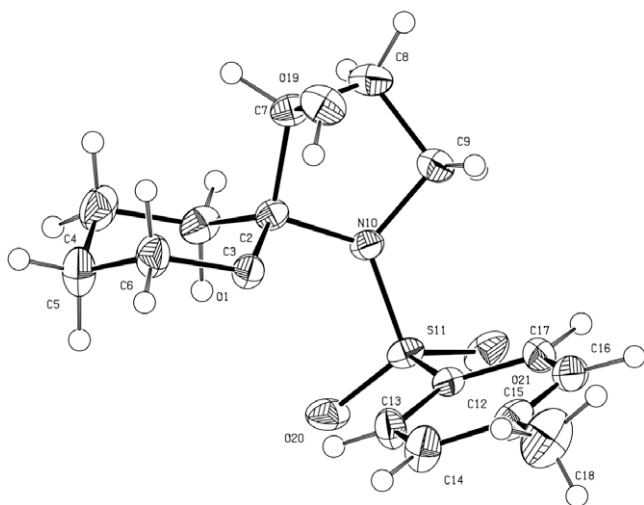
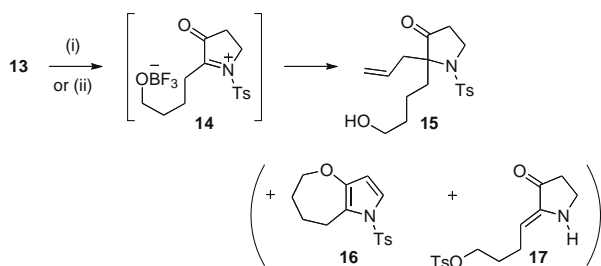


Figure 1. ORTEP view of spiro-*N,O*-acetal **11**.¹³



Scheme 3. Reagents: (i) allyl-SiMe₃, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 (**15**, 48%; **16**, 21%; **17**, 9%); (ii) allyl-SnBu₃, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 (95%; **15** only).

iminium intermediate **14**. Switching to the more reactive allyltributylstannane¹⁷ led to a much cleaner reaction that was complete within 2 h at 0 °C with little evidence of by-products.

Similar $\text{BF}_3\cdot\text{OEt}_2$ -mediated reactions of ketone **13** with triethylsilane¹⁸ or 2-(tributylstannyl)furan provided 3-pyrrolidinone adducts **18** and **20**, respectively (Fig. 2). In the former, some further cyclisation and reduction followed to give pyrrolidino-oxepane **19**. The reaction to form furyl adduct **20** was incomplete (29% of

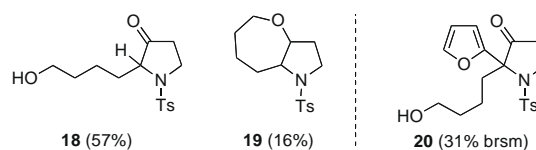
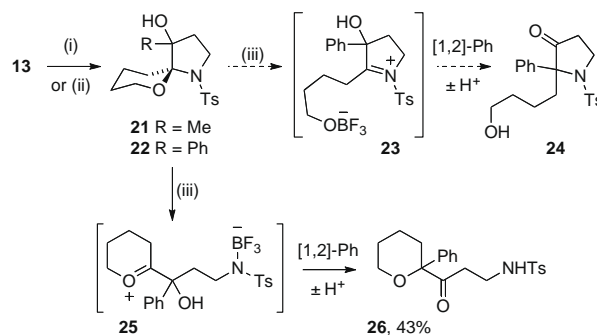


Figure 2. Products obtained from **13** + $\text{Et}_3\text{SiH}/\text{BF}_3\cdot\text{OEt}_2$ (\rightarrow **18**, **19**) and **13** + 2-(tributylstannyl)furan/ $\text{BF}_3\cdot\text{OEt}_2$ (\rightarrow **20**).

13 was recovered) and generated a complex mixture of by-products.

Despite promising literature precedent,¹⁹ an attempt to trap the iminium ion (**14**) with anisole returned only rearrangement products. Therefore, we briefly evaluated the possibility of intramolecular delivery of less reactive nucleophiles via a [1,2]-shift.²⁰ Addition of methyl lithium, in up to sixfold excess, to ketone **13** resulted in an incomplete reaction to produce alcohol **21** (Scheme 4) as a 4:1 ratio of diastereomers in 25% yield (57% brsm). In contrast, the addition of phenyllithium/ CeCl_3 provided alcohol **22** in excellent yield and with essentially complete stereoselectivity.²¹ Treatment of this alcohol with $\text{BF}_3\cdot\text{OEt}_2$ under conditions analogous to those used in the preparation of allyl adduct **15** was expected to initiate *C*-acyliminium formation (\rightarrow **23**) and a [1,2]-phenyl shift to afford pyrrolidinone **24**. In the event, the reaction took a different course and tetrahydropyran ketone **26** was produced via oxonium intermediate **25**. Considering that ions **23** and **25** might be in equilibrium, spirocycle **22** was treated with allyltributylstannane and then $\text{BF}_3\cdot\text{OEt}_2$. However, this reaction was uninformative, producing a mixture containing starting **22**, tetrahydropyran **26** and ring-opened material corresponding to the hydrolysis of **22**. Further experiments are needed in order to shed light on the origins of the differing outcomes in Schemes 3 and 4 but Lewis acid complexation at the hydroxy group in spirocycle **22** would generate a Brønsted acid ($\text{F}_3\text{B}^--\text{ORH}^+$) that may influence the course of the reaction.

In summary, we have demonstrated that spiro-*N,O*-acetals derived from simple dihydropyran derivatives can be used as *N*-sulfonylketoinimium precursors. Relatively reactive nucleophiles must then be present in order to generate 2,2-disubstituted pyrrolidin-3-ones effectively. A preliminary investigation of the



Scheme 4. Reagents: (i) MeLi, THF (dr = 4:1, 57% brsm); (ii) PhLi, CeCl_3 , THF (dr >95:5, 96%); (iii) $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 .

intramolecular delivery of other nucleophiles has revealed the operation of an alternative pathway via an oxonium intermediate.

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