Tetrahedron Letters 50 (2009) 7141–7143

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Jeremy Robertson [a,*], Andrew J. Tyrrell [a], Praful T. Chovatia [a], Sarah Skerratt [b]

[a] Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK
[b] Pfizer Global Research and Development, Ramsgate Road, Sandwich CT13 9NJ, UK

ARTICLE INFO

Article history:
Received 27 August 2009
Revised 23 September 2009
Accepted 2 October 2009
Available online 8 October 2009

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*-sulfonylketoiminium ion precursor. This route represents a formal synthesis of the indolizidine alkaloid core, with potential application to pyrrolizidines and quinolizidines.

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 ketoiminium 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-sulfonamidoalkyl)enol ether (cf. **2**→**3**) does not appear to have precedent; however, the intermolecular *N*-sulfonamidation of oxonium ions derived from enol ethers is well known.[3] In addition, within their synthesis of the EFGHI-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*-tosylketoiminiums 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]

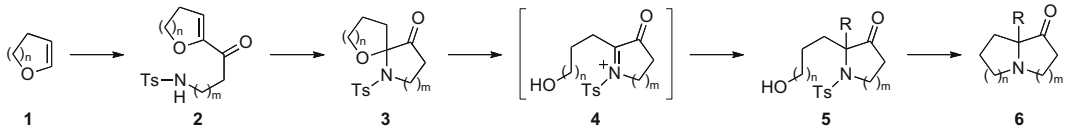
During the development of routes to substrates of the form **2** we discovered that 2-acyldihydrofurans are prone to oxidative rearrangement,[9] therefore we focused on the more tractable derivatives of dihydropyran and carried the oxygen functionality through as the alcohol rather than the ketone. A 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 literature[12] 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 preference[15]—and NOE experiments also support this as the preferred conformation in solution [the C*H*(O*H*) protons both correlate with just the axial CH_2O proton].

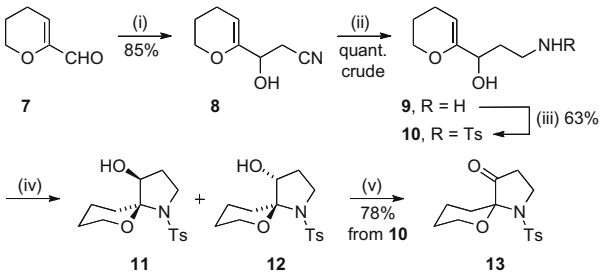
We were concerned in this initial work that hydride migration would terminate the intended iminium ion chemistry prematurely[16] therefore, the spirocyclic alcohols were oxidised to ketone **13** which was then treated with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ (Scheme 3) according 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

* Corresponding author. Tel.: +44 1865 275660.
E-mail address: jeremy.robertson@chem.ox.ac.uk (J. Robertson).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.018



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.

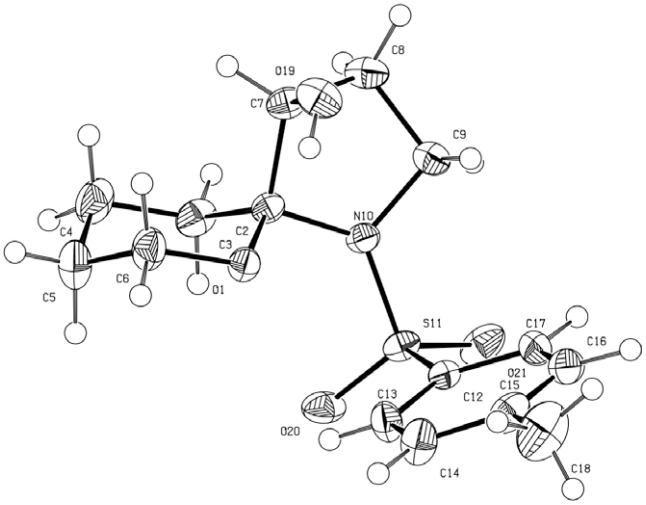
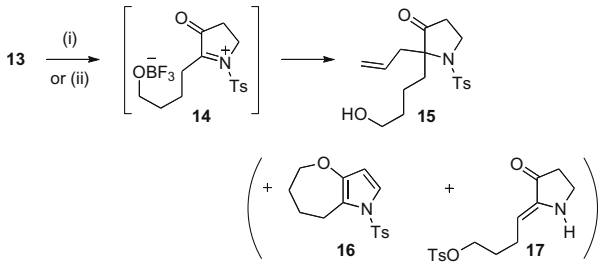


Figure 1. ORTEP view of spiro-*N*,*O*-acetal **11**.[13]



Scheme 3. Reagents: (i) allyl-$SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (**15**, 48%; **16**, 21%; **17**, 9%); (ii) allyl-$SnBu_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (95%; **15** only).

iminium intermediate **14**. Switching to the more reactive allyltributylstannane[17] led to a much cleaner reaction that was complete within 2 h at 0 °C with little evidence of by-products.

Similar $BF_3{\cdot}OEt_2$-mediated reactions of ketone **13** with triethylsilane[18] 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

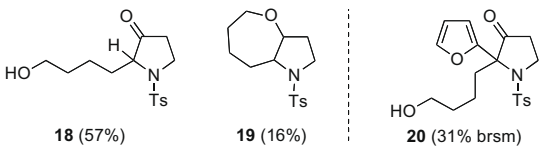
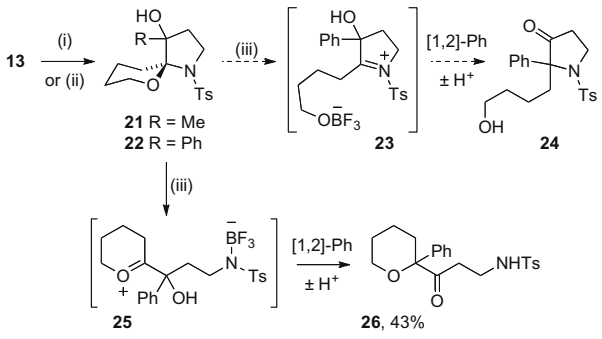


Figure 2. Products obtained from **13** + $Et_3SiH/BF_3{\cdot}OEt_2$ (→**18**, **19**) and **13** + 2-(tributylstannyl)furan/$BF_3{\cdot}OEt_2$ (→**20**).

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 methyllithium, 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 $BF_3{\cdot}OEt_2$ under conditions analogous to those used in the preparation of allyl adduct **15** was expected to initiate *C*-acyliminium formation (→**23**) and a [1,2]-phenyl shift to afford pyrrolidinone **24**. In the event, the reaction took a different course and tetrahydropyranyl 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 $BF_3{\cdot}OEt_2$. 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 (F_3B^-–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*-sulfonylketoiminium 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) $BF_3{\cdot}OEt_2$, CH_2Cl_2.

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

Acknowledgements

We thank Pfizer Global Research & Development and the EPSRC for a studentship for A.J.T. We also acknowledge the Oxford Chemical Crystallography Service for use of instrumentation, and Dr. Amber Thompson for assistance.

References and notes

1. (a) Hartmann, T.; Witte, L.. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1995; Vol. 9, pp 155–233; (b) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773–781; (c) Lopez, M. D.; Cobo, J.; Nogueras, M. *Curr. Org. Chem.* **2008**, *12*, 718–750.
2. Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825–5828.
3. (a) Reviews early literature: Speziale, A. J.; Ratts, K. W.; Marco, G. J. *J. Org. Chem.* **1961**, *26*, 4311–4314; (b) Colinas, P. A.; Bravo, R. D. *Org. Lett.* **2003**, *5*, 4509–4511.
4. Oikawa, M.; Uehara, T.; Iwayama, T.; Sasaki, M. *Org. Lett.* **2006**, *8*, 3943–3946.
5. (a) Nicolaou, K. C.; Pihko, P. M.; Diedrichs, N.; Zou, N.; Bernal, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 1262–1265; (b) Forsyth, C. J.; Hao, J. L.; Aiguade, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3663–3667; (c) Sasaki, M.; Iwamuro, Y.; Nemoto, J.; Oikawa, M. *Tetrahedron Lett.* **2003**, *44*, 6199–6201; (d) Nicolaou, K. C.; Chen, D. Y. K.; Li, Y. W.; Qian, W. Y.; Ling, T. T.; Vyskocil, S.; Koftis, T. V.; Govindasamy, M.; Uesaka, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 3643–3653; (e) Nicolaou, K. C.; Pihko, P. M.; Bernal, F.; Frederick, M. O.; Qian, W. Y.; Uesaka, N.; Diedrichs, N.; Hinrichs, J.; Koftis, T. V.; Loizidou, E.; Petrovic, G.; Rodriquez, M.; Sarlah, D.; Zou, N. *J. Am. Chem. Soc.* **2006**, *128*, 2244–2257; (f) Forsyth, C. J.; Xu, J.; Nguyen, S. T.; Samdal, I. A.; Briggs, L. R.; Rundberget, T.; Sandvik, M.; Miles, C. O. *J. Am. Chem. Soc.* **2006**, *128*, 15114–15116; (g) Nguyen, S.; Xu, J. Y.; Forsyth, C. J. *Tetrahedron* **2006**, *62*, 5338–5346; (h) Zhou, X. T.; Lu, L.; Furkert, D. P.; Wells, C. E.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7622–7626; see also: (i) Evans, D. A.; Dunn, T. B.; Kvaernø, L.; Beauchemin, A.; Raymer, B.; Olhava, E. J.; Mulder, J. A.; Juhl, M.; Kagechika, K.; Favor, D. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4698–4703; (j) Evans, D. A.; Kvaernø, L.; Dunn, T. B.; Beauchemin, A.; Raymer, B.; Mulder, J. A.; Olhava, E. J.; Juhl, M.; Kagechika, K.; Favor, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 16295–16309.
6. (a) Tursun, A.; Aboab, B.; Martin, A.-M.; Sinibaldi, M.-E.; Canet, I. *Synlett* **2005**, 2397–2399; (b) Sinibaldi, M.-E.; Canet, I. *Eur. J. Org. Chem.* **2008**, 4391–4399.
7. A similar intermediate is involved in the rearrangement of an *S,S*-dioxobenzothiazin-4-one derivative: Zinnes, H.; Shavel, J. *J. Heterocycl. Chem.* **1973**, *10*, 95–96.
8. Lead references: (a) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K.; Kanazawa, T.; Tsuda, K. *J. Org. Chem.* **1984**, *49*, 3711–3716; (b) Åhman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537–9544. For reviews on related *N*-acyliminium ion chemistry; (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856; (d) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.
9. Robertson, J.; Tyrrell, A. J.; Skerratt, S. *Tetrahedron Lett.* **2006**, *47*, 6285–6287.
10. Shimano, M.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 7727–7730.
11. Das, R.; Wilkie, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 4555–4557 and references cited therein.
12. Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661.
13. *Crystal data for* **11**: $C_{15}H_{21}NO_4S$, $M = 311.40$, colourless plate, monoclinic, $a = 12.5820(2)$, $b = 8.06930(10)$, $c = 15.2195(3)$ Å, $V = 1527.71$ Å^3, $T = 150$ K, space group $P2_1/c$, $Z = 4$, 6859 reflections measured, 3488 independent all of which were used for refinement ($R_{int} = 0.016$), final $wR = 0.116$. CCDC 745600 contains the full crystallographic data for this compound; this can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
14. The lowest energy conformation for each diastereomer (semi-empirical search) was used to derive a ΔH^* value at various levels of theory (PM3, HF/6-31G*, B3LYP/6-31G*, MP2/6-31G*). All methods showed isomer **11** to be more stable, ΔH increasing with increasing sophistication in the basis set, with the absolute values being sensitive to small peripheral conformational changes (e.g., rotation about the Ar–Me bond). SPARTAN'06, Wavefunction, Inc., Irvine, CA: Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio, R. A., Jr.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Van Voorhis, T.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C.-P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W. Z.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E.; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock, H. L., III; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172–3191.
15. See for example: Owens, J. M.; Yeung, B. K. S.; Hill, D. C.; Petillo, P. A. *J. Org. Chem.* **2001**, *66*, 1484–1486.
16. Whilst there are no direct *N*-sulfonyliminium precedents to draw from, an example of *N*-acyliminium quenching by [1,2]-H shift from an adjacent hydroxy has been reported in a related system: Chien, C. S.; Hasegawa, A.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1986**, *34*, 1493–1496.
17. The relative nucleophilicity of allylic silanes and stannanes is discussed in: Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954–4961.
18. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.
19. Buller, M. J.; Cook, T. G.; Kobayashi, Y. *Heterocycles* **2007**, *72*, 163–166.
20. See for example: (a) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169–1171; (b) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783–7786; (c) Choi, J.; Lee, G. H.; Kim, I. *Synlett* **2008**, 1243–1249; (d) Kim, I.; Choi, J.; Lee, S.; Lee, G. H. *Synlett* **2008**, 2334–2338.
21. The relative stereochemistry in **22** was not assigned.