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SYNTHESIS OF *N*-PROTECTED SPIROAMINES RELATED TO NATURAL PRODUCTS USING RADICAL CYCLISATIONS

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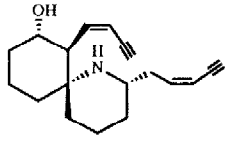
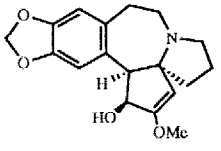
ABSTRACT: The use of radical cyclisations allows direct access to a family of azaspirocyclic ketones, including compounds having the azaspiro[4.4]nonane, and azaspiro[5.5]undecane structures which are found in the alkaloids cephalotaxine and histrionicotoxin.

The sustained interest in the synthesis of the alkaloids histrionicotoxin (**1**)[1] and cephalotaxine (**2**)[2] has resulted in the development of numerous strategies for the synthesis of the azaspirocyclic systems which constitute the structural cores of these molecules. Despite these efforts, there remains a need for a general method which allows the preparation of suitably functionalised azaspirocyclic systems having a variety of ring sizes, i.e. (**3**).[3]



(1)



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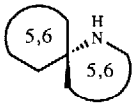
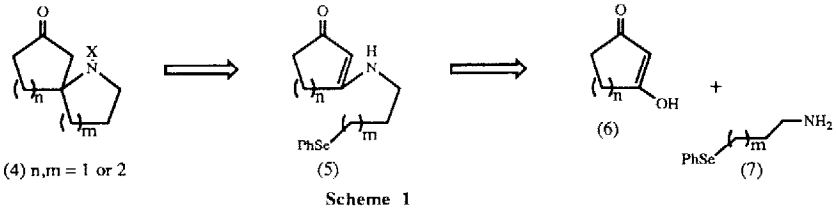


(3)

We recently described our results concerning the synthesis of oxaspirocyclic ketones by means of a radical cyclisation strategy,[4] and here we report the extension of this chemistry to the preparation of the more important aza-analogues (**4**).

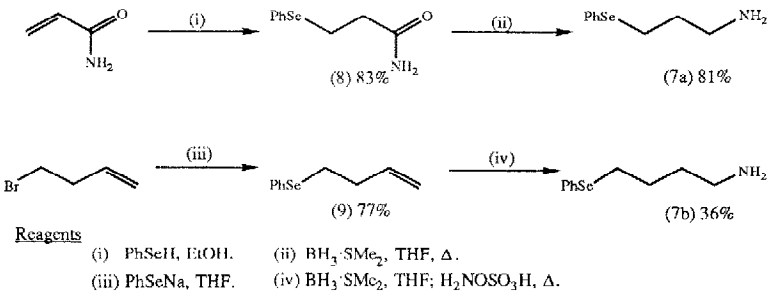
We initially anticipated obtaining the parent amines (**4**, X=H) by adopting an analogous procedure to that used previously to secure the corresponding spiroethers, thus (**4**, X=H) would be available by cyclisation of the precursor (**5**), Scheme 1.



(4) n,m = 1 or 2 (5) (6) (7)

Scheme 1

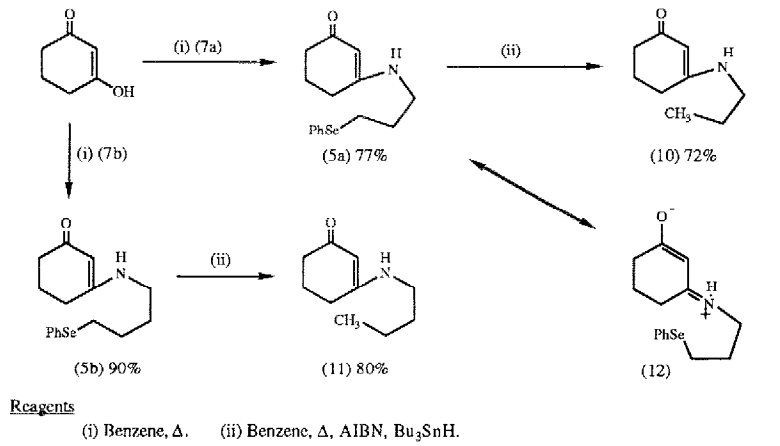
Since a number of cyclic diones (**6**) are available, our initial target was the synthesis of the required selenoamines (**7**). This was achieved in a very straightforward fashion as outlined in Scheme 2.



Scheme 2

Thus, addition of PhSeH to acrylamide gave the selenoamide (**8**),[5] m.p. 110-111°C, which was then smoothly reduced using BH_3·SMe_2 in refluxing THF to give (**7a**).[6] The preparation of (**7b**) involved the aminative hydroboration of the unsaturated selenide (**9**) which was easily prepared from the corresponding bromide. The yield of this reaction is only moderate since only two of the three chains of the intermediate trialkylborane are aminated; however this was compensated for by the directness of this route which allowed rapid preparation of multigram quantities of the desired amine.[7]

Condensation of the amines (**7a**) or (**7b**) with cyclohexane-1,3-dione in benzene under typical Dean-Stark conditions gave the desired vinylogous amides (**5a**) or (**5b**), Scheme 3.

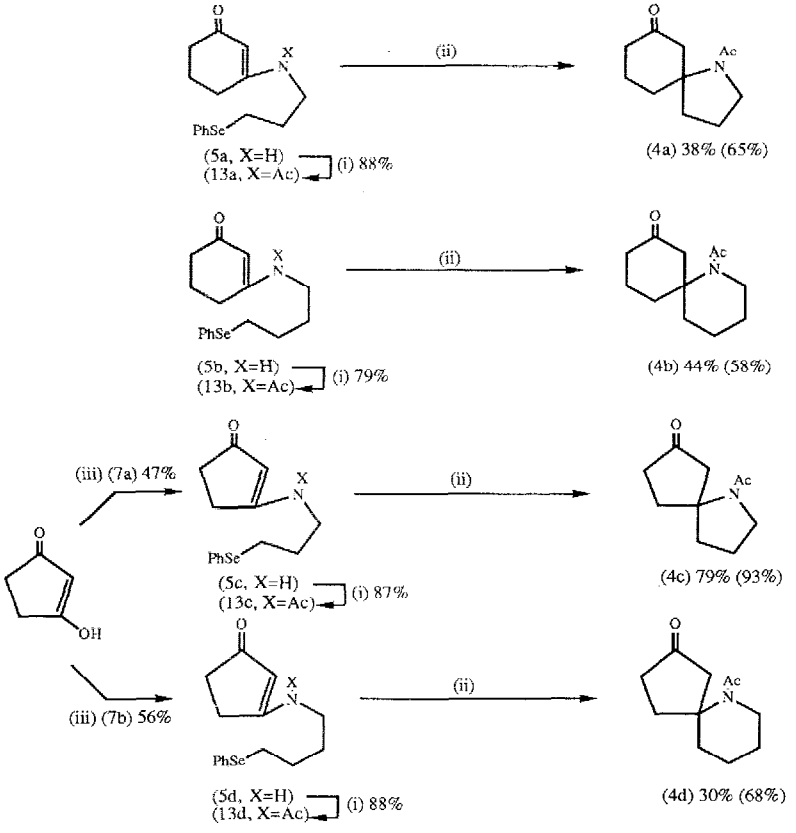


Scheme 3

We were surprised, and disappointed, when, upon treatment of (**5a**) or (**5b**) under the conditions used previously for cyclisation (Bu_3SnH, AIBN, benzene, reflux) we obtained only the reduced products (**10**) and (**11**) respectively, with no trace of cyclised material. Two possible explanations for this failure are that either H-transfer from the N-H group to the radical was occurring, or that a resonance contribution, e.g. (**5a**)↔(**12**), imparted an unfavourable degree of *endo*-trig character on the cyclisation process.[8] We therefore decided to *N*-acetylate (**5**) since this would hopefully aid the cyclisation by making the carbon-carbon double bond more electron deficient, and should be fairly easily removed after cyclisation if desired. Our attempts to acetylate compounds (**5**) under typical conditions (e.g. Ac_2O, NEt_3, CH_2Cl_2, DMAP, or NaH, AcCl, THF) were, however, totally unsuccessful until we eventually adopted a phase-transfer method used previously for vinylogous amides.[9] Thus exposure of (**5**) in a two phase system (CH_2Cl_2/50% $NaOH_{aq}$) to Ac_2O, using Adogen®464 as phase-transfer catalyst gave the desired acetylated materials in high yield, providing that the reaction was carefully monitored by TLC to avoid over-reaction.[10]

We were then pleased to find that each of these acetylated compounds, as well as their five-membered ring

analogues, underwent cyclisation to give the desired azaspirocyclic products (**4**, X=Ac), under standard conditions, Scheme 4.[11]



Reagents

(i) Ac_2O, CH_2Cl_2, 50% $NaOH_{aq}$, Adogen®464.
(ii) Bu_3SnH, AIBN, benzene, Δ, (0.01M).
(iii) Benzene, Δ.

Scheme 4

These cyclisations are unoptimised, and each product (**4**) was accompanied by varying amounts of reduced material and/or starting selenide (the yields of products based on recovered starting material are given in brackets). The incomplete conversion of starting materials to (**4a**), (**4b**), and (**4d**), is somewhat surprising, compared with the almost complete consumption of the corresponding spiroether precursors under similar conditions,[4] and especially considering the very efficient formation of (**4c**). We were very pleased that, as in the previous work, the relatively rare 6-*exo*-trig cyclisations were successful, as well as the far more common 5-*exo*-trig reactions. The moderate yields in the 6-*exo*-trig cyclisations are perhaps not surprising since these reactions are known to be slow compared with the corresponding 5-*exo*-trig analogues.[12]

This radical approach to azaspirocycles is thus quite general, and clearly the efficient formation of the azaspirononane (**4c**), and azaspiroundecane (**4b**) systems via radical cyclisation opens up new stategic possibilities for the synthesis of important targets such as (**1**) and (**2**). These are being actively pursued, and further results will be reported in due course.

Acknowledgements

We would like to thank the SERC, and Pfizer Central Research for a CASE studentship to DSM.

References and Notes

1. See R. J. Butlin, A. B. Holmes, and E. Mcdonald, Tetrahedron Lett., 1988, 29, 2989, and references therein.
2. For two very recent syntheses of cephalotaxine see, M. E. Kuehne, W. G. Bornmann, W. H. Parsons, T. D. Spitzer, J. F. Blount, and J. Zubieta, J. Org. Chem., 1988, 53, 3439; S. Yasuda, Y. Yamamoto, S. Yoshida, and M. Hanaoka, Chem. Pharm. Bull., 1988, 36, 4229.
3. For a previous attempt to develop a general strategy to azaspirocyclic systems see T. A. Bryson and C. A. Wilson, Synth. Commun., 1976, 521. The seemingly straightforward approach to these compounds involving intramolecular addition of an amine to an α,β–unsaturated ketone works in some cases, e.g. E. J. Corey, K. C. Nicolaou, R. D. Balanson, and Y. Machida, Synthesis, 1975, 590; S. A. Godleski and D. J. Heacock, J. Org. Chem., 1982, 47, 4820; but is problematic in others, see P. C. Conrad, P. L. Kwiatkowski, and P. L. Fuchs, J. Org. Chem., 1987, 52, 586.
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5. M. Miyashita and A. Yoshikoshi, Synthesis, 1980, 664.
6. H. C. Brown, S. Narasimhan, and Y. M. Choi, Synthesis, 1981, 441.
7. This problem can apparently be overcome if dimethylborane is used in the hydroboration step, but we have not yet explored this possibility, see H. C. Brown, K-W. Kim, M. Srebnik, and B. Singaram, Tetrahedron, 1987, 43, 4071.
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9. C. S. Swindell, B. P. Patel, S. J. DeSolms, and J. P. Springer, J. Org. Chem., 1987, 52, 2346.
10. In reference 9 Swindell *et al* note that *O*- and *C*-polyacetylation difficulties are encountered in the acetylation of vinylogous amides with acetyl chloride in pyridine. This probably explains our earlier failures to effect clean acetylation, and even using the phase-transfer method we suspect overacetylation occurs if the reaction is run for too long.
11. The preparation of **(4c)** is representative. To a refluxing solution of **(13c)** (420 mg, 1.25 mmol) in benzene (65 ml) was added a solution of Bu_3SnH (400 mg, 1.38 mmol) and AIBN (41 mg, 0.25 mmol) in benzene (65 ml) dropwise over 9.5 h. The mixture was then heated under reflux for a further 1h, cooled, and the solvent removed under reduced pressure. Flash chromatography of the residue on silica gel (5-50% acetone : ethyl acetate) gave spiroamide **(4c)** (179 mg, 79%) as a white solid, m.p. 58-59°C (acetone). (Found: C, 66.1; H, 8.2; N, 7.45. $C_{10}H_{15}NO_2$ requires C, 66.3; H, 8.3; N, 7.7%); ν_{max} ($CHCl_3$) 2940, 2890, 1740, 1635, 1400, and 1170 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.81-2.03(5H, m), 2.05(3H, s), 2.11(1H, d, J 18Hz), 2.19-2.29(1H, m), 2.58-2.67(1H, m), 2.77(1H, m), 3.32(1H, d, J 18Hz), and 3.49-3.59(2H, m); δ_C(23 MHz; $CDCl_3$) 23.0, 24.0, 33.3, 37.9, 41.4, 48.4, 49.3, 67.2, 169.2, and 216; *m/z* 181(M^+), 152, 122, 110, 96, and 83.
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