Pergamon

Tetrahedron Letters, Vol. 35, No. 38, pp. 7115-7118, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01472-8

Novel Spiro Cyclisations of *N*-Acyliminium Ions involving an Aromatic π-Nucleophile

Patrick D. Bailey,[a] Keith M. Morgan,[b] David I. Smith[c] and John M. Vernon[b]*

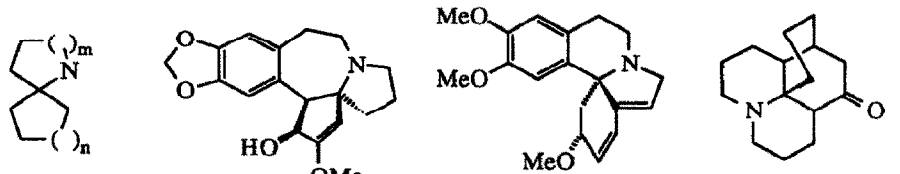
[a] Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, EH14 4AS, U.K.

[b] Department of Chemistry, University of York, Heslington, York, YO1 5DD, U.K.

[c] Department of Chemical Development, Sterling Winthrop Pharmaceuticals Research Division, Sterling Winthrop Research Centre, Alnwick, Northumberland, NE66 2JH, U.K.

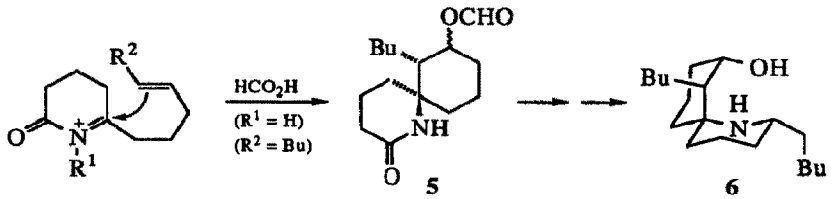
Abstract. Several spiro 2-pyrrolidin-5-ones were obtained by a two-step procedure from *N*-substituted succinimides, involving spiro cyclisation of *N*-acyliminium ion intermediates in refluxing trifluoroacetic acid; in all cases cyclisation utilised a tethered aromatic π-nucleophile, and ring-closure followed 5- or 6-*exo-trig* pathways.

Spiro amines of the type illustrated in structure **1** are key sub-units of several important natural products, including cephalotaxine **2**, erysotrine **3**, and lycopodine **4**.



1 (m = 1, 2; n = 1, 2) **2** **3** **4**

Spiro structures of this type can be accessed by the cyclisation of *N*-acyliminium ions, as shown in Scheme 1. For example, the spiro lactam **5** obtained by this approach is a key intermediate in formal total synthesis of perhydrohistrionicotoxin **6**.[1,2]

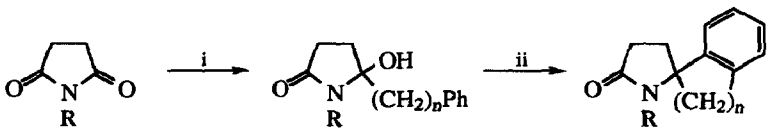


5 **6**

Scheme 1.

We wished to demonstrate that this approach could be extended to the formation of spiro lactams involving an aromatic ring as the π-nucleophile attached by a tether of variable length to the iminium carbon atom. The use of a chiral *N*-substituent would also open up the possibility of an enantioselective approach. We describe herein our preliminary results.

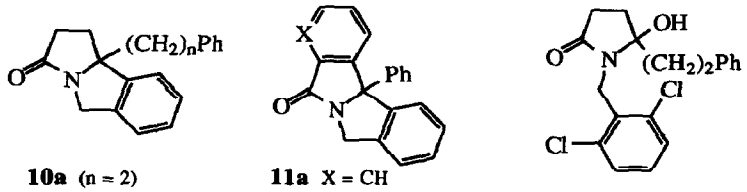
As an initial model system, the hydroxy lactam **8a** was prepared by Grignard addition to *N*-methyl-succinimide and found to undergo cyclisation in refluxing trifluoroacetic acid (TFA) to the 5,5-spiro lactam **9a** (69% yield). The same two-step procedure also afforded the 5,6-spiro lactam **9b** (Scheme 2).



7		
	8a R = Me, n = 2	**9a**
	b R = Me, n = 3	**b**
	c R = CH_2Ph, n = 2	**c**
	d R = CH_2Ph, n = 3	**d**

Scheme 2. i. $Ph(CH_2)_nMgBr$, THF, Et_2O; ii. TFA, Δ

Of more synthetic value were the *N*-benzyl derivatives **9c** and **9d**, which we obtained by the same two-step procedure *via* the hydroxy lactams **8c** and **8d**. However, for these *N*-benzyl spiro products **9c** and **9d** it was necessary to exclude the alternative structures **10a** and **10b**, which could arise by cyclisation of the same *N*-acyliminium ion intermediates to the *N*-benzyl group. Although this would be a disfavoured 5-*endo-trigonal* cyclisation (*endo* with respect to the C=N bond), two examples of this mode of cyclisation in polyphosphoric acid are known, yielding **11a**[3] and **11b**.[4]

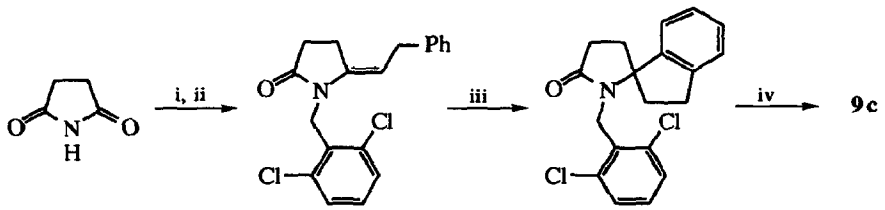


10a (n = 2)
b (n = 3)

11a X = CH
b X = N

12

For clarification of this point we thought to examine the acid-catalysed cyclodehydration of a hydroxy lactam **12** in which the *ortho*-positions of the *N*-benzyl group were blocked, thereby preventing formation of a product analogous to **10a**. However, attempted Grignard additions to *N*-2,6-dichlorobenzylsuccinimide **7** (R = $2,6\text{-}Cl_2C_6H_3CH_2$) afforded only dimeric products from a base-catalysed self condensation.



13 **14**

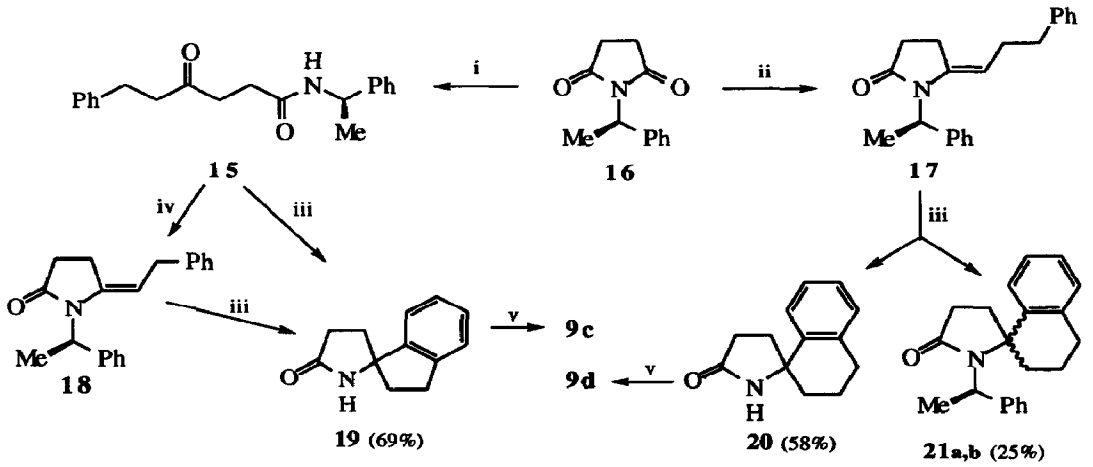
Scheme 3. i. $Ph(CH_2)_2MgBr$, THF; ii. $2,6\text{-}Cl_2C_6H_3CH_2Br$, Cs_2CO_3, MeCN; iii. TFA, Δ; iv. H_2, Pd-C, MeOH.

The alternative route shown in Scheme 3 afforded not **12** but its dehydration product, the enamide **13**. This material was isomerised in refluxing TFA to give spiro lactam **14**. Catalytic hydrogenation[5] over palladium then gave the spiro lactam **9c** directly, which was identical to the product already assigned as **9c** in Scheme 2. It would thus appear that the *exo-trig* mode of cyclisation is favoured in these systems.

We next turned our attention to *N*-α-methylbenzylsuccinimide **16**, as a readily available chiral starting material.[6] Once again, the increased steric bulk on the benzyl group prevented normal Grignard addition onto the succinimide carbonyl groups, and only dimeric products were isolated. However, by lowering the basicity of the Grignard reagent by the addition of a stoichiometric quantity of anhydrous cerium (III) chloride,[7] activated by ultrasonic dispersion,[8] we obtained the two possible iminium ion precursors **15** and **17**.[9]

Heating **15** in TFA achieved cyclisation, but this was accompanied by loss of the chiral directing group; attempts employing milder conditions led only to the formation of the enamide **18**. Since the spiro lactam **19** was racemic,[10] it would appear that the α-methylbenzyl group was lost prior to the cyclisation.

Of greater interest were the products obtained from the enamide **17**. Again, the major product (58% yield) was a racemic spiro lactam **20** which lacked the chiral directing group. This material was benzylated to confirm our assignment of **9d**, again indicating that *exo-trig* cyclisation was favoured from **8d**. The minor product (25% yield) was the desired spiro lactam, and ^{13}C NMR showed this material to be a *ca* 3:1 mixture of diastereoismers **21a,b** (Scheme 4 and Figure 1).



Scheme 4. i. $Ph(CH_2)_2MgBr$, Ce^{III}, THF; ii. $Ph(CH_2)_3MgBr$, Ce^{III}, THF; iii. TFA, Δ; iv. TFA (5 eq), DCM, r.t.; v. BnBr, Cs_2CO_3, MeCN.

A variety of catalytic hydrogenation conditions failed to remove the chiral directing group from the (inseparable) lactams **21a,b**. Treatment with sodium in liquid ammonia afforded a single product, but the endocyclic benzylic carbon-nitrogen bond had been cleaved with formation of the amide **22** in 66% yield (along with a small amount of unreacted starting material). The ^{13}C NMR spectrum of this material indicated that **22** was a single diastereoisomer (Figure 2), and thus a diastereoselective ring-opening must have occurred.

In summary, we have demonstrated that acyliminium cyclisations using tethered aromatic π-nucleophiles occur efficiently *via* 5- and 6-*exo-trigonal* pathways, giving access to 5,5- and 5,6-spiro amines. We are currently exploring the use of alternative chiral auxiliaries attached to the iminium nitrogen, and the application of the methodology to the total synthesis of biologically active spiro amines.

We thank Dr. G K Barlow, Mrs. B Chamberlain, Dr. T A Dransfield, Mr. B R Glennie & Dr. N R McLay for NMR and mass spectra at York, and SWPRD and SERC for a CASE studentship (to KMM).

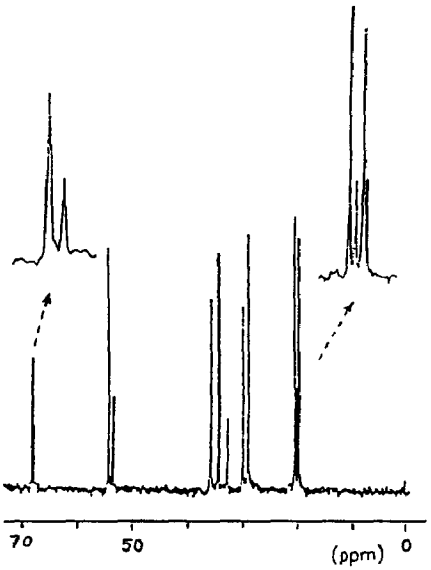
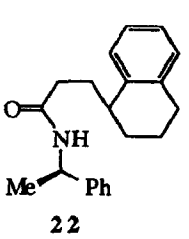


Figure 1. Portion of ^{13}C NMR of **21a,b**.



22

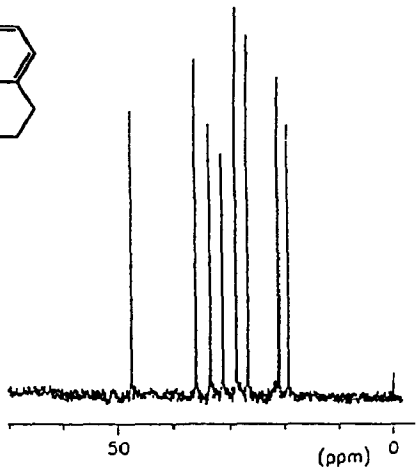


Figure 2. Portion of ^{13}C NMR of **22**.

References and Notes

1. Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.*, 1978, 1515; Schoemaker, H. E.; Kruk, C.; Speckamp, W. N. *ibid.*, 1979, 2437; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron*, 1980, **36**, 951.
2. Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.*, 1979, 411.
3. Winn, M.; Zaugg, H. E. *J. Org. Chem.*, 1968, **33**, 3779.
4. Hitchings, G. J.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1*, 1990, 1757.
5. For a review of hydrodehalogenation see Pandey, P. N.; Purkayasha, M. L. *Synthesis*, 1982, 877.
6. (*R*)-(+)-α-Methyl benzyl amine is refluxed with an equimolar quantity of succinic anhydride in THF for 2 h, then in acetic anhydride for 2 h. Aqueous work-up and flash chromatography on silica (DCM eluent) affords the (*R*)-α-methylbenzyl succinimide **16** in 65% yield.
7. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.*, 1989, **111**, 4392.
8. Greeves, N.; Lyford, L. *Tetrahedron Lett.*, 1992, **33**, 4759.
9. For example: $CeCl_3.7H_2O$ (1 mmol) was evacuated to 2 mmHg and heated to 140 °C for 1 h, and then for a further 2h with stirring. The flask was then cooled to -20 °C and dry THF (2 ml) added, with rapid stirring. After 30 min the flask was subjected to sonication for 1 h, then cooled to 0 °C. The Grignard reagent (1 mmol) in ether (3 ml) was added and the mixture stirred at r.t. for 2 h. After cooling to -78 °C, the chiral succinimide **16** (0.5 mmol) was added in THF (6 ml), and the reaction allowed to warm slowly to r.t. and stirred overnight. Aqueous work-up and chromatography on silica eluted with 1:9 ether/DCM afforded the 4-oxo amide **15** in 70% yield.
10. Both the racemic lactams **19** and **20** exhibited no optical rotation, and in their ^1H NMR spectra the amide NH peaks were split when a Eu(III) chiral shift reagent was added. Further evidence that the auxiliary was lost *first* was obtained by subjecting the lactams **21a,b** to the cyclisation conditions, when no debenzylation was observed.

(*Received in UK* 4 *July* 1994; *revised* 25 *July* 1994; *accepted* 29 *July* 1994)