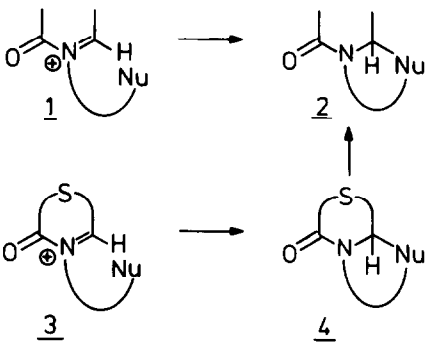
Tetrahedron Letters,Vol.23,No.37,pp 3811-3814,1982 0040-4039/82/373811-04$03.00/0
Printed in Great Britain

NOVEL SYNTHESIS OF AZA-HETEROCYCLES

Johannes A.M. Hamersma[1] and W. Nico Speckamp*,
Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands.

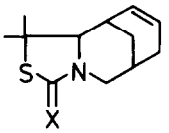
Abstract: N-formyl aza-heterocycles 15 - 24 can be prepared by Ra-Ni desulfurization of thiazolidine derived polycyclics 5 - 14 which in turn are obtained by intramolecular thiono α-acyliminium cyclisations of π-nucleophiles.

The wide variety of heterocyclic ring systems available via stereocontrolled α-acyliminium cyclisations[2] prompted the question whether this versatile method could be adapted to the synthesis of monocyclic systems. Such a procedure may in principle be based upon a ring closure of a linear precursor, e.g. 1 → 2, in analogy with the behaviour of the cyclic α-acyliminium ion[3]. In practice, however, preference is given to the route via a sulfur bridged α-acyliminium ion e.g. 3 → 4

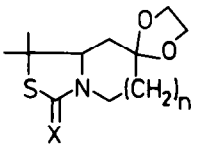


because of the easy handling and ready availability of the latter type of intermediate. The sequence then is completed by the reductive removal 4 → 2 of the sulfur atom from the initial ring system. Herein we report our results on the thiazolidinone derived polycyclics 5 - 13 as starting materials for the aimed conversions, together with one example of the 1,4-thiazine derivative 14[4].

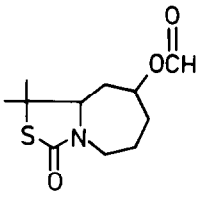
As discussed earlier[5], the thia-acyliminium ion 3 gives rise to stereoselective formation of systems 5, 6 and 8 on reaction with appropriate π-nucleophiles. A variety of other thiazolidinones, e.g. 7 and 9 - 13 possessing different



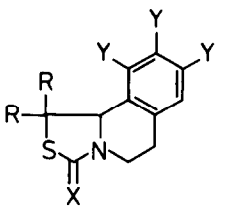
5



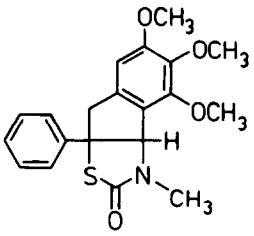
6 n = 1
7 n = 3



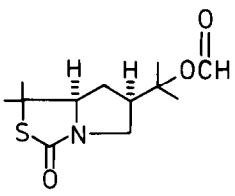
8



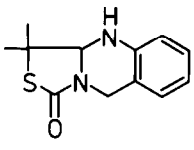
9 R = CH_3 Y = H
10 R = H Y = OCH_3



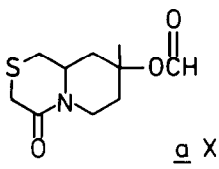
11



12



13

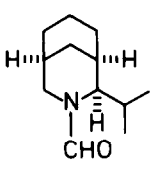


a X = O
b X = H_2

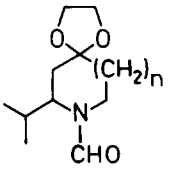
14

structural characteristics, have also been prepared by a similar methodology and will be described elsewhere[6]. In order to effect the transformation 4 → 2 it is necessary to remove the sulfur atom. This can be achieved either directly by treatment of the thiazolidinone with Ra-Ni or indirectly by prior LAH-reduction of the lactam carbonyl and subsequent Ra-Ni desulfurization.

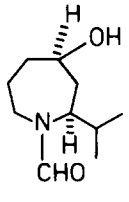
In the latter approach the LAH-reduction worked satisfactorily as demonstrated by the conversions of 5a → 5b, 6a → 6b, 7a → 7b and 9a → 9b which proceeded in yields up to 83% as indicated in the Table I. Ra-Ni desulfurization of 9b



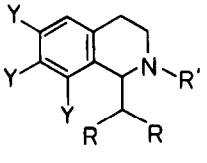
15



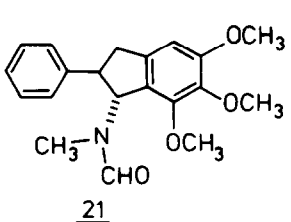
16 n = 1
17 n = 3



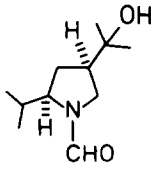
18



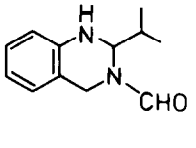
19a Y = H, R = CH_3, R' = CHO
19b Y = H, R = CH_3, R' = CH_3
20 Y = OCH_3, R = H, R' = CHO



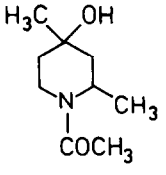
21



22



23



24

afforded the tetrahydroisoquinoline 19b as an oil (63%, ^{1}H NMR $\delta(CDCl_3)$: 0.85 (d, 3H, $C\underline{H}_3$), 1.0 (d, 3H, $C\underline{H}_3$), 1.95 (septet, 1H, $C\underline{H}(CH_3)_2$), 2.45 (s, 3H, $NC\underline{H}_3$)). In general, however, the Ra-Ni step gave irreproducible results, presumably as the result of the presence of a basic nitrogen atom. Therefore the direct desulfurization of the lactams 5 - 14 was attempted which in all experiments provided the

TABLE I

Lactam	Thiazolidine	Yield (%)	M.p.	^{1}H NMR[a] $NC\underline{H}_2S$	J_{AB}[b]
5a	5b	59	c)	3.31 , 4.05	7.0
6a	6b	43	c)	4.12 , 4.46	6.0
7a	7b	83	164-166	3.43 , 4.00	6.0
9a	9b	63	77-79	4.00 , 4.26	9.0

a) δ $CDCl_3$ b) ± 0.5 Hz c) oil.

N-formyl derivatives 15 - 24 in good yields. Thus upon reflux in EtOH of 5a with Ra-Ni (10-15 fold excess)[7] for 6 hrs the N-formylazabicyclo[3.3.1]nonane 15 was obtained in 91% as an oil; ^{1}H NMR $\delta(CDCl_3)$: 8.14 (s, $NC\underline{H}O$). Similarly the ketals 6a and 7a were refluxed with Ra-Ni and afforded the piperidine 16 and the azocine 17 in yields indicated in Table II. The remaining data are also summarized in Table II.

TABLE II

Starting lactam	Product	Yield (%)	M.p.	δ $CDCl_3$ $NC\underline{H}O$[b]
5a	15	91	a)	8.14
6a	16	71	a)	8.03-8.11
7a	17	81	a)	7.89
8	18	73	a)	7.97-8.16
9a	19a	40	a)	8.21-8.23
10a	20	79	85-88	8.09-8.28
11	21	63	a)	8.05-8.08
12	22	88	78-80	8.18-8.25
13	23	75	184-186	8.20-8.23
14	24	86	a)	-

a) oil b) mostly observed as two singlets, combined integrated area of 1 proton.

From the results of the table the following points deserve special attention: (i) the method is highly useful and allows the construction of varied heterocyclic systems of different ring sizes when combined with the appropriate thionocarbonyl iminium cyclisation (ii) coupled with the latter stereocontrolled ring closure the heterocycles formed eventually are obtained as single stereoisomers (iii) starting from C-substituted thiazolidinones, e.g. 11, the synthesis of a carbocyclic ring system carrying vicinal substituents in a defined spatial arrangement, e.g. 21, is also feasible (iv) lastly it may be remarked that the method allows an entry to otherwise difficultly accessible heterocycles, e.g. 22.

Given the variations possible in the structure of the sulfur containing ring as well as in the substituent pattern of the π-nucleophile it is concluded that the present method is highly flexible and allows the direct synthesis of novel complex heterocyclic structures.

LITERATURE AND REFERENCES

1) Part of the forthcoming Ph.D. Thesis of J.A.M. Hamersma, University of Amsterdam.

2) B.P. Wijnberg, W.N. Speckamp and A.R.C. Oostveen, Tetrahedron, 38, 209 (1982) and references contained therein.

3) W.N. Speckamp, Rec.Trav.Chim., 100, 345 (1981).

4) Results on the 1,3-thiazine system will be reported separately. In general our findings on the behaviour of the latter system are fully comparable. P.N.W. van der Vliet, unpublished observations.

5) J.A.M. Hamersma, H.E. Schoemaker and W.N. Speckamp, Tetrahedron Lett., 1347 (1979).

6) Compound 7 is obtained according to ref. 8.
Compound 12 is reported in the accompanying communication[9].
Compounds 8 - 11, 13 and 14 will be published separately.

7) H. Dannenberg and A. Rahman, Chem.Ber., 87, 1625 (1956).

8) H.E. Schoemaker, Tj. Boer-Terpstra, J. Dijkink and W.N. Speckamp, Tetrahedron, 36, 143 (1980).

9) P.M.M. Nossin, J.A.M. Hamersma and W.N. Speckamp, Tetrahedron Lett., preceding communication.

(Received in UK 7 July 1982)