Tetrahedron Letters No. 15, pp 1347 - 1350.
0040-4039/79/0408-1347$02.00/0

THE 2-OXO-THIAZOLIDINIUM MOIETY AS A NOVEL INITIATING CENTER FOR STEREOSELECTIVE OLEFIN CYCLISATIONS.

J.A.M. Hamersma, H.E. Schoemaker[1] and W.N. Speckamp*,
Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands.

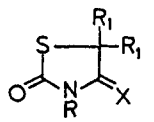
In recent years the synthetic utility of stereoselective α-acyliminium olefin cyclisations has been amply demonstrated[2]. Suitable structural variations in either the olefinic or in the α-acyliminium part could enlarge the scope of the method further. As an illustration of the latter modification some results on the 2-oxo-thiazolidinium moiety are reported herein.

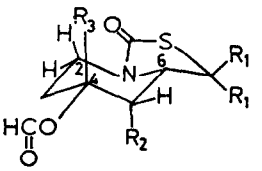
The starting imides used - 2,4-thiazolidinediones[3]- are coupled via the oxidation-reduction technique[5] with the appropriate alcohol to afford the N-alkylated derivatives 1a-7a in good yields. $NaBH_4/H^+$ reduction provided the mostly crystalline carbinollactams 1b-7b which were used after purification via columnchromatography or recrystallization. The observed regioselectivity effect in the reductions is either rationalized on the basis of a difference in ketonic character between the two carbonyl groups, viz 1a → 1b, 4a → 4b and 5a → 5b, or by steric approach control of the hydride reagent[6] or by a combination of both effects.

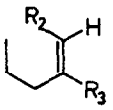
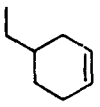
Cyclisations of the ω-carbinollactams 1b-7b were performed under essentially similar conditions as those described before[7]. Thus reaction of 1b in HCOOH for 142 hr afforded a 3 : 1 mixture (82% yield) of 1c and its C_4-epimer. The relative slowness of the reaction is most probably due to the reversible formation of the intermediate enamide 8 which in contrast to analogous derivatives in the succinimide and glutarimide series only gradually cyclizes.

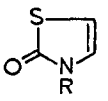
The rate of ring closure could be enhanced considerably by either blocking the adjacent CH_2-group thereby preventing enamide formation or by raising the nucleophilic character of the vinylic moiety. Within the latter context the cyclisation of 4b is completed after 18 hr thereby affording a 8 : 3 mixture of 4c and its C_4-epimer. 4c: 93-94°. IR($CHCl_3$): 1665 and 1720 cm^{-1} (C=O). NMR: δ($CDCl_3$) 8.02 (s, 1H, CHO), 3.68-4.07 (m, 2H, H_6ax and H_2eq), 1.58 (s, 3H, CH_3).

On the other hand complete ring closure of 2b (92% yield) proceeded within 2 hr upon HCOOH treatment at room temperature. A 3 : 1 mixture of 2c and its



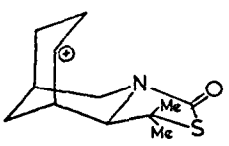


R	X=O[a]	X=	R_1	R_2	R_3	major isomer
	1a (87)	1b (50)	H	H	H	1c
	2a (62)	2b (78)	Me	H	H	2c
	3a (81)	3b (90)	Me	Et	H	3c
	4a (80)	4b (75)	H	H	Me	4c
	5a (72)	5b (55)	H	–	–	
	6a (69)	6b (75)	Me	–	–	
	7a (52)	7b (85)	Me	–	–	

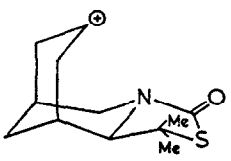


8

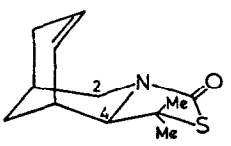
a : yields of purified products in parentheses



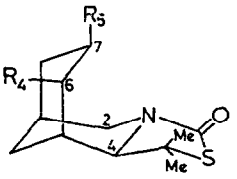
A



B



6c



6d R_4=H , R_5=OCH(=O)

6e R_4=OCH(=O) , R_5=H

C_4-epimer was obtained. 2c: mp. 137-138°. IR($CHCl_3$): 1670 and 1725 cm^{-1} (C=O). NMR: δ($CDCl_3$) 8.07 (s, 1H, CHO), 4.80-5.18 (m, 1H, H_4ax) 3.35 (d of d, J_1 = 12Hz, J_2 = 3Hz, H_6ax), 1.46 and 1.56 (s and s, 6H. 2 x CH_3).

The retardation of the cyclisation process by reversible enamide formation is also clearly indicated by the result of the cyclohexenyl derivative 5a which afforded only 8 (R = [3-cyclohexene]-methyl) as an oil.

On the contrary, ring closure of 6b was completed in less than 2 hr and yielded a mixture of three cyclisation products: 6c (50%), 6d (34%) and 6e (16%). 6c: mp. 116-118°. IR($CHCl_3$): 1655 cm^{-1} (C=O). NMR: δ($CDCl_3$) 5.85 (m, 2H, CH=CH), 4.26 (d of m, 1H, H_2eq), 3.34 (d, J = 2Hz, 1H, H_4ax), 3.05 (d of m, 1H, H_2ax). 6d: mp. 131-132°, IR($CHCl_3$): 1660 an 1725 cm^{-1} (C=O). NMR: δ($CDCl_3$) 8.00 (s, 1H, CHO), 5.22-5.60 (septet, 1H, H_7ax), 4.15 (d of m, J_d = 13 Hz, H_2eq), 3.38 (d, J = 2 Hz, H_4ax), 3.05 (d of m, 1H, H_2ax).

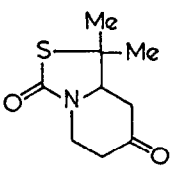
Compounds 6c and 6e originate from the C_6-carbenium intermediate A, while 6d is derived from the C_7- carbenium intermediate B which in turn is formed from A

via a [1,2]-hydride shift. Prolonged HCOOH treatment of 6c did not lead to any change thus excluding an acid catalyzed addition to the C=C bond in the formation of 6d.

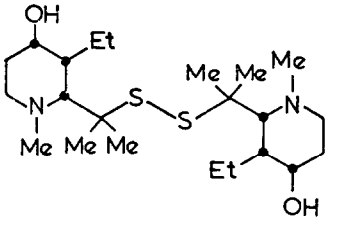
Finally the ability of the 2-oxo-thiazolidinium moiety to induce cyclisation of an acetylenic bond[8] was demonstrated in the conversion of 7b into the ketone 7c (72 hr, r.t., 80% yield), mp. 117-118°, IR (KBr): 1655 and 1708 cm^{-1} (C=O). NMR: δ($CDCl_3$) 4.25-4.50 (m, 1H, H_2eq), 3.58 (d of d, J_1= 11Hz, J_2= 5Hz, 1H, H_6ax), 2.95-3.25 (m, 1H, H_2ax), 1.43 and 1.63 (2 x s, 6H, 2 x CH_3).

The foregoing results have indicated the easy formation of a variety of thiazolidine derivatives of interesting pharmacological structure which hitherto were not accessible via simple routes.

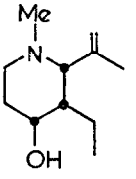
More important from a synthetic point of view, however, is the aptitude of the sulfur heterocycle to undergo further transformation resulting in a stereocontrolled synthesis of multiple substituted piperidine derivatives. As an example of this novel technique the preparation of an all-cis substituted derivative is described.



7c



9



10

Cyclisation of compound 3b (HCOOH, r.t., 72 hr) afforded in an essentially stereospecific manner compound 3c (96% yield): mp. 109-110°. IR($CHCl_3$): 1660 and 1720 cm^{-1} (C=O). NMR: δ($CDCl_3$) 8.01 (s, 1H, CHO), 4.93-5.23 (d of t, J_1= 12Hz, J_2= J_3 = 5Hz, 1H, H_4ax), 3.22 (d, J = 2.5Hz, 1H, H_6ax). LAH-reduction of 3c (THF, 16 hr, reflux) gave the crystalline disulfide 9[9], formed via reductive ring fission, followed by oxidative dimerization (51% yield), mp. 152-154°. ^{1}H NMR: δ($CDCl_3$): 3.74 (d of t, J_1 = 11z, J_2= J_3= 5Hz, 2H, C<u>H</u>OH), 2.57 (s, 6H, 2 x N-CH_3). The molecular weight of 432 was determined with the aid of Field-ionization mass spectroscopy. The "decoupled" ^{13}C-NMR spectrum showed 11 signals, indicating a symmetrical structure. ^{13}C NMR: δ($CDCl_3$) 73.56(d), 71.65(d), 55.56(t), 54.24(s), 45.07 (d), 43.58(q), 30.93(q), 27.58(q), 27.43(t), 18.63(t), 16.15(q). Treatment of compound 9 with Raney Ni (THF, 20 hr, reflux), afforded the crystalline cis-substituted piperidine 10 (67% yield), mp. 96-98°. NMR: δ($CDCl_3$) 3.65-3.92 (d of t, 1H, C<u>H</u>OH) 2.23 (s, 3H, NCH_3), 5.09 (m, 2H, >C=CH_2), 1.83 (br s, 3H, C=C-CH_3). Obvious ramifications of the latter procedure are under active investigation.

References

1. Part of the forthcoming Ph.D. Thesis of H.E. Schoemaker, University of Amsterdam.

2a. H.E. Schoemaker, J. Dijkink and W.N. Speckamp, Tetrahedron, 34, 163 (1978);

b. H.E. Schoemaker and W.N. Speckamp, Tetrahedron Letters, 4841 (1978).

3. Commercially available or prepared by simple standard procedures[4].

4a. cf. H. Erlenmeyer and H. von Meyenburg, Helv.Chim.Acta, 20, 1388 (1937);

b. E.E. Smissman, J.Amer.Chem.Soc., 76, 5805 (1954).

5. O. Mitsunobu, M. Wada and T. Sano, J.Amer.Chem.Soc., 94, 679 (1972) see also ref. 2a.

6a. J.B.P.A. Wijnberg, H.E. Schoemaker and W.N. Speckamp, Tetrahedron, 34, 179 (1978);

b. R.E. Rosenfield Jr. and J.D. Dunitz, Helv.Chim.Acta, 61, 2176 (1978).

7. See ref. 2a.

8. T. Boer-Terpstra, J. Dijkink, H.E. Schoemaker and W.N. Speckamp, Tetrahedron Letters, 939 (1977).

9. All new compounds gave correct analytical data.

(Received in UK 26 January 1979)

++++++++++++