RING TRANSFORMATIONS OF A THIAZOLINE FUSED δ-LACTONE INTO A γ-LACTAM AND A 1,4-THIAZINONE

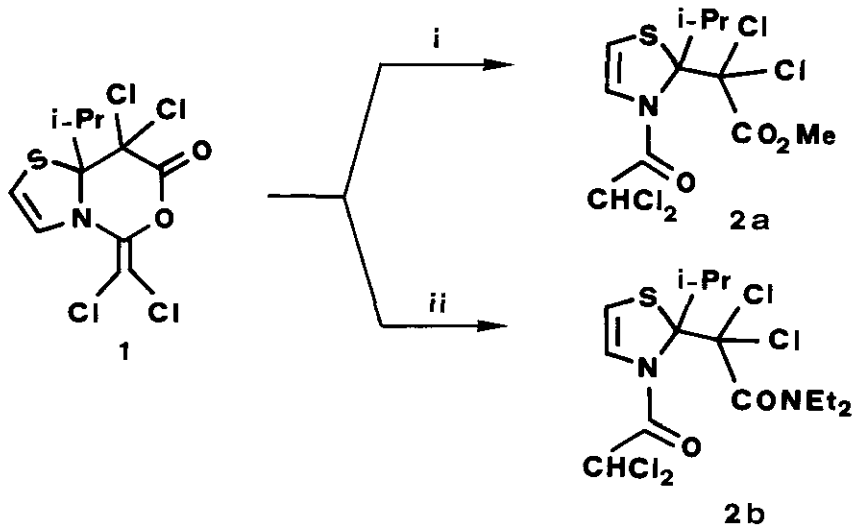
Alessandro Dondoni,* Giancarlo Fantin, Marco Fogagnolo and Alessandro Medici

Laboratory of Organic Chemistry, Faculty of Science, University of Ferrara, Ferrara, Italy

Abstract - The thiazoline fused δ-lactone 1 is converted via the methyl N-acyl-2-ethanoate 2a into the N-vinylthiazinone 3 or the thiazoline fused γ-lactam 4.

Ring transformations of heterocycles[1] are important in synthetic methodology because they provide, inter alia, the entry to a variety of heterocyclic systems which may be otherwise unaccessible. We report herein the conversion of a thiazoline fused oxazinone ring into a γ-lactam or alternatively into a thiazinone derivative via a common open-chain intermediate.

Treatment of the substituted 3-oxa-4-oxo-1-aza-7-thiabicyclo-[4.3.0]-non-8-ene (1) obtained from 2-i-propylthiazole and dichloroketene[2], with sodium methoxide in



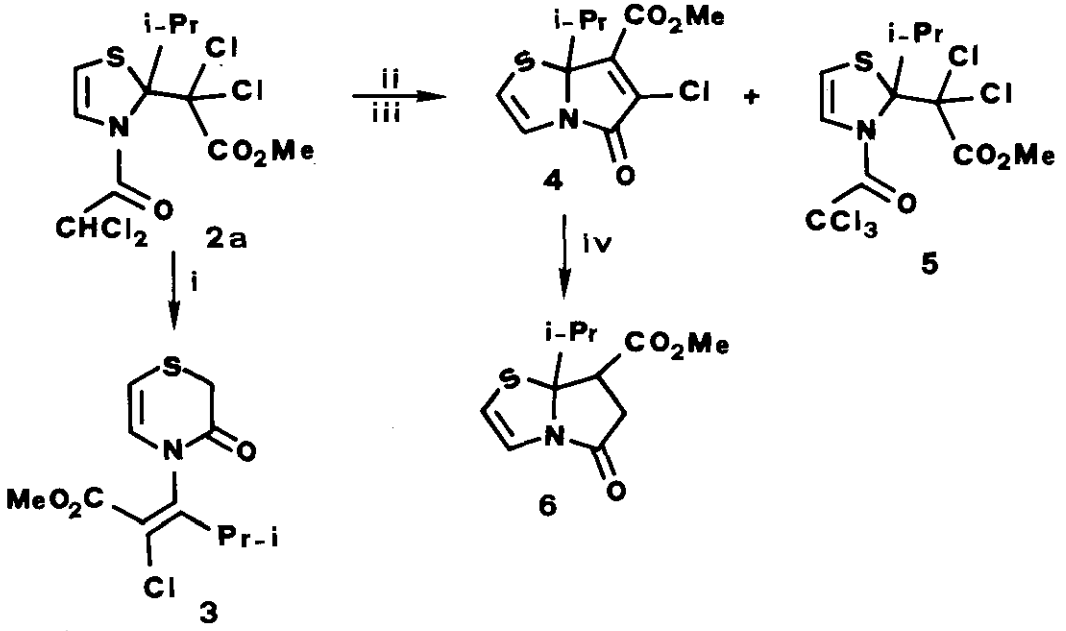
Reagents and conditions : i, MeONa, MeOH, r.t., 30 min.; ii, Et_2NH, C_6H_6, r.t., 2h.

methanol resulted in the opening of the oxazinone ring to give[3] the methyl N-acyl-thiazolin-2-yl-ethanoate (2a)[4] in almost quantitative yield. Similarly, the reaction of 1 with diethylamine in benzene produced the amide 2b[4].

Compounds 2a and 2b appeared to be set up for the intramolecular cyclization to a five-membered ring fused with the thiazoline ring across the C-N bond. The first route envisaged was unsuccessful since it afforded instead a monocyclic six-membered ring compound. The slow addition of 2a into a suspension of Zn in N-methylformamide - diethyl ether (1:8) and work-up gave the N-vinyl-1,4-thiazin-3-one (3) (70% yield)[5] (Scheme 1). This thiazoline-thiazine rearrangement is likely to take place from the Zn promoted dechlorination at C_α of the 2-ethanoate chain; the consequential carbon-sulfur bond fission in the thiazoline ring and the recyclization by chlorine displacement from the $CHCl_2$ group gives the product 3. The expected Zn promoted dechlorination and coupling between the C_α of the 2-ethanoate chain and the N-acyl group[6] to give a γ-lactam ring, was not observed.

As a second approach toward the intramolecular cyclization, the N-acylthiazoline 2a was treated with lithium diisopropylamide (LDA)[7] in THF at -78°C. The addition of DMSO[8] to the reaction mixture and warm up to room temperature, afforded after flash chromatography (silica, cyclohexane - ethyl acetate) the methyl 8-oxa-1-aza-4-thia-bicyclo-[3.3.0]-oct-2,6-diene-6-carboxylate (4) and the methyl N-trichloroacetyl-thiazolin-2-yl-ethanoate (5) in 2:1 ratio (overall yield 78%).[9] The reductive de-

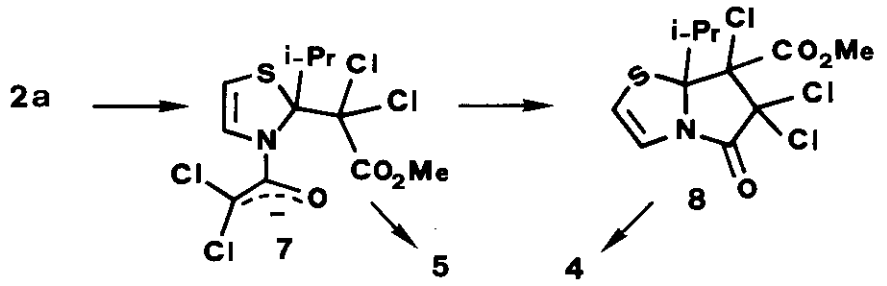
Scheme 1



Reagents and conditions: i, Zn (4 equiv.), MeNHCOH - Et_2O (1:8), r.t., 2h; ii, LDA (1 equiv.), THF, -78°C, 30 min.; iii, DMSO; iv, Zn - CH_3CO_2H, r.t., 2h.

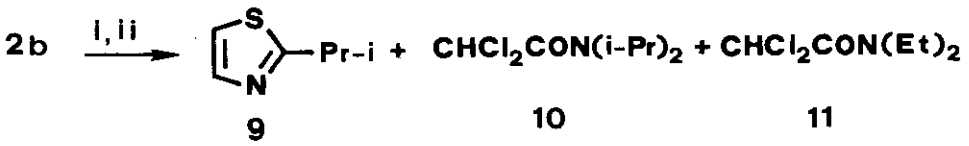
chlorination of 4 by Zn/CH_3COOH gave the γ-lactam 6 in modest yield (20%).[10]

The formation of products 4 and 5 can be explained by assuming as a common intermediate the thiazoline 7 bearing an enolate group at nitrogen due to the deprotonation of 2a at the N-dichloroacetyl moiety. The chloride ion displacement from the C_2 side-chain of 7 leads to the thiazoline fused γ-lactam 8 whereas the chlorination at the N-enolate group gives the product 5. The 1,2-dechlorination of 8 leads to the observed azathiabicyclo-[3.3.0]-octadiene 4. The relation between this dehalogenation reaction and the halogenation of 7 to 5 has to be clarified. Notwithstanding this and other mechanistic uncertainties, the above sequence provides the synthesis of a γ-lactam condensed across the carbon-nitrogen bond of a Δ^4-thiazoline ring. Therefore, the present ring transformation is of interest in connection with its possible extension to the synthesis of γ-lactam analogues of penems. At-



tention has been recently drawn to lactam antibiotics devoid of the β-lactam moiety.[11]

The attempt to apply tha same reactions to the N-acylthiazolin-2-ethanoyl amide (2b), failed. Treatment of 2b with LDA in THF at -78°C and addition of DMSO gave the compounds 9, 10 and 11. This suggests that the anion from 2b fragments into 2-isopropyl-2-thiazole (9), the carbanion of the N,N-diethyl-dichloroacetamide and dichloroketene. The latter product is trapped by LDA to give 10.



Reagents and conditions: i, LDA (1 equiv.), THF, -78°C, 30 min.; ii, DMSO.

REFERENCES AND NOTES

1. H.C. Van der Plas, "Ring Transformations of Heterocycles", Academic Press, New York, 1973, vol. 1 and 2.
2. A. Medici, G. Fantin, M. Fogagnolo, P. Pedrini, and A. Dondoni, J. Org. Chem., 1984, 49, 590.
3. All new compounds gave satisfactory elemental analyses. IR spectra were recorded on a Perkin-Elmer Model 297 grating spectrometer; NMR spectra were obtained on a 80-MHz WP80 Bruker spectrometer; mass spectra were recorded at 70 eV on a Varian Mat 112 high resolution mass spectrometer.
4. 2a: oil; IR (film) 1750, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (d, 1H, J = 5.13 Hz), 6.13 (s, 1H), 5.86 (d, 1H, J = 5.13 Hz), 3.91 (s, 3H), 3.70 (m, 1H), 1.29 (d, 3H), 1.07 (d, 3H); Mass spectrum m/e (relative intensity) 379 (M^+, 2.5), 344 (2.5), 296 (5), 238 (3), 226 (3), 198 (3), 128 (100), 112 (18), 84 (18), 59 (20).
   2b: m.p. 109-111°C (from diethyl ether - n-hexane); IR (KBr) 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.81 (d, 1H, J = 5.11 Hz), 6.23 (s, 1H), 5.83 (d, 1H, J = 5.11 Hz), 3.87 (m, 1H), 3.42 (m, 4H), 1.17 (m, 12H).
5. The structure of 3, m.p. 58-60°C (from diethyl ether - n-hexane) was established by X-ray crystallography (G. Gilli, V. Betrolasi, private communication). The main spectroscopic characteristics were: IR (KBr) 1720, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.12 (d, 1H, J = 7.00 Hz), 5.80 (dt, 1H, J = 7.00 Hz, J = 1.03 Hz), 3.90 (s, 3H), 3.72 (m, 1H), 3.38 (d, 2H, J = 1.03 Hz), 1.15 (d, 6H).
6. C. Chanin, E.A. Schmidt, and H.M.R. Hoffmann, J. Am. Chem. Soc., 1974, 96, 606.
7. R.G. Cregge, J.L. Herrmann, C.S. Lee, J.E. Richman, and H. Schlessinger, Tetrahedron Letters, 1973, 26, 2425.
8. No isolable products were obtained in the absence of DMSO.
9. The structures of 4 and 5 were established by X-ray crystallography (G. Gilli, V. Bertolasi, private communication).
   4: m.p. 78-79°C (from diethyl ether - n-hexane); IR (KBr) 1730, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.46 (d, 1H, J = 4.40 Hz), 6.04 (d, 1H, J = 4.40 Hz), 3.93 (s, 3H), 2.53 (m, 1H), 1.19 (d, 3H), 0.87 (d, 3H); Mass spectrum m/e (relative intensity) 273 (M^+, 20), 230 (100), 202 (15), 123 (10), 58 (18).
   5: m.p. 91-93°C (from diethyl ether - n-hexane); IR (KBr) 1750, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02 (d, 1H, J = 5.08 Hz), 5.86 (d, 1H, J = 5.08 Hz), 3.94 (s, 3H), 3.75 (m, 1H), 1.36 (d, 3H), 1.10 (d, 3H); Mass spectrum m/e (relative intensity) 272 (100), 190 (10), 166 (10), 126 (25), 121 (20), 119 (50), 117 (50), 112 (20), 59 (30), 43 (25).
10. The structure of 6, m.p. 81-83°C (from diethyl ether - n-hexane), was assigned by its spectroscopic characteristics. IR (KBr) 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 6.60 (d, 1H, J = 4.40 Hz), 5.90 (d, 1H, J = 4.40 Hz), 4.00 (m, 1H), 3.82 (s, 3H), 2.80 (m, 2H), 2.32 (m, 1H), 0,98 (d, 6H); Mass spectrum m/e (relative intensity) 241 (M^+, 20), 198 (100), 170 (40), 138 (100), 128 (40), 58 (40).

11. J.E. Baldwin, Fai Chan Ming, G. Gallacher, P. Monk, and K. Prout, J.C.S. Chem. Commun., 1983, 250.

Received, 11th June, 1984