

RING TRANSFORMATIONS OF A THIAZOLINE FUSED δ -LACTONE INTOA γ -LACTAM AND A 1,4-THIAZINONEAlessandro Dondoni,^{*} Giancarlo Fantin, Marco Fogagnolo and

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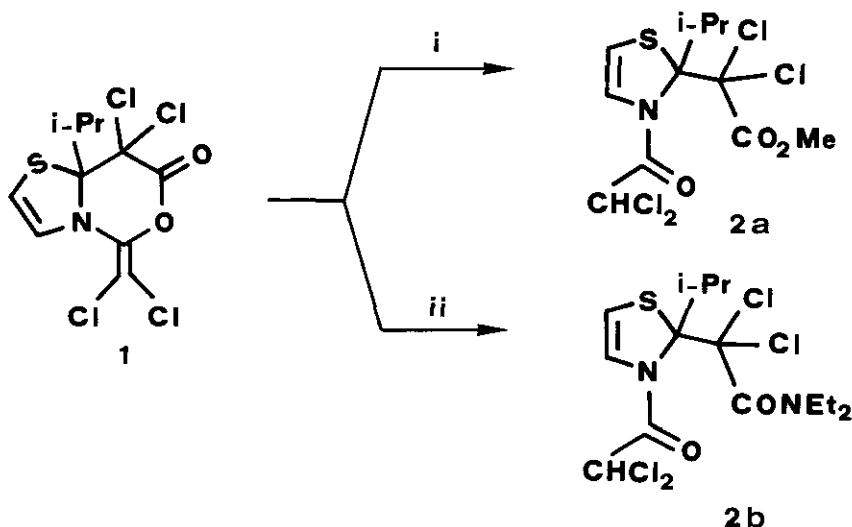
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Abstract - The thiazoline fused δ -lactone 1 is converted via the methyl N-acyl-2-ethanoate 2a into the N-vinylthiazinone 3 or the thiazoline fused γ -lactam 4.

Ring transformations of heterocycles¹ are important in synthetic methodology because they provide, inter alia, the entry to a variety of heterocyclic systems which may be otherwise inaccessible. 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 dichloroketene², with sodium methoxide in



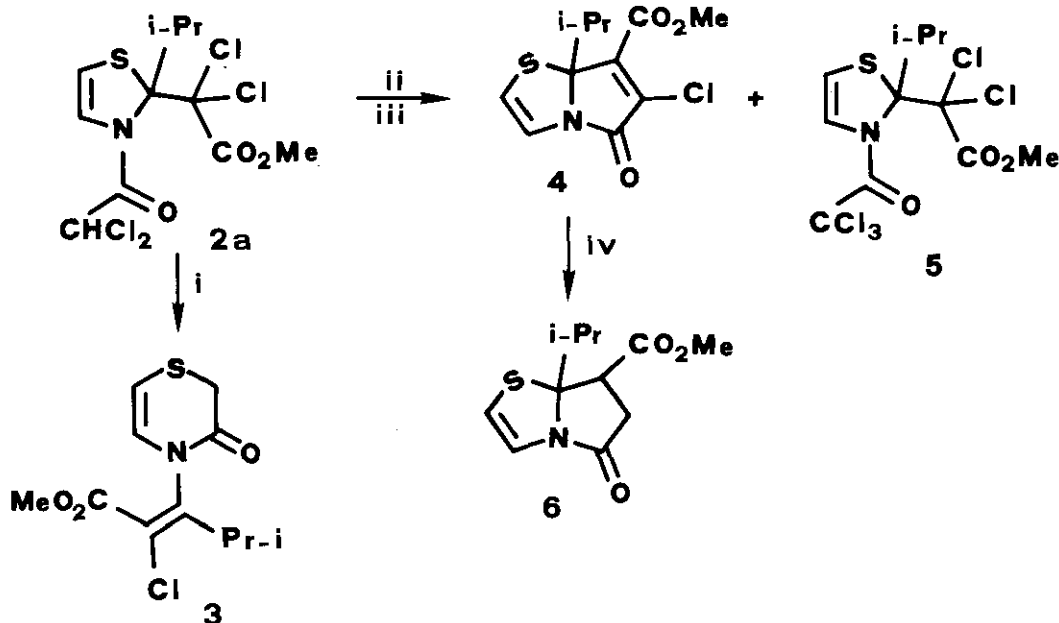
Reagents and conditions : i, MeONa, MeOH, r.t., 30 min.; ii, Et_2NH , C_6H_6 , r.t., 2h.

methanol resulted in the opening of the oxazinone ring to give³ 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 2b⁴.

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 CHCl₂ 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 group⁶ 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 DMSO⁸ 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*-trichloroacetylthiazolin-2-yl-ethanoate (5) in 2:1 ratio (overall yield 78%).⁹ The reductive de-

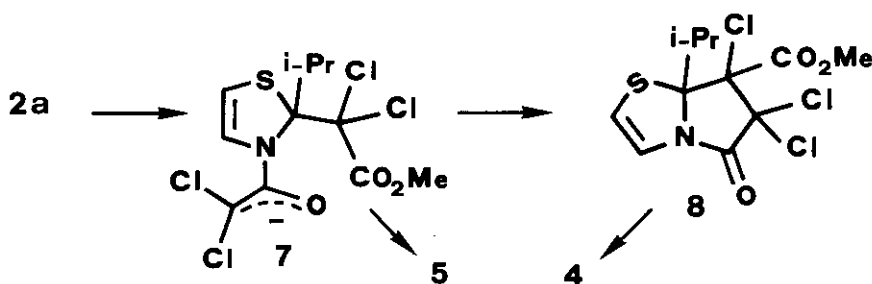
Scheme 1



Reagents and conditions: i, Zn (4 equiv.), MeNHCOH - Et₂O (1:8), r.t., 2h; ii, LDA (1 equiv.), THF, -78°C, 30 min.; iii, DMSO; iv, Zn - CH₃CO₂H, r.t., 2h.

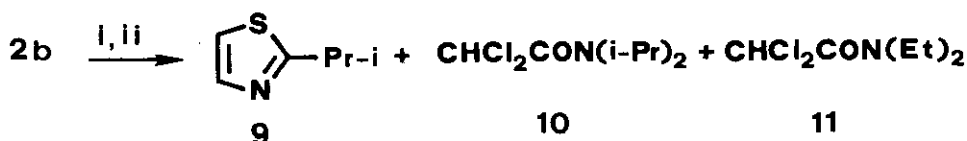
chlorination of 4 by $\text{Zn}/\text{CH}_3\text{COOH}$ gave the γ -lactam 6 in modest yield (20%).¹⁰

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 the 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 dichloro-rocketene. 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

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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. Bertolasi, 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).

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Received, 11th June, 1984