RING-CHAIN TRANSFORMATIONS OF SEMICYCLIC 3-CHLORO-PROPENIMINIUM SALTS TO ω-AMINOALKYL-1,2-OXAZOLES USING HYDROXYLAMINE[1]

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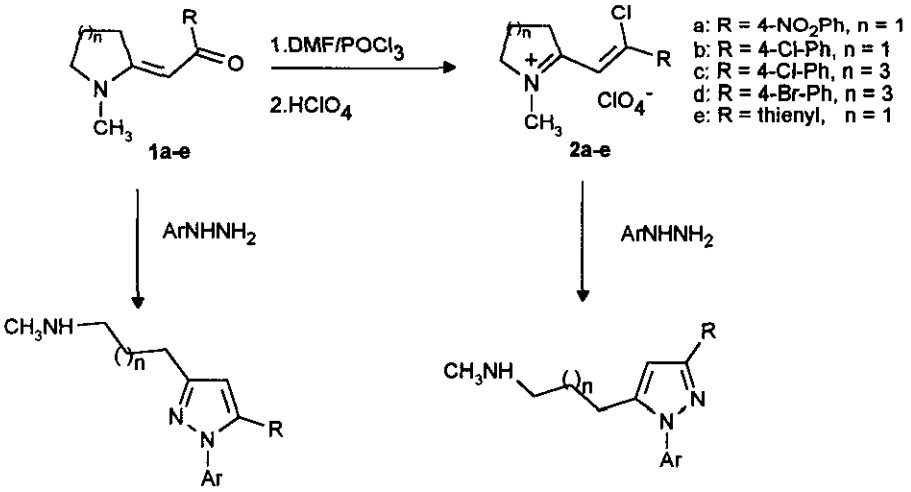
Abstract- Semicyclic 3-chloropropeniminium salts (**2**) or (**8**) react with hydroxylamine giving either ω-aminoalkyl-1,2-oxazoles (**4**, **6**, **10**) by ring chain transformation or chlorovinyloximes (**7**) by ring opening.

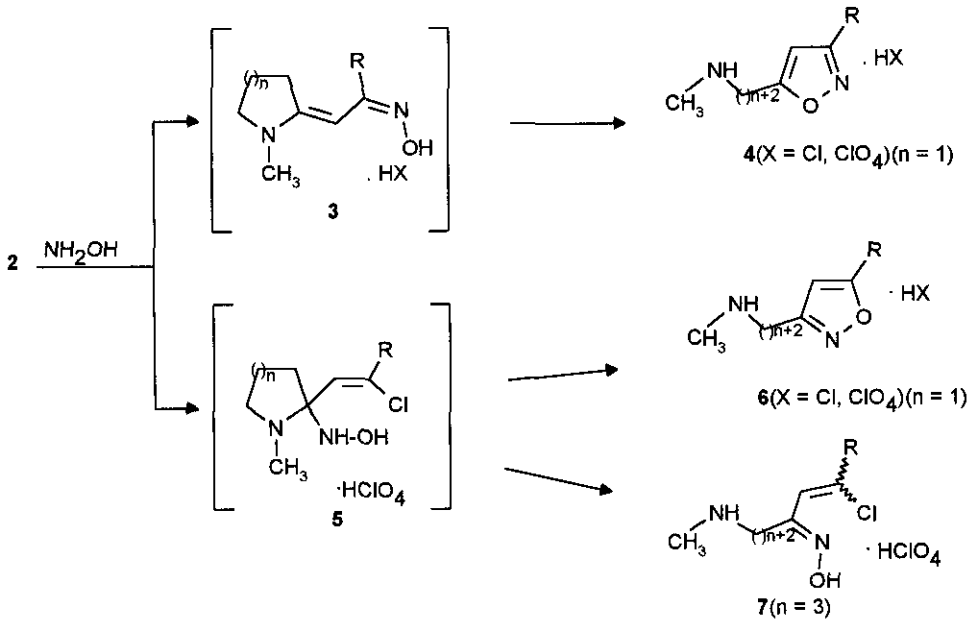
Semicyclic 3-chloropropeniminium salts (**2**) and their precursors (**1**) are 1,3-bielectrophiles reacting with hydrazines to give ω-aminoalkylpyrazoles by ring-chain transformation.[2-4] Since the regioselectivity in reactions with arylhydrazines is different, it



was possible to synthesize either the 1-aryl-3-(ω-aminoalkyl)pyrazoles or the 5-(ω-aminoalkyl) isomers if either enaminones (**1**) or 3-chloropropeniminium salts (**2**) were used.[3]

Enaminones (**1**) are known to react with hydroxylamine analogously giving 3- or 5-(ω-aminoalkyl)-1,2-oxazoles.[5] We now report on the reaction of 3-chloropropeniminium salts (**2**) with hydroxylamine.

Reacting salts (**2**) (n = 1) with hydroxylamine in methanol (procedure A) or in buffered aqueous solution of hydroxylamine hydrochloride (procedure B), affords mixtures of both isomeric ω-aminopropyl-1,2-oxazoles (**4**) (major isomer) and (**6**) in the ratio of 7:3 ~ 8 2. Under the same conditions the seven-membered ring 3-chloropropeniminium salts (**2**) (n = 3) surprisingly do not give 1,2-oxazoles but open chained ß-chlorovinyloximes (**7**), which resist further cyclisation. A similar situation was found in the reaction of open chain 3-chloropropeniminium salts with hydroxylamine.[6] Obviously the oximes (**7**) are formed by primary attack of the hydroxylamine at the iminium carbon atom giving intermediates (**5**). The formation of the 3-(ω-aminopropyl)-1,2-oxazoles (**6**) is initiated by the same primary step (formation of the adducts **5**). The next step of the ring-chain transformation to **6** could be explained by substitution of the chloride by the hydroxy group, rather than ring opening to give **7**. Probably the ring opening to **7** is faster in the case of azepane derivatives (**5**) (n = 3) than in the case of pyrrolidine derivatives (**5**) (n = 1), thus successfully competing with the ring transformation to 1,2-oxazoles (**6**)

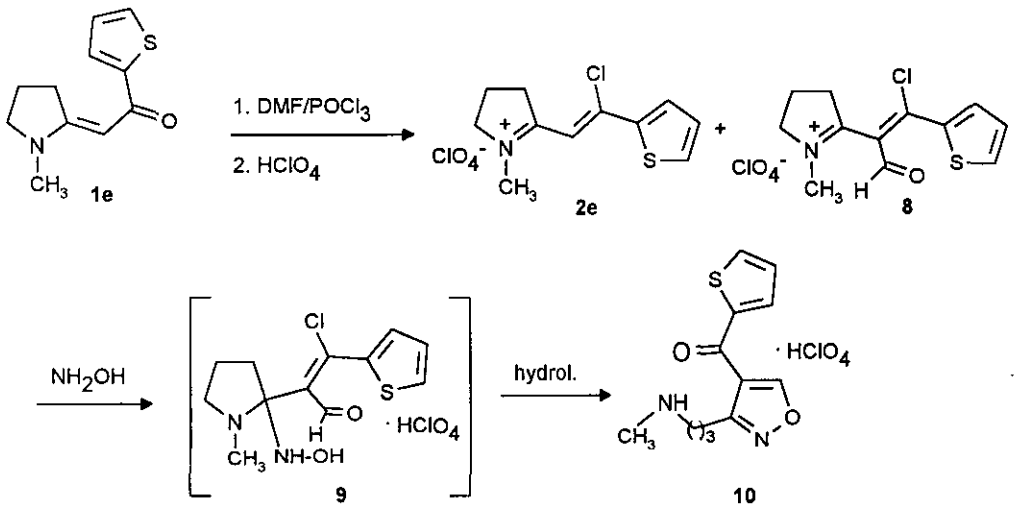


The isomeric 3-methylaminopropyl-1,2-oxazoles (**4**) and (**6**) can be distinguished by ^{13}C-nmr and by mass spectroscopy;[7] thus the 5-aryl-3-(3-methylaminopropyl)-1,2-oxazoles (**6**), unlike the major isomers (**4**), *exhibit an intense peak of* RCO^+ *in the ms* The major isomer (**4**) gives rise to ^{13}C-nmr shifts at δ = 161 ppm (C-3) and δ = 173 ppm (C-5) while the corresponding signals of the

5-aryl-3-(3-methylaminopropyl)-1,2-oxazoles (**6**) are found at δ = 163 ppm and δ = 165 ppm.

If the semicyclic thienyl-substituted 3-chloropropeniminium salt (**2e**) is treated with hydroxylamine as described above , no ring-transformation takes place. The crude starting material (**2e**) was found to contain a 3-chloropropeniminium salt (**8**) in the ratio **2e** . **8** = 7 . 3 with an additional formyl group , which had been formed by formylation with DMF/$POCl_3$.

Since **8** is relatively unstable it could not be obtained in a pure state. Obviously the thienyl substituted enaminone (**1e**) and 3-chloropropeniminium salt (**2e**) are relatively electron rich due to the thienyl substituent, thus explaining both the additional formylation giving **8** (for analogous formylation of open chain enaminones see ref.[8]) and the low electrophilicity disfavouring the reaction of **2e** with hydroxylamine. If hydroxylamine is reacted with the crude mixture of **2e** and **8** the latter almost quantitatively undergoes a ring-chain transformation to an ω-aminoalkyl-1,2-oxazole; however **8** does not react as a 3-chloro-



propeniminium salt but as a semicyclic enaminone. Hence the 3-(3-methylaminopropyl)-4-thienoyl-1,2-oxazole (**10**) is formed. Its structure was proved by X-ray crystal analysis (Figure 1) [9] The N and O atoms of the heterocycle were successfully

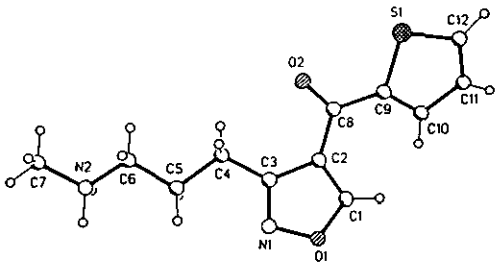


Figure 1· *X-ray crystal structure of compound (10)*

distinguished and the protonation site established as N2. Interestingly in the crystal lattice the molecules (**10**) are arranged in such a way that both the π-systems and the alkylammonium moieties form a separate layer.

Our results thus demonstrate that 3-chloropropeniminium salts are less suitable than semicyclic enaminones in the regioselective synthesis of ω-aminoalkyl-1,2-oxazoles.

EXPERIMENTAL

Nmr spectra were recorded with Bruker AC 300 and Tesla BS 587 spectrometers in DMSO-d_6. Mass spectra were obtained on HP 5995A (Hewlett Packard). Melting points are uncorrected. 3-Chloropropeniminium perchlorates (**2a-e**) were obtained according to known procedures [3]

Reaction of Hydroxylamine with 3-Chloro-propeniminium Salts (2)

Procedure A: 10 ml of 1 M freshly prepared methanolic NH_2OH solution were added to a solution of 10 mmol of (**2**) in 5 ml of methanol. The mixture was refluxed for 45 min. The solvent was evaporated and the residue recrystallized.

Procedure B: A solution of 15 mmol (1.04 g) of $NH_2OH \cdot HCl$ and 25 mmol (2.05 g) of sodium acetate in 20 ml of water was added to a solution of 10 mmol of (**2**) in 30 ml of methanol. After heating to reflux for 5 h the solvents were removed in vacuum. Water was added. The solution was extracted three times with 30 ml of CH_2Cl_2 and then three times with 30 ml of Et_2O. After evaporation of the solvents 10 ml of ethanol were added and with Et_2O (saturated with HCl gas) the 1,2-oxazole hydrochloride was obtained. It was filtered off and recrystallized.

5-[(3-Methylamino)prop-1-yl)]-3-(4-nitrophenyl)-1,2-oxazole · HCl/$HClO_4$ (4a) and 3-[(3-Methylamino)prop-1-yl)]-5-(4-nitrophenyl)-1,2-oxazole · HCl/$HClO_4$ (6a) (85/15, according to elemental analysis); from (**2a**);

procedure A; 69%; mp 215-216 °C (H_2O); ratio **4a/6a** = 72 28; ms [m/z, rel intensity (%)]· 261 (M^+ -HX, 2); 44 (100); ^{1}H-nmr, **4a (6a)**: 2.08 (q, 2H, J = 7 Hz, β-CH_2), 2 52 (s, 3H, CH_3), 2.97 (2.81) (m, 4H, α, γ-CH_2), 7.10 (7.28) (s, 1H, CH_{oxaz}), 8.10 (d, 2H, J = 7 Hz, CH_{arom}), 8.31 (8.32) (d, 2H, J = 7 Hz, CH_{arom}), 9.34 (s, 1H, NH); ^{13}C-nmr: 23.1 (22.7) (CH_2), 23.3 (23 7) (CH_2), 32.1, 47.2 (47.4) (CH_2), 100 2 (103.2)(CH_{oxaz}), 124.2 (124.4) (CH_{arom}), 127.8 (126.7) (CH_{arom}), 134.7 (132.3) (C_{arom}), 148.2 (147 9) (C_{arom}), 160.4 (166.6) (C-3_{oxaz}), 173.2 (163 8) (C-5_{oxaz}).

3-(4-Chlorophenyl)-5-(3-methylaminoprop-1-yl)-1,2-oxazole · HCl (4b) and 5-(4-Chlorophenyl)-3-(3-methylaminoprop-1-yl)-1,2-oxazole · HCl (6b); from (**2b**),

procedure B; 67%; mp 109-111 °C (acetic acid/ether); ratio **4b/6b** = 83 : 17; ms [m/z, rel. intensity (%)]. 250 (M^+ -HCl, 0.5); 44

(100); ^{1}H-nmr, 4b (6b). 2.03 (q, 2H, J = 7 Hz, β-CH_2), 2.61 (s, 3H, CH_3), 2 95 (m, 4H, α, γ-CH_2), 6.93 (7.02) (s, 1H, CH_{oxaz}), 7 62 (d, 2H, J = 7 Hz, CH_{arom}), 7.93 (d, 2H, J = 7 Hz, CH_{arom}), 8.90 (sb, 1H, NH); ^{13}C-nmr: 23.3 (22.7) (CH_2), 23.3 (23.8) (CH_2), 32.4, 47.5 (47 7) (CH_2), 99.8 (100.8) (CH_{oxaz}), 127.7 (C_{arom}), 128.3 (127.3) (CH_{arom}), 129.2 (129.4) (CH_{arom}), 134.8 (135.0) (C_{arom}), 161 0 (163.0) (C-3_{oxaz}), 173.0 (167.8) (C-5_{oxaz}); Anal. Calcd for $C_{13}H_{16}N_2OCl_2$: C, 54.36; H, 5.63; N, 9.76. Found: C, 54.22; H, 5.70; N, 9.55.

1-Chloro-1-(4-chlorophenyl)-8-methylaminooct-1-en-3-one Oxime · $HClO_4$ (7a); from (**2c**);

procedure A; 88%; mp 149-150 °C (H_2O); ms [m/z, rel. intensity (%)]. 248 (M^+ -$HClO_4$-HCl-30, 0.2); 44 (100); ^{1}H-nmr: 1.44 (m, 6H, 5-,6-,7-CH_2), 2 54 (s, 3H, CH_3), 2.55 (m, 2H, 4-CH_2), 2 86 (t, 2H, J = 7 Hz, 8-CH_2), 6.89 (s, 1H, CH), 7 52 (d, 2H, J = 7 Hz, CH_{arom}), 7 77 (d, 2H, J = 7 Hz, CH_{arom}), ^{13}C-nmr: 25.1 (CH_2), 25 1 (CH_2), 26.0 (CH_2), 26.2 (CH_2), 32.5 (CH_3), 48.2 (CH_2), 124.2 (2-CH), 128.2 (CH_{arom}), 128.6 (CH_{arom}), 130.7 (C_{arom}), 133.9 (C_{arom}), 136 6 (C-Cl), 155.6 (C=N); Anal. Calcd for $C_{15}H_{21}N_2O_5Cl_3$: C, 43.33; H, 5.10; N, 6.74. Found: C, 43.30; H, 5.09; N, 7.04

1-Chloro-1-(4-bromophenyl)-8-methylaminooct-1-en-3-one Oxime · $HClO_4$ (7b), from (**2d**);

procedure A; 75%; mp 149-156 °C (acetic acid/Et_2O); ms [m/z, rel. intensity (%)]: 323 (M^+ -$HClO_4$-HCl, 1.4); 44 (100); ^{1}H-nmr: 1.44 (m, 6H, 5-,6-,7-CH_2), 2.52 (s, 3H, CH_3), 2.70 (m, 4H, 4-,8-CH_2), 6.89 (s, 1H, CH), 7.70 (s, 4H, CH_{arom}); ^{13}C-nmr: 25.3 (CH_2), 25.3 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 32.7 (CH_3), 48.5 (CH_2), 122 7 (C_{arom}), 124.4 (2-CH), 128.7 (CH_{arom}), 131.1 (C_{arom}), 131.7 (CH_{arom}), 137.2 (C-Cl), 155.7 (C=N); Anal. Calcd for $C_{15}H_{21}N_2O_5BrCl_2$: C, 39.15; H, 4.61; N, 6.09. Found: C, 38 93; H, 4.78; N, 6.09

5-Thienoyl-3-[(3-methylamino)prop-1-yl)]-1,2-oxazole · $HClO_4$ (10), from **2e/8**;

procedure A; 28% (95% with respect to the ratio **2e/8**); mp 205-206 °C (acetic acid); ms [m/z, rel. intensity (%)]: 250 (M^+ - $HClO_4$, 0 5); 44 (100); ^{1}H-nmr. 2.00 (q, 2H, J = 7 Hz, β-CH_2), 2.53 (s, 3H, CH_3), 3.00 (m, 4H, α, γ-CH_2), 7.37 (dd, 1H, J = 7, J' = 5, C-$4_{thienyl}$), 8.15 (m, 2H, C-3,$5_{thienyl}$), 9.84 (s, 1H, CH_{oxaz}); ^{13}C-nmr 22 6 (CH_2), 23 3 (CH_2), 32.7 (CH_3), 48.0 (CH_2), 117.8 ($C_{thienyl}$), 129.2 ($CH_{thienyl}$) , 134.5 ($CH_{thienyl}$), 136.1 ($CH_{thienyl}$), 143.7 (C-4_{oxaz}), 161.3 (C-3_{oxaz}), 163.8 (CH_{oxaz}), 178.8 (C=O); Anal Calcd for $C_{12}H_{15}N_2O_6ClS$· C, 41.08; H, 4.32; N, 7.99. Found. C, 40.99; H, 4.50; N, 8.37.

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9. Full details of the structure determinations have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2, Federal Republic of Germany Any request for this material should quote a full literature citation and the reference number CSD-400506

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