

**RING-CHAIN TRANSFORMATIONS OF SEMICYCLIC 3-CHLORO-PROPENIMINIUM SALTS TO  $\omega$ -AMINOALKYL-1,2-OXAZOLES USING HYDROXYLAMINE<sup>1</sup>**

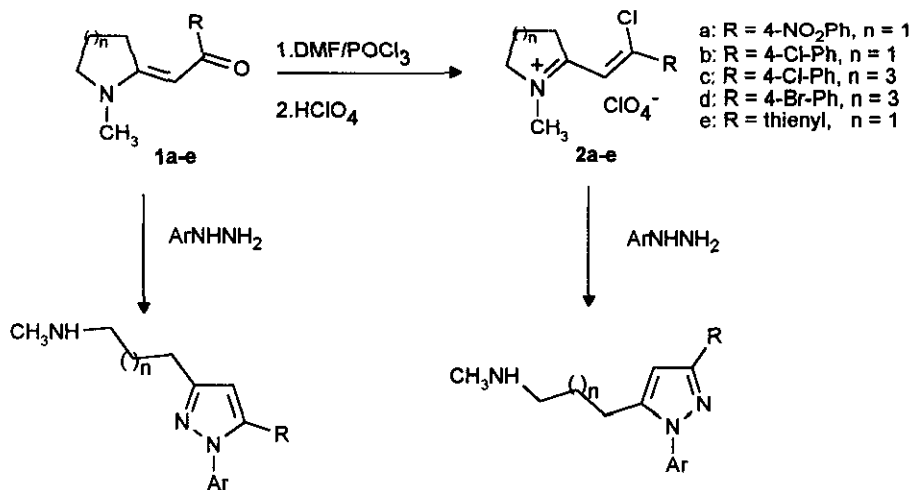
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**Abstract**—Semicyclic 3-chloropropeniminium salts (**2**) or (**8**) react with hydroxylamine giving either  $\omega$ -aminoalkyl-1,2-oxazoles (**4**, **6**, **10**) by ring chain transformation or chlorovinylloximes (**7**) by ring opening.

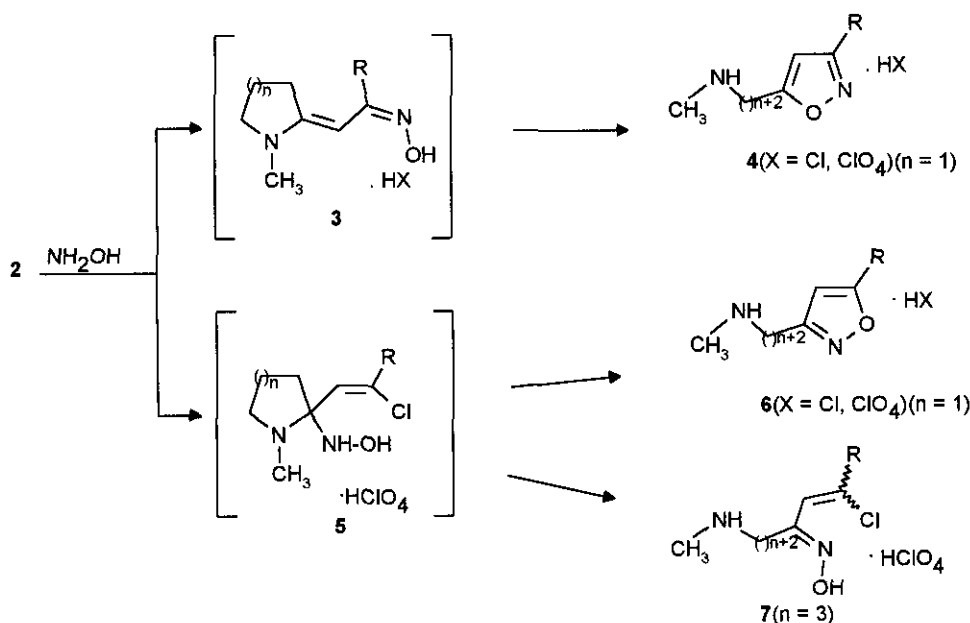
Semicyclic 3-chloropropeniminium salts (**2**) and their precursors (**1**) are 1,3-bielectrophiles reacting with hydrazines to give  $\omega$ -aminoalkylpyrazoles by ring-chain transformation.<sup>2-4</sup> Since the regioselectivity in reactions with arylhydrazines is different, it



was possible to synthesize either the 1-aryl-3-( $\omega$ -aminoalkyl)pyrazoles or the 5-( $\omega$ -aminoalkyl) isomers if either enaminones (**1**) or 3-chloropropeniminium salts (**2**) were used.<sup>3</sup>

Enaminones (1) are known to react with hydroxylamine analogously giving 3- or 5-( $\omega$ -aminoalkyl)-1,2-oxazoles.<sup>5</sup> 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  $\omega$ -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  $\beta$ -chlorovinylloximes (7), which resist further cyclisation. A similar situation was found in the reaction of open chain 3-chloropropeniminium salts with hydroxylamine.<sup>6</sup> 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-( $\omega$ -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)

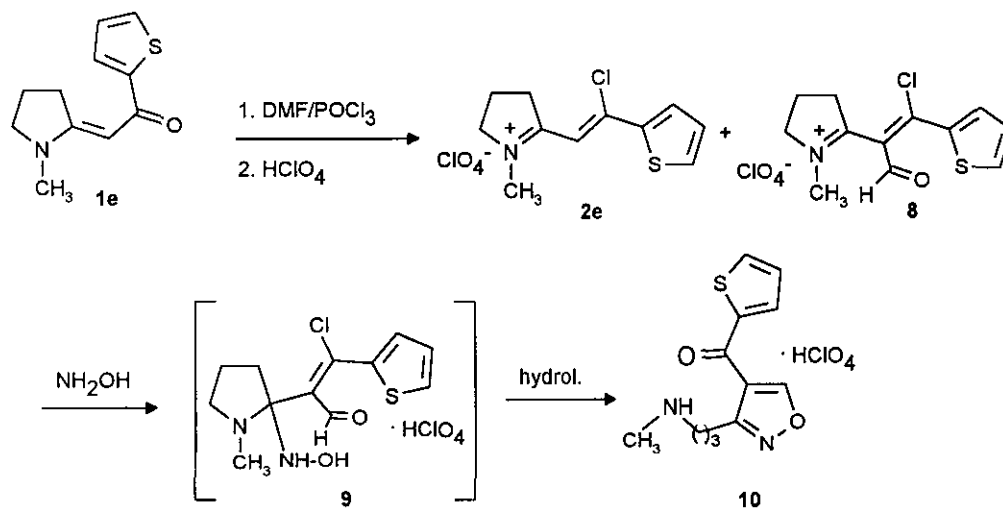


The isomeric 3-methylaminopropyl-1,2-oxazoles (4) and (6) can be distinguished by <sup>13</sup>C-nmr and by mass spectroscopy;<sup>7</sup> thus the 5-aryl-3-(3-methylaminopropyl)-1,2-oxazoles (6), unlike the major isomers (4), exhibit an intense peak of RCO<sup>+</sup> in the ms. The major isomer (4) gives rise to <sup>13</sup>C-nmr shifts at  $\delta = 161$  ppm (C-3) and  $\delta = 173$  ppm (C-5) while the corresponding signals of the

5-aryl-3-(3-methylaminopropyl)-1,2-oxazoles (**6**) are found at  $\delta = 163$  ppm and  $\delta = 165$  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<sub>3</sub>.

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.<sup>8</sup>) and the low electrophilicity disfavoring 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  $\omega$ -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)<sup>9</sup> The N and O atoms of the heterocycle were successfully

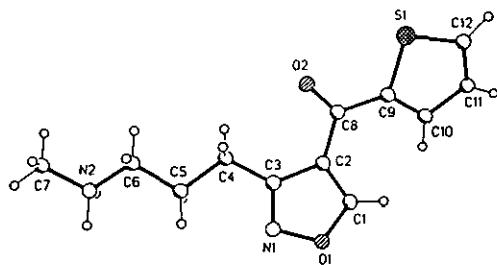


Figure 1 X-ray crystal structure of compound (**10**)

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  $\pi$ -systems and the alkylammonium moieties form a separate layer.

Our results thus demonstrate that 3-chloropropeniminium salts are less suitable than semicyclic enamminones in the regioselective synthesis of  $\omega$ -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<sup>3</sup>

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

Procedure A: 10 ml of 1 M freshly prepared methanolic  $\text{NH}_2\text{OH}$  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  $\text{NH}_2\text{OH} \cdot \text{HCl}$  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  $\text{CH}_2\text{Cl}_2$  and then three times with 30 ml of  $\text{Et}_2\text{O}$ . After evaporation of the solvents 10 ml of ethanol were added and with  $\text{Et}_2\text{O}$  (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  $\cdot$  HCl/HClO<sub>4</sub> (4a) and 3-[(3-Methylamino)prop-1-yl]-5-(4-nitrophenyl)-1,2-oxazole  $\cdot$  HCl/HClO<sub>4</sub> (6a)** (85/15, according to elemental analysis); from (2a);

procedure A; 69%; mp 215-216 °C ( $\text{H}_2\text{O}$ ); ratio 4a/6a = 72 : 28; ms [m/z, rel. intensity (%)] 261 ( $\text{M}^+ - \text{HX}$ , 2); 44 (100); <sup>1</sup>H-nmr, 4a (6a): 2.08 (q, 2H, J = 7 Hz,  $\beta$ -CH<sub>2</sub>), 2.52 (s, 3H, CH<sub>3</sub>), 2.97 (2.81) (m, 4H,  $\alpha$ ,  $\gamma$ -CH<sub>2</sub>), 7.10 (7.28) (s, 1H, CH<sub>oxaz</sub>), 8.10 (d, 2H, J = 7 Hz, CH<sub>arom</sub>), 8.31 (8.32) (d, 2H, J = 7 Hz, CH<sub>arom</sub>), 9.34 (s, 1H, NH); <sup>13</sup>C-nmr: 23.1 (22.7) (CH<sub>2</sub>), 23.3 (23.7) (CH<sub>2</sub>), 32.1, 47.2 (47.4) (CH<sub>2</sub>), 100.2 (103.2) (CH<sub>oxaz</sub>), 124.2 (124.4) (CH<sub>arom</sub>), 127.8 (126.7) (CH<sub>arom</sub>), 134.7 (132.3) (C<sub>arom</sub>), 148.2 (147.9) (C<sub>arom</sub>), 160.4 (166.6) (C-3<sub>oxaz</sub>), 173.2 (163.8) (C-5<sub>oxaz</sub>).

**3-(4-Chlorophenyl)-5-(3-methylaminoprop-1-yl)-1,2-oxazole  $\cdot$  HCl (4b) and 5-(4-Chlorophenyl)-3-(3-methylaminoprop-1-yl)-1,2-oxazole  $\cdot$  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 ( $\text{M}^+ - \text{HCl}$ , 0.5); 44

(100);  $^1\text{H-nmr}$ , 4b (6b). 2.03 (q, 2H,  $J = 7$  Hz,  $\beta\text{-CH}_2$ ), 2.61 (s, 3H,  $\text{CH}_3$ ), 2.95 (m, 4H,  $\alpha$ ,  $\gamma\text{-CH}_2$ ), 6.93 (7.02) (s, 1H,  $\text{CH}_{\text{oxaz}}$ ), 7.62 (d, 2H,  $J = 7$  Hz,  $\text{CH}_{\text{arom}}$ ), 7.93 (d, 2H,  $J = 7$  Hz,  $\text{CH}_{\text{arom}}$ ), 8.90 (sb, 1H, NH);  $^{13}\text{C-nmr}$ : 23.3 (22.7) ( $\text{CH}_2$ ), 23.3 (23.8) ( $\text{CH}_2$ ), 32.4, 47.5 (47.7) ( $\text{CH}_2$ ), 99.8 (100.8) ( $\text{CH}_{\text{oxaz}}$ ), 127.7 ( $\text{C}_{\text{arom}}$ ), 128.3 (127.3) ( $\text{CH}_{\text{arom}}$ ), 129.2 (129.4) ( $\text{CH}_{\text{arom}}$ ), 134.8 (135.0) ( $\text{C}_{\text{arom}}$ ), 161.0 (163.0) ( $\text{C-3}_{\text{oxaz}}$ ), 173.0 (167.8) ( $\text{C-5}_{\text{oxaz}}$ ); Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{OCl}_2$ : 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-methylaminoct-1-en-3-one Oxime  $\cdot$   $\text{HClO}_4$  (7a):** from (2c);

procedure A; 88%; mp 149-150  $^\circ\text{C}$  ( $\text{H}_2\text{O}$ ); ms [m/z, rel. intensity (%)]. 248 ( $\text{M}^+ - \text{HClO}_4 - \text{HCl} - 30$ , 0.2); 44 (100);  $^1\text{H-nmr}$ : 1.44 (m, 6H, 5-,6-,7- $\text{CH}_2$ ), 2.54 (s, 3H,  $\text{CH}_3$ ), 2.55 (m, 2H, 4- $\text{CH}_2$ ), 2.86 (t, 2H,  $J = 7$  Hz, 8- $\text{CH}_2$ ), 6.89 (s, 1H, CH), 7.52 (d, 2H,  $J = 7$  Hz,  $\text{CH}_{\text{arom}}$ ), 7.77 (d, 2H,  $J = 7$  Hz,  $\text{CH}_{\text{arom}}$ );  $^{13}\text{C-nmr}$ : 25.1 ( $\text{CH}_2$ ), 25.1 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 26.2 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_3$ ), 48.2 ( $\text{CH}_2$ ), 124.2 (2-CH), 128.2 ( $\text{CH}_{\text{arom}}$ ), 128.6 ( $\text{CH}_{\text{arom}}$ ), 130.7 ( $\text{C}_{\text{arom}}$ ), 133.9 ( $\text{C}_{\text{arom}}$ ), 136.6 (C-Cl), 155.6 (C=N); Anal. Calcd for  $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_5\text{Cl}_3$ : 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-methylaminoct-1-en-3-one Oxime  $\cdot$   $\text{HClO}_4$  (7b):** from (2d);

procedure A; 75%; mp 149-156  $^\circ\text{C}$  (acetic acid/ $\text{Et}_2\text{O}$ ); ms [m/z, rel. intensity (%)]: 323 ( $\text{M}^+ - \text{HClO}_4 - \text{HCl}$ , 1.4); 44 (100);  $^1\text{H-nmr}$ : 1.44 (m, 6H, 5-,6-,7- $\text{CH}_2$ ), 2.52 (s, 3H,  $\text{CH}_3$ ), 2.70 (m, 4H, 4-,8- $\text{CH}_2$ ), 6.89 (s, 1H, CH), 7.70 (s, 4H,  $\text{CH}_{\text{arom}}$ );  $^{13}\text{C-nmr}$ : 25.3 ( $\text{CH}_2$ ), 25.3 ( $\text{CH}_2$ ), 26.2 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ), 32.7 ( $\text{CH}_3$ ), 48.5 ( $\text{CH}_2$ ), 122.7 ( $\text{C}_{\text{arom}}$ ), 124.4 (2-CH), 128.7 ( $\text{CH}_{\text{arom}}$ ), 131.1 ( $\text{C}_{\text{arom}}$ ), 131.7 ( $\text{CH}_{\text{arom}}$ ), 137.2 (C-Cl), 155.7 (C=N); Anal. Calcd for  $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_5\text{BrCl}_2$ : 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  $\cdot$   $\text{HClO}_4$  (10):** from 2e/8;

procedure A; 28% (95% with respect to the ratio 2e/8); mp 205-206  $^\circ\text{C}$  (acetic acid); ms [m/z, rel. intensity (%)]: 250 ( $\text{M}^+ - \text{HClO}_4$ , 0.5); 44 (100);  $^1\text{H-nmr}$ : 2.00 (q, 2H,  $J = 7$  Hz,  $\beta\text{-CH}_2$ ), 2.53 (s, 3H,  $\text{CH}_3$ ), 3.00 (m, 4H,  $\alpha$ ,  $\gamma\text{-CH}_2$ ), 7.37 (dd, 1H,  $J = 7$ ,  $J = 5$ , C-4 $_{\text{thienyl}}$ ), 8.15 (m, 2H, C-3,5 $_{\text{thienyl}}$ ), 9.84 (s, 1H,  $\text{CH}_{\text{oxaz}}$ );  $^{13}\text{C-nmr}$ : 22.6 ( $\text{CH}_2$ ), 23.3 ( $\text{CH}_2$ ), 32.7 ( $\text{CH}_3$ ), 48.0 ( $\text{CH}_2$ ), 117.8 ( $\text{C}_{\text{thienyl}}$ ), 129.2 ( $\text{CH}_{\text{thienyl}}$ ), 134.5 ( $\text{CH}_{\text{thienyl}}$ ), 136.1 ( $\text{CH}_{\text{thienyl}}$ ), 143.7 (C-4 $_{\text{oxaz}}$ ), 161.3 (C-3 $_{\text{oxaz}}$ ), 163.8 ( $\text{CH}_{\text{oxaz}}$ ), 178.8 (C=O); Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_6\text{ClS}$ : 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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