RING-CHAIN TRANSFORMATIONS OF SEMICYCLIC 3-CHLOROPROPENIMINIUM SALTS TO \( \omega \)-AMINOALKYL-1,2-OXAZOLES USING HYDROXYLAMINE\(^1\)

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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.\(^2\)-\(^4\) 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 enamiones (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. 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 β-chlorovinyl oximes (7), which resist further cyclisation. A similar situation was found in the reaction of open chain 3-chloropropeniminium salts with hydroxylamine. 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).

![Chemical Structures](attachment:image.png)

The isomeric 3-methylaminopropyl-1,2-oxazoles (4) and (6) can be distinguished by $^{13}$C-nmr and by mass spectroscopy; thus the 5-aryl-3-(3-methylaminopropyl)-1,2-oxazoles (6), unlike the major isomers (4), exhibit an intense peak of $\textit{RCO}^+$ in the ms. The major isomer (4) gives rise to $^{13}$C-nmr shifts at $\delta = 161$ ppm (C-3) and $\delta = 173$ ppm (C-5) while the corresponding signals of the
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/POCl₃.

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 enaminoles 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 α-aminoalkyl-1,2-oxazole; however 8 does not react as a 3-chloropropeniminium salt but as a semicyclic enaminole. 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)](image-url)
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 enaminones in the regioselective synthesis of \( \alpha \)-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 \( \text{NH}_2\text{OH} \) 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 \( \cdot \text{HCl/\text{HClO}_4} \) (4a) and 3-[(3-Methylamino)prop-1-yl]-5-(4-nitrophenyl)-1,2-oxazole \( \cdot \text{HCl/\text{HClO}_4} \) (6a) (85/15, according to elemental analysis); from (2a);

procedure A; 69%, mp 215-216 °C (H\( _2\text{O} \)); ratio 4a/6a = 72 28; ms [m/z, rel. intensity (%)]: 261 (M\(^+\) -HX, 2); 44 (100); \( ^1\text{H-nmr, 4a (6a):} \) 2.08 (q, 2H, \( J = 7 \text{ Hz}, \beta-\text{CH}_2 \)), 2.52 (s, 3H, CH\(_3\)), 2.97 (2.81) (m, 4H, \( \gamma-\text{CH}_2 \)), 7.10 (7.28) (s, 1H, CH\(_{\text{oxaz}}\)), 8.10 (d, 2H, \( J = 7 \text{ Hz}, \text{CH}_{\text{arom}} \)), 8.31 (8.32) (d, 2H, \( J = 7 \text{ Hz}, \text{CH}_{\text{arom}} \)), 9.34 (s, 1H, NH); \( ^{13}\text{C-nmr:} \) 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\(_{\text{oxaz}}\)), 124.2 (124.4) (CH\(_{\text{arom}}\)), 127.8 (126.7) (CH\(_{\text{arom}}\)), 134.7 (132.3) (C\(_{\text{arom}}\)), 148.2 (147 9) (C\(_{\text{arom}}\)), 160.4 (166.6) (C-3\(_{\text{oxaz}}\)), 173.2 (163 8) (C-5\(_{\text{oxaz}}\)).

3-(4-Chlorophenyl)-5-(3-methylaminoprop-1-yl)-1,2-oxazole \( \cdot \text{HCl} \) (4b) and 5-(4-Chlorophenyl)-3-(3-methylaminoprop-1-yl)-1,2-oxazole \( \cdot \text{HCl} \) (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
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(100); 1H-nmr, 4b (6b). 2.03 (q, 2H, J = 7 Hz, β-CH₂), 2.61 (s, 3H, CH₃), 2.95 (m, 4H, α, γ-CH₂), 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 (6b, 1H, NH); 13C-nmr: 23.3 (22.7) (CH₂), 23.3 (23.8) (CH₂), 32.4, 47.5 (47 7) (CH₂), 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 C₁₃H₁₆N₂OCl₂: 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-methylenaminooct-1-en-3-one Oxime·HClO₄ (7a): from (2e):

procedure A; 88%; mp 149-150 °C (H₂O); ms [m/z, rel. intensity (%)]: 248 (M⁺-HClO₄-HCl-30, 0.2); 44 (100); 1H-nmr: 1.44 (m, 6H, 5-,6-,7-CH₂), 2.54 (s, 3H, CH₃), 2.70 (m, 4H, 4-,8-CH₂), 6.89 (s, 1H, CH), 7.52 (d, 2H, J = 7 Hz, CH arom), 7.77 (d, 2H, J = 7 Hz, CH arom), 13C-nmr: 25.1 (CH₂), 26.0 (CH₂), 26.2 (CH₂), 32.5 (CH₃), 48.2 (CH₂), 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=O); Anal. Calcd for C₁₅H₁₄N₂O₃Cl₃: 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-methylenaminooct-1-en-3-one Oxime·HClO₄ (7b): from (2d):

procedure A; 75%; mp 149-156 °C (acetic acid/Et₂O); ms [m/z, rel. intensity (%)]: 323 (M⁺-HClO₄-HCl, 1.4); 44 (100); 1H-nmr: 1.44 (m, 6H, 5-,6-,7-CH₂), 2.52 (s, 3H, CH₃), 2.70 (m, 4H, 4-,8-CH₂), 6.89 (s, 1H, CH), 7.70 (s, 4H, CH₂), 13C-nmr: 25.3 (CH₂), 26.2 (CH₂), 26.4 (CH₂), 32.7 (CH₃), 48.5 (CH₂), 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=O); Anal. Calcd for C₁₅H₁₂Br₂O₃Cl₂: C, 5.09; N, 7.04.

5-Thienoyl-3-[(3-methylamino)prop-1-yl]-2-oxazole·HClO₄ (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⁺-HClO₄, 0 5); 44 (100); 1H-nmr: 2.00 (q, 2H, J = 7 Hz, β-CH₂), 2.53 (s, 3H, CH₃), 3.00 (m, 4H, α, γ-CH₂), 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); 13C-nmr: 22 6 (CH₂), 23 3 (CH₂), 32.7 (CH₃), 48.0 (CH₂), 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 C₁₉H₁₄N₂O₆ClS: C, 41.08; H, 4.32; N, 7.99. Found: C, 40.99; H, 4.50; N, 8.37.

ACKNOWLEDGEMENT

We thank the Fonds der Chemischen Industrie for financial support.
REFERENCES


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.

Received, 11th January, 1994