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Kinetics and mechanism of methanolysis and cyclization of 1-acyl-3-(2-halo-5-nitrophenyl)thioureas

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ABSTRACT: The kinetics of methoxide ion-catalysed solvolysis of 1-acyl-3-(2-halo-5-nitrophenyl)thioureas and cyclization of fluoro derivatives were studied in methanol at 25 °C. The cyclization involved the substitution of fluorine by sulphur anion of thiourea and proceeded in two steps. With the acetyl derivative, the first step is methanolysis and the second step is much slower cyclization of the 2-fluoro-5-nitrophenylthiourea anion formed to give 2-amino-5-nitro-1,3-benzothiazole. With the benzoyl derivative, the first step involves parallel methanolysis of the benzoyl group and cyclization to 2-benzoylamino-5-nitro-1,3-benzothiazole. At concentrations of sodium methoxide higher than ca 0.01 mol l^{-1} the rates of solvolyses of all the acyl halothioureas decreased and at concentrations higher than ca 0.4 mol l^{-1} there was an increase in the formation of other product(s) than the product of cyclization. After the addition of 18-crown-6, the side products were not formed and the cyclizations of fluoro derivatives were considerably accelerated. The slowing of the solvolytic reaction and acceleration of the cyclization reaction are most probably due to the formation of dianions. Copyright © 2001 John Wiley & Sons, Ltd.

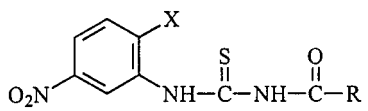
KEYWORDS: reaction kinetics; cyclization; benzothiazoles; acylthioureas; dissociation constants

INTRODUCTION

Phenylthioureas are suitable starting substrates for the preparation of 2-amino-1,3-benzothiazole derivatives. The presence of an oxidation agent, which oxidizes the leaving hydride anion to the proton, leads to ring closure. The most frequent oxidizing agents involve bromine in chloroform[1] or in acetic acid.[2] The reaction is not regioselective, and the cyclizations of 3-substituted phenylthioureas usually give mixtures of 5- and 7-substituted 2-amino-1,3-benzothiazoles.[2] Therefore, we have suggested the regioselective (S_NAr_i) cyclizations of 1-acyl-3-(2-halo-5-nitrophenyl)thioureas (**1a–d**), the mechanism of which we studied in some detail in the present work.

In earlier papers we described the kinetics and reaction mechanisms of intramolecular base-catalysed reactions[3–5] of ureas, thioureas and their benzoyl derivatives with an ester group in water and methanol. In all these cases the nitrogen atom reacted with the carbon atom of the carboxylic group. The benzoyl group was split off either during the cyclization or in the subsequent slower step.

The aim of this work was to study the kinetics and mechanism of methoxide-catalysed methanolysis and intramolecular nucleophilic aromatic substitution of fluorine in 1-acetyl-3-(2-fluoro-5-nitrophenyl)thiourea (**1a**) and substitution of fluorine in 1-benzoyl-3-(2-fluoro-5-nitrophenyl)thiourea (**1b**) complemented by the reactions of analogous chloro derivatives, 1-acetyl-3-(2-chloro-5-nitrophenyl)thiourea (**1c**) and 1-benzoyl-3-(2-chloro-5-nitrophenyl)thiourea (**1d**), with methoxide.



1	a	b	c	d
X	F	F	Cl	Cl
R	Me	Ph	Me	Ph

EXPERIMENTAL

The 1-acyl-3-(2-halo-5-nitrophenyl)thioureas (**1a–d**) were prepared by reactions of 2-fluoro- or 2-chloro-5-nitroaniline with acetyl or benzoyl isothiocyanate. The starting anilines were prepared by known methods.[6]

General procedure: 1-acyl-3-(2-halo-5-nitrophenyl)-thioureas (**1a–d**). A 100 ml flask was charged with

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40 mmol of 2-halo-5-nitroaniline and 20 ml of dry acetone. After dissolution, the mixture was treated with a solution of 45 mmol of acyl isothiocyanate[7] in 30 ml of acetone added in one portion. The reaction mixture was refluxed on a water-bath for 6 h (**1a, c**) and then cooled and left to stand at room temperature 2 h (**1b, d**). The separated crystalline solid was collected by filtration and recrystallized from a suitable solvent.

*1-Acetyl-3-(2-fluoro-5-nitrophenyl)thiourea (**1a**).* The yield after recrystallization from acetone was 4.9 g (48%) of white crystals with m.p. 173–175 °C (with decomposition). TLC [Silufol plates/$CHCl_3$-EtOAc (1:1)]: $R_F = 0.61$. ^{1}H NMR (δ): 2.24 (s, 3H, CH_3); 8.77 (bs, 1H, NH); 12.7 (bs, 1H, NH); 7.31 (m, 1H, H3); 8.14 (m, 1H, H4); 9.54 (m, 1H, H6).^{13}C NMR (δ): 24.2 (CH_3); 173.9 (C═O); 180.8 (C═S); 128.5 (C–NH); 159.3 (d, $J = 257$ Hz, C–F); 117.3 (d, $J = 22.6$ Hz, C3); 121.5 (d, 2.6, C4); 146.1 (d, $J = 254$ Hz, C–NO_2); 123.5 (d, $J = 10$, Hz, C6). MS (*m/z*,%): $[M + H + CH_3CN - HF]^+$ 279, 22.7; $[M + H]^+$ 258, 0.01; $[M + H + CH_3CN - HF - NO]^+$ 249, 38.7; $[M + H - HF]^+$ 238, 100; $[M + H - HF - NO]^+$ 208, 80.0. **Elemental analysis (% calculated/% found):** C 42.02/41.95; H 3.13/3.10; N 16.34/16.22; S 12.46/12.53.

*1-Benzoyl-3-(2-fluoro-5-nitrophenyl)thiourea (**1b**).* The yield after recrystallization from toluene was 10.2 g (80%) of yellowish needles with m.p. 199–200 °C. TLC (Silufol plates/$CHCl_3$): $R_F = 0.47$. ^{1}H NMR (δ): 7.92 (m, 2H, H-*o*); 7.56 (m, 2H, H-*m*); 7.68(m, 1H, H-*p*); 9.22 (bs, 1H, NH); 13.04 (bs, 1H, NH); 7.34 (m, 1H, H3); 8.16 (m, 1H, H4); 9.66 (m, 1H, H6). ^{13}C NMR (δ): 131.9 (C-*i*); 129.0 (C-*o*); 128.6 (C-*m*); 133.5 (C-*p*); 168.8 (C═O); 180.4 (C═S); 127.5 (d, $J = 13$ Hz, C–NH); 158.9 (d, $J = 257$ Hz, C–F); 117.0 (d, $J = 22.6$ Hz, C3); 121.8 (d, $J = 2.5$ Hz, C4); 144.9 (d, $J = 268$ Hz, C–NO_2); 123.5 (d, $J = 10.1$ Hz, C6). **Elemental analysis (% calculated/% found):** C 52.66/52.62; H 3.16/3.20; N 13.16/13.21; S 10.04/10.15.

*1-Acetyl-3-(2-chloro-5-nitrophenyl)thiourea (**1c**).* The yield after recrystallization from toluene was 5.5 g (50%) of white crystals with m.p. 194–195 °C. TLC [Silufol plates/ $CHCl_3$-EtOAc(1:1)]: $R_F = 0.49$. ^{1}H NMR (δ): 2.24 (s, 3H, CH_3); 11.90 (bs, 1H, NH); 12.87 (bs, 1H, NH); 7.91 (d, $J = 8.87$ Hz, 1H, H3); 8.16 (dd, $J = 8.87$, 2.73 Hz, 1H, H4); 9.21 (d, $J = 2.51$ Hz, 1H, H6). ^{13}C NMR (δ): 23.9 (CH_3); 173.1 (C═O); 179.9 (C═S); 136.4 (C–NH); 134.5 (C–Cl); 130.7 (C3); 122.1 (C4); 145.8 (C–NO_2); 121.4 (C6). **Elemental analysis (% calculated/% found):** C 39.50/39.60; H 2.95/2.91; Cl 12.95/13.02; N 15.35/15.20; S 11.71/11.80.

*1-Benzoyl-3-(2-chloro-5-nitrophenyl)thiourea (**1d**).* The yield after recrystallization from toluene was 10.8 g (80%) of yellowish needles with m.p. 203–204 °C. TLC [Silufol plates/$CHCl_3$–EtOAc(1:1)]: $R_F = 0.62$. ^{1}H NMR (δ): 8.06 (d, $J = 7.27$ Hz, 2H, H-*o*); 7.61 (t, $J = 7.66$ Hz, 2H, H-*m*); 7.73 (t, $J = 7.32$, 1H, H-*p*); 12.15 (bs, 1H, NH); 12.97 (bs, 1H, NH); 7.96 (d, $J = 8.87$ Hz, 1H, H3); 8.22 (dd, $J = 8.84$, 2.63 Hz, 1H, H4); 9.18 (d, $J = 2.25$ Hz, 1H, H6). ^{13}C NMR (δ): 131.8 (C-*i*); 128.5 (C-*o*); 128.9 (C-*m*); 133.4 (C-*p*); 168.7 (C═O); 180.4 (C═S); 136.7 (C–NH); 135.0 (C–Cl); 130.8 (C3); 122.2 (C4); 145.9 (C–NO_2); 121.9 (C6). **Elemental analysis (% calculated/% found):** C 50.74/50.81; H 3.28/3.21; Cl 11.52/11.63; N 13.65/13.72; S 10.42/10.35.

*2-Fluoro-5-nitrophenylthiourea (**2a**).* MS (*m/z*,%): $[M + H + CH_3CN]^+$ 256.6, 6.9; $[M + H + CH_3CN - HF]^+$ 236.6, 22.8; $[M+H]^+$ 215.5, 49.4; $[M + H - HF]^+$ 195.4, 100; $[M + H - HF - NO]^+$ 165.4, 41.1; $[M + H - HF - NO_2]^+$ 149.4, 7.0.

*2-Chloro-5-nitrophenylthiourea (**2b**).* A 100 ml Erlenmeyer flask was charged with 1 g (3 mmol) of **1d** together with 60 ml of 0.1 mol l^{-1} sodium methoxide solution. The yellow-orange solution formed was left to stand at room temperature overnight, then neutralized with methanolic hydrogen chloride to pH ≈ 7. The resulting yellow solution was treated with 10 ml of water and the mixture was concentrated to 20 ml by vacuum distillation. The separated yellow crystalline solid was collected by filtration. After recrystallization from water–acetone (2:1), the yield was 0.35 g (45%) of crystals with m.p. 167–168 °C. ^{1}H NMR (δ): 9.68 (bs, 1H, NH); 7.73 and 8.35 (2×bs, 2H, NH_2); 7.84 (d, $J = 8.87$ Hz, 1H, H3); 8.07 (dd, $J = 8.87$, 2.76 Hz, 1H, H4); 8.86 (d, $J = 2.52$ Hz, 1H, H6). ^{13}C NMR (δ): 182.2 (C═S); 138.7 (C–NH); 134.8 (C–Cl); 130.5 (C3); 122.7 (C4); 145.8 (C–NO_2); 120.7 (C6). **Elemental analysis (% calculated/% found):** C 36.29/36.24; H 2.61/2.55; Cl 15.30/15.38; N 18.14/18.21; S 13.84/13.87.

General procedure: 2-acylamino-5-nitro-1,3-benzothiazoles (**3a** and **b**). A 100 ml Erlenmeyer flask was charged with 0.5 g (1.94 mmol) of **1a** or **1b** and 30 ml of *tert*-butyl alcohol. After dissolution of the starting compound, the mixture was heated at 30–40 °C, whereupon 30 ml of 0.1 mol l^{-1} potassium *tert*-butoxide were added within several seconds. The mixture was stirred for another 5 min and then neutralized with acetic acid to pH ≈ 7. The solid substance was collected by filtration on a pre-heated sintered-glass filter and washed with 15 ml of methanol.

*2-Acetylamino-5-nitro-1,3-benzothiazole (**3a**).* Yield 0.37 g (80%). ^{1}H NMR (δ): 2.24 (s, 3H, CH_3); 8.47 (d, $J = 2.09$ Hz, 1H, H4); 8.12 (dd, $J = 8.69$, 2.23 Hz, 1H, H6); 8.23 (d, $J = 8.71$ Hz, 1H, H7). ^{13}C NMR (δ): 23.6 (CH_3); 171.5 (C═O); 163.0 (C2); 149.2 (C3a); 122.6 (C4); 146.2 (C–NO_2); 114.4 (C6); 117.1 (C7); 139.1 (C7a). MS(*m/z*,%): $[M + H + CH_3CN]^+$ 279, 22.6;

$[M + H + CH_3CN - NO]^+$ 249, 27.3; $[M + H]^+$ 238, 100; $[M + H - NO]^+$ 208, 55.3; 196, 17.6; 166, 21.3. **Elemental analysis (% calculated/% found):** C 45.57/45.49; H 2.97/2.80; N 17.71/17.84; S 13.51/13.64.

*2-Benzoylamino-5-nitro-1,3-benzothiazole (**3b**).* Yield 0.35 g (75%) of yellowish crystals, sublimation point at ambient pressure 233–235 °C lit.[2](m.p. 239–240 °C). ^{1}H NMR (δ): 8.17 (m, 3H, H-*o*); 7.59 (m, 2H, H-*m*); 7.69 (m, 1H, H-*p*); 13.21 (bs, 1H, NH); 8.51 (d, $J = 2.12$ Hz, 1H, H4); 8.17 (m, 3H, H6); 8.30 (d, $J = 8.71$ Hz, 1H, H7). ^{13}C NMR (δ): 131.8 (C-*i*); 128.5 (C-*o*); 128.7 (C-*m*); 133.1 (C-*p*); 166.5 (C=O); 162.5 (C2); 148.7 (C3a); 122.9 (C4); 146.4 (C-NO_2); 114.9 (C6); 117.8 (C7); 139.1 (C7a).

*2-Amino-5-nitro-1,3-benzothiazole (**4**).* A 100 ml Erlenmeyer flask equipped with a $CaCl_2$ closure was charged with 0.5 g (1.94 mmol) of **1a** and 40 ml of methanol. After dissolution of the starting compound, 13 ml of 0.5 mol l^{-1} sodium methoxide were added within several seconds. The yellow solution formed was left to stand at room temperature overnight to separate yellow crystals, which were collected by filtration on a sintered-glass filter. Yield 0.37 (97%), m.p. 308–310 °C lit.[8] (m.p. 308–309 °C).

A 100 ml Erlenmeyer flask equipped with a reflux condenser was charged with 0.5 g (2.16 mmol) of **2b** or 0.5 g (2.10 mmol) of **3a** and 50 ml of 0.5 mol l^{-1} sodium methoxide. The reaction mixture was refluxed for 2 h and then neutralized with methanolic hydrogen chloride to pH $\approx$ 7, whereupon 15 ml of water were added, and 30 ml of distillate were distilled off from the mixture. The residue on cooling separated 0.2 g (47% from **2b**) or 0.3 g (70% from **3a**) of product **4** with m.p. 310 °C.

^{1}H NMR (δ): 7.99 (bs, 2H, NH_2); 8.06 (d, $J = 2.20$ Hz, 1H, H4); 7.88 (dd, $J = 8.62$, 2.27 Hz, 1H, H6); 7.94(d, $J = 8.62$ Hz, 1H, H7). ^{13}C NMR (δ): 169.2 (C2); 153.2 (C3a); 121.6 (C4); 146.2 (C-NO_2); 111.5 (C6); 115.5 (C7); 139.2 (C7a). MS (*m/z*,%): $[M + H + CH_3CN]^+$ 237, 68.0; $[M + H]^+$ 196, 100; $[M + H - NO]^+$ 166, 33.3.

The data given agree with those given in the literature[9].

Balance experiment in 0.1 mol l^{-1} CH_3ONa. A 250 ml Erlenmeyer flask was charged with 0.5 g (1.6 mmol) of **1b** and 50 ml of 0.1 mol l^{-1} sodium methoxide. After mixing, the reaction mixture was left to stand for 15 h, whereupon 0.26 g (85%) of **4** was collected by filtration. The filtrate was neutralized with acetic acid, whereupon 0.07 g (15%) of white crystals of **3b** separated.

Balance experiment in 1.0 mol l^{-1} CH_3ONa. A 250 ml Erlenmeyer flask was charged with 0.5 of (1.6 mmol) of **1b** and 50 ml of 1.0 mol l^{-1} sodium methoxide. After mixing, the reaction mixture was left to stand for 15 h, whereupon it was neutralized with acetic acid to the final methoxide concentration of 0.1 mol l^{-1}. The separated white crystals of **3b** (0.21 g; 45%) were collected by filtration. The filtrate was evaporated until dry and the residue was washed with water. Yield 0.15 g (50%) of yellow crystals of **4**.

Measurements. ^{1}H and ^{13}C NMR spectra were measured at 360.14 and 90.57 MHz, respectively, on a Bruker AMX 360 spectrometer at 25 °C. Compounds **1a** and **b** were measured as saturated solutions in $CDCl_3$, and the chemical shifts were referenced to hexamethyldisiloxane [$\delta(^1H) = 0.05$] and to the solvent signal [$\delta(^{13}C) = 77.0$]. Compounds **1c** and **1d**, **2a**, **3a** and **3b** and **4** were measured as saturated solutions in hexadeuteriodimethyl sulfoxide, and the chemical shifts were referenced to tetramethylsilane [$\delta(^1H) = 0$] and the solvent signal [$\delta(^{13}C) = 39.6$]. The CH, CH_3 and C_{quart} groups in the ^{13}C NMR spectra were distinguished by the APT method.

Mass spectra of compounds **1a**, **2a**, **3a** and **4** were measured on a VG Platform II mass spectrometer (Micromass, Manchester, UK) with chemical ionization at atmospheric pressure (APCI) and a quadrupole analyser (0–3000 Da). The mass spectrometer was equipped with a preliminary separation unit composed of a Waters 616, high-pressure pump, Waters 717 autosampler Waters 996 UV detector (all from Waters, Milford, MA, USA) and a Separon SGX C_{18} HPLC column (Tessek, Prague, Czech Republic). For the mobile phase we used a 1:1 mixture of acetonitrile (Merck, Darmstadt, Germany) and redistilled water.

Kinetic measurements were carried out on an HP UV/VIS 8453 diode-array apparatus. A 1 cm quartz cell was charged with 2 ml of methanolic sodium methoxide or phenolate buffer. At 25 °C, 50 µl of a methanolic solution of substrate were injected and the absorbance was measured at the selected wavelength. In the experiment with 18-crown-6, the concentration of the latter was always 2×10^{-3} mol l^{-1} higher than that of sodium methoxide. The stability constant[10] for complexation of 18-crown-6 with Na^+ at 25 °C is log $K = 4.36$.

The percentages of individual products formed by the reactions **1b** $\rightarrow$ **3b** and **1b** $\rightarrow$ **2a** $\rightarrow$ **4** were determined spectrophotometrically using an HP UV/VIS 8453 diode-array apparatus and 1 cm closeable cells placed in the cell compartment of the apparatus kept at 25 °C. The following procedure was used: 10 ml calibrated flasks were charged with 5 ml of methanolic sodium methoxide (0.1–0.7 mol l^{-1}) (added from a pipette) and placed in a thermostat; after attaining a temperature of 25 °C, 1 ml of a methanolic solution of **1b** ($c = 2.11 \times 10^{-4}$ mol l^{-1}) was added and the flask contents were thoroughly mixed and left to stand at 25 °C for 6–7 h. Thereafter, the samples were taken and their absorbance was measured at 313 nm. The population of individual solvolysis and cyclization products

was calculated from Eqns (1) and (2):

$$A_{\infty}^{313\text{nm}} = \varepsilon_{3b}^{313\text{nm}} c_{3b} \cdot l + \varepsilon_{4}^{313\text{nm}} \cdot c_4 \cdot l \qquad (1)$$

$$c_{1b} = c_{3b} + c_4 \qquad (2)$$

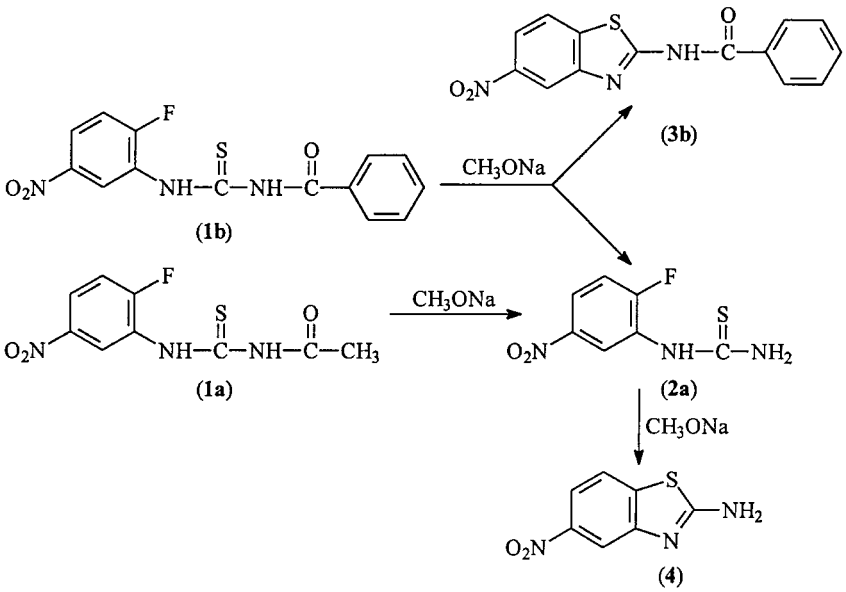
where A_{∞} is the absorbance of the reaction mixture after the completed reaction, ε_{3b} and ε_4 are the molar absorption coefficients of the respective substances and l is the optical pathlength.

The measurement was carried out at a wavelength of 313 nm, at which only the products in question absorb light.

The molar absorption coefficients at 313 nm were determined with the use of standards of substances **3b** and **4**: $\varepsilon_{3b} = 22\ 600\ \text{l mol}^{-1}\,\text{cm}^{-1}$ and $\varepsilon_4 = 5000\ \text{l mol}^{-1}\,\text{cm}^{-1}$. Similarly, the composition of reaction mixtures was estimated after the reactions **1a** → **3a** and **1a** → **2a** → **4** carried out in sodium methoxide solutions with added 18-crown-6. In this case, the measurements were carried out at 268 and 291 nm. The molar absorption coefficients of **3a** were $\varepsilon_{268\ \text{nm}} = 1290\ \text{l mol}^{-1}\,\text{cm}^{-1}$ and $\varepsilon_{291\ \text{nm}} = 4000\ \text{l mol}^{-1}\,\text{cm}^{-1}$. The molar absorption coefficients of **4** changed with changing sodium methoxide concentration, and its values are given in Table 3.

RESULTS AND DISCUSSION

The reaction of **1a** with 0.1 mol l^{-1} sodium methoxide gives 2-amino-5-nitro-1,3-benzothiazole (**4**) in an almost quantitative yield. With 2-acetylamino-5-nitro-1,3-benzothiazole (**3a**) prepared by the reaction of **1a** with *t*-



Scheme 1

Table 1. Rate constants k_{obs} (s^{-1}) of the methanolysis of 1-acyl-3-(2-halo-5-nitrophenyl)thioureas (**1a**, **c**, **d**) in methanolic solutions of *p*-bromophenoxide buffers (1:4–4:1) and the K_1(**1a**, **c**, **d**) (l mol^{-1}), pK_a and k_m (l $\text{mol}^{-1}\ \text{s}^{-1}$) values of **1a**, **c** and **d** in the same medium

	$k_{obs} \times 10^3$ (s^{-1})		
$[CH_3ONa] \times 10^4$ (mol l^{-1})	**1a**	**1c**	**1d**
1.24	2.28	2.06	0.71
1.65	3.30	2.83	0.82
2.47	5.14	4.13	0.96
4.94	7.42	6.99	1.10
9.90	11.4	8.79	1.23
14.8	12.1	9.45	1.40
19.8	12.4	9.61	1.34
K_1 **(1a, c, d)**	1658 ± 262	2086 ± 342	7257 ± 620
pK_a	13.70 ± 0.07	13.60 ± 0.07	13.06 ± 0.04
k_m	27.99 ± 2.91	26.05 ± 2.97	10.77 ± 0.76

BuOK in *t*-BuOH, the methanolysis takes place to only a slight extent under the same conditions. This means that the reaction goes in two steps. The first consists in methanolysis of **1a** giving 2-fluoro-5-nitrophenylthiourea (**2a**), and the second involves cyclization of **2a** to **4** (Scheme 1).

The reaction of **1b** with 0.1 mol l^{-1} sodium methoxide, after completion on a preparative scale, gave 15% 2-benzoylamino-5-nitro-1,3-benzothiazole (**3b**) and 85% **4**, whereas the analogous reaction in 1.0 mol l^{-1} sodium methoxide gave 45% **3b** and 50% **4** (as isolated without further purification).

Since **3b** (prepared also from **1b** by reaction with *t*-BuOK in *t*-BuOH) reacts with methoxide even more slowly than **3a**, the reaction must take two steps again: the first produces a mixture of **2a** and **3b** and the second involves cyclization of **2a** to **4** (in analogy with the reaction of **1a**; see Scheme 1).

Kinetics of methanolysis of *1a, c* and *d*

(a) The methanolysis kinetics were measured at 340 nm in *p*-bromophenoxide buffers at a constant concentration of sodium *p*-bromophenoxide (0.05 mol l^{-1}; see Table 1). The reactions exhibited pseudo-first-order kinetics up to 90% of reaction.

The *p*-bromophenol/*p*-bromophenoxide ratio varied from 1:4 to 4:1. The concentration of methoxide ion was

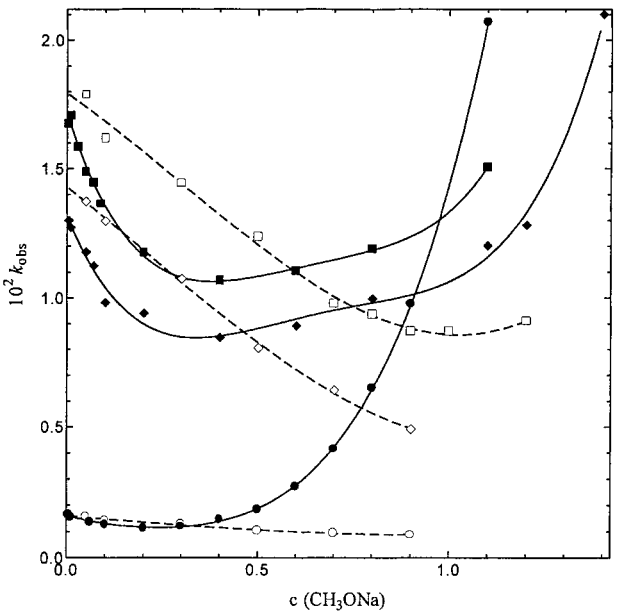


Figure 1. Dependence of observed rate constants k_{obs} (s^{-1}) of methanolysis of 1-acyl-3-(2-halo-5-nitrophenyl)thioureas **1a** (squares) **c** (diamonds) and **d** (circles) in sodium methoxide solution (concentration in mol l^{-1}), without addition (solid symbols) and with addition (open symbols) of 18-crown-6. The curves represent only the nature of the dependence

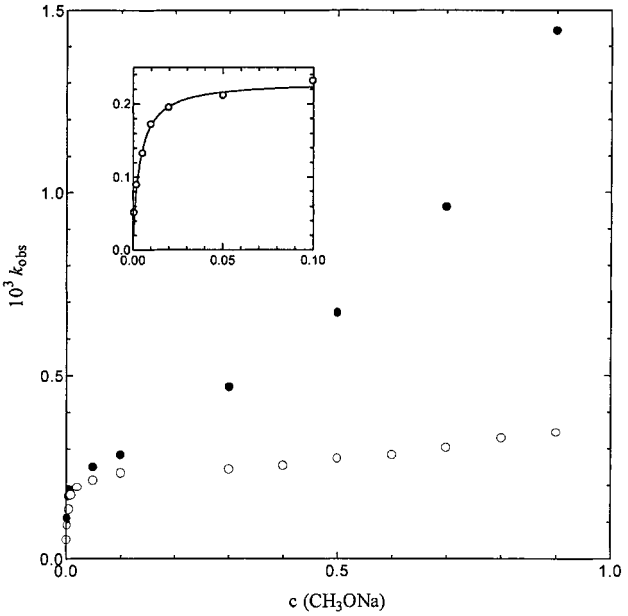


Figure 2. Dependence of observed rate constants k_{obs} (s^{-1}) of the cyclization reaction of 2-fluoro-5-nitrophenylthiourea (**2a**) on sodium methoxide concentration *c*(CH_3ONa) (mol l^{-1}) in the absence (○) and presence (●) of 18-crown-6. The inset represents the best fit of the measured data in the range 0.002–0.1 mol l^{-1} obtained by means Eqn. (7)

calculated from Eqn. (3):

$$pK_a(p-\text{bromophenol}) = pK_s(CH_3OH) + \log[CH_3O^-] - \log\frac{[p-\text{bromophenoxide}]}{[p-\text{bromophenol}]} \quad (3)$$

where the value of $pK_a(p-\text{bromophenol})$ is 13.61 in methanol[11] and the autoprotolytic constant of methanol[12] is $pK_S(CH_3OH) = 16.916$.

The reaction mechanism is presented in Scheme 2. The methanolysis rate constants k_m (l mol^{-1} s^{-1}) and the equilibrium constants K (l mol^{-1}) were calculated from Eqn. (4) and the pK_a values from Eqn. (6) (Table 1). The methanolysis rate constant k_m is defined by Eqn. (5).

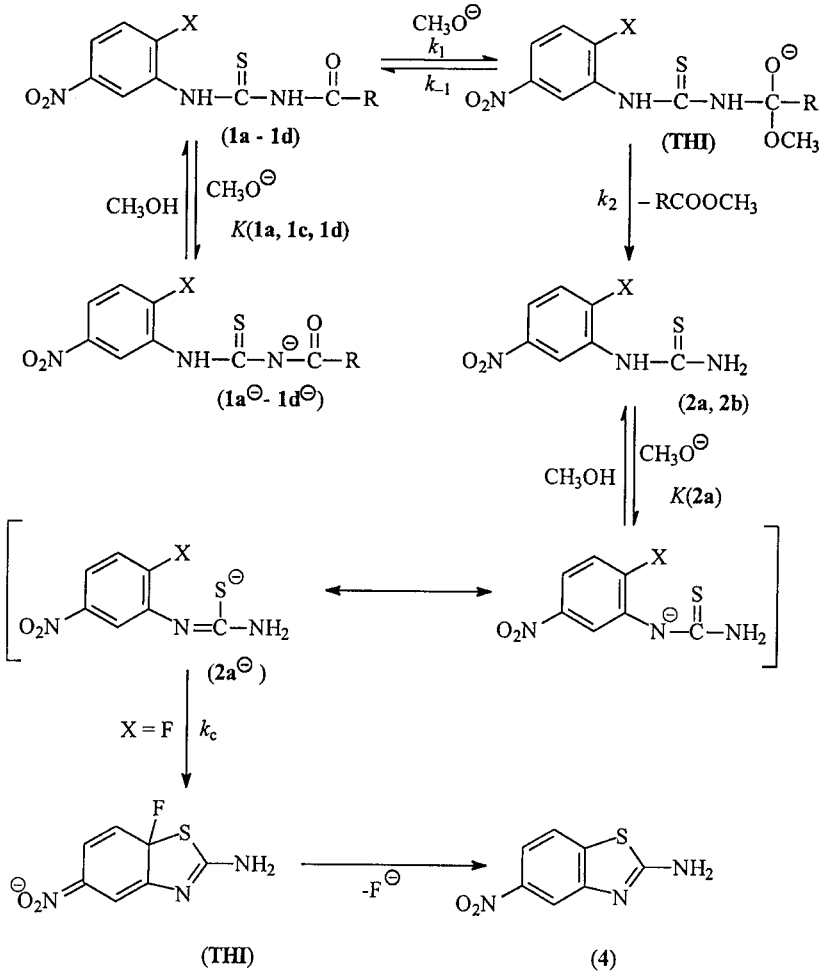
$$v_m = k_{obs} \cdot c_{1a} = \frac{k_m \cdot [CH_3O^-]}{1 + K \cdot [CH_3O^-]} \cdot c_{1a} \quad (4)$$

$$k_m = \frac{k_1 k_2}{k_{-1} + k_2} \quad (5)$$

$$pK_a = pK + pK_s(CH_3OH) \quad (6)$$

$$v_c = k_{obs} \cdot c_{2a} = \frac{k_c \cdot K \cdot [CH_3O^-]}{1 + K \cdot [CH_3O^-]} \cdot c_{2a} \quad (7)$$

There are only very small differences in pK_a and k_m values between the chloro- and fluoroacetyl derivatives



Scheme 2

1a and **c**. The methanolysis rate of acetyl derivative **1c** at sodium methoxide concentrations above 5×10^{-3} mol l^{-1} is about one order higher than that of the benzoyl derivative **1d** at the same sodium methoxide concentrations. We suppose that the difference between the methanolysis rates of the fluoro derivatives **1a** and **1b** is also the same.

(b) The methanolysis kinetics were measured in sodium methoxide solutions with concentrations from 0.01 to 1.4 mol l^{-1}. With all the three acyl derivatives (**1a**, **c**, and **d**), increasing methoxide concentration at first causes a drop in the observed rate constant but then, starting from about 0.4 mol l^{-1} methoxide concentration (for 1-acetyl derivatives **1a** and **c**) or 0.2 mol l^{-1} methoxide concentration (for 1-benzoyl derivative **1d**), the reaction rate shows an increase (Fig. 1), a new reaction product being gradually formed ($\lambda_{max} = 260$ and 360 nm for the 1-acetyl derivatives and $\lambda_{max} = 328$ and 455 nm for the 1-benzoyl derivative).

Within the whole methoxide concentration range used, the reaction is pseudo-first order, but the isosbestic points are not sharp at the higher concentrations, obviously owing to the formation of side product(s). From the mass spectra it was found out that neither of the chief products formed from **1c** and **d** at high methoxide concentrations contains a chlorine atom. However, the spectra in 2.0 mol l^{-1} methoxide (for **1c**) and 1.0 mol l^{-1} methoxide (for **1d**) [a further increase in methoxide concentration brings about only small changes in the spectra] differ substantially from those of the cyclizates **3a** and **b** and **4**, and also from those of 2-chloro-5-nitrophenylthiourea (**2b**) and 2-mercapto-5-nitro-1,3-benzoimidazole (the last being a conceivable cyclization product formed by the reaction of nitrogen atom) in the given medium. These products seem to be stable only in the given medium and their structures have not been determined. The formation of these products cannot involve methanolysis as the first step because the methanolysis product obtained from **2b** is stable under these conditions.

Kinetics of cyclization of *2a*

The cyclization kinetics were measured in sodium methoxide solutions. The kinetic experiments showed that the subsequent cyclization of **2a** is about two orders of magnitude slower than the methanolysis of **1a**, hence the kinetics of both the reactions can be measured

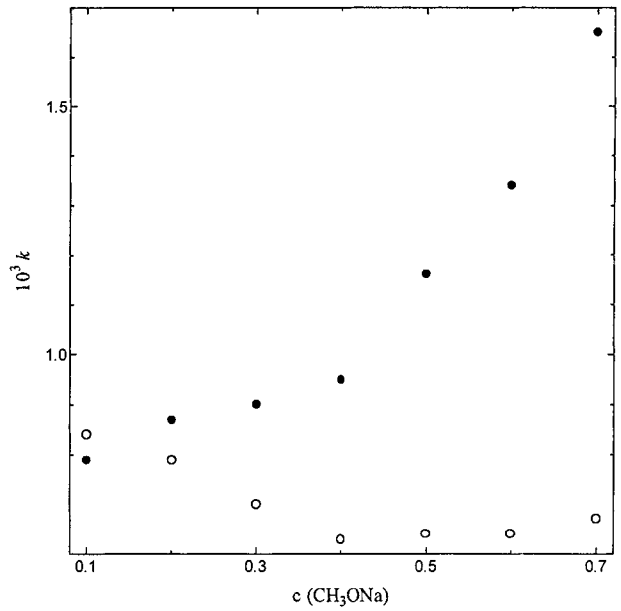


Figure 3. Dependence of rate constants of methanolysis k_m (s^{-1}) (○) and cyclization k_c (s^{-1}) (●) of 1-benzoyl-3-(2-fluoro-5-nitrophenyl)thiourea (**1b**) in sodium methoxide solution (concentration in mol l^{-1})

independently of each other starting from **1a**. [Note: attempts to isolate **2a** failed. Even at concentrations of **1a** as low as about 0.1 mol l^{-1} a rather small amount of **2a** besides the starting compound **1a** and cyclizate **4** was detected by means of HPLC in the reaction products. The decrease in the rate of methanolysis of **1a** is probably due to its association at higher concentrations. The formation of **2a** in kinetic runs was proved by combining HPLC with MS. After about seven half-lives of the methanolysis of **1a** at a concentration of sodium methoxide of 2×10^{-3} mol L^{-1} there was virtually only one compound detected by HPLC, which was proved by MS to be **2a**. The reaction exhibited pseudo-first-order kinetics within the whole range measured (six half-lives). At concentrations higher than 0.05 mol l^{-1} the observed rate constant k_{obs} of the cyclization reaction increases slowly and approximately linearly, although almost all thiourea **2a** is transformed into anion (Fig. 2).

The mechanism of the reaction is also presented in Scheme 2. The cyclization rate constant $k_c = (2.31 \pm 0.05) \times 10^{-4}$ l mol^{-1} s^{-1} and the equilibrium constant $K(\mathbf{2a}) = 284 \pm 27$ were calculated from Eqn. (7). The value of $pK_a(\mathbf{2a}) = 14.46 \pm 0.04$ was calculated from Eqn. (6).

Kinetics and mechanism of solvolysis and cyclization of *1b*

The methoxide-catalysed reaction of **1b** takes place in two steps again. However, the measured rate constants of the first step are equal to $k_m + k_c$, i.e. the sum of parallel methanolysis and cyclization of **1b** (Scheme 1). Their values are almost one order of magnitude higher than the rate constants of subsequent cyclization of thiourea **2a**, and the absorbance changes were measured at isosbestic points of the products from the first and the second steps. The dependence of the calculated constants k_m and k_c on the concentration of sodium methoxide is shown in Fig. 3. At methoxide concentrations above 0.7 mol l^{-1}, increasing amounts of side products were formed, hence it was impossible to determine the observed rate constants of cyclization and methanolysis in the first step.

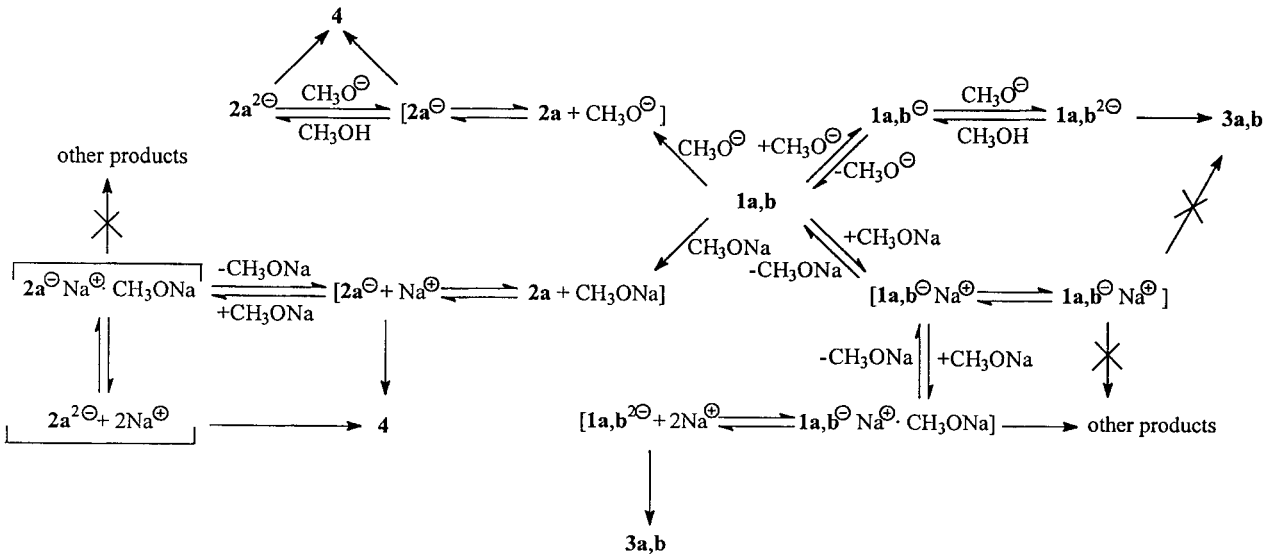
The subsequent cyclization of thiourea **2a** was usually measured at the λ_{max} of the cyclizate formed, i.e. at 263 nm. The observed rate constants of the second step were the same as those of the second step of reaction of **1a**, but the error of measurement gradually increased as the proportion of thiourea **2a** in the first step decreased with increasing methoxide concentration.

Study of reactions of *1a–d* and *2a* in the presence of 18-crown-6

The decrease in the observed rate constant k_{obs} in the reactions of **1a–1d** with methoxide at concentrations above 1×10^{-2} mol l^{-1} (Fig. 1) may be due to the fact that the anions formed in the acid-base reactions of **1a–1d** with sodium methoxide are stabilized by interaction with sodium cation, which shifts the acid-base equilibrium. The concentrations of starting thioureas are lower than corresponds to the methoxide concentrations, and the methanolysis rate decreases with increasing concentration of sodium methoxide. The subsequent increase can be caused by a reaction of the ion pair $CH_3O^-Na^+$ with the complexes of thiourea anions and sodium cation. Such an increase in reaction rate necessitates that the transition state of this reaction be stabilized more than methoxide anion with sodium cation.[13,14] In that case, the presence of a reagent forming firm complexes with sodium cation (e.g. 18-crown-6) should substantially change the reaction course. With the acyl derivatives **1c** and **d** the only reaction in the presence of 18-crown-6 was methanolysis of both substrates (Fig. 1), and even at the highest sodium methoxide concentrations neither the increase in the observed rate constant k_{obs} nor the formation of the products as in the absence of 18-crown-6 were observed. The most likely interpretation of the drop in observed rate constant k_{obs} is the increasing content of the dianion with increasing concentration of sodium methoxide and the corresponding drop in concentration of neutral starting substrate. In order to verify this presumption, we measured the spectra of **1a** immediately after mixing its solution with a solution of sodium methoxide and 18-crown-6. With increasing methoxide concentration, the absorbance of the solution gradually increased at $\lambda > 297$ nm and decreased at $\lambda < 297$ nm,

Table 2. Rate constants of methanolysis and cyclization of **1a** and of those of cyclization of **2a** in the presence of 18-crown-6 and molar absorption coefficients of **4** in the presence of 18-crown-6

$[CH_3ONa]$ (mol l^{-1})	4		$k_{obs} \times 10^3$ (s^{-1}) (1a)	$k_m \times 10^3$ (s^{-1}) (1a)	$k_c \times 10^3$ (s^{-1}) (1a)	$k_c \times 10^3$ (s^{-1}) (2a)
	268 nm	291 nm				
0.7	19000	9800	9.80	5.80	4.00	0.96
0.8	18400	10900	9.35	4.40	4.95	1.10
0.9	16500	12950	8.70	3.20	5.50	1.44
1.0	14600	14500	8.70	2.60	6.10	1.70
1.2	12400	18450	9.10	1.40	7.70	2.50



Scheme 3. (a) Upper part of the scheme is in the presence of 18-crown-6. (b) CH_3ONa is the sum of solvated ions and ion pair. (c) **1a**, $\mathbf{b}^-$ means anions of **1a**, **b** and similarly for other anions. (d) We have no idea about the mechanism of formation of other products but from the steep increase in K_{obs} of **1c** and **d** with increase in concentration of sodium methoxide (Fig. 1) we suggest that there are two sodium cations in the activated complex of the rate-limiting step. $\mathbf{1a}^-\ Na^+ \cdot CH_3ONa$ is the possible structure of the encounter complex, and similarly for $\mathbf{2a}^-\ Na^+ \cdot CH_3ONa$

which is characteristic of an acid–base equilibrium. In further experiments, we tried to find out the effect of 18-crown-6, and hence also increasing concentration of dianion, on the observed rate constants of cyclization in the two-step reaction of **1a** and in the first reaction step of **1b**. With **1b** we only used 18-crown-6 at a concentration of 0.8 mol l^{-1}; under these conditions, the cyclization to **3b** was almost the only reaction, so the whole reaction proceeded virtually in one step with observed rate constant $k_{obs} = 4.1 \times 10^{-3}$ s^{-1}, i.e. ca 50% higher than that in the absence of 18-crown-6.

In the reaction of sodium methoxide with **1a**, the effect of 18-crown-6 on both the reaction steps at concentrations of sodium methoxide from 0.7 to 1.2 mol l^{-1} was studied (Figs 1 and 2 and Table 2). In the first step the observed rate constant k_{obs} decreased except for the highest methoxide concentration (Table 2) whereas the rate of cyclization of thiourea **2a** in the second step increased rapidly (Fig. 2), hence at the highest methoxide concentration the second reaction step was only about four times as fast as the first step (Table 2).

At higher concentrations of methoxide ion, the cyclization of **1a** to **3a** gradually started to make itself felt (Table 2). In 0.8 mol l^{-1} sodium methoxide the rate of cyclization is already higher than the rate of methanolysis. In the absence of 18-crown-6 the ratio of cyclization to methanolysis rates and its increase with increase in sodium methoxide concentration is much smaller because the formation of complexes of anions with sodium cations decreases the rates of both methanolysis and cyclization reactions. The rate constant $k_c = 4.95 \times 10^{-3}$ s^{-1}, of **1a** in 0.8 mol l^{-1} sodium methoxide is almost the same as the observed rate constant of cyclization of benzoyl derivative **1b** ($k_{obs} = 4.3 \times 10^{-3}$ s^{-1}) measured under the same conditions. The 15% yield of benzoyl cyclizate **3b** and, on the other hand, the almost exclusive solvolysis of acetyl derivative **1a** at a sodium methoxide concentration of 0.1 mol l^{-1} in the absence of 18-crown-6 are obviously largely due to the fact that the solvolysis rate of **1a** is ca 10 times higher than that of **1b**.

The absence of cyclization reactions of chloro

derivatives **1c** and **d**, both with and without 18-crown-6, means that the rate-limiting step of the cyclization reactions is the formation of Meisenheimer adducts,[15] but a concerted reaction with advanced formation of a C—S bond and a small extent of C—F bond splitting cannot be excluded.

From the results of kinetic experiments with and without 18-crown-6, the sequence of reactions of **1a** and **b** as given in Scheme 3 can be suggested. The same scheme can be written for chloro derivatives with the exception of cyclization reactions.

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REFERENCES

1. Sprague KM, Land AH. In *Heterocyclic Compounds*, Elderfield RC (ed). Wiley: New York, 1989; 582–587, and references cited therein.
2. Sarkis GY, Faisal ED. *J. Heterocycl. Chem.* 1985; **22**: 725–728.
3. Kaválek J, Macháček V, Svobodová G, Štěrba V. *Collect. Czech. Chem. Commun.* 1986; **51**: 375–390.
4. Kaválek J, Kotyk M, El Bahaie S, Štěrba V. *Collect. Czech. Chem. Commun.* 1981; **46**: 246–255.
5. Kaválek J, Macháček V, Sedlák M, Štěrba V. *Collect. Czech. Chem. Commun.* 1993; **58**: 1122–1132.
6. Lawrence AR, Ferguson LN. *J. Org. Chem.* 1960; **25**: 1220–1224.
7. Frank ZR, Smith PV. *Org. Synth. Coll.* 1955; **Vol. 3**: 735–736.
8. Veltman RP. *Zh. Obsch. Khim.* 1960; **30**: 1363–1366.
9. Bartovič A, Ilavský D, Šimo O, Zalibera L, Belicová A, Seman M. *Collect. Czech. Chem. Commun.* 1995; **60**: 583–593.
10. Raevsky OA, Solovev VP, Solotnov AF, Schneider H-J, Rüdiger V. *J. Org. Chem.* 1996; **61**: 8113–8116.
11. Rochester CH, Rossal B. *Trans. Faraday Soc.* 1969; **65**: 1004–1013.
12. Rochester CH, Rossal B. *J. Chem. Soc. B* 1967; 743–748.
13. Msayib KJ, Watt CIF. *Chem. Soc. Rev.* 1992; **21**: 237–243.
14. Tee OS. *Adv. Phys. Org. Chem.* 1994; **29**: 1–69.
15. March J. *Advanced Organic Chemistry*. Wiley: New York, 1992; 652.