NUCLEOPHILIC SUBSTITUTION REACTIONS ON CHLORINATED THIOPHENE DERIVATIVES AS BASIS FOR THE SYNTHESIS OF THIENOANELLATED O,N- AND S,N-HETEROCYCLES 1

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Abstract-The reactivity of 5-acetyl-2-chloro-3-nitrothiophene with amines, alcohols, thiols and bifunctional compounds, as well as reactions of methyl 5-chloro-4-nitro-2-thiophene-carboxylate with various hydrazides are described. These substitution reactions provide an easy access to thienoanellated heterocycles.

A great variety of drugs show the following structure:

Two heteroatoms are positioned ortho on a benzene nucleus and linked via (-CH₂-)n. Because of the isosterity of benzene and thiophene pharmacological activity of various substances may be maintained if benzene is exchanged by this heteroaromatic ring. The chemistry of thienoanellated O,N- and S,N-heterocycles was studied to achieve compounds with the following basic structure:

Synthesis analogous to benzene derivatives was ruled out because of the instability of the required starting materials: neither aminomercaptothiophenes nor amino-hydroxythiophenes and diaminothiophenes could be synthesized. Thus an alter-
native synthetic concept was developed: halogenated nitrothiophenes were selected as starting materials, and nucleophilic substitution with the corresponding reagents should provide the desired result. Ring closure should occur after reduction of the nitro group if for instance an ester group is present in the structure.

To realize this project, nucleophilic substitution reactions with thiophene had to be studied in order to select the best solvent, the optimal reaction temperature and the most advantageous method for reprocessing.

5-Acetyl-2-chloro-3-nitrothiophene\textsuperscript{2} (1) was chosen for an initial trial since the acetyl group (another electron-withdrawing substituent) was supposed to support the nucleophilic attack at the thiophene.

1 was stirred with morpholine, pyrrolidine and dimethylamine hydrochloride at room temperature using $N,N$-dimethylformamide (dried over molecular sieve) as solvent, until tlc analysis indicated that these reactions were completed. After two hours the reaction mixture was poured into ice-water. The precipitated product was filtered off and recrystallized to provide 2, 3 and 4 in good yields (85%-89%).

The increase of the reaction temperature to 50°C shortened the reaction time, but the yield decreased to approx. 75%. Control experiments using ethanol or methanol as solvent, or reaction without a solvent resulted in lower yields.

Reaction of 1 with aniline brought up compound (5) in 82% yield. The method described by Kreuz and Hurd\textsuperscript{2} provided a 76% yield of the same product.
The surprisingly good results that were achieved by substitution of the chloro atom on the π-excessive heterocycle were also observed by using O-nucleophiles. Reaction with sodium methoxide, sodium ethoxide or sodium isopropoxide resulted in compounds (6, 7 and 8).

After the reaction of 1 with sodium hydrogen sulfide in methanol, 9 could be isolated. Increasing of reaction temperature to 80°C as described for pyrido analogue 3 produced a different compound. According to the mass spectrometric data the isolated crystals of this product correspond to structure (10).
The reaction of 1 with acetic hydrazide or ethyl carbazate yielded the expected hydrazones (11) and (12).

To be able to investigate nucleophilic substitution reactions at halogen-containing thiophene derivatives with hydrazides the acetyl group in position 2 had therefore to be replaced by a group less reactive toward these reagents. This was possible by oxidation of the acetyl group to a carboxyl group, which was subsequently esterified resulting in an electron-withdrawing group in position 2 as provided in compound (1). The oxidation of 2-acetyl-5-chlorothiophene with potassium permanganate and sodium hydroxide to the corresponding carboxylic acid resulted in 5-chloro-2-thienylglyoxylic acid, 4 which is known from the literature. However, 5-chloro-2-thiophenecarboxylic acid is easily synthesized from 5-acetyl-2-chloro-3-nitrothiophene by using hypobromite. The acid was esterified with an etheric diazomethane solution in methanol and after nitration methyl 5-chloro-4-nitro-2-thiophenecarboxylate (13) was obtained. 13 was reacted with several acyl hydrazides and under the previously described conditions (dry dimethylformamide/room temperature/reaction time 2 hours) to yield methyl 5-acylhydrazino-4-nitro-2-thiophenecarboxylates (14-18) as coloured crystals.

Since the experiments to substitute the chloro atom by different nucleophiles supported the proved concept, 1 was exposed to bifunctional reagents. Reaction of 1
with methyl 3-mercaptopropionate by using potassium carbonate in
tetrahydrofuran resulted in 19.

The catalytic hydrogenation of the nitro group was only completed
after applying molar amount of 10% Pd/C. Therefore, iron powder5 was used as reducing agent in
glacial acetic acid at 100°C for 2 hours. After working up a substance could be
isolated. The lack of signals of methoxycarbonyl- and amino protons in the 1H-nmr
spectrum and the appearance of 227 mass units in mass spectroscopy confirmed,
that not only the reduction of the nitro group, but also cyclisation to the expected
lactam (20) had occurred.

Compound (22) was synthesized in a similar way. 1 reacted with ethyl 2-
mercaptoacetate to give 21. Reduction and cyclisation led to 22 in a 68 % yield.
This approach provides a possibility to synthesize unknown thieno[2,3-b][1,4]thiaz-
epines as well as known thieno[2,3-b][1,4]thiazines6 in an easier way.
EXPERIMENTAL

Melting points were determined with a Kofler-apparatus and are uncorrected. 1H-Nmr spectra were recorded on a Bruker AC-80 spectrometer. Chemical shifts are reported in ppm downfield from internal TMS. Ms analyses were obtained with Shimadzu GC/MS QP 1000. All organic solvents were removed by evaporation under vacuum. The reaction progress was controlled by tlc analysis using Merck F254 silica gel sheets.

5-Acetyl-3-nitro-2-pyrrolidinylthiophene (2)
5-Acetyl-2-chloro-3-nitrothiophene (512 mg, 2.5 mmol) (1) in 10 ml of DMF was stirred with pyrrolidine (355 mg, 5 mmol) at room temperature under argon. After 1 h the reaction mixture was poured into ice-water. The precipitate was filtered off and recrystallized from 96% ethanol to give 510 mg (85%) of yellow crystals, mp 155°C, Anal. Caled for C_{10}H_{12}N_{2}O_{3}S: C, 49.99; H, 5.03; N, 11.66; Found: C, 50.23; H, 5.00; N, 11.62; ms m/z = 240 (M+), nmr (CDCl_{3}): δ: 1.95-2.25 (4H, m, -CH~2-CH~2), 2.50 (3H, s, -COCH~3), 3.35-3.65 (4H, m, -CH_{2}-N-CH_{2}-), 8.05 (1H, s, thiophene H)

5-Acetyl-2-(4-morpolinyl)-3-nitrothiophene (3)
1 (512 mg, 2.5 mmol) and morpholine (435 mg, 5 mmol) in 10 ml of DMF were stirred for 10 min at room temperature under argon. Then the mixture was poured into ice-water and stirred for another 30 min. The precipitate was filtered off and recrystallized from 96% ethanol to give 570 mg (89%) of dark yellow needles, mp 165°C, Anal. Caled for C_{12}H_{10}N_{2}O_{4}S: C, 46.87; H, 4.72; N, 10.93; Found: C, 46.66; H, 4.54; N, 10.82; ms m/z = 256 (M+), nmr (CDCl_{3}): δ: 2.50 (3H, s, -COCH~3), 3.39-3.49 (4H, m, -CH_{2}-O-CH_{2}-), 3.86-3.98 (4H, m, -CH_{2}-N-CH_{2}-), 8.05 (1H, s, thiophene H)

5-Acetyl-2-dimethylamino-3-nitrothiophene (4)
K₂CO₃ (1.104 g, 8 mmol) in 10 ml of DMF and dimethylamine hydrochloride (324 mg, 4 mmol) were stirred for 10 min at room temperature under argon, then 1 (512 mg, 2.5 mmol) was added and stirred for another 10 min. The mixture was poured into ice-water and the resulting precipitate was recrystallized from 96% ethanol to give 376 mg (87.8%) of yellow needles, mp 149°C, Anal. Caled for C_{8}H_{10}N_{2}O_{3}S: C, 44.85; H, 4.71; N, 13.08; Found: C, 44.66; H, 4.53; N, 12.83; ms m/z=214 (M+), nmr (CDCl_{3}): δ: 2.50 (3H, s, -COCH~3), 3.25 (6H, s, -N(CH_{3})_{2}), 8.05 (1H, s, thiophene H)

5-Acetyl-2-phenylamino-3-nitrothiophene (5)
1 (512 mg, 2.5 mmol) was stirred with aniline (465 mg, 5 mmol) and 10 ml of DMF at room temperature under argon. Tlc analysis indicated the reaction was complete,
then the reaction mixture was poured into ice-water and the precipitate was recrystallized from 96% ethanol to give 537 mg (82%) of orange needles, mp 138-140°C, Anal. Calcd for C_{12}H_{10}N_{2}O_{3}S: C, 54.95; H, 3.84; N, 10.68; Found: C, 54.78; H, 3.93; N, 10.41; ms m/z = 262 (M+), nmr (CDCl_{3}) δ: 2.50 (3H, s, -COCH_{3}), 7.43 (5H, s, aromatic protons), 8.05 (1H, s, thiophene H), 10.39 (1H, br s, -NH-)

**General procedure for compounds(6-8)**

From sodium (115 mg, 5 mmol) and 30 ml of the corresponding dry alcohol (methanol, ethanol, 2-propanol) the sodium alkoxides were obtained. To this solutions 1 (512 mg, 2.5 mmol) was added in small portions. After the reaction was completed (tlc analysis), the mixture was diluted with water and extracted three times with dichloromethane. The combined organic phases were dried over Na_{2}SO_{4} and the solvent evaporated. The product was isolated by chromatography on a silica gel column using toluene/ethyl acetate 8:2 as eluent. By this method the following compounds were obtained:

5-Acetyl-2-methoxy-3-nitrothiophene (6)
mp 161-163°C (lit.,^2 158-159°C)

5-Acetyl-2-ethoxy-3-nitrothiophene (7)
mp 122-124°C (lit.,^2 125-126°C)

5-Acetyl-2-isopropoxy-3-nitrothiophene (8)
mp 103°C, Anal. Calcd for C_{9}H_{14}N_{2}O_{4}S: C, 47.15; H, 4.84; N, 6.11; Found: C, 47.45; H, 4.56; N, 5.85; ms m/z = 229 (M+), nmr: δ: 1.52 (6H, d, J=5.9 Hz, -(CH_{3})_{2}), 2.51 (3H, s, -COCH_{3}), 4.70 (1H, q, J=5.9 Hz, -CH-), 8.05 (3H, s, thiophene H)

5-Acetyl-2-mercapto-3-nitrothiophene (9)
A solution of NaSH.H_{2}O (444 mg, 6 mmol) in 15 ml of dry methanol was added dropwise to a suspension of 1 (1.025 mg, 5 mmol) in 15 ml of dry methanol under argon at 0°C and was stirred for 30 min. Methanol was evaporated, 2N HCl was added to the residue and the resulting mixture stirred for another 30 min. The precipitated product was filtered off and recrystallized from ethyl acetate/toluene 9:1 to give light brown crystals, mp 205°C; Anal. Calcd for C_{6}H_{5}NO_{3}S_{2}: C, 35.46; H, 2.48; N, 6.89; Found: C, 35.88; H, 2.03; N, 6.58; ms m/z = 203 (M+), nmr: δ: 2.50 (3H, s, -COCH_{3}), 4.70 (1H, s, -SH), 8.10 (1H, s, thiophene H)

**General procedure for compounds(11) and(12)**

Acetic hydrazide (296 mg, 4 mmol) or ethyl carbazate (416 mg, 4 mmol) was stirred with 1 (615 mg, 3 mmol) in 15 ml of DMF. After tlc analysis indicated that the
reaction was complete, the reaction mixture was poured into ice-water, the resulting precipitate was filtered off and recrystallized from 96% ethanol.

\[ N'-[1-(5-Chloro-4-nitro-2-thienyl)ethylidene]acetohydrazide (11) \]
685 mg (87.5%) of yellow-green needles, mp 248-250°C, Anal. Calcd for C₉H₈N₃O₅S: C, 36.72; H, 3.08; N, 16.06; Found: C, 36.99; H, 2.98; N, 16.03; ms m/z=261 (M⁺), nmr (CDCl₃): δ: 2.20 (3H, s, H₃CC=N-), 2.34 (3H, s, H₃CCO-), 7.60 (1H, s, thiophene H)

\[ Ethyl N'-[1-(5-chloro-4-nitro-2-thienyl)ethylidene]carbazate (12) \]
692 mg (79.3%) of green crystals, mp 224-226°C, Anal. Calcd for C₉H₁₀N₃O₄ClS: C, 37.06; H, 3.45; N, 14.40; Found: C, 37.19; H, 3.31; N, 14.31; ms m/z=291 (M⁺); nmr (CDCl₃): δ: 1.43 (3H, t, J=6.7 Hz, CH₃-), 2.16 (3H, s, H₃CC=N-), 7.59 (1H, s, thiophene H)

\[ Methyl 5-(2-acetylhydrazino)-4-nitro-2-thiophenecarboxylate (general procedure) \]
Acylhydrazides (6 mmol) (acetic hydrazide, benzhydrazide, ethyl carbazate, nicotinic hydrazide, isonicotinic acid hydrazide) were dissolved in 10 ml of DMF (dried over molecular sieve) and stirred under argon for 10 min. Then methyl 5-chloro-4-nitro-2-thiophencarboxylate (13) (442 mg, 2 mmol) were added and the suspension was stirred for another 2 h at room temperature. The reaction mixture was poured into ice water, the precipitate was filtered off and recrystallized from methanol. By this method the following compounds were obtained:

\[ Methyl 5-(2-acetylhydrazino)-4-nitro-2-thiophenecarboxylate (14) \]
347 mg (67%) of yellow needles, mp 199-200°C, Anal. Calcd for C₉H₉N₃O₅S: C, 37.07; H, 3.50; N, 16.21; Found: C, 37.32; H, 3.29; N, 16.02; ms m/z = 259 (M⁺), nmr (CDCl₃/CF₃COOH): δ: 2.27 (3H, s, -COCH₃), 3.94 (3H, s, -OCH₃), 8.05 (1H, s, thiophene H), 9.5 (2H, br s, -NH-NH-)

\[ Methyl 5-(2-benzoylhydrazino)-4-nitro-2-thiophenecarboxylate (15) \]
552 mg (86%) of yellow needles, mp 193°C, Anal. Calcd for C₁₃H₁₁N₃O₅S x 1/4 CH₃OH: C, 48.32; H, 3.65; N, 12.76; Found: C, 48.07; H, 3.65; N, 12.36, ms m/z = 321 (M⁺), nmr (CDCl₃/CF₃COOH): δ: 3.89 (3H, s, -OCH₃), 6.50 (2H, br s, -NH-NH-), 7.59-7.83 (5H, m, aromatic protons), 8.02 (1H, s, thiophene H)
Methyl 5-[2-ethoxycarbonylhydrazino]-4-nitro-2-thiophenecarboxylate (16)
314 mg (54%) of orange needles, mp 197-200°C, Anal. Calcd for C9H11N3O6S: C, 37.37; H, 3.83; N, 14.53; Found: C, 37.62; H, 3.62; N, 14.53; ms m/z = 289 (M+), nmr (CDCl3/DMSO-d6): δ: 1.29 (3H, t, J=8 Hz, -CH3), 3.82 (3H, s, -OCH3), 4.20 (2H, q, J=8 Hz, -CH2-), 7.86 (1H, s, thiophene H), 10.15 (2H, br s, -NH-NH-)

Methyl 5-[2-(4-pyridyl)carbonyl]hydrazino]-4-nitro-2-thiophenecarboxylate (17)
304 mg (46%) of red crystals, mp 188-189°C, Anal. Calcd for C12H10N2O5S x ½ H2O: C, 43.51; H, 3.04; N, 16.91; Found: C, 43.24; H, 3.14; N, 16.76; ms m/z = 322 (M+), nmr (CDCl3/DMSO-d6): δ: 3.30 (2H, br s, -NH-NH-), 3.8 (3H, s, -OCH3), 7.90 (1H, s, thiophene H), 7.76-7.97 (2H, m, pyridine H), 8.70-8.90 (2H, m, pyridine H)

Methyl 5-[2-(3-pyridinyl)carbonyl]hydrazino]-4-nitro-2-thiophenecarboxylate (18)
420 mg (65.3%) of orange crystals, mp 195°C, Anal. Calcd for C12H10N4O5S: C, 44.72; H, 3.13; N, 17.38; Found: C, 44.91; H, 3.14; N, 17.15; ms m/z = 322 (M+), nmr (CDCl3/DMSO-d6): δ: 3.30 (2H, br s, -NH-NH-), 3.80 (3H, s, -OCH3), 7.49-7.58 (1H, m, pyridine H), 7.88 (1H, s, thiophene H), 8.15-8.41 (1H, m, pyridine H), 8.48-9.31 (2H, m, pyridine H)

Methyl 3-(5-acetyl-3-nitro-2-thienylthio)propionate (19)
Potassium carbonate (1.725 g, 12.5 mmol) and methyl 3-mercaptopropionate (720 mg, 6 mmol) were stirred in 20 ml of dry THF under argon at room temperature. Then 1 (1.024 g, 5 mmol) was slowly added and the suspension was stirred for another 7 h. The mixture was poured into ice-water, the precipitate filtered off and recrystallised from 96% ethanol to give 1.19 g (82%) of brown crystals, mp 110-112°C, Anal. Calcd for C10H11NO5S2: C, 41.62; H, 3.83; N, 4.84; Found: C, 41.31; H, 3.80; N, 5.01; ms m/z=289 (M+); nmr (CDCl3): δ: 2.56 (3H, s, -COCH3), 2.87 (2H, t, J=6.7 Hz, -CH2-), 3.38 (2H, t, J=6.7 Hz, -S-CH2-), 3.77 (3H, s, -COOCH3), 8.13 (1H, s, thiophene H)

Ethyl 2-(5-acetyl-3-nitro-2-thienylthio)acetate (21)
Potassium methoxide (350 mg, 5 mmol) in 5 ml of dry DMF was stirred with ethyl 2-mercaptoacetate (660 mg, 5.5 mmol) under argon for 15 min. Then 1 (510 mg, 2.5 mmol) was added slowly and the suspension was stirred at room temperature. After 3 h the mixture was poured into 700 ml of ice-water, the precipitate was filtered off and recrystallized from 96% ethanol to give 570 mg of dark yellow needles, mp 122-124°C, Anal. Calcd for C10H11NO5S2: C, 41.51; H, 3.83; N, 4.84; Found: C, 41.28; H, 3.56; N, 4.77; ms m/z=289 (M+); nmr (CDCl3): δ: 1.30 (3H, t, J=7 Hz, -CH3), 2.52 (3H, s, -COCH3), 3.88 (2H, s, -S-CH2-), 4.24 (2H, q, J=7 Hz, -OCH2-), 8.12 (1H, s, thiophene H)
General procedure for compounds (20) and (22)
Iron powder (1.4 g) was added in small portions to a suspension of 1 g of 19 or 21 in 14 ml of glacial acetic acid and 1.4 ml of water at 80°C. Then the reaction mixture was heated at 110°C for 2 h, filtered hot, washed with water and allowed to cool. The resulting precipitate was filtered off and recrystallized from 96% ethanol.

7-Acetyl-3,4-dihydrothieno[2,3-b][1,4]thiazepin-2(1H)-one (20)
490 mg (63%) of light brown crystals, mp 194-196°C, Anal. Calcd for C_{9}H_{9}NO_{2}S_{2} \times \frac{1}{2} H_{2}O: C, 45.74; H, 4.26; N, 5.99; Found: C, 45.52; H, 3.85; N, 5.79; ms m/z=227(M\textsuperscript{+}); nmr (CDCl\textsubscript{3}): \delta: 2.49 (3H, s, -COCH\textsubscript{3}), 2.76 (2H, t, J=7.2 Hz, -CH\textsubscript{2}-), 3.60 (2H, t, J=7.2 Hz, -S-CH\textsubscript{2}-), 7.39 (1H, s, thiophene H)

6-Acetyl-1H-thieno[2,3-b][1,4]thiazin-2(3H)-one (22)
500 mg (68%) of light grey needles, mp 211-213°C, Anal. Calcd for C_{8}H_{7}NO_{2}S_{2}: C, 45.05; H, 3.31; N, 6.57; Found: C, 44.96; H, 3.26; N, 6.57; ms m/z=213 (M\textsuperscript{+}), nmr (CDCl\textsubscript{3}/DMSO-d\textsubscript{6}): \delta: 2.42 (3H, s, -COCH\textsubscript{3}), 3.45 (2H, s, -CH\textsubscript{2}-), 7.51 (1H, s, thiophene H), 10.49 (1H, br s, -NH-)

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REFERENCES

1. Studies on the chemistry of thienoanellated O,N- and S,N-containing heterocycles-Part 1

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