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Short Paper

First Synthesis of 3-Acetyl-2-aminothiophenes Using the Gewald Reaction

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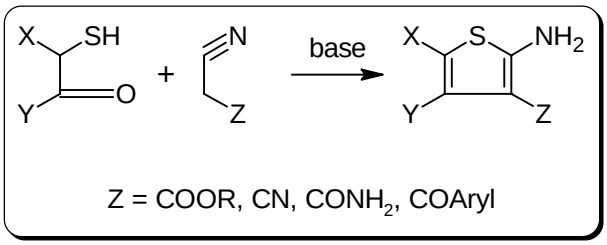
Abstract: Novel 3-acetyl-2-aminothiophenes were prepared from cyanoacetone and 1,4-dithianyl-2,5-diols using a modified Gewald reaction. The syntheses of the corresponding acetamides, as well as that of 3-acetyl-2-amino-5-nitrothiophene – an interesting building-block for thiophene azo dyes – are reported. Detailed spectroscopic investigations (^{1}H-NMR, ^{13}C-NMR, MS, IR) of the obtained compounds are presented.

Keywords: Gewald reaction; Thiophene synthesis; Cyclization; Condensation.

Introduction

Various substituted and fused 2-aminothiophenes have attracted considerable attention as structural motifs in numerous pharmaceuticals and dyes, whereof the tranquillizer brotizolam (Lendormin®), containing a thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine moiety, represents the best-known of such derivatives [1–3]. Although several thiophene ring syntheses are known in the literature [1] for the synthesis of thiophen-2-amines, the subsequent introduction of the amino group into an existing thiophene moiety is difficult and thus remains a challenging task. In contrast, during the classical Gewald thiophene synthesis – the reaction of an activated nitrile with an α-mercaptoaldehyde or with an α-mercaptoketone – an amino function is introduced right at the 2 position and therefore this reaction proves to be second to none for the construction of an 2-aminothiophene moiety (Scheme 1) [4].

Scheme 1. The classical Gewald thiophene synthesis.

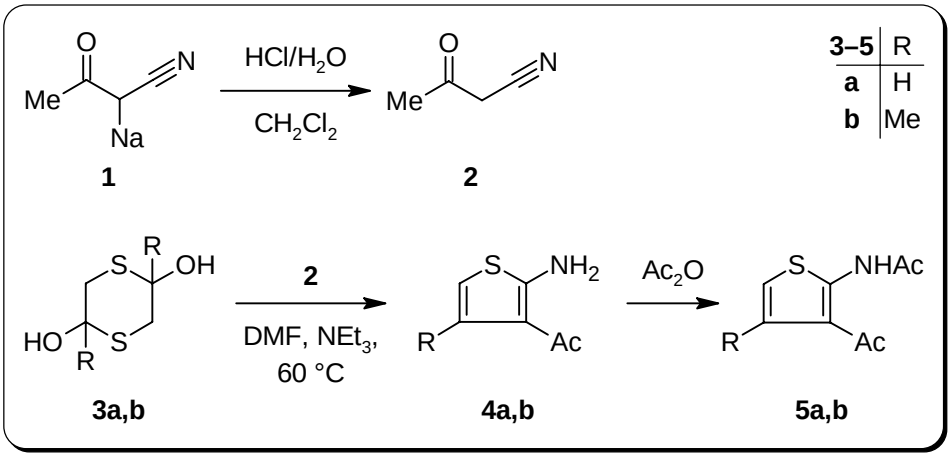


Activated nitriles used so far in the Gewald reaction are cyanoacetic acid esters, malonodinitrile, cyanoacetohydrazides and benzoylacetonitrile, which lead to the corresponding 3-alkoxycarbonyl-, 3-cyano-, 3-carbamoyl-, and 3-benzoylthiophen-2-amines, respectively [5]. To the best of our knowledge, however, the use of cyanoacetone for this purpose has not been reported yet. In this regard we now report an extension to the reaction's scope for the synthesis of 3-acetyl-2-aminothiophenes that are foreseen to be interesting building blocks.

Results and Discussion

In a modified Gewald reaction the labile cyanoacetone (**2**) – easily accessible from its commercially available sodium salt **1** – was cyclized with the appropriate α-mercaptoaldehyde dimers **3** using triethylamine in DMF at 60 °C to afford the novel 3-acetyl-2 aminothiophenes **4**, moderately stable at room temperature. Subsequent heating with acetic anhydride gave the stable acetamides **5** (Scheme 2).

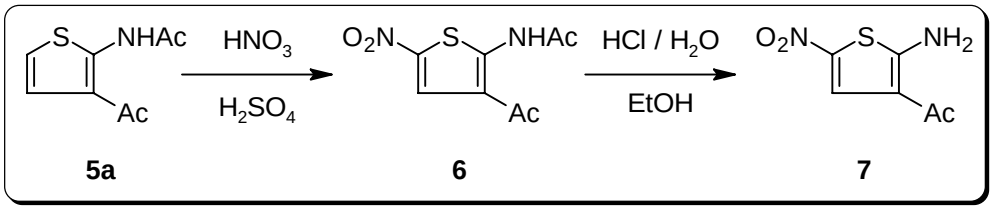
Scheme 2. Synthesis of the title compounds **4** and the corresponding acetamides **5**.



One potential practical application of acetamides **5** was realized in the synthesis of the azo-dye building-block **7**. It is well-known that related 3-alkoxycarbonyl and 3-cyanothiophenyl-2-amines containing an unsubstituted 5 position in the thiophene ring are labile compounds which undergo unwanted dimerization upon attempted diazotization [6]. However, this problem can be circumvented by 'blocking' this activated 5-position with a nitro group [7]. According to this strategy, compound **5a** was transformed into the corresponding 5-nitro derivative **6**, which after acidic hydrolysis gave the

nitrothiophenamine **7**. This deeply yellow colored compound has already been used in azo-couplings but neither its synthesis nor any analytical data have been reported so far [8].

Scheme 3. Preparation of the thiophene azo-dye building block **7**.



Conclusions

A variation of the Gewald thiophene synthesis was developed to yield novel 3-acetyl-2-aminothiophenes. Nevertheless, the possibility of adapting this new procedure to other 3-oxoalkanenitriles and other 1,4-dithianes of type **3** that are not yet commercially available requires further investigation.

Experimental Section

General

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV). IR spectra were recorded on a Perkin-Elmer FTIR 1605 spectrophotometer. Elemental analyses were performed at the Microanalytical Laboratory at the University of Vienna. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian UnityPlus 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28 °C. The centre of the solvent signal was used as an internal standard which was related to TMS with δ = 7.26 ppm (^{1}H in $CDCl_3$), δ = 2.49 ppm (^{1}H in DMSO-d_6), δ = 77.0 ppm (^{13}C in $CDCl_3$), and δ = 39.5 ppm (^{13}C in DMSO-d_6). All reagents and solvents were purchased from Sigma-Aldrich, except compounds **1**, **3a**, and **3b**, which were obtained from Merck, Fluka, and Oakwood Products, respectively.

3-Oxobutanenitrile (**2**) [9]

To a solution of cyanoacetone sodium salt (**1**, 5.25 g, 50 mmol) in water (150 mL) was added CH_2Cl_2 (100 mL). Whilst stirring, the mixture was adjusted to pH 1 with conc. HCl. The organic layer was separated, the aqueous layer was extracted once again with CH_2Cl_2 (100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. While keeping the bath temperature below 30 °C, the solvent was removed under reduced pressure to afford **2** (3.60 g, 87%) as a colorless and unstable oil (pure according to ^{1}H-NMR), which was used immediately and without further purification in the next reaction step. ^{1}H-NMR [10] ($CDCl_3$): δ = 2.34 (s, 3H, CH_3), 3.48 (s, 2H, CH_2); ^{13}C-NMR ($CDCl_3$): δ = 29.2 (CH_3, ^{1}J = 128.9 Hz), 32.7 (CH_2, ^{1}J = 128.9 Hz, $^{2}J(CH_2,CH_3)$ = 1.8 Hz), 113.7 (CN, $^{2}J(CN,CH_2)$ = 9.7 Hz), 195.0 (CO, $^{2}J(CO,CH_2)$ = 6.4 Hz, $^{2}J(CO,CH_3)$ = 6.4 Hz).

1-(2-Amino-3-thienyl)ethanone (**4a**)

Triethylamine (1 g, 10 mmol) was added with stirring to a solution of crude **2** (3.60 g, 43 mmol) and dithiane **3a** (3.35 g, 22 mmol) in DMF (10 mL), whereupon the temperature of the solution rose slightly. After 15 min, the solution was heated to 60 °C for 3 h. Then, the solvent was removed under reduced pressure and H_2O (50 mL), diethyl ether (50 mL), and glacial acetic acid (ca. 1–3 mL) were added to the oily residue until the organic layer became clear. After separation of the ethereal layer and further extraction of the aqueous layer with diethyl ether (50 mL), the combined organic layers were washed subsequently with 5% aqueous $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **4a** (3.98 g, 65%) as a yellow, slowly darkening oil, which was pure according to TLC and ^{1}H-NMR. B.p.: 148 °C (7 mbar); IR (KBr): 3382, 3283, 1616, 1589 cm-1; ^{1}H-NMR ($CDCl_3$): δ = 2.38 (s, 1H, CH_3), 6.12 (d, ^3J(H5,H4) = 5.8 Hz, 1H, H5), 6.84 (s, 2H, NH_2), 6.91 (d, ^3J(H5,H4) = 5.8 Hz, 1H, H4); ^{13}C-NMR ($CDCl_3$): δ = 28.1 (CH_3, ^1J = 127.1 Hz), 106.3 (C5, ^1J = 190.5 Hz, ^2J(C5,H4) = 5.6 Hz), 115.8 (C3, ^3J(C3,H5) = 8.6 Hz, ^3J(C3,H4) = 6.0 Hz, ^3J(C3,CH_3) = 1.4 Hz), 125.9 (C4, ^1J = 166.6 Hz, ^2J(C4,H5) = 3.9 Hz), 164.2 (C2, ^3J(C2,H4) = 10.2 Hz, ^3J(C2,H5) = 6.5 Hz), 193.8 (CO, ^2J(CO,CH_3) = 5.8 Hz); MS m/z (%) = 141 (M^+, 66), 126 (100), 98 (17); HRMS m/z calcd. for C_6H_7NOS: 141.0248. Found: 141.0251.

1-(2-Amino-4-methyl-3-thienyl)ethanone (**4b**)

Triethylamine (1 g, 10 mmol) was added with stirring to a solution of crude **2** (2.08 g, 25 mmol) and dithiane **3b** (2.25 g, 12.5 mmol) in DMF (10 mL) and the mixture was heated to 60 °C for 5 h. Then, the solvent was removed under reduced pressure and the semi-solid residue was recrystallized from cyclohexane–CH_2Cl_2 to afford 1.63 g (41%) of **4b** as yellowish to brownish crystals. M.p.: 145–148 °C; IR (KBr): 3332, 3228, 3127, 1602, 1575 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.34 (d, ^4J(CH_3,H5) = 1.2 Hz, 3H, CH_3), 2.44 (s, 3H, $COCH_3$), 5.97 (q, ^4J(H5,CH_3) = 1.2 Hz, 1H, H5), 7.00 (s, 2H, NH_2); ^{13}C-NMR ($CDCl_3$): δ = 19.6 (CH_3, ^1J = 127.8 Hz, ^3J(CH_3,H5) = 4.0 Hz), 30.6 ($COCH_3$, ^1J = 127.2 Hz), 103.2 (C5, ^1J = 187.7 Hz, ^3J(C5,CH_3) = 7.1 Hz), 116.0 (C3), 134.7 (C4, ^2J(C4,CH_3) = 6.3 Hz, ^2J(C4,H5) = 3.4 Hz), 166.3 (C2, ^3J(C2,H5) = 6.8 Hz), 194.5 (CO, ^2J(CO,CH_3) = 5.8 Hz); MS m/z (%) = 155 (M^+, 84), 140 (100); Anal. calcd. for $C_7H_9NOS \cdot 0.1\ H_2O$: C, 53.54; H, 5.91; N, 8.92. Found: C, 53.52; H, 5.57; N, 8.67.

N-(3-Acetyl-2-thienyl)acetamide (**5a**)

Thiophenamine **4a** (1.41 g, 10 mmol) and excess acetic anhydride (5 mL) were refluxed for 15 min. Then, H_2O (ca. 10 mL) was added and the mixture was heated again for a further 5 min. Upon cooling overnight, the product crystallized as slightly yellowish needles. Concentration of the mother liquor gave additional crystals. In total 1.74 g (95%) of **5a** were obtained. M.p.: 92–94 °C; IR (KBr): 1683, 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.29 (s, 3H, $NCOCH_3$), 2.52 (s, 3H, $COCH_3$), 6.72 (d, ^3J(H5,H4) = 5.8 Hz, 1H, H5), 7.18 (d, ^3J(H4,H5) = 5.8 Hz, 1H, H4), 11.88 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ = 23.5 ($NCOCH_3$, ^1J = 129.0 Hz), 28.7 ($COCH_3$, ^1J = 127.7 Hz), 116.0 (C5, ^1J = 187.0 Hz, ^2J(C5,H4) = 5.0 Hz), 120.8 (C3), 124.1 (C4, ^1J = 168.3 Hz, ^2J(C4,H5) = 3.6 Hz), 149.4 (C2), 167.7 (NCO, ^2J(NCO,NH) = 6.4 Hz, ^2J(NCO,$NCOCH_3$) = 4.6 Hz), 195.8 (CO, ^2J(CO,$COCH_3$) = 5.8 Hz); MS m/z

(%) = 183 (M^+, 18), 141 (68), 126 (100); Anal. calcd. for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.64. Found: C, 52.37; H, 4.74; N, 7.54.

N-(3-Acetyl-4-methyl-2-thienyl)acetamide (**5b**)

Applying a procedure similar to that used for the synthesis of acetamide **5a**, 0.91 g (92%) of **5b** were obtained as almost colorless needles starting from **4b** (0.78 g, 5 mmol) and excess acetic anhydride (3 mL). M.p.: 128–132 °C; IR (KBr): 1676, 1619 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.26 (s, 3H, $NCOCH_3$), 2.45 (d, ^3J(CH_3,H5) = 1.2 Hz, 3H, CH_3), 2.54 (s, 3H, $COCH_3$), 6.38 (q, ^3J(H5,CH_3) = 1.2 Hz, 1H, H5), 12.32 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ = 19.1 (CH_3, ^1J = 128.0 Hz, ^3J(CH_3,H5) = 4.0 Hz), 23.8 ($NCOCH_3$, ^1J = 128.9 Hz), 31.3 ($COCH_3$, ^1J = 127.9 Hz), 113.9 (C5, ^1J = 184.2 Hz, ^3J(C5,CH_3) = 6.6 Hz), 120.8 (C3), 133.2 (C4, ^2J(C4,CH_3) = 6.2 Hz, ^2J(C4,H5) = 3.2 Hz), 151.7 (C2), 167.9 (NCO), 196.9 (CO); MS m/z (%) = 197 (M^+, 32), 155 (66), 140 (100), 43 (71); Anal. calcd. for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10. Found: C, 54.52; H, 5.36; N, 7.19.

N-(3-Acetyl-5-nitro-2-thienyl)acetamide (**6**)

Acetamide **5b** (1.37 g, 7.5 mmol) was added carefully over a period of 30 min at 0 °C to a well stirred mixture of HNO_3 (65%, 2.5 mL, d = 1.4 g/mL, 36 mmol) and H_2SO_4 (98%, 2.5 mL, d = 1.8 g/mL, 46 mmol). After the addition was complete, the deeply colored reaction mixture was stirred for a further 10 min and was then poured cautiously into excess ice-water. The precipitate formed was filtered off, washed with H_2O, and dried under reduced pressure to afford 2.07 g (91%) of **6** (pure according to ^{1}H-NMR). An analytically pure sample was obtained by recrystallization from MeOH–DMF. M.p.: 178–179 °C; IR (KBr): 3182, 3079, 1683, 1655 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 2.36 (s, 3H, $NCOCH_3$), 2.57 (s, 3H, $COCH_3$), 8.55 (s, 1H, H4), 11.94 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 23.1 ($NCOCH_3$, ^1J = 129.7 Hz), 28.6 ($COCH_3$, ^1J = 128.3 Hz), 119.7 (C3, ^2J(C3,H4) = 3.6 Hz, ^3J(C3,$NCOCH_3$) = 1.4 Hz), 129.2 (C4, ^1J = 177.6 Hz), 139.8 (C2), 151.4 (C5, ^2J(C5,H4) = 11.9 Hz), 170.2 (NCO, ^2J(NCO,$NCOCH_3$) = 6.7 Hz), 195.6 (CO, ^2J(CO,$COCH_3$) = 6.1 Hz, ^3J(CO,H4) = 1.8 Hz); MS m/z (%) = 228 (M^+, 4), 186 (20), 69 (42), 43 (100); Anal. calcd. for $C_8H_8N_2O_4S$: C, 42.10; H, 3.53; N, 12.27. Found: C, 42.11; H, 3.66; N, 12.16.

1-(2-Amino-5-nitro-3-thienyl)ethanone (**7**)

A mixture of nitroacetamide **6** (1.14 g, 5 mmol), EtOH (5 mL), and conc. HCl (15 mL) was refluxed overnight (18 h). Removal of EtOH under reduced pressure and refrigeration of the reaction mixture for 48 h produced a dark precipitate. The solid was filtered off, washed with water, and dried under reduced pressure. The residue was treated three times with hot acetone (10 mL) and filtered. The combined acetone phases were concentrated to almost dryness to afford pure **7** (0.66 g, 70%) as a dark yellow powder. M.p.: 222–224 °C; ^{1}H-NMR (DMSO-d_6): δ = 2.40 (s, 3H, CH_3), 8.28 (s, 1H, H4), 9.11 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6): δ = 27.80 (CH_3, ^1J = 127.7 Hz), 114.5 (C3, ^2J(C3,H4) = 3.8 Hz, ^3J(C3,CH_3) = 1.5 Hz), 129.7 (C5), 133.4 (C4, ^1J = 174.6 Hz), 168.3 (C2, ^3J(C2,H4) = 12.1 Hz), 194.2 (CO, ^2J(CO,CH_3) = 5.8 Hz, ^3J(CO,H4) = 1.8 Hz); MS m/z (%) = 186 (M^+, 100), 69 (58); Anal. calcd. for $C_6H_6N_2O_3S$: C, 38.70; H, 3.25; N, 15.05. Found: C, 38.95; H, 3.33; N, 14.80.

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Sample Availability: Available from the authors.