REGIOSELECTIVITY OF ELECTROPHILIC ATTACKS TO 5-AMINO-3-THIOXO-3*H*-1,2-DITHIOLE-4-CARBOXYLIC ACID FUNCTIONAL DERIVATIVES. ELUCIDATION OF PRODUCT STRUCTURES.

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Abstract

Acylation of 5-amino-3-thioxo-3*H*-1,2-dithiole-4-carboxylic acid functional derivatives led to the formation of *N*-acyl compound *via* *S*-acyl intermediate. On the other hand, alkylation occurred only at the sulfur atom of thioxo group. Structure elucidation of both types of products was done by IR, ^{1}H, ^{13}C NMR and X-ray structural analysis.

Keywords

regioselectivity; 1,2-dithiole; alkylation; acylation; 1,2-dithiolium; hydrogen bonding; X-ray structural analysis.

Introduction

The regioselectivity as a basic phenomenon is very intensively studied along with looking for mechanism of the chemical reactions. Due to the presence of two exocyclic functional groups, the title compounds can serve as suitable models for studying electrophilic reactions such as alkylation and acylation. No systematic research has been done in this area so far. It might be owing to the instability of title compounds in basic medium (1).

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Experimental

General methods. Materials were obtained from commercial suppliers and were used without further purification. Melting points, determined with a Kofler hot-stage apparatus, are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz, and 75.5 MHz respectively (DRX 500 Avance Bruker). FTIR spectra (KBr) were measured on a Genesis ATI Mattson spectrometer. Both X-ray intensity data were collected at 150 K on a KUMA KM4 four-circle diffractometer with MoK_{α} radiation (λ = 0.71069 Å). The structures were solved by direct methods (program: SHELXS-97) and refined by weighted full-matrix least-squares on F^2 (SHELXL-97). All non-hydrogens were refined anisotropically, hydrogens were localized from difference Fourier map and refined isotropically.

Synthesis and identification of 5-amino-4-cyano-3-(methylsulfanyl)-1,2-dithiolium iodide (3a; R' = CH_3). To a solution of 1a (1.05 g, 6.00 mmol) (1) in DMF (10 mL) methyl iodide (0.75 mL, 12.05 mmol) was added. After the mixture was allowed to stand for 24 h at room temperature, precipitate was collected by filtration, and washed with ethanol. Compound was obtained in yield 1.25 g (66 %): mp 195 °C (decomp., DMF); IR $\tilde{\nu}$ / cm^{-1} 3217 (m), 3060 (m), 2218 (w), 1610 (s), 1500 (s), 1443 (w), 1416 (w), 1346 (w), 1315 (w), 1016 (w); ^{1}H NMR (DMSO-d_6) δ / ppm 3.01 (s, 3H, CH_3), 5.85 (s, br, 2H, NH_2);^{13}C NMR (DMSO-d_6) δ / ppm 16.54 (CH_3), 97.74, 109.33, 180.48, 188.79. Anal. Calcd for $C_5H_5N_2S_3I$: C, 18.99; H, 1.59; N, 8.86. Found: C, 18.64; H, 1.40; N, 8.70.

Compound 3a . DMF (R' = CH_3) was obtained in the same manner as 3a except for washing the isolated product with ethanol and drying in the vacuum oven.

Crystallographic data for 3a . DMF (R' = CH_3): $C_8H_{12}IN_3OS_3$, M = 389.28, triclinic crystal system, S.G. P-1, a = 6.038(2) Å, b = 9.560(6) Å, c = 12.659(4) Å, α = 93.23(5) °, β = 102.73(3) °, γ = 96.21(5) °, V = 706.1(5) $Å^3$, Z = 4, D_{calc} = 1.831 $Mg.m^{-3}$. Number of collected / independent reflections was 2747 / 2747; R_{int} = 0.0000. The final R indices [I>2o(I)] : R1 = 0.0500, wR2 = 0.1383, the largest diff. peak and hole were 2.028 and –1.682 e. $Å^{-3}$. Coordination have been deposited at the CCDC, deposition number CCDC 141128.

Synthesis and identification of ethyl 5-(acetylamino)-3-thioxo-3*H*-1,2-dithiole-4-carboxylate (2c; R = CH_3). A suspension of 1c (1.00 g, 5.20 mmol) (1) in acetic anhydride (25 mL, 263 mmol), was heated under reflux for 0.5 h. The solid resulting from solvent evaporation was crystallized to

afford 2.15 g (90 %) of product: mp 150-151 °C (chloroform); IR $\tilde{\nu}$ / cm^{-1} 3024 (w), 2999 (w), 2937 (w), 1689 (m), 1657 (s), 1495 (s), 1400 (m), 1365 (m), 1329 (s), 1281 (s), 1254 (s), 1203 (m), 1113 (w), 1038 (m), 1011 (s); ^{1}H NMR ($CDCl_3$) δ / ppm 1.42 (t, 3H, CH_3, J = 7.2 Hz), 2.39 (s, 3H, $COCH_3$), 4.42 (q, 2H, CH_2, J = 7.2 Hz), 12.68 (s, br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ / ppm 14.08 (CH_3), 23.86 (CH_3), 62.55 (CH_2), 118.67, 166.24, 170.50, 174.44, 208.08 (C=S). Anal. Calcd for $C_8H_9NO_3S_3$: C, 36.49; H, 3.44; N, 5.32. Found: C, 36.40; H, 3.33; N, 5.21.

Crystallographic data for 2c (R = CH_3): $C_8H_9NO_3S_3$, M = 263.34, monoclinic crystal system, S.G. P-2(1)/n, a = 7.460(4) Å, b = 16.392(4) Å, c = 9.539(4) Å, α = 90 °, β = 110.59(6) °, γ = 90 °, V = 1092.0(8) $Å^3$, Z = 4, D_{calc} = 1.602 $Mg.m^{-3}$. Number of collected / independent reflections was 2084 / 1929; R_{int} = 0.0291. The final R indices [I>2σ(I)]: R1 = 0.0434, wR2 = 0.1204, the largest diff. peak and hole were 0.433 and -0.356 e. $Å^{-3}$. Coordination have been deposited at the CCDC, deposition number CCDC 141129.

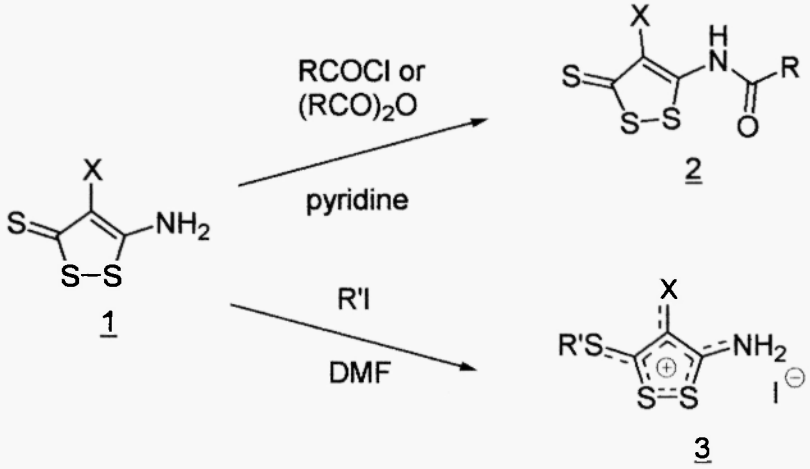
Acylation of 1c - ^{1}H NMR-experiment: To a solution of 1c in pyridine-d^5 was added an excess of freshly distilled acetic anhydride. Subsequently the solution was carefully mixed and the temperature was keep at 25 °C. Composition of the reaction mixture in the course of the reaction was monitored by ^{1}H NMR spectroscopy. After 30 min the acetylating of 1c to 2c was completed. In addition to bands of starting compound 1c [δ 1.36 (t, 3H, CH_3, J = 7.1 Hz), 4.42 ppm (q, 2H, CH_2, J = 7.1 Hz)], product 2c [δ 1.28 (t, 3H, CH_3, J = 7.1 Hz), 2.28 (s, 3H, $NCOCH_3$) and 4.22 ppm (q, 2H, CH_2, J = 7.1 Hz)], acetic anhydride (2.16 ppm) and acetic acid (2.15 ppm) the spectra were showed peaks at δ 2.37 (s, 3H, $SCOCH_3$) and 3.21 ppm (q, 2H, CH_2, J = 7.2 Hz), assigned to the methyl function of CH_3–CO–S– and the methylene of ethoxycarbonyl group. These bands gradually disappeared.

Results and discussion

Reaction of the alkylationing agents with the title substrate was first reported (2) in 1963. The article indicated a possibility of formation of *S*-acyl derivative in nitrile set 1a. The same author (1) corrected his previous idea and presented that *N*-acetyl derivatives 2a and 2c (R = CH_3) were easily available. In the case of ethyl ester the product was prepared by the reaction of 1c with acetyl chloride in pyridine as a solvent. The product was characterized by melting point and UV-VIS spectroscopic data. The synthesis of 2e was carried out by heating in acetic anhydride (product identity was deduced from elemental analysis) (3) A common way to prepare *N*-acyl compound was described in patent (4) (for methyl ester 1b and oleoyl chloride). The compound was identified on the basis of microanalysis and MS spectra. Furthermore, the authors (4)

reported that upon the treatment of 2e with alkylation agents gave $4\lambda^4$-[1,2]dithiole-[1,5-b][1,2,4]oxathiazole skeleton.

Methylation with methyl iodide in hot dimethylformamide solution furnished (5,6) S-methyl derivatives 3a and 3b (R' = CH_3). Their structures were confirmed by IR, UV-VIS spectra and elemental analysis. The alkaline hydrolysis into salt of methyl 2-cyano-3-methylsulfanyl-3-sulfanylacrylate and 2-cyano-3-methylsulfanyl-3-sulfanylacrylonitrile formed also during other reactions (7) supported the proposed arrangement. Alkylation without solvent (in excess of agent) was also feasible (8). A positive charge of salt 3 might be present at S(2)-atom of cycle (8), at nitrogen atom in the amino group (5), or delocalized over the whole dithiole ring (6).



Scheme 1. a: X = CN; b: X = $COOCH_3$; c: X = $COOCH_2CH_3$; d: X = $CONH_2$; e: X = $CSNH_2$; (R = CH_3, CH_3CH_2O, Ph, *t*-Bu; R' = CH_3, $PhCH_2$, cyclohexyl, *t*-Bu)

To explain results of transformation we selected representative series of alkylation and acylation agents (Scheme 1.) and studied their reactivity towards nitrile 1a, ethyl ester 1c and amide 1d. Examples of typical synthetic procedures are described. Though the possibility to acylate the nitrile 1a was reported (1), our attempts to perform this reaction failed. Amide 1d treated by an excess of the reagent for a long reaction time, gave a double acylated product showing that an additional attack on the amidic group occurred. The structures of 3a . DMF (X = CN, R' = CH_3) and 2c (X = $COOCH_2CH_3$, R = CH_3) were unambiguously assigned by single-crystal X-ray crystallographic analysis (Fig. 1, Fig. 2). It was found that alkylation provided *S*-alkyl derivative, while acylation proceeded on the nitrogen atom finally. However, according to the ^1H NMR experiment acylation of title compounds afforded kinetically preferred *S*-acyl derivative (an isolation was not successful). This intermediate was rearranged to *N*-acylated product 2.

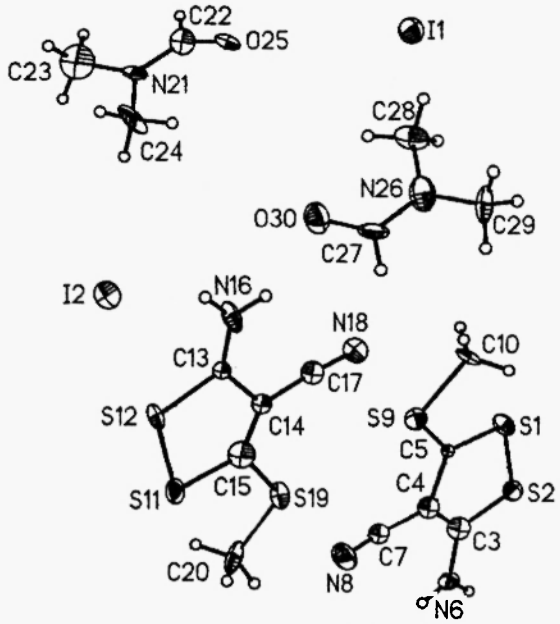


Fig. 1. X-ray structure of 5-amino-4-cyano-3-(methylsulfanyl)-1,2-dithiolium iodide–
–dimethyl formamide (1:1) (3a . DMF: X = CN, R' = CH_3).

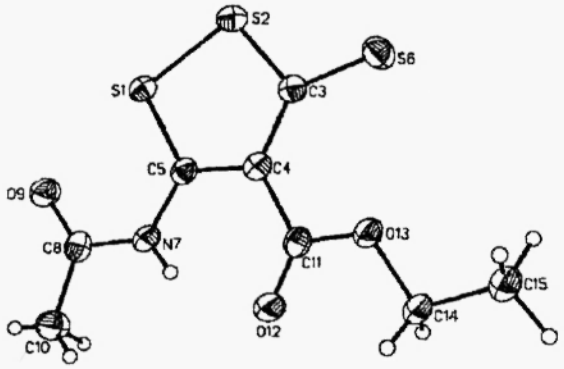
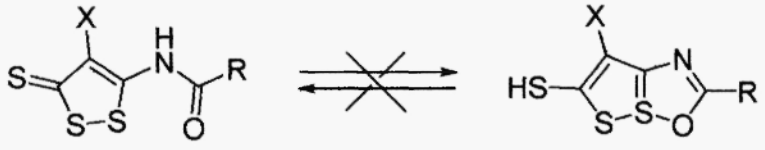


Fig. 2. X-ray structure of ethyl 5-(acetylamino)-3-thioxo-3*H*-1,2-dithioie-4-carboxylate
(2c; X = $COOCH_2CH_3$, R = CH_3)

On the basis of X-ray structural data, IR, ^1H and ^{13}C NMR spectra we prefer explanation of 3a . DMF (X = CN, R' = CH_3; Fig.1) structure in terms of charge delocalization to the whole molecule. The vibrational bands 3217 cm^{-1} and 3060 cm^{-1} of ν_{as}, ν_s (NH_2) are observed in wave number range between NH_2 and NH_2^+ groups. Both signals of methylsulfanyl group in ^1H and ^{13}C NMR spectra are shifted to higher values than they are frequent. On the other hand, the chemical shift of the cyano carbon is upfield due to an electron flow from the cyano group towards the

1,2-dithiolium ring. Furthermore, the bond length S-S in 3a . DMF (2.076 Å) obtained from crystal structure is as good as equal to the S-S bond length in 2c (2.066 Å), which supported structure 3a explanation, mentioned above.

Crystal structure of 2c (X = $COOCH_2CH_3$, R = CH_3; Fig. 2) also included a strong hydrogen bonding N–H(7)···O(12)=C(11). As a result, the dithiole cycle and amidic function are not coplanar, and therefore no interaction between O(9) and S(1) is possible. Therefore, the existence of 2c in the form of ethyl 2-methyl-6-sulfanyl-4λ^4-[1,2]dithiolo[1,5-b][1,2,4]oxathiazole-7-carboxylate 4c (Scheme 2.) like referred authors (4) are excluded.



2 4

Scheme 2.

Conclusion

The results of this study are in agreement with concept of interactions between electrophilic reagents and bifunctional amino-thioxo substrates (9,10).

Acknowledgments

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