Pergamon

Tetrahedron Letters 39 (1998) 4581–4584

TETRAHEDRON LETTERS

Polycarbonyl Heterocycles, Part IX[1] : Synthesis of Thiophene-2,3-dione Derivatives and Their Transformation to Pyrrolo[3,2-*c*]pyridine Systems.

Barbara Zaleska*, Dariusz Cież, Jerzy Klimek

Department of Organic Chemistry, Jagiellonian University, PL 30-060 Kraków, Poland

Received 11 February 1998; revised 16 April 1998; accepted 17 April 1998

Abstract: Thiophene-2,3-dione derivatives **2** were prepared in the reaction of β-aminovinylthioamides **1** with ethyl oxalyl chloride. Treatment of compounds **2b,c** with malonodinitrile led to the ring transformation of the thiophene-2,3-dione system to pyrrolo[3,2-*c*]pyridine derivatives **4b,c**.

The synthesis of the pyrrolo[3,2-*c*]pyridine system has attracted considerable attention from organic chemists in recent years[2,3] because of its broad range of biological activities. Derivatives of this system exhibit interesting activity as α_1-adrenergic antagonist[4] or as orally active renin inhibitors[5]. One major problem in the synthesis of 2,3-dioxo-pyrrolo[3,2-*c*]pyridine (5-azaisatin) is due to the presence of two neighbouring carbonyl groups.

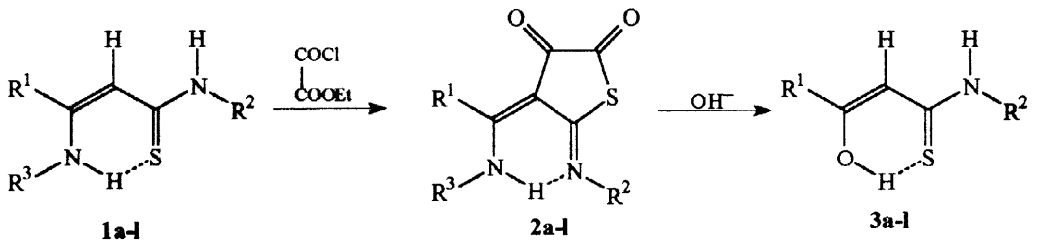
For some years we have employed the β-aminovinylthioamide derivatives[6] **1** as starting materials for a synthesis of several biologically active heterocyclic compounds such as furan,[7] pyridine,[8,9] thiazolidine[10,11] and thiazepine[12,13] derivatives. The high degree of functionalization allows these β-aminovinylthioamides **1** to react in all positions. [14]

We have investigated the reactivity of **1** towards ethyl oxalyl chloride expecting that the resulting polycarbonyl heterocyclic system may serve us as useful reagent in the synthesis of fused heterocyclic compounds. In contrast to our earlier results[9] the reaction of **1** with ethyl oxalyl chloride leads directly with good yields to a product of S and C2 acylations giving new thiophene-2,3-dione derivatives **2** (scheme 1).

The first synthesis of thiophene-2,3-dione derivatives was described by Mortensen[15] in 1971. It is known, that benzothiophene-2,3-dione derivatives react with malonodinitrile giving condensation products[16] but conversion into azaisatin derivatives **4** has not yet been reported in the literature.

Regiospecific S and C-2 acylation of **1** by means of ethyl oxalyl chloride in boiling benzene led to the thiophene-2,3-dione system **2**. Treatment of **2** with sodium hydroxide resulted in elimination of amine, ring opening and formation of β-hydroxyvinylthioamides **3** respectively. Product **2** is more stable in acidic medium: hydrolysis was observed after 3h of refluxing with ethanol/hydrochloride acid.

0040-4039/98/$19.00
PII: S0040-4039(98)00812-0



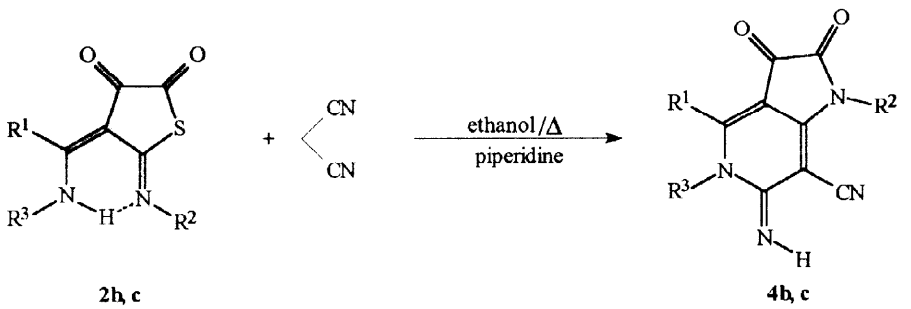
1a-l **2a-l** **3a-l**

a: $R^1=R^2=R^3=$ Ph ; **b:** $R^1=$ pTol , $R^2=$ Ph , $R^3=$ pAni ; **c:** $R^1=$ Ph , $R^2=$ pTol , $R^3=$ pAni ; **d:** $R^1=R^3=$ Ph , $R^2=$ pTol ; **e:** $R^1=R^3=$ Ph , $R^2=$ pCl-C_6H_4 ; **f:** $R^1=$ pCl-C_6H_4 , $R^2=$ Ph , $R^3=$ pTol ; **g:** $R^1=CH_3$, $R^2=R^3=$ Ph ; **h:** $R^1=$ pTol , $R^2=$ Ph, $R^3=$ pBr-C_6H_4; **i:** $R^1=$ pCl-C_6H_4 , $R^2=R^3=$ Ph ; **j:** $R^1=R^2=$ Ph, $R^3=$ pTol ; **k:** $R^1=$ pTol , $R^2=R^3=$ Ph ; **l:** $R^1=$ β-Naph , $R^2=$ Ph , $R^3=$ pTol ;

Scheme 1

The reaction of thiophene-2,3-dione **2b,c** with malonodinitrile in boiling ethanol in the presence of a catalytic amount of piperidine has resulted in formation of pyrrolo[3,2-*c*]pyridine derivatives **4b,c** (scheme 2).

The synthesis of the derivatives **4b,c** can be rationalised in terms of the formation and subsequent desulfurisation of an intermediate, open-chain condensation product, which undergoes cyclisation to pyrrolo [3,2-*c*]pyridine system **4**. It has been noticed that this ring transformation and the formation of a fused system **4** can be rationalized in the cases where in the amine R^3NH- ring of **2**, a π-electron releasing substituent such as OCH_3 influences the nucleophilicity of amine nitrogen.



2b, c **4b, c**

Scheme 2

The new thiophene-2,3-dione derivatives **2** as well as pyrrolo[3,2-*c*]pyridine **4** were characterized by elemental analyses and spectroscopic data. The electron impact (EI/MS) spectra of compounds **2** display diagnostic M^+ peaks and major characteristic ion **A** $[M - SCOCO]^{\bullet+}$ (100%) specific only for thiophene-2,3-diones as well as ions **B** and **C** respectively (figure 1). Completely different fragmentations were observed for thiazolidine-2,3-dione - isomeric diacylation products of β-aminovinylthioanilides with oxalyl chloride. [9]

The ^{1}H-nmr spectra of **2** confirmed C-2 acylation because CH vinyl is not observed in compounds **2**. In ^{13}C-nmr carbon atoms resonance was characteristic for thiophene-2,3-dione system and confirmed by means of DEPT-135 experiment. The analysis of ^{1}H and ^{13}C-nmr data of compounds **4b,c** clearly indicates the presence of α-dicarbonyls (174.6 and 159.4 ppm) in the pyrrolidine ring[17] fused with the pyridine system of pyrrolo

[3,2-*c*]pyridine derivatives **4b,c**. The structure of products **4b,c** is strongly supported by the IR spectrum and MS fragmentation (figure 1). The spectra of compounds **4** exhibit parent ions at m/z 460 and ion **B** m/z 404 $[M\text{-}COCO]^{\bullet+}$ characteristic for fragmentation of isatin[18] as well as ions **C**, **D** and **E**, which are formed due to the α and β cleavage of heterocyclic system **4**. [19]

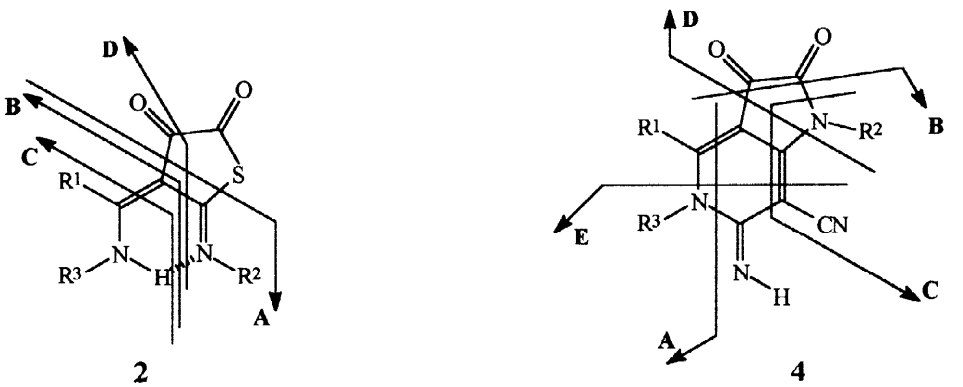


Figure 1

In summary, the reaction of β-aminovinylthioamides **1** with ethyl oxalyl chloride represents a very short, high yield procedure for synthesis of 4,5-substituted thiophene-2,3-diones **2**. Moreover, compounds **2b,c** are valuable intermediates for synthesis of some very interesting pyrrolo[3,2-*c*]pyridine (5-azaisatin) derivatives as well as for construction of other fused heterocyclic systems. [20-23]

EXPERIMENTAL

***Procedure for the preparation of thiophene-2,3-dione derivatives* 2.**

Ethyl oxalyl chloride (1.47 ml, 13 mmol) was added dropwise to a boiling solution of β-aminovinyl-thioamide **1** (12 mmol) in 200 ml anhydrous C_6H_6 and refluxed for 2-4 hrs. After cooling the yellow crystalline compound **2** was filtered off and crystallized from C_6H_6.

2a: $C_{23}H_{16}N_2O_2S$; MW 384.5; Mp. 266 °C; yield 85%; (% C, H, N): calc. 71.85, 4.19, 7.28; found. 72.01, 4.25, 7.32; IR (KBr): ν (cm^{-1})= 3272 (NH), 1739 (C=O), 1664 (C=O), 1609 (C=N); ^{1}H-nmr ($CDCl_3$): σ (ppm)= 13.46 (s. NH), 7.00-7.55 (m. 15H, aromatic protons); ^{13}C-nmr ($CDCl_3$): σ (ppm)= 197.50 (S-C=O), 175.78 (=C-C=O), 164.88 (N=C-S), 104.27 (=C-C=O); MS (EI): m/z (%)=384 (73) M^+, 295 (100) A, 193 (24) B, 180 (6) C, 220 (9) D.

***Procedure for the preparation of pyrrolo[3,2-c]pyridine derivatives* 4.**

The mixture of thiophene-2,3-dione **2b,c** (1 mmol) and malonodinitrile (1 mmol) dissolved in 50 ml C_2H_5OH was treated with 0.05 ml of piperidine (0.5 mmol). The solution was refluxed for 5 hrs. The red precipitate was filtered off.

4b: $C_{28}H_{20}N_4O_3$; MW 460.51; Mp. 327 °C; yield 63%; (% C, H, N): calc. 73.04, 4.35, 12.17; found. 72.95, 4.23, 12.17; IR (KBr): ν (cm^{-1})= 3281 (NH), 2220 (CN), 1759 (C=O), 1710 (C=O), 1550 (C=N); ^{1}H-nmr (DMSO-d_6): σ (ppm)= 9.76 (s, NH), 7.79-6.93 (m., 13H, aromatic protons), 3.83 (s. pCH_3O), 2.45 (s, pCH_3);

^{13}C-nmr (DMSO-d_6): σ (ppm)= 174.64 (=C-C=O), 161.58 (N-C=O), 159.54 (-C=N-), 113.51 (-CN), 55.24 (pCH_3O), 21.13 (pCH_3); MS (EI): m/z (%)=460 (27) M^+, 224 (7) A, 404 (14) B, 141 (18) C, 285 (25) D.
4c: $C_{28}H_{20}N_4O_3$; MW 460.51; Mp. 318 °C; yield 58%; (% C, H, N): calc. 73.04, 4.35, 12.17; found. 73.00, 4.25, 12.10; IR (KBr): ν (cm^{-1})= 3281 (NH), 2220 (CN), 1755 (C=O), 1705 (C=O), 1560 (C=N); ^{1}H-nmr (DMSO-d_6): σ (ppm)= 9.75 (s, NH), 7.81-6.97 (m., 13H, aromatic protons), 3.79 (s. pCH_3O), 2.41 (s, pCH_3); ^{13}C-nmr (DMSO-d_6): σ (ppm)= 174.52 (=C-C=O), 161.50 (N-C=O), 159.44 (-C=N-), 113.45 (-CN), 55.19 (pCH_3O), 21.03 (pCH_3); MS (EI): m/z (%)=460 (32) M^+, 209 (11) A, 404 (15) B, 156 (20) C, 300 (29) D.

REFERENCES

1. Zaleska B.; Kurdziel M. *Synth. Commun.* **1988**, *18*, 1863-73.
2. Nagafuji P.; Cushman M. *J. Org. Chem.* **1996**, *61*, 4999-5003.
3. Kadushkin A. V.; Bdanova L. I.; Kuleshova L. F.; Bogdanova G. A.; Granik V. G. *Khim.-Farm. Zh.* **1995**, *29*, 52-55.
4. Meyer M. D.; Altenbach R. J.; Basha F. Z.; Carroll W. A.; Drizin I.; Elmore S. W.; Kerwin Jr J. F.; Lebold S. A.; Lee E. L.; Sippy K. B.; Tietje K. R.; Wendt M. D. U.S.-Pat. 5,442,044; *C.A.* **1997**, *126*, P199575q.
5. Hoover D. J.; Lefker B. A.; Rosati R. L. U.S.-Pat. 5,442,044; *C.A.* **1996**, *124*, P87802p.
6. Liebscher J.; Knoll A. *Z. Chem.* **1987**, *27*, 8.
7. Zaleska B. *Monatsh. Chem.* **1986**, *117*, 671-8.
8. Zaleska B. *J. Prakt. Chem.* **1987**, *329*, 787-92.
9. Żankowska-Jasińska W.; Eilmes J. *Roczn. Chem.* **1973**, *47*, 2235.
10. Zaleska B.; Cież D.; Winnik W.; Chaczatrian K. *Pharmazie* **1995**, *50*, 537-40.
11. Coen S.; Ragonnet B.; Vieilescazes C.; Roggero J. P. *Heterocycles* **1985**, *23*, 1225.
12. Zaleska B.; Cież D.; Grochowski J.; Serda P.; Winnik W. *Liebigs Ann. Chem.* **1996**, 211-5.
13. Cocco M. T.; Congiu C.; Onnis V. *J. Heterocyclic Chem.* **1995**, *32*, 463.
14. Liebscher J.; Abegaz B.; Knoll A. *Phosphorus and Sulfur* **1988**, *35*, 5-34.
15. Mortensen J. Z.; Hedegaard B.; Lawesson S. -O. *Tetrahedron* **1971**, *27*, 3839.
16. Sallam M. M. M.; Ibraheim M. A.; Elnagdi M. M.; Sadek K. U. *J. Prakt. Chem.* **1985**, *327*, 333-6.
17. Zaleska B. *J. Prakt. Chem.* **1988**, *330*, 841-6.
18. Ballantine J. A.; Fenwick R. G.; Alam M. *Org. Mass Spectrom.* **1968**, *1*, 467.
19. Hubert R.; Wibberlay D. G. *J. Chem. Soc., B* **1970**, 459.
20. Ott W.; Kollenz G.; Ziegler E. *Synthesis* **1978**, *8*, 5467.
21. Kollenz G.; Penn G.; Ott W.; Peters K.; Peters E. M.; von Schnering G. H. *Chem Ber.* **1984**, *117*, 1310.
22. Kollenz G.; Penn G.; Ott W.; Peters K.; Peters E. M.; von Schnering G. H. *Heterocycles* **1989**, *26*, 625.
23. Terpetschnig E.; Ott W.; Kollenz G.; Peters K.; Peters E. M.; von Schnering G. H. *Monatsh. Chem.* **1988**, *119*, 367.