Pergamon

Tetrahedron Letters 40 (1999) 7553–7556

TETRAHEDRON LETTERS

Novel Route to *b*-Fused Thiazoles Starting from a 2-Chloro-1-Phenacylpyridinium Salt and KSCN. Crystal Structures of Thiazolo- and Oxazolo[3,2-a]pyridinium Thiocyanates

Eugene V. Babaev,* Alexander A. Bush, Irina A. Orlova, Viktor B. Rybakov, Sergey G. Zhukov

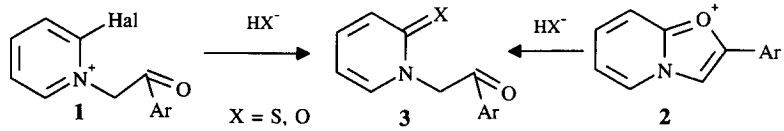
Chemistry Department, Moscow State University, 119899, Moscow, Russia
E-mail: babaev@org.chem.msu.su

Received 9 June 1999; accepted 24 August 1999

Abstract. Reaction of 2-chloro-1-phenacylpyridinium bromide **1a** with KSCN led to 2-amino-thiazolo[3,2-a]pyridinium salts **4a,b** thus opening a novel route to fused thiazoles. In reaction with KSCN oxazolo[3,2-a]pyridinium perchlorate **2a** was converted to thiocyanate **2b**. Crystal structures of thiocyanates **2b** and **4b** were determined. © 1999 Elsevier Science Ltd. All rights reserved.

In many reactions with nucleophiles 2-halogen-*N*-phenacylpyridinium salts **1** and 2-aryloxazolo[3,2-a]-pyridinium salts **2** yield the same products.[1-3] The origin of this similarity lies in formation of the same intermediates **3** which may undergo further cyclizations (as in the case of X = NH, NR). In a simple reaction with NaSH both types of the salts led to the same pyridinethione **3** (X = S),[3,4] see Scheme 1:

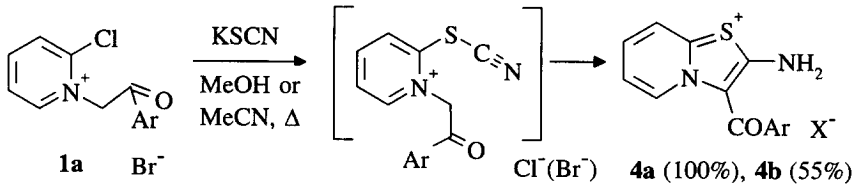
Scheme 1.

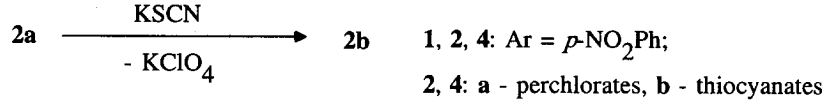


Attempts to involve the salts **1** and **2** in reactions with RS-nucleophiles (e.g., $PhCH_2SH$) under various conditions led only to disulfides and complex mixtures of products.[5] No other reactions with sulfur-containing nucleophiles have been reported for the salts **1** and **2**.

We found that during reaction with KSCN the salts **1** and **2** behave in different ways. Pyridinium bromide **1a** (Hal = Cl, Ar = *p*-NO_2Ph) readily and quantitatively gave previously unknown aminothiazole derivative **4** (isolated as perchlorate **4a** and thiocyanate **4b**),[6] whereas oxazolopyridinium perchlorate **2a** (Ar = *p*-NO_2Ph) underwent simple ionic exchange to the stable thiocyanate **2b**[7] (see Scheme 2).

Scheme 2.





PII: S0040-4039(99)01601-9

^{1}H NMR spectra of the oxazolopyridinium salts **2a** and **2b** showed no significant differences.[8] The crystal structure of **2b** was determined,[9] and X-ray data confirmed the presense of thiocyanate as the counter-ion in this salt (Fig. 1). The bond lengths in the molecule **2b** were the same as in the previously reported X-ray structure of 2-(*p*-nitrophenyl)oxazolo[3,2-a]pyridinium bromide.[10] Clear alternation of the bond lengths along the six-membered fragment (and around the whole perimeter of the bicycle) was observed in the case of **2b**. This confirms the earlier hypothesis[11] about the "pyridone-like" structure of bridgehead oxazolopyridines.

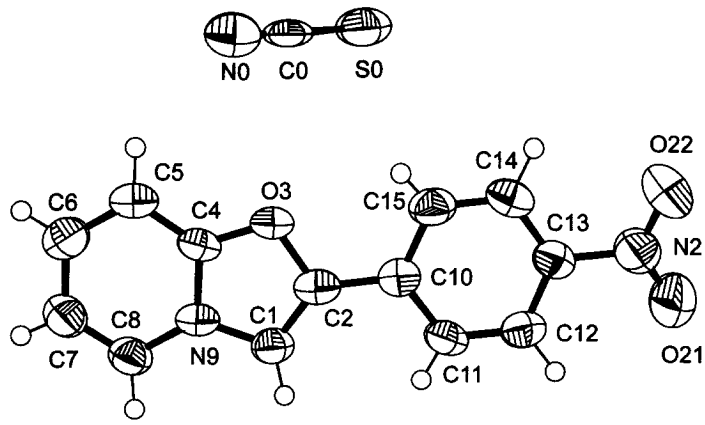


Fig. 1. Crystal structure and atoms numbering in the salt **2b**.

The conversion of **1a** to thiazolopyridine **4b** occurred easily either in solution (MeOH:H_2O 1:1, 80°C) or under heterogeneous conditions (MeCN, 80°C). Initially formed light-yellow thiocyanate **4b** (poorly soluble in most common solvents) was converted to the dark-yellow perchlorate **4a** by dissolving it in H_2SO_4 and addition of $HClO_4$. All signals in ^{1}H NMR spectra of cations **4a,b**[12] were clearly resolved and located exclusively in the aromatic region, thus indicating the presence of an unchanged *p*-nitrobenzoyl group and four pyridine protons. However, instead of a singlet for the CH_2-group, initially present in the spectrum of the salt **1a**, a new singlet of the NH_2-group appeared at 8.2 -- 8.5 ppm in the spectra of products **4**. This signal disappeared when D_2O was added to the solution of **4b** in DMSO, thus confirming the acidic character of NH_2-group. IR spectra clearly supported the presence of a new NH_2-group and benzoyl fragment in the salts **4**.

According to X-ray data,[13] the counter-ion in the initally formed salt **4b** was thiocyanate (Fig. 2). The angle between the carbonyl group and the plane of thiazolopyridinium bicycle was 23°, whereas such an angle for the *p*-nitrophenyl group was 42°. Slight alternation of single and double bond lengths around the pyridine ring (analogous to that in **2b**) was also observed in the molecule **4**. The length of the CS bond adjacent to the bridgehead carbon atom is slightly shorter than that of another CS bond, thus confirming bond alternation around the whole perimeter of the heterocycle **4**.

The cyclization of **1** into **4** opens a novel route to the previously unknown class of 2-aminoderivatives of thiazolo[3,2-a]pyridinium cations. One would expect formation of mesoionic (munchnone-like) derivatives by deprotonation of NH_2-group in the salts **4** (see, *e.g.* review[14]). Although the salts **4** are soluble in alkali, our attempts to obtain a crystalline mesoionic compound have so far failed.

The cyclization discovered corresponds to the novel disconnection scheme CNC + CS for the thiazole ring. Although thiocyanate ion is the standard reagent for SCN + CC synthetic strategy, it has never been used as the source of CS fragment in the chemistry of thiazoles.[15,16] The structural design of this reaction has some similarity with the known cyclocondensation of salts **1** with β-dicarbonyl compounds leading to indolizines[17] (with the disconnection scheme CNC + CC). In both cases displacement of halogen is followed by intramolecular cyclization, where the electrophilic component arises from an external reagent (CO group of CH-acid or CN-fragment of SCN anion), and the CH_2-group in the salt **1** serves as the nucleophilic center.

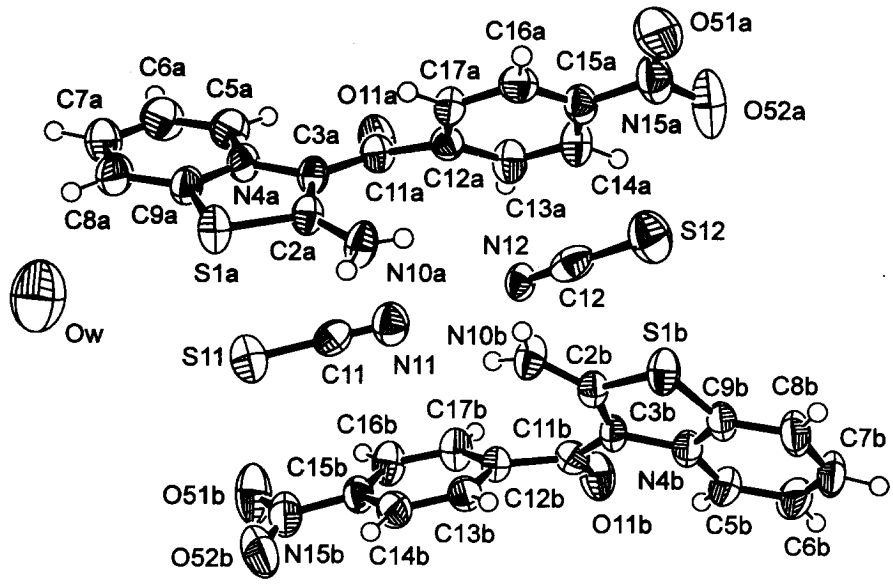


Fig. 2. Crystal structure and atoms numbering in the salt **4b**.

Supplementary Materials: the list of refined coordinates and e.s.d. for **2b** and **4b**; all materials are deposited in the Cambridge Crystal Database.

Acknowledgement
We thank Russian Foundation of Basic Research (RFBR, grant 99-03-33076a) and Nippon Soda Co. Ltd. for generous support of this work. We also thank RFBR for covering the licence fee for use of the Cambridge Structural Database (project 96-07-89187).

References and notes

1. (a) Bradsher, C. K.; Brandau, R. D.; Boilek, J. E.; Hough, T. L., *J. Org. Chem.* **1969**, *34*, 2129.
   (b) Hand, E. S.; Paudler, W. W., *J. Org. Chem.* **1978**, *43*, 658.
2. Babaev, E. V.; Tsisevich, A. A., *J. Chem. Soc., Perkin Trans. 1* **1999**, *4*, 399.
3. (a) Blank, B.; DiTullio, N. W.; Krog, A. J.; Saunders, H. L., *J. Med. Chem.* **1978**, *21*, 489.
   (b) Pauls, H.; Krohnke, F., *Chem. Ber.* **1976**, *109*, 3653.
4. Babaev, E. V.; Maiboroda, D. A.; Pasichnichenko, K. Yu., *Khim. Geterotsikl. Soedin.* **1997**, *3*, 397.
5. Babaev, E. V.; Tsisevich, A. A.; *unpublished results*.
6. Typical procedure for **4b**: A suspension of the salt **1a** (0.358 g, 1 mmol) and KSCN (0.194 g, 2 mmols) in 10 ml of MeCN was refluxed for 5 h. The mixture was filtered off, and the yellow precipitate was washed with water giving the thiocyanate **4b** in quantitative yield. To obtain a single crystal (mp 295-297°C) for X-ray analysis the compound **4b** was dissolved in solution of NaOH in 50% MeOH followed by neutralization with HOAc and addition of $CHCl_3$. Perchlorate **4a** (mp 245-247°C, 55%) was prepared by dissolving the salt **4b** (1.68 mmol) in 2 ml of H_2SO_4 followed by addition 1 ml of $HClO_4$.
7. Thiocyanate **2b** was obtained by heating suspension of perchlorate **2a** (0.15 g, 0.44 mmol) and KSCN (0.15 g, 1.55 mmol) in 5 ml of MeCN for 5 h. The resulting solid contained a white powder (inorganic products) and large yellow crystals (mp 205-207°C) of **2b**; the crystals were separated and used for X-ray analysis (the yield was not optimized).
8. Data for **2b**: ^{1}H NMR (in $(CD_3)SO$, 400 MHz): δ (ppm) 9.01 (H_3, s, 1H); 8.73 (H_5, d, 1H, J_{56}=7,3 Hz); 8.06 (m, H_7 and H_8, 2H, J_{78}=5.2 Hz); 7.99 and 7.80 (Ar, m, 4H); 7.48 (H_6, dd, 1H, J_{56}=7.3, J_{67}=6.9 Hz).

For spectral data of perchlorate **2a** see Ref. 23.

9. X-Ray structure determination and refinement. The intensitity data were collected on an Enraf-Nonius CAD-4 diffractometer[18] with graphite monochromated Mo radiation. The reference reflections showed no lost of intensity. Data were corrected for Lorentz and porarization effects using WinGX.[19] An absorption correction was not applied. The crystal structures were solved by SHELXS-97.[20] Refinement was performed by full-matrix least squares with the SHELXL-97[21] system of programs using F^2-values. The positions of the H-atoms were located by difference Fourier maps. Scattering factors were those included in SHELXL-97.[20] The ORTEP plots were prepared by PLATON-97[21] program.
Crystal structure of **2b**. (a) Crystal data: molecular formula $C_{13}H_9N_2O_3{\times}NCS$, Mr=299.30. Cell parameters a=12.370(3) Å; b=8.925(4) Å; c=24.425(5) Å; α=90.0°; β=90.0°; γ=90.0°. V=2696(2) Å^3. D_c=1.475 g×cm^{-3}. Z=8. Space group orthorhombic Pbca. Crystal size 0.5×0.5×0.5 mm. μ Mo K_α=0.254 mm^{-1}. (b) Data collection: temperature 293K, θ_{max} =27.96°. Reflections measured 2609. (c) Refinement: independent reflections observed with I>2σ(I) 2264. No. parameters in LS 227. R1=0.0587, wR2=0.1445. Residual electron density $(\Delta\rho)_{max}$ 0.239, $(\Delta\rho)_{min}$ -0.240.
10. Babaev, E. V.; Rybakov, V. B.; Zhukov, S. G.; Orlova, I. A., *Khim. Geterotsikl. Soedin.* **1999**, *4*, 542.
11. Babaev, E. V.; Bozhenko, S. V.; Maiboroda, D. A.; Rybakov, V. B.; Zhukov, S. G., *Bull. Soc. Chim. Belg.* **1997**, *106*, 631.
12. Data for **4a**. IR (KBr) ν (cm^{-1}) 3310 and 3445 (NH), 1612 and 1720 (CO). ^{1}H NMR (in $(CD_3)SO$, 400 MHz): δ (ppm) 9.30 (H_5, d, 1H, J_{56} = 6.6 Hz); 8.57 (H_8, d, 1H, J_{78}=8.6 Hz); 8.36 and 8.03 (Ar, m, 4H); 8.17 (NH_2, s, 2H); 8.14 (H_7, d, 1H, J_{67}=7.1 Hz); 7.78 (H_6, dd, 1H, J_{56}=6.6, J_{67}=7.1 Hz).
Data for **4b**. IR (KBr) ν (cm^{-1}) 3350 and 3420 (NH), 1610 and 1720 (CO). ^{1}H NMR (in $(CD_3)SO$, 400 MHz): δ (ppm) 9.24 (H_5, d, 1H, J_{56} = 6.7 Hz); 8.63 (H_8, d, 1H, J_{78}=8 Hz); 8.38 and 8.02 (Ar, m, 4H); 8.56 (NH_2, s, 2H); 8.15 (H_7, d, 1H, J_{67}=7.5 Hz); 7.78 (H_6, dd, 1H, J_{56}=6.7, J_{67}=7.5 Hz).
13. Crystal structure of **4b**. The compound contained a crystalline water molecule. (a) Crystal data: molecular formula $C_{14}H_{10}N_3O_3S{\times}NCS{\times}0.5H_2O$, Mr=365.39. Cell parameters a=5.975(7) Å; b=13.624(1) Å; c=20.17(2) Å; α=91.55(7)°; β=90.11(11)°; γ=102.66(8)°. V=1601(3) Å^3. D_c=1.516 g×cm^{-3}. Z=4. Space group triclinic P(-1). Crystal size 0.5×0.5×0.5 mm. μ Mo K_α 0.357 mm^{-1}. (b) Data collection: temperature 293K, θ_{max}=24.97°. Reflections measured 5174. (c) Refinement: independent reflections observed with I>2σ(I) 5174. No. of parameters in LS 523. R1=0.0643, wR2=0.1481. Residual electron density $(\Delta\rho)_{max}$ 0.399, $(\Delta\rho)_{min}$ -0.329.
14. Newton, C. G.; Ramsden, C. A., *Tetrahedron* **1982**, *38*, 2965.
15. Vernin, G. *Thiazole and Its Derivatives, Part 1* (The Chemistry of Heterocyclic Compounds, vol.34. Ed. Metzger, J. V.), New York: Interscience, 1979, p.165.
16. *Comprehensive Heterocyclic Chemistry.* Eds. Katritzky, A. R.; Rees, C. W., Oxford: Pergamon, 1984. Vol. 6, p. 305.
17. Nugent, R. A.; Murphy, M., *J. Org. Chem.* **1987**, *52*, 2206.
18. *Enraf-Nonius CAD-4 Software, version 5.0.* Enraf-Nonius, Delft, The Netherlands, 1989.
19. Farrugia, L. J., *WinGX-96. X-Ray Crystallographic Programs for Windows, version 1.5a.* University of Glasgow, UK, 1996.
20. Sheldrick, G. M., *SHELXS-97. Program for Solution of Crystal Structures.* University of Gottingen, Germany, 1997.
21. Sheldrick, G. M., *SHELXL-97. Program for Refinement of Crystal Structures.* University of Gottingen, Germany, 1997.
22. Spek, A. L., *PLATON-97. Molecular Geometry Program, version 1997.* University of Utrecht, The Netherlands, 1997.
23. Babaev, E. V.; Efimov, A. V.; Maiboroda, D. A.; Jug K., *Europ. J. Org. Chem.* **1998**, *1*, 193.