Pergamon

Tetrahedron Letters 43 (2002) 6767–6769

TETRAHEDRON LETTERS

The first synthesis and X-ray crystal structure of tetrahydropyrrolo[2,3-*d*]azocines

Alexey V. Varlamov,[a] Tatiana N. Borisova,[a] Leonid G. Voskressensky,[a,*] Tatiana A. Soklakova,[a] Larisa N. Kulikova,[a] Alexey I. Chernyshev[a] and Grigory G. Alexandrov[b]

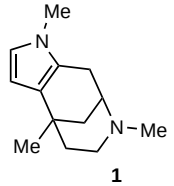
[a]*Organic Chemistry Department of the Russian Peoples Friendship University, 6, Miklukho-Maklayia St., Moscow 117198, Russia*

[b]*N.S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninsky Prospekt 31, Moscow GSP-1 119991, Russia*

Received 20 June 2002; revised 12 July 2002; accepted 19 July 2002

Abstract—Tetrahydropyrrolo[3,2-*c*]pyridines (THPP) upon the reaction with DMAD in acetonitrile or DMSO at rt underwent ring expansion, affording tetrahydropyrrolo[2,3-*d*]azocines; these latter compounds have not previously been reported in the literature. The crystal structure and conformation of these derivatives was established by X-ray crystallography. © 2002 Published by Elsevier Science Ltd.

The only example of the pyrrolo[2,3-*d*]azocine system described in the literature is a tricyclic pyrrolo[3,2-*f*]-morphan **1** (Scheme 1), synthesized via acid-induced intramolecular cyclization of a 2-(2-pyrrolylmethyl)-tetrahydropyridine.[1] Meanwhile, pyrrole-containing macrocyclic compounds are of great interest not only from a theoretical viewpoint (synthesis, reactivity, stereochemistry, etc.), but also for their biological activity.[2,3] We have recently reported an unusual cleavage process of tetrahydropyrrolo[3,2-*c*]pyridine (THPP) derivatives **2**–**4** under the action of the dimethyl acetylene dicarboxylate (DMAD) in anhydrous THF at rt leading to β-vinylpyrroles in moderate yields.[4] Taking into account the lack of availability of these compounds and their possible use in the synthesis of more elaborate substrates, we have undertaken further efforts aimed at the optimization of the reaction conditions.



1

Scheme 1.

The reaction of the THPP derivatives **2**–**4** with DMAD in anhydrous acetonitrile or DMSO in both cases led to the formation of the expected 3-vinylpyrroles **5**–**7** in 15–25% yields. In all cases, the second products isolated were the corresponding tetrahydropyrrolo[2,3-*d*]azocines **8**–**10** (20–35% yields). We presume that the reaction proceeds via the intermediate zwitterion **A**, resulting from the Michael addition of the tertiary nitrogen to DMAD (Scheme 2). Intramolecular attack of the resulting anion on the 4-CH_3 group (pathway a) leads to the corresponding vinylpyrroles, while the alternative nucleophilic attack on the C-4 position (pathway b) results in pyrrolo[2,3-*d*]azocine formation. In order to determine whether this reaction is general for all THPP derivatives, we have applied the synthetic protocol[5] to the THPP **11**, having an unsubstituted piperidine ring. The corresponding pyrrolo[2,3-*d*]-azocine **12** was isolated in 42% yield (Scheme 3).

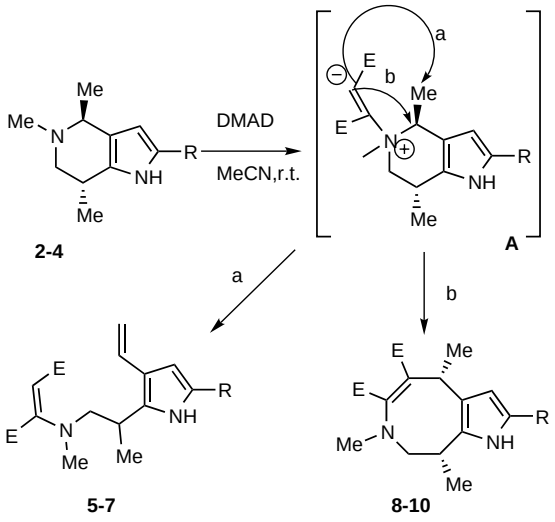
Proton and ^{13}C NMR spectra of compounds **8**,[6] **9**,[7] **10**[8] and **12**[9] in $CDCl_3$ showed the presence of only one isomer. However, it was difficult to determine the relative positions of the methyl groups for compounds **8**–**10** due to the absence of the standard NMR information for this class of compound.

In order to gain more information about the structure, compound **9** was studied by X-ray diffraction of a suitable monocrystal which was obtained by recrystallization from ethyl acetate by slow evaporation at room

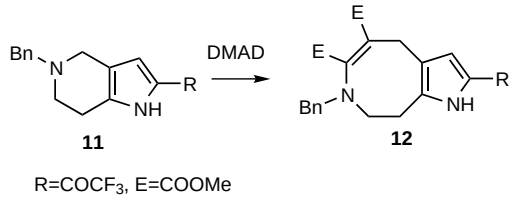
Keywords: pyrrole; azocine; cleavage; ring expansion.

* Corresponding author. Fax: 7 095 9540336; e-mail: lvoskressensky@sci.pfu.edu.ru

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01520-4



Scheme 2.



Scheme 3.

temperature. Crystal structure analysis for **9**: $C_{18}H_{21}F_3N_2O_5$, $M_r=402.37$ g mol^{-1}, monoclinic, space group $P2_1/n$, $a=7.300(4)$, $b=23.760(12)$, $c=11.633(6)$ Å, $\beta=104.62(1)°$, $V=1952(2)$ Å^3, $Z=4$, $\rho=1.369$ g cm^{-3}, $\mu=0.118$ cm^{-1}, $F(000)=840$, crystal size: 0.25×0.15×0.08 mm^3. Crystal data was collected on a Bruker AXS SMART 1000 area detector diffractometer[10] (three-circle goniometer with 1K CCD detector, MoK radiation, graphite monochromator; hemisphere data collection in ω at 0.3° scan width with 606, 435 and 230 frames ($\phi=0$, 90 and 180°) at a detector distance of 4.0 cm. A total of 5823 reflections ($1.5<\theta<30.0°$) were collected of which 3094 were unique ($R_{int}=0.0239$). The structure was solved with the program SHELXS-97[11] and refined using SHELXL-97[12] to $R_1=0.055$ and $wR(F^2)=0.1293$ for 2104 reflections with $I>2\sigma(I)$; max.\min. residual electron density 0.237 and −0.211 e Å^{-3}. All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometrical positions and gave thermal parameters equivalent to 1.2 times those of the atom to which they were attached.

The refined X-ray crystal structure of **9** is shown in Fig. 1. Crystallographic data (excluding structure factors) for compound **9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 185997. The conformation of the eight-membered ring is a twisted bath, in which the C(3), C(4), N(2) and C(7) atoms are almost coplanar, whilst the C(5), C(6), C(8) and C(9) atoms are located in the same direction from this plane within 0.69, 1.09, 0.45 and 0.79 Å, respectively. The N(2)–C(7) bond is shorter, than the N(2)–C(6) bond (1.370 and 1.444 Å, respectively), denoting the presence of conjugation in the enamine (N(2)–C(7)–C(8)) fragment. Molecules in the crystal are oriented by means of hydrogen bonds N(1)–H···O(1), forming chains along direction (101).

The 4-CH_3 and 9-CH_3 groups are in *cis*-positions, whilst the starting THPP **3** has been shown to have *trans*-di-equatorial methyl groups.[13] This observation is consistent with the proposed reaction mechanism.

In conclusion, we have demonstrated the synthesis of tetrahydropyrrolo[2,3-*d*]azocines via a one-step reaction from readily available THPP derivatives.[14] This reaction, upon optimization, could be regarded as a preparative method for the synthesis of this new heterocyclic system. Work aimed at optimization of the reaction conditions and new cleaving reagents is underway.

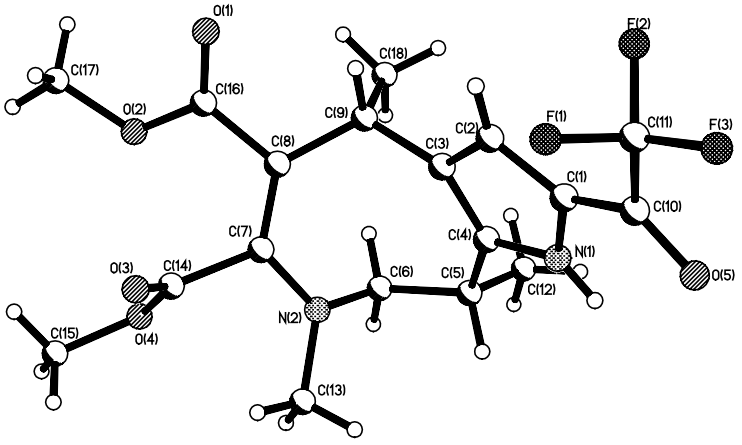


Figure 1. X-Ray crystal structure of **9**.

Acknowledgements

This work was supported by the Russian Foundation for Basic Research (grant # 02-03-32941).

References

1. Bosch, J.; Mauleon, D.; Boncompte, F.; Ganados, R. *J. Heterocyclic Chem.* **1981**, *18*, 263.
2. Hayakawa, J.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701.
3. For the pyrrole-containing alkaloid Rhazinilam and related compounds synthesis and biological activity evaluation, see for example: (a) Banwell, M.; Edwards, A.; Smith, J.; Hamel, E.; Verdier-Pinard, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1497; (b) Pascal, C.; Dubois, J.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **1998**, *63*, 6414; (c) David, B.; Sevenet, T.; Morgat, M.; Guenard, G.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Mobil. Cytoskel.* **1994**, *28*, 317.
4. Varlamov, A. V.; Borisova, T. N.; Voskressensky, L. G.; Nsabimana, B.; Chernyshev, A. I. *Heterocyclic Commun.* **2001**, *7*, 461.
5. **General**: All solvents were distilled and dried before use, DMAD was purchased from ACROS ORGANICS and was used without any additional purification. Column chromatography was performed with alumina oxide 60 from Fluka. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions, at 25°C using a Bruker WM 400 NMR spectrometer operating at 400 and 100 MHz, respectively. Mass-spectra were obtained by the EI technique (Finnigan-MAT 95 XL engine). **General synthetic protocol**: To a solution of 1 mmol of the THPP derivative in 10 ml of acetonitrile, 1.2 mmol of DMAD was added. The reaction mixture was stirred for 4–6 h at room temperature (TLC monitoring). Acetonitrile was evaporated under reduced pressure. The resulting residue was purified by column chromatography using ethyl acetate/hexane 1:1 mixture as eluent. The first fraction provided the corresponding pyrrolo[2,3-*d*]azocine derivatives as crystalline substances, which were recrystallized from ethyl acetate/hexane mixture.
6. **Dimethyl 2-formyl-4,7,9-trimethyl-4,7,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocine-5,6-dicarboxylate (8)**. Mp 226–228°C. Yield 35%. ^{1}H NMR: $\delta=10.6$ (bs, 1H, N*H*), 9.3 (s, 1H, C*H*O), 6.7 (d, 1H, $J=2.6$ Hz, *H*-3), 4.52 (q, 1H, $J=7.3$ Hz, *H*-4), 3.77 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.68–3.66 (m, 1H, *H*-8), 3.46 (m, 1H, *H*-9), 3.3 (dd, 1H, $J=9.0$ Hz, 5.6 Hz, *H*-8), 2.68 (s, 3H, N-CH_3), 1.44 (d, 3H, $J=7.3$ Hz, CH_3-4), 1.25 (d, 3H, $J=6.9$ Hz, CH_3-9). EI MS: *m*/*z* (relative intensity): 334 (M^+, 17), 319(3), 303(8), 275(22), 200(100), 135(78). $C_{17}H_{22}N_2O_5$: calcd C, 61.07; H, 6.63; N, 8.38; found C, 61.13; H, 6.56; N, 8.40.
7. **Dimethyl 2-trifluoroacetyl-4,7,9-trimethyl-4,7,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocine-5,6-dicarboxylate (9)**. Mp 234–236°C. Yield 28%. ^{1}H NMR: $\delta=9.96$ (bs, 1H, N*H*), 7.01 (d, 1H, $J=1.5$ Hz, *H*-3), 4.56 (q, 1H, $J=7.3$ Hz, *H*-4), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.80–3.30 (m, 3H, CH_2-8+*H*-9), 2.69 (s, 3H, N-CH_3), 1.46 (d, 3H, $J=7.3$ Hz, CH_3-4), 1.31 (d, 3H, $J=6.7$ Hz, CH_3-9). ^{13}C NMR $\delta=169.4$, 167.4, 154.1, 146.7, 126.3, 126.1, 124.0, 119.4, 115.6, 108.0, 60.6, 52.7, 52.1, 37.8, 33.9, 32.9, 25.5, 17.8. EI MS: *m*/*z* (relative intensity): 402 (M^+, 12), 343(22), 204(40), 200(100), 140(30), 134(50), 118(10), 59(20). $C_{18}H_{21}F_3N_2O_5$: calcd C, 53.73; H, 5.26; N, 6.96; found C, 53.88; H, 5.65; N, 6.90.
8. **Dimethyl 2-(2,2-dicyanovinyl)-4,7,9-trimethyl-4,7,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocine-5,6-dicarboxylate (10)**. Mp 236–238°C. Yield 20%. ^{1}H NMR: $\delta=9.35$ (bs, 1H, N*H*), 7.3 (s, 1H, *H*C=C$(CN)_2$), 6.72 (bs, 1H, *H*-3), 4.52 (q, 1H, $J=7.3$ Hz, *H*-4), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.75–3.20 (m, 3H, CH_2-8+*H*-9), 2.69 (s, 3H, N-CH_3), 1.44 (d, 3H, $J=7.3$ Hz, CH_3-4), 1.32 (d, 3H, $J=6.7$ Hz, CH_3-9). ^{13}C NMR $\delta=169.2$, 167.1, 146.3, 144.5, 130.3, 126.7, 125.5, 118.4, 118.1, 116.9, 115.2, 112.1, 67.3, 60.7, 52.9, 52.0, 38.3, 33.5, 25.4, 17.6. EI MS: *m*/*z* (relative intensity): 382 (M^+, 29), 367(6), 351(12), 323(32), 200(100), 183(67). $C_{20}H_{22}N_4O_4$: calcd C, 62.82; H, 5.80; N, 14.65; found C, 62.85; H, 5.65; N, 14.43.
9. **Dimethyl 2-trifluoroacetyl-7-benzyl-4,7,8,9-tetrahydro-1*H*-pyrrolo[2,3-*d*]azocine-5,6-dicarboxylate (12)**. Mp 208–210°C. Yield 42%. ^{1}H NMR: $\delta=9.1$ (bs, 1H, N*H*), 7.20–7.10 (m, 3H, C*H*-Ar), 7.05–6.95 (m, 3H, 2 C*H*-Ar+*H*-3), 4.12 (s, 2H, CH_2-benzyl), 3.87 (t, 2H, $J=6.3$ Hz, CH_2-8), 3.79 (s, 2H, CH_2-4), 3.76 (s, 3H, O-CH_3), 3.74 (s, 3H, O-CH_3), 2.9 (t, 2H, $J=6.3$ Hz, CH_2-9). ^{13}C NMR $\delta=168.7$, 168.2, 167.4, 152.9, 140.9, 137.4, 128.1, 128.1, 127.3, 127.3, 127.3, 124.2, 122.5, 123.6, 117.1, 103.9, 60.0, 52.6, 51.9, 50.28, 27.2, 24.8. EI MS: *m*/*z* (relative intensity): 450 (M^+, 10), 359(39), 299(35), 267(8), 189(10), 91(100), 65(15). $C_{22}H_{21}F_3N_2O_5$: calcd C, 58.67; H, 4.70; N, 6.22; found C, 58.39; H, 4.72; N, 6.31.
10. SMART (control) and SAINT (integration) software, version 5.0 Bruker AXS Inc., Madison, WI, 1997.
11. Sheldrick, G. M. SHELXS, Program for Crystal Structure Solution, University of Göttingen: Germany, 1997.
12. Sheldrick, G. M. SHELXL, Program for Crystal Structure Refinement, University of Göttingen: Germany, 1997.
13. Borisova, T. N.; Stazharova, I. A.; Aliev, A. E.; Prostakov, N. S.; Varlamov, A. V. *Chem. Heterocyclic Compd. (Engl. Transl.)* **1991**, *27*, 1105.
14. For the review on THPP synthesis, see: Varlamov, A. V.; Borisova, T. N.; Voskressensky, L. G. *Synthesis* **2002**, *2*, 155.