Brief Communications

Mannich reaction in the synthesis of *N*,*S*-containing heterocycles. 2.* Convenient one-pot synthesis of 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene derivatives

*V. V. Dotsenko,[a] S. G. Krivokolysko,[a] and V. P. Litvinov[b]**

[a]*V. Dal East Ukrainian National University, 20 kv. Molodezhnyi, 91034 Lugansk, Ukraine. Fax: +38 (064 2) 41 9151. E-mail: ksg@lep.lg.ua*
[b]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (495) 135 5328. E-mail: vpl@ioc.ac.ru*

The reactions of *N*-methylmorpholinium 6-amino-3,5-dicyano-1,4-dihydropyridine-2-thiolates with formaldehyde and primary aromatic amines produce 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-1,9-dicarbonitrile derivatives.

Key words: Mannich reaction, *N*-methylmorpholinium 6-amino-4-aryl-3,5-dicyano-1,4-dihydropyridine-2-thiolates, formaldehyde, primary amines, 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-1,9-dicarbonitrile derivatives.

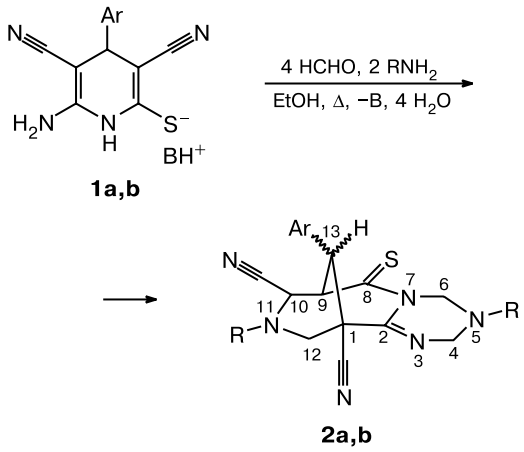
Recently, we have demonstrated[1] that "double" aminomethylation of 1,2,3,4-tetrahydropyridine-6-thiolates afforded the previously unknown pyrido[2,1-*b*][1,3,5]thiadiazine derivatives in high yields. In this connection, it was of interest to study the behavior of other pyridine-2-thiones and pyridine-2-thiolates, which are very variable and readily available synthons,[2] in the Mannich reaction. 6-Amino-4-aryl-3,5-dicyano-1,4-dihydropyridine-2-thiolates **1** (see Ref. 3) have attracted our attention as suitable reagents. These compounds contain several active nucleophilic centers, which can be subjected to aminomethylation. It was found that thiolates **1a,b** are readily involved in the previously unknown reaction with 4 equiv. of formaldehyde and 2 equiv. of primary amines giving rise to 5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene-1,9-dicarbonitrile derivatives (**2a,b**). It is worthy of note that this reaction is highly regioselective, which is surprising taking into account the presence of several reactive centers and possible combinations of their interactions in the course of the one-pot synthesis. Tricyclic compounds **2** were isolated as the only products, their yields being as high as 72—77% (Scheme 1).

It should be noted that procedures for the synthesis of compounds containing the pyrido[1,2-*a*][1,3,5]triazine fragment are few in number.[4—6] Nevertheless, these compounds are of practical interest because they are strong

* For Part 1, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2605—2607, November, 2005.

Scheme 1



B is *N*-methylmorpholine

1, 2: Ar = 2-ClC$_6$H$_4$, R = 3,4-Me$_2$C$_6$H$_3$ (**a**); Ar = 2-MeOC$_6$H$_4$, R = 4-EtOC$_6$H$_4$ (**b**).

5-hydroxytryptamine receptor antagonists (5-HT$_2$ and 5-HT$_{2a}$ antagonists)[7—9] and active anthelmintic and fungicidal agents.[10] The structures of tricyclic products **2** were confirmed by spectroscopic studies. The IR spectra of the reaction products have no absorption bands corresponding to stretching vibrations of the N—H bond and the conjugated C—N group, which would be expected in the case of another structure alternative to structure **2**. To the contrary, the spectrum shows a weak broadened absorption band at ν = 2250 cm^{-1}, which is indicative of the presence of nonconjugated C—N groups. Absorption bands of the C=N fragment (ν = 1660—1655 cm^{-1}) and the C=S group (ν = 1510—1480 cm^{-1}, a strong thioamide II band)[11] are observed at lower frequencies. The ^{1}H NMR spectra of compounds **2** have three sets of signals of aromatic substituents. One set is assigned to the *C*-aryl substituent, and two other sets belong to the R groups bound to the nitrogen atoms. The signals for the protons of the methylene groups C(10)H$_2$ and C(12)H$_2$ are observed at δ 3.70—4.09 as two pairs of doublets (**2a**) or as a complex multiplet due to partial overlap with the signals for the CH$_2$ protons of the EtO groups (**2b**). The protons of the 1,3,5-triazine ring are resolved as two quadruplets at δ 5.03—5.12 (C(6)H$_2$) and δ 5.70—5.76 (C(4)H$_2$). The signal for the C(13)H proton is observed as a narrow singlet at δ 4.60—4.71. To reveal the stereochemical aspects of the reaction, the structure of compound (**2a**) was studied by X-ray diffraction. The results of this study will be published elsewhere.

Experimental

The ^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument (200 MHz) in DMSO-d$_6$ with Me$_4$Si as the internal standard. The IR spectra were measured on an IKS-29 spectrophotometer in Nujol mulls. Elemental analysis was carried out on a Perkin—Elmer C,H,N-Analyzer. The purities of the reaction products were checked by TLC on Silufol UV 254 plates in a 1 : 1 acetone—heptane system, spots were visualized with iodine vapor, and an UV detector was used. The melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Thiolates **1a,b** were synthesized according to a known procedure.[3]

Synthesis of compounds 2a,b (general procedure). An excess of 37% HCHO (3 mL) was added to a suspension of thiolate **1a,b** (1.5 mmol) in EtOH (20 mL). The reaction mixture was heated with stirring until complete dissolution was achieved. Then the corresponding amine (3.1 mmol) was added in one portion. The reaction mixture was refluxed with vigorous stirring for 3 min and then stirred at ~20 °C for 5 h. The precipitate of compound **2a,b** was filtered off and washed with EtOH and heptane.

13-(2-Chlorophenyl)-5,11-di(3,4-dimethylphenyl)-8-thioxo-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-1,9-dicarbonitrile (2a). Yellow crystals, the yield was 72%, m.p. 209—211 °C (Me$_2$CO). Found (%): C, 67.88; H, 5.43; N, 14.55. C$_{33}$H$_{31}$ClN$_6$S. Calculated (%): C, 68.44; H, 5.40; N, 14.51. IR, ν/cm^{-1}: 2250 (CN); 1655 (C=N); 1480 (C=S). ^{1}H NMR (DMSO-d$_6$), δ: 1.98, 2.08, 2.15, and 2.17 (all s, 3 H each, 4 Me); 3.82 and 3.99 (both d, 1 H each, C(10)H$_2$ or C(12)H$_2$, ^2J = 11.9 Hz); 3.89 and 4.09 (both d, 1 H each, C(12)H$_2$ or C(10)H$_2$, ^2J = 12.2 Hz); 4.71 (s, 1 H, C(13)H); 5.12 (q, 2 H, C(6)H$_2$, ^2J = 17.1 Hz); 5.70 (q, 2 H, C(4)H$_2$, ^2J = 13.3 Hz); 6.40—7.59 (m, 10 H, 3 Ar).

5,11-Di(4-ethoxyphenyl)-13-(2-methoxyphenyl)-8-thioxo-3,5,7,11-tetraazatricyclo[7.3.1.0^{2,7}]tridec-2-ene-1,9-dicarbonitrile (2b). Yellow crystals, the yield was 77%, m.p. 207—208 °C (Me$_2$CO : MeOH = 1 : 1). Found (%): C, 66.70; H, 5.69; N, 13.94. C$_{34}$H$_{34}$N$_6$O$_3$S. Calculated (%): C, 67.31; H, 5.65; N, 13.85. IR, ν/cm^{-1}: 2250 (CN); 1660 (C=N); 1510 (C=S). ^{1}H NMR (DMSO-d$_6$), δ: 1.38* (q, 6 H, 2 C$\underline{H}_3$CH$_2$O, ^3J = 7.0 Hz); 3.70—4.00 (m, 8 H, 2 CH$_3$C$\underline{H}_2$O, C(10)H$_2$, C(12)H$_2$); 3.91 (s, 3 H, MeO); 4.60 (s, 1 H, C(13)H); 5.03 (q, 2 H, C(6)H$_2$, ^2J = 16.8); 5.76 (q, 2 H, C(4)H$_2$, ^2J = 13.2 Hz); 6.44—7.41 (m, 12 H, 3 Ar).

This study was financially supported by the Russian Foundation for Basic Research (Project No. 05-03-32031).

References

1. V. V. Dotsenko, S. G. Krivokolysko, A. N. Chernega, and V. P. Litvinov, *Dokl. Akad. Nauk,* 2003, **389**, 763 [*Dokl. Chem.*, 2003, **389**, 92 (Engl. Transl.)].
2. (a) V. P. Litvinov, S. G. Krivokolysko, and V. D. Dyachenko, *Khim. Geterotsikl. Soedin.*, 1999, 579 [*Chem. Heterocycl. Compd.*, 1999 (Engl. Transl.)]; (b) V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 2123 [*Russ. Chem. Bull.*, 1998, **47**, 2053 (Engl. Transl.)].
3. (a) Yu. A. Sharanin, S. G. Krivokolysko, and V. D. Dyachenko, *Zh. Org. Khim.*, 1994, **30**, 581 [*Russ. J. Org.*

* Overlap of the signals.

Chem., 1994, **30**, 620 (Engl. Transl.)]; (b) S. G. Krivokolysko, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, 1997, 214 pp. (in Russian).

4. (a) B. Stanovnik and M. Tišler, *Synthesis*, 1972, 308; (b) B. Zaleska, B. Trzewik, E. Stodolak, J. Grochowski, and P. Serba, *Synthesis*, 2004, 2975; 2005, 674; and references cited therein.
5. J. Bödeker, A. Köckrotz, and H. Köppel, *J. Prakt. Chem.*, 1987, **329**, 108.
6. A. Fiksdahl and C. Wentrup, *ARKIVOK*, 2000, **1** (*iii*), 438. Avail. URL: http://www.arkat-usa.org/ark/journal/2000/I03_Jones/GJ-028E/copy.pdf
7. Y. Watanabe, H. Usui, S. Kobayashi, H. Yoshiwara, T. Shibano, T. Tanaka, Y. Morishima, M. Yasuoka, and M. Kanao, *J. Med. Chem.*, 1992, **35**, 189.
8. D. Pawlak, K. Pawlak, E. Chabielska, J. Małyszko, A. Takada, M. Myśliwiec, and W. Buczko, *Thromb. Res.*, 1998, **90**, 259.
9. D. Pawlak, M. Adamkiewicz, J. Małyszko, A. Takada, M. Myśliwiec, and W. Buczko, *J. Cardiovasc. Pharmacol.*, 1998, **32**, 266.
10. (a) R. J. Bochis, GB Pat. 1503046 (1978), http://ep.espacenet.com/; (b) R. J. Bochis, US Pat. 3984549 (1976), http://patft.uspto.gov/netahtml/srchnum.htm.
11. Koji Nakanishi, *Infrared Absorption Spectroscopy*, Holden-Day, Inc., San Francisco, Nakanodo Company Ltd, Tokyo, 1962.

Received September 5, 2005;
in revised form October 3, 2005