Synthesis of 7-thia-1,4,6,8-tetraazabenzo[*de*]anthracenes

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Abstract

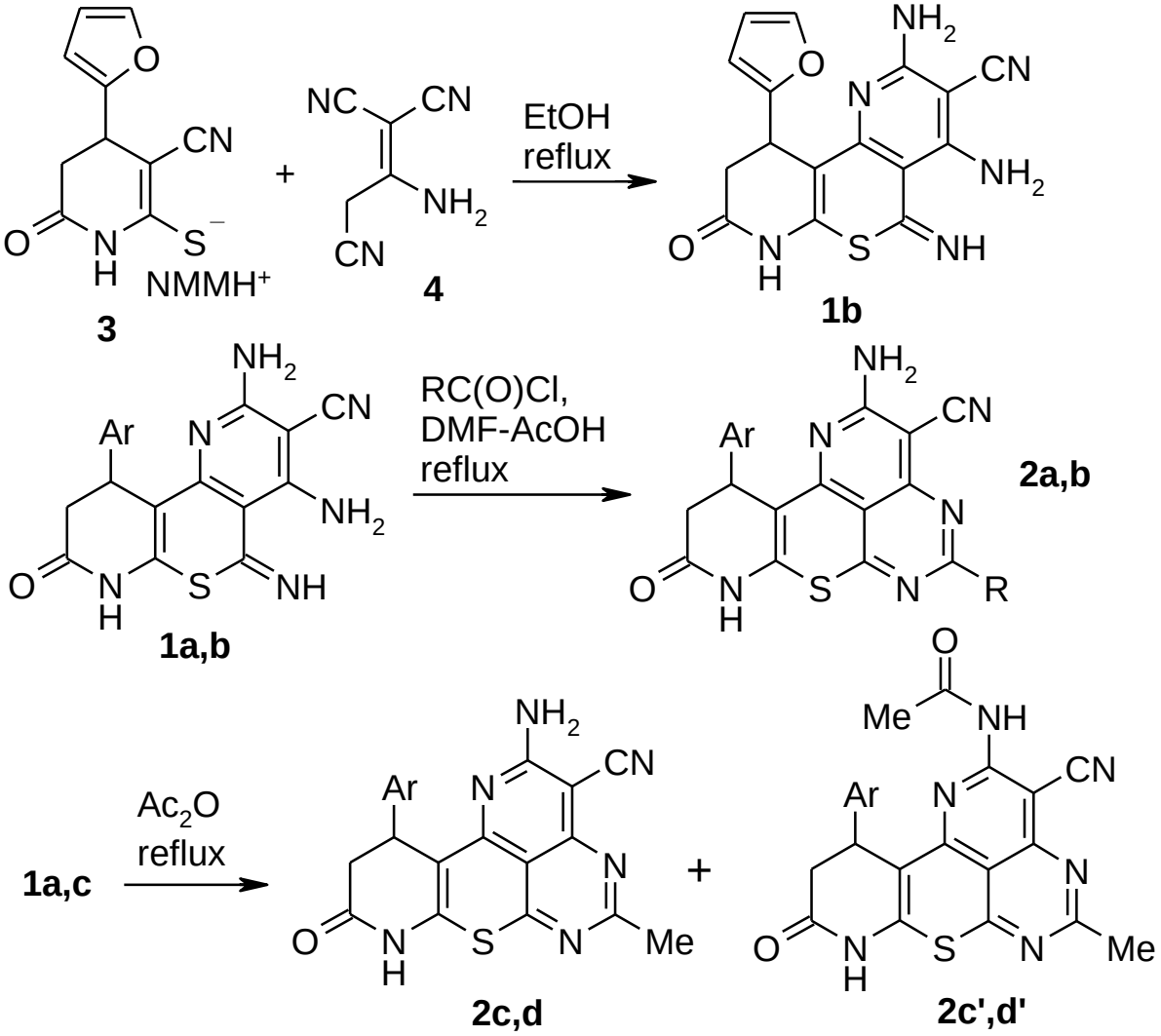
New polyheterocyclic ensembles of 8,9,10,11-tetrahydro-7-thia-1,4,6,8-tetraazabenzo[de]anthracenes were prepared by reaction of easily available 5H-pyrido[2',3':2,3]thiopyrano[4,5-b]pyridines with Ac_2O or acyl chlorides. The starting 5H-pyrido[2',3':2,3]thiopyrano[4,5-b]pyridines were prepared by reaction of N-methylmorpholinium 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates with malononitrile dimer.

Keywords
malononitrile dimer, thiatetraazabenzo[de]anthracene, tetrahydropyridine-2-thiolates, acylation, heterocyclization, Meldrum's acid

Earlier we have shown [1,2] that 3-cyanopyridine-2-thiolates react with malononitrile dimer (2-amino-1,1,3-tricyanopropene) in hot EtOH to afford 2,4-diamino-5-imino-5H-pyrido[2',3':2,3]thiopyrano[4,5-b]pyridines **1**. The compounds **1** are promising reagents to prepare polyheterocyclic ensembles. We found that compounds **1a,b** easily react with acid chlorides with the closure of the pyrimidine ring and the formation of new polyheterocyclic ensembles, 8,9,10,11-tetrahydro-7-thia-1,4,6,8-tetraazabenzo[de]anthracenes

2a,b in modest (34-57%) yields (Scheme 1). The relatively low yields of the polycycles **2** are due to non-optimal reaction conditions, the presence of several nucleophilic centers in the molecule of **1** and associated ambiguity of acylation. A confirmation of this assumption resulted from the fact that acylation of compounds **1a,c** with Ac_2O gives mixtures. Thus, when **1a,c** were heated under reflux in Ac_2O, products of acylation at the 2-NH_2 group **2c',d'** were obtained along with the expected compounds **2c,d** (the molar ratio of compounds **2d:2d'** was ~1:2 (~24% and ~47%, respectively), whereas the molar ratio of compounds **2c:2c'** was ~3:1 (~59% and ~20%, respectively). The starting compound **1b** was prepared by analogy with known procedure [1] from pyridine-2-thiolate **3b** and malononitrile dimer **4**.

Scheme 1



1 a Ar = Ph; **b** Ar = 2-furyl; **c** Ar = 2-ClC_6H_4; **2 a** Ar = Ph, R = $ClCH_2$; **b** Ar = 2-furyl, R = Ph; **c,c'** Ar = 2-ClC_6H_4; **d,d'** Ar **=** Ph.

Presumably, the formation of the tetracyclic system of **2** proceeds as a cascade process starting with acylation of the 4-NH_2 group of compound **1** followed by the intramolecular cyclization involving the imino group at the *peri* position. Thiatetraazabenzo[*de*]anthracenes **2** are yellow-brown or green-brown powders that are insoluble in EtOH, sparingly soluble in acetone, AcOH, DMF, and moderately soluble in hot DMSO. As we have shown prior [3-5], such polycyclic assemblies can be used as chemical protection agents for plants, corrosion inhibitors, antitumor agents, DNA intercalators, etc. The structure of polyheterocyclic ensembles **2** was confirmed by the results of spectral studies (IR spectroscopy, ^{1}H NMR spectroscopy, HPLC-MS) and elemental analysis. ^{1}H NMR spectra of tetraazabenzo[*de*]anthracenes **2** showed the *ABX* pattern of protons 10-CH_2 and 11-CH_2: the signals of protons 10-CH*cis* are observed upfield (δ 2.60–2.81 ppm) as a pseudo doublet (unresolved doublet of doublets) with coupling constants in the range *J* 16.3–16.4 Hz, while signals of proton 10-CH*trans* appeared as doublet of doublets with ^2J = 16.3–16.4 Hz and ^3J = 7.0–7.4 Hz at δ 3.17–3.28 ppm. The signals of protons 11-CH were observed as a pseudo doublet (unresolved doublet of doublets) in the region of δ 4.91–5.22 ppm. In addition, ^{1}H NMR spectra of compounds **2** showed the signals of 8-NH protons at δ 11.21–11.40 ppm as well as the characteristic signals of substituents at C-5 and C-11. The signals of the 2-NH_2 group appeared as a broadened peak at 7.42–7.76 ppm, whereas in the case of NHAc derivatives **2c'**,**d'** this signal disappeared and singlets at δ 10.51 and δ 10.68 ppm were observed, respectively.

In summary, we have demonstrated that polyheterocyclic ensembles of 1,4,6,8-tetraaza-7-thiabenzo[*de*]anthracene may be prepared in moderate yields by acylation of the available 2,4-diamino-5-imino-5*H*-pyrido[2',3':2,3]thiopyrano[4,5-*b*]pyridines. In the presence of a large excess of the acylating agent, acylation may take place concurrently at the 2-NH_2 group.

Experimental

IR spectra were recorded on a Thermo Nicolet Magna-IR 750 spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 MHz) in DMSO-d_6 using TMS as an internal standard. HPLC-MS analysis was performed on a Shimadzu LC-10AD LC with a Shimadzu SP D-10A UV–Vis (254 nm) detector and Sedex 75 ELSD, combined

with a PE SCIEX API 150EX mass spectrometer, atmospheric pressure electrospray ionization. Selected experimental procedures are given.

2,4-Diamino-10-(2-furyl)-5-imino-8-oxo-7,8,9,10-tetrahydro-5*H*-pyrido[2',3' : 4,5]thiopyrano[2,3-*b*]pyridine-3-carbonitrile (1b), DMF solvate (2:1). A mixture of thiolate **3b** [6,7] (3.0 g, 9.34 mmol), malononitrile dimer **4** [8] (1.85 g, 14.0 mmol) in 96% EtOH (30 ml) was heated under reflux for 25 h. The mixture was then kept for 48 h at 20°C, and black precipitate was filtered and dried at 60°C. After recrystallization from DMF, the solvate containing 0.5 molecules of DMF was obtained. Yield was 1.72 g (52%), large greenish-brown crystals, decomp. temp. >250°C. IR spectrum, ν, cm^{-1}: 3464, 3320, 3223, 3171 (NH, NH_2), 2206 (C≡N), 1705 (C=O). ^1H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.61 (1H, br. d, ^2J = 16.4, 9-CH_A); 2.72 (1.5H, s) and 2.87 (1.5H, s, 0.5N$(CH_3)_2$ of DMF); 2.96 (1H, dd, ^2J = 16.4, ^3J = 7.0, 9-CH_B); 5.04–5.05 (1H, m, 10-CH); 6.06–6.07 (1H, m) and 6.26–6.27 (1H, m, H-3,4 furyl); 6.85 (2H, br. s, 2-NH_2); 7.16 (1H, br. s, 4-NH_A); 7.45–7.46 (1H, m, H-5 furyl); 7.94 (0.5H, br. s, 0.5 HC(O) of DMF); 10.09 (1H, br. s, =NH); 10.48 (1H, s, C(O)NH); 10.80 (1H, br. s, 4-NH_B). Mass spectrum, *m*/*z*: 647 $[2M-C_4H_3O]^+$, 613 $[2M-2C_4H_3O+H+MeCN]^+$, 353 $[M+H]^+$, 285 $[M-C_4H_3O]^+$. Found, %: C 54.01; H 4.08; N 23.37. $C_{16}H_{12}N_6O_2S \cdot 0.5C_3H_7NO$. Calculated, %: C 54.05; H 4.02; N 23.41.

2-Amino-5-chloromethyl-9-oxo-11-phenyl-8,9,10,11-tetrahydro-7-thia-1,4,6,8-tetraazabenzo[*de*]anthracene-3-carbonitrile (2a). Chloroacetyl chloride (1 ml, 12.6 mmol) was added to a suspension of compound **1a** [1] (1.0 g, 2.76 mmol) in dry DMF (5 ml), and a mixture was stirred for 20 min (the suspension turns into a solution). Then AcOH (7 ml) was added to the prepared solution (an exothermic reaction observed), and stirring continued for another 30 min, while a mixture was slowly heated to the boiling point. The mixture was heated under reflux with stirring for another 2 h for complete conversion and then cooled to room temperature. Product **2a** was filtered off and washed with EtOH. Yield was 0.66 g (57%), yellow-brown fine crystalline powder, decomp. temp. >250°C. IR spectrum, ν, cm^{-1}: 3455, 3319, 3214, 3154 (NH), 2214 (C≡N), 1701 (C=O). ^1H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.74 (1H, br. d, ^2J = 16.4) and 3.23 (1H, dd, ^2J = 16.4, ^3J = 7.4, 10-CH_2); 4.67 (2H, s, CH_2Cl); 4.92–4.93 (1H, m, 11-CH); 7.19–7.27 (5H, m, H Ph); 7.76 (2H, br. s, NH_2); 11.31 (1H, s, NH). Mass spectrum, *m*/*z*: 421 $[M(^{35}Cl)+H]^+$, 423 $[M(^{37}Cl)+H]^+$.

References

1. Dotsenko, V. V.; Krivokolysko, S. G.; Chernega, A. N.; Litvinov, V. P. *Russ. Chem. Bull., Int. Ed*. 2003, 52, 969.

2. Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. *Chem. Heterocycl. Compd*. 2007, 43, 599.

3. Litvinov, V. P.; Dotsenko, V. V.; Krivokolysko, S. G. *Chemistry of Thienopyridines and Related Systems* [in Russian]; Belenkiy, L. I., (Ed.); Nauka: Moscow, 2006, p. 406.

4. Litvinov, V. P.; Dotsenko, V. V.; Krivokolysko, S. G. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Elsevier: New York, 2007, Vol. 93, p. 117.

5. Litvinov, V. P.; Dotsenko, V. V.; Krivokolysko, S. G. *Russ. Chem. Bull., Int. Ed*. 2005, 54, 864.

6. Dotsenko, V. V.; Lebedeva, I. A.; Krivokolysko, S. G.; Povstyanoi, M. V.; Povstyanoi, V. M.; Kostyrko, E. O. *Chem. Heterocycl. Compd*. 2012, 48, 462.

7. Dotsenko, V. V.; Frolov, K. A.; Pekhtereva, T. M.; Papaianina, O. S.; Suykov, S. Yu.; Krivokolysko, S. G. *ACS Comb. Sci*. 2014, 16, 543.

8. Mittelbach, M. *Monatsh. Chem*. 1985, 116, 689.