UNEXPECTED SIMPLE ROUTE TO NOVEL DIPYRIDO-1,4-THIAZINE SYSTEM[1]

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Abstract

Reaction of 4-chloro-3-nitropyridine **1** with sodium sulfide led to different novel tricyclic ring systems depending on the nature of a solvent: in DMSO to expected dipyrido-1,4-dithiins **2** and **3** but in DMF unexpectedly to dipyrido-1,4-thiazines **4** and **5**.

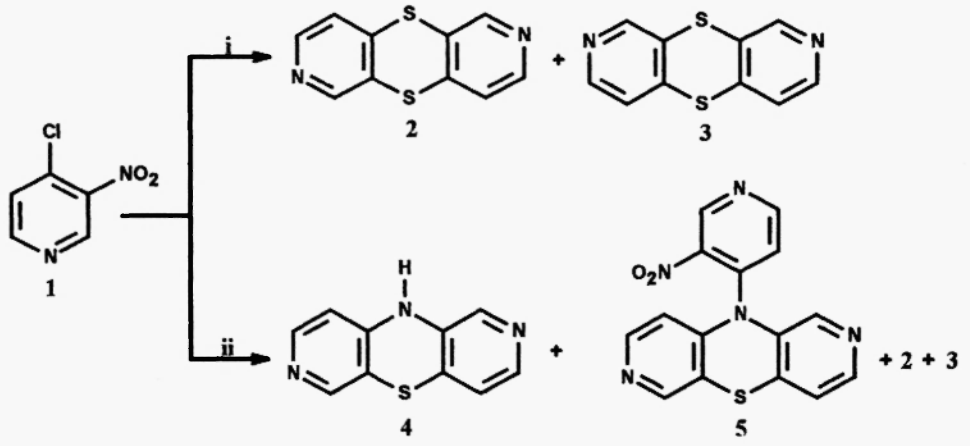
Introduction

Tricyclic diareno-1,4-thiazines (phenothiazines and azaphenothiazines) attract attention in consideration of the structure, reactivity, electronic properties and biological activity. They are very important compounds because they constitute a major class of pharmaceutical agents with beneficial antipsychotic, CNS depressant and recently anticancer properties.[2] Modification of the diareno-1,4-thiazine structure has been achieved by a change of the benzo ring into the azine (pyridine, pyridazine, pyrimidine and pyrazine).

Results and Discussions

Our interest in the chemistry of azinyl sulfides has brought original syntheses of multicyclic heteroaromatic systems containing various heteroatoms (N, S, O or Se)[3]. In an attempt to synthesize the remained unknown dipyrido-1,4-dithiin, we carried out a reaction of 4-chloro-3-nitropyridine **1** with sodium sulfide in DMSO at 140-150°C for 10 hours and we obtained two isomeric dithiins with predominance of the C_{2h} symmetric isomer, 2,7-diazathianthrene **2** (systematic name: dipyrido[3,4-b;3',4'-e][1,4]dithiin,[4] 25% yield), over to the C_{2v} symmetric isomer, 2,8-diazathianthrene **3**[5] (systematic name: dipyrido[3,4-b;4',3'-e][1,4]dithiin, 5% yield) (Scheme 1). To improve the yield we repeated the reaction in boiling DMF for longer time[6] and to our surprise we obtained four compounds: two expected dithiins **2** and **3** as the minor products (12 and 2% yield) and two unknown major products. The elemental analyses showed unexpected excess of nitrogen (the N:S ratio was 3:1 and 5:1, respectively) and the mass spectra (molecular peaks at m/z = 201 and 323) suggested the dipyridothiazine and nitropyridyldipyridothiazine structures. Furthermore, the ^{1}H NMR spectra excluded the C_{2v} symmetric dipyridothiazine structures because they contained 7 and 9 protons signals instead of 4 and 6.

On these grounds we concluded that the major products are 10*H*-2,7-diazaphenothiazine **4**[5] (systematic name: 10*H*-dipyrido[3,4-b;3',4'-e][1,4]thiazine, 30% yield) and 10-(3'-nitro-4'-pyridyl)-2,7-diazaphenothiazine **5**[5] (systematic name: 10-(3'-nitro-4'-pyridyl)dipyrido[3,4-b;3',4'-e][1,4]thiazine, 26% yield).



Scheme 1. *Reactions and conditions:* i, DMSO, Ar, rt, 2h,140-150°C, 10h; ii, DMF, Ar, rt, 2h, reflux, 72h.

The structure of intriguing compound **5**, containing three pyridine rings, was confirmed by means of an X-ray crystal analysis (Fig.1).[7] Since biological activity of phenothiazines has been described to their structural specificity of having a fold along the nitrogen-sulfur axis, the X-ray studies have been undertaken to determine the effect of different substituents in tricyclic 10-aryldiarenothiazines on the configuration and conformation.[8-10] As expected, phenothiazine **5** is not planar and the butterfly angle between two pyridine rings in tricyclic system is 28.27(4)°. The central thiazine ring is in a boat conformation with the 3'-nitropyridyl substituent in the quasi-equatorial location (the S(1)...N(3)-C(21) angle of 160.57(1)°). The pyridyl group plane nearly bisects the tricyclic ring system with the dihedral angle of 73.04(9)° between the pyridyl plane and the C(3), C(4), C(13), C(14) plane in contrast to the similar electron withdrawing azinyl group - 2'-pyrazyl, which is perpendicular to the bisecting plane and in the quasi-axial location.[9] The nitro group plane is tilted from the pyridyl ring by 33.3(2)° due to a steric hindrance with the tricyclic ring system and is directed inside the butterfly structure, which is contrary to that observed in 2'-nitrophenylphenothiazine[10].

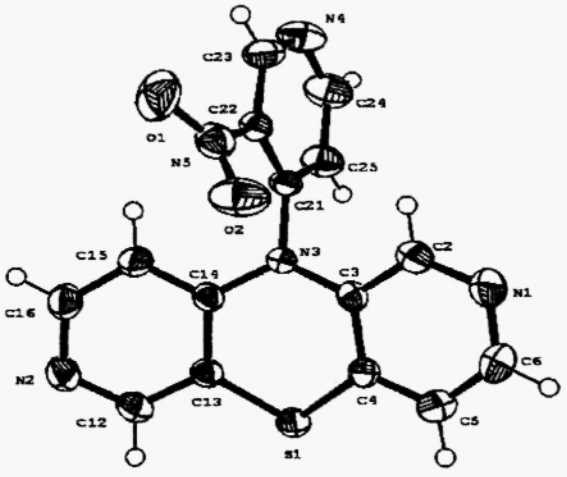
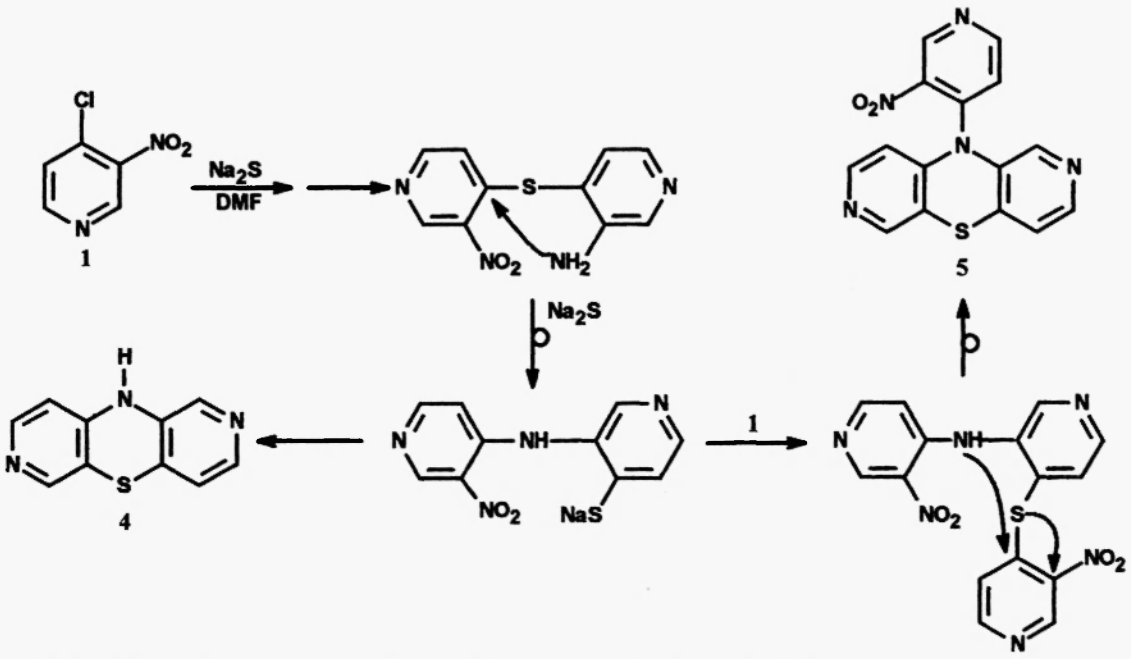


Fig. 1. ORTEP drawing of **5**. Selected bond lengths (Å) and angles (°); N(1)-C(2) 1.329(3), N(3)-C(3) 1.408(3), N(3)-C(14) 1.411(3), N(3)-C(21) 1.434(3), N(5)-C(22) 1.471(3), C(4)-S(1)-C(13) 99.86(10), C(3)-N(3)-C(14) 121.82(7), C(3)-N(3)-C(21) 117.07(18), C(14)-N(3)-C(21) 120.28(19).



Scheme 2. Possible reaction pathway for the formation of phenothiazines **4** and **5**.

To our knowledge, there are known only two dipyrido-1,4-thiazine structure systems (*i.e.* 1,6- and 3,7-diaza-phenothiazines)[11,12] and our plausible reaction pathway is reminiscent of that proposed by Rodig *et al.*[11] for the formation of the former thiazine (Scheme 2). The first key step is a reductive action of DMF[13] on the substrates to form 3'-amino-3-nitro-4,4'-dipyridyl sulfide. The next key step is the S→N type of the Smiles rearrangement of the sulfide to give 3',4-dipirydyl amine followed by the thiazine ring closure through intramolecular nucleophilic substitution of the nitro group by the thiolate anion (thiazine **4**). On the other hand, the amine can also react with the substrate **1** to form tripyridyl compound which undergoes the Smiles rearrangement and the ring closure (thiazine **5**). It is worth noting that *ab initio* calculations[14] of dipyridyl sulfides showed possibilities of the Smiles rearrangement only for the 2,2'-, 2,3'- and 2,4'-isomers and in fact, the rearrangement was observed only for the 2,2'- and 2,4'-isomers[15] and our finding is the first example of the rearrangement of 4,4'-dipyridyl sulfide.

Dithiin **3** was obtained in better yield (60%) in isomerization of dithiin **2** *via* the 1,4-dithiin ring opening with sodium methanethiolate, the S→S type of the Smiles rearrangement of the formed 3,4'-dipyridyl sulfide and the 1,4-dithiin ring closure in similar way as described for the quinoline analogue.[16]

Conclusion

We have established here a simple one-pot synthesis of the novel diazaphenothiazine system. N-unsubstituted compound **4** seems to be very useful substrate to obtain 10-substituted diazaphenothiazines by a simple N-alkylation of the thiazine nitrogen in conditions described for diquino-1,4-thiazines.[3b] Synthesis and biological activity of these compounds will be reported elsewhere.

References and Notes

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5. Spectroscopic data: **3**: ^{1}H NMR ($CDCl_3$): δ 7.37 (d, 2H, *J* 5.1 Hz), 8.45 (d, 2H, *J* 5.1 Hz), 8.62 (s, 2H); MS: *m/z* 218(M^+, 100); **4**: ^{1}H NMR (DMSO-d_6): δ 6.53 (d, 1H, *J* 5.4 Hz), 6.97 (d, 1H, *J* 5.1 Hz), 7.78 (s, 1H), 7.87 (d, 1H, *J* 1.2 Hz), 7.89 (s, 1H), 7.98 (d, 1H, *J* 5.14 Hz), 9.26 (br s, 1H); MS: *m/z* 201(M^+, 100), 174(M-HCN, 23.3); **5**: ^{1}H NMR ($CDCl_3$): δ 5.79 (d, 1H, *J* 5.7 Hz), 6.93 (d, 1H, *J* 5.1 Hz), 7.14 (s, 1H), 7.61 (d, 1H, *J* 5.1 Hz), 8.00 (d, 1H, *J* 5.7 Hz), 8.05 (s, 1H), 8.06 (d, 1H, *J* 1.2 Hz), 9.20 (d, 1H, *J* 5.1 Hz), 9.57 (s, 1H); MS: *m/z* 323(M^+, 100), 277(M-NO_2, 58.0), 22(M-nitropyridyl, 17.4).
6. A solution of 1.0 g (6.3 mmol) of **1** in dry DMF (10 mL) was stirred with 1.47 g (18.9 mmol) of anhydrous sodium sulfide at room temperature for 2 h and at reflux for 72 h under atmosphere of argon. After cooling and evaporation to the dryness the residue was extracted with chlorofom. The extract was washed, dried ($CaCl_2$), concentrated and the oily residue was separated by column chromatography on silica gel 60, using chloroform-ethanol as eluent.
7. Crystal data: $C_{15}H_9N_5O_2S$, M_r = 323.32, orthorhombic, a = 18.3530(2). b = 7.5690(5), c = 20.2400(7), space group *Pbca*, Z = 8, V = 2811.6 Å^3, D_c = 1.528 g cm^{-3}, F (000) = 1328. Mo-Kα radiation (0.71070 Å), T = 293(2), μ(Mo-Kα) = 0.248 cm^{-1}. Data were measured on a Nonius Kappa CCD diffractometer in the range of θ between 3.08 and 28.33°. 5560 reflections were collected of which 2960 were unique and 2054 with $I > 2\sigma(I)$ (R_{eq} = 0.027). The structure was solved by direct methods (SHELXS-86)[17] and refined by full-matrix least-squares based on all unique F^2 (SHELXL-93)[18] to give R = 0.0483, R_w = 0.1168, *GOF* = 1.110 for 209 refined parameters. The max. and min. residual densities were 0.311 and -0.285 e Å^{-3}. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were 'riding' on their carbon atoms (d_{C-H} = 0.93 Å, U_{iso} = 1.2U_{eq} of the attached C-atom. Atomic coordinates, bond lengths, bond angles, torsion angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
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