UNEXPECTED PRODUCTS IN THE REACTIONS OF s-TETRAZINE HYDRAZONES WITH ENAMINES

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Abstract. For the first time in the reactions of some 1,2,4,5-tetrazine hydrazones with enamines in addition to the expected products of Carbony-Lindsey reaction the unusual addition and cyclization products at cyclic and exocyclic nitrogen atom of tetrazine ring have been isolated

Introduction. [4+2]Cycloaddition of alkenes and other compounds with multiple bonds to s-tetrazines is known as Carbony-Lindsey reaction. It is classified as an inverse electron demand Diels-Alder reaction, in which electron-deficient tetrazine molecule acts as a diene. The characteristic feature of the reaction is high instability of the adducts, that cannot be isolated. The reaction proceeds through nitrogen release usually yielding substituted pyridazines.

Discussion. It is known that electron withdrawing substituents in 3,6-disubstituted s-tetrazines facilitate their [4+2]cycloaddition to alkenes, whereas electron donating groups, such as amino or hydrazino ones suppress this reaction.[1-5] Recently we have demonstrated that dimethylpyrazole groups in the 3rd and the 6th position of the tetrazine ring are suitable substituents for cycloaddition reaction with alkenes including enamines.[6]

In this paper we wish to present the results of our studies in which we have found that the displacement of one of pyrazolyl moieties by electron donating hydrazono fragment retains the tetrazine molecule ability to react with enamine yielding the expected products of the Carbony-Lindsey reaction and the unexpected enamine addition products. Hydrazones **1a-d** were obtained according to the known procedure[7] from 6-hydrazino-3-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine and benzaldehyde, cyclopentanone, acetone and 4-bromoacetophenone. Enamines derived from cyclopentanone, cyclohexanone and secondary cyclic amines (pyrrolidine, piperidine and morpholine) were used as dienophiles.

Reactivity of hydrazones **1a-d** significantly depends on both substituents in enamino and hydrazono moiety, and on the solvent used. In acetonitrile all hydrazones except **1b** reacted with cyclopentyl enamines according to Carbony-Lindsey pathway to yield the corresponding tetrahydropyridazines (**2a-e**). The reaction proceeded smoothly through release of nitrogen even at room temperature. N-Benzylideno-N′-{6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl}-hydrazine (**1b**) in acetonitrile did not react either at room temperature or on heating.

However, in methanol under the same conditions compound **1b** reacted with the same enamines rather unexpectedly. No nitrogen evolution was detected, but after 5-10 minutes the red color of the solution disappeared, and light yellow or colorless needles were formed in high yields (80-85%). These were identified as the enamine addition products at cyclic and exocyclic nitrogen atoms of tetrazine molecule, 8a-aminosubstituted 9-benzylideneamino-3-(3,5-dimethylpyrazol-1-yl)-5a,6,7,8,8a,9-hexahydro-2*H*-cyclopenta[4,5]imidazo[1,2-*b*]-1,2,4,5-tetrazines (**3a-c**).

Hydrazones **1a** and **1d** reacted with 1-pyrrolidinocyclohexene-1 in the same manner to give 10-(4-bromophenyl)ethylideneamino- and 10-cyclopentylideneamino-3-(3,5-dimethylpyrazol-1-yl)-9a-pyrrolidin-1-yl-2,5a,6,7,8,9,9a,10a-octahydrobenzo[4,5]imidazo[1,2-*b*]-1,2,4,5-tetrazines (**3d,e**), respectively.

We suppose that methanol promotes the proton migration of the hydrazine moiety in hydrazones **1** to a ring nitrogen atom and stabilizes the imino tautomer formed. The latter reacts with enamines resulting in cycloaddition products **3a-e**.

The structures of **2c** and **3d** were confirmed by X-ray analysis (Fig. 1 and 2). The compound **2c** is substituted cyclopentyltetrahydropyridazine, in which both pyridazine N(1) and cyclopentyl C(5) rings are not planar. Six-membered ring has a flattened chair conformation with atoms C(2) and C(3) displaced for 0.14 and -0.33 Å out of the plane of the other four atoms, respectively. In the five-membered ring C(2) and C(7) deviate from the other three atoms for -0.35 and 0.29 Å, respectively. The second cyclopentyl ring C(18) (also in a twist conformation) is more flattened - analogous distances are -0,25 Å for C(20) and 0,13 Å for C(21). Piperidyl has a chair conformation, and the N(5)-C(2) bond is in a pseudo equatorial position. The five- membered pyrazolyl ring is planar. The geometrical parameters of the molecule are compared with that of other nitrogen-containing heterocyclic systems.[8] The molecules of **2c** in crystals are linked together by hydrogen bonding (N(1)-H(N1)...N(6)(x,1.5-y,-.5+z) 2.887(4), 2.16(4) Å, N-H..N 153(4)°. Selected bond distances (Å) and angles (°): N(7)-C(18) 1.263(4); C(4)-N(6) 1.282(4); N(6)-N(7) 1.420(4); C(4)N(6)N(7)C(18) -145.4; C(1)C(2)C(3)H(3) -156.9; C(1)C(2)C(3)C(4) -34.7; N(5)C(2)C(3)H(3) -34.8; N(5)C(2)C(3)C(4) 87.4.

The tetrazine ring in **3d** has a twist chair conformation. The saturated six-membered (C8-C13) and unsaturated five-membered (N1-N7) rings have *cis* ring junctions. Unsaturated five membered ring N14-N18 is nearly planar (±0.02 Å). Along C3-N14 bond the hindered conformation is stabilized by intramolecular hydrogen bonding N4: N4...N18 2.705(4), N4-H 0.95(4), H...N18 2.16 (4) Å, angle N4-H... N18 is 115(3)°. Five-membered C22-C26 and N27 rings have an envelope conformation with C25 and N27 atom displaced out of the corresponding plane of the other four atoms.

The X-ray data of the compounds **2c** and **3d** were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated λMo Kα radiation (for **2c:** omega scan technique, $2\theta_{max}$=56°. 4800 reflections, 2409 from that have of $F^2>3\sigma(I)$; for **3d**: ω/2θ scan technique, 4957 reflections, 1647 of that have $I>3\sigma$.). Tetrahydropyridazine **2c** and adduct **3d** crystallize in the monoclinic system with for **2c** a=8.337(3), b=30.167(14), c=8.477(5) E, β=95.60(4)°, Z=4, D_c=1.168 g·cm^{-3}, μ=0.073 mm^{-1}, V=2249(2) Å^3, space group $P2_1/c$; for **3d** a=8.6984(9), b=22.638(3), c=11.692(1) Å, β=104.58(1)°, V=2229.5(2) Å^3, D_C=1.26 g·cm^{-3} Z=4, space group $P2_1/c$.

The structure of **2c** was solved by direct method (SHELXS-86[9]) and refined by full-matrix least-squares on F^2 with SHELXL-93[10] anisotropically (isotropically for H atoms); R_1=0.065, $wR_2(F^2)$=0.160 for 2409 unique reflections with $F^2>3\sigma$, GOOF=1.096. The structure of **3d** was resolved by direct method using SIR[11] and refined in the isotropic and next anisotropic approximation. R=0.046, R_w=0.049 for 1579 reflections with $F^2>3\sigma$. All calculations were made using MolEN[12] at Alpha Station 200. Hydrogen bonds and conformations of the molecule were analyzed with PLUTON.[13]

All new compounds gave satisfactory analytical and spectroscopic data.

Experimental.

^{1}H NMR spectra were measured on a Bruker DRX400 spectrometer. All signals are expressed in ppm (δ) with TMS as an internal standard. Melting points (uncorrected) were obtained on a Boetius apparatus.

General procedure for preparing tetrahydropyridazines (2a-e).

0.5 Mmol of corresponding hydrazone **1** was suspended in 15 ml of warm CH_3CN. Then 1.0 mmol of enamine was added dropwise. Nitrogen was released and the color of mixture was changed from light-red to dark brown. The precipitate was filtered off and recrystallized from CH_3CN.

2a: yield: 64.0%, mp 130°C (decomp.). ^{1}H NMR ($CDCl_3$): 1.80-1.84, 2.40-2.70, 2.90-3.30 (all m,19H, $N(CH_2)_2$, cyclopentyl, cyclopentylideno), 2.22, 2.39 (both s, 6H, $2CH_3$), 3.58 (t, 4H, $O(CH_2)_2$, *J*=4.5 Hz), 5.89 (s, 1H, CHpyrazolyl), 8.78 (br.s, 1H, NH-N=). Found (%): C, 63.36; H, 7.85; N, 24.69. Calc. for $C_{21}H_{31}N_7O$ (%): C, 63.45; H, 7.86; N, 24.67.

2b: yield: 50.7%, mp 144°C (decomp.). ^{1}H NMR ($CDCl_3$): 1.6-2.0 (m, 4H, $2CH_2$), 2.04 (s, 6H, $=C(CH_3)_2$), 2.22, 2.40 (both s, 6H, $2CH_3$), 2.50-2.64, 2.80-3.05, 3.1-3.35 (all m, 7H, 2Hcyclopentyl; 1H; $N(CH_2)_2$), 3.59 (t, 4H, $O(CH_2)_2$, *J*=4.7 Hz), 5.90 (s, 1H, CHpyrazolyl), 8.79 (br.s, 1H, NH-N=). Found (%): C, 61.47; H, 7.88; N, 26.41. Calc. for $C_{19}H_{29}N_7O$ (%): C, 61.43; H, 7.87; N, 26.40.

2c: yield: 67.2% , mp 127°C (decomp). ^{1}H NMR ($CDCl_3$): 1.32-1.35 (m, 2H), 1.42-1.46 (m, 4H), 1.70-1.84 (m, 8H), 2.21 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.39-2.45 (m, 5H), 2.49-2.58 (m, 4H), 2.98 (t, 1H, *J*=9.5 Hz), 3.30-3.33 (m, 1H), 5.88 (s, 1H, CHpyrazolyl), 8.57 (br.s, 1H, NH-N=). Found (%): C, 66.85; H, 8.42; N, 24.77. Calc. for $C_{22}H_{33}N_7$ (%): C, 66.80; H, 8.41; N, 24.79.

2d: yield: 75.9% , mp 110°C (decomp.). ^{1}H NMR ($CDCl_3$): 1.3-1.65, 1.7-1.9 (both m, 10H, piperidino), 2.03 (s, 6H, $=C(CH_3)_2$), 2.22 (s, 3H, CH_3pyrazolyl), 2.30-2.60, 2.88-3.08, 3.27-3.39 (all m, 10H, CH_3pyrazolyl, cyclopentyl), 5.88 (s, 1H, CHpyrazolyl), 8.73 (br.s, 1H, NH-N=). Found (%): C, 64.99; H, 8.84; N, 26.57. Calc. for $C_{20}H_{31}N_7$ (%): C, 65.01; H, 8.46; N, 26.53.

2e: yield: 75.1% , mp 137°C (decomp.). ^{1}H NMR ($CDCl_3$): 1.30-1.65 (m, 6H, piperidino), 1.79-1.95 (m, 4H, $N(CH_2)_2$), 2.23 (s, 3H, CH_3), 2.41, 2.43 and 2.36-2.58 (s, s, m, 11H, $2CH_3$, cyclopentyl, CH), 2.35-2.78 (m, 2H, cyclopentyl), 5.89 (s, 1H, CHpyrazolyl), 7.44-7.78 (m, 4H, Har), 8.92 (s, 1H, NH-N=). Found (%): C, 58.90; H, 6.48; N, 19.23. Calc. for $C_{25}H_{32}BrN_7$ (%): C, 58.82; H, 6.32; N, 19.21.

General procedure for preparing adducts (3a-e).

1.0 Mmol of corresponding hydrazone **1** was suspended in 30 ml of CH_3OH. Then 1.5 mmol of enamine was added dropwise under stirring. The color of the reaction mixture was changed to dark brown. After a few minutes the precipitate was filtered off and recrystallized from DMF:CH_3OH (10:1) or CH_3CN.

3a: yield: 94.5% , mp 193-195°C. ^{1}H NMR (CDCl$_3$): 1.68-2.15 (m, 8H, 4CH$_2$), 2.22 and 2.22 (both s, 6H, 2CH$_3$), 2.74-2.90 and 3.10-3.25 (both m, 6H, CH$_2$), 3.95-4.0 (m, 1H, CHCH$_2$), 5.95 (s, 1H, CHpyrazolyl), 7.31-7.47 and 7.58-7.68 (both m, 5H, Har), 7.79 (s, 1H, NH), 9.30 (s, 1H, CH=N). Found (%): C, 64.14; H, 6.80; N, 29.16. Calc. for $C_{23}H_{29}N_9$ (%): C, 64.01; H, 6.77; N, 29.21.

3b: yield: 50.7%, mp 220°C. ^{1}H NMR (CDCl$_3$): 1.58-1.95 (m, 6H, N(CH$_2$)$_2$, CH$_2$), 2.22, 2.48 (both s, 6H, 2CH$_3$); 2.64-3.12 (m, 4H, 2CH$_2$), 3.67 (t, 4H, O(CH$_2$)$_2$, *J*=4,5 Hz), 3.91-3.96 (m, 1H, CHCH$_2$), 5.95 (s, 1H, CHpyrazolyl), 7.32-7.42 and 7.59-7.68 (both m, 5H, Har), 7.81 (s, 1H, NH), 9.31 (s, 1H, CH=N). Found (%): C, 62.24; H, 6.40; N, 28.15. Calc. for $C_{23}H_{29}N_9O$ (%): C, 61.73; H, 6.53; N, 28.17.

3c: yield: 85.3% , mp 183-184°C. ^{1}H NMR (CDCl$_3$): 1.46-1.81 (m, 10H, piperidino), 2.22, 2.49 (both s, 6H, 2CH$_3$), 2.76-2.95 (m,6H, cyclopentyl), 3.91-3.97 (m, 1H, CHCH$_2$), 5.95 (s, 1H, CH in pyrazolyl), 7.32-7.48 and 7.60-7.69 (both m, 5H, Har), 7.77 (s, 1H, NH), 9.30 (s, 1H, N=CHAr). Found (%): C, 64.30; H, 6.89; N, 28.01. Calc. for $C_{24}H_{31}N_9$ (%): C, 64.70; H, 7.01; N, 28.29.

3d: yield: 74.5% , mp 193-195°C. ^{1}H NMR.(CDCl$_3$): 1.50-1.90 (m, 16H, 8CH$_2$), 2.20 (s, 3H, CH$_3$) 2.46, 2.30-2.70 and 2.85-3.05 (s, m, m, 11H, CH$_3$, N(CH$_2$)$_2$, 2CH$_2$, 3.37 (br.s, 1H, CHCH$_2$), 5.93 (s, 1H, CH in pyrazolyl), 7.55 (s, 1H, NH). Found (%): C, 62.20; H, 7.70; N, 29.70. Calc. for $C_{22}H_{33}N_9$ (%): C, 62.38; H, 7.85; N, 29.77.

3e: yield: 75.1% , mp 161-163°C. ^{1}H NMR (CDCl$_3$): 1.50-2.10 (m, 10H, 5CH$_2$), 2.21, 2.38, 2.48 (all s, 9H, 3CH$_3$), 2.75-3.03 (m, 6H, 3CH$_2$), 3.51 (br. s, 1H, CHCH$_2$), 5.94 (s, 1H, CH in pyrazolyl), 7.60 and 7.45-7.75 (s and m, 5H, NH and 4Har), 7.75 (s, 1H, NH). Found (%): C, 56.00; H, 6.02; N, 23.25. Calc. for $C_{25}H_{32}BrN_9$ (%): C, 55.76; H, 5.99; N, 23.41.

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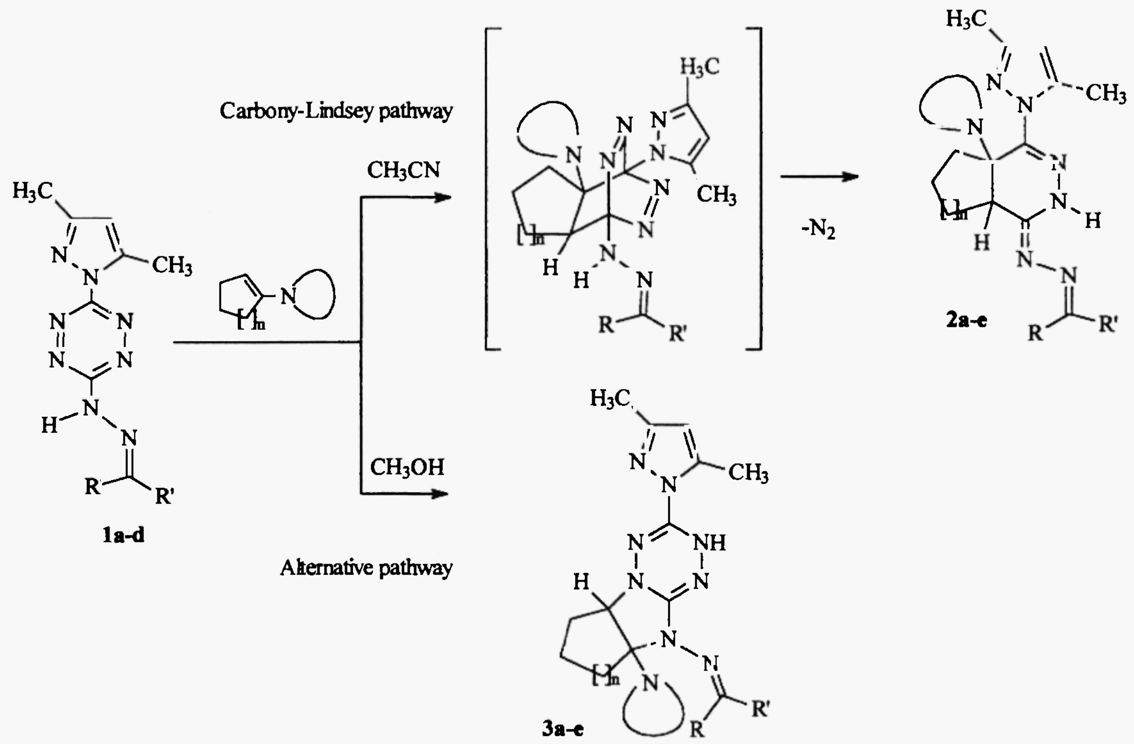

1	R	R'	R+R'
a			(CH$_2$)$_4$
b	H	C$_6$H$_5$	
c	CH$_3$	CH$_3$	
d	CH$_3$	4-BrC$_6$H$_4$	

2	R	R'	R+R'	-N	n
a			(CH$_2$)$_4$	-N O	1
b	CH$_3$	CH$_3$		-N O	1
c			(CH$_2$)$_4$	-N	1
d	CH$_3$	CH$_3$		-N	1
e	CH$_3$	4-BrC$_6$H$_4$		-N	1

3	R	R'	R+R'	-N	n
a	H	C$_6$H$_5$		-N	1
b	H	C$_6$H$_5$		-N O	1
c	H	C$_6$H$_5$		-N	1
d			(CH$_2$)$_4$	-N	2
e	CH$_3$	4-BrC$_6$H$_4$		-N	2

Scheme

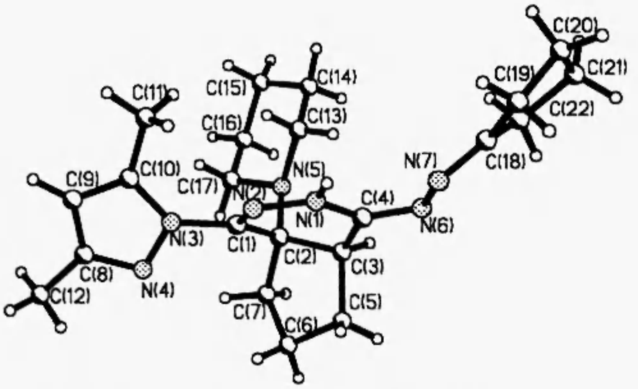

Fig. 1. X-ray crystal structure of compound **2c**

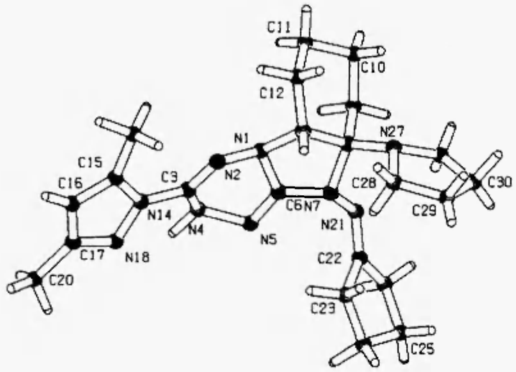

Fig. 2. X-ray crystal structure of compound **3d**