[4+2]-Cycloaddition of 3,6-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines with alkenes

G. L. Rusinov,[a] R. I. Ishmetova,[a] N. I. Latosh,[a] I. N. Ganebnych,[a] O. N Chupakhin,[a] and V. A. Potemkin[b]*

[a]Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20 ul. S. Kovalevskoy, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343 2) 74 1189. E-mail: rusinov@ios.uran.ru

[b]Chelyabinsk State University, 129 ul. Br. Kashirinykh, 454136 Chelyabinsk, Russian Federation

A number of 1,4-dihydropyridazines and pyridazines were prepared by the Diels—Alder reaction with an inverse electron demand from cyclic heterodiene systems, 3,6-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines, and some enamines as well as from 4-vinylpyridine, butyl vinyl ether, phenylacetylene, and acrylamide. The reaction of 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine with styrene afforded 4,5-dihydropyridazine, which was readily oxidized by atmospheric oxygen to form the corresponding pyridazine. Electron-withdrawing substituents (Br or Cl) in the pyrazole rings accelerate [4+2]-cycloaddition. When heated, 1,4-dihydropyridazines, which were synthesized from tetrazines and enamines, eliminated amine to give pyridazines. The reactivities of tetrazines were evaluated by quantum-chemical methods.

Key words: 1,2,4,5-tetrazine, 1,4-dihydropyridazine, pyridazine, enamine, Carboni—Lindsey reaction, [4+2]-cycloaddition, azadiene, dienophile, quantum-chemical calculations.

[4+2]-Cycloaddition of 3,6-disubstituted 1,2,4,5-tetrazines, which are used as heterodienes with a reversed electronic character of addends, is known as the Carboni—Lindsey reaction.[1] This reaction is accelerated by electron-withdrawing groups and is slowed down by electron-donating substituents at positions 3 and 6 of the tetrazine fragment.[2—5] The effects of π-deficient, π-excessive, and π-amphoteric heterocyclic substituents bound to the tetrazine ring through the C—C bond have been studied previously.[6]

We studied the [4+2]-cycloaddition reactions of 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**1a**) and its 4′-Br- and 4′-Cl derivatives (**1b,c**) with styrene, 4-vinylpyridine, butyl vinyl ether, acrylamide, phenylacetylene, and some enamines in which the π-amphoteric dimethylpyrazole ring is bound to the tetrazine fragment through an N—C bond.

Previously, it has been demonstrated that both dimethylpyrazolyl groups are readily replaced by different *N*-nucleophiles.[7—9] Thus, one would expect that the reactions of tetrazines **1a—c** with unsaturated compounds, such as enamines, which can also act as *C*-nucleophiles, will afford substitution products along with the cycloaddition products. However, the reactions gave only the cycloaddition products, *viz.*, 1,4-dihydropyridazines **3a—j**, 4,5-dihydropyridazine **2** (in the reaction of tetrazine **1a** with styrene), and pyridazines **4a—c,g**, in rather high yields (Scheme 1, Table 1). Compound **2** was oxidized by atmospheric oxygen upon storage both in the crystalline state and in a chloroform solution in the presence of acetic acid to give aromatic derivative **4b**. The reaction of tetrazine **1a** with acrylamide proceeded much more slowly to form pyridazine **4g**. Prolonged heating promoted oxidation of the dihydropyridazine that formed by atmospheric oxygen as well as by the initial tetrazine **1a**, as evidenced by partial reduction of **1a** to the 1,2-dihydro derivative.

As expected, the introduction of electron-withdrawing substituents (Br or Cl) into the dimethylpyrazole ring accelerated cycloaddition (see Table 1). This substitution had also a pronounced effect on the rate of aromatization of the resulting dihydropyridazines. Compound **3b** underwent deamination upon storage as a melt (150 °C) for 30 min to form pyridiazine **4d**. Chlorine-containing aromatic analog **4e** can be prepared at room temperature by the reaction of tetrazine **1c** with 1-piperidinocyclopentene, along with the major reaction product, *viz.*, dihydropyridazine **3h**. In attempting to recrystallize the latter from an acetonitrile—chloroform mixture, it was completely deaminated. However, the reaction product of tetrazine **1c** with 1-morpholinocyclopentene, which was prepared and purified under the same conditions, retained the morpholine residue in the molecule, and, consequently, it was identified as dihydropyridazine **3i**. Therefore, the nature of the amine group at position 4 of the dihydropyridazine

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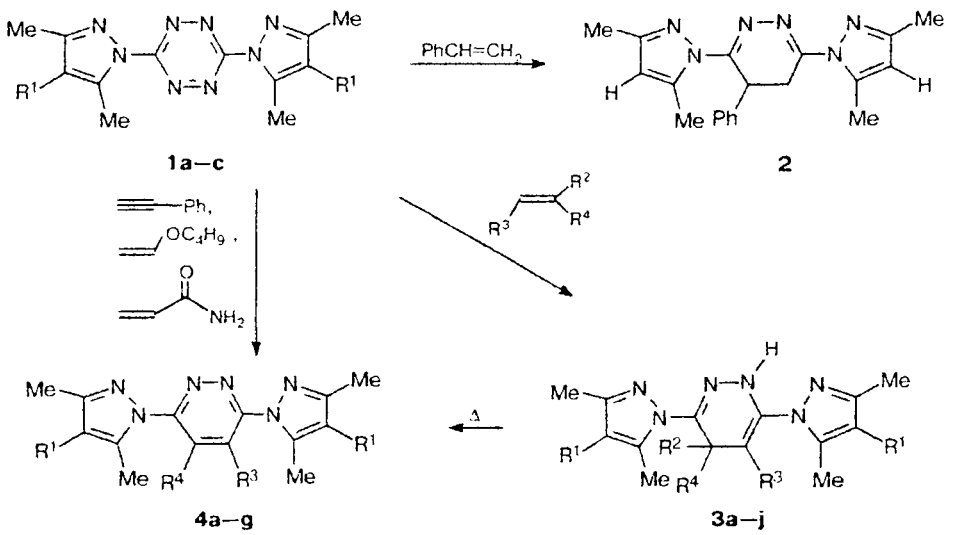


1: R^1 = H (**a**); Br (**b**); Cl (**c**)

3	R^1	R^2	R^3+R^4
a	H	—N	$(CH_2)_3$
b	H	—N	$(CH_2)_3$
c	H	—N O	$(CH_2)_3$
d	H	—N	$(CH_2)_4$
e	H	—N	$(CH_2)_4$

3	R^1	R^2	R^3+R^4
f	H	—N O	$(CH_2)_4$
g	Br	—N O	$(CH_2)_4$
h	Cl	—N	$(CH_2)_3$
i	Cl	—N O	$(CH_2)_3$
j	H	H	R^3 = H; R^4 = 4-Py

4	R^1	R^3	R^4
a	H	H	H
b	H	Ph	H
c	Br	Ph	H
d	H	R^3+R^4=$(CH_2)_3$	
e	Cl	R^3+R^4=$(CH_2)_3$	
f	H	R^3+R^4=$(CH_2)_4$	
g	H	H	$CONH_2$

Table 1. Principal characteristics of compounds **3a–j** and **4a–f**

Compound	Reaction time/h	Yield (%)	M.p. /°C	Found (%) / Calculated C	H	N	Molecular formula	^{1}H NMR, δ (*J*/Hz)
3a	0.08	59	158	66.22 66.46	7.95 7.70	25.85 25.84	$C_{21}H_{29}N_7$	5.92, 5.95 (both s, 2 H, 2 CH, Pyr); 2.68–2.57 (m, 10 H, 4 H, 2 Me); 3.31 (t, 4 H, $-CH_2-N-CH_2$, *J* = 7.5); 4.01–3.85 (m, 1 H, —NH—N=); 2.55, 2.54 (both s, 6 H, 2 Me); 2.47–1.62 (m, 6 H, 3 CH_2)
3b	0.08	63	145	67.23 67.14	7.97 7.94	24.81 24.92	$C_{22}H_{31}N_7$	5.92, 5.95 (both s, 2 H, 2 CH, Pyr); 2.67, 2.66 (both s, 3 H, Me); 2.53, 2.52 (both s, 6 H, 2 Me); 4.02–3.78 (m, 1 H,—NH—N=); 3.41–3.23 (m, 2 H, CH_2); 2.30–2.24 (m, 7 H, Me, 2 CH_2); 2.06–1.36 (m, 10 H, 5(CH_2)N)

(*to be continued*)

Table 1. (*continued*)

Compound	Reaction time/h	Yield (%)	M.p. /°C	Found (%) / Calculated C	H	N	Molecular formula	^{1}H NMR, δ (*J*/Hz)
3c	0.08	58	158	63.79 63.77	7.28 7.39	24.87 24.79	$C_{21}H_{29}N_7O$	5.99, 5.95 (both s, 2 H, 2 CH, Pyr); 3.57 (t, 4 H, $-CH_2-O-CH_2-$, *J* = 4.6); 4.08–3.85 (m, 1 H, $-NH-N=$); 2.64–2.24 (m, 18 H, 4 Me, 3 CH_2); 2.21–1.70 (m, 4 H, $-CH_2-N-CH_2-$)
3d	0.16	48	150	67.16 67.14	7.88 7.94	24.98 24.92	$C_{22}H_{31}N_7$	5.96, 5.92 (both s, 2 H, 2 CH, Pyr); 3.84–3.78 (m, 1 H, NH–N=); 3.11–2.79 (m, 4 H, 2 CH_2); 2.63, 2.64 (both s, 3 H, Me); 2.49, 2.26 (both s, 6 H, 2 Me); 2.24–1.66 (m, 11 H, Me, 4 CH_2)
3e	0.25	51	131–132	67.74 67.78	8.05 8.16	24.22 24.06	$C_{23}H_{33}N_7$	5.95, 5.92 (both s, 2 H, 2 CH, Pyr); 3.89–3.86 (m, 1 H, NH–N=); 3.04–2.67 (m, 7 H, Me, 2 CH_2); 2.52 (s, 3 H, Me); 2.23, 2.24 (both s, 6 H, 2 Me); 1.95–1.28 (m, 14 H, 7 CH_2)
3f	10.0	63	165–166	64.48 64.55	7.62 7.58	24.02 23.96	$C_{22}H_{31}N_7O$	5.97, 5.96 (both s, 2 H, 2 CH, Pyr); 3.51 (t, 4 H, $-CH_2-O-CH_2-$, *J* = 4.5); 2.67, 2.52 (both s, 6 H, 2 Me); 2.07–2.83 (m, 4 H, 2 CH_2); 3.84–3.77 (m, 1 H, $-NH-N=$); 2.24–1.29 (m, 14 H, 2 Me, $-CH_2-N-CH_2$, 4 H, 2 CH_2)
3g	0.25	65	148–151	47.10 47.15	5.25 5.28		$C_{22}H_{29}Br_2N_6O$	3.50 (t, 4 H, $-CH_2-O-CH_2$, *J* = 4.5); 3.94–3.78 (m, 1 H, NH–N=); 3.04–2.80 (m, 7 H, Me, 2 CH_2); 2.52 (s, 3 H, Me); 2.25 (br. s, 6 H, 2 Me); 1.98–1.22 (m, 8 H, $-CH_2-N-CH_2$, 2 CH_2)
3h	0.08	65	122–124	57.30 57.14	6.64 6.32	21.42 21.21	$C_{22}H_{29}Cl_2N_7$	3.99–2.67 (m, 2 H, CH_2); 2.65 (s, 3 H, Me); 2.56–2.25 (m, 14 H, 3 Me, 2 CH_2, –NH–N=); 1.77–1.39 (m, 10 H, 5 $(CH_2)_5N$)
3i	0.08	81	188–191	54.38 54.31	5.98 5.86	21.32 21.11	$C_{21}H_{27}Cl_2N_7O$	3.32 (t, 4 H, $-CH_2-O-CH_2$, *J* = 7.5); 4.07–3.73 (m, 1 H, NH–N=); 3.58 (t, 2 H, CH_2, *J* = 4.6); 2.65 (s, 3 H, Me); 3.23–2.37 (m, 7 H, Me, 2 CH_2); 2.30–1.59 (m, 10 H, 2 Me, $-CH_2-N-CH_2$)
3j	2.0	41	184	65.66 65.71	6.04 6.05	28.25 28.24	$C_{19}H_{21}N_7$	6.06, 6.05 (both s, 2 H Pyr); 8.29–8.27, 6.52–6.49 (both m, 4 H, Py); 3.88 (s, 2 H, CH_2); 10.19 (s, 1 H, $-NH-N=$); 2.50, 2.46, 2.21 (all s, 12 H, 4 Me)
4a	0.5	91	178–180	62.66 62.81	6.01 6.00	31.33 31.53	$C_{14}H_{16}N_6$	8.22 (s, 2 H, CH_2); 6.00 (s, 2 H, 2 CH, Pyr); 2.75, 2.74 (both s, 6 H, 2 Me); 2.31 (s, 6 H, 2 Me)
4b	20.0	62	159–160	69.76 69.58	5.81 5.89	24.42 24.38	$C_{20}H_{20}N_6$	8.33 (s, 1 H, CH); 7.40–7.13 (m, 5 H, Ph); 6.09, 5.90 (both s, 2 CH, Pyr); 2.80, 2.32, 2.23, 1.97 (all s, 12 H, 4 Me)
4c	3.0	91	182–184	47.83 47.93	3.61 3.54	16.74 16.83	$C_{20}H_{18}Br_2N_6$	8.31 (s, 1 H, CH); 7.42–7.02 (m, 5 H, Ph); 2.82, 2.32, 2.20, 2.02 (all s, 12 H, 4 Me)
4d	0.5	76	195–197	66.18 66.21	6.47 6.54	27.41 27.25	$C_{17}H_{20}N_6$	6.04 (s, 2 H, 2 CH, Pyr); 3.32 (t, 4 H, 2 CH_2, *J* = 7.6); 2.29–2.07 (m, 2 H, CH_2); 2.55, 2.54 (both s, 6 H, 2 Me); 2.30 (s, 6 H, 2 Me)
4e	0.25	85	268–269	54.44 54.12	5.37 4.80	22.28 22.34	$C_{17}H_{18}Cl_2N_6$	3.32 (t, 4 H, 2 CH_2, *J* = 7.5); 2.28–1.99 (m, 2 H, CH_2); 2.57 (s, 6 H, 2 Me); 2.30 (s, 6 H, 2 Me)
4f	0.25	93	183–185	66.96 67.05	6.89 6.88	26.42 26.07	$C_{18}H_{22}N_6$	6.03 (s, 2 H, 2 CH, Pyr); 2.30 (s, 12 H, 4 Me); 2.85–2.69, 2.00–1.67 (both m, 8 H, 4 CH_2)

fragment also substantially affects the process of aromatization, *viz.*, less basic amines are more difficultly eliminated, all other factors being the same. This is also evidenced by the results of prolonged storage of dihydropyridazine **3c** as a melt (~160 °C). In this case, the initial compound was present in the reaction mixture along with pyridazine **4d**. We failed to prepare aromatic products from dihydropyridazines, which have been synthesized by the reactions of tetrazines with cyclohexanone-derived enamines, according to this procedure. However, refluxing of compound **3d** in toluene in the presence of acetic acid even for 15 min afforded the corresponding pyridazine **4f**.

All the compounds obtained (**2**, **3a—j**, and **4a—g**) are colorless crystalline substances which are readily soluble in chloroform and acetone, moderately soluble in alcohols, and insoluble in water.

The chemical shifts of the protons of the —NH—N= groups in the pyridazine rings are observed as multiplets at δ 4.07—3.73 (see Table 1). We succeeded in assigning these multiplets only upon addition of CD_3OD, because the addition of CD_3CO_2D induced aromatization of dihydropyridazines. Thus after acidification of a solution of dihydropyridazine **3c** with CD_3CO_2D, the ^1H NMR spectrum immediately showed resonance signals as a triplet with the center at δ 3.32. These signals belong to four protons of the cyclopenteno substituent in pyridazine **4d**.

The IR spectra of all the synthesized 1,4-dihydropyridazines, unlike the spectra of their aromatic analogs, have an intense band in the region of 1600—1590 cm^{-1}, which is characteristic of the NH bond. This fact agrees well with the published data.[10] The IR spectrum of compound **4g** has two medium-intensity broad bands in the region of stretching vibrations at 3130 and 3290 cm^{-1}. These bands belong to the NH_2 fragment. The low-frequency shifts of these bands compared to the usual positions of the signals of the nonassociated amino group (at 3400 and 3500 cm^{-1}) are indicative of the existence of a hydrogen bond.[11] This is also confirmed by the nonequivalence of the protons of the amino group in the ^1H NMR spectrum.

With the aim of explaining the high reactivity of 3,6-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines, we performed quantum-chemical calculations. The preliminary results agree well with the regularities described previously.[2,3] The *ab initio* calculations with the STO-3G basis set for these compounds and for a large number of other symmetrical 3,6-disubstituted *s*-tetrazines demonstrated that the logarithms of the rate constants of the Carboni—Lindsey reaction are actually determined by the energy of the lowest unoccupied molecular orbital (LUMO) of the diene, provided that the dienophile remains the same. The quantitative kinetic characteristics for the reactions of a number of symmetrical 3,6-disubstituted *s*-tetrazines with Me—C≡C—NMe_2 have been reported previously.[3] It was demonstrated that the rate constants for the reactions of tetrazines with other dienophiles linearly correlate with the constants of their reactions with Me—C≡C—NMe_2. The arrangement of the tetrazines in order of increasing activity with respect to other dienophiles also completely corresponds to their arrangement in order of increasing activity with respect to Me—C≡C—NMe_2. This allows one to make the qualitative arrangement of the newly synthesized symmetrical 3,6-disubstituted *s*-tetrazines in the order of increasing activity in the series of the known compounds based on theoretical estimates of the rate constants for the reactions with Me—C≡C—NMe_2. However, it should be taken into account that when the energies of the highest occupied molecular orbital (HOMO) and of LUMO of the diene have close values, this electron transition becomes possible, resulting in competition with the transition between HOMO of the dienophile and LUMO of the diene, thus decreasing the rate of cycloaddition. It is this process that can explain, for example, the anomalously low rate constants for cycloaddition of 3,6-dimethoxytetrazine and some other compounds with relatively low energies of LUMO. In this case, the reactivities of dienes in the reactions with the same dienophile should be determined by the ratio between the $(E_{HOMO} - E_{LUMO})$ difference and the E_{LUMO} value of the diene. Actually, a correlation between the $E_{LUMO}/(E_{HOMO} - E_{LUMO})$ value and the logarithm of the rate constant is observed in the series of different symmetrically substituted tetrazines. The charges on the nitrogen atoms (Q_N) of the tetrazine ring also have a pronounced effect on the reactivity of substituted tetrazines. This is attributable to the fact that charges on these atoms serve as an indirect estimate of the electron-withdrawing ability of substituents at positions 3 and 6. In this case, the C(3) and C(6) atoms should be more sensitive to the electronic properties of the substituent. However, analysis of the charges and the coefficients of the wave functions of HOMO and LUMO on these atoms did not reveal an essential dependence of the rate constants on these functions. The fact that the electron density on the N atom determines to a large extent its characteristics as a leaving group provides yet another explanation for the dependence of cycloaddition on the charge on the N atom. Based on the aforesaid, the following empirical equation for the rate constants for the Carboni—Lindsey reactions of a series of substituted tetrazines with Me—C≡C—NMe_2 at 20 °C in nitrobenzene was obtained

$$\ln(K \cdot 10^4) = 49.86 - 52.6\ E_{LUMO}/(E_{LUMO} - E_{HOMO}) + 173.9\ Q_N;$$

(where $R = 0.956$ is the correlation coefficient of the equation; $F = 43$ is the Fisher coefficient; and $\sigma = 2.3$ is the standard deviation). The corresponding equation for acetonitrile solutions can be written as follows:

$$\ln(K \cdot 10^4) = 49.94 - 58.9\ E_{LUMO}/(E_{LUMO} - E_{HOMO}) + 153.5\ Q_N,$$

$R = 0.980$; $F = 156$; $\sigma = 1.1$.

Apparently, the differences in the coefficients of the equations for different solvents are determined by solvation effects. The experimental kinetic characteristics and those calculated according to both equations are given in Table 2. The coefficients of both equations have rather close values, which allows one to construct a general equation for the total selection from Table 2 if the effect of the solvent is neglected:

$$\ln(K \cdot 10^4) = 50.9 - 52.5\, E_{LUMO}/(E_{LUMO} - E_{HOMO}) + 180\, Q_N.$$

$$R = 0.965;\ F = 164;\ \sigma = 1.6.$$

These dependences do not contradict the regularities described previously[3] and supplement these regularities due to the possibility of taking into account electron transitions in the diene and the effect of the electron density on the N atoms of the tetrazine ring.

The logarithms of the constant rates for 3,6-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines can be calculated based on this dependence. The calculated data for the reactions in nitrobenzene and acetonitrile are given in Table 2 ($\ln(K \cdot 10^4)_{calc}$). Taking into account the fact that, according to the published data,[3,6,12] the rates of the Carboni—Lindsey reactions in different solvents correlate with each other, the values obtained indicate that 3,6-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines (**1a—c**) are highly reactive compounds. They can be arranged in the series containing other symmetrical 3,6-disubstituted *s*-tetrazines (see Table 2) in the following order of increasing activity: R = CN > CF_3 > COOMe ≈ COOEt ≈ 4-chloro-3,5-dimethylpyrazolyl > 4-bromo-3,5-dimethylpyrazolyl ≈ 2-pyridyl ≈ 3,5-dimethylpyrazolyl > 2-furyl >> SMe ≈ OMe > NH_2.

Therefore, due to the high reactivity of 3,6-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines and the nucleofugality of substituents at positions 3 and 6 of the tetrazine fragment, these compounds are very promising in the synthesis of new symmetrically and unsymmetrically substituted pyridazines provided that the Carboni—Lindsey reactions are combined with the nucleophilic substitution of the dimethylpyrazole groups.

Experimental

The melting points were measured on a Boetius table. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Tesla BS-567A spectrometer operating at 80 MHz with Me_4Si as the internal standard. The IR spectra were obtained on a Specord IR-75 instrument in KBr pellets and in Nujol mulls.

3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (1a) and enamines were synthesized according to procedures reported previously.[13,14]

3,6-Bis(4-bromo-3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (1b). Bromine (1.29 g, 25 mmol) was added to a solution of tetrazine **1a** (2.7 g, 10 mmol) in $CHCl_3$ (30 mL) at a temperature below 25 °C, and precipitation immediately started. The solvent was distilled off, the residue was dissolved in water, and the solution was neutralized with a solution of $NaHCO_3$. The precipitate that formed was filtered off and recrystallized from MeCN. M.p. 263 °C. The yield was 3.8 g (89%). Found (%): C, 33.68; H, 2.78; N, 25.95. $C_{12}H_{12}Br_2N_8$. Calculated (%): C, 33.67; H, 2.83; N, 26.18. ^{1}H NMR, δ: 2.75 (s, Me); 2.42 (s, Me).

3,6-Bis(4-chloro-3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (1c). *N*-Chlorosuccinimide (3.4 g, 25 mmol) was added to a solution of tetrazine **1a** (3.0 g, 11 mmol) in $CHCl_3$ (40 mL). The reaction mixture was refluxed for 40 min. The solvent was distilled off and the residue was washed with water and recrystallized from MeCN. Bright-red crystals were obtained, m.p. 247—248 °C. The yield was 3.0 g (81%). Found (%): C, 42.71; H, 3.42; N, 32.97. $C_{12}H_{12}Cl_2N_8$. Calculated (%): C, 42.48; H, 3.57; N, 33.04. ^{1}H NMR, δ: 2.73 (s, Me); 2.41 (s, Me).

4,5-Dihydro-3,6-bis(3,5-dimethylpyrazol-1-yl)-4-phenylpyridazine (2). A mixture of tetrazine **1a** (0.5 g, 1.85 mmol) and styrene (0.25 mL, 2.16 mmol) in toluene (10 mL) was refluxed for 0.5 h. The solvent was distilled off and the product was recrystallized from MeOH. The yield was 0.57 g (94%). M.p. 163 °C. Found (%): C, 69.30; H, 6.43; N, 24.43. $C_{20}H_{22}N_6$. Calculated (%): C, 69.34; H, 6.40; N, 24.26. ^{1}H NMR, δ: 7.21—7.18 (m, 5 H, Ph); 5.98 and 5.93 (both s, 2 H, 2 CH, Pyr); 2.64 (d, 3 H, Me, J = 0.7 Hz); 2.61 (d, 3 H, Me, J = 0.8 Hz); 2.20 (s, 6 H, 2 Me); 5.28, 4.05, and 3.08 (all dd, 1 H, H(4): J = 9 and 1.2 Hz; H_A(5): J = 17.5 and 1.2 Hz; H_B(5): J = 17.5 and 9 Hz).

4a-Amino-1,4-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-4a,5,6,7-tetrahydro-2*H*-cyclopenta[*d*]pyridazines and 4a-amino-1,4-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-2,4a,5,6,7,8-hexahydrophthalazines. Compounds (3a—e and g—i). Tetrazine **1** (1.0 mmol) was added portionwise to a solution of enamine (1.5 mmol) in MeCN (20 mL) for 5—7 min. The reaction proceeded with vigorous evolution of nitrogen and disappearance of the red color of the reaction mixture at room temperature.* After completion of gas evolution, the reaction mixture was cooled with ice. The precipitate that formed was filtered off and recrystallized from acetonitrile.** In the synthesis of compound **3h**, its aromatic analog **4e** was also isolated from the reaction mixture in 26% yield. The principal characteristics of compounds **3a—e** and **g—i** are given in Table 1.

Compounds (3f,j). The corresponding dienophile (1-morpholinocyclohexene or 4-vinylpyridine) (2.0 mmol) was added to a solution of tetrazine **1a** (1.0 mmol) in toluene (5.0 mL) and the reaction mixture was refluxed for 2—10 h. The solvent was distilled off and the residue was recrystallized from methanol.

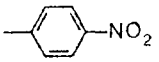
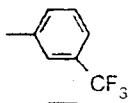
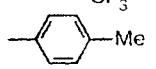
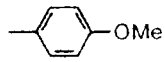
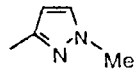
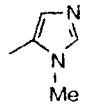
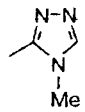
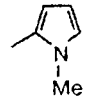
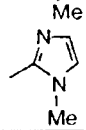
3,6-Bis(3,5-dimethylpyrazol-1-yl)pyridazine (4a). A mixture of tetrazine **1a** (1.0 g, 3.7 mmol) and butyl vinyl ether (2 mL, 15.6 mmol) in toluene (10 mL) was refluxed for 0.5 h. The solvent was distilled off and the compounds were recrystallized from ethanol. The yield was 0.93 g (93.8%) (see Table 1).

3,6-Bis(3,5-dimethylpyrazol-1-yl)-4-phenylpyridazine (4b). A mixture of tetrazine **1a** (0.5 g, 1.85 mmol) and phenylacetylene (0.3 mL, 2.73 mmol) in toluene (5 mL) was refluxed for 20 h.

* For the preparation of compounds **3e,g**, the reaction mixtures were slowly heated to boiling over 5 min.

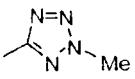
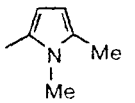
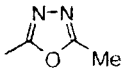
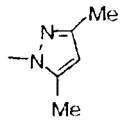
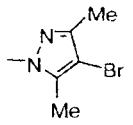
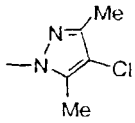
** Compound **3c** was purified by recrystallization from methanol, compound **3h** was washed on a filter with methanol, and compound **3i** was recrystallized from a 10 : 1 acetonitrile—chloroform mixture.

Table 2. Results of quantum-chemical calculations for 3,6-bis-R-1,2,4,5-tetrazines and the experimental[3] (exp) and calculated (calc) characteristics of the Carboni—Lindsey reactions of tetrazine derivatives with Me—C≡C—NMe_2 in nitrobenzene or acetonitrile

R	Q_N/au	E_{HOMO}	E_{LUMO}	$(K \cdot 10^4)_{exp}$	$\ln(K \cdot 10^4)$		
		eV		/L (mol s)$^{-1}$	exp	calc ($PhNO_2$)	calc (MeCN)
—OMe	−0.2130	−3.576	0.985	4.22	1.440	1.449	4.525
$-CF_3$	−0.1725	−4.660	−0.249	$>4 \cdot 10^9$	>22.127	22.830	26.791
—H	−0.1890	−3.839	0.689	$5.8 \cdot 10^4$	10.968	8.981	11.967
—SMe	−0.1440	−6.473	5.079	170	5.136	1.675	1.934
—Me	−0.1355	−7.738	4.737	65.3	4.179	6.309	6.770
	−0.1310	−7.759	2.466	$17.4 \cdot 10^4$	12.067	14.383	15.624
—COOMe	−0.1060	−8.514	2.761	$4 \cdot 10^9$	22.127	18.536	19.242
—COOEt	−0.1070	−8.436	2.863	—	—	17.914	18.588
$-NH_2$	−0.2270	−2.986	1.522	—	—	−7.388	−4.792
—CN	−0.0890	−9.515	1.692	—	—	26.434	27.384
	−0.1350	−7.250	3.151	14400	9.575	10.436	11.370
	−0.1400	−6.426	3.717	155	5.043	6.224	6.861
	−0.1425	−5.952	3.842	34.7	3.547	4.430	4.956
Ph in nitrobenzene	−0.1380	−6.727	3.608	685	6.529	7.485	—
Ph in acetonitrile	−0.1380	−6.727	3.608	1820	7.507	—	8.190
	−0.1385	−6.041	3.491	1150	7.048	6.496	7.104
	−0.1350	−6.361	3.258	10050	9.215	8.554	9.263
	−0.1235	−6.783	2.980	$2.5 \cdot 10^6$	14.756	12.316	13.000
	−0.1405	−6.224	4.023	525	6.263	4.761	5.244
	−0.1305	−6.447	4.114	1100	7.003	6.661	6.958
	−0.1290	−6.619	3.748	16600	9.717	8.396	8.839
	−0.1370	−6.589	3.836	426	6.054	6.667	7.233
	−0.1370	−6.087	3.411	319	5.765	7.131	7.753
	−0.1185	−7.194	2.759	$4.6 \cdot 10^6$	15.355	14.661	15.419
	−0.1430	−5.337	3.931	11.2	2.416	2.666	3.001
	−0.1270	−6.146	3.431	9770	9.187	8.917	9.339

(to be continued)

Table 2. *continued*

R	Q_N/au	E_{HOMO}	E_{LUMO}	$(K \cdot 10^4)_{exp}$	ln($K \cdot 10^4$)		
		eV		/L (mol s)$^{-1}$	exp	calc ($PhNO_2$)	calc (MeCN)
	−0.1100	−7.873	3.023	$15 \cdot 10^6$	16.563	16.126	16.710
	−0.1450	−5.023	4.054	3.69	1.306	1.135	1.370
	−0.1395	−7.040	3.964	10200	9.230	6.639	7.304
	−0.1055	−7.684	2.305	$2.9 \cdot 10^8$	19.496	19.366	20.151
	−0.1260	−7.207	3.331	—	—	11.309	11.977
	−0.1275	−6.242	3.385	—	—	9.179	9.654
	−0.1180	−7.075	3.805	—	—	10.931	11.200
	−0.1160	−6.937	3.514	—	—	11.988	12.325
	−0.0960	−7.333	3.346	—	—	16.672	16.744

The solvent was distilled off and the product was recrystallized from ethanol. The yield was 0.394 g (62%) (see Table 1).

3,6-Bis(4-bromo-3,5-dimethylpyrazol-1-yl)-4-phenylpyridazine (4c). A mixture of tetrazine **1b** (0.428 g, 1.0 mmol) and phenylacetylene (0.5 mL, 4.55 mmol) in toluene (5.0 mL) was refluxed for 3 h. The color of the reaction mixture changed from bright-orange to pale-yellow. Toluene was distilled off and the residue was recrystallized from methanol. The yield was 0.46 g (91.6%) (see Table 1).

1,4-Bis(3,5-dimethylpyrazol-1-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine (4d). Dihydropyridazine **3b** (50 mg, 0.13 mmol) was kept as a melt at 160 °C for 30 min until liberation of the amine ceased. The residue was cooled and recrystallized from methanol. Colorless crystals were obtained. The yield was 30 mg (76.9%) (see Table 1).

1,4-Bis(4-chloro-3,5-dimethylpyrazol-1-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine (4e). Dihydropyridazine **3h** (186 mg, 0.4 mmol) was dissolved in a 10 : 1 acetonitrile–chloroform mixture (5 mL) upon heating. The precipitate that formed on cooling was filtered off and dried. The yield was 130 mg (85.5%) (see Table 1).

1,4-Bis(3,5-dimethylpyrazol-1-yl)-5,6,7,8-tetrahydrophthalazine (4f). A solution of 1,4-bis(3,5-dimethylpyrazol-1-yl)-4a-pyrrolidino-2,4a,5,6,7,8-hexahydrophthalazine (**3d**) (197 mg, 0.5 mmol) in toluene (5.0 mL) and AcOH (0.1 mL) was refluxed for 15 min. The solvent was distilled off, the residue was dissolved in MeOH (5.0 mL), and the mixture was added dropwise to chilled distilled water (100 mL). The colorless flocculent precipitate that formed was filtered off and dried. The yield was 150 mg (93.2%) (see Table 1).

3,6-Bis(3,5-dimethylpyrazol-1-yl)pyridazine-4-carboxamide (4g). Et_3N (0.05 mL, 0.36 mmol) was added to a mixture of tetrazine **1a** (200 mg, 0.74 mmol) and acrylamide (56 mg, 0.78 mmol) in toluene (5 mL) and the mixture was refluxed for 20 h.* The cream-colored precipitate that formed was filtered off and recrystallized from ethanol. The yield was 86 mg (37%). M.p. 246–247 °C. Found (%): C, 57.41; H, 5.82; N, 31.36. $C_{15}H_{17}N_7O$. Calculated (%): C, 57.86; H, 5.51; N, 31.50. ^{1}H NMR (DMSO-d_6), δ: 8.17 (s, 1 H, CH); 8.09 (br.s, 1 H, NH_2); 7.73 (br.s, 1 H, NH_2); 6.27 and 6.13 (both s, 1 H, 2 CH, Pyr); 2.68, 2.41, 2.26, and 2.16 (all s, 3 H, 4 Me).

References

1. R. A. Carboni and R. V. Lindsey, *J. Am. Chem. Soc.*, 1959, **81**, 4342.
2. E. G. Kovalev, I. Ya. Postovskii, G. L. Rusinov, and I. L. Shegal, *Khim. Geterotsikl. Soedin.*, 1981, **11**, 1462 [*Chem. Heterocycl. Compd.*, 1981, **11** (Engl. Transl.)].

* The completion of the reaction was monitored by TLC; the formation of 1,2-dihydro-3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine was also detected chromatographically.

3. J. Sauer, *Khim. Geterotsikl. Soedin.*, 1995, **25**, 1307 [*Chem. Heterocycl. Compd.*, 1995, **25** (Engl. Transl.)].
4. D. L. Boger and S. M. Sakya, *J. Org. Chem.*, 1988, **53**, 1415.
5. S. M. Sakya, K. K Groskopf, and D. L. Boger, *Tetrahedron Lett.*, 1997, **38**, 3805.
6. J. Sauer, in *Comprehensive Heterocycl. Chem. II*, 1996, **6**, 901.
7. G. L. Rusinov, N. I. Latosh, I. N. Ganebnych, R. I. Ishmetova, and O. N. Chupakhin, *16th International Congress of Heterocyclic Chemistry. Abstracts Book*, Bozeman, USA, 1997, 196.
8. N. I. Latosh, G. L. Rusinov, and E. G. Polovinko, *International Memorial I. Postovsky Conference on Organic Chemistry. Abstracts Book*, Ekaterinburg, Russia, 1998, 90.
9. C. Glidewell, P. Lightfoot, B. Royles, and D. Smith, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1167.
10. M. Avram, I. G. Dinulescu, E. Marica, and C. D. Nenitzescu, *Chem. Ber.*, 1962, **95**, 2250.
11. K. Nakanishi, *Infrared Absorption Spectroscopy*, Holden-Day, San Francisco, 1962.
12. J. W. Wijnen, S. Zavarise, J. B. F. N. Engberts, and M. Charton, *J. Org. Chem.*, 1996, **61**, 2001.
13. M. D. Coburn, G. A. Buntain, B. W. Harris, M. A. Hiskey, K.-Y. Lee, and D. G. Ott, *J. Heterocycl. Chem.*, 1991, **28**, 2049.
14. S. Hünig and W. Lendle, *Chem. Ber.*, 1960, **93**, 909.

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