Synthesis of Novel 1,2,4-Triazino[5,6-*b*]quinoxalines and Their Tri-*N*-oxides

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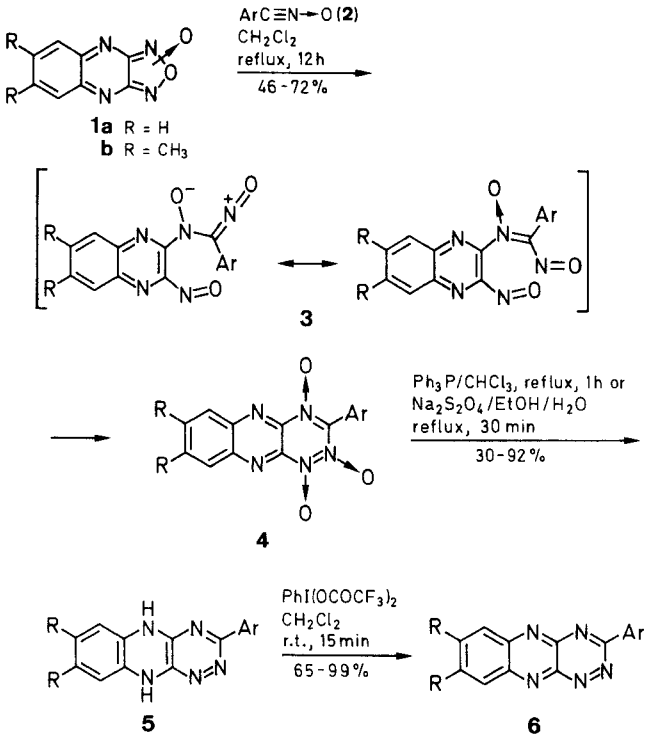
Reaction of [1,2,5]oxadiazolo[3,4-*b*]quinoxaline 1-oxides with stable nitrile oxides in refluxing dichloromethane affords good yields of 1,2,4-triazino[5,6-*b*]quinoxaline 1,2,4-tri-*N*-oxides, a novel class of compounds containing the pyrazino[2,3-*e*]triazine skeleton and also bearing three *N*-oxides in the same triazine ring. The tri-*N*-oxides are reduced with triphenylphosphine or sodium dithionite to the corresponding 5,10-dihydro-1,2,4-triazino[5,6-*b*] quinoxalines, which are converted to 1,2,4-triazino[5,6-*b*] quinoxalines upon oxidation with iodosobenzene bis(trifluoroacetate).

The reactivity of benzofurazan 1-oxide towards 1,3-dipoles or dienes[1-5] has not been well explored. The benzofurazan ring is often inert in these reactions, and if a reaction does occur, it usually affords cycloaddition products from the benzene ring.[3,5] We have recently reported[6] that benzofurazan 1-oxides react with nitrile oxides affording both the benzene and furazan ring addition products. The furazan 1-oxide ring addition reaction led to an unexpected 1,2,4-benzotriazine tri-*N*-oxide, whose structure was unequivocally assigned by X-ray analysis.[6]

We report here a further synthetic application of this unusual cycloaddition by reaction of [1,2,5]oxadiazolo-[3,4-*b*]quinoxaline 1-oxides **1** with the stable nitrile oxides **2** in refluxing dichloromethane, which affords good yields of 1,2,4-triazino[5,6-*b*]quinoxalines **4**, while no cycloadducts to the quinoxaline ring are isolated.



2	Ar	4–6	R	Ar
a	2,4,6-$Me_3C_6H_2$	a	H	2,4,6-$Me_3C_6H_2$
b	2,6-$Cl_2C_6H_3$	b	H	2,6-$Cl_2C_6H_3$
		c	Me	2,4,6-$Me_3C_6H_2$
		d	Me	2,6-$Cl_2C_6H_3$

Readily available[7,8] [1,2,5]oxadiazolo[3,4-*b*]quinoxaline 1-oxides **1** have been found to be more reactive[8,9] than simple benzofurazan 1-oxides, evidently because of the electron-withdrawing fused pyrazine ring, which activates the neighboring furoxan ring towards nucleophiles. These compounds **1** are easily prepared[7,8] in high yields by oxidation of the corresponding 2,3-bis[hydroxyimino]tetrahydroquinoxalines, which can be obtained in good yields by reaction of 1,2-phenylenediamines with 1,2-dichloroglyoxime.[10]

1,2,4-Triazino[5,6-*b*]quinoxalines **4**, separated from the reaction mixture by column chromatography, were characterized on the basis of their spectral data (IR, ^{1}H- and ^{13}C-NMR, UV/VIS, and MS) and elemental analyses, as well as from their reduction products. The infrared spectra of these products indicate the lack of the strong absorption bands at ca $\nu = 1600\ cm^{-1}$, characteristic for a furazan 1-oxide ring, implying the addition of nitrile oxides **2** to the furazan ring of compounds **1**. Their ^{1}H- and ^{13}C-NMR spectra also show the presence of an unsymmetrically substituted quinoxaline ring system, the H-7, H-8 protons being less deshielded in comparison to H-6, H-9 protons.[11] The parent ions of compounds **4** do not appear at 70 eV, while the peaks at $m/z = M^+ - 16$, $M^+ - 32$, $M^+ - N_2O$, $M^+ - NO_3$ and $M^+ - N_2O_3$ can be easily observed.

The generation of tri-*N*-oxides **4** can be explained as a [4 + 2] cycloaddition between the reactants, where the furazans **1** and nitrile oxides **2** contribute four and two electrons respectively. This reaction may involve in situ generation of an intermediate bis(nitroso)nitrone **3**, possibly by an nucleophilic attack from the carbon of the nitrile oxides, which carries a considerable negative charge[12] on the nitrogen of the furazan ring. A nitroso-sonitrone intermediate analogous to **3** has been reported to be generated in the reaction of aromatic nitroso compounds with nitrile oxides.[13] The formation of **3** seems reasonable, when considering the "*o*-dinitroso" equivalence of furazan 1-oxides.[1]

Tri-*N*-oxides **4** are reduced by triphenylphosphine or sodium dithionite, affording in good to high yields the deoxygenated 5,10-dihydro-1,2,4-triazino[5,6-*b*]-quinoxalines **5**, which are further oxidized by iodosobenzene bis(trifluoracetate) to the 1,2,4-triazino[5,6-*b*]-quinoxalines **6**. Tables 1 and 2 record the spectral data of compounds **5** and **6**. The characteristic N–H stretching bands of compounds **5** appear in its IR spectrum at ca. $\nu = 3200\ cm^{-1}$. Due to the slow invesion of the unsymmetrically substituted nitrogen atoms in the dihydropyrazine ring of these compounds, their ^{1}H- and ^{13}C-NMR spectra possess broad peaks. For this reason, ^{13}C-NMR spectra are not reported for compounds **5**. The mass spectra of compounds **6** do not show the parent ion,

but peaks at $M^+ + 2$, a characteristic tendency of quinonoid and related compounds when introduced into the mass spectrometer by means of a heated inlet.[14] The additional atoms probably originate from absorbed water.

The hydrogenation of pyrazine ring in compounds **5** by triphenylphosphine in chloroform seems unusual, since, to our knowledge, no other simple example of hydrogenation of a heterocyclic ring with triphenylphosphine has been reported in the literature. In a similar reaction,[15] the

Table 1. Compounds **4–6** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	UV/VIS (THF) λ_{max}(nm) (log ε)	^{1}H-NMR[c] δ, J(Hz)	MS (70 eV) m/z (%)
4a	46	210 (dec)[d]	$C_{18}H_{15}N_5O_3$ (349.3)	329 (4.34), 380 (sh) (3.60), 466 (3.36), 488 (sh) (3.34), 540 (3.37)	2.16 (s, 6H, CH_3-2′, 6′), 2.34 (s, 3H, CH_3-4′), 7.06 (s, $2H_{arom}$), 8.27 (m, 2H, H-7, H-8), 8.51 (m, 2H, H-6, H-9)	317 ($M^+ - 16$, 1), 30 (100)
4b	72	215 (dec)[d]	$C_{15}H_7Cl_2N_5O_3$ (376.2)	330 (4.41), 388 (3.60), 475 (3.34), 533 (3.40)	7.77 (s, $3H_{arom}$), 8.28 (m, 2H, H-7, H-8), 8.51 (m, 2H, H-6, H-9)	359, 361, 363 ($M^+ - 16$, 1), 44 (100)
4c	57	206–207[d] (dec)	$C_{20}H_{19}N_5O_3$ (377.4)	332 (4.60), 395 (3.88), 472 (3.61), 532 (3.58)	2.16 (s, 6H, CH_3-2′, 6′), 2.34 (s, 3H, CH_3-4′), 2.62, 2.63 (2s, 3H each, CH_3-7,8), 7.04 (s, $2H_{arom}$), 8.26, 8.28 (2s, 1H each, H-6, 9)	345 ($M^+ - 16$, 2), 130 (100)
4d	52	214 (dec)[d]	$C_{17}H_{11}Cl_2N_5O_3$ (404.2)	332 (4.43), 399 (3.78), 460 (sh) (3.49), 495 (3.38), 525 (3.41)	2.62, 2.63 (2s, 3H each, CH_3-7, 8), 7.77 (s, $3H_{arom}$), 8.27 (s, 2H, H-6, 9)	387, 389, 391 ($M^+ - 16$, 2, 2, 1), 44 (100)
5a[e]	92[f] 64[g]	293–296 (EtOH)	$C_{18}H_{17}N_5$ (303.4)	362 (4.01), 380 (4.11), 401 (4.10), 424 (3.83)	2.24 (s, 3H, CH_3-4′), 2.27 (s, 6H, CH_3-2′, 6′), 6.80 (br s, 4H, H-6-9), 6.88 (s, $2H_{arom}$), 10.03 (br s, 2H, NH)	303 (M^+, 100)
5b[e]	72[f] 30[g]	314–319 (EtOH)	$C_{15}H_9Cl_2N_5$ (330.2)	361 (4.02), 377 (4.08), 397 (4.04), 421 (3.78)	6.65 (m, 4H, H-6-9), 7.52 (m, $3H_{arom}$), 10.15 (br s, 2H, NH)	329, 331, 333 (M^+, 100, 55, 12)
5c[e]	73[f] 51[g]	285–290 (EtOH)	$C_{20}H_{21}N_5$ (331.4)	366 (4.10), 384 (4.21), 405 (4.22), 428 (3.94)	2.09, 2.10 (2s, 3H each, CH_3-7, 8), 2.23 (s, 3H, CH_3-4′), 2.28 (s, 6H, CH_3-2′, 6′), 6.65 (s, br, 2H, H-6, H-9), 6.87 (s, $2H_{arom}$), 9.92 (br s, 2H, NH)	331 (M^+, 100)
5d[e]	48[f] 55[g]	305–308 (EtOH)	$C_{17}H_{13}Cl_2N_5$ (358.2)	365 (4.09), 383 (4.17), 403 (4.16), 426 (3.95)	1.99, 2.02 (2s, 3H each, CH_3-7, 8), 6.35 (br s, 2H, H-6, 9), 7.53 (m, $3H_{arom}$), 10.13 (br s, 2H, NH)	357, 359, 361 (M^+, 100, 61, 10)
6a	67	190–192 (benzene)	$C_{18}H_{13}N_5$ (299.3)	371 (4.06), 397 (sh) (4.03)	2.26 (s, 6H, CH_3-2′, 6′), 2.41 (s, 3H, CH_3-4′), 7.08 (s, $2H_{arom}$), 8.1 (m, 2H, H-7, 8), 8.4 (d, 1H, J = 8, H-6 or H-9), 8.54 (d, 1H, J = 8, H-9 or H-6)	303 ($M^+ + 2$, 63), 273 ($M^+ - N_2$, 100)
6b	99	218–220 (benzene)	$C_{15}H_7Cl_2N_5$ (328.2)	375 (4.27)	7.55 (m, $3H_{arom}$), 8.16 (m, 2H, H-7, 8), 8.44 (d, 1H, J = 8.5, H-6 or H-9), 8.56 (d, 1H, J = 8, H-9 or H-6)	329, 331, 333 ($M^+ + 2$, 10, 6, 1), 171, 173, 175 (100, 67, 11)
6c	74	245 (dec) (benzene)	$C_{20}H_{19}N_5$ (329.4)	388 (4.21)	2.23 (s, 6H, CH_3-2′, 6′), 2.40 (s, 3H, CH_3-4′), 2.66 (s, 6H, CH_3-7, 8), 7.06 (s, $2H_{arom}$), 8.12, 8.23 (2s, 1H each, H-6, 9)	331 ($M^+ + 2$, 100)
6d	65	242 (dec) (benzene)	$C_{17}H_{11}Cl_2N_5$ (356.2)	375 (sh) (4.24), 390 (4.28)	2.68 (s, 6H, CH_3-7, 8), 7.54 (m, $3H_{arom}$), 8.12, 8.26 (2s, 1H each, H-6, 9)	357, 359, 361 ($M^+ + 2$, 11, 7, 1), 156 (100)

[a] Yields of **4**, **5** and **6** were based on **1**, **4** and **5**, respectively.
[b] Satisfactory microanalyses obtained: C ±0.23, H ±0.31, N ±0.31.
[c] Solvents: DMSO-d_6 for compounds **4** and **5**, and $CDCl_3$ for **6**.
[d] Due to their sparing solubility in common organic solvents, compounds **4a–d** could not be recrystallized, but were washed thoroughly with EtOAc/hexane (1 : 1) after their chromatographic separation.
[e] IR (Nujol), ν(cm^{-1}): **5a**: 3210, 3180; **5b**: 3225, 3120; **5c**: 3180, 3130; **5d**: 3230, 3120.
[f] Method A.
[g] Method B.

Table 2. ^{13}C-NMR Assignments of Compounds **4** and **6**, δ ($CDCl_3$ or DMSO-d_6/TMS)[a]

Product	C-3	C-4a C-10a	C-5a C-9a	C-6 C-9	C-7 C-8	C-1′	C-2′ C-6′	C-3′ C-5′	C-4′	CH_3-7 CH_3-8	CH_3-2′ CH_3-6′	CH_3-4′
4a	149.6	140.8 142.6	138.4 138.8	129.3 129.6	134.4 135.1	121.5	138.5	128.3	140.9	–	18.7	20.9
4b	145.1	141.1 143.2	138.4 138.5	129.4 129.6	134.4 134.8	123.9	135.5	128.7	135.0	–	–	–
4c	149.1	140.2 142.0	137.9 138.4	127.5 127.7	146.5 147.2	121.7	138.5	128.2	140.8	20.37 20.40	18.7	20.9
4d	144.6	140.5 142.6	137.9 138.1	127.6 127.8	147.1 147.9	124.1	135.0	128.8	134.4	20.38 20.43	–	–
6a	165.9	145.8 149.7	141.2 144.9	129.9 130.9	133.6 135.4	132.6	137.1	129.0	139.9	–	20.4	21.3
6b	161.2	146.4 149.9	141.1 145.8	130.0 131.0	134.2 135.8	134.5	134.8	128.3	131.7	–	–	–
6c	165.6	145.5 149.3	141.4 145.5	128.0 128.8	146.0 148.4	132.9	137.0	128.9	139.6	21.0 21.3	20.4	21.3
6d	161.1	146.1[b] 149.5	141.3 146.3[b]	128.1 128.8	146.8 149.0	134.8	134.8	128.3	131.5	21.0 21.3	–	–

[a] Solvent, DMSO-d_6 for compounds **4** and $CDCl_3$ for compounds **6**.
[b] Assignments interchangeable.

pyrazine ring of [1,2,5]oxadiazolo[3,4-*b*]quinoxalines has been hydrogenated by phosphorus ylides. The hydrogen atoms probably come from the atmospheric moisture, in a reaction pathway analogous to Mitsunobu reaction.[16]

In conclusion, we have developed a method for the synthesis of the novel 1,2,4-triazino[5,6-*b*]quinoxaline 1,2,4-tri-*N*-oxides and the corresponding deoxygenated compounds, which are the first examples of compounds containing the pyrazino[2,3-*b*][1,2,4]triazine ring system and moreover the first examples of their tri-*N*-oxides, taking into account that previous attempts[17] to synthesize pyrazino[2,3-*b*][1,2,4]triazine derivatives afforded the enhydrated compounds. Considering the pharmaceutical interest of *N*-oxides[1] and of the pyrazino[2,3-*b*][1,2,4]triazine ring,[17] which is an aza analogue of pteridine, the compounds reported here are expected to be of potential biological interest.

1,2,4-Triazino[5,6-*b*]quinoxaline 1,2,4-Tri-*N*-oxides, 4; General Procedure:
A solution of [1,2,5]oxadiazolo[3,4-*b*]quinoxaline-1-oxide **1**[7,8] (1 mmol) and nitrile oxide **2**[18] (2 mmol) in anhydrous CH_2Cl_2 (25 mL) is refluxed for 12 h. The solvent is then evaporated and the mixture is chromatographed on a silica gel column, using at first a mixture of EtOAc/hexane (1:1) to elute the reaction byproducts; then with EtOAc to obtain the deep red compounds **4** (Table 1). For further purification, compounds **4** are washed thoroughly with EtOAc/hexane (1:1).

5,10-Dihydro-1,2,4-triazino[5,6-*b*]quinoxalines 5:
Method A: A solution of **4** (1 mmol) and an excess of Ph_3P (2.62 g, 10 mmol) in $CHCl_3$ (50 mL) is refluxed for 1 h. The solvent is then evaporated and the mixture chromatographed on silica gel using at first a mixture of hexane/EtOAc (1:1) and then EtOAc as eluent. The excess of Ph_3P is eluted first, afterwards the yellow desired compounds **5** and at last Ph_3PO. Compounds **5** are further purified by recrystallization from EtOH.

Method B: To a suspension of **4** (1 mmol) in EtOH (10 mL), a solution of $Na_2S_2O_4$ (2.48 g, 20 mmol) in H_2O (30 mL) is added and the mixture is refluxed for 30 min. Upon addition of H_2O (100 mL) the yellow solid produced is collected by filtration, washed thoroughly with H_2O, and then with CH_2Cl_2, and recrystallized from EtOH, to give compounds **5** (Table 1).

1,2,4-Triazino[5,6-*b*]quinoxalines 6; General Procedure:
A solution of **5** (0.5 mmol) and iodosobenzene bis(trifluoroacetate)[19] (0.215 g, 0.5 mmol) in CH_2Cl_2 (10 mL) is allowed to stand at r.t. for 15 min. The solvent is then evaporated and the mixture is chromatographed on silica gel with CH_2Cl_2 as eluent to give first PhI, and then the yellow compounds **6**, which can be further purified by recrystallization from benzene (Table 1).

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