ν-Triazolines; 33.[1] Synthesis of 3-Aminoquinoxaline 1-Oxides and 2-Aminopyrido[3,4-*b*]-pyrazine 4-Oxides

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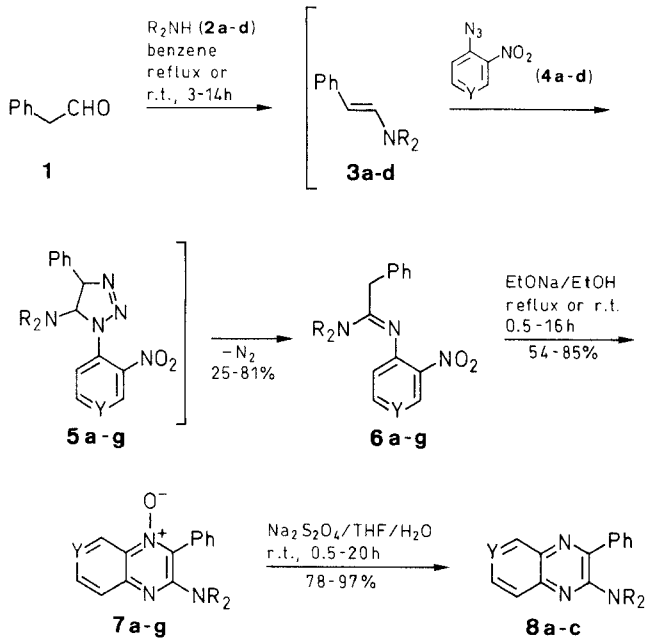
N^1,N^1-Disubstituted N^2-(2-nitrophenyl)- and N^2-(2-nitropyridyl)-phenylacetamidines, derived from the thermal rearrangement of 5-amino-4,5-dihydro-1-(2-nitroaryl)-4-phenyl-1*H*-1,2,3-triazoles, are obtained in a one-pot reaction from phenylacetaldehyde, a secondary amine and an aryl azide and undergo ring closure to the title compounds on reaction with sodium ethoxide in ethanol.

5-Amino-1-aryl-4,5-dihydro-1*H*-1,2,3-triazoles are readily accessible compounds whose synthetic usefulness, apart from the straightforward deamination to aromatic 1,2,3-triazoles, has not yet been fully exploited. Of importance is their relatively high thermal lability which allows an easy entry to substituted amidine synthons from which nitrogen-containing heterocycles can be derived. In line with this synthetic strategy a new 2-aminobenzimidazole synthesis starting from 5-amino-4,5-dihydro-1-(2-nitroaryl)-1*H*-1,2,3-triazoles has been described by us.[1] Now, we report on a synthesis of 3-aminoquinoxaline 1-oxides and 2-aminopyrido[3,4-*b*]pyrazine 4-oxides. As far as we are aware both class of compounds have not been described previously.

The reaction of phenylacetaldehyde **(1)** with equimolar amounts of secondary amines **2a–d** and aromatic azides **4a–d** in benzene solution at room temperature readily afforded the corresponding 4,5-dihydro-1,2,3-triazoles **5a–g** through cycloaddition of the azide to the 2-aminostyrenes **3a–d** formed in situ from the aldehyde and the amine. Though identifiable during the reaction course by TLC, compounds **5** could not be isolated because they suffered a quick rearrangement with ring cleavage, nitrogen elimination and hydrogen transfer according to a well established reaction path.[2]

As final reaction products the corresponding N^2-(2-nitrophenyl)- and N^2-(2-nitropyridyl)-substituted phenylacetamidines **6a–g** were obtained. The thermal lability of intermediates **5** is not surprising since it is known that both electron-poor substituents on N-1 and aryl groups on C-4 are detrimental for the stability of the 4,5-dihydro-1,2,3-triazole ring.[3]

Analytical and spectral data of compounds **6** are given in Table 1 and confirm their structure. Cyclization of amidines **6a–g** to the corresponding 3-aminoquinoxaline 1-oxides **7a–e** or 2-aminopyrido[3,4-b]pyrazine 4-oxides **7f,g**, respectively, was readily obtained by reaction with bases. Best results were achieved using sodium ethoxide in ethanol. This ring-closure reaction occurs via deprotonation of the benzyl group and intramolecular nucleophilic addition to the nitro group. This reaction, though already



2,3	NR_2	4	Y	5–8	NR_2	Y
a	morpholino	a	CH	a	morpholino	CH
b	pyrrolidin-1-yl	b	CMe	b	morpholino	CCl
c	NMe_2	c	CCl	c	morpholino	N
d	NEt_2	d	N	d	morpholino	CMe
				e	pyrrolidin-1-yl	CCl
				f	NMe_2	CH
				g	NEt_2	N

applied to the preparation of 1,2-dihydro-2-oxoquinoxaline 4-oxides[4,5] was never applied to amidine substrates and appears of utility giving structurally definite compounds with respect to the mono-*N*-oxidation reaction of the parent heterocycles which must face a selectivity problem,[6] expectedly even more complicated by the presence of an amino substituent.

Deoxygenated quinoxalines **8a,b** and pyrido[3,4-*b*]pyrazine **8c** were readily formed on reduction of the corresponding mono-*N*-oxides **7** with sodium dithionite in water/tetrahydrofuran.

All reagents including phenylacetaldehyde (**1**) and amines **2** were commercial products. Azides **4** were prepared according to described methods: 2-nitrophenyl azide;[7] 2-nitro-4-methylphenyl azide;[8] 2-nitro-4-chlorophenyl azide;[8] 3-nitro-4-azidopyridine.[9]

Analytical TLC plates and silica gel 60 F 254 Merck. Melting points were taken using a Büchi 510 (capillary) apparatus. IR spectra were measured using a Pye Unicam SP3-200 S Philips infrared spectrophotometer. ^1H NMR spectra were obtained on a Bruker AC-200 spectrometer. Column chromatography was performed on silica gel using silica gel 60/70–230 ASTM/Merck.

Phenylacetamidines 6a–g; General Procedure:
In a round-bottomed flask, phenylacetaldehyde (**1**; 5.85 mL, 50 mmol) was added to a stirred solution of azide **4a–d** (50 mmol) dissolved in benzene (100 mL). A solution of amine **2a–d** (50 mmol) in benzene (20 mL) was immediately added dropwise and stirring was continued, at r.t. or at reflux, for the time indicated (Table 1). The mixture was dried (Na_2SO_4) and the solvent was evaporated at reduced pressure and the crude product **6** was chromatographed on a silica gel column using as eluent EtOAc cyclohexane (35:65). The main fraction, containing the product, was crystallized from *i*-Pr_2O (except for **6g** for which Et_2O was used).

3-Aminoquinoxaline 1-Oxides 7a–e and 2-Aminopyrido[3,4-*b*]pyrazine 4-Oxides 7f,g; General Procedure:
NaOEt was prepared by dissolving Na (0.25 g, 10 mmol) in anhydr. EtOH (20 mL). A suspension of amidine **6a–g** (7.7 mmol) in EtOH (10 mL) was added to the stirred solution and stirring was continued, at r.t. or at reflux, for 1–16 h (Table 2). The solvent was evaporated at reduced pressure and the residue was dissolved in CH_2Cl_2, washed thoroughly with H_2O (3 × 30 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product **7** was crystallized from *i*-Pr_2O.

3-Aminoquinoxalines 8a,b and 2-Morpholino-3-phenylpyrido[3,4-*b*]-pyrazine (8c); General Procedure:
Quinoxaline 1-oxides **7a,b**, or aminopyrido[3,4-*b*]pyrazine 4-oxide-**7c** (4.5 mmol) was dissolved in THF (10 mL); a solution of NaS_2O_4 (2.54 g, 15 mmol) in H_2O (15 mL) was added and the mixture was stirred for 0.5–20 h (Table 3) at r.t. The organic solvent was evaporated at reduced pressure and the watery residue was

Table 1. Compounds **6a–g** Prepared

Product	Time (h), Temp.	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR[b] (cm^{-1}) $\nu_{C=N}$	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
6a	8, reflux	34	91 (*i*-Pr_2O)	$C_{18}H_{19}N_3O_3$ (325.3)	1600	3.48–3.59 (m, 4H, CH_2NCH_2), 3.61–3.63 (m, 4H, CH_2OCH_2), 3.71 (s, 2H, CH_2), 6.8–7.9 (m, 9H_{arom})
6b	5, reflux	25	oil	$C_{19}H_{21}N_3O_3$ (339.4)	1605	2.30 (s, 3H, CH_3), 3.40–3.53 (m, 4H, CH_2NCH_2), 3.58–3.62 (m, 4H, CH_2OCH_2), 3.69 (s, 2H, CH_2), 6.69–7.91 (m, 8H_{arom})
6c	12, r.t.	43	oil	$C_{18}H_{18}ClN_3O_3$ (359.8)	1605	3.48–3.62 (m, 4H, CH_2NCH_2), 3.59 (s, 2H, CH_2), 3.63–4.14 (m, 4H, CH_2OCH_2), 6.74–7.88 (m, 8H_{arom})
6d	3, reflux	74	oil	$C_{18}H_{18}ClN_3O_2$ (343.8)	1600	1.85–1.92 [m, 4H, $(CH_2)_2$], 3.28–3.55 (m, 4H, CH_2NCH_2), 3.68 (s, 2H, CH_2), 6.74–7.84 (m, 8H_{arom})
6e	14, r.t.	26	83 (*i*-Pr_2O)	$C_{16}H_{17}N_3O_2$ (283.3)	1605	2.99 (s, 6H, $2CH_3$), 3.72 (s, 2H, CH_2), 6.80–7.87 (m, 9H_{arom})
6f	4, r.t.	81	111 (*i*-Pr_2O)	$C_{17}H_{18}N_4O_3$ (326.3)	1595	3.54–3.57 (m, 4H, CH_2NCH_2), 3.57–3.65 (m, 4H, CH_2OCH_2), 3.72 (s, 2H, CH_2), 6.71 (d, 1H, J = 5.5, H-5_{pyr}), 7.14–7.37 (m, 5H_{arom}), 8.36 (d, 1H, J = 5.5, H-6_{pyr}), 9.03 (s, 1H, H-2_{pyr})
6g	12, r.t.	70	84 (Et_2O)	$C_{17}H_{20}N_4O_2$ (312.3)	1595	0.99–1.15 (m, 6H, CH_3), 3.66–3.90 (m, 4H, CH_2NCH_2), 3.69 (s, 2H, CH_2), 6.65 (d, 1H, J = 5.6, H-5_{pyr}), 7.11–7.48 (m, 5H_{arom}), 8.29 (d, 1H, J = 5.6, H-6_{pyr}), 8.99 (s, 1H, H-2_{pyr})

[a] Satisfactory microanalyses obtained: C ±0.32, H ±0.32, N ±0.22. [b] Nujol or neat for oily compounds.

Table 2. Compounds **7a–g** Prepared

Product	Time (h), Temp.	Yield (%)	mp (°C) *i*-Pr_2O	Molecular Formula[a]	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
7a	1, reflux	54	140	$C_{18}H_{17}N_3O_2$ (307.3)	3.15–3.20 (m, 4H, CH_2NCH_2), 3.54–3.59 (m, 4H, CH_2OCH_2), 7.46–7.86 (m, 8H_{arom}), 8.47 (d, 1H, J = 8, H-8)
7b	6, reflux	54	164	$C_{19}H_{21}N_3O_2$ (323.4)	2.54 (s, 3H, CH_3), 3.11–3.16 (m, 4H, CH_2NCH_2), 3.53–3.58 (m, 4H, CH_2OCH_2), 7.45–7.75 (m, 7H_{arom}), 8.27 (s, 1H, H-8)
7c	5, reflux	55	167	$C_{18}H_{16}ClN_3O_2$ (341.8)	3.11–3.19 (m, 4H, CH_2NCH_2), 3.23–3.70 (m, 4H, CH_2OCH_2), 7.26–7.78 (m, 7H_{arom}), 8.46 (d, 1H, J = 3, H-8)
7d	2, reflux	85	161	$C_{18}H_{16}ClN_3O$ (325.8)	1.70–1.86 [m, 4H, $(CH_2)_2$], 3.07–3.23 (m, 4H, CH_2NCH_2), 7.29–7.70 (m, 7H_{arom}), 8.39 (d, 1H, J = 2.6, H-8)
7e	1, reflux	48	118	$C_{16}H_{15}N_3O$ (265.3)	2.77 (s, 6H, 2CH_3), 7.37–7.81 (m, 8H_{arom}), 8.44 (dd, 1H, J_m = 1.42, J_o = 8.42, H-8)
7f	0.5, r.t.	65	178	$C_{17}H_{16}N_4O_2$ (308.3)	3.23–3.49 (m, 4H, CH_2NCH_2), 3.51–3.60 (m, 4H, CH_2OCH_2), 7.49–7.71 (m, 5H_{arom}, H-8), 8.69 (d, 1H, J = 5.8, H-7), 9.68 (s, 1H, H-5)
7g	16, r.t.	67	151	$C_{17}H_{18}N_4O$ (294.3)	0.99 (t, 6H, CH_3), 3.30 (q, 4H, CH_2NCH_2), 7.48–7.57 (m, 5H_{arom}, H-8), 8.63 (d, 1H, J = 5.8, H-7), 9.61 (s, 1H, H-5)

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.26, N ±0.32.

Table 3. Compounds **8a–c** Prepared

Product	Time (h), Temp.	Yield (%)	mp (°C) *i*-Pr_2O	Molecular Formula[a]	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
8a	14, r.t.	78	129	$C_{18}H_{17}N_3O$ (291.3)	3.26–3.31 (m, 4H, CH_2NCH_2), 3.69–3.74 (m, 4H, CH_2OCH_2), 7.44–8.02 (m, 9H_{arom})
8b	20, r.t.	93	126	$C_{18}H_{16}ClN_3O$ (325.8)	3.25–3.27 (m, 4H, CH_2NCH_2), 3.68–3.73 (m, 4H, CH_2OCH_2), 7.45–8.01 (m, 8H_{arom})
8c	0.5, r.t.	97	128	$C_{17}H_{16}N_4O$ (292.3)	3.28–3.55 (m, 4H, CH_2NCH_2), 3.56–3.85 (m, 4H, CH_2OCH_2), 7.49–7.61 (m, 5H_{arom}), 7.80–8.00 (m, 1H, H-8), 8.55–8.70 (m, 1H, H-7), 9.20–9.35 (m, 1H, H-5)

[a] Satisfactory microanalyses obtained: C ±0.28, H ±0.11, N ±0.19.

extracted with CH_2Cl_2 (3 × 45 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated giving the crude product **8** which was crystallized from *i*-Pr_2O.

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