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INTRAMOLECULAR DIELS-ALDER REACTIONS OF PYRAZINES WITH ALKYNYLPHENYL MOIETIES AS SIDE-CHAIN DIENOPHILES.

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Abstract: Intramolecular Diels-Alder reactions of (2-alkynylphenyl-X)-pyrazines (X = O, NAc, S) under neutral and acidic conditions are described. The isomer distribution of the resulting tricyclic *b*- and *c*-annelated pyridines is discussed.

Inverse-electron-demand ($LUMO_{diene}$-controlled) Diels-Alder reactions of cyclic azadienes represent a versatile tool in heterocyclic chemistry.[1] In particular, the intramolecular version of this reaction type has been attracting increasing attention.[2-5] The entropic assistance provided by linkage of the dienophilic component to the heteroaromatic diene precludes the need for electron-rich dienophiles and has given rise to the synthesis of a variety of condensed ring systems, as demonstrated by our laboratory and others, employing appropriately substituted 1,2,4,5-tetrazines,[3] 1,2,4-triazines,[4] pyridazines,[5] pyrimidines,[2a,b,d,e,f,i] pyrazines,[2c,g,j] and pyridines[2b,m] as starting materials. Interestingly, intramolecular cycloaddition reactions of pyrazines containing an -X-CH_2-CH_2-C≡CH side chain (X = NAc, O, S, SO, SO_2) have been found to result in the formation of *b*-annelated as well as of *c*-annelated pyridine derivatives, depending on the nature of X.[2c] In continuation of these studies, we here report on investigations of the behaviour of pyrazines bearing an -X-(2-phenylene)-C≡C-R moiety (X = O, NAc, S; R = $SiMe_3$, CH_2OH) in thermally induced intramolecular Diels-Alder reactions.

For the preparation of the required cycloaddition educts **2**, we used a similar route as that employed recently for the synthesis of structurally related pyrimidine derivatives.[2i] Starting from chloropyrazine, nucleophilic displacement reactions (analoguous to those described in ref.[6]) with sodium 2-bromophenolate, 2-bromoaniline, or sodium 2-aminothiophenolate, respectively, afforded the substituted pyrazines **1a,b,d**. Refluxing of **1b** in acetic anhydride gave the N-acetyl derivative **1c**.[7] The iodo compound **1e** was obtained by diazotation of **1d** and subsequent reaction with potassium iodide. Introduction of the required alkynyl substructures

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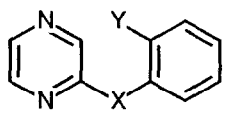
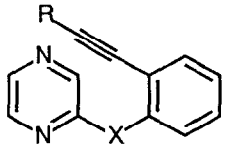
finally was accomplished by Pd°-catalysed cross-coupling reactions of the halogeno precursors **1a,c,e** with trimethylsilylacetylene or propargyl alcohol, respectively, at elevated temperature (see Experimental).



1a-e

	a	b	c	d	e
X	O	NH	NAc	S	S
Y	Br	Br	Br	NH_2	I

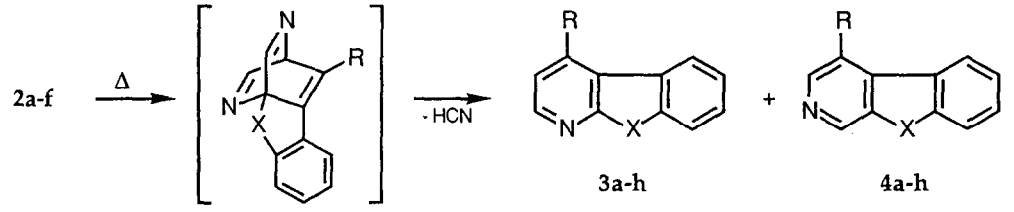


2a-f

	a	b	c	d	e	f
X	O	O	NAc	NAc	S	S
R	$SiMe_3$	CH_2OH	$SiMe_3$	CH_2OH	$SiMe_3$	CH_2OH

Indeed, heating of compounds **2a-f** in bromobenzene solutions at 155°C for 2.5-4 hours[8] smoothly effected intramolecular cycloaddition reactions, followed by a cycloreversion step (elimination of hydrogen cyanide) (Scheme 1). The resulting mixtures of *b*- and *c*-annelated pyridines **3** and **4** could be easily separated by column chromatography. In the case of the N-acetylated pyridoindoles **3c/4c** and **3e/4e**, it proved to be convenient to subject the crude reaction mixtures to alkaline hydrolysis prior to chromatography, leading to the isolation of the corresponding NH-congeners **3d/4d**, **3f/4f**.[9] The structures of the new compounds of type **3** and **4** thus obtained are in full agreement with their spectroscopic and microanalytical data;[10] the *b*-annelated trimethylsilylpyridines **3a,g** were identified by comparison with authentic material.[2i]

Scheme 1.



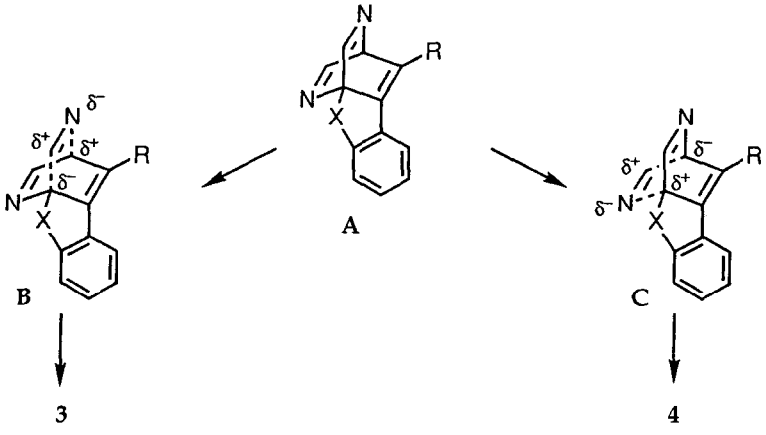
3a-h **4a-h**

	a	b	c	d	e	f	g	h
X	O	O	NAc	NH	NAc	NH	S	S
R	$SiMe_3$	CH_2OH	$SiMe_3$	$SiMe_3$	CH_2OH	CH_2OH	$SiMe_3$	CH_2OH

Whereas employment of pyrazines containing an -X-CH_2-CH_2-C≡CH side chain, where X = O, NAc, or S, as cycloaddition educts has been reported to give predominantly *c*-annelated pyridines,[2c] we now find that cyclisation of compounds **2a-d** (X = O, NAc) preferentially leads to the formation of *b*-fused pyridine derivatives; in the case of **2e,f** (X = S), the expected isomer distribution of the reaction products is observed (**3** : **4** ≈ 1:3).

The marked differences in the reaction behaviour of compounds **2e,f** and, on the other hand, compounds **2a-d** may be interpreted in terms of the electron distribution in the intermediate cycloadducts of type **A** (Scheme 2). In analogy to a mechanism proposed recently,[2c] we suggest two competing pathways for hydrogen cyanide elimination from **A**, which are characterised by the formation of partial charges (with opposite signs) at the two bridgehead carbon atoms (transition states **B** and **C**). Thus, the stabilisation/destabilisation of the developing partial charges by the local electron densities at these carbon atoms in **A** should determine whether transition state **B** or **C** predominates in the final retro Diels-Alder reaction. This assumption is supported by MNDO[11] calculations which we carried out for the cycloadducts **A**: whereas in the case of X = S the bridgehead carbon atom adjacent to the heteroatom X exhibits an electron density significantly higher than that at the carbon atom being originally C-5 of the starting pyrazine (thus favouring transition state **C** which leads to formation of compounds **4**), this situation is reversed in the case of X = O or X = NAc (stabilising transition state **B** to afford compounds **3**).

Scheme 2.



Recently, it has been found in our laboratory that protonation of (-X-CH_2-CH_2-C≡CH)-substituted pyrazines (which was established by NMR spectroscopy to occur at N-4 rather than at N-1) shifts the isomer distribution of the bicyclic products resulting from intramolecular cycloaddition reactions almost exclusively towards *c*-annelated pyridines, even if X represents a strongly electron-withdrawing SO or SO_2 function;[2j] sulfoxides and sulfones of this type have been reported earlier to yield predominantly *b*-annelated pyridines on heating in neutral solvents.[2c] These findings reflected the stabilising effect of the protonated, positively charged nitrogen atom on the negative partial charge at the adjacent bridgehead carbon atom in a transition state comparable to **C**. A similar effect on product distribution, albeit less pronounced, now was also found when solutions of compounds **2a-f** in dioxane were heated in the presence of trifluoroacetic acid (Table).[12] Thus, under these conditions the **3** : **4** ratio is shifted from 10:1 to 3:1 (for X = O), from 3:1 to 1:1 (for X = NAc), and from 1:3 to 1:10 (for X = S).

Besides the fact that the $HOMO_{dienophile}/LUMO_{diene}$ energy separation as well as conformational/entropic aspects play a key role[1c] in the initial [4+2] cycloaddition reaction of heteroaromatic azadienes with side-chain dienophiles it appears, in conclusion, that local electron densities in the cycloadducts thus formed have a marked influence on the course of the subsequent cycloreversions, in particular, if there exist competing pathways for the latter.

Table. Intramolecular Diels-Alder Reactions of Pyrazines **2**: Reaction Conditions, Products, and Yields.

Solvent, Temp.	Starting Compound	Reaction Time	Reaction Products Compounds (% isolated yield)	
bromobenzene, 155°C	**2a**	4 h	**3a** (76)	**4a** (7)
	2b	3.5 h	**3b** (72)	**4b** (6)
	2c	3.5 h	**3d**[a] (67)	**4d**[a] (21)
	2d	3 h	**3f**[a] (55)	**4f**[a] (22)
	2e	3 h	**3g** (27)	**4g** (62)
	2f	2.5 h	**3h** (23)	**4h** (68)
dioxane/CF_3COOH, 100°C	**2a**	5.5 d	**3a** (71)	**4a** (23)
	2b	5.5 d	**3b** (58)	**4b** (17)
	2c	5 d	**3d**[a] (39)	**4d**[a] (43)
	2d	4.5 d	**3f**[a] (42)	**4f**[a] (48)
	2e	4.5 d	**3g** (9)	**4g** (87)
	2f	4 d	**3h** (8)	**4h** (83)

[a] Isolated after cleavage of the N-acetyl groups in initially formed compounds **3c,e**, **4c,e**.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM 390 (90 MHz) spectrometer; chemical shifts are reported in ppm downfield from tetramethylsilane. Mass spectral data were obtained on a AEI MS 902 instrument equipped with a VG ZAB console. Column chromatography was performed on Merck silica gel 60 (230-400 mesh ASTM). Light petroleum, unless specified, refers to the fraction of bp 40-60°C.

(2-Bromophenoxy)pyrazine (**1a**).
Sodium 2-bromophenolate (6 mmol) was prepared by dissolving sodium metal (138 mg; 6 mmol) in 2-bromophenol (4 ml) kept under a nitrogen atmosphere at 70°C. To the stirred solution was then added chloropyrazine (687 mg; 6 mmol), and the mixture was heated to 140°C for 24 h. It was then diluted with methylene chloride, washed with water, and evaporated under reduced pressure (excess 2-bromophenol was recovered by bulb-to-bulb distillation). The residue was taken up in ether and washed successively with 30% aqueous sodium hydroxide and water. After drying ($MgSO_4$), the solution was evaporated to afford almost colourless crystals (47%), mp 75-76°C (light petroleum, bp 80-100°C).

^{1}H-NMR ($CDCl_3$) δ 8.50 (d, J = 1.5 Hz, 1 H), 8.25 (d, J = 3.0 Hz, 1 H), 8.05 (dd, J_1= 1.5 Hz, J_2= 3.0 Hz, 1 H), 7.75-7.55 (m, 1 H), 7.40-7.00 (m, 3 H).
HRMS Calcd. for $C_{10}H_7BrN_2O$: m/z 249.9741. Found: 249.9743.
Anal. Calcd.: C, 47.8; H, 2.8; N, 11.1. Found: C, 48.1; H, 2.7; N, 11.1.

(2-Bromophenylamino)pyrazine (**1b**).
A mixture of 2-bromoaniline (4.13 g; 24 mmol) and chloropyrazine (916 mg; 8 mmol) was heated under a nitrogen atmosphere to 150°C for 24 h. The resulting dark mixture was partitioned between methylene chloride and water. The organic layer was evaporated under reduced pressure (excess 2-bromoaniline was recovered by bulb-to-bulb distillation). The residue was subjected to column chromatography (eluting first with ether/light petroleum, 1:1, then with ether) to afford a brownish oil (27%).
^{1}H-NMR ($CDCl_3$) δ 8.25 (d, J = 1.5 Hz, 1 H), 8.20-8.05 (m, 2 H), 8.00 (d, J = 3.0 Hz, 1 H), 7.65-7.55 (m, 1 H), 7.40-6.75 (m, 3 H).
HRMS Calcd. for $C_{10}H_8BrN_3$: m/z 248.9901. Found: 248.9902.

(N-Acetyl-2-bromophenylamino)pyrazine (**1c**).
A solution of **1b** (750 mg; 3 mmol) in acetic anhydride (15 ml) was refluxed for 2 h. The residue obtained on evaporation under reduced pressure was taken up in methylene chloride and washed successively with saturated aqueous sodium hydrogencarbonate and water. After removal of the solvent, the residue was purified by column chromatography (ether as eluent) to give almost colourless crystals (77%), mp 95-97°C (ethyl acetate/light petroleum, bp 60-80°C).
^{1}H-NMR ($CDCl_3$) δ 9.25 (d, J = 1.3 Hz, 1 H), 8.30 (d, J = 2.5 Hz, 1 H), 8.20 (dd, J_1= 1.3 Hz, J_2= 2.5 Hz, 1 H), 7.75-7.60 (m, 1 H), 7.55-7.15 (m, 3 H), 2.05 (s, 3 H).
HRMS Calcd. for $C_{12}H_{10}BrN_3O$: m/z 291.0008. Found: 291.0002.
Anal. Calcd.: C, 49.3; H, 3.4; N, 14.4. Found: C, 49.2; H, 3.4; N, 14.5.

(2-Aminophenylthio)pyrazine (**1d**).
Sodium ethanolate (4 mmol) was prepared by dissolving sodium metal (92 mg; 4 mmol) in absolute ethanol (4 ml) under a nitrogen atmosphere. 2-Aminothiophenol (500 mg; 4 mmol) and chloropyrazine (458 mg; 4 mmol) were added, and the solution was refluxed for 16 h. The mixture was diluted with ether, filtered, and evaporated under reduced pressure. Column chromatography (eluting first with ether/light petroleum, 1:1, then with ether) afforded colourless needles (90%), mp 90-92°C (ethyl acetate/light petroleum).
^{1}H-NMR ($CDCl_3$) δ 8.30 (dd, J_1= 1.5 Hz, J_2= 2.8 Hz, 1 H), 8.20 (d, J = 2.8 Hz, 1 H), 8.10 (d, J = 1.5 Hz, 1 H), 7.60-7.15 (m, 2 H), 6.90-6.65 (m, 2 H), 4.40 (br s, 2 H).
HRMS Calcd. for $C_{10}H_9N_3S$: m/z 203.0517. Found: 203.0518.
Anal. Calcd.: C, 59.1; H, 4.5; N, 20.7. Found: C, 59.1; H, 4.5; N, 21.0.

(2-Iodophenylthio)pyrazine (**1e**).
A solution of sodium nitrite (690 mg; 10 mmol) in water (5 ml) was added dropwise during a period of 0.5 h to a stirred suspension of **1d** (1.83 g; 9 mmol) in a mixture of concentrated hydrochloric acid (3 ml) and water (5 ml) at 0°C. After stirring of the mixture at this temperature for 2 h, a solution of potassium iodide (3.32 g; 20 mmol) in water (10 ml) was added. The mixture was extracted with methylene chloride; the organic layer was washed with water, dried ($MgSO_4$), and evaporated. Column chromatography (eluting with ether/light petroleum, 1:1) gave an almost colourless oil (56%).
^{1}H-NMR ($CDCl_3$) δ 8.35 (dd, J_1= 1.5 Hz, J_2= 2.8 Hz, 1 H), 8.25 (d, J = 2.8 Hz, 1 H), 8.20 (d, J = 1.5 Hz, 1 H), 8.10-7.95 (m, 1 H), 7.80-7.65 (m, 1 H), 7.50-7.30 (m, 1 H), 7.20-7.00 (m, 1 H).
HRMS Calcd. for $C_{10}H_7IN_2S$: m/z 313.9377. Found: 313.9372.

(2-Trimethylsilylethynylphenoxy)pyrazine (**2a**).
To a solution of **1a** (502 mg; 2 mmol) and trimethylsilylacetylene (392 mg; 4 mmol) in triethylamine (6 ml) were added $PdCl_2(PPh_3)_2$ (25 mg) and CuI (5 mg), and the mixture was heated in a sealed tube to 80°C for 24 h. The residue left on evaporation under reduced pressure was purified by column chromatography (eluting with ether/light petroleum, 2:3) to give a colourless oil (54%).

^{1}H-NMR ($CDCl_3$) δ 8.55 (d, J = 1.4 Hz, 1 H), 8.30 (d, J = 2.8 Hz, 1 H), 8.15 (dd, J_1= 1.4 Hz, J_2= 2.8 Hz, 1 H), 7.65-7.15 (m, 4 H), 0.10 (s, 9 H).
HRMS Calcd. for $C_{15}H_{16}N_2OSi$: m/z 268.1032. Found: 268.1031.

[2-(3-Hydroxy-1-propynyl)phenoxy]pyrazine (**2b**).
Preparation as described for **2a**, starting from **1a** (502 mg; 2 mmol) and propargyl alcohol (224 mg; 4 mmol). Column chromatography (eluting with ethyl acetate/light petroleum, 2:1) afforded a colourless oil (66%).

^{1}H-NMR ($CDCl_3$) δ 8.45 (d, unresolved, 1 H), 8.20 (d, unresolved, 1 H), 8.10 (dd, unresolved, 1 H), 7.60-7.05 (m, 4 H), 4.25 (s, 2 H), 3.05 (br s, 1 H).
HRMS Calcd. for $C_{13}H_{10}N_2O_2$: m/z 226.0742. Found: 226.0741.

(N-Acetyl-2-trimethylsilylethynylphenylamino)pyrazine (**2c**).
To a suspension of **1c** (584 mg; 2 mmol) and trimethylsilylacetylene (392 mg; 4 mmol) in triethylamine (8 ml) was added $Pd(PPh_3)_4$ (30 mg), and the mixture was heated in a sealed tube to 80°C for 24 h. After evaporation under reduced pressure, the residue was subjected to column chromatography (eluting with ethyl acetate/light petroleum, 1:1) to give colourless crystals (68%), mp 101-103°C (light petroleum, bp 60-80°C).

^{1}H-NMR ($CDCl_3$) δ 9.20 (d, J = 1.3 Hz, 1 H), 8.30-8.15 (m, 2 H), 7.65-7.30 (m, 4 H), 2.05 (s, 3 H), 0.10 (s, 9 H).
HRMS Calcd. for $C_{17}H_{19}N_3OSi$: m/z 309.1297. Found: 309.1296.
Anal. Calcd.: C, 66.0; H, 6.2; N, 13.6. Found: C, 65.9; H, 6.3; N, 13.5.

[N-Acetyl-2-(3-hydroxy-1-propynyl)phenylamino]pyrazine (**2d**).
Preparation as described for **2c**, starting from **1c** (584 mg; 2 mmol) and propargyl alcohol (224 mg; 4 mmol). Column chromatography (eluting with ethyl acetate/light petroleum, 3:1) afforded a pale yellow oil (52%).

^{1}H-NMR ($CDCl_3$) δ 9.10 (s, 1 H), 8.25 (s, 2 H), 7.75-7.20 (m, 4 H), 4.30 (s, 2 H), 2.10 (s, 3 H).
HRMS Calcd. for $C_{15}H_{13}N_3O_2$: m/z 267.1008. Found: 267.1016.

(2-Trimethylsilylethynylphenylthio)pyrazine (**2e**).
Preparation as described for **2a**, starting from **1e** (628 mg; 2 mmol) and trimethylsilylacetylene (392 mg; 4 mmol); reaction time: 4 h. Column chromatography (eluting with ether/light petroleum, 1:1) gave an almost colourless oil (88%).

^{1}H-NMR ($CDCl_3$) δ 8.35 (dd, J_1= 1.5 Hz, J_2= 2.8 Hz, 1 H), 8.30-8.20 (m, 2 H), 7.70-7.55 (m, 2 H), 7.45-7.25 (m, 2 H), 0.10 (s, 9 H).
HRMS Calcd. for $C_{15}H_{16}N_2SSi$: m/z 284.0803. Found: 284.0800.

[2-(3-Hydroxy-1-propynyl)phenylthio]pyrazine (**2f**).
Preparation as described for **2a**, starting from **1e** (628 mg; 2 mmol) and propargyl alcohol (224 mg; 4 mmol); reaction time: 4 h. Column chromatography (eluting with ethyl acetate/light petroleum, 2:1) afforded an almost colourless oil (91%).

^{1}H-NMR ($CDCl_3$) δ 8.30 (dd, unresolved, 1 H), 8.25-8.15 (m, 2 H), 7.70-7.20 (m, 4 H), 4.30 (s, 2 H), 3.25 (br s, 1 H).
HRMS Calcd. for $C_{13}H_{10}N_2OS$: m/z 242.0514. Found: 242.0527.

General Procedure for the Intramolecular Diels-Alder Reactions of the Pyrazines **2**.
Method A. A solution of the pyrazine derivative (1 mmol) in bromobenzene (1 ml) was heated under a nitrogen atmosphere to 155°C (for reaction times cf. Table). Then the solvent was removed under reduced pressure [in the case of the transformations **2c** —> **3c/4c** and **2d** —> **3e/4e**, the residue thus obtained was taken up in a mixture of methanol (10 ml) and 10% aqueous potassium hydroxide (0.5 ml), heated to 60°C for 2 h, then concentrated under reduced pressure]. Column chromatography, eluting with the appropriate solvent system yielded the reaction products **3** and **4**.
Method B. To a solution of the pyrazine derivative (0.5 mmol) in dioxane (1 ml) was added trifluoroacetic acid (228 mg; 2 mmol), then the mixture was heated under a nitrogen atmosphere to 100°C (for reaction times cf. Table). Work-up was performed as described for method A.

Cyclisation of (2-Trimethylsilylethynylphenoxy)pyrazine (**2a**).
Column chromatography (eluting first with ether/light petroleum, 2:3, then with ether) gave compounds **3a** and **4a**.
First fraction: 4-Trimethylsilylbenzofuro[2,3-*b*]pyridine (**3a**); yield: 76% (method A), 71% (method B); identical with an authentic sample.[2i]
Second fraction: 4-Trimethylsilylbenzofuro[2,3-*c*]pyridine (**4a**); yield: 7% (method A), 23% (method B); colourless crystals, mp 75-78°C (light petroleum).
^{1}H-NMR ($CDCl_3$) δ 9.00 (s, 1 H), 8.65 (s, 1 H), 8.20-8.05 (m, 1 H), 7.70-7.30 (m, 3 H), 0.55 (s, 9 H).
HRMS Calcd. for $C_{14}H_{15}NOSi$: m/z 241.0923. Found: 241.0923.
Anal. Calcd.: C, 69.7; H, 6.3; N, 5.8. Found: 69.7; H, 6.5; N, 5.9.

Cyclisation of [2-(3-Hydroxy-1-propynyl)phenoxy]pyrazine (**2b**).
Column chromatography (eluting with ethyl acetate) gave compounds **3b** and **4b**.
First fraction: 4-Hydroxymethylbenzofuro[2,3-*b*]pyridine (**3b**); yield: 72% (method A), 58% (method B); colourless needles, mp 171-175°C (methanol).
^{1}H-NMR (d_6-DMSO) δ 8.40 (d, J = 5.0 Hz, 1 H), 8.15-8.00 (m, 1 H), 7.80-7.30 (m, 4 H), 5.75 (t, J = 4.5 Hz, 1 H), 5.10 (d, J = 4.5 Hz, 2 H).
HRMS Calcd. for $C_{12}H_9NO_2$: m/z 199.0633. Found: 199.0629.
Anal. Calcd.: C, 72.3; H, 4.5; N, 7.0. Found: C, 72.1; H, 4.5; N, 6.9.
Second fraction: 4-Hydroxymethylbenzofuro[2,3-*c*]pyridine (**4b**); yield: 6% (method A), 17% (method B); colourless crystals, mp 143-146°C (ethanol/ether).
^{1}H-NMR (d_6-DMSO) δ 8.95 (br s, 1 H), 8.55 (br s, 1 H), 8.30-8.15 (m, 1 H), 7.90-7.35 (m, 3 H), 5.60 (t, J = 5.0 Hz, 1 H), 5.05 (d, J = 5.0 Hz, 2 H).
HRMS Calcd. for $C_{12}H_9NO_2$: m/z 199.0633. Found: 199.0631.
Anal. Calcd.: C, 72.3; H, 4.5; N, 7.0. Found: C, 72.2; H, 4.5; N, 6.9.

Cyclisation of (N-Acetyl-2-trimethylsilylethynylphenylamino)pyrazine (**2c**).
Column chromatography (eluting first with ethyl acetate/light petroleum, 1:1, then with ethyl acetate) gave compounds **3d** and **4d**.
First fraction: 4-Trimethylsilylpyrido[2,3-*b*]indole (**3d**); yield: 67% (method A), 39% (method B); colourless crystals, mp 175-176°C (ethyl acetate/light petroleum).
^{1}H-NMR ($CDCl_3$) δ 12.40 (br s, 1 H), 8.50 (d, J = 4.5 Hz, 1 H), 8.25-8.10 (m, 1 H), 7.65-7.10 (m, 4 H), 0.55 (s, 9 H).
Anal. Calcd. for $C_{14}H_{16}N_2Si$: C, 70.0; H, 6.7; N, 11.7. Found: C, 70.0; H, 6.8; N, 11.7.
Second fraction: 4-Trimethylsilylpyrido[3,4-*b*]indole (**4d**); yield: 21% (method A), 43% (method B); colourless crystals, mp 190-191°C (ethyl acetate/light petroleum).
^{1}H-NMR ($CDCl_3$) δ 10.60 (br s, 1 H), 9.00 (s, 1 H), 8.55 (s, 1 H), 8.30-8.15 (m, 1 H), 7.60-7.45 (m, 2 H), 7.40-7.15 (m, 1 H), 0.55 (s, 9 H).
Anal. Calcd. for $C_{14}H_{16}N_2Si$: C, 70.0; H, 6.7; N, 11.7. Found: C, 70.0; H, 6.8; N, 11.7.

Cyclisation of [N-Acetyl-2-(3-hydroxy-1-propynyl)phenylamino]pyrazine (**2d**).
Column chromatography (eluting first with ethyl acetate, then with ethyl acetate/ethanol, 9:1) gave compounds **3f** and **4f**.
First fraction: 4-Hydroxymethylpyrido[2,3-*b*]indole (**3f**); yield: 55% (method A), 42% (method B); colourless needles, mp 244-245°C (methanol).

^{1}H-NMR (d_6-DMSO) δ 11.80 (br s, 1 H), 8.40 (d, J = 4.5 Hz, 1 H), 8.10-7.95 (m, 1 H), 7.60-7.10 (m, 4 H), 5.60 (t, J = 5.0 Hz, 1 H), 5.15 (d, J = 5.0 Hz, 2 H).
HRMS Calcd. for $C_{12}H_{10}N_2O$: m/z 198.0793. Found: 198.0792.
Anal. Calcd.: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.5; H, 5.0; N, 14.0.
Second fraction: 4-Hydroxymethylpyrido[3,4-*b*]indole (**4f**); yield: 22% (method A), 48% (method B); colourless needles, mp 216-219°C (methanol).

^{1}H-NMR (d_6-DMSO) δ 11.65 (br s, 1 H), 8.85 (br s, 1 H), 8.35 (br s, 1 H), 8.30-8.15 (m, 1 H), 7.70-7.45 (m, 2 H), 7.40-7.10 (m, 1 H), 5.45 (t, unresolved, 1 H), 5.10 (d, unresolved, 2 H).
HRMS Calcd. for $C_{12}H_{10}N_2O$: m/z 198.0793. Found: 198.0790.
Anal. Calcd.: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.5; H, 5.0; N, 14.0.

Cyclisation of (2-Trimethylsilylethynylphenylthio)pyrazine (**2e**).
Column chromatography (eluting with ether/light petroleum, 2:3) gave compounds **3g** and **4g**.
First fraction: 4-Trimethylsilylbenzothieno[2,3-*b*]pyridine (**3g**); yield: 27% (method A), 9% (method B); identical with an authentic sample.[2i]
Second fraction: 4-Trimethylsilylbenzothieno[2,3-*c*]pyridine (**4g**); yield: 62% (method A), 87% (method B); colourless crystals, mp 130-131°C (light petroleum).

^{1}H-NMR ($CDCl_3$) δ 9.15 (br s, 1 H), 8.70 (br s, 1 H), 8.50-8.30 (m, 1 H), 7.95-7.75 (m, 1 H), 7.60-7.35 (m, 2 H), 0.55 (s, 9 H).
HRMS Calcd. for $C_{14}H_{15}NSSi$: m/z 257.0694. Found: 257.0697.
Anal. Calcd.: C, 65.3; H, 5.9; N, 5.4. Found: C, 65.1; H, 5.8; N, 5.3.

Cyclisation of [2-(3-Hydroxy-1-propynyl)phenylthio]pyrazine (**2f**).
Column chromatography (eluting with ethyl acetate/light petroleum, 3:1) gave compounds **3h** and **4h**.
First fraction: 4-Hydroxymethylbenzothieno[2,3-*b*]pyridine (**3h**); yield: 23% (method A), 8% (method B); colourless needles, mp 223-224°C (methanol).

^{1}H-NMR (d_6-DMSO) δ 8.65 (d, J = 5.0 Hz, 1 H), 8.35-8.00 (m, 2 H), 7.75-7.50 (m, 3 H), 5.85 (t, J = 4.5 Hz, 1 H), 5.20 (d, J = 4.5 Hz, 2 H).
HRMS Calcd. for $C_{12}H_9NOS$: m/z 215.0405. Found: 215.0400.
Anal. Calcd. for $C_{12}H_9NOS \cdot 1/8\,H_2O$: C, 66.3; H, 4.3; N, 6.4. Found: C, 66.4; H, 4.3; N, 6.4.
Second fraction: 4-Hydroxymethylbenzothieno[2,3-*c*]pyridine (**4h**); yield: 68% (method A), 83% (method B); colourless crystals, mp 174-176°C (2-propanol).

^{1}H-NMR (d_6-DMSO) δ 9.20 (s, 1 H), 8.65 (s, 1 H), 8.60-8.45 (m, 1 H), 8.25-8.05 (m, 1 H), 7.75-7.45 (m, 2 H), 5.60 (t, J = 5.0 Hz, 1 H), 5.10 (d, J = 5.0 Hz, 2 H).
HRMS Calcd. for $C_{12}H_9NOS$: m/z 215.0405. Found: 215.0399.
Anal. Calcd. for $C_{12}H_9NOS \cdot 1/4\,H_2O$: C, 65.6; H, 4.4; N, 6.4. Found: C, 65.8; H, 4.1; N, 6.3.

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7. It is known from (3-butynylamino)pyrazine as well as from 2-(2-trimethylsilylethynylphenylamino)pyrimidine that, for electronic reasons, intramolecular cycloaddition reactions can be achieved only with the corresponding N-acylated derivatives.[2c,i]

8. The trimethylsilyl-substituted acetylenes **2a,c,e**, in general, required slightly longer reaction times than compounds **2b,d,f** (bearing CH_2OH moieties), obviously due to the steric requirements of the bulky $SiMe_3$ group.

9. ^{1}H-NMR monitoring of the cycloaddition reactions of compounds **2c,d** indicated limited stability of the N-acetyl groups in the tricyclic products (particularly, for the pyrido[3,4-*b*]-indoles **4c,e**), resulting in partial deacetylation before the reactions were complete.

10. Elemental analyses of compounds **3h, 4h** indicated partial hydration; however, the molecular formulae for these compounds follow unambiguously from high-resolution mass spectrometry.

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12. To circumvent solubility problems with the protonated pyrazines **2**, dioxane was used as a solvent instead of bromobenzene, although the lower reflux temperature required longer reaction times. On the other hand, employment of neat trifluoroacetic acid as solvent (as described in ref.[2j]), predominantly led to decomposition.