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INTRAMOLECULAR DIELS-ALDER REACTIONS OF QUATERNARY PYRAZINIUM SALTS AND PROTONATED PYRAZINIUM CATIONS. SYNTHESIS OF ANNELATED PYRIDINIUM SALTS AND ANNELATED PYRIDINES.

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Abstract: Quaternization of alkynyl substituted pyrazines with triethyloxonium tetrafluoroborate in dichloromethane occurs exclusively at N-4 yielding 3-alkynyl-1-ethylpyrazinium salts, as shown by the ^{13}C NMR data. Protonation of the same pyrazines with trifluoroacetic acid also occurs at N-4. The quaternary pyrazinium salts as well as the protonated pyrazines undergo an intramolecular Diels-Alder reaction under considerably milder conditions than the corresponding neutral pyrazines. The products of the reactions were [c]-annelated quaternary pyridinium salts and [c]-annelated protonated pyridinium cations, respectively.

INTRODUCTION

Inverse electron demand Diels-Alder reactions of pyrimidines[1,2], pyrazines[3,4], 1,2,4-triazines[5,6] and other heteroazadienes[7,8] with appropriate alkenes or alkynes have been shown to be useful routes to new heterocyclic compounds. Particularly, the intramolecular version of these reactions has received considerable attention[2,4,5,6,8]. Introduction of electron withdrawing substituents into the azaaromatic ring enhances the reactivity of the azadiene fragment as a result of a lower $HOMO_{dienophile}/LUMO_{diene}$ energy separation[8]. Since quaternization of the azaaromatic system is an alternative way to reduce the HOMO/LUMO energy separation, it was supposed that quaternization may facilitate intramolecular Diels-Alder reactions. For this reason the current research at our laboratory on intramolecular Diels-Alder reactions was extended to similar reactions of quaternary pyrazinium salts. Support for the justness of our supposal was obtained recently by the observation that 3-(3-butynylthio)- and 3-(4-pentynylthio)-1-ethyl-5-phenyl-1,2,4-triazinium salts cyclize under considerably milder conditions than the corresponding neutral 1,2,4-triazines[9]. In this paper we report on the behaviour of 3-(alkynyl-substituted)-1-ethylpyrazinium salts in intramolecular cyclization reactions. We included in our study the intramolecular Diels-Alder reaction of alkynyl-substituted pyrazinium cations. Similar to quaternization, protonation may accelerate this type of cyclization and can provide an useful and simple approach to annelated heterocyclic systems.

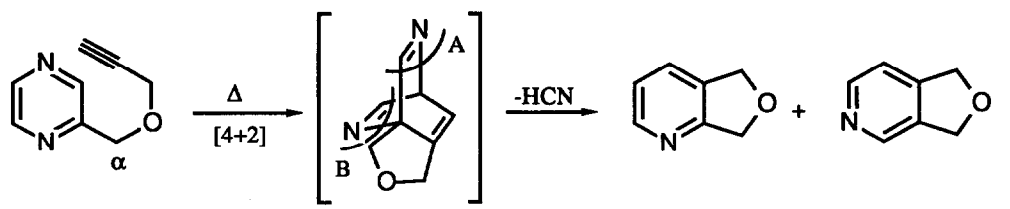
RESULTS AND DISCUSSION

In order to compare the behaviour of quaternary pyrazinium salts in intramolecular Diels-Alder reactions with that of the corresponding neutral pyrazines we tried to prepare the N-quaternary salts **2** of the neutral compounds (3-butynyloxy)pyrazine (**1a**), (3-butynylthio)-pyrazine (**1b**), (3-butynylsulfinyl)pyrazine (**1c**), (3-butynylsulfonyl)pyrazine (**1d**) and (3-propynyl-oxymethyl)pyrazine (**1e**). The compounds **1a-d** are known and their intramolecular cycloaddition reactions have already been studied, so that good comparison is possible. Compound **1e** was unknown and could be prepared in good yield from chloromethylpyrazine and the sodium salt of propargylalcohol.

Scheme 1

Compound **1e** was found to undergo an intramolecular Diels-Alder reaction in high yield on heating in the solvent nitrobenzene at 130°C for 2.5 h, resulting in the formation of a mixture of 5,7-dihydrofuro[3,4-b]pyridine (**3**) and 1,3-dihydrofuro[3,4-c]pyridine (**4**) in a ratio 4:1 (scheme 2). The formation of **3** as main product implies that cleavage A is favoured over that indicated by B. This result is in agreement with previous observations[4].

Scheme 2



It is interesting to note that the conditions required for the cyclization of **1e** are comparable to those required for the highly electron deficient sulfoxide (**1c**) (120°C, 3h). A similar result was found in the pyrimidine series[10]. We suppose that the presence of an oxygen atom at the β–

position of the side chain of **1e** favours the perpendicular conformation between the C_α-O group and the aromatic ring leading to a higher reactivity[11].

Triethyloxonium tetrafluoroborate (Meerwein reagent) in dichloromethane was used as alkylating reagent in the quaternization reaction of pyrazines **1a-e** (scheme 1). Refluxing pyrazines **1a** and **1b** with 1 equiv. of the Meerwein reagent yielded 3-(3-butynyloxy)-1-ethylpyrazinium tetrafluoroborate (**2a**) and 3-(3-butynylthio)-1-ethylpyrazinium tetrafluoroborate (**2b**), respectively, as stable crystalline solids.

The position of the ethyl group in **2a,b** was established by ^{13}C NMR spectroscopy (table 1). Comparison of the ^{13}C NMR spectra of **1a**[12a] and **2a** shows downfield shifts for the ring carbon atoms at a β–position to the quaternary nitrogen. Furthermore, upfield shifts of 5.5 and 7.9 ppm are observed for the resonances of the ring carbon atoms of **2a** adjacent to the quaternary nitrogen. Upfield shifts with this magnitude are characteristic for pyrazine carbon atoms adjacent to a quaternized nitrogen atom[13]. Similar upfield shifts are observed on comparison of the ^{13}C NMR spectra of **1b**[12b] and **2b**. The ^1H NMR spectra of **2a,b** and **2e** (see table 2) show that

TABLE 1 ^{13}C NMR spectral data of pyrazinium salts **2a** and **2b** in acetone-d_6 and **6b** in trifluoroacetic acid.

Compound	^{13}C chemical shift (ppm) of the ring carbons				other signals
	C-2	C-3	C-5	C-6	
2a	130.9	164.0	149.0	129.9	80.8, 71.8, 67.8,
Δδ (ppm) to neutral **1a**[a]	-5.5	3.0	7.6	-7.9	59.3, 19.2, 16.2.
2b	136.7	164.5	150.5	131.6	82.1, 71.6, 59.0,
Δδ (ppm) to neutral **1b**[a]	-7.9	7.6	5.6	-9.1	30.0, 18.8, 15.7.
6b	136.4	168.9	152.4	129.8	83.7, 73.2, 32.5,
Δδ (ppm) to neutral **1b**[a]	-8.2	12.0	7.5	-10.9	21.0.

a: in acetone-d_6

TABLE 2 ^1H NMR spectral data of pyrazinium salts **2a, b** and **e** in acetone-d_6.

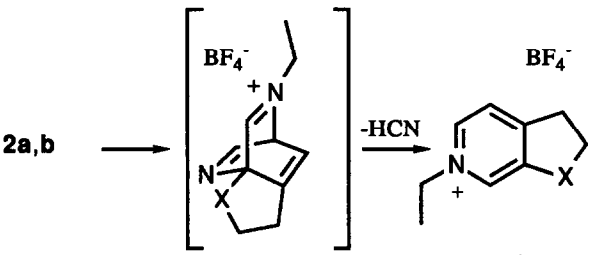
Compound	^1H chemical shifts (ppm) and coupling constants (Hz)				
	H-6	H-5	H-2	R	N-CH_2-CH_3
2a	8.72 (d, J = 2.9)	9.03 (d, J = 2.9)	8.91 (s)	2.39 (t, J = 2.8, 1H), 2.72 (dt, J_1 = 7.5, J_2 = 2.8, 2H), 4.66 (t, J = 7.5, 2H)	4.82 (q, J = 7.5, 2H), 1.72 (t, J = 7.5, 3H)
2b	8.85 (d, J = 2.9)	9.30 (d, J = 2.9)	9.14 (s)	2.42 (t, J = 3.0, 1H), 2.66 (dt, J_1 = 7.5, J_2 = 3.0, 2H), 3.53 (t, J = 7.5, 1H)	4.85 (q, J = 7.5,2H), 1.72 (t, J = 7.5, 3H)
2e	8.97 (d, J = 2.9)	9.39 (d, J = 2.9)	9.06 (s)	2.90 (t, J = 3.0, 1H), 4.42 (d, J = 3.0, 2H), 5.00 (s)	4.81 (q, J = 7.5, 2H), 1.72 (t, J = 7.5, 3H)

the resonance of all aromatic protons are shifted downfield when compared to those of the corresponding neutral pyrazines. The assignment of the aromatic protons was deduced from

the fact that the signal of protons β to the quaternary nitrogen shifts more downfield than that of protons α to the quaternary nitrogen[13]. Therefore the conclusion is justified that in **1a, b** and **e** the less sterically hindered nitrogen atom is the site of quaternization.

Heating of **2a,b** in D_2O at 100°C afforded in good yields 6-ethyl-2,3-dihydrofuro[2,3-c]pyridinium tetrafluoroborate (**5a**) and 6-ethyl-2,3-dihydrothieno[2,3-c]pyridinium tetrafluoroborate (**5b**), respectively (see scheme 3). The structure of **5a** was established by an independent synthesis of **5a** from 2,3-dihydrofuro[2,3-c]pyridine as described in the experimental part. The structure of **5b** was proven by ^1H NMR spectrometry, mass spectrometry and elemental analysis.

Scheme 3

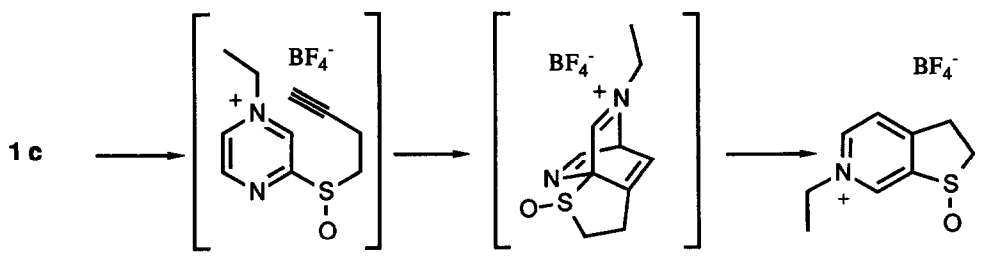


a X = O; **b** X = S

5a,b

Reacting **1c** with the Meerwein reagent in refluxing dichloromethane did not give the required salt **2c**, but 6-ethyl-2,3-dihydro-1-oxothieno[2,3-c]pyridinium tetrafluoroborate (**5c**) (scheme 4) as sole product. Apparently due to the presence of the electron deficient sulfinyl group and the quaternary nitrogen the reactivity is so high that **2c**, when formed, immediately reacts to give **5c**. Even on treatment of **1c** with the Meerwein reagent at room temperature **5c** is exclusively formed. Attempts to quaternize **1d** failed; no quaternary salt and also no Diels-Alder product could be isolated.

Scheme 4

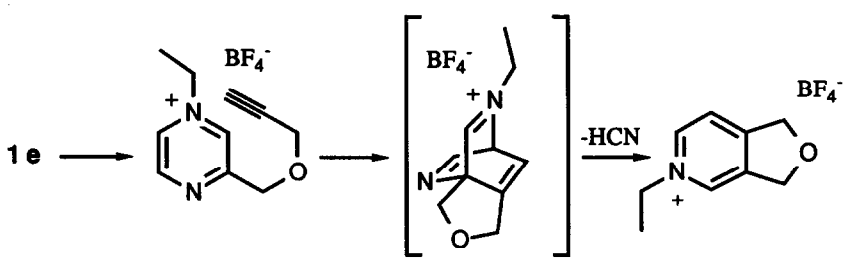


2c **5c**

Ethylation of **1e** does not yield the quaternary salt **2e** as sole product; always 5-10% of the Diels-Alder product 5-ethyl-1,3-dihydrofuro[3,4-c]pyridinium tetrafluoroborate **5e** was present in

the material obtained as is shown by ^1H NMR spectroscopy. The formation of both **5c** and **5e** evidently occurs via the intermediacy of the salts **2c** and **2e**, being cyclized to **5c** and **5e**. The structure of **5e** was established by an independent synthesis of **5e** from 1,3-dihydrofuro[3,4-c]-pyridine (**4**) as described in the experimental part. The possibility of formation of **5c** and **5e** via a route involving an intramolecular Diels-Alder reaction of **1c** and **1e** and subsequent quaternization of the cyclization products can be excluded since cyclization of **1c** and **1e** requires much longer reaction times and leads to [b]-annelated pyridines as main products.

Scheme 5



2e **5e**

The conditions mentioned in table 3 are considerably milder then those required for the intramolecular Diels-Alder reaction of the neutral pyrazines **1a**[4] (210°C, 4h), **1b**[4] (180°C, 3h), **1c**[4] (120°C, 3h) and **1e** (130°C, 2.5h) in nitrobenzene.

TABLE 3 Intramolecular Diels-Alder reactions of the quaternary pyrazinium salts **2a-c** and **2e**. Reaction conditions, products and yields.

Starting compounds	Reaction time[a]	Reaction products	% Yield
2a	7 h	**5a**	65
2b	15 min	**5b**	71
2c	<< 1 min	**5c**	65
2e	8 min	**5e**	75

(a) All reactions were carried out in D_2O at 100°C.

It is clear that the quaternary pyrazinium salts **2a-c** and **2e** cyclize considerably faster then the corresponding neutral species. Comparing the reaction conditions for cyclization (see table 3) of the salts **2a-c** and **2e** we notice that the reacti-vity increases in the order X = O < X = S < X = CH_2O < X = SO. This order is similar to those found in the pyrazine[4], pyrimidine[14,15] and 1,2,4-triazine[6a] series. Therefore, we suppose that in the cyclization of **2a-c** and **2e** cycloadducts are intermediates being formed by addition of the triple bond across C-3/C-6 of the pyrazine ring. Loss of hydrogen cyanide leads to the [c]-an-nelated products **5a-c** and **5e**. The exclusive formation of quaternary pyridinium salts indicates that loss of hydrogen cyanide from the intermediate cycloadducts is more facile than loss of pro-tonated ethylisocyanide. It means that,

contrary to our observations in the neutral pyrazine series, the side chain, particularly the character of the atom directly attached to the ring, does not influence the mode of decomposition of the cycloadduct. The way of ring opening of the cycloadducts originating from the salts **2** is governed by the C=N$^+$-ethyl moiety due to its strong electron withdrawing effect.

Now it has been established that quaternary salts **2** are more easily and exclusively converted into [c]-annelated pyridines than the neutral compounds **1**, we were induced to study the behaviour of the alkynyl-substituted pyrazines **1a-e** on heating in strong acidic medium. As protonating solvent we chose trifluoroacetic acid.

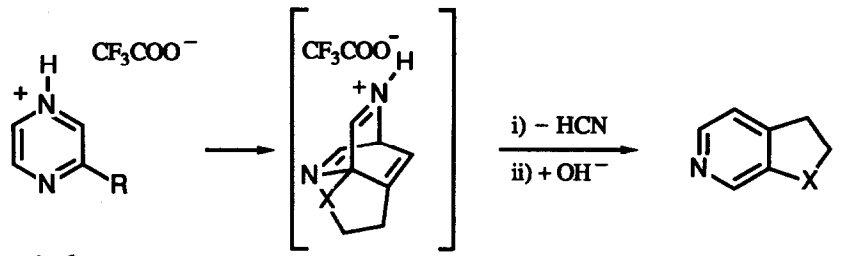
TABLE 4 ^{1}H NMR spectral data for the protonated cations **6a-e** and **10** in trifluoroacetic acid.

Compound	^{1}H chemical shifts (ppm) and coupling constants (Hz). H-6	H-5	H-2	R
6a	8.42 (d, J = 2.9)	9.06 (d, J = 2.9)	8.50 (s)	2.06 (t, J = 2.7, 1H), 2.75 (dt, J_1 = 7.5, J_2 = 2.7,2H), 4.75 (t, J = 7.5, 2H)
6b	8.09 (d, J = 2.9)	8.87 (d, J = 2.9)	8.39 (s)	2.00 (t, J = 2.7, 1H), 2.65 (dt, J_1 = 7.5, J_2 = 2.7, 2H), 3.51 (t, J = 7.5, 2H)
6c	9.00 (d, J = 2.7)	9.30 (d, J = 2.7)	9.42 (s)	1.91 (t, J = 2.5, 1H), 2.80 (m, 2H), 3.33-375 (m, 2H)
6d	9.12 (d, J = 2.7)	9.24 (d, J = 2.7)	9.50 (s)	1.72 (t, J = 2.7, 1H), 2.75 (dt, J_1 = 7.5, J_2 = 2.7, 2H), 3.78 (t, J = 7.5, 2H)
6e	9.09 (d, J = 2.7)	9.39 (d, J = 2.7)	9.24 (s)	2.59 (t, J = 2.7, 1H), 4.53 (d, J = 2.7,2H), 5.24 (s, 2H)
10	9.06 (d, J = 2.7)	9.33 (d, J = 2.7)	9.27 (s)	2.03 (t, J = 2.7, 1H), 2.57 (dt, J_1 = 7.5, J_2 = 2.7, 2H), 3.92 (t, J = 7.5, 2H), 5.16 (s, 2H)

When dissolving the pyrazines **1a-e** in trifluoroacetic acid we could establish the site of protonation by ^{13}C NMR spectroscopy (**6b**) (table 1) and ^{1}H NMR spectroscopy (table 4). Comparison of the ^{13}C NMR spectra of **1b** and **6b** shows shifts downfield (C_3) and upfield (C_2 and C_6) similar to those observed in the ^{13}C NMR spectra of **1b** and **2b**. The effect of protonation on the chemical shifts of the aromatic protons as observed for **6a,b** and **e** is comparable to the effect of quaternization. Also on comparison of the ^{1}H NMR spectra of protonated compounds **6c** and **6d** with those of the pyrazine **1c** and **1d** it appears that the protons ortho to the protonated ring nitrogen (H-2 and H-6) are shifted less downfield than H-5. Therefore we concluded that in the pyrazines **1a-e** protonation takes place at the less steric hindered nitrogen atom.

Cyclization of the N-protonated pyrazinium cations **6a-d** (scheme 6) in trifluoroacetic acid at reflux temperature yielded, after work up of the reaction mixtures, the corresponding [c]-annelated pyridines **7** (X = O, S, SO, SO_2) in moderate to reasonable yields (table 5), while from **6e** the 1,3-dihydrofuro[3,4-c]pyridine **4** was formed (scheme 7).

Scheme 6



6a-d **7a-d**

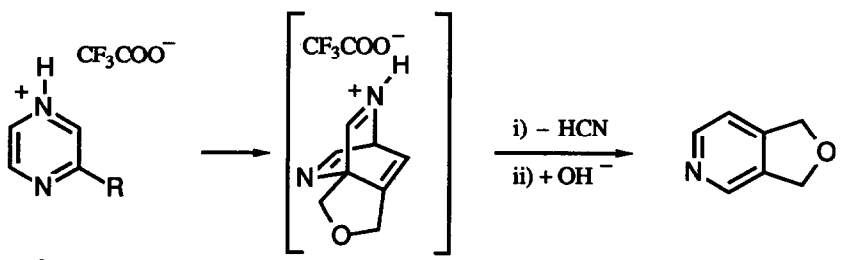
a X = O; **b** X = S; **c** X = SO; **d** X = SO_2

TABLE 5 Intramolecular Diels-Alder reactions of the protonated pyrazinium cations **6a-e**. Reaction conditions[a], reaction products and yields.

Starting compounds	Reaction time[b]	Reaction products	% Yield
6a	20 h	**7a**	5
6b	25 min	**7b**	73
6c	< 5 min	**7c**	55
6d	70 min	**7d**	46
6e	20 min	**4**	88

(a) Reactions were carried out at reflux temperature (72°C) of trifluoroacetic acid.
(b) Times for complete conversion of **6a-e** were found by monitoring the reactions by ^1H NMR spectroscopy.

Scheme 7

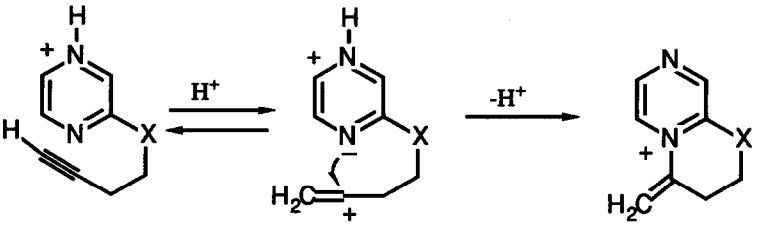


6e **4**

Compounds **7** and **4** are the main reaction products from the cations **6b-e**. However, on cyclization of **6a** the main product is supposed to be 3,4-dihydro-4-methylene-2*H*-pyrazino[2,1-b][1,3]oxazinium trifluoroacetate (**8a**) (scheme 8) based on the presence of a pair of doublets at 5.80 ppm (J = 3.0 Hz) in the ^1H NMR spectrum and a triplet at 115.5 ppm characteristic for the exocyclic $=CH_2$ in the ^{13}C NMR spectrum of the reaction mixture. Similar observations were made when reacting **1b** in trifluoroacetic acid: the presence of a small amount of 3,4-dihydro-4-methylene-2*H*-pyrazino[2,1-b][1,3]thiazinium trifluoroacetate (**8b**) was found. The formation of **8a,b** can be ascribed to a competitive intramolecular coplanar cycloamination reaction[16-18]

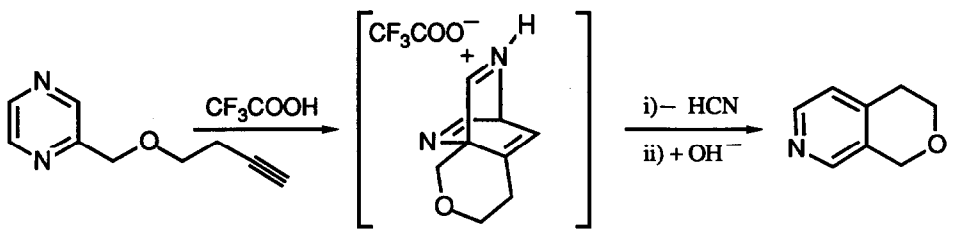
(scheme 8). This reaction probably proceeds via protonation on the terminal acetylenic carbon, followed by attack of the unprotonated nitrogen upon the internal acetylenic carbon (**9a,b**), and subsequent loss of a proton[19]. It is possible that the electron donating effect of oxygen and sulfur stimulates the cycloamination reaction. In case of cyclization of **6d** besides **7d** 1,1-dioxo-2,3-dihydrothieno[2,3-b]pyridine was obtained (ratio of 7:1). The formation of the latter compound may be ascribed to cyclization of unprotonated **1d**.

Scheme 8



Because protonation seems to be a very useful tool to promote the inverse electron demand Diels-Alder reaction, we also investigated the behaviour of (3-butynyloxymethyl)pyrazine (**10**) in trifluoroacetic acid since it is known that in neutral solution strenuous conditions (135h, 195°C, undecane) are required for cyclization[20]. It is interesting that protonation enables **10** to undergo the ring transformation at moderate temperature (72°C). In this way **10** could be converted on heating in trifluoroacetic acid (45 h) into 1*H*-3,4-dihydropyrano[3,4-c]pyridine (**11**) in good yield (Scheme 9).

Scheme 9



In conclusion, the conditions for these protonated intramolecular Diels-Alder reactions are considerably milder than those required for the neutral pyrazines and even milder then those for the N-alkylated pyrazinium salts. Similar to the quaternary salts the protonated (3-alkynyl)pyrazinium cations are exclusively converted into [c]-annelated pyridines.

EXPERIMENTAL SECTION

Melting points are uncorrected. The ^1H NMR spectra were recorded on a Varian (90 MHz) EM 390 spectrometer with Me_4Si as internal standard (δ = 0 ppm). The ^{13}C NMR spectra were recorded at 75.46 MHz on a Bruker CXP-300 spectrometer. Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was performed on Merck silica gel 60 (230-400 mesh ASTM).

Starting materials and reference compounds: (3-butynyloxy)pyrazine (**1a**), (3-butynylthio)-pyrazine (**1b**), (3-butynylsulfinyl)-pyrazine (**1c**), (3-butynylsulfonyl)pyrazine (**1d**) and (3-butynyl-oxymethyl)pyrazine (**10**) were synthesized as described in the literature[4,20].

(3-Propynyloxymethyl)pyrazine (**1e**). Sodium (0.46 g, 20.0 mmole) was dissolved at 0°C in propargyl alcohol (5 ml). To this cooled solution was added a solution of chloromethyl-pyrazine[21,22] (2.6 g, 20.0 mmole) in tetrahydrofuran (10 ml). The mixture was heated at reflux temperature for 3 h and after cooling to room temperature ether (75 ml) was added. Sodium chloride was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by bulb to bulb distillation (160-175°C, 15 mm Hg) to yield **1e** (47%) as an oil. ^1H NMR ($CDCl_3$) δ 8.74 (s, 1H), 8.53 (s, 2H), 4.78 (s, 2H), 4.35 (d, J = 3.0 Hz, 2H), 2.60 (t, J = 3.0 Hz, 1H). HRMS Calcd. for $C_8H_8N_2O$ (M^+): 148.0637. Found; 148.0637.
Anal. Calcd. for $C_8H_8N_2O$: C, 64.9; H, 5.4; N, 18.9. Found: C, 64.8; H, 5.4; N, 19.0.

3-(3-Butynyloxy)-1-ethylpyrazinium tetrafluoroborate (**2a**). To a solution of **1a** (0.44 g, 3 mmole) in dichloromethane (5 ml) was added triethyloxonium tetrafluoroborate (0.57 g, 3 mmole). This solution was heated at reflux temperature for 15 min. The solvent was removed at reduced pressure. The residual solid material was crystallized from absolute ethanol to yield **2a** (51%); m.p. 96-97°C. ^1H and ^{13}C NMR spectral data are given in table 2 and 1.
Anal. Calcd. for $C_{10}H_{13}BF_4N_2O$: C, 45.5; H, 5.0; N, 10.6. Found: C, 45.2; H, 4.9; N, 10.6.

3-(3-Butynylthio)-1-ethylpyrazinium tetrafluoroborate (**2b**). To a solution of **1b** (0.49 g, 3 mmole) in dichloromethane (5 ml) was added triethyloxonium tetrafluoroborate (0.57 g, 3 mmole). This solution was heated at reflux temperature for 5 min. The solvent was removed at reduced pressure. The residual oily material solidified on standing at room temperature and was crystallized from absolute ethanol to yield **2b** (72%); m.p. 103-104°C. ^1H and ^{13}C NMR spectral data are given in table 2 and 1.
Anal. Calcd. for $C_{10}H_{13}BF_4N_2S$: C, 42.9; H, 4.7; N, 10.0. Found: C, 42.7; H, 4.7; N, 9.9.

3-(2-Propynyloxymethyl)-1-ethylpyrazinium tetrafluoroborate (**2e**). A mixture of **1e** (0.44 g, 3.0 mmole), triethyloxonium tetrafluoroborate (0.57 g, 3.0 mmole) and dichloromethane (20 ml) was refluxed for 5 min. After evaporation of the solvent under reduced pressure, a residue was obtained which contained > 95% **2e** based on the ^1H NMR spectrum (table 2). This residue was used without further purification in the intramolecular cyclization reaction.

6-Ethyl-2,3-dihydrofuro[2,3-c]pyridinium tetrafluoroborate (**5a**). To a solution of 2,3-dihydro[2,3-c]pyridine (0.11 g, 0.8 mmole) in dichloromethane (2 ml) was added triethyloxonium tetrafluoroborate (0.13 g, 0.8 mmole). This solution was heated at reflux temperature for 15 min. The separated oil was washed with dichloromethane and dried *in vacuo* to yield 0.17 g (86%) of **5a**. ^1H NMR (acetone-d_6) δ 8.58 (d, J = 6.0 Hz, 1H), 8.44 (s, 1H), 8.00 (d, J = 6.0 Hz, 1H), 4.94 (t, J = 9.0 Hz, 2H), 4.33 (q, J = 6.0 Hz, 2H), 3.63 (t, J = 9.0 Hz, 2H), 1.63 (t, J = 6.0 Hz, 3H). MS (FD): m/e 150 (M^+- 87).
Anal. Calcd. for $C_9H_{12}BF_4NO$: C, 45.6; H, 5.1; N, 5.9. Found: C, 45.7; H, 5.1; N, 6.0.

5-Ethyl-1,3-dihydrofuro[3,4-c]pyridinium tetrafluoroborate (**5e**). To a solution of 1,3-dihydrofuro[3,4-c]pyridine (**4**) (0.24 g, 2.0 mmole) in dichloromethane (10 ml) was added triethyloxonium tetrafluoroborate (0.38 g, 2.0 mmole). This solution was heated at reflux temperature for 15 min. The solvent was removed under reduced pressure. The resulting oil was purified by column chromatography (acetonitrile/dichloromethane 1:1) to yield 0.42 g (80%) of **5e** as an oil. ^1H NMR (acetone-d_6) δ 8.91 (s, 1H), 8.88 (d, J = 6.5 Hz, 1H), 8.09 (d, J = 6.5 Hz, 1H), 5.24 (m, 4H), 4.75 (q, J = 6.5 Hz, 2H), 1.65 (t, J = 6.5 Hz,3H).
Anal. Calcd. for $C_9H_{12}BF_4NO$: C, 45.6; H, 5.1; N, 5.9. Found: C, 45.9; H, 5.4; N, 6.2.

Cyclization of (2-propynyloxymethyl)pyrazine (**1e**) into 5,7-dihydrofuro[3,4-b]pyridine (**3**) and 1,3-dihydrofuro[3,4-c]pyridine (**4**). A solution of **1e** (0.5 g, 3.4 mmole) in nitrobenzene (5 ml) was heated under nitrogen at 130°C for 2.5 h. The reaction mixture was chromatographed over silica gel. Elution first with ether yielded **3** (61%) as an oil. HRMS Calcd. for C_7H_7NO (M^+): 121.0528. Found: 121.0536. ^1H NMR ($CDCl_3$) δ 8.47 (d, J = 3.2 Hz, 1H), 7.53 (d, J = 6 Hz, 1H), 7.15 (m, 1H), 5,15 (s, 2H), 5.06 (s, 2H). Subsequent elution with ether/ethylacetate 1:1 yielded **4** (15%) as an oil. This product was identical with a specimen isolated before[10].

Cyclization of 3-(3-butynyloxy)-1-ethylpyrazinium tetrafluoroborate (**2a**) to 6-ethyl-2,3-dihydrofuro[2,3-c]pyridinium tetrafluoroborate (**5a**). A solution of **2a** (2.0 g, 7.6 mmole) in D_2O (20 ml) was heated with stirring at 100°C under nitrogen for 7 h. The solvent was removed under reduced pressure. The residual oil was dried and purified by column chromatography (acetonitrile as eluent) to yield 1.7 g (65%) **5a** as an oil. Its ^1H NMR (acetone-d_6) and IR spectrum were identical with those of the reference compound synthesized as described above in this experimental part.

Cyclization of 3-(3-butynylthio)-1-ethylpyrazinium tetrafluoroborate (**2b**) to 6-ethyl-2,3-dihydrothieno[2,3-c]pyridinium tetrafluoroborate (**5b**). A solution of **2b** (0.25 g, 0.9 mmole) in D_2O (2.5 ml) was heated with stirring at 100°C under nitrogen for 15 min. The solvent was removed under reduced pressure and the residue crystallized from ethyl acetate/methanol/ether to yield 0.16 (71%) of **5b**; m.p. 124-125°C. ^1H NMR ($CDCl_3$) δ 8.63 (s, 1H), 8.53 (d, J =6.0 Hz, 1H), 7.88 (d, J = 6.0 Hz, 1H), 4.63 (q, J = 6.0 Hz, 2H), 3.66 (s, 4H), 1.66 (t, J = 6.0 Hz, 3H).
Anal. Calcd. for $C_9H_{12}BF_4NS$: C, 42.7; H, 4.8; N, 5.5. Found: C, 42.4; H, 4.8; N, 5.5.

Alkylation of (3-butynylsulfinyl)pyrazine (**1c**) and subsequent cyclization of the reaction product to 6-ethyl-2,3-dihydro-1-oxothieno[2,3-c]pyridinium tetrafluoroborate (**5c**). A mixture of (3-butynylylsulfinyl)pyrazine (**1c**) (0.54 g, 3.0 mmole), triethyloxonium tetrafluoroborate (0.57 g, 3.0 mmole) and dichloromethane (20 ml) was stirred at room temperature for 30 min. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in D_2O (2 ml) and heated for 1 min. at 100°C. The solvent was removed under reduced pressure. The residue was crystallized from methanol to yield 0.52 g (65%) of **5c**; m.p. 103-104°C. ^1H NMR (acetone-d_6, CD_3OD) δ 9.72 (s, 1H), 9.18 (d, J = 6.5 Hz, 1H), 8.36 (d, J = 6.5 Hz, 1H), 4.84 (q, J = 6.5 Hz, 2H), 4.00 (m, 2H), 3.59 (m, 2H), 1.72 (t, J = 6.5 Hz, 3H).
Anal. Calcd. for $C_9H_{12}BF_4NOS$: C, 40.2; H, 4.5; N, 5.2. Found: C, 39.9; H, 4.5; N, 5.2.

Cyclization of 1-ethyl-3-(2-propynyloxymethyl)pyrazinium tetrafluoroborate (**2e**) to 5-ethyl-1,3-dihydrofuro[3,4-c]pyridinium tetrafluoroborate (**5e**). The residue isolated in the reaction of **1e** with the Meerwein reagent was dissolved in D_2O (2 ml) and heated at 100°C for 8 min. The solvent was removed at reduced pressure. The residue was purified over silica gel eluting with acetonitrile/dichloromethane 1:1 to yield 0.59 g (75%; based on **1e**) of pure **5e** as an oil. The product was identified by comparison of its ^1H NMR (acetone-d_6) and IR spectrum with those of the reference compound synthesized as described above.

General procedure for the intramolecular Diels-Alder reaction of pyrazines **1a-e** and **10** in trifluoroacetic acid.
A stirred solution of the pyrazine in trifluoroacetic acid (200 mg/1 ml) was heated at reflux temperature (72°C). The reaction was monitored by ^1H NMR spectroscopy. After all the protonated starting material had disappeared (see table 5) the reaction mixture was cooled, poured into water (5 ml/1 ml trifluoroacetic acid) and made slightly alkaline with 25% aqueous sodium hydroxide solution. This solution was extracted with dichloromethane, the organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed over silica gel with the appropriate solvent system to yield the reaction products mentioned below. Characterization of the products was established by comparison of their ^1H NMR ($CDCl_3$) spectra with those of the already known compounds.

Cyclization of (3-butynyloxy)pyrazine (**1a**) to 2,3-dihydrofuro[2,3-c]pyridine (**7a**). Column chromatography (ether) of the reaction mixture obtained from **1a** (2.0 mmole) yielded **7a** (5%). According to the ^1H NMR measurements of the reaction mixture in trifluoroacetic acid there was also about 70% of compound **8a** present. This was established by its ^{13}C NMR spectrum which shows the expected triplet of the exocyclic $=CH_2$ carbon atom.

Cyclization of (3-butynylthio)pyrazine (**1b**) to 2,3-dihydrothieno[2,3-c]pyridine (**7b**). Column chromatography (ether) of the reaction mixture obtained from **1b** (2.0 mmole) yielded **7b** (73%). According to the ^{1}H NMR measurements of the reaction mixture in trifluoroacetic acid there was also about 5% of compound **8b** present.

Cyclization of (3-butynylsulfinyl)pyrazine (**1c**) to 2,3-dihydro-1-oxothieno[2,3-c]pyridine (**7c**). Column chromatography (dichloromethane /methanol 10:1) of the reaction mixture obtained from **1c** (2.0 mmole) yielded **7c** (55%); m.p. 106-108°C. ^{1}H NMR ($CDCl_3$) δ 9.09 (s, 1H), 8.72 (d, J = 6.0 Hz, 1H), 7.47 (d, J = 6.0 Hz, 1H), 4.15-3.15 (m, 4H).
Anal. Calcd. for C_7H_7NOS : C, 54.9; H, 4.6; N, 9.1. Found: C, 54.6; H, 4.6; N, 9.0.

Cyclization of (3-butynylsulfonyl)pyrazine (**1d**) to 2,3-dihydro-1,1-dioxothieno[2,3-c]pyridine (**7d**) and 2,3-dihydro-1,1-dioxothieno[2,3-b]pyridine. Column chromatography (ethyl acetate) of the reaction mixture obtained from **1d** (4 mmole) yielded **7d** (46%); m.p. 205-207°C. ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H), 8.77 (d, J = 6.0 Hz, 1H), 7.37 (d, J = 6.0 Hz, 1H), 3.47 (m, 4H).
Anal. Calcd. for $C_7H_7NO_2S$: C, 49.7; H, 4.2; N, 8.3. Found: C, 49.4; H, 4.1; N, 8.1.
Besides this product the already described [b]-annelated product (7%) was obtained.

Cyclization of (3-propynyloxymethyl)pyrazine (**1e**) to 1,3-dihydrofuro[3,4-c]pyridine (**4**). Column chromatography (ethyl acetate) of the reaction mixture obtained from **1e** yielded **4** (88%).

Cyclization of (3-butynyloxymethyl)pyrazine (**10**) to 1*H*-3,4-dihydropyrano[3,4-c]pyridine (**11**). Column chromatography (ether/petroleum ether 1:1) of the reaction mixture obtained from **10** after a reaction time of 45h yielded **11** (85%).

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