Spectral Assignments and Reference Data

Magnetic Resonance in Chemistry

Received: 21 January 2009 Revised: 13 March 2009 Accepted: 14 March 2009 Published online in Wiley Interscience: 28 April 2009

(www.interscience.com) DOI 10.1002/mrc.2437

Derivatives of pyrazinecarboxylic acid: ^{1}H, ^{13}C and ^{15}N NMR spectroscopic investigations

Wolfgang Holzer,* Gernot A. Eller,* Barbara Datterl and Daniela Habicht

NMR spectroscopic studies are undertaken with derivatives of 2-pyrazinecarboxylic acid. Complete and unambiguous assignment of chemical shifts (^{1}H, ^{13}C, ^{15}N) and coupling constants (^{1}H,^{1}H; ^{13}C,^{1}H; ^{15}N,^{1}H) is achieved by combined application of various 1D and 2D NMR spectroscopic techniques. Unequivocal mapping of ^{13}C,^{1}H spin coupling constants is accomplished by 2D (δ,*J*) long-range INEPT spectra with selective excitation. Phenomena such as the tautomerism of 3-hydroxy-2-pyrazinecarboxylic acid are discussed.

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; ^{15}N NMR; pyrazines

Introduction

In the course of a program devoted to the synthesis of new heterocyclic scaffolds,[1–6] we recently presented the synthesis of pyrazolo[4′,3′:5,6]pyrano[2,3-b]pyrazin-4(1*H*)-ones of type **16** via reaction of 1-substituted or 1,3-disubstituted 2-pyrazolin-5-ones (**15**) and 3-chloro-2-pyrazinecarbonyl chloride (**13**), the latter being available from the corresponding 3-chloro-2-pyrazinecarboxylic acid (**12**) by treatment with thionyl chloride (Scheme 1).[7]

As convenient approaches regarding the synthesis of acid **12** – the key educt of the described synthesis – are not well documented in the literature, we tested different pathways for the synthesis of **12** as given in Scheme 2. Except for **8**, which was obtained upon attempted transformation of nitrile **7** into **12**, all other compounds represented in Scheme 2 are known compounds, some of them being also commercially available. Since the quoted reaction types are well known, the synthetic details will not be discussed here. Nevertheless, in the present paper we want to present the results of the extensive NMR (^{1}H, ^{13}C, ^{15}N) studies undertaken with compounds **1**–**14** (Scheme 2), which – except for chloropyrazine (**3**) – can be all considered as derivatives of pyrazinecarboxylic acid (**1**). Although, from most of these essential pyrazine derivatives more or less, NMR data are available (selected references are specified in Tables 1–3), particularly with 2,3-disubstituted pyrazines almost persistently no assignments of chemical shifts and spin coupling constants are given and the lack of reliable ^{13}C NMR data is noticeable. However, the availability of such unambiguously assigned chemical shift data is crucial, as reference material for databases used in NMR prediction programs such as CSEARCH[8] or ACD/C + H Predictor,[9] programs that have become more and more popular in the last years, especially for the prediction of ^{13}C NMR chemical shifts. Nevertheless, the quality of such predictions is considerably dependent on the availability of authentic reference data of related structures, a criterion which is frequently not fulfilled for heteroaromatic systems such as pyrazine.

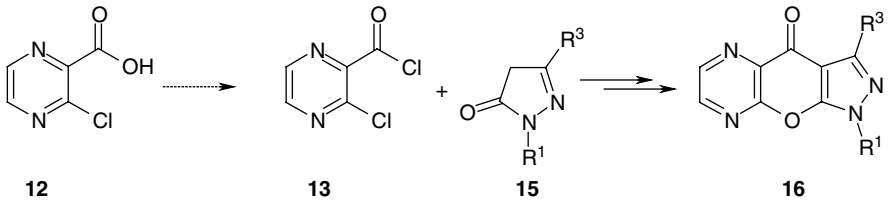
Results and Discussion

^{1}H NMR

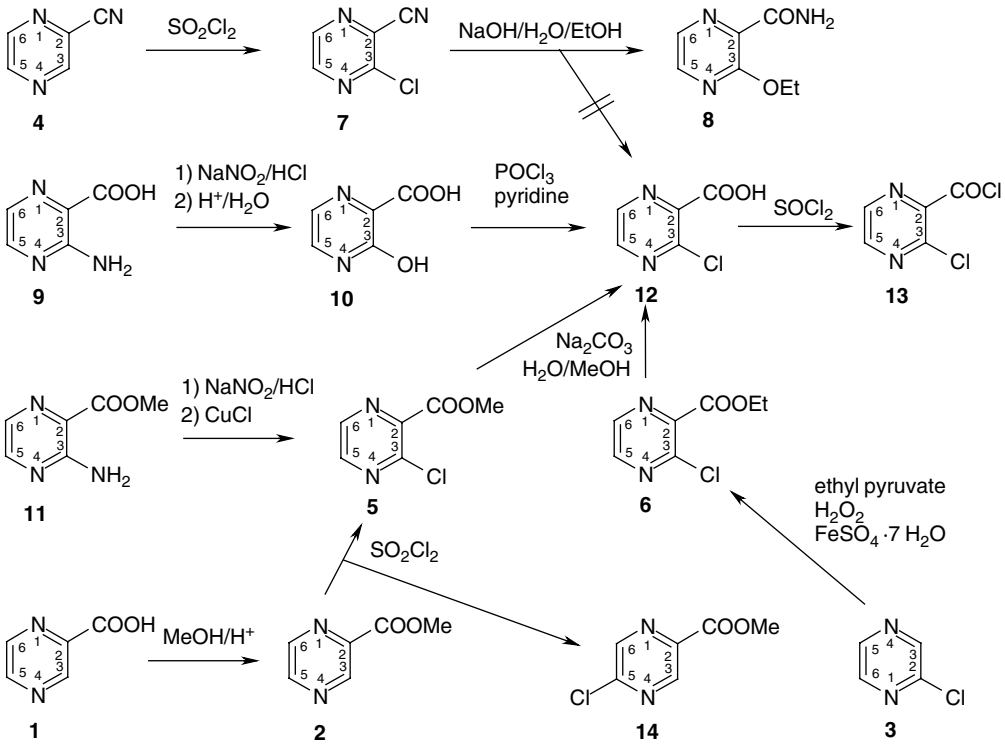
The ^{1}H NMR data of compounds **1**–**14** are collected in Table 1. Assignment of signals in the ^{1}H NMR spectra of 2-monosubstituted pyrazines **1**–**4** is facile considering the known characteristic ^{1}H,^{1}H coupling behaviour in monosubstituted pyrazines: ^{3}J(H5,H6) > ^{5}J(H3,H6) > ^{4}J(H3,H5); the latter coupling constant approximating 0 Hz. Thus, for instance, for ester **2** in DMSO-d_6 values of 2.43 (5,6), 1.49 (3,6) and 0.30 Hz (3,5) are given in the literature.[10] For **1**–**4,** we found coupling constants of 2.2–2.7 Hz for ^{3}J(H5,H6) and 1.5 Hz for ^{5}J(H3,H6), whereas ^{4}J(H3,H5) was not resolved. This leads to doublets for the signals due to H-3 (1.5 Hz) and H-5 (~2.4 Hz) and a double doublet for the H-6 resonance. Introduction of an additional substituent into the 3-position results in the reduction of the pyrazine-H spectrum into two doublets (or an AB-system) of H-5 and H-6; however, an assignment on basis of the splitting pattern is not possible by now. From Table 1 it emerges that the order of signals due to H-5 and H-6 is strongly dependent on the substituents attached to positions 2 and 3 and also from the solvent (compare compound **12**). The difficulty in the unambiguous distinction between the signals of H-5 and H-6 on basis of chemical shift considerations may be the main reason that in the relevant literature assignments are not given with 2,3-disubstituted pyrazines in nearly all cases. Nevertheless, reliable and unequivocal assignments can be achieved considering the ^{13}C,^{1}H and ^{15}N,^{1}H spin coupling constants of the mentioned protons (see below). In compound **10**, the magnitude of the vicinal *J*(H5,H6) coupling (3.7 Hz) is considerably larger than those of all other compounds, thus giving a hint for its special status (presence as 3-oxo-3,4-dihydropyrazine rather than as 3-hydroxypyrazine tautomer in DMSO-d_6 solution) (Scheme 3).

* *Correspondence to: Wolfgang Holzer and Gernot A. Eller, Department of Drug and Natural Product Synthesis, Faculty of Life Sciences, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria. E-mail: wolfgang.holzer@univie.ac.at; gernot.eller@univie.ac.at*

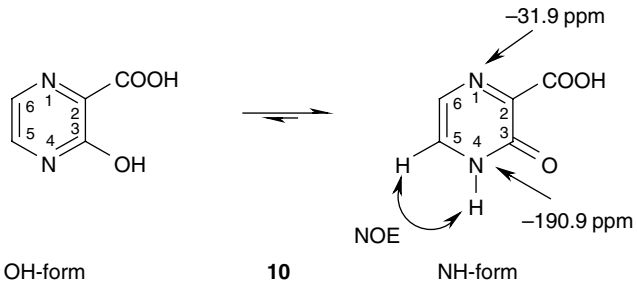
Department of Drug and Natural Product Synthesis, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria



Scheme 1. Synthesis of tricycles **16**.



Scheme 2. Compounds investigated (with atom numbering).



Scheme 3. Tautomeric forms of compound **10**.

^{13}C NMR

In Table 2, the ^{13}C NMR data of the investigated compounds are summarized. In monosubstituted pyrazines **1**–**4**, the signal of C-5 can be smoothly distinguished from those of C-3 and C-6 on basis of the splitting patterns in the ^{1}H-coupled spectra. Whereas the signals of C-3 and C-6 in each case exhibit one larger and one smaller long-range coupling (for instance, C-3 in **1** gives a 10.2 Hz and a 1.4 Hz splitting, the C-6 signal is split with 10.8 and 1.3 Hz), the C-5 resonance shows two larger splittings [**1**: ^{2}J(C5,H6) = 10.8 Hz and ^{3}J(C5,H3) = 9.6 Hz]. The latter couplings can be unequivocally discriminated employing 2D (δ,J) long-range INEPT spectra with selective excitation[11] of the resonances due to H-6 and H-3, respectively. Besides, unequivocal assignment of C-3 and C-6 in **1**–**4** can also be easily achieved by consulting the ^{1}J(C-H) correlations from the HSQC spectra, as H-3 and H-6 can be easily identified as described above. A characteristic attribute observed with pyrazines **1**, **2** and **4** is the ^{5}J(CO,H5) or ^{5}J(CN,H5) coupling constant of 1.0–1.5 Hz, which was unambiguously assigned via 2D long-range INEPT experiments with selective excitation. In contrast, a ^{4}J coupling of H-6 to CO or CN could not be observed.

With 2,3-disubstituted pyrazines, the situation is a little bit more tricky. The quaternary carbon atoms C-2 and C-3 show very similar coupling patterns and similarly this is the case for C-5 and C-6. With compounds **8, 9** and **11** the substituent in 3-position (OEt, NH_2) is characterized by a pronounced −I but +M effect, thus enabling a smooth distinction between C-2 and C-3 on basis of chemical shift considerations (δ C-3 $\gg$ δ C-2) and also between C-5 and C-6 (δ C-5 $>$ δ C-6). However, these differences in chemical shifts are less pronounced in compounds **5**, **6**, **12** and **13** with a chloro atom linked to pyrazine C-3. Here, a safe identification of H-5 and thus the starting point for unambiguous assignments of all carbon atoms can be accomplished by 2D (δ,J) long-range

Table 1. ^{1}H NMR data of **1**–**14** (δ in ppm, J in Hz)

Compound	Solvent	δ (H-3)	δ (H-5)	δ (H-6)	δ other H	^{3}J(5,6)	Other J
1	DMSO-d_6	9.16	8.82	8.77	10–14 (OH)	2.4	1.5 J(3,6)
2	$CDCl_3$	9.17	8.65	8.59	3.90 (OMe)	2.4	1.5 J(3,6)
	DMSO-d_6	9.16	8.86	8.79	3.90 (OMe)	2.4	1.5 J(3,6)
3	$CDCl_3$	8.55	8.43	8.32	–	2.5	1.5 J(3,6)
	DMSO-d_6	8.76	8.63	8.50	–	2.5	1.4 J(3,6)
4	$CDCl_3$	8.91	8.79	8.71	–	2.5	1.5 J(3,6)
	DMSO-d_6	9.20	8.95	8.85	–	2.5	1.5 J(3,6)
5	$CDCl_3$	–	8.50	8.56	4.01 (OMe)	2.4	–
	DMSO-d_6	–	8.72	8.75	3.93 (OMe)	2.4	–
6	$CDCl_3$	–	8.51	8.57	4.49 (OCH_2), 1.43 (Me)	2.3	7.2 (CH_2,CH_3)
7	$CDCl_3$	–	8.61	8.65	–	2.4	–
	DMSO-d_6	–	8.83	8.85	–	2.4	–
8	$CDCl_3$	–	8.23	8.22	7.62, 6.90 ($CONH_2$), 4.53 (OCH_2), 1.45 (Me)	2.4	7.1 (CH_2,CH_3)
	DMSO-d_6	–	8.28	8.17	7.88, 7.61 ($CONH_2$), 4.38 (OCH_2), 1.32 (Me)	2.7	7.1 (CH_2,CH_3)
9	DMSO-d_6	–	8.19	7.86	7.38 (NH_2), 5.50 (OH)	2.3	–
10	DMSO-d_6	–	7.80	7.65	8–15 (OH, NH)	3.7	–
11	$CDCl_3$	–	8.14	7.94	3.93 (OMe), 6.56 (NH_2)	2.3	–
	DMSO-d_6	–	8.23	7.87	3.82 (OMe), 7.29 (NH_2)	2.0	–
12	$CDCl_3$	–	8.70	8.69	9.21 (OH)	2.2	–
	DMSO-d_6	–	8.65	8.71	10–16 (OH)	2.3	–
13	$CDCl_3$	–	8.62	8.68	–	2.2	–
14	$CDCl_3$	9.01	–	8.63	3.97 (OMe)	–	1.3 J(3,6)
	DMSO-d_6	9.01	–	8.91	3.91 (OMe)	–	1.3 J(3,6)

selected references: **1**,[20] **2**,[21] **3**,[22,23,24] **4**,[23,25] **5**,[26,27] **6**,[28] **7**,[29] **9**,[30] **10**,[31] **11**,[32] **12**,[33] **14**,[27]

INEPT experiments with selective excitation considering the above mentioned characteristic ^{5}J(CO,H5) coupling.

From Table 2 it is apparent that, for **5**–**9** and **11**–**13** the absolute value of ^{2}J(C5,H6) is slightly larger than ^{2}J(C6,H5); however, the relationship ^{3}J(C3,H5) $>$ ^{3}J(C2,H6) is not true stringent in every case.

The excellent utility of 2D (δ,J) long-range INEPT spectra with selective excitation for the definitive mapping of ^{13}C,^{1}H coupling constants is demonstrated in Fig. 1. In chloropyrazine **3**, the signal of C-5 is splitted by 185.6, 10.3 and 9.5 Hz. Discrimination of the two latter – quite similar – couplings on basis of the known values for the parent pyrazine molecule – ^{2}J(C2,H3) $= +10.4$ Hz, ^{3}J(C2,H6) $= +9.8$ Hz[12] – seems to be less trustable. However, upon selective excitation of the H-3 resonance, in the 2D (δ,J) INEPT spectrum the signal of C-5 is split by 9.5 Hz, thus assigning ^{2}J(C5,H3) to be 9.5 Hz and – indirectly – ^{2}J(C5,H6) must be 10.3 Hz (Fig. 1). Moreover, from this experiment the magnitude of ^{2}J(C2,H3) is unequivocally assigned with 7.8 Hz, thus, ^{3}J(C2,H6) must be 11.3 Hz. In the same way, all long-range ^{13}C,^{1}H coupling constants given in Table 2 were unequivocally allocated by corresponding experiments.

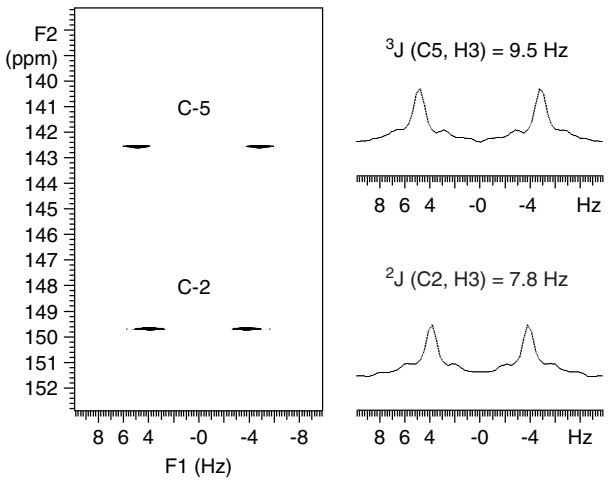


Figure 1. Longe-range 2D (δ,J) INEPT spectrum of **3** obtained upon selective irradiation of the H-3 resonance.

^{15}N NMR

Table 3 comprises the ^{15}N NMR data of **1**–**14**. The values we found for monosubstituted pyrazines **1**–**4** are in nearly perfect agreement with those published by *Günther* and coworkers[13] (but not with those given by *Jovanovic*[14]). Compounds **1**–**3** exhibit somewhat larger chemical shifts for N-4 when compared with those of N-1, whereas in disubstituted compounds **5**–**14** the situation is reverted due to the more or less pronounced π-donating properties of the chloro, amino or ethoxy substituent in position 3 affecting the ortho located N-4 atom. The ^{2}J(N,H) couplings of N-1 and N-4 are very congruent and cover the range of 10.4–11.6 Hz (absolute value), being characteristic for pyridine-type nitrogen atoms with the axis of the nitrogens lone-pair being coplanar with the N-C-H system.[13,15] The large difference between the geminal (~11 Hz) and the vicinal (~1.5 Hz) ^{15}N,^{1}H coupling constants also affects the form and intensity of the corresponding signals in the HMBC spectra, which helps to identify the N–H connectivities. The N-4 signal of monosubstituted pyrazines **1**–**4** can be easily identified due to its characteristic triplet structure (dt) in the ^{1}H-coupled ^{15}N NMR spectra (two geminal N,H couplings).[13]

Table 2. ^{13}C NMR data of **1**–**14** (δ in ppm, J in Hz)

Compound	Solvent	^{13}C chemical shifts (δ, ppm)					$^{13}C,^{1}H$ spin coupling constants (Hz)								
		C-2	C-3	C-5	C-6	other C	C-2		C-3		C-5		C-6		other J
							$^{3}J(2,6)$	$^{4}J(2,5)$	$^{3}J(3,5)$	$^{4}J(3,6)$	$^{1}J(5,5)$	$^{2}J(5,6)$	$^{1}J(6,6)$	$^{2}J(6,5)$	–
1	DMSO-d_6	144.0	145.7	147.8	144.7	165.3 (CO)	9.7	1.5	10.2	1.4	185.8	10.8	186.4	10.8	CO: 1.2 (H5)
							$J(2,3) = 8.1$		$J(3,3) = 187.6$		$J(5,3) = 9.6$		$J(6,3) = 1.3$		
2	$CDCl_3$	143.0	146.0	147.5	144.1	164.0 (CO), 52.8 (OMe)	9.7	1.5	10.1	1.4	184.6	11.1	185.5	11.0	OMe: 148.1; CO: 3.9 (Me), 1.0 (H5)
							$J(2,3) = 8.1$		$J(3,3) = 188.6$		$J(5,3) = 9.7$		$J(6,3) = 1.3$		
	DMSO-d_6	142.9	145.6	148.2	144.8	52.7 (OMe)	9.9	1.6	10.3	1.4	186.2	10.8	187.0	10.8	OMe: 148.2; CO: 3.8 (Me), 1.1 (H5)
							$J(2,3) = 8.1$		$J(3,3) = 188.1$		$J(5,3) = 9.6$		$J(6,3) = 1.3$		
3	$CDCl_3$	149.6	144.9	142.4	143.8	–	11.3	1.9	10.5	1.5	185.6	10.3	186.1	11.7	–
							$J(2,3) = 7.5$		$J(3,3) = 192.4$		$J(5,3) = 9.5$		$J(6,3) = 1.3$		–
	DMSO-d_6	148.6	144.8	143.4	144.5	–	11.4	1.9	10.7	1.6	187.3	10.0	188.2	11.6	–
							$J(2,3) = 7.6$		$J(3,3) = 194.0$		$J(5,3) = 9.5$		$J(6,3) = 1.4$		–
4	$CDCl_3$	130.9	148.2	147.3	145.4	115.2 (CN)	11.3	1.7	10.4	1.5	186.8	10.7	187.6	11.0	CN: 1.5 (H3), 1.5 (H5)
							$J(2,3) = 9.4$		$J(3,3) = 190.4$		$J(5,3) = 9.4$		$J(6,3) = 1.3$		
	DMSO-d_6	129.8	148.7	148.2	145.8	115.9 (CN)	11.3	1.8	10.4	1.4	188.5	10.4	189.5	10.8	CN: 1.5 (H3), 1.5 (H5)
							$J(2,3) = 9.3$		$J(3,3) = 192.6$		$J(5,3) = 9.3$		$J(6,3) = 1.3$		
5	$CDCl_3$	144.2	147.6	145.6	141.7	163.6 (CO), 53.3 (OMe)	10.8	1.4	11.6	1.8	187.5	11.8	187.9	10.5	OMe: 148.5; CO: 3.9 (Me), 1.1 (H5)
	DMSO-d_6	143.7	145.6	146.7	143.0	163.6 (CO), 53.2 (OMe)	10.9	1.6	11.9	1.8	190.4	11.8	190.2	10.3	OMe: 148.7; CO: 4.0 (Me), 1.1 (H5)
6	$CDCl_3$	144.6	147.5	145.4	141.8	163.3 (CO), 62.8 (OCH_2), 14.0 (Me)	10.8	1.7	11.6	1.8	187.5	11.8	187.8	10.5	CO: 3.3 (OCH_2), 1.2 (H5); OCH_2: 148.9, 4.4; Me: 127.5, 2.7

Table 2. (*Continued*)

Compound	Solvent	^{13}C chemical shifts (δ, ppm)					^{13}C,^{1}H spin coupling constants (Hz)								
		C-2	C-3	C-5	C-6	other C	C-2		C-3		C-5		C-6		other *J*
							$^{3}J(2,6)$	$^{4}J(2,5)$	$^{3}J(3,5)$	$^{4}J(3,6)$	$^{1}J(5,5)$	$^{2}J(5,6)$	$^{1}J(6,6)$	$^{2}J(6,5)$	–
7	$CDCl_3$	130.4	151.3	146.4	143.0	113.5 (CN)	12.0	1.7	11.9	1.7	189.5	11.8	190.3	10.5	CN: 1.3 (H5)
	DMSO-d_6	129.6	150.5	147.8	144.1	114.4 (CN)	12.1	1.5	12.1	1.7	192.1	11.6	192.3	10.4	CN: 1.4 (H5)
8	$CDCl_3$	133.6	158.7	143.8	136.0	165.1 (CO), 63.4 (OCH_2), 14.3 (Me)	not unambiguously determined				183.1	12.0	186.5	10.3	OCH_2: 148.5, 4.4; Me: 127.1, 2.5
	DMSO-d_6	138.8	156.8	142.2	135.2	165.6 (CO), 62.1 (OCH_2), 14.2 (Me)	10.0	1.6	10.4	1.5	184.2	11.7	186.2	10.2	OCH_2: 147.8, 4.4; Me: 126.7, 2.5
							$J(2, NH_2) = 8.0$		$J(3, OCH_2) = 2.9$						
9	DMSO-d_6	124.8	156.1	147.3	132.0	168.1 (CO)	10.0	1.5	11.0	1.2	180.5	11.8	186.1	10.3	CO: 1.2 (H5)
10	DMSO-d_6	143.6	156.6	132.5	125.5	164.2 (CO)	10.4		6.7		185.6	13.1	192.0	5.5	
11	$CDCl_3$	124.1	155.8	147.4	133.4	166.7 (CO), 52.7 (OMe)	10.0	1.6	11.0	1.2	180.4	12.0	186.9	10.4	CO: 3.8 (OMe), 1.3 (H5); OMe: 147.9
							$J(C2,NH_2) = 3.5$				$J(C5,NH_2) = 1.2$				
	DMSO-d_6	123.3	155.9	147.8	132.5	166.5 (CO), 52.1 (OMe)	10.2	1.4	11.1	1.1	180.9	12.0	186.7	10.3	CO: 3.8 (OMe), 1.2 (H5); OMe: 147.8
							$J(C2,NH_2) = 3.4$								
12	$CDCl_3$	140.7	149.3	147.2	141.0	162.8 (CO)	10.0	1.3	11.8	1.2	188.6	11.6	189.3	10.7	–
	DMSO-d_6	145.8	144.8	145.9	142.8	164.9 (CO)	10.7	1.5	11.9	1.8	189.8	11.6	189.5	10.4	CO: 1.1 (H5)
13	$CDCl_3$	143.4	147.3	147.2	142.0	165.7 (CO)	10.6	1.6	11.9	1.8	188.7	11.9	189.5	10.6	CO: 1.6 (H5)
14	$CDCl_3$	141.1	145.5	152.5	144.2	163.4 (CO), 53.1 (OMe)	9.5	–	–	1.2	–	8.1	195.0	–	OMe: 148.3; CO: 3.9 (OMe)
							$J(2, 3) = 7.8$		$J(3, 3) = 191.6$		$J(5, 3) = 11.4$		$J(6, 3) = 1.4$		
	DMSO-d_6	141.4	145.4	151.4	144.6	163.3 (CO), 52.9 (OMe)	9.6	–	–	1.3	–	8.1	197.0	–	OMe: 148.3; CO: 3.9 (OMe)
							$J(2, 3) = 7.8$		$J(3, 3) = 192.2$		$J(5, 3) = 11.3$		$J(6, 3) = 1.4$		

selected references: **2**,[21] **3**,[23,24] **4**,[23,25,29,34] **5**,[26] **6**,[28] **7**,[29] **11**,[32]

The exceptional position of compound **10** is best reflected by its ^{15}N NMR spectrum: The chemical shift of −190.9 ppm for N-4 definitely rules out an 'aromatic' pyrazine system (Scheme 3). The predominance of the NH-form is further confirmed by the distinctly smaller chemical shifts for H-5 (7.90 ppm) and H-6 (7.65 ppm) compared to the corresponding shifts in all other compounds (>8.17 ppm), furthermore by the larger H5,H6 coupling (3.7 Hz instead of ∼2.4 Hz, see above), by the markedly smaller ^2J(C6,H5) of 5.5 Hz (instead of 10.2–11.7 Hz) and by an obvious NOE on H-5 upon irradiation of the (broad) NH resonance (Scheme 3). In contrast, the corresponding 3-amino-2-pyrazinecarboxylic acid **9**, which in principle is capable of prototropic tautomerism as well, does not show such behaviour and thus can be considered to be existent in the amino form in DMSO-d_6 solution. These findings are in full agreement with those published for related compounds.[16]

An interesting phenomenon was observed with 3-chloro-2-pyrazinecarboxylic acid **12**. In this compound, obvious differences were evident between spectra observed in DMSO-d_6 and those in $CDCl_3$ solution (Fig. 2). The situation in the ^{15}N NMR spectra seems to be especially striking whereas, in DMSO-d_6 δ(N-1) is larger than δ(N-4) (−44.2 vs −51.5 ppm) – as observed in all other 2,3-disubstituted pyrazines **5**–**11** and **13** – a reverse situation appears for **12** in $CDCl_3$, namely δ(N-1) < δ(N-4) (−51.7 vs −46.6 ppm). Moreover, in $CDCl_3$ a significantly smaller absolute value for ^2J(N1,H6) (10.0 Hz) was determined compared to that in DMSO-d_6 (11.5 Hz), whereas, ^2J(N4,H5) remained almost unaffected by the change of the solvent (11.3 Hz in DMSO-d_6, 11.2 Hz in $CDCl_3$). A possible explanation for the mentioned effects can be given by the assumption that, in $CDCl_3$ the pyrazine N-1 atom of **12** is involved in an intramolecular hydrogen bond (Fig. 2). The so-caused stress of the nitrogen's lone-pair leads to a decrease in the magnitude of ^2J(N1,H6) and also to a decrease of δ(N-1).[15,17,18] It is well known from the literature that, lone-pair effects can drastically influence a large variety of different spin coupling constants. Additionally, the involvement of pyridine-type nitrogen atoms in hydrogen bonding, complexation or protonation is known to decrease the magnitude of the corresponding geminal $^{15}N,^1H$ coupling constant.[17,18] Furthermore, it is well documented that, the involvement of pyridine-type nitrogen atoms in hydrogen bonding or – more drastically – in protonation causes an upfield shift of the corresponding ^{15}N resonance.[19] In DMSO-d_6, which exhibits strong acceptor properties, intramolecular hydrogen bonds are usually broken and such distinctive features can not be observed. In contrast, esters **2** and **5** having no capability for hydrogen bonding exhibit only small differences between the concerning chemical shifts and coupling constants in DMSO-d_6 and $CDCl_3$ solution. Investigations with regard to similar phenomena in other pyrazinecarboxylic acids (**1, 9**) were not possible owing to the very low solubility of the latter compounds in $CDCl_3$.

In conclusion, we have presented full and unambiguous assignments of ^1H, ^{13}C and ^{15}N NMR chemical shifts of a variety of 2-substituted and 2,3-disubstituted pyrazines as well as a complete analysis of the connected scalar spin coupling constants ($^1H,^1H$; $^{13}C,^1H$; $^{15}N,^1H$) employing an extensive combination of different 1D and 2D NMR spectroscopic techniques.

Experimental

All NMR experiments were performed using standard NMR spectroscopic techniques.[36] The ^1H NMR and ^{13}C NMR spectra were recorded either on a Varian UnityPlus NMR spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C) or on a Bruker Avance 500 instrument (500 MHz for ^1H, 125 MHz for ^{13}C) at 25 °C from approximately 0.5 M solutions using 5 mm direct detection broadband probes and deuterium lock. The center of the solvent signal was used as an internal standard which was related to tetramethylsilane with δ 2.49 ppm (^1H) and δ 39.5 ppm (^{13}C). The recording conditions were the following: ^1H NMR: pulse angle 30°, acquisition time 5 s, digital resolution 0.2 Hz/data point, spectral width 20 ppm, 16 transients, relaxation delay 5 s; broadband decoupled ^{13}C-NMR spectra: pulse angle 30°, acquisition time 2 s, digital resolution 0.5 Hz/data point, spectral width 220 ppm, 256–2048 transients, relaxation delay 2 s, exponential multiplication with 1.0 Hz line broadening factor before FT; gated decoupled ^{13}C-NMR spectra: as above but acquisition time 2.5 s, digital resolution 0.4 Hz/data point, 512–8192 transients, relaxation delay 2.5 s, resolution enhancement by Gaussian weighting (Varian: lb = −0.15, gf = 0.7; Bruker: lb = −0.6, gb = 0.2) before FT. Full and unambiguous assignments were achieved by consequent application of fully ^1H-coupled ^{13}C-NMR spectra (gated decoupling), gs-HSQC[37] (1024 × 256 data matrix, 10 ppm for ^1H, 160 ppm for ^{13}C, four transients accumulated per t_1 increment; optimized for J = 160 Hz, qsine multiplication in both dimensions) and gs-HMBC[38] (1024 × 256 data matrix, 10 ppm for ^1H, 180 ppm for ^{13}C, 16 transients accumulated per t_1 increment; optimized for J = 8 Hz, sine multiplication in both dimensions) techniques to all compounds. The unequivocal mapping of $^{13}C,^1H$ coupling constants was performed via 2D long-range INEPT (δ,J) spectra with selective excitation (DANTE)[11] of pyrazine-H resonances (12 Hz excitation width, optimized for J = 8 Hz, 64 increments for 20 Hz width in F1, 128 transients accumulated per t_1 increment; zero-filling to 128 data points in the F1 dimension, shifted sine multiplication in F1). The ^{15}N-NMR spectra were obtained on a Bruker Avance 500 instrument (50.69 MHz) equipped with a 5 mm broadband observe probe at 25 °C and were referenced against external, neat nitromethane. Chemical shifts of pyrazine nitrogen atoms were determined employing refocused, ^1H-decoupled INEPT spectra optimized for an $^{15}N,^1H$ coupling of 11 Hz (acquisition time 1 s, digital resolution 1 Hz/data point, spectral width 400 ppm, 512–4K transients), nitrile N-atoms were covered by inverse gated decoupled ^{15}N NMR spectra (pulse width 7 μs (50°), relaxation delay 10 s, 8 K transients). The $^{15}N,^1H$ coupling constants were determined either from ^1H-coupled ^{15}N-NMR spectra (30° pulse angle, 10 s relaxation delay) of from DEPT experiments without ^1H-decoupling [both: acquisition time 3s, digital resolution 0.33 Hz/data point, resolution enhancement by Lorentz-to-Gauss transformation (lb = −0.6, gb = 0.2)]. For the assignment of pyrazine N-signals $^1H,^{15}N$ gs-HMBC experiments (Bruker standard program 'inv4gplplrndqf',[38] 2048 × 128 data matrix, 10 ppm for ^1H, 200 ppm for ^{15}N, 32 transients accumulated per t_1 increment; 65 (45) ms delay for the evolution of the $^{15}N,^1H$ long-range coupling, optimized for J = 8 (11) Hz, zero-filling to 1K data points in the F1 dimension, sine multiplication in both dimensions) were undertaken.

The melting point was determined on a Reichert–Kofler hot-stage microscope and is uncorrected. The mass spectrum was obtained on a Shimadzu QP 1000 instrument (EI, 70 eV), the IR spectrum on a Perkin-Elmer FTIR 1605 spectrophotometer. The elemental analysis (C, H, N) was performed at the Microanalytical Laboratory, University of Vienna.

Table 3. ^{15}N NMR data of **1**–**14** (δ in ppm, J in Hz)

Compound	Solvent	δ (N-1)	δ (N-4)	δ other N	^2J(N1,H6)	^3J(N1,H5)	^2J(N4,H5)	^3J(N4,H6)
1	DMSO-d_6	−47.3	−45.2	–	11.0	1.5	10.6	1.3
					J(N1,H3) = 1.0		J(N4,H3) = 10.6	
2	$CDCl_3$	−51.2	−46.0	–	10.9	1.6	10.4	1.1
					J(N1,H3) = 0.9		J(N4,H3) = 10.4	
	DMSO-d_6	−47.8	−45.0	–	11.1	1.5	10.7	1.4
					J(N1,H3) = 0.8		J(N4,H3) = 10.7	
3	$CDCl_3$	−57.8	−40.2	–	11.0	1.7	10.6	1.6
					J(N1,H3) = 0.9		J(N4,H3) = 10.6	
	DMSO-d_6	−57.0	−37.1	–	11.2	1.7	10.7	1.4
					J(N1,H3) = 0.9		J(N4,H3) = 10.7	
4	$CDCl_3$	−44.5	−44.7	−118.9 (CN)	11.2	1.4	10.5	1.4
					J(N1,H3) = 0.7		J(N4,H3) = 10.5	
	DMSO-d_6	−46.6	−44.5	−119.5 (CN)	11.3	1.3	10.7	1.1
					J(N1,H3) = 0.7		J(N4,H3) = 10.2	
5	$CDCl_3$	−43.8	−50.3	–	11.3	1.2	11.2	1.3
	DMSO-d_6	−42.6	−50.8	–	11.5	1.4	11.3	1.5
6	$CDCl_3$	−44.1	−50.7	–	11.3	1.4	11.2	1.6
7	$CDCl_3$	−35.5	−52.1	−112.7 (CN)	11.7	1.5	11.3	1.6
	DMSO-d_6	−38.2	−53.9	−114.0 (CN)	11.6	1.5	11.3	1.6
8	$CDCl_3$	−42.2	−92.7	−279.6 (NH_2)	not determined due to low solubility			
	DMSO-d_6	−45.2	−95.8	−271.6 (NH_2) J = 88.3, 89.5	11.1	1.6	11.2	1.7
9	DMSO-d_6	−43.2	−92.3	−300.3 (NH_2)	11.1	1.5	11.2	1.4
10	DMSO-d_6	−31.9	−190.9	–	10.8	2.4	not found	not found
11	$CDCl_3$	−47.3	−93.6	−305.5 (NH_2)	11.0	1.5	11.0	1.3
							J(N4,NH_2) = 4.0	
	DMSO-d_6	−41.9	−91.0	−300.0 (NH_2, J = 90.4)	11.4	1.5	11.3	1.3
12	$CDCl_3$	−51.7	−46.6	–	10.0	1.6	11.2	1.6
	DMSO-d_6	−44.2	−51.5	–	11.5	1.4	11.3	1.6
13	$CDCl_3$	−39.5	−47.8	–	11.6	1.4	11.3	1.6
14	$CDCl_3$	−42.8	−55.2	–	11.0	–	–	0.9
					J(N1,H3) = 0.9		J(N4,H3) = 11.3	
	DMSO-d_6	−39.2	−55.9	–	11.1	–	–	0.8
					J(N1,H3) = 0.9		J(N4,H3) = 11.1	

selected references: **1**,[13,35] **2**,[13] **3**,[13] **4**,[13]

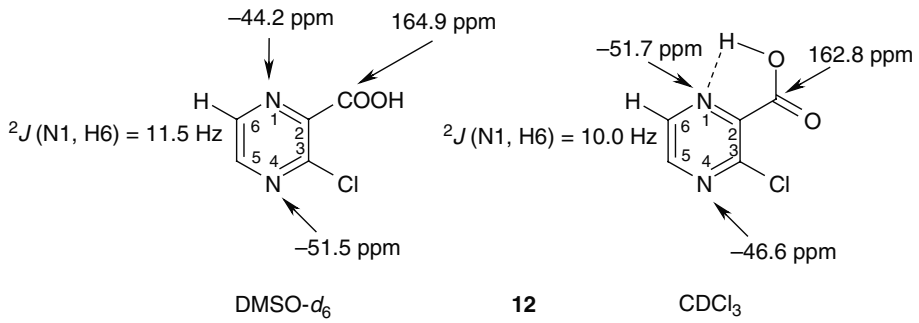


Figure 2. Differences in the NMR spectra of **12** recorded from DMSO-d_6 and $CDCl_3$ solution.

3-Ethoxypyrazine-2-carboxamide (8)

Compound **7** (10.4 g, 75 mmol) was suspended in EtOH (150 mL) and a solution of NaOH (10%, 30 mL) was added. The reaction mixture was heated 2 h under reflux. Then H_2O (30 mL) was added and the EtOH was evaporated under reduced pressure. Upon adjusting the pH to 2–3 with 2N HCl a precipitate was formed, which was filtered off, and washed with H_2O; Yield: 3.62 g (29%); M.p.: 165–166 °C; IR (KBr): ν = 1639 cm^{-1}; MS (70 eV): m/z (%) = 167 (M^+, 19), 150 (76), 123 (37), 96 (45), 80 (45), 68 (100), 44 (76). Anal. Calculated for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.51; H, 5.36; N, 24.92.

References

[1] G. A. Eller, V. Wimmer, A. W. Haring, W. Holzer, *Synthesis* **2006**, 4219.
[2] G. A. Eller, A. W. Haring, B. Datterl, M. Zwettler, W. Holzer, *Heterocycles* **2007**, *71*, 87.
[3] G. A. Eller, W. Holzer, *Molecules* **2007**, *12*, 60.
[4] G. A. Eller, B. Datterl, W. Holzer, *J. Heterocycl. Chem.* **2007**, *44*, 1139.
[5] (a) G. A. Eller, V. Wimmer, W. Holzer, *Khim. Geterotsikl. Soedin.* **2007**, 1251; (b) G. A. Eller, V. Wimmer, W. Holzer, *Chem. Heterocycl. Comp.* **2007**, *43*, 1060.
[6] (a) G. A. Eller, D. Habicht, W. Holzer, *Khim. Geterotsikl. Soedin.* **2008**, 884; (b) G. A. Eller, D. Habicht, W. Holzer, *Chem. Heterocycl. Comp.* **2008**, *44*, 709.
[7] G. A. Eller, Q. Zhang, D. Habicht, B. Datterl, W. Holzer, *Acta Chim. Slov.* **2009**, in press.
[8] *NMR Predict, version 3.2.8.*, Modgraph Consultants, Ltd, Herts, **2004**, www.modgraph.co.uk.
[9] *ACD/C+H NMR Predictors and DB, version 10.04*, Advanced Chemistry Development, Inc., Toronto, **2006**, www.acdlabs.com.
[10] R. H. Cox, A. A. Bothner-By, *J. Phys. Chem.* **1968**, *72*, 1646.
[11] T. Jippo, O. Kamo, N. Nagayama, *J. Magn. Reson.* **1986**, *66*, 344.
[12] F. J. Weigert, J. Husar, J. D. Roberts, *J. Org. Chem.* **1973**, *38*, 1313.
[13] S. Tobias, P. Schmitt, H. Günther, *Chem. Ber.* **1982**, *115*, 2015.
[14] M. V. Jovanovic, *Spectrochim. Acta.* **1984**, *40*, 637.
[15] (a) W. von Philipsborn, R. Müller, *Angew. Chem.* **1986**, *98*, 381; (b) W. von Philipsborn, R. Müller, *Angew. Chem. Int. Ed.* **1986**, *25*, 383.
[16] S. Tobias, H. Günther, *Tetrahedron Lett.* **1982**, *23*, 4785.
[17] W. Holzer, W. von Philipsborn, *Magn. Reson. Chem.* **1989**, *27*, 511.
[18] V. M. S. Gil, W. von Philipsborn, *Magn. Reson. Chem.* **1989**, *27*, 409.
[19] R. O. Duthaler, J. D. Roberts, *J. Am. Chem. Soc.* **1978**, *100*, 4969.
[20] (a) I. G. Iovel, M. V. Shimanskaya, *Zhurn. Prikladboi Khim.* **1992**, *65*, 2075; (b) I. G. Iovel, M. V. Shimanskaya, *J. Appl. Chem. USSR (Engl. Transl.)* **1992**, *65*, 1696.
[21] R. Takeuchi, K. Suzuki, N. Sato, *Synthesis* **1990**, 923.
[22] M. Hashimoto, N. Izuchi, K. Sakata, *J. Heterocycl. Chem.* **1988**, *25*, 1705.
[23] K. Dlabal, K. Palat, A. Lycka, Z. Odlerova, *Collect. Czech. Chem. Commun.* **1990**, *55*, 2493.
[24] P. Cmoch, *Magn. Reson. Chem.* **2003**, *41*, 693.
[25] A. Littke, M. Soummeillant, R. F. Kaltenbach III, R. J. Cherney, C. M. Tarby, S. Kiau, *Org. Lett.* **2007**, *9*, 1711.
[26] T. Okawa, S. Eguchi, A. Kakehi, *J. Chem. Soc. Perkin Trans. 1* **1996**, 247.
[27] N. Sato, M. Fujii, *J. Heterocycl. Chem.* **1994**, *31*, 1177.
[28] N. Haider, *Molbank* **2002**, M287.
[29] N. Sato, Y. Shimomura, Y. Ohwaki, R. Takeuchi, *J. Chem. Soc. Perkin Trans 1* **1991**, 2877.
[30] P. R. Buckland, *J. Heterocycl. Chem.* **1980**, *17*, 397.
[31] A. P. Krapcho, C. E. Gallagher, A. Hammach, M. Ellis, E. Menta, A. Oliva, *J. Heterocycl. Chem.* **1997**, *34*, 27.
[32] M. A. Farran, R. M. Claramunt, C. Lopez, E. Pinilla, M. R. Torres, J. Elguero, *J. Mol. Struct.* **2005**, *741*, 67.
[33] A. Turck, L. Mojovic, G. Queguiner, *Synthesis* **1988**, *881*.
[34] G. Orellana, C. Alvarez-Ibarra, M. L. Quiroga, *Bull. Soc. Chim. Belg.* **1988**, *97*, 731.
[35] L. Carlton, M.-P. Belciug, *J. Organomet. Chem.* **1989**, *378*, 469.
[36] S. Braun, H.-O. Kalinowski, S. Berger, *150 and More Basic NMR Experiments* (2nd edn), Wiley-VCH, Weinheim-New York, **1998**.
[37] L. E. Kay, P. Keifer, T. Saarinen, *J. Am. Chem. Soc.* **1992**, *114*, 10663.
[38] W. Willker, D. Leibfritz, R. Kerssebaum, W. Bermel, *Magn. Reson. Chem.* **1993**, *31*, 287.