5-ALKYL-2-PYRAZINECARBOXAMIDES, 5-ALKYL-2-PYRAZINECARBONITRILES AND 5-ALKYL-2-ACETYLPYRAZINES AS SYNTHETIC INTERMEDIATES FOR ANTIINFLAMMATORY AGENTS

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2-Pyrazinecarbonitrile, 2-acetylpyrazine, 5-alkyl-2-pyrazinecarboxamides, 5-alkyl-2-pyrazinecarbonitriles and 5-alkyl-2-acetylpyrazines were prepared as intermediates for use in synthesis of potential antiinflammatory agents. The results of the homolytic alkylation of pyrazinecarboxamide were compared with published data. 2-Acetylpyrazine and its 5-(1,1-dimethylethyl) derivative were screened for biological activity, but no interesting effect was found.

Key words: Pyrazinecarboxamide; Pyrazinecarbonitrile; Homolytic alkylation; 5-Alkyl-2-acetylpyrazines; Antiinflammatory agents intermediates.

Homolytic substitution reactions are suitable for preparation of various derivatives of heteroaromatic bases. In the pyrazine series, homolytic alkylation[1–3], alkoxycarbonylation[4], carbamoylation[4,5], acylation[6–9], and aroylation[10] have been studied. In this paper, preparation of 5-alkyl-2-pyrazinecarboxamides **1b–1e**, 2-pyrazinecarbonitrile **2a** and 5-alkyl-2-pyrazinecarbonitriles **2b–2e** is described. The mixture of a carboxylic acid, ammonium peroxydisulfate and silver nitrate was used as a source of the alkyl radical. Pyrazinecarbonitrile **2a** and its 5-alkylated analogues **2b–2e** were then converted to the corresponding acetyl derivatives **3a–3e** via the Grignard reaction (Scheme 1).

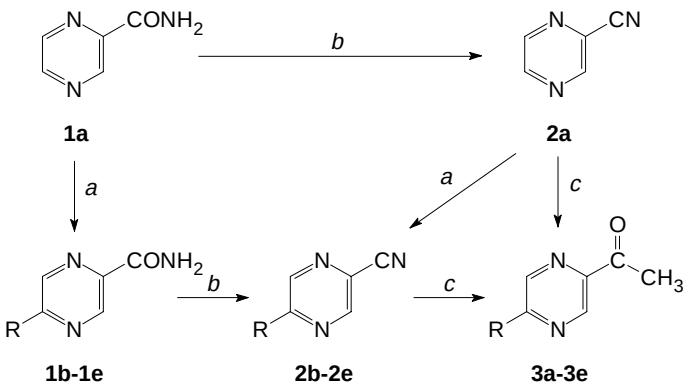
Two synthetic procedures were used for the preparation of 5-alkyl-2-pyrazinecarbonitriles. In method *A*, 2-pyrazinecarboxamide (**1a**) is first alkylated to give 5-alkyl-2-pyrazinecarboxamides **1b–1e**. These components are then dehydrated to the corresponding 5-alkyl-2-pyrazinecarbonitriles **2b–2e**. Alkylation of the amide was performed using the method of Nalepa[3]. The results were only satisfactory and comparable with reported data[1–3] in the case of alkylation with pivalic acid. In all other prepara-

tions, separation of the 5-alkyl derivative from the reaction mixture was found to be difficult. Crystallization had to be repeated several times, and the yields were consequently low (Table I).

Dehydration of the amides **1b–1e** to the corresponding nitriles **2b–2e** proceeded without problems. Total yields of method *A* (Table II) were, however, low due to the low yields of the first reaction step.

It was, therefore, decided to try method *B* in which 2-pyrazinecarboxamide (**1a**) is first dehydrated to 2-pyrazinecarbonitrile (**2a**), and the nitrile is then alkylated to give the corresponding 5-alkyl-2-pyrazinecarbonitriles **2b–2e**. Dehydration with phosphoryl chloride is widely used for the preparation of 2-pyrazinecarbonitrile[11–15] (**2a**) and gave a high yield (Table II). Alkylation of nitrile **2a** gave a mixture in each case from which the 5-alkyl derivative was separated by means of flash column chromatography on silica gel using petroleum ether–ethyl acetate 80 : 20 as the eluent. Since alkylation of nitrile **2a** gave better yields (40 to 80%) than alkylation of amide **1a**, total yields of method *B* were higher compared to method *A* (Table II).

The pyrazinecarbonitriles **2a–2e** were converted to the acetyl derivatives **3a–3e** by the Grignard reaction[13,15].



1-3	R
a	H
b	$(CH_3)_3C$
c	$(CH_3)_2CHCH_2$
d	$CH_3CH_2CH_2CH_2$
e	$CH_3CH_2CH_2$

a) R-COOH, $AgNO_3$, $(NH_4)_2S_2O_8$; *b*)$POCl_3$, Δ; *c*) CH_3MgI, ether

SCHEME 1

Infrared spectra (Tables I, II and III) of unsubstituted 2-pyrazinecarbonitrile (**2a**) and 2-acetylpyrazine (**3a**) conformed to literature data[16]. Infrared spectra of alkylated products **1b–1e**, **2b–2e** and **3b–3e** were compared with available data of various pyrazine derivatives[17]. Weak to medium intensity bands between 1 529–1 542 cm^{-1} and 1 550–1 590 cm^{-1}, which are usually present in all spectra of pyrazine derivatives, except in those of tetrasubstituted pyrazines[17], were observed in the spectra of all the prepared pyrazine derivatives. 2,5-Disubstituted pyrazines usually show a characteristic absorption in the region 1 033–1 040 cm^{-1} (ref.[17]). In contrast, a strong absorption band only occurred between 1 050–1 060 cm^{-1} in the infrared spectra of the products described in this paper. 2,5-Disubstitution was, however, confirmed from ^1H NMR spectroscopic analysis where the magnitude of the coupling constant extracted for the pyrazine ring protons (H-3 and H-6) for all the compounds examined is consistently 1.5 Hz, which is comparable with literature values[5] (J(3,6) = 1.33–1.45 Hz).

TABLE I
Characteristic data, infrared and mass spectra of amides **1b–1e**

Compound	M.p., °C Yield, %	Formula M.w.	Calculated/Found			$\tilde{\nu}$, cm^{-1}			*m/z*, %
			% C	% H	% N	NH_2	CH-aliph.	C=O	
1b	155–157.5, sublim.[a]	$C_9H_{13}N_3O$	60.32	7.31	23.45	3 440	2 985	1 670	179 (M^+, 34)
	50	179.2	60.25	7.08	23.09	3 290 3 220	2 960 2 895		164 (100) 137 (41) 121 (6)
1c	158–178, sublim.[b]	$C_9H_{13}N_3O$	60.32	7.31	23.45	3 420	2 975	1 670	179 (M^+, 17)
	20	179.2	60.03	7.46	22.89	3 280 3 180	2 950 2 890		164 (19) 137 (100) 121 (13)
1d	141–150, sublim.[c]	$C_9H_{13}N_3O$	60.32	7.31	23.45	3 430	2 980	1 670	179 (M^+, 34)
	20	179.2	60.33	7.20	22.88	3 290 3 200	2 950 2 890		164 (8) 137 (100) 121 (28)
1e	152–165, sublim.[d]	$C_8H_{11}N_3O$	58.17	6.71	25.44	3 410	2 975	1 670	165 (M^+, 29)
	20	165.2	58.43	6.66	25.07	3 280 3 240	2 950 2 890		150 (23) 137 (100) 121 (16)

[a] Crystallized from ethanol–water; ref.[1] 155–157 °C. [b] Crystallized from water; ref.[2] 155–156 °C, ref.[3] 171–174 °C. [c] Crystallized from water; refs[1,2] 150–152 °C. [d] Crystallized from water; ref.[1] 154–156 °C, ref.[2] 154–155 °C.

^{1}H and ^{13}C NMR chemical shift assignments were assisted by the use of the DEPT technique. In addition, 2D hetero (^{1}H, ^{13}C) nuclear correlation studies were carried out on compounds **2b**, **3b** and **3e**. Both ^{1}H and ^{13}C NMR chemical shifts (Tables IV and V) of the pyrazine nuclei are similar for all the compounds except those (**1b**, **2b**, **3b**) substituted by a *tert*-butyl group. In these compounds the ^{13}C NMR signals for C-5 (167.7, 168.0 and 167.9, respectively) are shifted relatively downfield and those for C-6 (139.4, 142.5 and 140.1, respectively) are shifted relatively more upfield compared to compounds with other alkyl chains. In the ^{1}H NMR spectra of compounds **2b** and **3b**, the signal for H-6 (8.78 and 8.71, respectively) is shifted downfield compared to that obtained from substitution with other alkyl groups. The respective signal for **1b** (8.37) is surprisingly unaffected and follows the trend set by the related amide analogues.

The mass spectra of the pyrazine derivatives (Tables I, II and III) showed that compounds such as **1c**, **1d** and **1e** which have alkyl groups with a methylene group directly bonded to the pyrazine ring, gave a characteristic base peak (*m/z* 137, 100%). This results from fragmentation of the alkyl chain from the penultimate carbon (for

TABLE II
Characteristic data, infrared and mass spectra of nitriles **2a–2e**

Compound	M.p., °C Yield, %	Distillation temperature °C/kPa	Formula M.w.	$\tilde{\nu}$, cm^{-1}		*m/z*, %
				CH-aliph.	CN	
2a	–	90–91/1.99[a]	$C_5H_3N_3$	–	2 280	–
	85		105.1			
2b	59–61[b]	–	$C_9H_{11}N_3$	2 985	2 280	161 (M^+, 24)
	42[c]		161.2	2 925		146 (100)
	69[d]			2 890		119 (12)
2c	–	94–96/0.33	$C_9H_{11}N_3$	2 970	2 280	161 (M^+, 9)
	17[c]		161.2	2 940		146 (13)
	47[d]			2 890		119 (100)
2d	–	127–128/0.40	$C_9H_{11}N_3$	2 970	2 280	161 (M^+, 3)
	17[c]		161.2	2 940		146 (5)
	47[d]			2 880		119 (100)
2e	–	114–115/0.33	$C_8H_9N_3$	2 980	2 280	147 (M^+, 34)
	17[c]		147.2	2 950		132 (33)
	33[d]			2 890		119 (100)

[a] Refs[11,15] 87 °C/0.79 kPa; ref.[12] 96–100 °C/1.99 kPa. [b] Crystallized from ethanol. [c] Method *A*, related to pyrazinecarboxamide **1a**. [d] Method *B*, related to pyrazinecarboxamide **1a**.

1c, **1d** and **1e**; $M^+ - C_nH_{2n} = m/z$ 137). Branching by substitution of the hydrogens of the methylene group (e.g. **2b** and related analogues) alters the fragmentation pattern as reflected by the observed base peak (**2b** gave $M^+ - CH_3 = m/z$ 146).

Structurally, 2-acetylpyrazines may be considered to be related to acetophenone and since acetophenone derivatives show antirheumatic[18] and antiasthmatic[19] activity, some of the pyrazine derivatives (**3a** and **3b**) were tested for biological activity. The final concentrations ranged from 2–40 μg/ml. None of the compounds exhibited any activity. They can, however, be used as intermediates for the synthesis of other potential anti-inflammatory agents.

EXPERIMENTAL

Pyrazinecarboxamide, granted by Bracco s.p.a., Milano, was used as the starting material. Alkylation was carried out with pivalic acid (Merck), isovaleric acid (Aldrich), valeric acid (Fluka) and butyric

TABLE III
Characteristic data, infrared and mass spectra of acetylpyrazines **3a–3e**

Compound	M.p., °C Yield, %	Distillation temperature °C/kPa	Formula M.w.	$\tilde{\nu}$, cm^{-1}		*m/z*, %
				CH-aliph.	C=O	
3a	74–76.5[a] 40	79/1.87	$C_6H_6N_2O$ 122.1	–	1 695	–
3b	45–47 51	108–110.5/1.47	$C_{10}H_{14}N_2O$ 178.2	2 980 2 920 2 885	1 690	178 (M^+, 26) 163 (100) 136 (55) 121 (17)
3c	– 58	115–120/1.47	$C_{10}H_{14}N_2O$ 178.2	2 970 2 945 2 890	1 690	178 (M^+, 10) 163 (19) 136 (100) 121 (28)
3d	– 56	125–130/1.99	$C_{10}H_{14}N_2O$ 178.2	2 970 2 940 2 880	1 690	178 (M^+, 6) 163 (6) 136 (100) 121 (54)
3e	– 64	118–122/1.99	$C_9H_{12}N_2O$ 164.2	2 980 2 950 2 890	1 690	164 (M^+, 33) 149 (25) 136 (100) 121 (49)

[a] Ref.[13] 74–76 °C, ref.[15] 76–78 °C.

TABLE IV
^{1}H NMR spectra (δ, ppm; *J*, Hz) of the compounds **1**, **2** and **3**

Compound	^{1}H NMR spectrum
1b	1.44 s, 9 H ((C**H**$_3$)$_3$C); 5.84 and 7.62 (CON**H**$_2$); 9.31 d, 1 H, *J* = 1.5 (H-3); 8.37 d, 1 H, *J* = 1.5 (H-6)
1c	0.96 d, 6 H, *J* = 6.8 ((C**H**$_3$)$_2$CH–CH$_2$); 2.16 m, 1 H, *J* = 6.8 and 7.2 ((CH$_3$)$_2$C**H**–CH$_2$); 2.77 d, 2 H, *J* = 7.2 ((CH$_3$)$_2$CH–C**H**$_2$); 5.97 and 7.62 (CON**H**$_2$); 9.32 d, 1 H, *J* = 1.5 (H-3); 8.37 d, 1 H, *J* = 1.5 (H-6)
1d	0.96 t, 3 H, *J* = 7.3 (C**H**$_3$–CH$_2$–CH$_2$–CH$_2$); 1.41 m, 2 H, *J* = 7.3 and 7.7 (CH$_3$–C**H**$_2$–CH$_2$–CH$_2$); 1.77 m, 2 H, *J* = 7.7 and 7.7 (CH$_3$–CH$_2$–C**H**$_2$–CH$_2$); 2.91 t, 2 H, *J* = 7.7 (CH$_3$–CH$_2$–CH$_2$–C**H**$_2$); 6.56 and 7.67 (CON**H**$_2$); 9.31 d, 1 H, *J* = 1.5 (H-3); 8.40 d, 1 H, *J* = 1.5 (H-6)
1e	1.00 t, 3 H, *J* = 7.3 (C**H**$_3$–CH$_2$–CH$_2$); 1.80[a] m, 2 H (CH$_3$–C**H**–CH$_2$); 2.88[a] m, (CH$_3$–CH$_2$–C**H**$_2$); 7.15 and 7.75 (CON**H**$_2$); 9.27 d, 1 H, *J* = 1.5 (H-3); 8.42 d, 1 H, *J* = 1.5 (H-6)
2b	1.43 s, 9 H ((C**H**$_3$)$_3$C); 8.84 d, 1 H, *J* = 1.6 (H-3); 8.78 d, 1 H, *J* = 1.6 (H-6)
2c	0.99 d, 6 H, *J* = 6.6 ((C**H**$_3$)$_2$CH–CH$_2$); 2.19 m, 1 H, *J* = 6.6 and 7.3 ((CH$_3$)$_2$C**H**–CH$_2$); 2.82 d, 2 H, *J* = 7.3 ((CH$_3$)$_2$CH–C**H**$_2$); 8.88 d, 1 H, *J* = 1.5 (H-3); 8.58 d, 1 H, *J* = 1.5 (H-6)
2d	0.96 t, 3 H, *J* = 7.3 (C**H**$_3$–CH$_2$–CH$_2$–CH$_2$); 1.41 m, 2 H, *J* = 7.3 and 7.3 (CH$_3$–C**H**$_2$–CH$_2$–CH$_2$); 1.77 m, 2 H, *J* = 7.3 and 7.7 (CH$_3$–CH$_2$–C**H**$_2$–CH$_2$); 2.94 t, 2 H, *J* = 7.7 (CH$_3$–CH$_2$–CH$_2$–C**H**$_2$); 8.84 d, 1 H, *J* = 1.5 (H-3); 8.59 d, 1 H, *J* = 1.5 (H-6)
2e	1.01 t, 3 H, *J* = 7.3 (C**H**$_3$–CH$_2$–CH$_2$); 1.83 m, 2 H, *J* = 7.3 and 7.6 (CH$_3$–C**H**–CH$_2$); 2.92 t, 2 H, *J* = 7.6 (CH$_3$–CH$_2$–C**H**$_2$); 8.85 d, 1 H, *J* = 1.5 (H-3); 8.59 d, 1 H, *J* = 1.5 (H-6)
3b	1.44 s, 9 H ((C**H**$_3$)$_3$C); 2.71 s, 3 H (COC**H**$_3$); 9.15 d, 1 H, *J* = 1.6 (H-3); 8.71 d, 1 H, *J* = 1.6 (H-6)
3c	0.96 d, 6 H, *J* = 6.8 ((C**H**$_3$)$_2$CH–CH$_2$); 2.16 m, 1 H, *J* = 6.8 and 7.2 ((CH$_3$)$_2$C**H**–CH$_2$); 2.77 d, 2 H, *J* = 7.2 ((CH$_3$)$_2$CH–C**H**$_2$); 2.71 s, 3 H (COC**H**$_3$); 9.15 d, 1 H, *J* = 1.5 (H-3); 8.46 d, 1 H, *J* = 1.5 (H-6)
3d	0.96 t, 3 H, *J* = 7.3 (C**H**$_3$–CH$_2$–CH$_2$–CH$_2$); 1.40 m, 2 H, *J* = 7.3 and 7.3 (CH$_3$–C**H**$_2$–CH$_2$–CH$_2$); 1.76 m, 2 H, *J* = 7.3 and 7.7 (CH$_3$–CH$_2$–C**H**$_2$–CH$_2$); 2.93 t, 2 H, *J* = 7.7 (CH$_3$–CH$_2$–CH$_2$–C**H**$_2$); 2.71 s, 3 H (COC**H**$_3$); 9.13 d, 1 H, *J* = 1.5 (H-3); 8.48 d, 1 H, *J* = 1.5 (H-6)
3e	1.01 t, 3 H, *J* = 7.5 (C**H**$_3$–CH$_2$–CH$_2$); 1.81 m, 2 H, *J* = 7.5 and 7.3 (CH$_3$–C**H**$_2$–CH$_2$); 2.89 t, 2 H, *J* = 7.3 (CH$_3$–CH$_2$–C**H**$_2$); 2.71 s, 3 H (COC**H**$_3$); 9.14 d, 1 H, *J* = 1.5 (H-3); 8.50 d, 1 H, *J* = 1.5 (H-6)

[a] Non-first order.

acid (Fluka). Purity of the products was checked by TLC on Silufol UV 254 plates (Kavalier, Votice). The following solvent systems were used: toluene–acetone 50 : 50 (v/v), petroleum ether–ethyl acetate 25 : 75 (v/v), and petroleum ether–ethyl acetate 80 : 20 (v/v). Silpearl (Kavalier, Votice) was used for flash column chromatography. Melting points were determined with a Boetius apparatus and are uncorrected. Elemental analyses were performed with CHN Analyzer (Laboratorni pristroje, Prague). Infrared spectra of the amides were recorded in KBr pellets with an IR spectrophotometer Perkin–Elmer 577. Infrared spectra of the nitriles and acetyl derivatives were recorded in chloroform solution with the same apparatus. ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ in 5 mm tubes using a JEOL GSX-270 (^{1}H, ^{13}C) FT spectrometer at 270.16 (^{1}H) and 67.97 (^{13}C) MHz, using the deuterium signal of the solvent as the lock and TMS as internal standard. The

TABLE V
^{13}C NMR spectra (δ, ppm) of the compounds **1**, **2** and **3**

Compound	^{13}C NMR spectrum
1b	29.7 (($\mathbf{C}H_3)_3C$), 37.0 (($CH_3)_3\mathbf{C}$), 166.0 ($\mathbf{C}ONH_2$), 141.2 (C-2), 142.3 (C-3), 167.7 (C-5), 139.4 (C-6)
1c	22.3 (($\mathbf{C}H_3)_2CH–CH_2$), 29.2 (($CH_3)_2\mathbf{C}H–CH_2$), 44.6 (($CH_3)_2CH–\mathbf{C}H_2$), 165.3 ($CONH_2$), 141.6 (C-2), 142.7 (C-3), 160.5 (C-5), 143.7 (C-6)
1d	13.8 ($\mathbf{C}H_3–CH_2–CH_2–CH_2$), 22.4 ($CH_3–\mathbf{C}H_2–CH_2–CH_2$), 31.4 ($CH_3–CH_2–\mathbf{C}H_2–CH_2$), 35.4 ($CH_3–CH_2–CH_2–\mathbf{C}H_2$), 166.1 ($CONH_2$), 141.7 (C-2), 142.3 (C-3), 161.3 (C-5), 143.6 (C-6)
1e	13.7 ($\mathbf{C}H_3–CH_2–CH_2$), 22.4 ($CH_3–\mathbf{C}H_2–CH_2$), 37.4 ($CH_3–CH_2–\mathbf{C}H_2$), 166.0 ($CONH_2$), 142.0 (C-2), 142.3 (C-3), 160.7 (C-5), 143.4 (C-6)
2b	29.5 (($\mathbf{C}H_3)_3C$), 37.4 (($CH_3)_3\mathbf{C}$), 115.9 (CN), 127.7 (C-2), 146.8 (C-3), 168.0 (C-5), 142.5 (C-6)
2c	22.3 (($\mathbf{C}H_3)_2CH–CH_2$), 29.0 (($CH_3)_2\mathbf{C}H–CH_2$), 44.7 (($CH_3)_2CH–\mathbf{C}H_2$), 115.8 (CN), 128.0 (C-2), 147.5 (C-3), 161.1 (C-5), 145.7 (C-6)
2d	13.8 ($\mathbf{C}H_3–CH_2–CH_2–CH_2$), 22.4 ($CH_3–\mathbf{C}H_2–CH_2–CH_2$), 31.0 ($CH_3–CH_2–\mathbf{C}H_2–CH_2$), 35.6 ($CH_3–CH_2–CH_2–\mathbf{C}H_2$), 115.8 (CN), 127.9 (C-2), 147.5 (C-3), 161.8 (C-5), 145.3 (C-6)
2e	13.7 ($\mathbf{C}H_3–CH_2–CH_2$), 22.3 ($CH_3–\mathbf{C}H_2–CH_2$), 37.8 ($CH_3–CH_2–\mathbf{C}H_2$), 115.8 (CN), 127.9 (C-2), 147.5 (C-3), 161.6 (C-5), 145.3 (C-6)
3b	29.7 (($\mathbf{C}H_3)_3C$), 37.0 (($CH_3)_3\mathbf{C}$), 199.3 ($\mathbf{C}OCH_3$), 25.8 ($CO\mathbf{C}H_3$), 145.1 (C-2), 142.0 (C-3), 167.9 (C-5), 140.1 (C-6)
3c	22.4 (($\mathbf{C}H_3)_2CH–CH_2$), 29.1 (($CH_3)_2\mathbf{C}H–CH_2$), 44.7 (($CH_3)_2CH–\mathbf{C}H_2$), 199.4 ($\mathbf{C}OCH_3$), 25.8 ($CO\mathbf{C}H_3$), 145.5 (C-2), 142.8 (C-3), 160.8 (C-5), 143.5 (C-6)
3d	13.8 ($\mathbf{C}H_3–CH_2–CH_2–CH_2$), 22.4 ($CH_3–\mathbf{C}H_2–CH_2–CH_2$), 31.4 ($CH_3–CH_2–\mathbf{C}H_2–CH_2$), 35.5 ($CH_3–CH_2–CH_2–\mathbf{C}H_2$), 199.4 ($\mathbf{C}OCH_3$), 25.9 ($CO\mathbf{C}H_3$), 145.5 (C-2), 142.8 (C-3), 161.7 (C-5), 143.0 (C-6)
3e	13.8 ($\mathbf{C}H_3–CH_2–CH_2$), 22.6 ($CH_3–\mathbf{C}H_2–CH_2$), 37.6 ($CH_3–CH_2–\mathbf{C}H_2$), 199.3 ($\mathbf{C}OCH_3$), 25.8 ($CO\mathbf{C}H_3$), 25.8 ($CO\mathbf{C}H_3$), 145.5 (C-2), 142.7 (C-3), 161.4 (C-5), 143.1 (C-6)

parameters were: spectral width 3 kHz (^{1}H) and 18 kHz (^{13}C), pulse width 3 μs (^{1}H) and 4.2 μs (^{13}C) (ca 40 and 45° flip angle, respectively), acquisition time 5.46 or 0.90 s, number of scans 16 (^{1}H) and 600 (^{13}C). Mass spectra were determined on a JEOL JMS-DX303 mass spectrometer.

Alkylated Pyrazinecarboxamides **1b–1e**. General Procedure

To a solution of pyrazinecarboxamide **1a** (12.3 g, 0.1 mol) in water (300 ml) heated to 80 °C, silver nitrate (1.7 g, 0.01 mol) and the corresponding carboxylic acid (0.1 mol) were added. Ammonium peroxydisulfate (25.1 g, 0.11 mol) in water (70 ml) was then added dropwise whilst stirring and temperature maintained between 75–80 °C. The reaction mixture was stirred for 1 h. After cooling, the pH was adjusted to 9 with 10% solution of sodium hydroxide, and the mixture continuously extracted with 1,2-dichloroethane. The organic extract was dried over anhydrous sodium sulfate before evaporating to dryness. Crystallization of the residue yielded amides **1b–1e**. Their characteristic data, infrared and mass spectra are given in Table I, their NMR spectra in Tables IV and V.

Pyrazinecarbonitrile **2a**

Pyrazinecarboxamide **1a** (6.15 g, 0.05 mol) was stirred with phosphorylchloride (31.2 ml) for 90 min in a bath heated to 100 °C. Excess phosphoryl chloride was then removed in mild vacuo and water aspirated. The residue was dropped to ice, the pH adjusted to 9 with saturated solution of sodium carbonate, and the mixture continuously extracted with ether. The organic portion was dried over anhydrous sodium sulfate, and the solvent evaporated. Distillation of the residue gave pyrazinecarbonitrile **2a**. Its characteristic data and infrared spectra are given in Table II.

Alkylated Pyrazinecarbonitriles **2b–2e**. General Procedure

Method A. Alkylated pyrazinecarboxamides **1b–1e** were first prepared as described above, and then dehydrated under the same conditions as the unsubstituted pyrazinecarboxamide **1a**.

Method B. Pyrazinecarbonitrile **2a** was first prepared and then alkylated using the procedure similar to that of preparation of alkylated amides **1b–1e**. Reaction products were extracted with ether and then separated chromatographically. Nitrile **2b** was purified by crystallization, nitriles **2c–2e** were distilled. Their characteristic data, infrared and mass spectra are given in Table II, their NMR spectra in Tables IV and V.

2-Acetylpyrazines **3a–3e**. General Procedure

The nitriles **2a–2e** (0.064 mol) in 25 ml (in case of the nitrile **2b** 110 ml) absolute ether were added dropwise to methylmagnesium iodide (24.9 g, 0.15 mol) in 100 ml absolute ether whilst stirring at –10 to +10 °C. The reaction mixture was stirred at the same temperature for 1 h and then poured on cracked ice. Dilute hydrochloric acid (25 ml, 1 : 1, v/v) was then added and the mixture extracted continuously with ether. The organic portion was dried over anhydrous sodium sulfate, and solvent removed. Distillation of the respective residues yielded acetyl derivatives **3a–3e**. Their characteristic data, infrared and mass spectra are given in Table III, their NMR spectra in Tables IV and V.

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