A New, Convenient Synthesis of Monoaroylpyrazines via Homolytic Substitution

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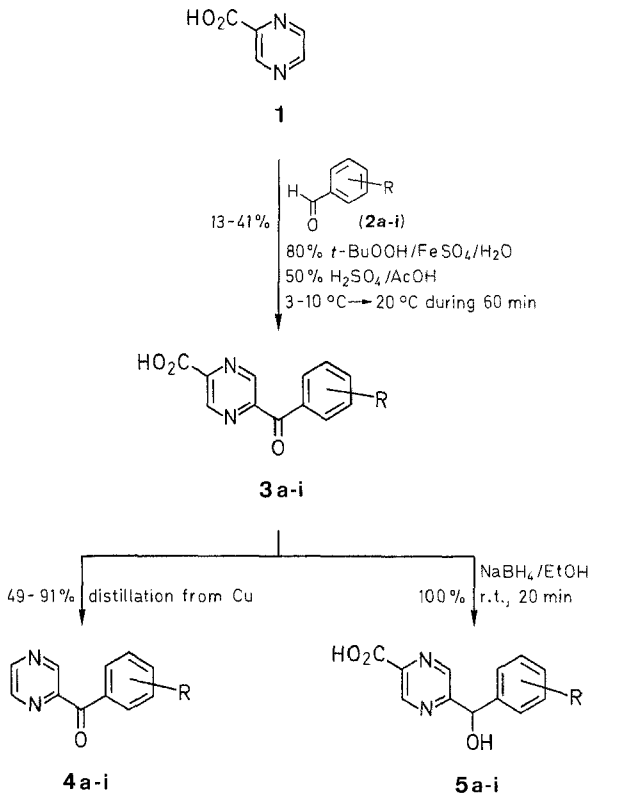
Reactions of 2-pyrazinecarboxylic acid **(1)** with aroyl radicals to give 5-aroyl-2-pyrazinecarboxylic acids **3** followed by decarboxylation provide convenient access to aryl 2-pyrazinyl ketones (2-aroylpyrazines) **4**.

The direct introduction of a single electron-withdrawing substituent (e.g. an acyl or alkoxycarbonyl group) into parent systems of π-deficient *N*-heteroarenes by means of homolytic substitution (Minisci-type reactions[1-3]) remains a challenging problem, since in general these reactions lead to di- or polysubstituted products.[4-7] In previous papers we have demonstrated[8-10] that radical alkoxycarbonylation frequently can be restricted to monosubstitution when the reactions are performed in the presence of an organic phase. This methodology enabled us to prepare ethyl 2-pyrazinecarboxylate in 89% yield from pyrazine.[9] Independently, Williams and co-workers[11] succeeded in the preparation of monoalkanoylpyrazines employing a similar strategy. By carrying out reactions of protonated pyrazine with alkanoyl radicals in the absence of acetic acid, and thus in a heterogeneous medium, further radical attack to give 2,5-diacylpyrazines[12] could be avoided due to removal of the monoacylated product into the organic layer. This procedure, however, is not applicable to the preparation of aryl pyrazinyl ketones, since the low water solubility of the radical precursors in this case requires acetic acid as co-solvent.

We now report on a convenient access to these diaza-analogs of benzophenone, employing a two-step reaction sequence previously applied to efficient syntheses of aryl 4-pyridazinyl ketones.[13,14] The procedure (Scheme) is based on the consideration that homolytic aroylation of protonated 2-pyrazinecarboxylic acid **(1)** should afford 2,5-disubstituted pyrazine derivatives **(3)**, which can be anticipated[15] to readily undergo decarboxylation at elevated temperatures. Thus, the carboxylic moiety



2–5	a	b	c	d	e	f	g	h	i
R	H	4-CH_3	4-CH_3O	2-F	4-F	4-Br	3-Cl	4-Cl	3,4-Cl_2

Table 1. 5-Aroyl-2-pyrazinecarboxylic Acids **3** Prepared[a]

Product	Yield[b] (%)	Molecular Formula[c]	IR (KBr) $\nu_{(C=O)}$ (cm^{-1})	^{1}H-NMR δ, J(Hz)	MS *m/z* (%)
3a	14	$C_{12}H_8N_2O_3 \cdot H_2O$ (246.2)	1692, 1658	8.19–8.54 (m, 5H, phenyl); 9.29–9.40 (m, 2H, pyrazine)	228 (M^+, 12); 105 (100)
3b	22	$C_{13}H_{10}N_2O_3$ (242.2)	1740, 1716	2.42 (s, 3H, CH_3); 7.42, 7.98 (AA'BB' system, 4H, J = 8.7, phenyl); 9.26, 9.32 (2d, 2H, J = 1.3, pyrazine)	242 (M^+, 13); 119 (100)
3c	28	$C_{13}H_{10}N_2O_4 \cdot \frac{1}{4}H_2O$ (262.7)	1748, 1722	3.91 (s, 3H, OCH_3); 7.14, 8.10 (AA'BB' system, 4H, J = 8.7, phenyl); 9.26, 9.33 (2d, 2H, J = 1.4, pyrazine)	258 (M^+, 11); 135 (100)
3d	13	$C_{12}H_7FN_2O_3 \cdot \frac{1}{4}H_2O$ (250.7)	1698, 1668	7.22–7.93 (m, 4H, phenyl); 9.30, 9.35 (2d, 2H, J = 1.5, pyrazine)	246 (M^+, 14); 123 (100)
3e	41	$C_{12}H_7FN_2O_3 \cdot H_2O$ (264.2)	1692, 1658	7.32–7.60, 8.06–8.31 (2m, 4H, phenyl); 9.28–9.38 (m, 2H, pyrazine)	246 (M^+, 10); 123 (100)
3f	22	$C_{12}H_7BrN_2O_3 \cdot H_2O$ (325.1)	1737, 1725, 1650	7.80, 8.00 (AA'BB' system, 4H, J = 8.4, phenyl); 9.27–9.33 (m, 2H, pyrazine)	306/308 (M^+, 13/13); 183/185 (100/92)
3g	29	$C_{12}H_7ClN_2O_3 \cdot H_2O$ (280.7)	1692, 1658	7.48–8.10 (m, 4H, phenyl); 9.29–9.35 (m, 2H, pyrazine)	262/264 (M^+, 15/5); 139/141 (100/33)
3h	24	$C_{12}H_7ClN_2O_3 \cdot H_2O$ (280.7)	1692, 1660	7.70, 8.11 (AA'BB' system, 4H, J = 8.7, phenyl); 9.29–9.35 (m, 2H, pyrazine)	262/264 (M^+, 11/4); 139/141 (100/33)
3i	22	$C_{12}H_6Cl_2N_2O_3 \cdot H_2O$ (315.1)	1735, 1696, 1658	7.80–8.32 (m, 3H, phenyl); 9.30–9.36 (m, 2H, pyrazine)	296/298/300 (M^+, 15/10/2); 173/175/177 (100/63/11)

[a] Melting points can not be determined due to sublimation and/or decarboxylation.
[b] Based on **1**.
[c] Satisfactory microanalyses obtained: C ±0.38, H ±0.17, N +0.35.

Table 2. 2-Aroylpyrazines **4** Prepared

Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c] or Lit. mp (°C)	IR (KBr) $\nu_{(C=O)}$ (cm^{-1})	^{1}H-NMR δ, J(Hz)	MS m/z (%)
4a	84	50–52	47–49[19]	1655	7.50–8.17 (m, 5H, phenyl); 8.88, 9.00, 9.26 (3m, 3H, H-3, H-5, H-6)	–[22]
4b	87	60–62	62.5[19]	1643	7.41, 7.99 (AA'BB' system, 4H, J = 8.4, phenyl); 8.83, 8.98, 9.20 (3m, 3H, H-3, H-5, H-6)	198 (M^+, 23); 119 (100)
4c	62	122–124	125.6[19] "oil"[11]	1640	–[11]	–[11]
4d	82	62–63	$C_{11}H_7FN_2O$ (202.2)	1662	7.26–7.91 (m, 4H, phenyl); 8.85, 9.01, 9.30 (3m, 3H, H-3, H-5, H-6)	202 (M^+, 20); 123 (100)
4e	49	70–72	$C_{11}H_7FN_2O$ (202.2)	1658	7.28–7.60 (m, 4H, phenyl); 8.89, 9.00, 9.26 (3m, 3H, H-3, H-5, H-6)	202 (M^+, 17); 123 (100)
4f	66	87–88	$C_{11}H_7BrN_2O$ (263.1)	1640	7.80, 8.01 (AA'BB' system, 4H, J = 8.7, phenyl); 8.86, 9.00, 9.24 (3m, 3H, H-3, H-5, H-6)	262/264 (M^+, 26/25); 182/184 (100/94)
4g	83	49–50	$C_{11}H_7ClN_2O$ (218.6)	1658	7.50–8.14 (m, 4H, phenyl); 8.88, 9.00, 9.28 (3m, 3H, H-3, H-5, H-6)	218/220 (M^+, 29/10); 139/141 (100/32)
4h	91	73–74	$C_{11}H_7ClN_2O$ (218.6)	1658	7.68, 8.10 (AA'BB' system, 4H, J = 8.7, phenyl); 8.88, 8.99, 9.25 (3m, 3H, H-3, H-5, H-6)	218/220 (M^+, 18/6); 139/141 (100/31)
4i	72	120–122	$C_{11}H_6Cl_2N_2O$ (253.1)	1662	7.80–8.32 (m, 3H, phenyl); 8.90, 9.01, 9.26 (3m, 3H, H-3, H-5, H-6)	252/254/256 (M^+, 36/22/4); 173/175/177 (100/64/10)

[a] Based on **3**.
[b] Products recrystallized from i-Pr_2O.
[c] Satisfactory microanalyses obtained: C ±0.38, H ±0.15, N ±0.22.

Table 3. 5-(Arylhydroxymethyl)-2-pyrazinecarboxylic Acids **5** Prepared[a,b]

Product	Molecular Formula[c]	IR (KBr) $\nu_{(C=O)}$ (cm^{-1})	^{1}H-NMR δ, J(Hz)	MS m/z (%)
5a	$C_{12}H_{10}N_2O_3 \cdot 1\frac{1}{4}H_2O$ (252.7)	1690	6.50 (br, 1H, CHOH); 7.20–7.59 (m, 5H, phenyl); 5.92, 9.06, 9.12 (ABX system, 3H, J_{AB} = 1.3, H-3, H-6, CHOH)	230 (M^+, 100)
5b	$C_{13}H_{12}N_2O_3$ (224.3)	1703	2.25 (s, 3H, CH_3); 6.42 (br, 1H, CHOH); 7.16, 7.37 (AA'BB' system, 4H, J = 8.7, phenyl); 5.89, 9.02, 9.12 (ABX system, 3H, J_{AB} = 1.4, H-3, H-6, CHOH)	244 (M^+, 49); 121 (100)
5c	$C_{13}H_{12}N_2O_4 \cdot \frac{1}{4}H_2O$ (264.8)	1690	3.72 (s, 3H, OCH_3); 6.40 (br, 1H, CHOH); 6.91, 7.37 (AA'BB' system, 4H, J = 8.7, phenyl); 5.86, 9.01, 9.09 (ABX system, 3H, J_{AB} = 1.4, H-3, H-6, CHOH)	260 (M^+, 2); 44 (100)
5d	$C_{12}H_9FN_2O_3 \cdot H_2O$ (266.2)	1692	6.67 (br, 1H, CHOH); 7.03–7.70 (m, 4H, phenyl); 6.17, 9.08, 9.12 (ABX system, 3H, J_{AB} = 1.3, H-3, H-6, CHOH)	248 (M^+, 53); 125 (100)
5e	$C_{12}H_9FN_2O_3$ (248.2)	1712	6.58 (br, 1H, CHOH); 7.04–7.68 (m, 4H, phenyl); 5.95, 9.07, 9.13 (ABX system, 3H, J_{AB} = 1.3, H-3, H-6, CHOH)	248 (M^+, 41); 125 (100)
5f	$C_{12}H_9BrN_2O_3$ (309.1)	1712	6.59 (br, 1H, CHOH); 7.41, 7.57 (AA'BB' system, 4H, J = 8.7, phenyl); 5.91, 9.03, 9.11 (ABX system, 3H, J_{AB} = 1.4, H-3, H-6, CHOH)	308/310 (M^+, 21/19); 44 (100)
5g	$C_{12}H_9ClN_2O_3 \cdot \frac{1}{4}H_2O$ (269.2)	1720	6.72 (br, 1H, CHOH); 7.28–7.61 (m, 4H, phenyl); 5.95, 9.09, 9.18 (ABX system, 3H, J_{AB} = 1.4, H-3, H-6, CHOH)	264/266 (M^+, 39/13); 77 (100)
5h	$C_{12}H_9ClN_2O_3$ (264.7)	1712	6.60 (br, 1H, CHOH); 7.39, 7.52 (AA'BB' system, 4H, J = 8.7, phenyl); 5.96, 9.03, 9.12 (ABX system, 3H, J_{AB} = 1.4, H-3, H-6, CHOH)	264/266 (M^+, 47/16); 77 (100)
5i	$C_{12}H_8Cl_2N_2O_3$ (299.1)	1712	6.71 (br, 1H, CHOH); 7.36–7.82 (m, 3H, phenyl); 5.99, 9.08, 9.15 (ABX system, 3H, J_{AB} = 1.4, H-3, H-6, CHOH)	298/300/302 (M^+, 18/11/2); 124 (100)

[a] Characteristic melting points cannot be determined due to sublimation and/or decarboxylation.
[b] The yields of compounds **5** are quantitative.
[c] Satisfactory microanalyses obtained: C ±0.39, H ±0.32, N ±0.23.

serves as a protecting group against diaroylation and, in addition, activates the heteroaromatic system for the attack by nucleophilic carbon-centered radicals.

As shown in Table 1, reactions of **1** with aroyl radicals, generated from various aromatic carbaldehydes according to a reported procedure,[16] afford reasonable yields[17] of 5-aroyl-2-pyrazinecarboxylic acids **3a–i**, which are conveniently separated by precipitation from the reaction mixtures upon addition of water. Analytically pure products are obtained in 13–41% yield by recrystallization from ethanol.

In addition, we also succeeded in preparing of 5-acyl-2-pyrazinecarboxylic acids by homolytic substitution of **1** employing acetyl and butanoyl radicals. However, due to low yields, these oxocarboxylic acids cannot be considered as appropriate intermediates for preparing alkyl pyrazinyl ketones.

^{1}H-NMR data enabled us to assign the pyrazine substitution pattern for compounds **3b, c, d, j,** and **k** ($J_{3,6}$ = 1.3–1.5 Hz; see Table 1 and experimental section); the signals of the two pyrazine protons in the spectra of compounds **3a,e–i**, however, did not permit the determination of coupling constants. In this case structure proof unambigously follows from evaluation of the ^{1}H-NMR spectra of the alcohols **5** (Table 3), obtained in quantitative yields upon reduction by sodium borohydride. Due to the markedly different electronic effects of the substituents in compounds **5a–i**, the pyrazine ring protons form two well separated signals. The observed coupling constants J = 1.3–1.4 Hz correspond to the values reported in the literature[18] for *para* substituted pyrazines.

The oxocarboxylic acids **3a–i** were found to decarboxylate smoothly when heated in a Kugelrohr apparatus, affording the target monoaroylpyrazines **4a–i** in satisfactory yields (Table 2). The analytical and spectral data of all novel compounds are in full agreement with the assigned structures. Structure proof of compounds **4a–c** rests on comparison with authentic samples.[19]

The proposed procedure provides access to a variety of aryl pyrazinyl ketones under very simple experimental conditions starting from commercially available, low cost 2-pyrazinecarboxylic acid (**1**), and thus appears to be advantageous in comparison to methods previously used[11,19,20,21] for the preparation of these important synthetic building blocks.

Melting points (uncorrected) were determined with a Kofler apparatus. IR spectra were recorded on a Jasco IRA-1 spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM 390 (90 MHz), using DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were obtained on a Varian MAT 311A and on a Hewlett Packard HP5970-MSD.

5-Aroyl-2-pyrazinecarboxylic Acids 3; General Procedure:
To a stirred mixture of the carbaldehyde **2** (120 mmol), and pyrazinecarboxylic acid (**1**; 4.96 g, 40 mmol) in 50% H_2SO_4 (80 mL), AcOH is added until complete solution of the carbaldehyde is achieved (max. 200 mL). To this mixture 80% *t*-BuOOH (13.5 g, 120 mmol) and a solution of $FeSO_4 \cdot 7H_2O$ (33.4 g, 120 mmol) in water are added simultaneously at 3–10 °C. The resulting mixture is stirred for additional 60 min, during which the temperature is allowed to rise to 20 °C. The reaction product is precipitated by dilution with water (200 mL). [The reaction products of **1** with acetyl and butanoyl radicals (**3j** and **3k**, respectively) are isolated after exhaustive extraction with CH_2Cl_2, followed by evaporation of the solvent *in vacuo*]. The precipitate is washed with CH_2Cl_2; analytically pure compounds **3a–k** are obtained by recrystallization from EtOH/charcoal. (For data of compounds **3a–i** see Table 1).

5-Acetyl-2-pyrazinecarboxylic acid (**3j**): Yellow crystals; yield: 0.8 g (12%).

$C_7H_6N_2O_3$	calc.	C 50.61	H 3.64	N 16.86
(166.1)	found	50.25	3.66	16.76

IR (KBr): $\nu_{(C=O)}$ = 1722, 1690 cm^{-1}.

^{1}H-NMR: δ = 2.71 (s, 3H, CH_3); 9.23, 9.32 (2 d, 2H, J = 1.4 Hz, pyrazine).

MS (70 eV): m/z (%) = 166 (M^+, 12), 43 (100).

5-Butanoyl-2-pyrazinecarboxylic acid (**3k**): Yellow crystals; yield: 0.24 g (3%).

$C_9H_{10}N_2O_3 \cdot \frac{1}{8} H_2O$	calc.	C 55.03	H 5.26	N 14.26
(196.4)	found	55.01	5.17	14.31

IR (KBr): $\nu_{(C=O)}$ = 1685 cm^{-1}.

^{1}H-NMR: δ = 0.96 (t, 3H, J = 7.5 Hz, $CH_2C\underline{H}_3$); 1.46–1.84 (m, 2H, $C\underline{H}_2CH_3$); 3.17 (t, 2H, J = 7.2 Hz, $COCH_2$); 9.23, 9.33 (2 d, 2H, J = 1.3 Hz, pyrazine).

MS (70 eV): m/z (%) = 194 (M^+, 3), 43 (100).

Melting points for **3j, k** could not be determined due to sublimation and/or decomposition.

2-Aroylpyrazines 4; General Procedure:
A mixture of 5-aroyl-2-pyrazinecarboxylic acid **3** (300 mg) with copper powder (300 mg) is distilled (temperatures: **3a**: 150 °C; **3b**: 180 °C; **3c**: 245 °C; **3d**: 140 °C; **3e**: 200 °C; **3f**: 180 °C; **3g**: 210 °C; **3h**: 170 °C; **3i**: 215 °C) in a Kugelrohr apparatus under reduced pressure. Analytically pure compounds **4a–i** (for data see Table 2) are obtained by recrystallization from i-Pr_2O.

5-(Arylhydroxymethyl)-2-pyrazinecarboxylic Acids 5; General Procedure:
To a stirred solution of **3** (1 mmol) in EtOH (80 mL), $NaBH_4$ (190 mg, 5 mmol) is added and the solution is stirred for an additional 20 min at room temperature. The reaction mixture is then suction filtered and the solvent removed *in vacuo* to yield a residue, which is dissolved in 2N $NaHCO_3$ solution. Products are then precipitated by addition of 2N HCl, washed with water and dried *in vacuo* to yield analytically pure compounds **5a–i** (for data see Table 3).

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