Homolytic Acylation of Methyl 3-Amino-2-pyrazinecarboxylates

W. Ried,* Th. Russ[1]

Institut für Organische Chemie der Universität Frankfurt am Main, Laboratorium Niederrad, Theodor-Stern-Kai 7, D-6000 Frankfurt a.M. 70, Germany

Homolytic acylation of methyl 3-amino-2-pyrazinecarboxylates **1a–c** under standard Minisci conditions affords the corresponding 5- or 6-monoacylated pyrazines **3a–d** or **4a,b** in reasonable yields. With **1a**, complete selectivity in favor of the 5-acyl products is observed.

As first shown by Minisci and co-workers,[2] homolytic substitution of strongly electron-deficient nitrogen heteroaromates by nucleophilic radicals, e.g. alkyl, acyl, α-oxyalkyl, alkoxycarbonyl, and aminocarbonyl, provides a general and convenient method for adding functionality to such otherwise rather poorly reactive compounds.

Due to the high reactivity of these short-lived intermediates, some lack of selectivity and a tendency for polysubstitution are two major difficulties frequently accompanying these reactions and have been subject of further investigations in this field.[3–7]

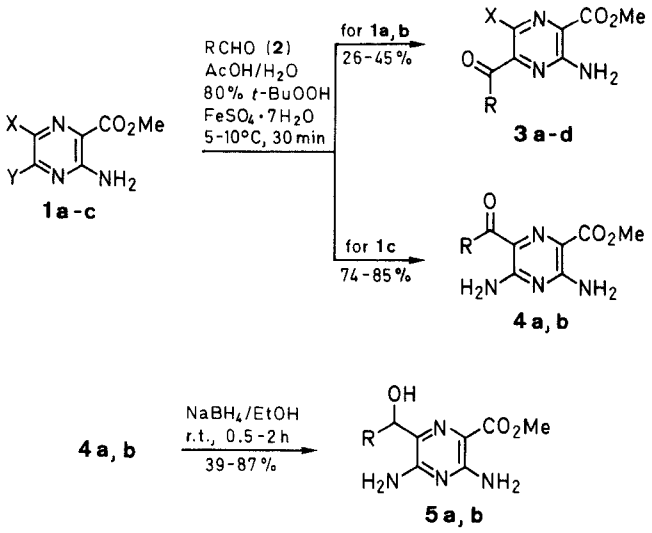
During our recent work on pyrazines and pteridines, we have applied this method to the acylation of methyl 3-amino-, 3-amino-6-bromo- and 3,5-diamino-2-pyrazinecarboxylates **1a–c** by aromatic or aliphatic aldehydes **2**, using a mixture of acetic acid and water as solvent and iron(II) sulfate/*tert*-butyl hydroperoxide as the redox system.

In each case, a single monoacyl product was isolated within 30 minutes upon addition of water to the reaction mixture.

Yields were generally markedly improved when the amino-2-pyrazinecarboxylates (which are only sparingly soluble as their acetates) were finely suspended in the reaction medium by means of an ultrasound bath prior to cooling and addition of the reagents.

For compound **1a**, complete selectivity in favor of the 5-substituted products **3a–c** was established from their spectral data (^{1}H- and ^{13}C-NMR) and independently proven by subsequent bromination of **3c** to yield **3d**, which is also obtained by homolytic benzoylation of **1b**.

With **1c**, the expected 3,5-diamino-6-acyl derivatives **4a,b** were formed, which could be further reduced to the corresponding alcohols **5a,b** by sodium borohydride in ethanol.



1	X	Y	2	R	3	X	R	4,5	R
a	H	H	a	Me	a	H	Me	a	Me
b	Br	H	b	Et	b	H	Et	b	Ph
c	H	NH_2	c	Ph	c	H	Ph		
					d	Br	Ph		

Melting points (uncorrected) were determined with a Gallenkamp MFB-595 apparatus. IR spectra (KBr) were recorded on a Perkin-Elmer 398 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on Varian XL 200 and VXR 300 instruments.

Table 1. Homolytic Acylation of 3-Amino-2-pyrazinecarboxylates **1a–c**

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})
3a	31	229–231 (MeOH)	$C_8H_9N_3O_3$ (195.2)	3420 (s), 3250 (s-m), 3180 (s-m), 3130 (s-m, NH), 2960, 2840 (w, CH_3), 1690 (br s, 2 × C=O), 1610 (br s, C=N, C=C)
3b	41	200–202 (MeOH)	$C_9H_{11}N_3O_3$ (209.2)	3440 (s), 3250 (s-m), 3180 (s-m), 3130 (s-m, NH), 2980–2820 (m-w, CH_{aliph}), 1690 (br s, 2 × C=O), 1610 (br s, C=N, C=C)
3c	45	166–167 (EtOH)	$C_{13}H_{11}N_3O_3$ (257.3)	3440 (s), 3260 (s), 3180 (s), 3130 (m, NH), 3050 (sh), 2990 (CH_{arom}), 2940, 2840 (w, CH_3), 1700 (s), 1655 (s, 2 × C=O), 1610, 1590 (s, C=N, C=C_{arom})
3d	26	172–173 (EtOH)	$C_{13}H_{10}BrN_3O_3$ (336.2)	3440 (s), 3330 (s), 3180 (w), 3120 (w, NH), 3060, 3000 (w, CH_{arom}), 2950, 2850 (w, CH_3), 1705 (s), 1675 (s, 2 × C=O), 1600 (br s, C=N, C=C_{arom})
4a	74	215–216 (EtOH)	$C_8H_{10}N_4O_3$ (210.2)	3460 (s), 3380 (s), 3350 (m), 3310 (s), 3270 (sh), 3160 (m, NH), 2980 (w), 2940, 2840 (w, CH_3), 1690, 1655 (s, 2 × C=O), 1625, 1585 (s, C=N, C=C_{arom})
4b	85	201–203 (EtOH)	$C_{13}H_{12}N_4O_3$ (272.3)	3470 (m), 3430 (s), 3330 (s), 3160 (m, NH), 3050, 3020 (sh, CH_{arom}), 2950, 2840 (w, CH_3), 1690 (s), 1665 (m, 2 × C=O), 1630, 1660 (s), 1590 (s, C=N, C=C)

[a] Satisfactory microanalyses obtained: C, H, N ±0.3.

Table 2. NMR Data of Compounds **3, 4** Prepared

Compound	^{1}H-NMR (DMSO-d_6/TMS), δ, J (Hz)	^{13}C-NMR (DMSO-d_6/TMS), δ
3a	2.57 (s, 3H, $COCH_3$), 3.88 (s, 3H, CO_2CH_3), 7.58 (s, 2H, NH_2), 8.32 (s, 1H, CH)	–
3b	1.07 (t, 3H, J = 7.2, CH_2CH_3), 3.08 (q, 2H, J = 7.2, CH_2CH_3), 3.87 (s, 3H, OCH_3), 7.56 (s, 2H, NH_2), 8.32 (s, 1H, CH)	7.5 (CH_2CH_3), 30.7 (CH_2CH_3), 52.4 (CO_2CH_3), 125.8 (C2), 129.5 (C6), 147.9 (C5), 154.7 (C3), 165.1 (CO_2CH_3), 201.5 (COEt)
3c	3.91 (s, 3H, CH_3), 7.28 (br s, 2H, NH_2), 7.53–7.97 (m, 5H_{arom}), 8.27 (s, 1H, CH)	52.8 (OCH_3), 129 (C3′, C5′), 130.9 (C2′, C6′), 132 (C4′), 134.1 (C6), 136 (C1′), 152 (C5), 154.6 (C3), 192.7 (COPh)[a]
3d	3.9 (s, 3H, CH_3), 7.5–7.9 (m, 5H_{arom}), 7.8 (br, 2H, NH_2)	52.5 (OCH_3), 117.4 (C2), 124.2 (C6), 129.2 (C3′, C5′), 129.9 (C2′, C6′), 133.5 (C1′), 135.1 (C4′), 153.9 (2 signals C2, C3), 164.5 (CO_2CH_3), 191.6 (COPh)
4a	2.47 (s, 3H, $COCH_3$), 3.80 (s, 3H, CO_2CH_3), 7.62 (s, 1H, NH), 7.68 (s, 2H, NH_2), 8.25 (s, 1H, NH)	25.1 ($COCH_3$), 51.6 (OCH_3), 114.4 (C2), 123 (C6), 156 (C5), 156.8 (C3), 165.7 (CO_2CH_3), 198.5 ($COCH_3$)
4b	3.75 (s, 3H, CH_3), 7.4–8.1 (m, 8H, 5H_{arom}, 3NH), 8.46 (br s, 1H, NH)	51.7 (CO_2CH_3), 113.8 (C2), 121.3 (C6), 127.4 (C3′, C5′), 130.5 (C2′, C6′), 131.2 (C4′), 138.3 (C1′), 156 (C5), 157.3 (C3), 165.7 (CO_2CH_3), 191.2 (COPh)

[a] Two quaternary C-atoms not resolved.

Homolytic Acylation of Methyl 3-Amino-2-pyrazinecarboxylates 1; General Procedure:

The appropriate methyl 3-amino-2-pyrazinecarboxylate **1** (10 mmol) is finely suspended in a mixture of AcOH (30 mL) and H_2O (20 mL) by means of an ultrasound bath during 10 min and then cooled to 5–7 °C. After addition of the aldehyde **2** (30 mmol), a solution of $FeSO_4 \cdot 7H_2O$ (5.6 g, 20 mmol) in H_2O (10 mL) and 80% *t*-BuOOH (2.2 g, 20 mmol) are simultaneously added and the mixture is stirred for additional 30 min, allowing the temperature to rise to about 10 °C. Upon addition of cold H_2O (50–60 mL), the product is isolated by filtration, washed with H_2O, and dried. Purified samples are obtained by recrystallization from MeOH or EtOH.

Methyl 3,5-Diamino-6-(α-hydroxybenzyl)-2-pyrazinecarboxylate (5b); Typical Procedure:

To a stirred suspension of the amino ketone **4b** (545 mg, 2 mmol) in abs. EtOH (200 mL) $NaBH_4$ (380 mg, 20 mmol) is added in two portions, and the resulting solution is stirred for 2 h. Excessive $NaBH_4$ is destroyed by addition of 1 N HCl (20 mL) and the mixture is taken to dryness on a rotary evaporator. To the residue H_2O is added (40 mL), and the mixture is made slightly alkaline with sat. aq $NaHCO_3$. The product is extracted with EtOAc (3 × 50 mL), the organic phase dried (Na_2SO_4), and the solvent removed *in vacuo*. The residue is then stirred with Et_2O/pentane, isolated by filtration and dried; yield: 478 mg (87%); mp 162–164 °C (dec.).

IR (KBr): ν = 3480 (s), 3460 (s), 3415 (s), 3360 (s), 3305 (s, NH, OH), 1680 (m, C=O), 1655 (s), 1610 (s), 1590 (s, C=N, C=C_{arom}).

Methyl 3,5-Diamino-6-(1-hydroxyethyl)-2-pyrazinecarboxylate **(5a)**: yield: 39%; mp 198–200 °C (dec.).

IR (KBr): ν = 3420 (s), 3300 (s), 3190 (br s, NH, OH), 1690 (s, C=O), 1635 (s), 1605 (s, C=N, C=C).

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