Studies on Pyrazine. 23 [1]. Homolytic Acylation of 2-Amino-3-cyanopyrazine and the Related Compounds with α-Keto Acids: A Synthesis of 5-Acyl-3-aminopyrazinecarboxylic Acid Derivatives

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Received July 14, 1992

Homolytic acylation of 2-amino-3-cyanopyrazine (**1**) with α-keto acids led to the formation of 6-acylated compounds in 74-85% yields. Methyl 3-aminopyrazinecarboxylate (**2**) and 3-aminopyrazinecarboxamide (**3**) were also acylated under the same conditions although in lower yields. The observed reactivity of acylation is explained by comparison with the homolytic reactions of related pyrazines.

J. Heterocyclic Chem., **29**, 1685 (1992).

Homolytic acylation is certainly a unique methodology for introducing a carbonyl functionality directly into electron-deficient nitrogen heteroaromatics [2] inert to the Friedel-Crafts aromatic substitution. A variety of syntheses for parent [3], alkyl [4,5], methoxy [5], chloro [5], acyl [3,5], ethoxycarbonyl [5], carbamoyl [5], and carboxy [6] substituted acylpyrazines was achieved by the radical reaction using the *tert*-butyl hydroperoxide/ferrous sulfate redox system in the presence of aldehydes. In the course of our work on the synthesis of pyrazines, we were interested in the homolytic acylation of 2-amino-3-cyanopyrazine (**1**) because of its potential as useful building blocks for the synthesis of functionalized pteridine compounds. This paper reports a successful acylation of the above **1** as well as methyl 3-aminopyrazinecarboxylate (**2**), 3-aminopyrazinecarboxamide (**3**) and related pyrazines with a different source of acyl radicals involving silver-catalyzed oxidative decarboxylation of α-keto acids by persulfate [7].

The homolytic reactions were carried out in 1*N* sulfuric acid at 40°, and the results are summarized in Table 1. The yields of 60-85% in acylation of **1** to **4a-c** were emphasized as compared with the earlier preparation of pyrazinyl ketones obtained usually in 20-30% yields sometimes reaching 50%. Most recently [8] preceding this project, homolytic acylation of the ester **2** with aldehydes in aqueous acetic acid was reported to furnish the same products **5a-c** in 31-45% yields. To determine the site of substitution, ketone **4b** was subjected to reduction with triethylsilane and boron trifluoride, but a 40% yield of the α-hydroxypropyl compound **7** was obtained only instead of the desired propylpyrazine comparable with an authentic 2-amino-3-cyano-5-propylpyrazine [9]. An attempt to positively establish the structure by the coupling constant of the disubstituted pyrazine in the ^{1}H nmr spectrum [10] was also frustrated by the inhibition of decarboxylation of the hydrolysis product from **4b** or its hydrazine-reducing material. Consequently, **4b** was confirmed to be 2-amino-3-cyano-6-propionylpyrazine independently prepared by acylation of 2-amino-3-cyano-5-bromopyrazine followed by reductive debromination of the resulting tetrasubstituted compound **8**. Meanwhile, the nitrile **4c** underwent oxidative hydrolysis with hydrogen peroxide yielding the carboxamide which was identified with **6c**.

The reactivity and regioselectivity of homolytic acylation are opposite to those of the traditional electrophilic aromatic acylation due to the nucleophilic character of the acyl radical [11]. This feature of the reaction is clearly exemplified by the behavior of various monosubstituted pyrazines on the radical reactions [5]. For instance, an electron-withdrawing acyl, ethoxycarbonyl, or carbamoyl

Table 1

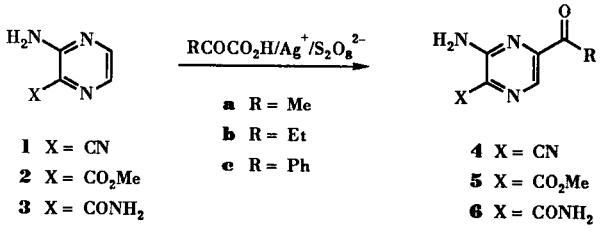
Homolytic Acylation of Aminopyrazine Derivatives by α-Keto acids

Starting material	Substituent X	Product	Substituent R	Yield (%) H_2O [a]	Yield (%) H_2O/CH_2Cl_2 [a]
1	CN	**4a**	Me	60	74
		4b	Et	75	74
		4c	Ph	85	81
2	CO_2Me	**5a**	Me	10	51
		5b	Et	50	53
		5c	Ph	47	51
3	$CONH_2$	**6a**	Me	≈0	20
		6b	Et	9	25
		6c	Ph	63	45

[a] Solvent system.

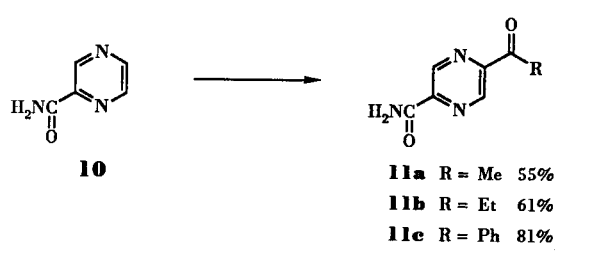
group provokes the substitution reaction at the *para* position. This direction is compatible with that in the acylation of **1** regardless of carrying an additional amino substituent. That amino group is strongly electron-donating but is protonated in the acidic medium to dissipate the distinctive electronic influence. The resulting ammonium group is conversely electron-withdrawing, but the homolytic reaction of 2-aminopyrazine (**9**) with 2-ketobutyric acid led to 2-amino-3-propionyl- and 2-amino-3,6-dipropionylpyrazines in less than a 10% combined yields with no reproducible ratio. In comparison with the radical reaction of the parent pyrazine giving a 17% yield of 2-propionylpyrazine, the amino group of **1** evidently impedes the homolytic acylation. The ammonium moiety preferably plays an important role in increasing the solubility of the substrate in acidic reaction mixture.

Scheme 1



In contrast, the amino group of carboxamide **3** prevents strikingly the homolytic substitution, especially the formation of **6a,b**. The reduction of their yields affected by the substituent is evident in comparison with acylation of pyrazinecarboxamide (**10**) which products **11a-c** were now found to be increased to 55-81% yields (Scheme 2) by changing the radical source to the α-keto acids from aldehyde in only 25% for **11b** [5]. Similar suppression was observed in homolytic acylation of the ester **2**. A discernible decrease in yields of **5** and **6** is presumably rationalized to exhibit the mesomeric interaction of the methoxycarbonyl or the carbamoyl functionality with the pyrazine ring by the steric hindrance with the adjacent ammonium group. Conversely, acylation in **2** and **3** could be attributed to control by the inductive effect of the substituent without the mesomeric one.

Scheme 2



An interesting item to note is that a dichloromethane/water two-phase system is effective for improving of acetylation. The observed outcome in the solvent system is more conceivable than that in the aqueous one on taking into account the strength of the substituent effects as well as the stability of the acyl radicals. We have not yet clarified the reason why the acetylation is only restricted in aqueous media and improved in the two-phase solvent system but the work is in progress.

EXPERIMENTAL

All melting points were taken on a Büchi 535 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded on a JACSO IR-810 spectrometer. The ^1H and ^{13}C nmr spectra were measured in dimethyl sulfoxide-d_6 with tetramethylsilane as the internal standard and recorded on a JEOL JNM EX270 instrument.

General Procedure of the Homolytic Acylation.

To a solution of the substrate (1.0 mmole), ammonium persulfate (1.14 g, 5.0 mmoles), silver nitrate (26 mg, 0.15 mmole) in 1*N* sulfuric acid (18 ml, 9.0 mmoles) was added under argon the α-keto acid (1.3 mmoles), and the resulting solution was stirred and heated at 40° for 2 hours. After cooling to room temperature, the solution was basified at *p*H 8 with sodium hydrogen carbonate. The precipitate which formed was collected by filtration, and the mother liquor was extracted with ethyl acetate (3 x 25 ml). The combined precipitates and extracts were evaporated and then subjected to flash chromatography over silica gel. Analytical samples were obtained by recrystallization. Isolated yields are summarized in Table 1 and Scheme 2, unless otherwise noted.

2-Acetyl-6-amino-5-cyanopyrazine (**4a**).

This compound was obtained as pale yellow needles (benzene), mp 214°; ir: 3360, 3160, 2220, 1700, 1650, 1220 cm^{-1}; ^1H nmr: δ 2.54 (s, 3H), 7.61 (br s, 2H), 8.27 (s, 1H); ^{13}C nmr: δ 25.7, 114.1, 115.5, 130.6, 147.6, 156.1, 198.7.

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.95; H, 3.74; N, 34.50.

2-Amino-3-cyano-6-propionylpyrazine (**4b**).

This compound was obtained as pale yellow needles (benzene), mp 195-196°; ir: 3390, 3160, 2200, 1705, 1650, 1220 cm^{-1}; ^1H nmr: δ 1.07 (t, J = 7.3 Hz, 3H), 3.04 (q, J = 7.3 Hz, 2H), 7.59 (br s, 2H), 8.27 (s, 1H); ^{13}C nmr: δ 7.4, 30.7, 114.1, 115.5, 130.6, 147.5, 156.6, 201.0.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.75; H, 4.58; N, 31.86.

2-Amino-6-benzoyl-3-cyanopyrazine (**4c**).

This compound was obtained as pale yellow needles (benzene), mp 185-186°; ir: 3420, 3150, 2230, 1640, 1550, 1205 cm^{-1}; ^1H nmr: δ 7.51-7.95 (m, 5H), 7.63 (br s, 2H), 8.25 (s, 1H); ^{13}C nmr: δ 113.4, 115.6, 130.5, 132.4, 133.9, 135.0, 150.8, 155.5, 192.0.

Anal. Calcd. for $C_{12}H_8N_4O$: C, 64.28; H, 3.60; N, 24.99. Found: C, 64.70; H, 3.48; N, 24.99.

Methyl 5-Acetyl-3-aminopyrazinecarboxylate (**5a**).

This compound was obtained as pale yellow crystals (methanol), mp 235-236°, lit [8] mp 229-231°; ir: 3440, 1690,

1610, 1210, 1110 cm^{-1}; ^1H nmr: δ 2.57 (s, 3H), 3.87 (s, 3H), 7.54 (br s, 2H), 8.30 (s, 1H); ^{13}C nmr: δ 25.8, 52.4, 129.2, 147.8, 154.5, 165.4, 180.8, 198.7.

Methyl 3-Amino-5-propionylpyrazine (**5b**).

This compound was obtained as pale yellow needles (methanol), mp 205-206°, lit [8] mp 200-202°; ir: 3460, 1700, 1615, 1115 cm^{-1}; ^1H nmr: δ 1.07 (t, J = 7.3 Hz, 3H), 3.07 (q, J = 7.3 Hz, 2H), 3.86 (s, 3H), 7.51 (br s, 2H), 8.28 (s, 1H); ^{13}C nmr: δ 7.4, 30.7, 52.4, 125.9, 129.5, 147.9, 154.7, 165.7, 201.4.

Methyl 3-Amino-5-benzoylpyrazinecarboxylate (**5c**).

This compound was obtianed as yellow needles (ethanol), mp 167-168°, lit [8] mp 166-167°; ir: 3450, 1705, 1615, 1330, 1190 cm^{-1}; ^1H nmr: δ 3.90 (s, 3H), 7.54-8.00 (m, 5H), 7.60 (br s, 2H), 8.30 (s, 1H); ^{13}C nmr: δ 52.4, 125.2, 128.5, 130.5, 131.3, 133.8, 135.2, 151.1, 154.2, 165.8, 192.3.

5-Acetyl-3-aminopyrazinecarboxamide (**6a**).

This compound was obtained as yellow tiny needles (2-propanol), mp 231-322° dec; ir: 3500, 3350, 1650, 1590, 1150, 690 cm^{-1}; ^1H nmr: δ 2.56 (s, 3H), 7.73 (br s, 2H), 7.80 (br s, 1H), 8.20 (br s, 1H), 8.22 (s, 1H); ^{13}C nmr: δ 25.7, 128.2, 128.5, 147.8, 154.3, 167.7, 199.1.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.67; H, 4.48; N, 31.10. Found: C, 47.01; H, 4.44; N, 30.74.

3-Amino-5-propionylpyrazinecarboxamide (**6b**).

This compound was obtained as yellow tiny needles (2-propanol), mp 191-192°; ir 3500, 3420, 3360, 1670, 1580, 1210, 920 cm^{-1}; ^1H nmr: δ 1.07 (t, J = 7.3 Hz, 3H), 3.68 (q, J = 7.3 Hz, 2H), 7.72 (br s, 3H), 8.19 (br s, 1H), 8.21 (s, 1H); ^{13}C nmr: δ 7.5, 30.7, 128.2, 128.5, 147.7, 154.3, 167.7, 201.5.

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.56; H, 4.93; N, 28.69.

3-Amino-5-benzoylpyrazinecarboxamide (**6c**).

This compound was obtined as yellow crystals (2-propanol), mp 173-174°; ir: 3450, 3400, 1660, 1580, 1190, 900, 700 cm^{-1}; ^1H nmr: δ 7.54-7.99 (m, 5H), 7.77 (br s, 2H), 8.20 (s, 1H), 8.25 (br s, 2H); ^{13}C nmr: δ 127.7, 128.4, 130.1, 130.4, 133.6, 135.4, 150.6, 153.7, 167.8, 192.3.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.63; H, 3.83; N, 22.70.

2-Amino-6-benzoyl-5-bromo-3-cyanopyrazine (**8**).

This compound was obtained in 57% yield as pale yellow needles (hexane-ethyl acetate), mp 159-160°; ir: 3380, 3210, 2220, 1680, 1650, 1540, 1200, 890 cm^{-1}; ^1H nmr: δ 7.57-7.93 (m, 5H), 7.87 (br s, 2H); ^{13}C nmr: δ 112.1, 114.7, 118.1, 129.2, 130.1, 133.5, 135.2, 153.8, 155.5, 191.0.

Anal. Calcd. for $C_{12}H_7N_4OBr$: C, 47.55; H, 2.33; N, 18.48. Found: C, 47.69; H, 2.18; N, 18.38.

5-Acetylpyrazinecarboxamide (**11a**).

The compound was obtained as colorless prisms (2-propanol), mp 253° dec; ir: 3450, 3200, 1670, 1270, 1030 cm^{-1}; ^1H nmr: δ 2.67 (s, 3H), 7.97 (br s, 1H), 8.36 (br s, 1H), 9.07 (d, J = 1.4 Hz, 1H), 9.25 (d, J = 1.4 Hz, 1H); ^{13}C nmr: δ 25.9, 141.2, 142.7, 147.2, 148.6, 164.3, 198.4.

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.89; H, 3.99; N, 25.33.

5-Propionylpyrazinecarboxamide (**11b**).

This compound was obtained as colorless crystals (2-propanol), mp 222°, lit [5] mp 217-218° dec; ir: 3430, 3200, 1700, 1670, 1030, 570 cm^{-1}; ^1H nmr: δ 1.12 (t, J = 7.0 Hz, 3H), 3.19 (q, J = 7.0 Hz, 2H), 7.97 (br s, 1H), 8.36 (br s, 1H), 9.07 (d, J = 1.4 Hz, 1H), 9.24 (d, J = 1.4 Hz, 1H); ^{13}C nmr: δ 7.4, 30.9, 141.2, 142.7, 147.2, 148.5, 164.3, 200.8.

5-Benzoylpyrazinecarboxamide (**11c**).

This compound was obtained as pale yellow tiny needles (2-propanol), mp 205°; ir: 3430, 3130, 1700, 1670, 1270, 680 cm^{-1}; ^1H nmr: δ 7.5-7.6 (m, 2H), 7.7-7.8 (m, 1H), 7.96-8.02 (m, 3H), 8.41 (br s, 1H), 9.16 (d, J = 1.4 Hz, 1H), 9.26 (d, J = 1.4 Hz, 1H); ^{13}C nmr: δ 128.4, 130.6, 133.7, 135.1, 142.0, 143.6, 146.3, 151.1, 164.4, 191.9.

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.40; H, 3.76; N, 18.30.

Reduction of 2-Amino-3-cyano-6-propionylpyrazine (**4b**) to 2-Amino-3-cyano-6-(1-hydroxypropionyl)pyrazine (**7**).

Triethylsilane (0.63 ml, 1.4 mmoles) was added under argon to a solution of **4b** (176 mg, 1.0 mmole) in boron trifluoride etherate (2.5 ml, 20 mmoles), and the resulting mixture was stirred at room temperature for 48 hours. After adding saturated aqueous sodium chloride, the mixture was extracted with chloroform (3 x 25 ml). The extracts were washed with saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluted with hexane-ethyl acetate (5:1) to give colorless prisms (72 mg, 44%). The analytical sample was prepared by recrystallization from benzene as colorless crystals, mp 109-110°; ir: 3380, 3170, 2210, 1660, 1560, 1440, 1200 cm^{-1}; ^1H nmr: δ 0.86 (t, J = 7.8 Hz, 3H), 1.63 (d of q, J = 7.8, 5.0 Hz, 2H), 4.37 (q, J = 5.0 Hz, 1H), 5.51 (d, J = 5.0 Hz, 1H), 7.22 (br s, 2H), 7.98 (s, 1H); ^{13}C nmr: δ 9.6, 29.6, 73.0, 109.1, 116.2, 131.3, 156.0, 162.9.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.71; H, 5.62; N, 31.28.

Reductive Debromination of 2-Amino-6-benzoyl-5-bromo-3-cyanopyrazine (**8**) to **4c**.

A mixture of **8** (156 mg, 0.54 mmole), sodium formate (37 mg, 0.54 mmole) and tetrakis(triphenylphosphine)palladium (62 mg, 0.054 mmole) in dry DMF (3 ml) was stirred under argon and heated at 100° for 2 hours. The resulting mixture was evaporated *in vacuo*, and the residue was triturated with ethyl acetate. An insoluble matter was removed by filtration and the filtrate was evaporated. Column chromatography of the residue on silica gel (10 g) eluted with hexane-ethyl acetate (4:1 to 1:1) gave **4c** (65 mg, 58%), mp 183-184°, which was identified with the authentic sample in all respects.

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