Novel Syntheses of Heterocycles from α-Oxonitriles; Part III.[1] 2-Amino-3-arylpyrazines

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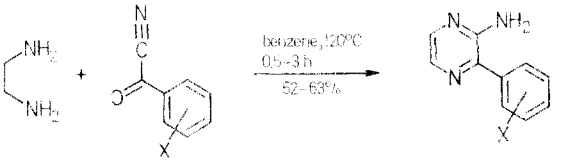
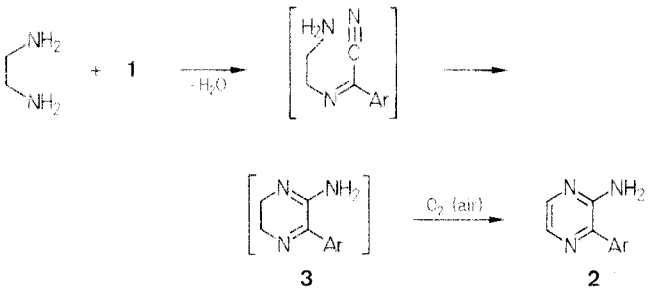
A facile synthesis of 2-amino-3-arylpyrazines **2** by the interaction of equimolecular amounts of α-oxonitriles (aroyl cyanides) **1** with ethylenediamine in refluxing benzene is described.

In connection with our investigations[2,3] on the preparation of novel heterocycles from the reaction of α-oxonitriles (aroyl cyanides) **1** with bidentate nucleophiles, we report here a facile synthesis of 2-amino-3-arylpyrazines **2** from **1** and ethylenediamine. The heteroaromatic ring formed simply by heating the regaents in benzene at 120°C in an oil bath. Other routes to 2-aminopyrazines and their 3-carboxamide derivatives are *via* the condensation of 1,2-dicarbonyl compounds with aminoacetamidine[4] and aminomalonamide,[5] respectively.



1a-e **2a-e**

The synthesis of 2-amino-3-arylpyrazines **2a–e** from aroyl cyanides **1a–e** and ethylenediamine usually proceeds in good yields and invariably without the formation of any by-products. A plausible reaction mechanism is suggested below. Ethylenediamine condenses with **1** through one of its amino groups forming an intermediate which cyclizes by attack of the remaining amino group to the nitrile function to form a dihydropyrazine derivative **3**. The latter oxidizes spontaneously by air to form the heteroaromatic 2-amino-3-arylpyrazines **2**.



3 **2**

1, 2	X	1, 2	X
a	H	**d**	4-Cl
b	3-CH_3	**e**	4-NO_2
c	4-CH_3		

Such dihydropyrazines are in fact known to oxidize readily by means of air[6,7] to give the corresponding pyrazines. An electron withdrawing group (e.g., chloro or nitro) at the *para* position in the aroyl cyanides requires heating for a relatively shorter period (see Table). The reaction fails with *o*-toluoyl cyanide.

The structure of 2-amino-3-arylpyrazines was established on the basis of spectral (IR and ^{1}H-NMR) and microanalytical data and suitable derivatization (e.g. 2-Benzamido-3-phenylpyrazine, see experimental). Typically the IR spectrum of **2b** shows bands at 3470, 3390 and 3065 cm^{-1} for the NH_2 and aromatic C–H stretchings and at 1620 cm^{-1} for C=N stretching. Its ^{1}H-NMR spectrum shows overlapping multiplets of 6 H intensity for *m*-tolyl and pyrazine ring protons between $\delta = 7.00$–8.80. A broad signal of 2 H intensity is observed at $\delta = 3.20$–3.60 for the amino protons. A sharp singlet also appears at $\delta = 2.33$ (3 H intensity) for the methyl protons of *m*-tolyl group.

α-Oxonitriles **1** were prepared by known methods.[8,9]

2-Amino-3-phenylpyrazine (2a); Typical Procedure:

To a cold solution of ethylenediamine (1.2 g, 20 mmol) in dry benzene (15 mL) is added dropwise a solution of benzoyl cyanide (**1a**; 2.62 g, 20 mmol) in dry benzene (10 mL) during 2 h. The resulting solution

Table. 2-Amino-3-arylpyrazines **2** Prepared

Product	Reaction Time (h)	Yield (%)	m.p. (°C) (solvent)	Appearance	Molecular Formula[a]	IR (KBr or Nujol) ν (cm^{-1})[b]	^{1}H-NMR (DMSO-d_6/TMS) δ, J (Hz)[c]
2a	2	60	261 (C_6H_6)/EtOH, 1:1)	colorless	$C_{10}H_9N_3$ (171.2)	3300, 3100, 3080, 1640, 1580	–
2b	3	55	180 (C_6H_6)	colorless	$C_{11}H_{11}N_3$ (185.2)	3470, 3390, 3065, 1620, 1570	2.33 (s, 3H, CH_3); 3.20–3.60 (br, 2H, NH_2); 7.00–8.80 (m, 6H, *m*-tolyl and pyrazine ring protons)
2c	2	58	230 (C_6H_6)	colorless	$C_{11}H_{11}N_3$ (185.2)	3480, 3390, 3070, 1620, 1590	2.33 (s, 3H, CH_3); 3.73–4.20 (br, 2H, NH_2); 7.00–7.80 (q, 4H, J = 9, *p*-tolyl); 8.26 (s, 2H, pyrazine ring protons)
2d	1	52	274 (EtOH)	colorless	$C_{10}H_8ClN_3$ (205.7)	3400, 3280, 3080, 1610, 1580	–
2e	0.5	63	268 (EtOH)	yellow	$C_{10}H_8N_4O_2$ (216.2)	3320, 3120, 3080, 1620, 1580, 1530	–

[a] Satisfactory microanalyses obtained: C ±0.19, H ±0.34, N ±0.36.
[b] Recorded with a Perkin-Elmer 720 grating IR spectrophotometer.
[c] Recorded with a Jeol FX 90Q Fourier transform spectrometer.

becomes hot but no solid formation takes place. The mixture is heated under reflux at 120 °C for 2 h. The solution on cooling deposits white crystals of 2-amino-3-phenylpyrazine (**2a**). It is recrystallized from a mixture of benzene ethanol (1:1); yield (60%); m.p. 261 °C (Table).

2-Benzamido-3-phenylpyrazine:
Purified benzoyl chloride (1 mL) is added dropwise to a solution of 2-amino-3-phenylpyrazine (**2a**; 0.5 g, 3 mmol) in pyridine (5 mL). The mixture is stirred at 10 °C for 1 h, and then allowed to stand overnight at room temperature. The solid mass obtained is stirred with water, filtered and crystallized from ethanol to give colorless plates; yield (75%); m.p. 61 °C.

$C_{17}H_{13}N_3O$ (275.3) calc. C 74.18 H 4.72
found 74.34 4.38

IR (Nujol): ν = 3410 (br, NH), 1710 (s, C=O), 1620 (m), 1590 cm^{-1} (m).

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