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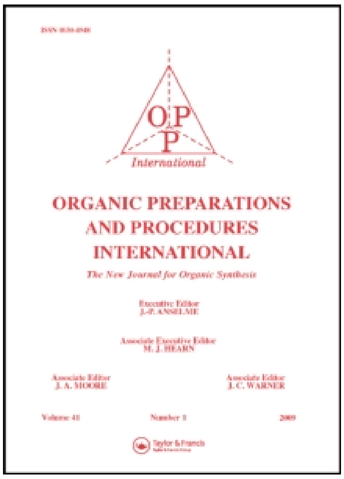

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A SIMPLE PREPARATION OF 2-UNSUBSTITUTED 4-AMINOOXAZOLES

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ORGANIC PREPARATIONS AND PROCEDURES INT. 21(2), 141-146 (1989)

A SIMPLE PREPARATION OF 2-UNSUBSTITUTED 4-AMINOOXAZOLES†

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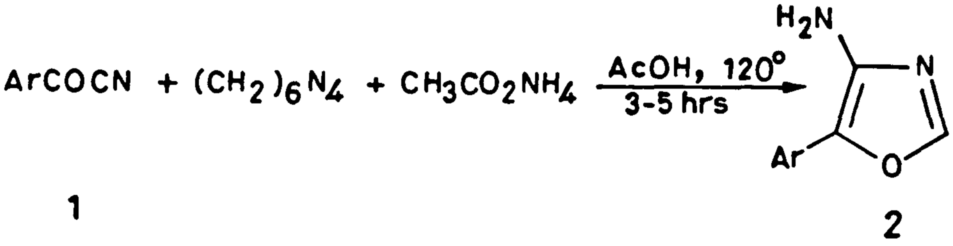
In continuation of our earlier work[1] on the utilization of α-oxonitriles 1 in heterocyclic syntheses and our interest in the oxazole chemistry,[2,3] we now report a simple preparation of 2-unsubstituted 4-amino-5-aryl-oxazoles 2 by heating a mixture of 1, hexamethylenetetramine and an excess of anhydrous ammonium acetate in glacial acetic acid under reflux at 120°C for 3-5 hrs. A literature survey reveals that there is no report of the synthesis of 4-aminooxazoles.



a) Ar = C_6H_5 b) Ar = 2-MeC_6H_4 c) Ar = 3-MeC_6H_4
d) Ar = 4-MeC_6H_4 e) Ar = 4-$MeOC_6H_4$ f) Ar = 4-ClC_6H_4
g) Ar = 4-$NO_2C_6H_4$

The present synthesis of 2a-g from 1a-g proceeds in moderate yields and affords the aminooxazoles as the only isolable product. In this reaction, ammonium acetate behaves as the source of ammonia[3,4] and hexamethylenetetramine as a precursor of formaldehyde.[5] A plausible reaction mechanism for

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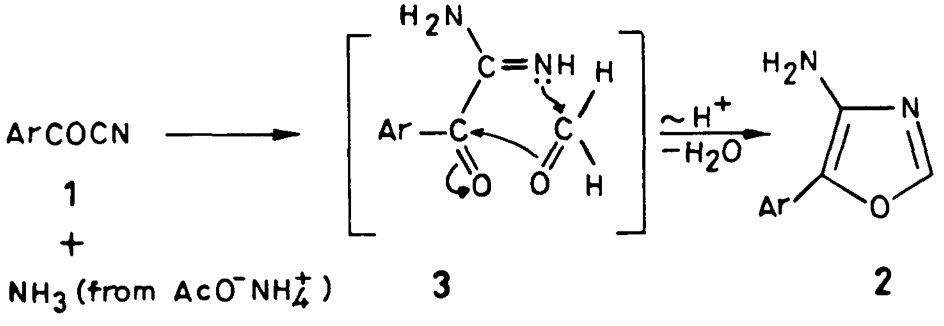
the formation of 2 is outlined below.



Acyl cyanides with electron-withdrawing groups gave slightly higher yields of 2 than those with electron-donating groups (see Table 1). The reaction was also successful with o-toluoyl cyanide 1b.

The structural assignments of 4-amino-5-aryloxazoles were based on spectral (IR and ^{1}H-NMR) and microanalytical data and suitable derivatization (e.g., 4-acetamido-5-phenyloxazole). The IR spectra of 2 as nujol mull display bands between 3460-3200 cm^{-1} for the NH_2 stretchings, at 1650 cm^{-1} for C=N stretching and several characteristic bands at 1600, 1580, 1310,1110,1025,915, 760, 715 cm^{-1}. The ^{1}H-NMR spectrum of 4-amino-5-phenyloxazole 2a in dimethylsulfoxide-d_6 exhibits a broad signal of 2H intensity for the amino protons at δ3.25-3.62 and an overlapping multiplet of 6H intensity between δ7.29-8.25 for the five aromatic protons of phenyl ring and one hydrogen at C-2 of the oxazole ring. The isomeric 2-amino-4-phenyloxazole was reported[5] to melt at 142°. Other aryl aminooxazoles are not known.

EXPERIMENTAL SECTION

Mps were obtained with a Gallenkamp apparatus and are uncorrected. The purity of compounds was routinely checked by TLC

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Table 1. 4-Amino-5-aryloxazoles (2)[a]

No.	Time (hrs)	Yield (%)	mp.(°C)[b]	Chemical shifts δ (ppm)	Found	Calcd.
2a	3	65	117-118	3.25-3.62 (br, 2H, $N\underline{H}_2$), 7.29-8.25 (m, 6H, ArH)	C 67.28 H 5.20 N 17.10	67.49 5.03 17.49
2b	4	40	172-173	2.37 (s, 3H, $C\underline{H}_3$), 4.73-5.43 (br, 2H, $N\underline{H}_2$), 7.10-8.15 (m, 5H, ArH)	C 68.76 H 5.54 N 16.20	68.95 5.78 16.08
2c	4	40	211-212	2.42 (s, 3H, $C\underline{H}_3$), 5.25-6.22 (br, 2H, $N\underline{H}_2$), 7.09-7.92 (m, 5H,ArH)	C 68.82 H 5.91 N 15.94	68.95 5.78 16.08
2d	3	45	162-163	2.22 (s, 3H, $C\underline{H}_3$), 3.42 (s, 2H, $N\underline{H}_2$), 6.45-7.29 (m, 5H, ArH)	C 68.78 H 5.42 N 16.19	68.95 5.78 16.08
2e	5	40	206-207[d]	1.44-2.00 (br,2H, $N\underline{H}_2$), 3.87 (s, 3H, $OC\underline{H}_3$), 6.83-8.10 (m, 5H, ArH)	C 63.40 H 5.39 N 14.36	63.15 5.30 14.73
2f	3	55	263-264[e]	3.56 (s, 2H, $N\underline{H}_2$), 6.44-7.53 (m, 5H, ArH)	C 55.71 H 3.89 N 14.12	55.54 3.62 14.39
2g	3	60	115-116[d]	3.12-3.45 (br, 2H, $N\underline{H}_2$), 7.14-8.43 (m, 5H, ArH)	C 52.97 H 3.76 N 20.19	52.69 3.44 20.48

a) All are colorless except for 2g which is pale yellow.
b) Crystallized from aqueous ethanol unless otherwise indicated.
c) In $CDCl_3$ except for 2a and 2g run in DMSO-d_6. d) From ethanol. e) From methanol.

using silica gel G (E.Merck). Elemental analyses (C,H and N) were performed by a Coleman analyser. The IR spectra were recorded with a Perkin-Elmer 783 grating spectrophotometer as nujol mull. The ^{1}H-NMR spectra were run on a JEOL FX 90Q Fourier transform spectrometer (90 MHz instrument) at the probe temperature (27°) as deuteriochloroform or dimethylsulfoxide-d_6 solutions using tetramethylsilane as an internal standard. α-Oxonitriles 1 were prepared by known methods.[7]

4-Amino-5-phenyloxazole (2a). Typical Procedure.- A mixture of benzoyl cyanide (1a, 6.55 g, 0.05 mol), hexamethylenetetramine (7.0 g, 0.05 mol) and anhydrous ammonium acetate (10.0 g, 0.13 mol) in glacial acetic acid (30 ml) was heated under reflux in an oil bath at 110-120° for 3 hrs. The reaction mixture was cooled and poured with stirring into 100 ml of water. It was basified to pH 8.0 with aqueous ammonia (50 ml, sp. gr. 0.91) and filtered. The filtrate was extracted with ether (3 x 100 ml) and the ethereal extract dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum left a residue which was crystallized from aqueous ethanol to give 5.25 g (65%) of 2a as colorless needles, mp. 117-118°.

4-Acetamido-5-phenyloxazole. - A mixture of 4-amino-5-phenyloxazole (2a, 0.8 g, 5 mmol) and acetyl chloride (1.0 g, 13 mmol) was heated on a steam bath for 30 min. After cooling, the oil was triturated with water and solid was collected and crystallized from ethanol to afford 0.72 g (70%) of colorless crystals, mp. 136°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85
Found : C, 65.52; H, 5.13; N, 13.60

IR (Nujol) : 3300 (m, NH), 1660 (s, C=O), 1600 (s), 1540 (m), 1500 (m), 1320 (m), 1260 (m), 740 (m) cm^{-1}.

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^{1}H-NMR ($CDCl_3$): δ3.52 (s, 3H, COC$\underline{H}_3$), 7.02-7.93 (m, 6H, phenyl and oxazole ring protons), 8.39-8.56 (br, 1H, N$\underline{H}$CO, D_2O exchangeable) ppm.

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4-Chloroacetamido-5-p-chlorophenyloxazole.- To a chilled solution of 2f (0.5 g, 2.5 mmol) in dry benzene (10 ml), chloroacetyl chloride (0.4 g, 3.5 mmol) in benzene (5 ml) was added with stirring. The mixture was heated under reflux for 1 hr. Benzene and excess chloroacetyl chloride were removed by distillation and the residue was washed with 5% $NaHCO_3$ solution. The product was agitated with water and crystallized from ethanol to give 0.47 g (70%) of colorless needles, mp. 152-153°.

Anal. Calcd. for $C_{11}H_8Cl_2N_2O_2$: C, 48.71; H, 2.95; Cl, 26.20
Found : C, 48.84; H, 3.12; Cl, 26.28

IR (Nujol) : 3240 (m,NH), 1680 (s, C=O), 1640 (s), 1600 (m), 1550 (m), 1085 (m), 1010 (m), 830 (s), 705 (m) cm^{-1}.

4-Chloroacetamido-5-p-nitrophenyloxazole.- This compound was prepared from 2g as described above and crystallized from ethanol to give 0.56 g (80%) of pale yellow crystals, mp.192-193°.

Anal. Calcd. for $C_{11}H_8ClN_3O_4$: C, 46.89; H, 2.83; N, 14.92
Found : C, 47.04; H, 3.10; N, 14.75

IR (Nujol) : 3250 (m, NH), 1690 (s, C=O), 1630 (m), 1580 (s), 1510 (s), 1260 (m), 1180 (m), 850 (s), 750 (s) cm^{-1}.

^{1}H-NMR ($CDCl_3$) : δ4.46 (s, 2H, COC$\underline{H}_2$Cl), 7.55-8.05 (m, 5H, aromatic protons), 8.74-9.12 (br, 1H, N$\underline{H}$CO) ppm.

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