A New Synthesis of 4-Aminooxazoles from α-Oxonitriles [1,2]

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A general synthesis is described for the preparation of 4-amino-2,5-disubstituted oxazoles **2**. The interaction of α-oxonitriles **1** with equimolecular amounts of aromatic or aliphatic aldehydes, and excess of anhydrous ammonium acetate in glacial acetic acid at 110-120° for 3-6 hours gives **2** in 40-65% yields. A plausible reaction mechanism for the formation of **2** is also suggested.

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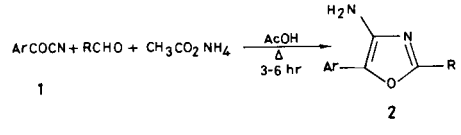
Introduction.

In recent years α-oxonitriles (acyl cyanides, **1**) have emerged as versatile synthons for the formation of 5- and 6-membered heterocyclic compounds. Reactions between acyl cyanides **1** and aromatic aldehydes in the presence of hydrogen chloride (or hydrogen bromide) in absolute ether give good yields of 2,5-diaryl-4-chloro (or bromo)oxazoles [3]. Reductive dimerization of benzoyl cyanide takes place when an ethereal solution of the nitrile is saturated with dry hydrogen iodide and the reaction mixture is kept at 0° for a week; 2,5-diphenylpyrazine is obtained in low yield [4]. Recently, α-oxonitriles **1** have been developed as building blocks in the formation of 5- and 6-membered heterocycles, such as 3-amino-4-aryl-1,2,5-oxadiazoles [5] and 2-amino-3-arylpyrazines [6] *via* condensation with hydroxylamine and ethylenediamine, respectively.

Scheme 1



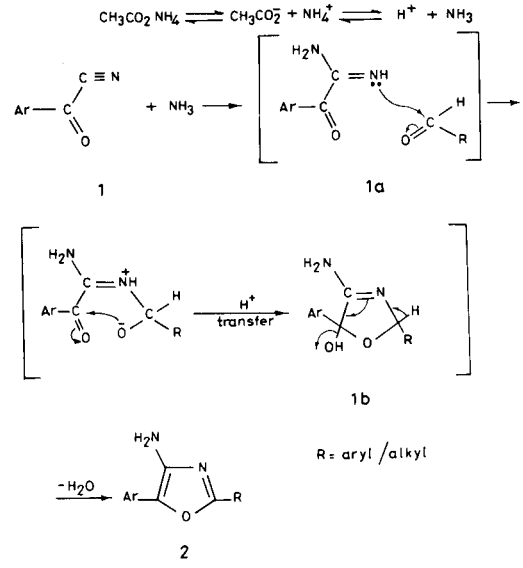
1 2

2	Ar	R
a	Ph	Ph
b	Ph	*p*-MeOPh
c	Ph	*p*-ClPh
d	Ph	*o*-O_2NPh
e	Ph	*p*-O_2NPh
f	*p*-MePh	*p*-MeOPh
g	*p*-MePh	*p*-ClPh
h	*p*-MePh	*o*-O_2NPh
i	*p*-MePh	*p*-O_2NPh
j	*p*-ClPh	Ph
k	*p*-ClPh	*p*-MeOPh
l	*p*-ClPh	*p*-O_2NPh
m	*p*-MeOPh	Ph
n	*p*-MeOPh	*p*-O_2NPh
o	Ph	Me
p	Ph	Et
q	Ph	*n*-Pr

As part of our continuing program to investigate the potential of α-oxonitriles as synthons in the chemistry of oxazoles [3,7], we now report a general synthesis of 4-amino-2,5-disubstituted oxazoles. It is observed that the reaction of α-oxonitriles **1** with aromatic or aliphatic aldehydes in equimolecular amounts in the presence of excess anhydrous ammonium acetate in glacial acetic acid at 110-120° for 3-6 hours affords 4-amino-2,5-disubstituted oxazoles **2** (Scheme 1). The yields are 40-65% and the reaction proceeds without the formation of any by-products; in several instances the unreacted starting materials are recovered to account for the low yields.

The present method thus provides the first direct synthesis of 4-aminooxazoles **2** from readily available starting materials. Though some derivatives of 4-aminooxazoles, such as urethanes and ureas, have been prepared earlier [8-10] *via* the Curtius degradation and the involvement of a 4-aminooxazole as intermediate in the synthesis of 4-arylideneaminooxazoles has been proposed [11], the

Scheme 2



4-aminooxazole system with a free amino group has not been isolated previously.

Results and Discussion.

A reaction mechanism for the formation of 4-amino-2,5-disubstituted oxazoles **2** from α-oxonitriles **1** is outlined in Scheme 2.

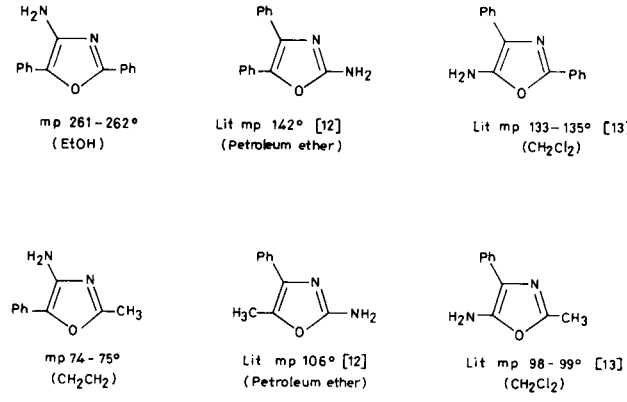
In this reaction ammonium acetate behaves as a source of ammonia which, by way of nucleophilic attack on the nitrile function of **1**, gives an α-oxoamidine **1a** as an intermediate. Subsequently, through one of its amidino nitrogens, **1a** adds onto the carbonyl carbon of the aldehyde, which is followed by cyclization forming **1b**. This aromatizes by the loss of a molecule of water, producing **2**. The driving force for the overall reaction is presumably the formation of the heteroaromatic oxazole ring. The intermediates **1a** and **1b** have not been isolated.

Acyl cyanides **1** with or without an electron-attracting *para*-substituent in the benzene ring (*e.g.*, chloro) provide the aminooxazoles **2** in high yields, whereas those with an electron-releasing group (*e.g.*, methoxy) afford the desired products in lower yields. With respect to the aldehyde component, a variety of these containing electron-attracting and donating groups at *ortho* and *para* positions in the phenyl rings of benzaldehydes undergo the reaction smoothly. The reaction, however, fails when both the acyl cyanide and aromatic aldehyde contain *p*-methoxy substituents. This result is in accordance with our earlier observations [3]. Straight-chain aliphatic aldehydes such as acetaldehyde (in the form of paraldehyde), propionaldehyde and *n*-butyraldehyde give 50-65% yields of the corresponding 2-alkyl-5-phenyl-4-aminooxazoles.

The establishment of the structures of 4-aminooxazoles **2** is based not only from their elemental analyses, spectral studies (ir and ^{1}H-nmr) and suitable derivatization, but also indirectly from literature analogies of related structural isomers. For example, the compound having the molecular formula $C_{15}H_{12}N_2O$, obtained from benzoyl cyanide, benzaldehyde and ammonium acetate (by Scheme 1) is assigned the structure of 4-amino-2,5-diphenyloxazole (*cf.* Scheme 3). Its melting point is found to be 261-262° (ethanol). Two other heterocyclic ring-substituted aminooxazoles with the same formula are 2-amino-4,5-diphenyloxazole, mp 142° (petroleum ether) [12], and 5-amino-2,4-diphenyloxazole, mp 133-135° (methylene chloride) [13]. Thus, our aminooxazole in question is certainly different from those described in the literature and is a new compound.

By a similar argument, the compound $C_{10}H_{10}N_2O$ produced from benzoyl cyanide and paraldehyde is thought to be 4-amino-2-methyl-5-phenyloxazole (*cf.* Scheme 3), mp 74-75° (methylene chloride). In principle, five other hetero ring-substituted aminooxazoles of this formula are possible but only two of them are reported in the literature, namely 2-amino-5-methyl-4-phenyloxazole, mp 106° (petroleum ether) [12] and 5-amino-2-methyl-4-phenyloxazole, mp 98-99° (methylene chloride) [13]. Once again, our aminooxazole is not similar to any of those cited in the literature and therefore it must be the 4-aminooxazole proposed.

Scheme 3



The conclusions derived from ir and ^{1}H-nmr data are also documented here. The ir spectrum of 4-amino-2-methyl-5-phenyloxazole (**2o**) in nujol shows absorption bands at 3310 (m) and 3200 (m) assigned to NH_2 stretchings, at 1665 (s) for C=N stretching and at 1620 (s), 1565 (m) cm^{-1} for the heteroaromatic ring. Its ^{1}H-nmr spectrum in deuteriochloroform shows a multiplet of five aromatic protons between δ 7.21 to 8.24 and a broad signal of 2H intensity at 4.04-4.58 ppm for the primary amino group. A sharp singlet of 3H intensity for the methyl protons appears at δ 2.72 ppm. The ir spectrum of 4-amino-2-ethyl-5-phenyloxazole (**2p**) as a thin film shows absorptions at 3400-3200 (br) for NH_2 stretchings, at 1660 (m) for C=N stretching and several bands at 2950 (s), 2870 (m), 1600 (w), 1500 (w) and 1460 (s) cm^{-1}. Its ^{1}H-nmr spectrum in deuteriochloroform shows a triplet at δ 1.84 (J = 7 Hz) for the methyl protons and a quartet at 4.44 (J = 7 Hz) for the methylene protons. The five aromatic protons appear as a multiplet at δ 7.32 to 8.54 and a sharp singlet of 2H intensity is observed at δ 2.10 ppm for the amino group.

The 4-aminooxazole ring system **2** reported herein is quite stable towards treatment with various reagents and the amino group of **2** undergoes some typical reactions such as acylation with acetyl chloride, trifluoroacetic anhydride and benzoyl chloride, and thiourea formation with alkyl (or aryl) isothiocyanates.

EXPERIMENTAL

Melting points were observed with a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed by a Coleman analyser. The ir spectra were recorded on a Perkin-Elmer 783 grating spectro-

photometer and ^{1}H-nmr on a Jeol FX 90Q Fourier transform spectrometer at the probe temperature (27°) as deuteriochloroform/DMSO-d_6 solutions using tetramethylsilane as an internal standard. The purity of compounds was checked by tlc using silica gel G (Merck).

Acyl cyanides **1** were prepared by the literature method [14] from the corresponding acyl chloride and cuprous cyanide : benzoyl cyanide [14], *p*-toluoyl cyanide [15], *p*-chlorobenzoyl cyanide [15], and *p*-methoxybenzoyl cyanide [15].

4-Amino-2,5-diphenyloxazole (**2a**).

A mixture of benzoyl cyanide (6.55 g, 0.05 mole), benzaldehyde (5.3 g, 0.05 mole), anhydrous ammonium acetate (10 g, 0.13 mole) and glacial acetic acid (30 ml) was heated in an oil bath at 110-120° for 3 hours. The reaction product was cooled and poured with stirring into 100 ml of water. It was basified with ammonia solution (sp gr, 0.91) and filtered. The filtrate was extracted with ether (3 x 100 ml). The ethereal extract was dried over anhydrous magnesium sulfate and the solvent removed. The product was crystallized from ethanol to give 7.1 g (60%) of **2a** as colorless plates, mp 261-262°; ir (nujol): ν max 3400 w, 3180 m (NH_2), 1645 s (C=N), 1610 m, 1590 m, 1560 m (ring str.), 1220 m, 790 s, 700 s cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 6.02-6.62 (broad, 2H, NH_2), 7.43-8.25 (m, 10H, aromatic protons).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.3; H, 5.1; N, 11.9. Found: C, 76.7; H, 5.3; N, 11.6.

Reaction of **2a** with Methyl Isothiocyanate. Formation of 1-Methyl-3-(2,5-diphenyloxazol-4-yl)-2-thiourea.

The aminooxazole **2a** (0.5 g, 2 mmoles) was heated with methyl isothiocyanate (0.22 g, 3 mmoles) in dry benzene (10 ml) for an hour on a steam bath. A solid mass was formed. Benzene was removed and the residue washed with aqueous ethanol and crystallized from ethanol to give 0.42 g (65%) of the methyl thiourea derivative of 4-amino-2,5-diphenyloxazole, mp 212-213°; ir (nujol): ν max 3380 m, 3240 m, 1630 s, 1610 s, 1560 m, 1215 m, 1080 m, 760 s, 730 s cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}N_3OS$: C, 66.0; H, 4.8; N, 13.6. Found: C, 65.9; H, 5.0; N, 13.3.

4-Amino-2-*p*-methoxyphenyl-5-phenyloxazole (**2b**).

A mixture of benzoyl cyanide (2.62 g, 0.02 mole), anisaldehyde (2.72 g, 0.02 mole), anhydrous ammonium acetate (4.0 g, 0.05 mole) and glacial acetic acid (20 ml) was refluxed in an oil bath at 110-120° for 5 hours. The product was worked up in the usual manner and crystallized from ethanol to afford colorless crystals of **2b**, yield 2.7 g (50%), mp 240-241°; ir (nujol): ν max 3230 m, 3100 m, 1660 s, 1630 m, 1520 m, 1280 s, 1200 m, 1020 m, 920 m, 830 m, 760 m cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.5; H, 5.4; N, 10.4.

4-Amino-2-*p*-chlorophenyl-5-phenyloxazole (**2c**).

This compound, prepared from benzoyl cyanide and *p*-chlorobenzaldehyde in a manner analogous to that described above (heating for 4 hours at 120°), was obtained as pale yellow crystals from ethanol, yield 45%, mp 232-233°; ir (nujol): ν max 3460 w, 3280 w, 1640 m, 1600 m, 1540 s, 1030 m, 815 m, 720 s cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.21 (broad, 2H, NH_2), 7.29-8.85 (m, 9H, aromatic protons).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.5; H, 4.1; N, 10.3. Found: C, 66.7; H, 4.2; N, 10.1.

Acylation of **2c**.

A. Preparation of 4-Acetamido-2-*p*-chlorophenyl-5-phenyloxazole.

A mixture of the aminooxazole **2c** (1.35 g, 5 mmoles) and acetyl chloride (0.8 g, 10 mmoles) was heated on a steam bath for 30 minutes. The product was cooled and triturated with water. Crystallization from ethanol afforded colorless crystals of the acetyl derivative, yield 1.17 g (75%), mp 228°; ir (nujol): ν max 3270 m, 1660 s, 1650 s, 1600 m, 1580 m, 1530 s, 910 s, 760 s, 710 s cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.97 (broad, 3H, CH_3), 4.82 (s, 1H, >N*H*, deuterium oxide-exchangeable), 6.78-8.12 (m, 9H, aromatic protons).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$: C, 65.3; H, 4.2; N, 9.0. Found: C, 65.0; H, 4.0; N, 8.8.

B. Preparation of 4-Benzamido-2-*p*-chlorophenyl-5-phenyloxazole.

Purified benzoyl chloride (0.6 g, 4 mmoles) was added to a solution of **2c** (0.6 g, 2 mmoles) in 5 ml of pyridine. The reaction mixture was stirred at 5-10° for 1 hour and then allowed to stand overnight at room temperature. The solid mass was agitated with water, filtered and crystallized from ethanol to give colorless needles, 0.6 g (70%), mp 108-109°; ir (nujol): ν max 3450 br, 1700 m, 1680 s, 1600 m, 1580 m, 1290 s, 920 m, 700 m cm^{-1}.

Anal. Calcd. for $C_{22}H_{15}ClN_2O_2$: C, 70.5; H, 4.0; N, 7.5. Found: C, 70.3; H, 4.2; N, 7.1.

4-Amino-2-*o*-nitrophenyl-5-phenyloxazole (**2d**).

This compound was prepared by the reaction of benzoyl cyanide (24 mmoles) with *o*-nitrobenzaldehyde (24 mmoles) and ammonium acetate (90 mmoles) in glacial acetic acid (50 ml) in the usual manner. Basification with aqueous ammonia gave a red precipitate which was recrystallized from benzene to afford **2d** as red crystals, yield 3.4 g (50%), mp 197-198°; ir (nujol): ν max 3320 m, 3200 m, 1665 s, 1625 m, 1570 m, 1100 s, 840 s, 740 s cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.85 (broad, 2H, NH_2), 7.29-8.24 (m, 9H, aromatic protons).

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.0; H, 3.9; N, 14.9. Found: C, 64.3; H, 4.0; N, 15.1.

4-Amino-2-*p*-nitrophenyl-5-phenyloxazole (**2e**).

This compound was obtained from *p*-nitrobenzaldehyde by the procedure described above for **2d**. Crystallization from ethanol gave **2e** as red crystals, yield 55%, mp 310-312°; ir (nujol): ν max 3450 w, 3180 w, 1660 s, 1600 m, 1510 m, 1100 m, 850 s, 760 m cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.0; H, 3.9; N, 14.9. Found: C, 63.9; H, 4.2; N, 14.8.

Trifluoroacetylation of **2e**. Preparation of 4-Trifluoroacetamido-2-*p*-nitrophenyl-5-phenyloxazole.

An ice cooled solution of trifluoroacetic anhydride (1.1 g, 50 mmoles) in 10 ml of benzene was added portionwise to a suspension of **2e** (0.7 g, 25 mmoles) in 10 ml of benzene. The mixture was stirred at 10° for 1 hour and then allowed to stand overnight at room temperature. The product was triturated with water, and crystallized from ethanol to give 0.56 g (60%) of 4-trifluoroacetamido-2-*p*-nitrophenyl-5-phenyloxazole, mp 340°; ir (nujol): ν max 3450 br, 1695 s, 1610 m, 1300 m, 860 m, 770 m cm^{-1}.

Anal. Calcd. for $C_{17}H_{10}F_3N_3O_4$: C, 54.1; H, 2.6; N, 11.1. Found: C, 53.8; H, 2.7; N, 10.9.

4-Amino-2-*p*-methoxyphenyl-5-*p*-tolyloxazole (**2f**).

This compound was obtained by heating a mixture of 2.9 g *p*-toluoyl cyanide, 2.76 g anisaldehyde, 5.0 g anhydrous ammonium acetate and 50 ml of glacial acetic acid at 120° for 6 hours and working up the product in the usual manner. Crystallization from DMF-ethanol (1:3) afforded colorless crystals of **2f**, yield 3.5 g (62%), mp 165-166°; ir (nujol): ν max 3400-3200 br, 1655 s, 1620 m, 1600 m, 1570 m, 1095 m, 1015 m, 855 s, 750 s cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.8; H, 5.7; N, 10.0. Found: C, 72.9; H, 5.9; N, 9.8.

4-Amino-2-*p*-chlorophenyl-5-*p*-tolyloxazole (**2g**).

The reaction between *p*-toluoyl cyanide and *p*-chlorobenzaldehyde under the usual conditions followed by crystallization of the product from aqueous ethanol gave **2g** as colorless crystals, yield 55%, mp 156-157°; ir (nujol): ν max 3440 m, 3250 m, 1630 s, 1600 s, 1535 s, 1525 s, 775 m, 720 m cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.42 (s, 3H, CH_3), 3.72 (broad, 2H, NH_2), 6.72-7.80 (m, 8H, aromatic protons).

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.5; H, 4.6; Cl, 12.5. Found: C, 67.3; H, 4.8; Cl, 12.8.

Preparation of 4-Benzamido-2-*p*-chlorophenyl-5-*p*-tolyloxazole.

A mixture of **2g** (0.86 g, 3 mmoles), benzoyl chloride (0.84 g, 6 mmoles) and 10% sodium hydroxide solution (10 ml) was shaken at 0-5° for 30 minutes. A solid mass formed which was poured into cold water, stirred and filtered. Crystallization from ethanol formed colorless crystals of the benzoyl derivative of **2g**, 0.78 (70%), mp 303-304°; ir (nujol): ν max 3240 m, 1660 s, 1630 s, 1530 s, 1500 m, 1280 s, 1200 s, 800 s, 750 s cm^{-1}.

Anal. Calcd. for $C_{23}H_{17}ClN_2O$: C, 74.1; H, 4.6; N, 7.5. Found: C, 74.4; H, 4.6; N, 7.4.

4-Amino-2-*o*-nitrophenyl-5-*p*-tolyloxazole (**2h**).

It was prepared from *p*-toluoyl cyanide and *o*-nitrobenzaldehyde as described before and obtained as light yellow crystals from ethanol, yield 40%, mp 72-73°; ir (nujol): ν max 3420 w, 3230 w, 1655 s, 1625 m, 1615 m, 1515 m, 1180 m, 970 s, 865 m, 820 s cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.1; H, 4.4; N, 14.2. Found: C, 65.4; H, 4.6; N, 14.0.

4-Amino-2-*p*-nitrophenyl-5-*p*-tolyloxazole (**2i**).

It was obtained by replacing *o*-nitrobenzaldehyde with *p*-nitrobenzaldehyde in the above preparation. The product was crystallized from ethanol-benzene (1:1) to give **2i** as pale yellow crystals, yield 60%, mp 179-180°; ir (nujol): ν max 3460 br, 1670 s, 1620 m, 1500 w, 1190 m, 1120 w, 750 m cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.1; H, 4.4; N, 14.2. Found: C, 65.0; H, 4.7; N, 14.3.

4-Amino-5-*p*-chlorophenyl-2-phenyloxazole (**2j**).

This compound was prepared by heating a mixture of *p*-chlorobenzoyl cyanide (3.3 g, 0.02 mole), benzaldehyde (2.33 g, 0.022 mole), anhydrous ammonium acetate (5.0 g) and glacial acetic acid (50 ml) at 120° for 3 hours and working up the product as described earlier. Crystallization from methanol afforded **2j** as shining yellow crystals, 3.0 g (55%), mp 263-264°; ir (nujol): ν max 3400 br, 3170 w, 1680 s, 1610 m, 1520 m, 1200 m, 1100 w, 850 m, 720 m cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.5; H, 4.1; Cl, 13.1. Found C, 66.8; H, 4.0; Cl, 13.0.

Reaction of *p*-Ethoxyphenyl Isothiocyanate with **2j**. Formation of 1-*p*-Ethoxyphenyl-3-(5-*p*-chlorophenyl-2-phenyloxazol-4-yl)-2-thiourea.

Equimolar quantities of **2j** and *p*-ethoxyphenyl isothiocyanate were heated in benzene for 1 hour in a steam bath. The solvent was removed, the residue washed with aqueous ethanol and crystallized to give colorless crystals from ethanol (75%), mp 194-195°; ir (nujol): ν max 3400 m, 3260 m, 1665 s, 1635 m, 1605 s, 1540 m, 1510 m, 1210 m, 1030 m, 920 s, 770 m, 700 m cm^{-1}.

Anal. Calcd. for $C_{24}H_{20}ClN_3O_2S$: C, 64.1; H, 4.4; N, 9.3; S, 7.1. Found: C, 63.8; H, 4.1; N, 9.2; S, 7.3.

4-Amino-5-*p*-chlorophenyl-2-*p*-methoxyphenyloxazole (**2k**).

This compound was prepared from *p*-chlorobenzoyl cyanide and anisaldehyde, and the product worked up as usual. Crystallization from aqueous ethanol gave **2k** in the form of shining white crystals (60%), mp 226-227°; ir (nujol): ν max 3400-3200 br, 1640 s, 1610 m, 1565 m, 1500 m, 1065 m, 785 m, 700 m cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.9; H, 4.3; N, 9.3. Found: C, 63.6; H, 4.2; N, 9.4.

4-Amino-5-*p*-chlorophenyl-2-*p*-nitrophenyloxazole (**2l**).

The reaction between *p*-chlorobenzoyl cyanide (3.3 g, 0.02 mole) and *p*-nitrobenzaldehyde (3.2 g, 0.021 mole) in the usual manner followed by crystallization from benzene afforded red plates, yield 4.1 g (65%), mp 258-259°; ir (nujol): ν max 3420-3260 br, 1660 s, 1600 m, 1510 m, 1090 m, 840 m, 750 m cm^{-1}.

Anal. Calcd. for $C_{15}H_{10}ClN_3O_3$: C, 57.1; H, 3.2; N, 13.3. Found: C, 57.2; H, 3.4; N, 13.0.

Preparation of 1-*p*-tolyl-3-(5-*p*-chlorophenyl-2-*p*-nitrophenyloxazol-4-yl)-2-thiourea.

A mixture of **2l** (1.3 g, 4 mmoles), *p*-tolyl isothiocyanate (1.2 g, 8 mmoles) and dry benzene (15 ml) was refluxed for 1.5 hours to form a solid mass. The solvent was removed and the residue washed with aqueous ethanol. It was crystallized from benzene to give colorless crystals of the thiourea, 1.24 g (65%), mp 330°; ir (nujol): ν max 3300 m, 3210 m, 1660 s, 1620 s, 1520 m, 1255 m, 965 m, 905 m, 860 m, 750 s cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 4.64 and 4.86 (two singlets, 1H each, for two NH groups), 6.79-7.82 (m, 12H, aromatic protons).

Anal. Calcd. for $C_{23}H_{17}ClN_4O_3S$: C, 59.4; H, 3.6; N, 12.0. Found: C, 59.0; H, 3.7; N, 12.2.

4-Amino-5-*p*-methoxyphenyl-2-phenyloxazole (**2m**).

The reaction between 1.61 g anisoyl cyanide and 1.1 g benzaldehyde in the presence of 3.0 g anhydrous ammonium acetate in 20 ml of acetic acid as described above and working up of the product gave **2m** as colorless crystals from ethanol, 1.06 g (40%), mp 92-93°; ir (nujol): ν max 3490-3200 br, 1640 s, 1600 m, 1580 m, 1030 m, 750 m cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.4; H, 5.3; N, 10.4.

Attempted Preparation of 4-Amino-2,5-di-(*p*-methoxyphenyl)oxazole.

The reaction of anisoyl cyanide with anisaldehyde under the usual conditions failed to give the expected oxazole.

4-Amino-5-*p*-methoxyphenyl-2-*p*-nitrophenyloxazole (**2n**).

It was prepared by heating anisoyl cyanide (1.61 g) with *p*-nitrobenzaldehyde (1.51 g) in the presence of anhydrous ammonium acetate (3.0 g) in glacial acetic acid (20 ml) at 120° for 5 hours. After cooling, it was poured into 50 ml of water and filtered. The filtrate was basified with aqueous ammonia (40 ml, sp gr, 0.91) and extracted with ether (3 x 50 ml). The extract was dried over anhydrous magnesium sulfate and the solvent evaporated. The residue on crystallization from ethanol afforded **2n** as light yellow crystals, 1.55 g (50%), mp 215-216°; ir (nujol): ν max 3400 m, 3200 m, 1660 m, 1600 m, 1560 m, 1310 m, 1260 m, 840 m, 740 m cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.91 (s, 3H, OCH_3), 4.72 (broad, 2H, NH_2), 6.72-7.69 (m, 8H, aromatic protons).

Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.7; H, 4.2; N, 13.5. Found: C, 61.9; H, 4.3; N, 13.3.

4-Amino-2-methyl-5-phenyloxazole (**2o**).

This compound was obtained by heating a mixture of benzoyl cyanide (3.0 g, 23 mmoles), paraldehyde (5.0 g, 38 mmoles), anhydrous ammonium acetate (10 g, 130 mmoles) and glacial acetic acid (50 ml) in an oil bath at 110-120° for 3 hours and working up the product as before. Crystallization from dichloromethane afforded colorless crystals of **2o**, yield 2.4 g (60%), mp 74-75°; ir (nujol): ν max 3310 m, 3200 m, 1665 s, 1620 s, 1565 m, 1115 m, 1100 s, 1015 m, 840 s, 735 s, 675 m cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.72 (s, 3H, CH_3), 4.04-4.58 (broad, 2H, NH_2), 7.21-8.24 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.7; N, 16.1. Found: C, 69.2; H, 5.8; N, 16.0.

Preparation of 4-Benzamido-2-methyl-5-phenyloxazole.

A mixture of **2o** (0.9 g, 5 mmoles), benzoyl chloride (1.4 g, 10 mmoles) and 10 ml of pyridine was stirred at 5-10° for 30 minutes to form a solid mass. It was agitated with water, filtered and crystallized from aqueous ethanol to give monobenzoyl derivative of **2o** as colorless needles, 1.0 g (70%), mp 138-139°; ir (nujol): ν max 3300 br, 1700 s, 1640 m, 1600 m, 1580 s, 1500 s, 1310 m, 1240 m, 1120 m, 1050 m, 800 m cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.0; N, 10.1. Found: C, 73.6; H, 5.1; N, 10.0.

4-Amino-2-ethyl-5-phenyloxazole (**2p**).

A mixture of benzoyl cyanide (23 mmoles), propionaldehyde (68 mmoles) and anhydrous ammonium acetate (10.0 g) in 50 ml of glacial

acetic acid was heated in an oil bath at 120° for 4 hours. The product was cooled and basified with aqueous ammonia. It was extracted with ether, the ethereal extract dried (anhydrous magnesium sulfate) and the solvent evaporated to give a colorless oil. It was distilled to afford **2p** as a colorless liquid, bp 155-157° at 760 mm, yield 2.8 g (65%); ir (liquid film): ν max 3400-3200 br, 2950 s, 2870 m, 1660 m, 1600 w, 1500 w, 1460 s, 1330 s, 1230 s, 1170 m, 1100 m, 1020 m, 700 s cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.84 (t, J = 7 Hz, 3H, CH_2CH_3), 2.10 (s, 2H, NH_2), 4.44 (q, J = 7 Hz, 2H, CH_3CH_2), 7.32-8.54 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 69.8; H, 6.6; N, 15.1.

Preparation of 4-Benzamido-2-ethyl-5-phenyloxazole.

Benzoyl chloride (2.0 g) was added to a stirred solution of **2p** (1.3 g) in 10% sodium hydroxide (10 ml) at 0-5°. The stirring was continued for 30 minutes when a solid mass formed. Crystallization from ethanol afforded white crystals, 1.5 g (75%), mp 162-163°; ir (nujol): ν max 3280 m (sharp), 1660 s, 1600 m, 1590 m, 1530 s, 1320 m, 760 m cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 74.0; H, 5.5; N, 9.6. Found: C, 73.6; H, 5.7; N, 9.4.

4-Amino-2-propyl-5-phenyloxazole (**2q**).

The reaction between benzoyl cyanide (3.2 g, 24 mmoles) and *n*-butyraldehyde (3.0 g, 36 mmoles) as described above and work up of the product gave **2q** as light yellow crystals from benzene, yield 2.5 g (50%), mp 135°; ir (nujol): ν max 3320 m, 3200 m, 1665 m, 1645 m, 1620 s, 1560 m, 1100 m, 840 s, 735 s cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.3; H, 6.9; N, 13.9. Found: C, 71.4; H, 7.1; N, 13.7.

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REFERENCES AND NOTES

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