# Electrophilic Substitution of Diazonium Salts in 2-Amino-4-(alkyl or aryl)oxazoles



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Aryl diazonium fluoborates react readily with 2-amino-4-alkyloxazoles and 2-amino-4-aryloxazoles under mild conditions. The products are the corresponding 5-arylazo derivatives formed, in 44-98% yield free from side products.

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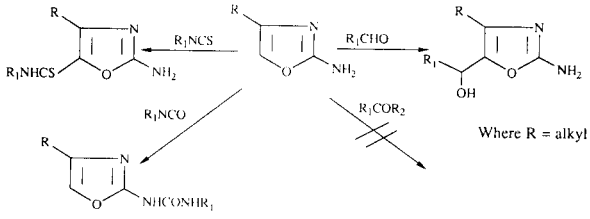
In our earlier investigations it has been shown that in 2-aminooxazoles the presence of alkyl or aryl substituents at C-4 of the ring activities C-5 to electrophilic substitutions which do not occur in 2-aminooxazole itself. 4-Alkyl and 4-aryl-2-aminooxazoles react with isothiocyanates to give good yields of 5-thioamides [1,2]. On the other hand these oxazoles react with isocyanates only at the amino group to form substituted ureas [3].

The reaction of 4-substituted-2-aminooxazoles with aldehydes is also highly selective. Compounds having a 4-alkyl substituent give high yields of 5-hydroxyalkyl or 5-hydroxyaryl derivatives from aliphatic and aromatic aldehydes but 4-aryl substituted compounds do not react with aldehydes [4,5]. A free amino group is also necessary for this electrophilic substitution at C-5 since acetylation of the amino group blocks substitution. The degree of ring activation conferred by alkyl substituents at the C-4 is also insufficient for reaction to occur with ketones.



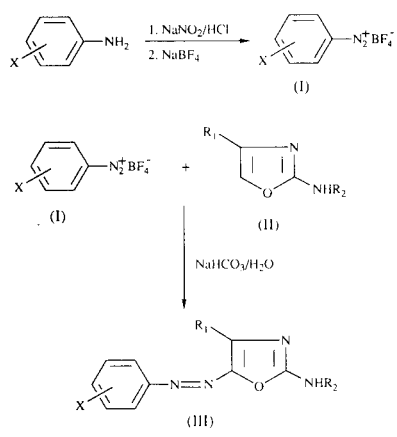

Where R = alkyl or aryl
and $R_1$ = alkyl or aryl

In the present paper we report the facile reaction of diazonium salts at C-5 of 4-alkyl and 4-aryl-2-aminooxazoles to give excellent yields of the azo compounds.

## Results and Discussion.

When 2-amino-4-methyloxazole **(IIa)** was treated with diazotized aromatic amines in neutral, mildly acidic or mildly basic solutions highly coloured yellow or brown precipitates formed but it was difficult to isolate pure products. A much better procedure was found by isolation of crystalline diazonium fluoborate salts and reaction of these with oxazoles in sodium bicarbonate solution. Azo derivatives were formed free of side products and structures were established by standard spectroscopic techniques. The position of substitution of the azo group on the oxazole ring was clearly indicated by pmr spectra showing the absence of the signal for the proton at C-5. The reaction sequence is shown in Scheme I below, and the range of structures prepared is illustrated in Table 1.

Scheme I




Identities of X, $R_1$ and $R_2$ are shown in table 1

Aryl diazonium salts are relatively weak electrophiles and normally require activated aromatics for substitution reactions to occur. In the oxazoles studied the activation of the ring system provided by 4-alkyl or 4-aryl substituents in conjunction with a free or acetylated amino group is sufficient to promote efficient substitution by the diazonium salts at C-5.

The degree of activation of the oxazole ring required for electrophilic substitution by diazonium salts is less than that required for the aldehyde reaction, where alkyl substituents at C-4 and a free amino group were both necessary [4,5].

The amino group in 2-amino-4-methyloxazole could not be diazotized by treatment with nitrous acid using a variety of experimental conditions. The diazonium salts used in this study did not show any reactivity to the amino group

Table 1

Products of The Reaction of Aminooxazole (**II**) With Sustituted Phenyldiazonium Fluoborate (**I**)

| Diazonium Salt | | Oxazole | | | Azo Product | | | | Yield |
|---|---|---|---|---|---|---|---|---|---|
| No. | X | No. | $R_1$ | $R_2$ | No. | X | $R_1$ | $R_2$ | % |
| **Ia** | H | **IIa** | $CH_3$ | H | **IIIa** | H | $CH_3$ | H | 91 |
| **Ib** | *p*-Br | **IIa** | $CH_3$ | H | **IIIb** | *p*-Br | $CH_3$ | H | 95 |
| **Ic** | *p*-Cl | **IIa** | $CH_3$ | H | **IIIc** | *p*-Cl | $CH_3$ | H | 89 |
| **Id** | *m*-Cl | **IIa** | $CH_3$ | H | **IIId** | *m*-Cl | $CH_3$ | H | 76 |
| **Ie** | *o*-Cl | **IIa** | $CH_3$ | H | **IIIe** | *o*-Cl | $CH_3$ | H | 72 |
| **If** | *p*-$OCH_3$ | **IIa** | $CH_3$ | H | **IIIf** | *p*$OCH_3$ | $CH_3$ | H | 57 |
| **Ig** | *p*-$CH_3$ | **IIa** | $CH_3$ | H | **IIIg** | *p*-$CH_3$ | $CH_3$ | H | 65 |
| **Ih** | *p*-$NO_2$ | **IIa** | $CH_3$ | H | **IIIh** | *p*-$NO_2$ | $CH_3$ | H | 96 |
| **Ia** | H | **IIb** | $CH_3$ | $COCH_3$ | **IIIi** | H | $CH_3$ | $COCH_3$ | 98 |
| **If** | *p*-$OCH_3$ | **IIb** | $CH_3$ | $COCH_3$ | **IIIj** | *p*-$OCH_3$ | $CH_3$ | $COCH_3$ | 44 |
| **Id** | *m*-Cl | **IIb** | $CH_3$ | $COCH_3$ | **IIIk** | *m*-Cl | $CH_3$ | $COCH_3$ | 90 |
| **Ia** | H | **IIc** | $C_6H_5$ | H | **IIIl** | H | $C_6H_5$ | H | 73 |

of the oxazoles and there was no evidence for the formation of diazoamino derivatives. When the reaction was tried with 2-amino-4,5-dimethyloxazole and phenyl diazonium fluoborate no product was obtained.

## EXPERIMENTAL

Melting points were recorded on a Leitz hot stage microscope and are uncorrected. Elemental analysis were carried out by the Microanalytical Laboratory, University of New South Wales. Infrared spectra were recorded on a Perkin Elmer 298 Infrared Spectrophotometer and pmr spectra on a Bruker CXP-300 Spectrometer. Mass spectra were obtained from an AEI MS 12 spectrometer (70 eV). Starting materials were analytical grade reagents and were checked for purity before use and all solvents were distilled before use.

Reaction of 2-Amino-4-methyloxazole (**IIa**) With Phenyldiazonium Fluoborate (**Ia**).

Aniline (1.86 g, 0.02 mole) was dissolved in hydrochloric acid (10 ml of 3*M*) and the solution was cooled to 0°. Sodium nitrite (5 ml of 4.2*M*) was added slowly keeping the temperature of the reaction mixture below 5°. After standing for 10 minutes the mixture was filtered and then treated with sodium fluoborate solution (5 ml of 4.4*M*). After 15 minutes the solid formed was collected by filtration and washed with cold water (6 ml), cold methanol (8 ml) and cold water (5 ml). Phenyldiazonium fluoborate was obtained as colourless crystals and was dried over phosphorus pentoxide *in vacuo*.

2-Amino-4-methyloxazole (0.98 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) and cooled to 0°. Phenyldiazonium fluoborate (1.92 g, 0.01 mole), suspended in water (25 ml) cooled to 0°, was added with stirring and the mixture was kept below 10° for 15 minutes. The product 2-amino-4-methyl-5-phenylazooxazole (**IIIa**) was collected by filtration and recrystallized from aqueous ethanol. It formed orange needles (1.84 g, 91%) mp 178-180°; ms: m/z 202 ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 1.70 (s, 3H, 4-$CH_3$), 6.7-7.25 (m, 5H, aromatic H), 8.20 (broad s, 2H, exchanged with deuterium oxide, $NH_2$); ir (potassium bromide): 680, 760, 1020, 1070, 1280, 1310, 1600, 1680, 3060-3300 $cm^{-1}$.

*Anal.* Calcd. for $C_{10}H_{10}N_4O$: C, 59.4; H, 5.0; N, 27.7. Found: C, 59.3; H, 5.2; N, 28.0.

Reaction of 2-Amino-4-methyloxazole (**IIa**) with *p*-Bromophenyldiazonium Fluoborate (**Ib**).

2-Amino-4-methyloxazole (0.98 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) and cooled to 0°. *p*-Bromophenyldiazonium fluoborate (2.71 g, 0.01 mole), prepared as in the previous experiment, suspended in water (25 ml), was cooled to 0° and was added to the oxazole. The mixture was stirred and kept below 10° for 15 minutes. The product 2-amino-4-methyl-5-(*p*-bromophenylazo)oxazole (**IIIb**) was collected by filtration and recrystallized from aqueous ethanol. It formed dark red crystals (2.67 g, 95%) mp 160-161°; ms: m/z 283, 281 (1:1) ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 1.85 (s, 3H, 4-$CH_3$), 6.55-7.67 (m, 4H, aromatic H), 8.60 (broad s, 2H, exchanged with deuterium oxide, $NH_2$); ir (potassium bromide): 820, 1070, 1280, 1305, 1600, 1690, 3120-3500 $cm^{-1}$.

*Anal.* Calcd. for $C_{10}H_9BrN_4O$: C, 42.7; H, 3.2; N, 19.9. Found: C, 42.4; H, 3.5; N, 20.0.

Reaction of 2-Amino-4-methyloxazole (**IIa**) With *p*-Chlorophenyldiazonium Fluoborate (**Ic**).

2-Amino-4-methyloxazole (0.98 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) cooled to 0°. *p*-Chlorophenyldiazonium fluoborate (2.26 g, 0.01 mole) prepared in the usual way, was suspended in water (25 ml), cooled to 0° and added to the oxazole. The mixture was stirred and kept below 10° for 15 minutes. The product 2-amino-4-methyl-5-(*p*-chlorophenylazo)oxazole (**IIIc**) was collected by filtration and was recrystallized from aqueous ethanol. It formed yellow crystals (2.10 g, 89%) mp 153-155°; ms: m/z 238, 236 (1:3) ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 1.81 (s, 3H, 4-$CH_3$), 6.85-7.70 (m, 4H, aromatic H), 8.52 (broad s, 2H, exchanged with deuterium oxide, $NH_2$); ir (potassium bromide): 740, 825, 1020, 1070, 1275, 1300, 1600, 1690, 3020-3400 $cm^{-1}$.

*Anal.* Calcd. for $C_{10}H_9ClN_4O$: C, 50.7; H, 3.8; N, 23.7. Found: C,

50.6; H, 3.7; N, 23.4.

Reaction of 2-Amino-4-methyloxazole (**IIa**) With *m*-Chlorophenyldiazonium Fluoborate (**Id**).

2-Amino-4-methyloxazole (0.98 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) cooled at 0°. *m*-Chlorophenyldiazonium fluoborate (2.26 g, 0.01 mole), prepared in the usual way, was suspended in water (25 ml), cooled to 0° and added to the oxazole. The mixture was stirred at less than 10° for 15 minutes. The product 2-amino-4-methyl-5-(*m*-chlorophenylazo)oxazole (**IIId**) was collected by filtration and recrystallized from aqueous ethanol. It formed yellow crystals (1.80 g, 76%) mp 165-166°; ms: m/z 238, 236 (1:3) ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 1.75 (s, 3H, 4-$CH_3$), 6.55-7.45 (m, 4H, aromatic H), 9.0 (broad s, 2H, exchanged with deuterium oxide, $NH_2$); ir (potassium bromide): 775, 1070, 1310, 1600, 1680, 3130-3400 $cm^{-1}$.

*Anal.* Calcd. for $C_{10}H_9ClN_4O$: C, 50.7; H, 3.8; N, 23.7. Found: C, 50.8; H, 3.8; N, 23.4.

Reaction of 2-Amino-4-methyloxazole (**IIa**) With *o*-Chlorophenyldiazonium Fluoborate (**Ie**).

2-Amino-4-methyloxazole (0.98 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) cooled at 0°. *o*-Chlorophenyldiazonium fluoborate (2.26 g, 0.01 mole), prepared by the usual way, was suspended in water (25 ml), cooled to 0° and added to the oxazole. The mixture was stirred for 15 minutes at less than 10°. The product 2-amino-4-methyl-5-(*o*-chlorophenylazo)oxazole (**IIIe**) formed yellow crystals (1.70 g, 72%) mp 163-164°; ms: m/z 238, 236 (1:3) ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 1.65 (s, 3H, 4-$CH_3$), 6.55-7.55 (m, 4H, aromatic H), 8.45 (broad s, 2H, exchanged with deuterium oxide, $NH_2$); ir (potassium bromide): 750, 1030, 1050, 1300, 1600, 1680, 3200-3400 $cm^{-1}$.

*Anal.* Calcd. for $C_{10}H_9ClN_4O$: C, 50.7; H, 3.8; N, 23.7. Found: C, 50.6; H, 3.5; N, 23.4.

Reaction of 2-Amino-4-methyloxazole (**IIa**) With *p*-Methoxyphenyldiazonium Fluoborate (**If**).

2-Amino-4-methyloxazole (0.98 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%), cooled to 0°. *p*-Methoxyphenyldiazonium fluoborate (2.22 g, 0.01 mole), prepared in the usual way, was suspended in water (25 ml), cooled to 0°, and added to the oxazole. The mixture was stirred at less than 10° for 15 minutes. The product 2-amino-4-methyl-5-(*p*-methoxyphenylazo)oxazole (**IIIf**) was collected by filtration and recrystallized from aqueous ethanol. It formed light brown crystals (1.32 g, 57%) mp 150-151°; ms: m/z 232 ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 2.32 (s, 3H, 4-$CH_3$), 3.67 (s, 3H, O-$CH_3$), 6.65-7.10 (m, 4H, aromatic H), 7.75 (broad s, 2H, exchanged with deuterium oxide, $NH_2$); ir (potassium bromide): 825, 1035, 1250, 1310, 1600, 1695, 3100-3400 $cm^{-1}$.

*Anal.* Calcd. for $C_{11}H_{12}N_4O_2$: C, 56.9; H, 5.2; N, 24.1. Found: C, 56.8; H, 5.0; N, 23.8.

Reaction of 2-Amino-4-methyloxazole (**IIa**) With *p*-Tolyldiazonium Fluoborate (**Ig**).

2-Amino-4-methyloxazole (0.98 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) and cooled to 0°. *p*-Tolyldiazonium fluoborate (2.06 g, 0.01 mole), prepared in the usual way, was suspended in water (25 ml), cooled to 0° and added to the oxazole. The mixture was stirred for 15 minutes at less than 10°. The product 2-amino-4-methyl-5-(*p*-tolylazo)oxazole (**IIIg**) was collected by filtration and recrystallized from aqueous ethanol. It formed yellow crystals (1.40 g, 65%) mp 147-148°; ms: m/z 216 ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 2.16 (s, 3H, 4-$CH_3$), 2.18 (s, 3H, Ar-$CH_3$), 6.50-7.12 (m, 4H, aromatic H), 7.65 (broad s, 2H, exchanged with deuterium oxide, $NH_2$); ir (potassium bromide): 710, 820, 1020, 1075, 1280, 1310, 1600, 1690, 3080-3350 $cm^{-1}$.

*Anal.* Calcd. for $C_{11}H_{12}N_4O$: C, 61.1; H, 5.6; N, 25.9. Found: C, 61.0; H, 5.3; N, 25.6.

Reaction of 2-Amino-4-methyloxazole (**IIa**) With *p*-Nitrophenyldiazonium Fluoborate (**Ih**).

2-Amino-4-methyloxazole (0.98 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) and cooled to 0°. *p*-Nitrophenyldiazonium fluoborate (2.37 g, 0.01 mole), prepared in the usual way, was suspended in water (25 ml), cooled to 0° and added to the oxazole. The mixture was stirred for 15 minutes at less than 10°. The product 2-amino-4-methyl-5-(*p*-nitrophenylazo)oxazole (**IIIh**) was collected by filtration and was recrystallized from aqueous ethanol. It formed dark red hygroscopic crystals (2.37 g, 96%) mp 215° dec; ms: m/z 247 ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 1.90 (s, 3H, 4-$CH_3$), 3.40 (broad s, $H_2O$), 6.70-7.12 (m, 4H, aromatic H), 9.20 (broad s, 2H, exchanged with deuterium oxide, $NH_2$); ir (potassium bromide): 850, 1100, 1260, 1330, 1600, 1690, 3070-3400 $cm^{-1}$.

*Anal.* Calcd. for $C_{10}H_9N_5O_3 \cdot {}^3/_4H_2O$: C, 46.1; H, 4.0; N, 26.8. Found: C, 45.9; H, 3.8; N, 26.4.

Reaction of 2-Acetamido-4-methyloxazole (**IIb**) With Phenyldiazonium Fluoborate (**Ia**).

2-Acetamido-4-methyloxazole (1.40 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) cooled to 0°. Phenyldiazonium fluoborate (1.92 g, 0.01 mole) was suspended in water (25 ml), cooled to 0° and added to the oxazole. The mixture was stirred for 15 minutes at less than 10°. The product 2-acetamido-4-methyl-5-phenylazooxazole (**IIIi**) was collected by filtration and recrystallized from aqueous ethanol. It formed yellow crystals (2.39 g, 98%) mp 145-147°; ms: m/z 244 ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 2.48 (s, 3H, 4-$CH_3$), 3.33 (s, 3H, NHCO-$CH_3$), 7.55-7.80 (2t, 4H, aromatic H), 11.8 (s, 1H, exchanged with deuterium oxide, NH); ir (potassium bromide): 695, 785, 1245, 1295, 1585, 1610, 1630, 1710, 3200 $cm^{-1}$.

*Anal.* Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.0; H, 5.0; N, 22.9. Found: C, 58.8; H, 4.8; N, 22.8.

Reaction of 2-Acetamido-4-methyloxazole (**IIb**) With *p*-Methoxyphenyldiazonium Fluoborate (**If**).

2-Acetamido-4-methyloxazole (1.40 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) cooled to 0°. *p*-Methoxyphenyldiazonium fluoborate (2.22 g, 0.01 mole) was suspended in ice water (25 ml) and added to the oxazole. The mixture was stirred for 15 minutes at less than 10°. The product 2-acetamido-4-methyl-5-(*p*-methoxyphenylazo)oxazole (**IIIj**) was collected by filtration and was recrystallized from aqueous ethanol. It formed yellow crystals (1.21 g, 44%) mp 173-174°; ms: m/z 274 ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 2.16 (s, 3H, $NHCOCH_3$), 2.44 (s, 3H, 4-$CH_3$), 7.55-7.80 (2t, 4H, aromatic H), 11.8 (s, 1H, exchanged with deuterium oxide, NH).

*Anal.* Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.0; H, 5.0; N, 23.0. Found: C, 58.8; H, 4.8; N, 22.8.

Reaction of 2-Acetamido-4-methyloxazole (**IIb**) With *m*-Chlorophenyldiazonium Fluoborate (**Id**).

2-Acetamido-4-methyloxazole (1.40 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) cooled to 0°. *m*-Chlorophenyldiazonium fluoborate (2.26 g, 0.01 mole) was suspended in ice water (25 ml) and added to the oxazole. The mixture was stirred for 15 minutes at less than 10°. The product 2-acetamido-4-methyl-5-(*m*-chlorophenylazo)oxazole (**IIIk**), was collected by filtration and was recrystallized from aqueous ethanol. It formed yellow crystals (2.50 g, 90%) mp 151-152°; ms: m/z 280, 278 (1:3) ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 2.22 (s, 3H, 4-$CH_3$), 2.45 (s, 3H, $NHCOCH_3$), 7.15-7.85 (m, 4H, aromatic H), 11.9 (s, 1H, exchanged with deuterium oxide, NH); ir (potassium bromide): 790, 1020, 1280, 1500, 1620, 1705, 3220 $cm^{-1}$.

*Anal.* Calcd. for $C_{12}H_{11}ClN_4O_2$: C, 51.7; H, 4.0; N, 20.1. Found: C, 51.5; H, 3.8; N, 19.9.

Reaction of 2-Amino-4-phenyloxazole (**IIc**) With Phenyldiazonium Fluoborate (**Ia**).

2-Amino-4-phenyloxazole (1.60 g, 0.01 mole) was dissolved in aqueous ethanol (1:1) (30 ml) saturated with sodium bicarbonate and cooled to 0°. Phenyldiazonium fluoborate (1.92 g, 0.01 mole) was suspended in ice water (25 ml) and added to the oxazole. The mixture was stirred for 15 minutes at less than 10°. The product 2-amino-4-phenyl-5-phenylazooxazole (**IIIl**) was collected by filtration and recrystallized from aqueous ethanol. It formed red crystals (1.93 g, 73%) mp 99-100°; ms: m/z 264 ($M^+$); pmr (deuterated dimethyl sulfoxide): δ 7.15 (s, 2H, exchanged with deuterium oxide, $NH_2$), 7.30-8.26 (m, 10H, aromatic H); ir (potassium bromide): 695, 780, 1140, 1260, 1320, 1340, 1500, 1580, 1680, 3050-3400 $cm^{-1}$.

*Anal.* Calcd. for $C_{15}H_{12}N_4O$: C, 68.2; H, 4.6; N, 21.2. Found: C, 68.3; H, 4.3; N, 20.9.

Reaction of 2-Amino-4,5-dimethyloxazole with Phenyldiazonium Fluoborate.

2-Amino-4,5-dimethyloxazole (1.12 g, 0.01 mole) was dissolved in sodium bicarbonate solution (30 ml, 5%) cooled to 0°. Phenyldiazonium fluoborate (1.92 g, 0.01 mole) was suspended in water (25 ml), cooled to 0° and added to the oxazole. The mixture was stirred for 15 minutes at less than 10°. No new product formed, and only the fluoborate salt was recovered.

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