Friedel-Crafts Reactions of 2-Amino-4-(alkyl or aryl)oxazoles with Acid Chlorides and Acid Anhydrides: Synthesis of 5-Acyl-2-amino-4-alkyloxazoles

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Acid chlorides and anhydrides react with 2-amino-4-alkyloxazoles in the presence of aluminum chloride to produce 5-acyl substituted 2-amino-4-alkyloxazoles in modest yields. However, in the absence of the Lewis acid reaction occurs at the amino group to give the corresponding amides. This provides a viable entry for functionalising and making carbon-carbon bond at C-5 of this heterocyclic system.

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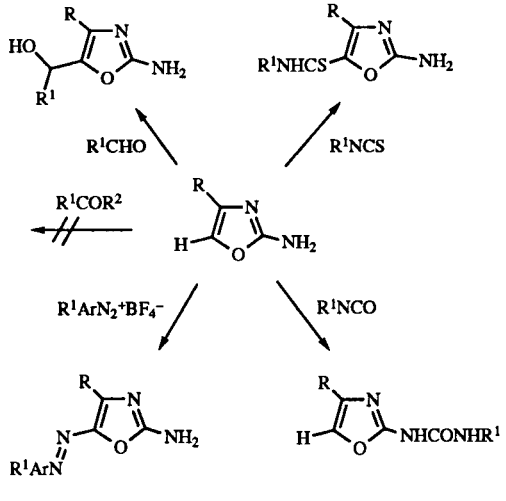
In addition to their potential use as pharmacodynamics agents, heterocycles bearing transposable functional groups are of great importance in modern organic synthesis. Several derivatives of 2-aminooxazoles have been shown to exhibit antiinflammatory activity as well as to cause moderate CNS depression in mice [1]. However, the difficulties associated with their synthesis does appear to be sufficient not to elicite many studies of the chemistry of these heterocycles. Previous work from this laboratory demonstrated that 4-activated 2-aminooxazoles react with electrophiles in a different pattern, depending on conditions, to give the corresponding substitution products. 4-Alkyl and 4-aryl-2-aminooxazoles react with isothiocynates to give good yields of thioamides [2,3]. On the other hand these oxazoles react with isocyanates only at the amino group to form substituted ureas [1].

The reaction of 4-substituted-2-aminooxazoles with aldehydes is also highly selective. Compounds having a 4-alkyl substituents give high yields of 5-hydroxyalkyl or 5-hydroxyaryl derivatives from aliphatic and aromatic aldehydes but 4-aryl substituted compounds do not react with aldeydes [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 C-4 is also insufficient for reaction to occur with ketones. Facile electrophilic substitution at C-5 of 4-alkyl and 4-aryl-2-aminooxazoles occurs also with diazonium salts to give excellent yields of the azo compounds [6].

As a part of our continuing studies on the reactivity of 4-alkyl and 4-aryl-2-aminooxazoles we now wish to report the Friedel-Crafts acylations of this ring system to provide a series of 5-acyl derivatives.

Scheme 1

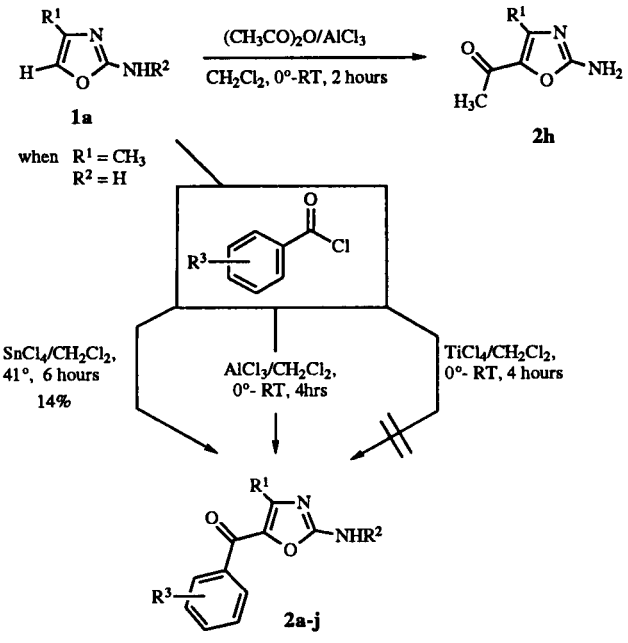


Results and Discussion.

Generally 4-substituted 2-aminooxazoles are prepared by the condensation of cyanamide with either an α-hydroxy or a halogenated ketones. In order to introduce an acyl group at C-5 it would be necessary to employ a 2-hydroxy (or halogenated) 1,3-diketone with cyanamide. In an unsymmetric 1,3-diketone it would be impossible to control the structure of the product, *i.e.*, the substituents at C-4 and C-5 since either carbonyl could be involved in the condensation. In addition, the α-hydroxy diketones are not easily accessible. Thus, in order to avoid separating mixtures and to control the regiochemistry of the product we undertook an investigation of the reaction of acid chlorides with 2-amino-4-methyloxazole (**1a**). The reaction was initially performed in carbon disulfide in the presence of an equimolar amount of aluminum chloride. The product, **2a**, was obtained in low yield. However, an investigation of the reaction conditions found that the use of dichloromethane and two equivalents of aluminum chloride yielded the product in modest yield. Attempts to increase the yield by employing stannic chloride or other Lewis acids were unsuccessful.

The two molar equivalent amount of aluminum chloride is essential, presumably due to a formation of a stable donor-acceptor complex between the Lewis acid and the oxazole, which would tie up at least one equivalent of the reagent thereby reducing the effective concentration of unassociated Lewis acid, and consequently a second equivalent then being necessary to effectuate the reaction.

Scheme 2



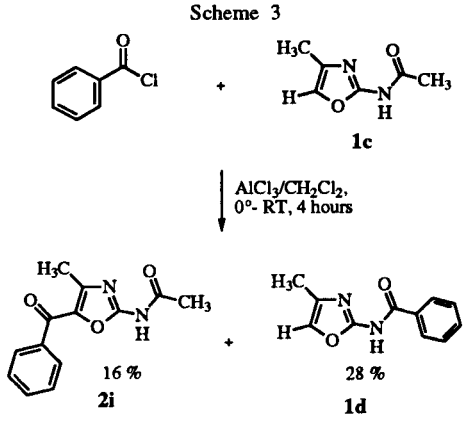
The identities of R^1, R^2, and R^3 are shown in Table 1.

Since the aluminum chloride gives only modest yields (*vide infra*) it became necessary to explore the effects of other Lewis acids, in particular in conjunctions to the coordination effect with this class of heterocycles. As it was anticipated the acylation with the less reactive stannic chloride required an elevated temperature and relatively longer time, nonetheless, neither the yield nor the cleanness was better than that of the aluminum chloride reaction. On the other hand, the reaction with titanium(IV) chloride produced only an interactable polymeric material which proved difficult to purify and characterise.

The scope of the reaction was probed by systematically varying the nature of the substituents on the oxazole nucleus and also the acyl chloride. For example, in one of the cases a deactivating acetyl group replaced one of the hydrogens on the amino group, **1c**, and in the other instance the 4-methyl group was replaced by a phenyl group, **1b** which is a weak resonance donor but an inductive acceptor. These oxazoles were then subjected to acylations under identical conditions to that of the model oxazole **1a**. The 4-phenyloxazole failed to undergo the acylation. This seems to be more of a steric factor than electronic control, where most probably the bulkier phenyl group at position four causes a steric congestion and therefore an attack on the acylium ion might have been hindered.

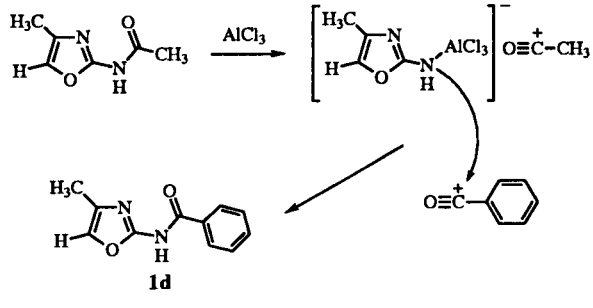
However, when 2-acetyl substituted aminooxazole **1c** was subjected to the same conditions, Scheme 3, the reaction took an unexpected course and gave compound **1d** along with a small amount of the expected product **2i**. These products were easily separable by thin layer chromatography and characterised thoroughly.

Scheme 3



The structure of **1d** was also confirmed unambiguously by comparison with its reported spectroscopic and physical data [3]. The most plausible mechanistic rationalisation that can be offered for product **1d** formation is delineated in Scheme 4, in which an exchange of the acetyl moiety by the benzoyl group has occured on the amino functionality.

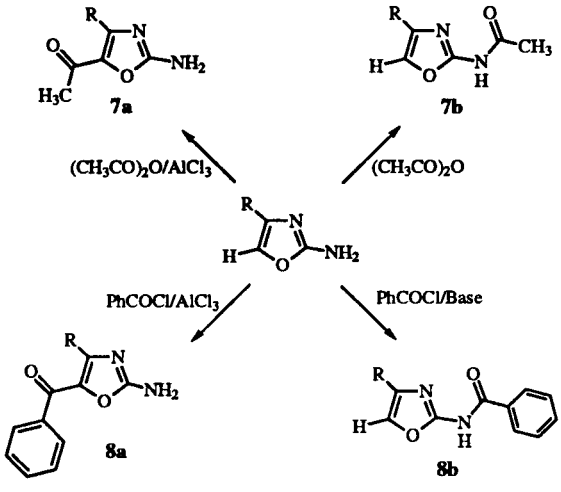
Scheme 4



This new pattern of reactivity has produced a method by which regio control on the orientation of acid chlorides and acid anhydrides substitutions into 2-aminooxazoles can be achieved, through careful adjustment of the experimental conditions. For instance, benzoylation in the presence of a Lewis acid occurs at position five whereas without a Lewis acid catalyst and under basic conditions such as in pyridine, it is the amino group which would be benzoylated to the corresponding amide product in good yield, Scheme 5. In the same way, the reaction of the oxazole with neat acetic anhydride would cause acetylation of the amino group whereas this same reaction in the presence of a Lewis acid acetylates position five of the oxazole ring to give 5-acetyl-2-amino-4-methyloxazole (**2h**). The position of this substitutions of the acyl group on the oxazole was

clearly deduced by comparative analysis of the spectra of the products. In those products where substitution occurs at C-5 the proton magnetic resonance shows the absence of signal attributable for the proton at C-5. This was also substantiated by their ^{13}C nmr spectra.

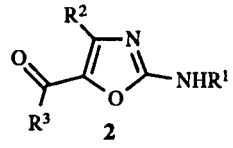
Scheme 5



Besides the need to attest the generality of this reaction it was also of interest to synthesise a core number of 5-aroyloxazoles **2a-g** having different substituents on the phenyl ring for biological screening. The range of products that have been prepared are outlined in Table 1.

Table 1

The Friedel-Crafts Reaction Products of 2-Aminooxazoles



2

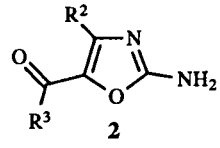
Compound No. 2	R^1	R^2	R^3	Yield %
a	H	CH_3	Ph	47
b	H	CH_3	2-ClPh	40
c	H	CH_3	3-ClPh	43
d	H	CH_3	4-ClPh	49
e	H	CH_3	3-CH_3OPh	46
f	H	CH_3	4-CH_3OPh	36
g	H	CH_3	β-Naphthyl	61
h	H	CH_3	CH_3	35
i	$COCH_3$	CH_3	Ph	16
j	H	$HOCH_2$	3-CH_3OPh	19

Although no clear reasoning can be given for the observed trend of yields versus substituents effects, there are some points which deserve a brief mention. The reaction of 4-methoxybenzoyl chloride required relatively longer time and slightly stronger conditions. This apparently could be due to the strong electron releasing ability of the methoxy group which would stabilise the intermediate carbonium ion significantly, and hence extend its transition state life time before being attacked.

Another peculiar feature also worth pointing out, from the spectral properties of these compounds **2a-g**, is the proton resonance of the NH_2 group which showed a marked shift depending on the nature of substituent (R^3), most likely due to a long range aromatic π-electron interaction with the lone pair electrons of the amino nitrogen. The substituents, depending on their position and electron withdrawing or releasing character, may have a significant role in affecting the extent of this conjugation. These chemical shifts are presented in Table 2.

Table 2

Proton Chemical Shifts of NH_2 group in Compounds **2a-g**.



2

Compound No. 2	R^2	R^3	NH_2 (ppm) [a] [b]
a	CH_3	Ph	7.77
b	CH_3	2-ClPh	8.29
c	CH_3	3-ClPh	8.83
d	CH_3	4-ClPh	8.35
e	CH_3	3-CH_3OPh	9.11
f	CH_3	4-CH_3OPh	8.06
g	CH_3	β-Naphthyl	9.03
h	CH_3	CH_3	7.52
j	$HOCH_2$	3-CH_3OPh	9.09

[a] Spectra were recorded in DMSO-d_6 (300MHz). [b] All these signals disappeared when exchanged with deuterium oxide.

Generally, as already mentioned above these Friedel-Crafts reactions give an important entry to put activated benzoyl or acetyl groups at position five which otherwise proved difficult to obtain either by oxidation of the alcohol of the 5-hydroxyaryloxazole **3** (obtained from the reaction of oxazole and aromatic aldehydes [4,5]) or by utililizing the available synthetic methods for 2-amino-oxazoles and its derivatives.

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 obtained from a Perkin Elmer 298 Infrared Spectrophotometer and mass spectra from an AEI MS 12 mass

spectrometer at 70 eV ionising potential and 8000V accelerating voltage with an ion source temperature of 210°. ^1H and ^{13}C nmr spectra were recorded on a Bruker CXP 300 (300 MHz), A Bruker AC 300F (300 MHz) or a Bruker AM 500 (500 MHz) spectrometer. The ^1H nmr data is reported as follows: chemical shift measured in parts per million (ppm) downfield from TMS (δ), multiplicity, observed coupling constant (J) in Hertz (Hz), proton count. Multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q) and multiplet (m). The ^{13}C nmr chemical shifts (δ) are reported in ppm downfield from TMS and identifiable carbons are given.

Column chromatography was carried out using Merck silica gel 7736 60H, whilst preparative thin layer chromatography (ptlc) was performed using Merck silica gel 7730 60 GF_{254}. Starting materials were analytical grade reagents and were checked for purity before use and all solvents were distilled before use. 2-Amino-4-methyloxazole (**1a**) [8], 2-amino-4-phenyloxazole (**1b**) [2], and 2-acetamido-4-methyloxazole (**1c**) [5] were prepared according to literature procedures.

2-Amino-5-benzoyl-4-methyloxazole (**2a**).

Into a three necked round bottom flask (50 ml), which was equipped with a thermometer, a pressure equalizing dropping funnel, and a double layer condenser fitted with a calcium chloride guard tube, was placed 2-amino-4-methyloxazole (**1a**) (1.0 g, 0.01 mole) and dry dichloromethane (20 ml). This homogenous solution was cooled with an ice-salt bath, and anhydrous finely powdered aluminum chloride (2.72 g, 0.02 mole) was introduced portionwise over 15 minutes. with stirring, while controlling the internal temperature below 5°. The mixture was stirred until all the aluminum chloride was dissolved. Then, dry benzoyl chloride (1.43 g, 0.01 mole) was added slowly dropwise over 20 minutes. The ice bath was removed, the mixture was allowed to warm to room temperature, and stirred for 4 hours. This was poured onto crushed ice and neutralized with saturated aqueous sodium bicarbonate solution (50 ml). The organic layer was separated. The aqueous phase was extracted with chloroform (3 x 30 ml). The combined organic phase was washed with sodium bicarbonate solution (10%, 50 ml) and dried over sodium sulfate. The solvent was removed *in vacu'o*. The resulting yellow solid was filtered off and recrystallised from ethyl acetate/petroleum ether (60-80°). It formed a yellow crystalline product **2a** (0.96 g, 47%) mp 196-197°; ir (potassium bromide): 675 (m), 735 (s), 928 (s), 942 (s), 1030 (m), 1230 (m), 1305 (s), 1407 (m), 1580 (s), 1625 (s), 1680 (vs), 3120 (m), 3305 (s) cm^{-1}; ms: m/z (relative intenensity %) 202 (M^+, 74), 201 (M-1, 100), 185 (4), 159 (8), 125 (M-Ph, 17), 105 (PhCO, 36), 97 (125-CO, 17), 77 (38), 69 (97-CO, 33), 51 (17), 42 (43); ^1H nmr (deuterated dimethyl sulfoxide): δ 2.23 (s, 3H, CH_3), 7.46-7.55 (m, 3H, aromatic H), 7.77 (s, 2H, exchanged with deuterium oxide, NH_2), 7.81 (d, J = 8.56 Hz, 2H, aromatic H); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 14.9 (CH_3), 128.6 (C-3', aromatic C), 128.6 (C-2', aromatic C), 131.9 (C-4', aromatic C), 138.7 (C-1', aromatic C), 139.6 (C-4), 152.6 (C-5), 162.9 (C-2), 179.7 (CO).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.85. Found: C, 65.02; H, 5.19; N, 13.94.

2-Amino-5-(2'-chlorobenzoyl)-4-methyloxazole (**2b**).

To an ice cold solution of 2-amino-4-methyloxazole (**1a**) (1.0 g, 0.01 mole) in dry dichloromethane (20 ml) was added portionwise anhydrous finely powdered aluminum chloride (2.72 g, 0.02 mole) followed by dropwise addition of 2-chlorobenzoyl chloride (1.78 g, 0.01 mole). The reaction mixture was stirred at room temperature for 24 hours, heated under reflux for 1 hour and poured onto crushed ice and neutralized with saturated aqueous sodium bicarbonate solution (50 ml). The organic layer was separated. The aqueous phase was further extracted with chloroform (3 x 30 ml). The combined organic phase was passed through potassium carbonate, dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting residue was triturated with diethyl ether and filtered. This gave **2b** as light green crystals (0.93 g, 40%) mp >240° dec; ir (potassium bromide): 760 (m), 780 (m), 915 (s), 1010 (s), 1050 (m), 1290 (s), 1320 (m), 1370 (m), 1590 (s), 1650 (vs), 1690 (s), 3400 (m) cm^{-1}; ms: m/z (relative intenensity %): 238 (M+2, 25), 236 (M^+, 78), 235 (M-1, 21), 201 (M-Cl, 100), 159 (M-77, 24), 139 (M-97, 36), 125 (M-ClPh, 14), 111 (139-CO, 21), 97 (M-ClPhCO, 29), 75 (16), 69 (97-CO, 37), 42 (56); ^1H nmr (deuterated dimethyl sulfoxide): δ 1.92 (s, 3H, CH_3), 7.45-7.58 (m, 4H, aromatic H), 8.29 (bs, 2H, exchanged with deuterium oxide, NH_2); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 13.6 (CH_3), 127.9, 129.0, 130.0, 130.1, 131.8, 138.7, 139.3 (C-4), 151.2 (C-5), 162.7 (C-2), 178.0 (CO).

Anal. Calcd. for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.83. Found: C, 55.62; H, 3.89; N, 11.53.

2-Amino-5-(3'-chlorobenzoyl)-4-methyloxazole (**2c**).

To an ice cold solution of 2-amino-4-methyloxazole (1.0 g, 0.01 mole) in dry dichloromethane (20 ml) was added portionwise anhydrous finely powdered aluminum chloride (2.72 g, 0.02 mole) followed by dropwise addition of 3-chlorobenzoyl chloride (1.78 g, 0.01 mole). The reaction mixture was stirred at room temperature for 24 hours and poured onto crushed ice and neutralized with saturated aqueous sodium bicarbonate solution (50 ml). The organic layer was separated. The aqueous phase was further extracted with chloroform (3 x 30 ml). The combined organic phase was passed through a short column of potassium carbonate, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to dryness. The resulting yellowish residue was triturated with diethyl ether and filtered. This gave **2c** as brown crystals (1.04 g, 43%) mp 186-188°; ir (potassium bromide): 720 (s), 740 (s), 885 (w), 955 (m), 1025 (s), 1080 (m), 1180 (s), 1260 (m), 1315 (s), 1370 (s), 1585 (m), 1615 (s), 1660 (s), 1690 (vs), 3100 (w), 3275 (w) cm^{-1}; ms: m/z (relative intenensity %): 238 (M+2, 11), 236 (M^+, 35), 235 (M-1, 50), 201 (M-Cl, 13), 158 (20), 156 (59), 139 (M-97, 100), 113 (29), 111 (86), 97 (M-ClPhCO, 28), 76 (20), 75 (74), 69 (77), 42 (64); ^1H nmr (deuterated dimethyl sulfoxide): δ 2.29 (s, 3H, CH_3), 7.55 (dd, J = 7.86, 7.78 Hz, aromatic H), 7.68 (d, J = 8.30 Hz, 1H, aromatic H), 7.78 (d, J = 7.70 Hz, 1H, aromatic H), 7.82 (s, 1H, aromatic H), 8.83 (bs, 2H, exchanged with deuterium oxide, NH_2); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 13.3 (CH_3), 127.6, 128.5, 130.8, 132.4, 133.6, 138.7, 139.6 (C-4), 147.3 (C-5), 160.5 (C-2), 178.7 (CO).

Anal. Calcd. for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.83. Found: C, 55.56; H, 4.02; N, 11.94.

2-Amino-5-(4'-chlorobenzoyl)-4-methyloxazole (**2d**).

This was prepared in the same way as compound **2c** from 2-amino-4-methyloxazole (1.0 g, 0.01 mole), anhydrous aluminum chloride (2.72 g, 0.02 mole), and 4-chlorobenzoyl chloride (1.78 g, 0.01 mole). The crude product was recrystallised from ethyl acetate/petroleum ether (60-80°). This gave **2d** as

brown crystals (1.19 g, 49%) mp 203-205°; ir (potassium bromide): 745 (w), 780 (m), 830 (m), 915 (m), 1010 (s), 1080 (m), 1265 (m), 1320 (m), 1580 (m), 1610 (s), 1660 (m), 1680 (vs), 3200 (bm) cm^{-1}; ms: m/z (relative intenensity %): 238 (M+2, 26), 236 (M^+, 26), 235 (M-1, 54), 201 (M-Cl, 27), 159 (M-77), 141 (14), 139 (M-97, 47), 125 (M-ClPh, 8), 113 (19), 111 (97-CO, 46), 97 (M-ClPhCO, 28), 75 (111-HCl, 37), 69 (97-CO, 76), 42 (100), 36 (HCl, 73); ^1H nmr (deuterated dimethyl sulfoxide): δ 2.28 (s, 3H, CH_3), 7.59 (d, J = 8.54 Hz, 2H, aromatic H), 7.85 (d, J = 8.54 Hz, 2H, aromatic H), 8.35 (bs, 2H, exchanged with deuterium oxide, NH_2); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 13.4 (CH_3), 128.9 (C-3', aromatic C), 130.8 (C-2', aromatic C), 136.4, 137.5, 138.8, 147.2 (C-5), 160.6 (C-2), 178.9 (CO).

Anal. Calcd. for $C_{11}H_9N_2O_2Cl$: C, 55.83; H, 3.83; N, 11.83. Found: C, 55.50; H, 4.07; N, 11.61.

2-Amino-5-(3'-methoxybenzoyl)-4-methyloxazole (**2e**).

This was prepared in a similar manner as compound **2a** from 2-amino-4-methyloxazole (1.0 g, 0.01 mole), anhydrous aluminum chloride (2.72 g, 0.02 mole), and 3-methoxybenzoyl chloride (1.74 g, 0.01 mole). The crude product was crystallised from ethyl acetate/petroleum ether (60-80°). This gave **2e** as shiny yellow crystals (1.10 g, 46%) mp 166-168°; ir (potassium bromide): 752 (m), 850 (m), 910 (s), 1005 (s), 1145 (m), 1310 (s), 1360 (m), 1575 (s), 1590 (s), 3120 (w), 3390 (m) cm^{-1}; ms: m/z (relative intenensity %): 232 (M^+, 53), 231 (M-1, 55), 217 (M-CH_3, 12), 201 (21), 189 (17), 135 (M-97, 35), 107 (135-CO, 21), 97 (M-CH_3OPhCO, 22), 92 (35), 77 (39), 69 (97-CO, 66), 42 (100); ^1H nmr (deuterated dimethyl sulfoxide): δ 2.28 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 7.17 (d, J = 7.40 Hz, 1H, aromatic H), 7.34 (s, 1H, aromatic H), 7.38-7.46 (m, 2H, aromatic H), 9.11 (bs, 2H, exchanged with deuterium oxide, NH_2); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 12.3, 130.1, 138.7, 138.8, 144.4, 159.5, 159.6, 180.4 (CO).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.21; N, 12.06. Found: C, 61.92, H, 5.34; N, 11.89.

2-Amino-5-(4'-methoxybenzoyl)-4-methyloxazole (**2f**).

This was obtained in the same manner as compound **2a** from 2-amino-4-methyloxazole (1.0 g, 0.01 mole), anhydrous aluminum chloride (2.72 g, 0.02 mole), and 4-methoxybenzoyl chloride (1.74 g, 0.01 mole), except the reaction mixture was refluxed for an additional 2 hours. The crude product was recrystallised from ethyl acetate/petroleum ether (60-80°). This gave **2f** as a yellowish-brown solid (0.86 g, 36%) mp 236-238°; ir (potassium bromide): 750 (m), 840 (m), 840 (m), 1010 (s), 1160 (s), 1250 (s), 1300 (s), 1340 (m), 1360 (m), 1570 (s), 1595 (s), 1690 (vs), 3125 (w), 3380 (m) cm^{-1}; ms: m/z (relative intenensity %): 232 (M^+, 33), 231 (M-1, 59), 217 (M-CH_3, 8), 201 (M-CH_3O, 31), 189 (13), 152 (18), 135 (M-97, 100), 107 (135-CO, 18), 92 (41), 77 (45), 69 (97-CO, 50), 42 (87); ^1H nmr (deuterated dimethyl sulfoxide): δ 2.27 (s, 3H, CH_3), 3.83 (s, 3H, CH_3O), 7.02 (d, J = 8.84 Hz, 2H, aromatic H), 7.87 (d, J = 8.83 Hz, 2H, aromatic H), 8.06 (bs, 2H, exchanged with deuterium oxide, NH_2); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 14.3 (CH_3), 55.8 (CH_3O), 113.9 (C-3', aromatic C), 130.5 (C-1', aromatic C), 131.2 (C-2', aromatic C), 139.3 (C-4), 149.2 (C-5), 161.6 (C-2), 162.7 (C-4', aromatic C), 178.6 (CO).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.21; N, 12.06. Found: C, 61.88; H, 5.38; N, 12.19.

2-Amino-4-methyl-5-(β–naphthoyl)oxazole (**2g**).

To an ice cold solution of 2-amino-4-methyloxazole (1.0 g, 0.01 mole) in dry dichloromethane (20 ml) was added portionwise anhydrous finely powdered aluminum chloride (2.72 g, 0.02 mole) followed by dropwise addition of a solution of β-naphthoyl chloride (1.94 g, 0.01 mole) in dry dichloromethane (15 ml). The mixture was stirred at room temperature for 24 hours and poured onto ice and neutralized with saturated aqueous sodium bicarbonate solution (50 ml). The organic layer was separated. The aqueous layer was extracted with chloroform (3 x 30 ml). The combined organic phase was passed through a short column of potassium carbonate, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. The resulting residue was triturated with diethyl ether and filtered. This gave **2g** as an off-white hygroscopic solid (1.55g, 61%) mp 191-193°; ir (potassium bromide): 750 (s), 770 (s), 825 (m), 910 (m), 1025 (m), 1110 (m), 1160 (m), 1310 (m), 1375 (s), 1600 (s), 1650 (s), 1695 (vs), 3225 (m) cm^{-1}; ms: m/z (relative intenensity %): 253 (M+1, 2), 252 (M^+, 11), 172 (100), 155 (NaphthCO, 57), 127 (OxazCO, 53), 36 (27); ^1H nmr (deuterated dimethyl sulfoxide): δ 2.31 (s, 3H, CH_3), 3.68 (bs, H_2O), 7.55-7.67 (m, 2H, naphthalene H), 7.87 (d, J = 8.55 Hz, 1H, naphthalene H), 7.96-8.14 (m, 3H, naphthalene H), 8.53 (s, 1H, naphthalene H), 9.03 (bs, 2H, exchanged with deuterium oxide, NH_2); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 13.1 (CH_3), 125.0, 127.2, 128.0, 128.5, 128.8, 129.8, 130.4, 132.5, 135.3, 139.0, 145.3 (C-4), 160.1 (C-5), 167.8 (C-2), 180.3 (CO).

Anal. Calcd. for $C_{15}H_{12}N_2O_2 \cdot 3/5H_2O$: C, 68.49; H, 5.06; N, 10.64. Found: C, 68.18; H, 5.38; N, 10.26.

5-Acetyl-2-amino-4-methyloxazole (**2h**).

To an ice cold solution of 2-amino-4-methyloxazole (1.0 g, 0.01 mole) in dry dichloromethane (20 ml) was added portionwise anhydrous finely powdered aluminum chloride (2.72 g, 0.02 mole) followed by a dropwise addition of acetic anhydride (1.04 g, 0.01 mole) solution in dry dichloromethane (10 ml). The mixture was stirred at room temperature for 2 hours and poured onto ice and neutralized with saturated aqueous sodium bicarbonate solution (50 ml). The organic layer was separated. The aqueous phase was further extracted with ethyl acetate (2 x 30 ml). The combined organic phase was passed through potassium carbonate, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The resulting residue was crystallised from diethyl ether and collected by filtration. This gave **2h** as white crystals (0.50 g, 35%) mp 185-187°; ir (potassium bromide): 950 (s), 1105 (s), 1295 (vs), 1325 (m), 1370 (s), 1570 (vs), 1635 (s), 1670 (s), 3075-3125 (m), 3340 (s) cm^{-1}; ms: m/z (relative intenensity %): 140 (M^+, 98), 125 (M-CH_3, 100), 97 (M-CH_3CO, 34), 69 (97-CO, 62), 43 (CH_3CO, 45), 42 (76); ^1H nmr (deuterated dimethyl sulfoxide): δ 2.23 (s, 3H, CH_3-4), 2.25 (s, 3H, CH_3CO), 7.52 (s, 2H, exchanged with deuterium oxide, NH_2); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 14.4 (CH_3-4), 27.2 (CH_3CO), 140.1 (C-4), 148.9 (C-5), 162.3 (C-2), 183.5 (CO).

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.43; H, 5.75; N, 19.98. Found: C, 51.28; H, 5.73; N, 19.86.

Reaction of 2-Acetamido-4-methyloxazole with Benzoyl Chloride and Aluminum chloride.

To an ice cold solution of benzoyl chloride (1.41 g, 0.01 mole) in dry dichloromethane (20 ml) was added finely powdered anhydrous

aluminum chloride (2.72 g, 0.02 mole) followed by a dropwise addition of 2-acetamido-4-methyloxazole (1.49 g, 0.01 mole) solution in dry dichloromethane (10 ml). The mixture was stirred at room temperature for 2.5 hours, while protected from moisture with a calcium chloride guard tube, and poured onto ice water (30 ml) and neutralized with saturated aqueous sodium bicarbonate solution (50 ml). The organic phase was separated. The aqueous layer was further extracted with chloroform (3 x 30 ml). The combined organic phase was passed through potassium carbonate, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The resulting residue was purified by preparative thin layer chromatography (dichloromethane/ethyl acetate, 70:30) which gave 2-benzamido-4-methyloxazole (**1d**) (0.56 g, 28%) as a white crystalline solid mp 87-89° (lit [3] 84-86°), and 2-acetamido-5-benzoyl-4-methyloxazole (**2i**) as a white solid (0.40 g, 16%) mp 233-235° which had the following data: ir (potassium bromide): 940 (s), 1115 (s), 1295 (vs), 1330 (m), 1365 (m), 1575 (s), 1640 (s), 1675 (vs), 1680 (vs), 3125 (m) cm^{-1}; ms: m/z (relative intenensity %): 244 (M^+, 16), 229 (11), 186 (M-$COCH_3$, 24), 167 (M-Ph, 73), 124 (15), 105 (PhCO, 37), 97 (10), 69 (58), 43 (61), 42 (100); ^1H nmr (deuterated dimethyl sulfoxide): δ 2.13 (s, 3H, CH_3-4), 2.36 (s, 3H, CH_3CO), 7.22-7.54 (m, 5H, aromatic H), 11.23 (bs, 1H, exchanged with deuterium oxide, NH).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.46. Found: C, 63.66; H, 5.21; N, 11.07.

2-Amino-4-hydroxymethyl-5-(3'-methoxybenzoyl)oxazole (**2j**).

This was prepared in the same way as compound **2a** from 2-amino-4-hydroxymethyloxazole [7] (**5**) (1.14 g, 0.01 mole), anhydrous aluminum chloride (2.72 g, 0.02 mole), and 3-methoxybenzoyl chloride (1.74 g, 0.01 mole). This gave **2j** as a white hygroscopic solid (0.22g, 19%) mp 201-203°, which had the following spectral data: ir (potassium bromide): 755 (m), 830 (m), 850 (m), 1015 (s), 1170 (s), 1255 (s), 1310 (s), 1345 (m), 1575 (s), 1595 (s), 1685 (vs), 3130-3490 (m) cm^{-1}; ms: m/z (relative intenensity %): 248 (M^+, 17), 247 (M-1, 74), 233 (M-CH_3, 13), 230 (M-H_2O, 21), 217 (M-CH_3O, 23), 179 (11), 141 (M-CH_3OPh, 71), 135 (CH_3OPhCO, 100), 113 (18), 107 (21), 93 (33), 55 (9), 28 (84); ^1H nmr (deuterated dimethyl sulfoxide): δ 3.23 (s, 2H, $HOCH_2$), 3.83 (s, 3H, CH_3O), 4.31 (s, 1H, exchanged with deuterium oxide, OH), 7.33-7.62 (m, 4H, aromatic H), 9.09 (bs, 2H, exchanged with deuterium oxide, NH_2).

REFERENCES AND NOTES

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[1] G. Crank and M. J. Foulis, *J. Med. Chem.*, **14**, 1075 (1971).

[2] G. Crank and H. R. Khan, *Aus. J. Chem.*, **38**, 447 (1985).

[3] G. Crank, *Tetrahedron Letters*, 4537 (1974).

[4] G. Crank and H. R. Khan, *Tetrahedron Letters*, **28**, 3381 (1987).

[5] H. R. Khan, G. Crank and S. Jesdapaulpaan, *J. Heterocyclic Chem.*, **25**, 815 (1988).

[6] G. Crank and B. Mekonnen, *J. Heterocyclic Chem*, **29**, 1469 (1992).

[7] B. Mekonnen, *PhD Thesis*, University of New South Wales, Australia, 1993.

[8] A. F. Cockerill, A. Deacon, R. G. Harrison, D. J. Osborne, D. M. Prime, W. J. Ross, A. Todd, and J. P. Verge, *Synthesis*, 591 (1976).