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Ethyl 5-oxo-3-arylamino-2,5-dihydroisoxazole-4-carboxylates as sources of imidazopyrimidine and aminoindole derivatives

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The reaction of ethyl 5-oxo-3-arylamino-2,5-dihydroisoxazole-4- carboxylates with 2-chloropyrimidine and 2-chlorobenzoxazole gave the corresponding isoxazolones with pyrimidine and benzoxazole rings substituted on N-2. Their rearrangements with triethylamine in ethanol produced the corresponding imidazopyrimidine and aminoindole derivatives, respectively, through intramolecular cyclisation.

Key Words: Isoxazolones, 2-chloropyrimidine, 2-chlorobenzoxazole, rearrangements, imidazopyrimidines, aminoindoles

Introduction

The synthesis of some mono- and bis-isoxazolinyl derivatives of pyrimidine **1** and benzothiazole **2** as central nervous system-active compounds and their base-catalysed rearrangements to the corresponding annelated heterocycles have been reported.[1,2]

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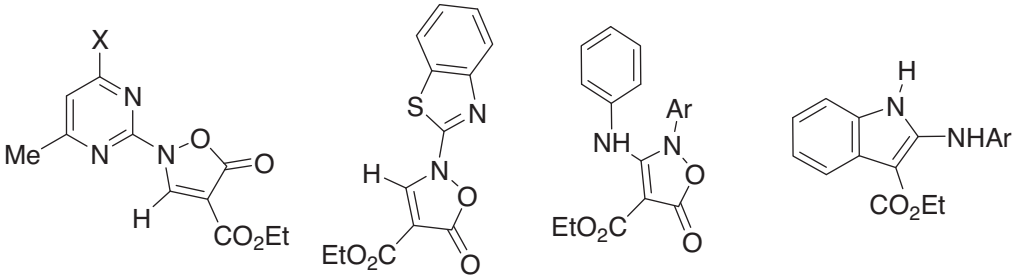
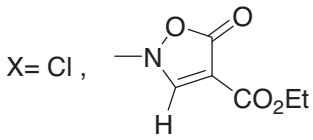
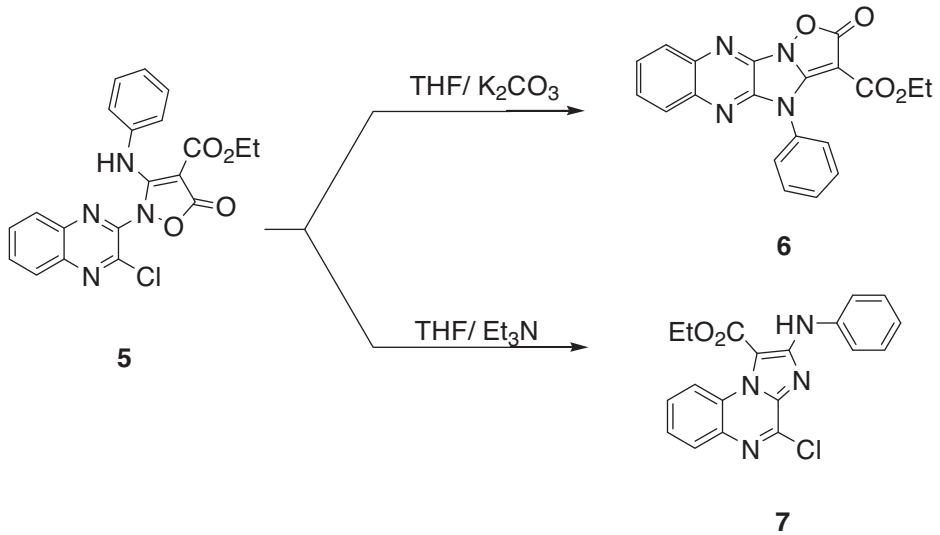


1 **2** **3** **4**



We have recently reported[3] that the reaction of 2-pyridyl-3-arylaminoisoxazolones **3** with triethylamine leads to the formation of indoles **4** and carbon dioxide, an outcome that is formally the same as that achieved by photolysis.[4] The evidence for the indole structure, rather than that of an isomer, rested on the number of aryl proton signals visible in the ^{1}H-NMR spectrum.

We have recently reported[5] that the treatment of quinoxaline **5** with base afforded 2 different rearranged products depending on the kind of base. Its reaction with potassium carbonate in THF under reflux conditions produced tetracyclic compound **6** via intramolecular nucleophilic substitution, but with triethylamine under similar conditions the tricyclic compound **7** was formed (Scheme 1).



5 **6** **7**

Scheme 1

In the present study a number of ethyl 5-oxo-3-arylamino-2,5-dihydroisoxazole-4-carboxylates substituted with nitrogen heterocycles on N-2 were synthesised. Annelated imidazopyrimidine and aminoindole derivatives

were obtained in excellent yields on their treatment with triethylamine in ethanol, which were presumed to arise by intramolecular cyclisation of an imino carbene intermediate.

Experimental section

General procedures. Melting points were determined on a digital melting point apparatus (electrothermal) and remain uncorrected. Infrared spectra were recorded on a Thermonicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as film or KBr disks. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in $CDCl_3$ using TMS as the internal reference. Microanalyses were performed on a Carlo-Erba Analyser 1104.

Ethyl 2-(benzo[d]oxazol-2-yl)-5-oxo-3-(2-bromophenylamino)-2,5-dihydroisoxazole-4-carboxylate (10a)

Ethyl 5-oxo-2-bromophenylamino-2,5-dihydroisoxazole-4-carboxylate (**9a**) (100 mg, 0.3 mmol) and 2-chlorobenzoxazole (47 mg, 0.3 mmol) were refluxed in chloroform (10 mL) for 48 h. The solvent was removed under reduced pressure to give colourless oil; the residue was recrystallised from ethanol to afford ethyl 2-(benzo[d]oxazol-2-yl)-5-oxo-3-(2-bromophenyl amino)-2,5-dihydroisoxazole-4-carboxylate as white needles (82 mg, 60%), mp 130-132 °C. Anal calcd for $C_{19}H_{14}BrN_3O_5$: C, 51.37; H, 3.18; N, 9.46%. Found: C, 51.22; H, 3.28; N, 9.61%. ^{1}H-NMR ($CDCl_3$): δ 1.40 (t, J = 7.2 Hz, 3H, CH_3), 4.41 (q, J = 7.2 Hz, 2H, CH_2), 6.82 (t, J = 7.8 Hz, 1H, Ar), 6.99 (t, J = 7.8 Hz, 1H, Ar), 7.25 (t, J = 8.4 Hz, 1H, Ar), 7.29 (d, J = 7.2 Hz, 1H, Ar), 7.34 (d, J = 7.2 Hz, 1H, Ar), 7.41 (d, J = 7.8 Hz, 1H, Ar), 7.46 (t, J = 7.8 Hz, 1H, Ar), 7.48 (d, J = 8.7 Hz, 1H, Ar), 10.05 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.38, 61.27, 79.48, 110.84, 118.06, 120.65, 123.13, 125.47, 126.78, 127.96, 128.21, 133.29, 134.16, 139.31, 149.62, 150.93, 163.27, 163.62, 164.46 ppm; FT-IR (KBr): ν 3189, 3097, 2992, 1784, 1671, 1624, 1570, 1499, 1449, 1237, 1023, 983, 791, 753 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-yl)-5-oxo-3-(3-bromophenylamino)-2,5-dihydroisoxazole-4-carboxylate (10b)

This compound was prepared as described for **10a** using the corresponding isoxazolone (**9b**)[6] (100 mg, 0.3 mmol) and 2-chlorobenzoxazole (47 mg, 0.3 mmol) and recrystallising from ethanol to afford the desired product as cream needles (87 mg, 64%), mp 149-151 °C. Anal calcd for $C_{19}H_{14}BrN_3O_5$: C, 51.37; H, 3.18; N, 9.46%. Found: C, 51.41; H, 3.01; N, 9.69%. ^{1}H-NMR ($CDCl_3$): δ 1.42 (t, J = 7.2 Hz, 3H, CH_3), 4.42 (q, J = 7.2 Hz, 2H, CH_2), 7.05 (d, J = 7.5 Hz, 1H, Ar), 7.08-7.12 (m, 2H, Ar), 7.32 (dd, J_1 = 8.7 Hz, J_2 = 1.2 Hz, 1H, Ar), 7.35 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H, Ar), 7.39 (td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H, Ar), 7.48 (t, J = 8.7 Hz, 1H, Ar), 7.51 (t, J = 7.8 Hz, 1H, Ar), 9.98 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.37, 61.34, 79.28, 110.98, 120.62, 122.82, 125.55, 125.58, 126.97, 129.79, 130.56, 132.31, 136.56, 139.23, 149.71, 150.95, 163.21, 163.76, 164.75 ppm; FT-IR (KBr): ν 3282, 3074, 2981, 1786, 1668, 1628, 1582, 1488, 1450, 1288, 1198, 1031, 767, 792 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-yl)-5-oxo-3-(*o*-tolylamino)-2,5-dihydroisoxazole-4-carboxylate (10c)

This compound was prepared as described for **10a** using the corresponding isoxazolone (**9c**)[7] (100 mg, 0.38 mmol) and 2-chlorobenzoxazole (58 mg, 0.38 mmol) and recrystallising from ethanol to afford the desired product as white needles (78 mg, 54%), mp 130-132 °C. Anal calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08%. Found: C, 63.43; H, 4.44; N, 11.01%. ^{1}H-NMR ($CDCl_3$): δ 1.41 (t, J = 7.2 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.40 (q, J = 7.2 Hz, 2H, CH_2), 6.84 (d, J = 8.4 Hz, 1H, Ar), 6.87 (t, J = 8.4 Hz, 1H, Ar), 7.01 (t, J = 8.7 Hz, 1H, Ar), 7.12 (dd, J_1 = 6.9 Hz, J_2 = 1.5 Hz, 1H, Ar), 7.26-7.35 (m, 2H, Ar), 7.37 (dd, J_1 = 7.4 Hz, J_2 = 1.5 Hz, 1H, Ar), 7.46 (dd, J_1 = 6.9 Hz, J_2 = 1.5 Hz, 1H, Ar), 9.71 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.42, 17.81, 61.04, 78.26, 110.79, 120.55, 123.73, 125.35, 126.55, 126.79, 127.67, 130.93, 133.07, 133.55, 139.37, 149.64, 151.16, 163.66, 165.04, 165.10 ppm; FT-IR (KBr): ν 3266, 3078, 2983, 1782, 1632, 1487, 1388, 1351, 1287, 1231, 1028, 796, 754 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-yl)-5-oxo-3-(*m*-tolylamino)-2,5-dihydroisoxazole-4-carboxylate (10d)

This compound was prepared as described for **10a** using the corresponding isoxazolone (**9d**)[6] (100 mg, 0.38 mmol) and 2-chlorobenzoxazole (58 mg, 0.38 mmol) and recrystallising from ethanol to afford the desired product as cream prisms (84 mg, 58%), mp 121-123 °C. Anal calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08%. Found: C, 63.50; H, 4.44; N, 11.15%. ^{1}H-NMR ($CDCl_3$): δ 1.43 (t, J = 7.2 Hz, 3H, CH_3), 2.11 (s, 3H, CH_3), 4.42 (q, J = 7.2 Hz, 2H, CH_2), 6.74 (d, J = 6.9 Hz, 1H, Ar), 6.75-7.2 (m, 3H, Ar), 7.31 (d, J= 9 Hz, 1H, Ar), 7.39 (d, J = 8.7 Hz, 1H, Ar), 7.46 (d, J= 9 Hz, 1H, Ar), 7.51 (d, J = 7.5 Hz, 1H, Ar), 9.90 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.41, 20.91, 61.13, 78.53, 110.82, 119.43, 120.64, 123.03, 125.4, 126.83, 127.60, 129.17, 135.01, 139.41, 139.57, 149.7, 151.24, 163.6, 164.23, 164.93 ppm; FT-IR (KBr): ν 3281, 3069, 1785, 1670, 1630, 1607, 1583, 1489, 1288, 1216, 1030, 986, 792 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-yl)-3-(3-methoxyphenylamino)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (10e)

This compound was prepared as described for **10a** using the corresponding isoxazolone (**9e**) (100 mg, 0.36 mmol) and 2-chlorobenzoxazole (55 mg, 0.36 mmol) and recrystallising from ethanol to afford the desired product as brown needles (85 mg, 60%), mp 133-135 °C. Anal calcd for $C_{20}H_{17}N_3O_6$: C, 60.76; H, 4.33; N, 10.63%. Found: C, 60.45; H, 4.62; N, 10.50%. ^{1}H-NMR ($CDCl_3$): δ 1.43 (t, J = 7.2 Hz, 3H, CH_3), 3.65 (s, 3H, CH_3), 4.43 (q, J = 7.2 Hz, 2H, CH_2), 6.49 (d, J = 8.4 Hz, 1H, Ar), 6.71 (bs, 1H, Ar), 6.76 (d, J= 8.1 Hz, 1H, Ar), 7.01 (t, J = 8.1 Hz, 1H, Ar), 7.32 (d, J = 7.5 Hz, 1H, Ar), 7.38 (t, J = 7.8 Hz, 1H, Ar), 7.46 (d, J = 7.8 Hz, 1H, Ar), 7.51 (t, J = 8.7 Hz, 1H, Ar), 9.95 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.41, 55.33, 61.21, 78.81, 107.63, 110.88, 112.9, 114.23, 120.68, 125.44, 126.83, 130.18, 136.26, 139.39, 149.73, 151.34, 160.28, 163.51, 164.06, 164.91 ppm; FT-IR (KBr): ν 3182, 2972, 1783, 1682, 1640, 1608, 1589, 1493, 1296, 1155, 1029, 796, 795, 765, 752 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-yl)-5-oxo-3-(4-nitrophenylamino)-2,5-dihydroisoxazole-4-carboxylate (10f)

This compound was prepared as described for **10a** using the corresponding isoxazolone (**9f**)[6] (100 mg, 0.34 mmol) and 2-chlorobenzoxazole (52 mg, 0.34 mmol) and recrystallising from ethanol to afford the desired product as yellow needles (95 mg, 68%), mp 157-159 °C. Anal calcd for $C_{19}H_{14}N_4O_7$: C, 55.61; H, 3.44; N, 13.65%. Found: C, 55.74; H, 3.21; N, 13.52%. ^{1}H-NMR ($CDCl_3$): δ 1.43 (t, J = 7.2 Hz, 3H, CH_3), 4.44 (q, J = 7.2 Hz, 2H, CH_2), 7.31 (d, J = 8.4 Hz, 2H, Ar), 7.33 (d, J = 8.7 Hz, 1H, Ar), 7.38 (d, J = 8.1 Hz, 1H, Ar), 7.46 (t, J = 8.1 Hz, 1H, Ar), 7.52 (t, J = 8.1 Hz, 1H, Ar), 8.07 (d, J = 8.4 Hz, 2H, Ar), 10.33 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.41, 61.74, 81.30, 111.08, 119.41, 120.57, 121.14, 125.21, 125.68, 127.12, 138.93, 141.43, 144.94, 149.68, 151.01, 162.98, 164.54 ppm; FT-IR (KBr): ν 3230, 3086, 2981, 1783, 1666, 1626, 1590, 1506, 1344, 1208, 1027, 788, 748 cm^{-1}.

Ethyl 3-(3-bromophenylamino)-5-oxo-2-(pyrimidin-2-yl)-2,5-dihydroisoxazole-4-carboxylate (11b)

A mixture of 2-chloropyrimidine (34 mg, 0.3 mmol) and ethyl 3-(3-bromophenyl) amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate[6] (100 mg, 0.3 mmol) was heated neat under the atmosphere of nitrogen in oil bath at 130 °C for 20 min. The residue was recrystallised from ethanol to give the desired isoxazolone as white needles (100 mg, 81%), mp 181-183 °C. Anal calcd for $C_{16}H_{13}BrN_4O_4$: C, 47.43; H, 3.23; N, 13.83%. Found: C, 47.22; H, 3.10; N, 14.02%. ^{1}H-NMR ($CDCl_3$): δ 1.34 (t, J = 7.2 Hz, 3H, CH_3), 4.31 (q, J = 7.2 Hz, 2H, CH_2), 7.07 (t, J = 7.5 Hz, 1H, Ar), 7.09 (dt, J_1= 6.6 Hz, J_2 = 1.8 Hz, 1H, Ar), 7.15 (t, J = 4.8 Hz, 1H, Ar), 7.21 (dt, J_1 = 6.6 Hz, J_2 = 2.0 Hz, 1H, Ar), 7.32 (bt, J = 1.8 Hz, 1H, Ar), 8.58 (d, J = 4.8 Hz, 2H, Ar), 10.26 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.32, 60.97, 79.35, 119.27, 120.19, 122.69, 124.89, 128.86, 130.40, 138.65, 156.01, 158.57, 160.62, 163.36, 164.33 ppm; FT-IR (KBr): ν 3207, 3075, 2981, 1759, 1695, 1575, 1550, 1395, 1069, 780 cm^{-1}.

The following compounds were prepared by the same method.

Ethyl 5-oxo-2-(pyrimidin-2-yl)-3-(*m*-tolylamino)-2,5-dihydroisoxazole-4-carboxylate (11d)

Isoxazolone **9d**[6] (100 mg, 0.38 mmol) and 2-chloropyrimidine (43 mg, 0.38 mmol) gave **11d** (98 mg, 75%) as yellow prisms after recrystallisation from ethanol, mp 168-170 °C. Anal calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46%. Found: C, 60.21; H, 4.55; N, 16.52%.^{1}H-NMR ($CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.31 (q, J = 7.2 Hz, 2H, CH_2), 6.85 (d, J = 7.5 Hz, 1H, Ar), 6.93 (bt, J = 7.5 Hz, 1H, Ar), 6.96 (bs, 1H, Ar), 7.04 (d, J = 7.8 Hz, 1H, Ar), 7.10 (t, J = 4.8 Hz, 1H, Ar), 8.54 (d, J = 4.8 Hz, 2H, Ar), 10.13 (s, 1H, NH, removed by D_2O addition) ppm;^{13}C-NMR ($CDCl_3$) δ 14.34, 21.13, 60.78, 78.73, 118.71, 119.26, 122.27, 126.63, 128.99, 137.08, 139.32, 156.28, 158.47, 161.23, 163.82, 164.62 ppm; FT-IR (KBr): ν 3203, 3078, 2979, 1758, 1698, 1578, 1394, 1070, 834, 781, 691 cm^{-1}.

Ethyl 5-oxo-2-(pyrimidin-2-yl)-3-(*p*-tolylamino)-2,5-dihydroisoxazole-4-carboxylate (11j)

Isoxazolone **9j**[8] (100 mg, 0.38 mmol) and 2-chloropyrimidine (43 mg, 0.38 mmol) gave **11j** (94 mg, 74%) as pale yellow prisms after recrystallisation from ethanol, mp 187-189 °C. Anal calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H,

4.74; N, 16.46%. Found: C, 60.11; H, 4.61; N, 16.46%. ^{1}H-NMR ($CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.32 (q, J = 7.1 Hz, 2H, CH_2), 6.98 (d, J = 8.7 Hz, 2H, Ar), 7.03 (d, J = 8.7 Hz, 2H, Ar), 7.09 (t, J = 4.8 Hz, 1H, Ar), 8.53 (d, J = 4.8 Hz, 2H, Ar), 10.10 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.36, 20.85, 60.78, 78.62, 119.24, 121.71, 129.73, 134.64, 135.83, 156.35, 158.48, 161.61, 163.87, 164.74 ppm; FT-IR (KBr) ν 3207, 3083, 2985, 1761, 1699, 1579, 1558, 1393, 1371, 1069, 781 cm^{-1}.

Ethyl 5-oxo-3-(4-bromophenylamino)-2-(pyrimidin-2-yl)-2,5-dihydroisoxazole-4-carboxylate (11h)

Isoxazolone **9h**[8] (100 mg, 0.3 mmol) and 2-chloropyrimidine (34 mg, 0.3 mmol) gave **11h** (110 mg, 85%) as white prism after recrystallisation from ethanol, mp 202-204 °C. Anal calcd for $C_{16}H_{13}BrN_4O_4$: C, 47.43; H, 3.23; N, 13.83%. Found: C, 47.29; H, 3.32; N, 14.09%. ^{1}H-NMR ($CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 3H, CH_3), 4.33 (q, J = 7.2 Hz, 2H, CH_2), 7.05 (d, J = 8.7 Hz, 2H, Ar), 7.14 (t, J = 4.8 Hz, 1H, Ar), 7.32 (d, J = 8.7 Hz, 2H, Ar), 8.57 (d, J = 4.8 Hz, 2H, Ar), 10.19 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.33, 60.96, 79.27, 118.96, 119.37, 123.24, 132.29, 136.56, 156.16, 158.59, 161.13, 163.44, 164.58 ppm; FT-IR (KBr): ν 3310, 3208, 3083, 1759, 1698, 1601, 1578, 1556, 1392, 1069, 835, 781 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-ylamino)-7-bromo-1H-indole-3-carboxylate (12a)

N-aryl isoxazolone (**10a**) (100 mg, 0.22 mmol) and triethylamine (0.4 mL) were refluxed in ethanol (10 mL) for 48 h. The reaction mixture was left to cool to room temperature and the resulting precipitate was collected to afford ethyl 2-(benzoxazol-2-ylamino)-7-bromo-1H-indole-3-carboxylate as white prisms (62 mg, 69%), mp 128-130 °C. Anal calcd for $C_{18}H_{14}BrN_3O_3$: C, 54.02; H, 3.53; N, 10.50%. Found: C, 53.99; H, 3.45; N, 10.65%. ^{1}H-NMR ($CDCl_3$): δ 1.55 (t, J = 7.2 Hz, 3H, CH_3), 4.55 (q, J = 7.2 Hz, 2H, CH_2), 6.85 (t, J = 7.5 Hz, 1H, Ar), 7.30-7.40 (m, 3H, Ar), 7.55 (t, J = 6.9 Hz, 2H, Ar), 8.21 (bs, 1H, NH, removed by D_2O addition), 8.58 (d, J = 8.1 Hz, 1H, Ar), 9.35 (bs, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 15.02, 60.57, 112.07, 113.89, 114.19, 118.55, 122.23, 124.08, 124.14, 124.81, 127.37, 128.35, 132.41, 134.19, 138.12, 149.89, 153.39, 156.64 ppm; FT-IR (KBr): ν 3289, 2998, 1668, 1628, 1613, 1596, 1569, 1557, 1272, 1199, 1076, 1021, 756, 742 cm^{-1}.

The following aminoindoles were made by the same procedure.

Ethyl 2-(benzo[d]oxazol-2-ylamino)-6-bromo-1H-indole-3-carboxylate (12b)

N-aryl isoxazolone **10b** (100 mg, 0.22 mmol) gave **12b** as cream prisms (61 mg, 68%), mp 155-157 °C. Anal calcd for $C_{18}H_{14}BrN_3O_3$: C, 54.02; H, 3.53; N, 10.50%. Found: C, 53.91; H, 3.36; N, 10.71%. ^{1}H-NMR ($CDCl_3$): δ 1.58 (t, J = 7.2 Hz, 3H, CH_3), 4.52 (q, J = 7.2 Hz, 2H, CH_2), 7.19-7.39 (m, 4H, Ar), 7.52 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H, Ar), 7.54 (d, J = 7.5 Hz, 1H, Ar), 7.93 (bs, 1H, NH, removed by D_2O addition), 8.75 (bs, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.84, 60.46, 112.20, 113.40, 116.43, 120.61, 122.85, 124.15, 124.61, 124.81, 127.34, 130.32, 132.41, 133.65, 141.38, 145.31, 149.86, 158.32 ppm; FT-IR (KBr): ν 3423, 3305, 2979, 1660, 1628, 1617, 1593, 1568, 1552, 1477, 1444, 1197, 741 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-ylamino)-7-methyl-1H-indole-3-carboxylate (12c)

N-aryl isoxazolone **10c** (100 mg, 0.25 mmol) gave **12c** as cream prisms (53 mg, 60%), mp 168-170 °C. Anal calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%. Found: C, 67.95; H, 5.22; N, 12.63%. ^{1}H-NMR ($CDCl_3$): δ 1.54 (t, J = 6.9 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.52 (q, J = 6.9 Hz, 2H, CH_2), 6.96 (t, J = 7.2 Hz, 1H, Ar), 7.20 (d, J = 7.2 Hz, 1H, Ar), 7.25-7.38 (m, 3H, Ar), 7.51 (d, J = 7.8 Hz, 1H, Ar), 7.94 (bs, 1H, NH, removed by D_2O addition), 8.33 (d, J = 8.4 Hz, 1H, Ar), 8.78 (bs, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.92, 17.92, 60.28, 112.05, 113.30, 114.35, 118.07, 121.86, 123.86, 124.70, 125.48, 126.99, 127.47, 130.29, 137.31, 138.48, 149.83, 151.83, 155.09 ppm; FT-IR (KBr): ν 3326, 2979, 1652, 1625, 1592, 1477, 1441, 1267, 1193, 1077, 749 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-ylamino)-6-methyl-1H-indole-3-carboxylate (12d)

N-aryl isoxazolone **10d** (100 mg, 0.25 mmol) gave **12d** as pale yellow needles (56 mg, 64%), mp 125-127 °C. Anal calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%. Found: C, 67.89; H, 5.28; N, 12.59%. ^{1}H-NMR ($CDCl_3$): δ 1.57 (t, J = 6.9 Hz, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.51 (q, J = 6.9 Hz, 2H, CH_2), 6.84 (d, J= 7.2 Hz, 1H, Ar), 7.22 (d, J = 7.2 Hz, 1H, Ar), 7.27-7.40 (m, 3H, Ar), 7.45 (bs, 1H, Ar), 7.54 (d, J = 8.1 Hz, 1H, Ar), 7.96 (bs, 1H, NH, removed by D_2O addition), 8.73 (bs, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.87, 21.65, 60.25, 112.10, 113.30, 114.51, 115.27, 117.64, 118.75, 122.82, 123.90, 124.74, 127.50, 128.97, 133.34, 138.96, 139.95, 149.83, 155.09 ppm; FT-IR (KBr): ν 3310, 3072, 2986, 1696, 1652, 1601, 1561, 1487, 1276,1160, 1071, 840, 745, 720 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-ylamino)-6-methoxy-1H-indole-3-carboxylate (12e)

N-aryl isoxazolone **10e** (100 mg, 0.24 mmol) gave **12e** as pale yellow prisms (58 mg, 66%), mp 134-136 °C. Anal calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96%. Found: C, 64.85; H, 5.02; N, 12.10%. ^{1}H-NMR ($CDCl_3$): δ 1.58 (t, J = 7.2 Hz, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.52 (q, J = 7.2 Hz, 2H, CH_2), 6.58 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H, Ar), 7.12 (bs, 1H, Ar), 7.18-7.41 (m, 4H, Ar), 7.54 (d, J = 8.4 Hz, 1H, Ar), 7.96 (bs, 1H, NH, removed by D_2O addition), 8.79 (bs, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.85, 55.29, 60.30, 103.83, 107.64, 110.60, 112.12, 113.39, 115.81, 121.41, 123.96, 124.75, 127.48, 129.79, 141.79, 144.27, 149.86, 155.03, 160.44 ppm; FT-IR (KBr): ν 3315, 2979, 1663, 1628, 1598, 1561, 1422, 1155, 1074, 865, 752, 684 cm^{-1}.

Ethyl 2-(benzo[d]oxazol-2-ylamino)-5-nitro-1H-indole-3-carboxylate (12f)

N-aryl isoxazolone **10f** (100 mg, 0.24 mmol) gave **12f** as yellow prisms (54 mg, 61%), mp 198-200 °C. Anal calcd for $C_{18}H_{14}N_4O_5$: C, 59.02; H, 3.85; N, 15.29%. Found: C, 58.95; H, 4.00; N, 15.32%. ^{1}H-NMR ($CDCl_3$): δ 1.58 (t, J = 7.2 Hz, 3H, CH_3), 4.55 (q, J = 7.2 Hz, 2H, CH_2), 7.36-7.61 (m, 4H, Ar), 7.76 (d, J = 9 Hz, 2H, Ar), 8.23 (d, J = 8.4 Hz, 1H, Ar), 8.51 (bs, 1H, NH, removed by D_2O addition), 9.19 (bs, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.79, 60.88, 112.38, 112.74, 113.77, 114.95, 115.77, 116.69, 124.66, 125.01, 125.56, 126.15, 127.12, 131.40, 141.42, 145.89, 149.95, 155.61 ppm; FT-IR (KBr): ν 3304, 1662, 1590, 1566, 1509, 1477, 1458, 1331, 1317, 1282, 1200, 1078, 748 cm^{-1}.

Ethyl 2-(3-bromophenylamino)imidazo[1,2-a]pyrimidine-3-carboxylate (13b)

N-aryl isoxazolone **11b** (100 mg, 0.24 mmol) and triethylamine (0.4 mL) were refluxed in ethanol (10 mL) for 48 h. The reaction mixture was left to cool to room temperature and the resulting precipitate was collected to give ethyl 2-(3-bromophenylamino)imidazo[1,2-*a*]pyrimidine-3-carboxylate (**13b**) as white prisms (64 mg, 72%), mp 174-176 °C. Anal calcd for $C_{15}H_{13}BrN_4O_2$: C, 49.88; H, 3.63; N, 15.51%. Found: C, 50.01; H, 3.55; N, 15.41%. ^{1}H-NMR ($CDCl_3$): δ 1.50 (t, J = 7.2 Hz, 3H), 4.50 (q, J = 7.2 Hz, 2H, CH_2), 7.02 (dt, J_1 = 6.9 Hz, J_2 = 4.8 Hz, 1H, Ar), 7.12-7.22 (m, 2H, Ar), 7.73 (d, J = 7.8 Hz, 1H, Ar), 8.03 (bs, 1H, Ar), 8.54-8.57 (m, 2H, Ar), 9.21 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.68, 60.79, 96.52, 109.58, 116.99, 121.03, 122.76, 125.16, 130.32, 134.89, 141.02, 149.01, 151.21, 154.32, 160.92 ppm; FT-IR (KBr): ν 3395, 2986, 2925, 1673, 1613, 1592, 1571, 1461, 1094, 793 cm^{-1}.

The following imidazopyrimidines were made by the same procedure.

Ethyl 2-(m-tolylamino)imidazo[1,2-a]pyrimidine-3-carboxylate (13d)

N-aryl isoxazolone **11d** (100 mg, 0.26 mmol) gave **13d** as green prisms (56 mg, 64%), mp 138-140 °C. Anal calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91%. Found: C, 64.65; H, 5.61; N, 19.01%. ^{1}H-NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.52 (q, J = 7.1 Hz, 2H, CH_2), 6.86 (d, J = 7.5 Hz, 1H, Ar), 6.99 (dd, J_1 = 6.6 Hz, J_2 = 4.5 Hz, 1H, Ar), 7.25 (t, J = 7.8 Hz, 1H, Ar), 7.64 (t, J = 9 Hz, 2H, Ar), 8.53-8.56 (m, 2H, Ar), 9.23 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.69, 21.64, 60.60, 96.22, 109.34, 115.81, 119.15, 123.35, 128.94, 134.81, 138.10, 139.56, 149.25, 150.10, 158.23, 161.01 ppm; FT-IR (KBr): ν 3398, 2986, 1665, 1616, 1584, 1548, 1465, 1098, 808, 753 cm^{-1}.

Ethyl 2-(p-tolylamino)imidazo[1,2-a]pyrimidine-3-carboxylate (13j)

N-aryl isoxazolone **11j** (100 mg, 0.26 mmol) gave **13j** as yellow needles (52 mg, 61%), mp 147-149 °C. Anal calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91%. Found: C, 64.71; H, 5.65; N, 19.11%. ^{1}H-NMR ($CDCl_3$): δ 1.51 (t, J = 7.2 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.52 (q, J = 7.2 Hz, 2H, CH_2), 7.01 (t, J = 6.6 Hz, 1H, Ar), 7.18 (d, J = 8.4 Hz, 2H, Ar), 7.71 (d, J = 8.4 Hz, 2H, Ar), 8.48-8.70 (m, 2H, Ar), 9.24 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.66, 20.79, 60.70, 96.42, 109.55, 119.07, 121.73, 129.66, 131.92, 134.96, 137.73, 150.98, 158.46, 161.23 ppm; FT-IR (KBr): ν 3225, 2984, 2923, 1699, 1653, 1611, 1568, 1264, 1180, 1094, 760 cm^{-1}.

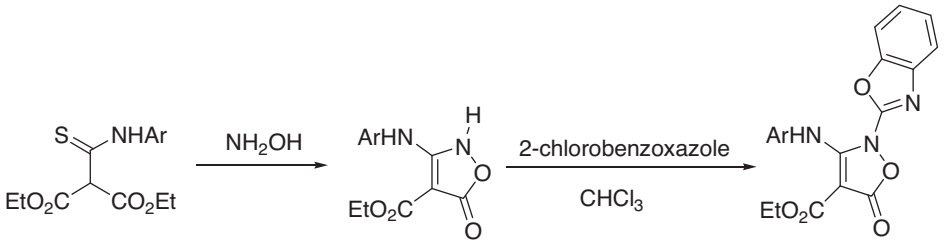
Ethyl 2-(4-bromophenylamino)imidazo[1,2-a]pyrimidine-3-carboxylate (13h)

N-aryl isoxazolone **11h** (100 mg, 0.24 mmol) gave **13h** as yellow prisms (68 mg, 76%), mp 148-150 °C. Anal calcd for $C_{15}H_{13}BrN_4O_2$: C, 49.88; H, 3.63; N, 15.51%. Found: C, 50.18; H, 3.47; N, 15.66%. ^{1}H-NMR ($CDCl_3$): δ 1.52 (t, J = 7.0 Hz, 3H, CH_3), 4.52 (q, J = 7.0 Hz, 2H, CH_2), 7.02 (t, J = 6.9 Hz, 1H, Ar), 7.45 (d, J = 9 Hz, 2H, Ar), 7.75 (d, J = 9 Hz, 2H, Ar), 8.54-8.58 (m, 2H, Ar), 9.20 (s, 1H, NH, removed by D_2O addition) ppm; ^{13}C-NMR ($CDCl_3$): δ 14.68, 60.74, 96.43, 109.52, 114.57, 119.94, 120.02, 131.92, 134.85, 138.84, 149.17, 151.20, 162.48 ppm; FT-IR (KBr): ν 3319, 2975, 1667, 1618, 1566, 1448, 1186, 1092, 920, 757 cm^{-1}.

Results and discussion

The required isoxazolones (**10a-f**) were synthesised by *N*-arylation of the corresponding 2*H*-isoxazolones (**9a-f**), which in turn were made by a modification of the procedure of Worrall.[9,10] Thus, the reaction of the sodium salt of diethyl malonate in ethanol with aryl isothiocyanates gave the thiocarbamates (**8a-h**) in high yield, and these were converted to the corresponding isoxazolone (**9a-h**) by reaction with hydroxylamine.

N-arylation of **9a-f** with 2-chlorobenzoxazole in chloroform under reflux afforded the corresponding *N*-benzoxazole derivatives (**10a-f**) in good yield (Scheme 2).



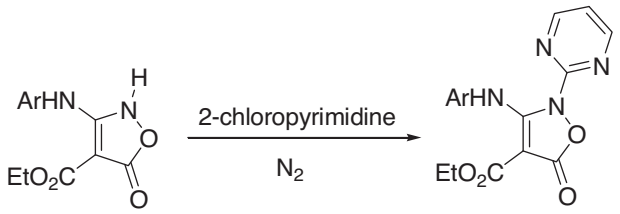
8a-f **9a-f** **10a-f**

a, Ar =2-BrC_6H_4 **b**, Ar = 3-BrC_6H_4 **c**, Ar = 2-MeC_6H_4

d, Ar = 3-MeC_6H_4 **e**, Ar = 3-$OMeC_6H_4$ **f**, Ar = 4-$NO_2C_6H_4$

Scheme 2

The reaction of the isoxazolones **9b-h** with 2-chloropyrimidine gave the desired *N*-pyrimidine derivatives **11b-h** (Scheme 3). While the formation of **11b-h** appears trivial, the reaction generally proceeded best in the absence of solvent, by heating the required reagents under nitrogen atmosphere at 130 °C.

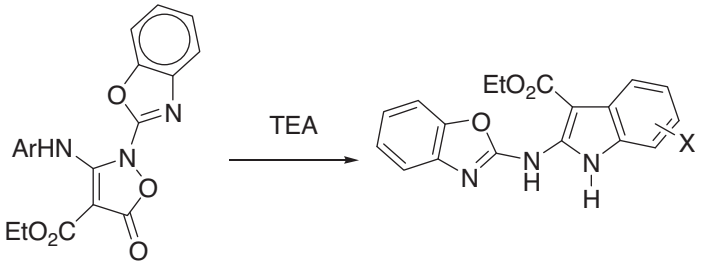


9b-h **11b-h**

b, Ar = 3-BrC_6H_4 **d**, Ar = 3-MeC_6H_4 **j,** Ar = 4-MeC_6H_4 **h,** Ar = 4-BrC_6H_4

Scheme 3

The reaction of the corresponding isoxazolones, substituted on nitrogen with a benzoxazole group **10a-f** with triethylamine, afforded the rearranged aminoindoles **12a-f** in 60%-69% yield (Scheme 4).

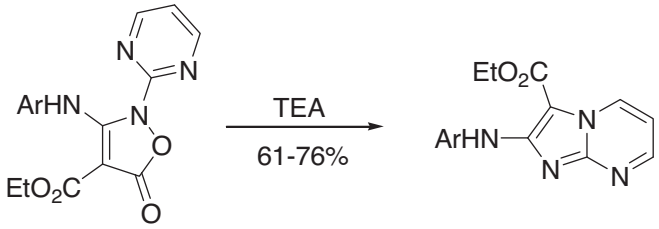


10a-f **12a-f**

a, Ar =2-BrC_6H_4 **b**, Ar = 3-BrC_6H_4 **c**, Ar = 2-MeC_6H_4
d, Ar = 3-MeC_6H_4 **e**, Ar = 3-$OMeC_6H_4$ **f**, Ar = 4-$NO_2C_6H_4$

Scheme 4

The rearrangement of 2-arylisoxazolones **11b-h** in the presence of triethylamine in ethanol under reflux afforded the rearranged imidazopyrimidines **13b-h** (Scheme 5).



11b-h **13b-h**

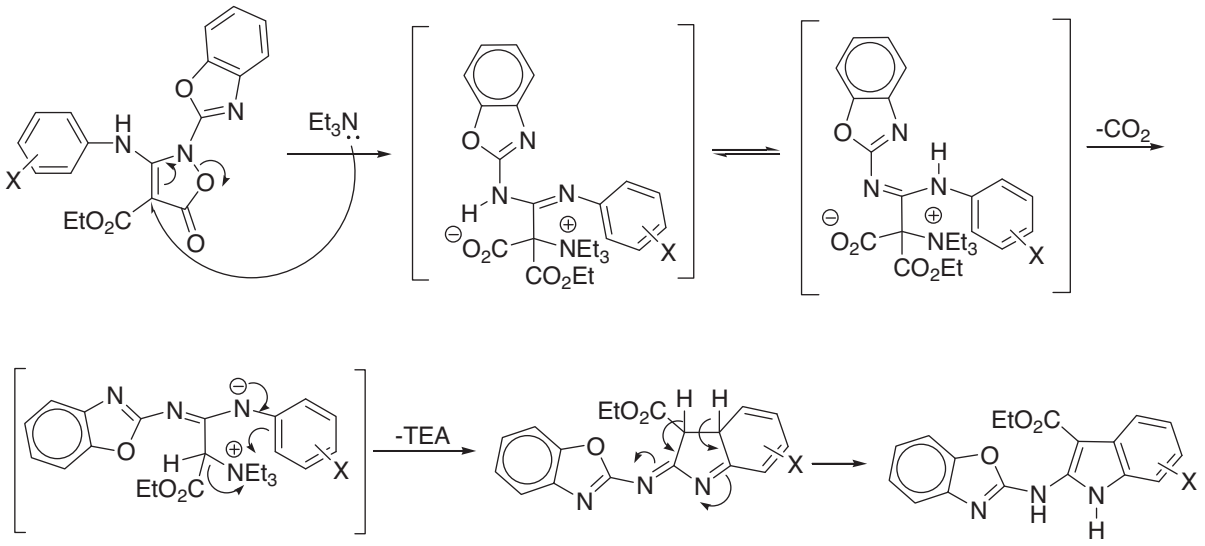
b, Ar = 3-BrC_6H_4 **d**, Ar = 3-MeC_6H_4 **j,** Ar = 4-MeC_6H_4 **h,** Ar = 4-BrC_6H_4

Scheme 5

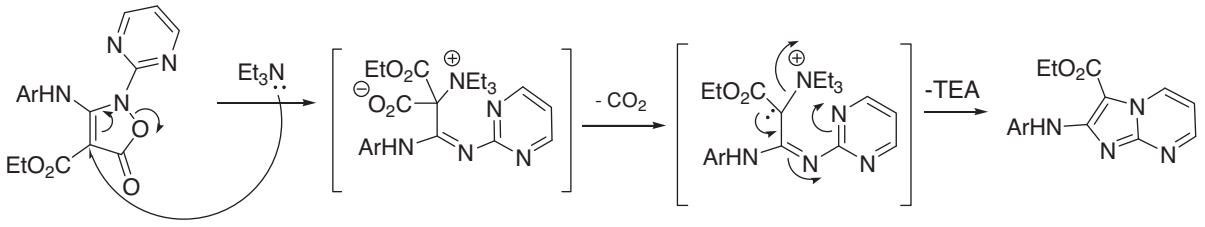
The structures of all new compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR, FT-IR spectral data, and microanalyses.

The mechanisms of rearrangements are consistent with our earlier suggestions[3,11] for the formation of aminoindoles and imidazopyrimidine (Scheme 6). The present results, when considered with those obtained previously,[3,12] suggest that in the case of imidazopyrimidine formation the heteroaryl group of the heteroaryl isoxazolones is most likely to intercept the ylide intermediate formed by reaction with a base, unless the 3-aryl group is both electron rich and sterically unhindered.

It is interesting that in the case of pyrimidine derivative the rearrangement gave only imidazopyrimidine, as shown in Scheme 5, but in the case of benzoxazole derivatives, aminoindoles are formed with no sign of any imidazobenzoxazole derivative formation as shown in Scheme 4, which may be due to the fact that oxygen in the benzoxazole ring is more electronegative than nitrogen in the pyrimidine ring and, therefore, the lone pair on nitrogen of the pyrimidine ring is more available than that in the benzoxazole ring.



a, X = 2-BrC_6H_4 **b**, X = 3-BrC_6H_4 **c**, X = 2-MeC_6H_4
d, X = 3-MeC_6H_4 **e**, X = 3-$OMeC_6H_4$ **f**, X = 4-$NO_2C_6H_4$



b, Ar = 3-BrC_6H_4 **d**, Ar = 3-MeC_6H_4 **j**, Ar = 4-MeC_6H_4 **h**, Ar = 4-BrC_6H_4

Scheme 6

Conclusion

These rearrangements of 2-heterocyclyl isoxazolones appear to be generally applicable to the synthesis of heterocycles, which are suitable synthetic intermediates for a series of new polycyclic heterocycles with possible pharmaceutical applications and could be expected to intercalate with DNA.[13–15]

Acknowledgements

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