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Synthesis of optically active imidazo[1,2-*a*]pyrimidin-3(2*H*)-ones

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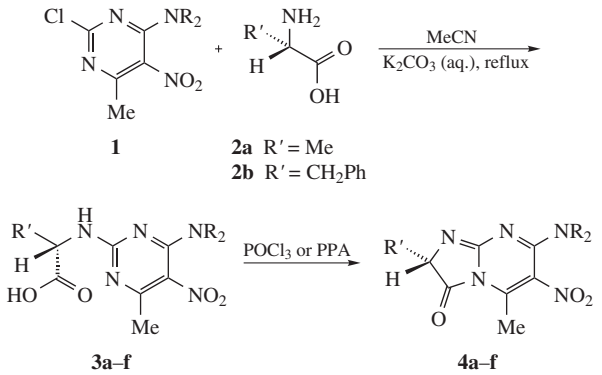
The reactions of 2-chloro-4-(substituted amino)-6-methyl-5-nitropyrimidine 1 with (L)-α-amino acids gave substituted derivatives 3, which were converted to optically active imidazo[1,2-*a*]pyrimidines 4 by treatment with either phosphorus oxychloride or polyphosphoric acid.

Imidazopyrimidines are of chemical and pharmacological interest because of their similarity to purines, which are important moieties in biologically active compounds.[1] Biological activities of imidazopyrimidines, such as antiinflammatory,[2] antibacterial,[3] antiulcer,[4] local anesthetic and calcium channel blocking activity,[5] were reported. Continuing our studies on bioactive heterocycles,[6] we synthesised six new optically active imidazo[1,2-*a*]pyrimidin-3(2*H*)-ones *via* the cylisation of N-heteroarylamino acids in either phosphorus oxychloride or polyphosphoric acid.

The synthesis of imidazo[1,2-*a*]pyrimidin-3(2*H*)-ones **4a–f** is shown in Scheme 1. The key compound, 2-chloro-4-(substituted amino)-6-methyl-5-nitropyrimidine **1**, was prepared according to the published method.[7] Treatment of **1** with appropriate (L)-α-amino acids **2a**,**b** in the prersence of potassium carbonate gave corresponding N-heteroarylamino acids **3a–f**.† The subsequent chlorination of **3a**,**c**,**e**,**f** with phosphorus oxychloride (Method A) followed by cyclisation at moderate temperatures furnished chiral imidazo[1,2-*a*]pyrimidin-3(2*H*)-ones **4a**,**c**,**e**,**f**.‡ Amino acids **3b**,**d** were directly converted to imidazo[1,2-*a*]pyrimidin-3(2*H*)-ones **4b**,**d** on stirring with polyphosphoric acid (Method B) at 70–75 °C.‡



1 **2a** R′ = Me; **2b** R′ = CH_2Ph

3a–f **4a–f**

a R′ = Me, NR_2 = diethylamine
b R′ = Me, NR_2 = pyrrolidine
c R′ = Me, NR_2 = morpholine
d R′ = CH_2Ph, NR_2 = diethylamine
e R′ = CH_2Ph, NR_2 = pyrrolidine
f R′ = CH_2Ph, NR_2 = morpholine

Scheme 1

The structural assignment of compounds **4a–f** was based upon the spectral data. The IR spectra exhibited stretching vibration bands at 3300 (ν, sharp, NH), 2800–2200 (ν, broad, NH_2^+), 1630–1620 (ν_{as}) and 1396–1375 cm^{-1} (ν_s, CO_2^-)[8] due to precursors but showed a band at 1718–1744 cm^{-1} for C=O absorption. Further proofs came from the ^1H NMR spectra, which showed the disappearance of two broad 1H signals belonging to NH and COOH moieties of compounds **3a–f**.

During cyclisation, the racemization of chiral centres could occur. However, by addition of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato]europium(III) as a chiral shift reagent to the chloroform solutions of the bicyclic compounds with a chiral side chain, we observed only one set of peaks in the ^1H NMR spectra. On this basis, we suggest that no racemization took place during cyclisation and, therefore, since only (L)-α-amino acids were employed, the chirality of the side chains in imidazo[1,2-*a*]pyrimidin-3(2*H*)-ones is (*S*). However, racemi-

zation can occur during the isolation of the final products since at the workup stage they were treated with an alkaline solution.

In conclusion, the reaction of **1** with (L)-α-amino acids in the presence of potassium carbonate proceeded smoothly to give corresponding heteroarylamino acids **3a–f**. The intramolecular cyclisation of these compounds with $POCl_3$ or PPA afforded optically active products **4a–f**.

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† The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian CH-7 instrument at 70 eV. Optical rotations were measured at the sodium D-line with a Schmidt Haensch polartonic NH8 polarimeter (concentrations are given as 0.5 g dm^{-3} of ethanol). Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

General procedure for the preparation of N-heteroarylamino acids **3a–f**. To a solution of 2-chloro-4-(substituted amino)-6-methyl-5-nitropyrimidine **1a–f** (0.01 mol) in acetonitrile (25 ml), appropriate amino acid **2a**,**b** (0.02 mol) and potassium carbonate (0.03 mol) in water (5 ml) were slowly added. The solution was stirred at reflux for a time (see below). After the completion of the reaction (monitored by TLC using $CHCl_3$–MeOH, 3:1) the solution was reduced in volume under reduced pressure, then cooled and acidified with dilute acetic acid. The precipitate was filtered off and recrystallised from a suitable solvent to give **3a–f** as pale yellow powders.

(2S)-2-{[4-(diethylamino)-6-methyl-5-nitropyrimidin-2-yl]amino}propanoic acid **3a**: recrystallised from light petroleum–diethyl ether, (40:60); reaction time, 4.5 h; yield 76%; $[\alpha]_D^{25}$ = –7; mp 155 °C. ^{1}H NMR ($CDCl_3$) δ: 1.20 (t, 6H, 2Me, *J* 7.1 Hz), 1.53 (d, 3H, Me, *J* 7.1 Hz), 2.32 (s, 3H, Me), 3.37 (q, 4H, 2CH_2, *J* 7.1 Hz), 4.58 (br., changed to quartet after addition of D_2O, 1H, CH), 8.22 (br. s, 1H, NH, exchangeable with D_2O), 11.0 (br. s, 1H, COOH, exchangeable with D_2O). IR (KBr disk, ν/cm^{-1}): 3397 (NH), 2800–2200 (br., NH_2^+), 1597 (ν_{as}) and 1320 (ν_s, CO_2^-). MS, *m*/*z*: 297 (M^+).

(2S)-2-[(4-methyl-5-nitro-6-pyrrolidin-1-ylpyrimidin-2-yl)amino]propanoic acid **3b**: recrystallised from MeOH; reaction time, 12 h; yield 85%; $[\alpha]_D^{25}$ = –8; mp 180–182 °C. ^{1}H NMR ($CDCl_3$) δ: 1.70 (d, 3H, Me, *J* 6.96 Hz), 1.94 (m, 4H, 2CH_2), 2.30 (s, 3H, Me), 3.30 (m, 4H, 2N–CH_2), 4.60 (br., changed to quartet after addition of D_2O, 1H, CH, *J* 7.0 Hz), 8.14 (br. s, 1H, NH, exchangeable with D_2O), 10.90 (br. s, 1H, COOH, exchangeable with D_2O). MS, *m*/*z*: 295 (M^+).

(2S)-2-[(4-methyl-6-morpholin-4-yl-5-nitropyrimidin-2-yl)amino]propanoic acid **3c**: recrystallised from EtOH–H_2O; reaction time, 8 h; yield 85%; $[\alpha]_D^{25}$ = –9; mp 182–184 °C. ^{1}H NMR ($CDCl_3$) δ: 1.60 (d, 3H, Me, *J* 7.0 Hz), 2.40 (s, 3H, Me), 3.55 (m, 4H, 2N–CH_2), 3.70 (m, 4H, 2O–CH_2), 4.60 (q, 1H, CH, *J* 7.0 Hz), 8.50 (br. s, 1H, NH, exchangeable with D_2O), 11.20 (br. s, 1H, COOH, exchangeable with D_2O). MS, *m*/*z*: 311 (M^+).

(2S)-2-{[4-(diethylamino)-6-methyl-5-nitropyrimidin-2-yl]amino}-3-phenylpropanoic acid **3d**: recrystallised from EtOH–H_2O; reaction time, 4.5 h; yield 95%; $[\alpha]_D^{25}$ = –3; mp 201–203 °C. ^{1}H NMR ($CDCl_3$) δ: 1.06 (t, 6H, 2Me, *J* 7.1 Hz), 2.22 (s, 3H, Me), 3.18 (m, 6H, 2N–CH_2, Ph–CH_2), 4.45 (q, 1H, CH, *J* 7.0 Hz), 7.27 (s, 5H, Ph), 7.60 (br. s, 1H, NH, exchangeable with D_2O), 9.30 (br. s, 1H, COOH, exchangeable with D_2O). MS, *m*/*z*: 373 (M^+).

(2S)-2-[(4-methyl-5-nitro-6-pyrrolidin-1-ylpyrimidin-2-yl)amino]-3-phenylpropanoic acid **3e**: recrystallised from EtOH; reaction time, 6.0 h; yield 95%; $[\alpha]_D^{25}$ = –10; mp 220–222 °C. ^{1}H NMR ($CDCl_3$) δ: 1.90 (m, 4H, 2CH_2), 2.27 (s, 3H, Me), 3.20 (d, 2H, Ph–CH_2, *J* 6.9 Hz), 3.30 (m, 4H, 2N–CH_2), 4.76 (q, 1H, CH, *J* 6.9 Hz), 7.24 (s, 5H, Ph), 6.10 (br. s, 1H, NH, exchangeable with D_2O), 7.75 (br. s, 1H, COOH, exchangeable with D_2O). MS, *m*/*z*: 371 (M^+).

(2S)-2-[(4-methyl-6-morpholin-4-yl-5-nitropyrimidin-2-yl)amino]-3-phenylpropanoic acid **3f**: recrystallised from EtOH; reaction time, 8 h; yield 90%; $[\alpha]_D^{25}$ = –5; mp 203–205 °C. ^{1}H NMR ($CDCl_3$) δ: 2.29 (s, 3H, Me), 3.20 (d, 2H, Ph–CH_2, *J* 6.9 Hz), 3.20 (m, 4H, 2N–CH_2), 3.40 (m, 4H, 2O–CH_2), 4.76 (q, 1H, CH, *J* 6.9 Hz), 7.24 (s, 5H, Ph), 7.75 (br. s, 1H, NH, exchangeable with D_2O), 8.15 (br. s, 1H, COOH, exchangeable with D_2O). MS, *m*/*z*: 387 (M^+).

‡ *General procedure for the preparation of optically active imidazo[1,2-*a*]-pyrimidin-3(*2H*)-ones* **4a–f**.

Method A. A solution of N-heteroarylamino acid **3a**,**c**,**e**,**f** (0.001 mol) in $POCl_3$ was heated at 50–55 °C with stirring for a time (see below). The excess $POCl_3$ was removed *in vacuo*, and the residue was poured onto ice and then basified with a dilute sodium hydroxide solution. The resulting solution was extracted with chloroform. The organic layer was separated, dried, filtered, and evaporated to dryness *in vacuo*. The residue was purified either by silica gel column chromatography (CC) or silica gel TLC as pale yellow powder (see below).

Method B. A mixture of N-heteroarylamino acid **3b**,**d** (0.001 mol) and polyphosphoric acid (3 g) was heated with stirring at 70–75 °C for 3.0 h. The mixture was poured onto crushed ice; the aqueous solution was basified with a dilute potassium hydroxide solution and then extracted with dichloromethane. The organic layer was separated, washed with water and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by chromatography as pale yellow powder (see below).

*(2S)-7-(diethylamino)-2,5-dimethyl-6-nitroimidazo[1,2-*a*]pyrimidin-3(*2H*)-one* **4a**: purified by TLC (ethyl acetate–hexane, 1:1); reaction time, 18.0 h; yield 45%; $[\alpha]_D^{25}$ = –4.2, mp 122–124 °C. ^{1}H NMR ($CDCl_3$) δ: 1.24 (m, 6H, 2Me), 1.40 (d, 3H, Me, *J* 7.2 Hz), 2.30 (s, 3H, Me), 3.30 (q, 4H, 2CH_2, *J* 7.1 Hz), 4.30 (q, 1H, CH). IR (KBr disk, ν/cm^{-1}): 1718 (C=O). MS, *m*/*z*: 279 (M^+). Found (%): C, 51.61; H, 6.13; N, 25.07. Calc. for $C_{12}H_{17}N_5O_3$ (%): C, 51.51; H, 6.15; N, 24.96.

*(2S)-2,5-dimethyl-6-nitro-7-pyrrolidin-1-ylimidazo[1,2-*a*]pyrimidin-3(*2H*)-one* **4b**: purified by TLC (ethyl acetate–hexane, 95:5); reaction time, 4.5 h; yield 45%; $[\alpha]_D^{25}$ = –5.5, mp 155–157 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (d, 3H, Me, *J* 7.0 Hz), 1.95 (m, 4H, 2CH_2), 2.37 (s, 3H, Me), 3.30 (m, 4H, 2N–CH_2), 5.30 (br., 1H, CH). MS, *m*/*z*: 279 (M^+). Found (%): C, 51.98; H, 5.45; N, 25.26. Calc. for $C_{12}H_{15}N_5O_3$ (%): C, 52.09; H, 5.49; N, 25.22.

*(2S)-2,5-dimethyl-7-morpholin-4-yl-6-nitroimidazo[1,2-*a*]pyrimidin-3(*2H*)-one* **4c**: purified by CC ($CHCl_3$–MeOH, 9:1); reaction time, 18.0 h; yield 52%; $[\alpha]_D^{25}$ = –7.0, mp 142–144 °C. ^{1}H NMR ($CDCl_3$) δ: 1.40 (d, 3H, Me, *J* 7.2 Hz), 2.3 (s, 3H, Me), 3.3 (m, 4H, 2N–CH_2), 3.6 (m, 4H, 2O–CH_2), 4.2 (q, 1H, CH, *J* 7.2 Hz). MS, *m*/*z*: 293 (M^+). Found (%): C, 49.14; H, 5.15; N, 23.88. Calc. for $C_{12}H_{15}N_5O_4$ (%): C, 49.23; H, 5.18; N, 23.81.

*(2S)-2-benzyl-7-(diethylamino)-5-methyl-6-nitroimidazo[1,2-*a*]pyrimidin-3(*2H*)-one* **4d**: purified by CC (ethyl acetate–hexane, 2.5:97.5); reaction time, 4.5 h; yield 52%; $[\alpha]_D^{25}$ = –1.3, mp 110–112 °C. ^{1}H NMR ($CDCl_3$) δ: 1.15 (m, 6H, 2Me), 2.20 (s, 3H, Me), 3.15 (m, 4H, 2CH_2), 3.60 (dd, 2H, CH_2, *J* 7.0 Hz), 4.20 (dd, 1H, CH, *J* 7.0 Hz), 7.15–7.50 (m, 5H, Ph). IR (KBr disk, ν/cm^{-1}): 1741 (C=O). MS, *m*/*z*: 355 (M^+). Found (%): C, 60.83; H, 5.96; N, 19.71. Calc. for $C_{18}H_{21}N_5O_3$ (%): C, 61.03; H, 5.94; N, 19.59.

*(2S)-2-benzyl-5-methyl-6-nitro-7-pyrrolidin-1-ylimidazo[1,2-*a*]pyrimidin-3(*2H*)-one* **4e**: purified by CC (ethyl acetate–hexane, 1:1); reaction time, 1.5 h; yield 50%; $[\alpha]_D^{25}$ = –6.58; mp 102–105 °C. ^{1}H NMR ($CDCl_3$) δ: 1.84 (m, 4H, 2CH_2), 2.26 (s, 3H, Me), 3.06 (dd, 2H, CH_2, *J* 6.9 Hz), 3.11 (m, 4H, 2N–CH_2), 4.5 (dd, 1H, CH, *J* 6.9 Hz), 7.24 (s, 5H, Ph). MS, *m*/*z*: 353 (M^+). Found (%): C, 61.18; H, 5.42; N, 19.82. Calc. for $C_{18}H_{19}N_5O_3$ (%): C, 61.04; H, 5.47; N, 19.86.

*(2S)-2-benzyl-5-methyl-7-morpholin-4-yl-6-nitroimidazo[1,2-*a*]pyrimidin-3(*2H*)-one* **4f**: purified by CC ($CHCl_3$–MeOH, 1:1); reaction time, 48 h; yield 57%; $[\alpha]_D^{25}$ = –5.0, mp 180–182 °C. ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H, Me), 3.40 (dd, 2H, CH_2, *J* 6.9 Hz), 3.60 (m, 4H, 2N–CH_2), 3.70 (m, 4H, 2O–CH_2), 4.75 (dd, 1H, CH, *J* 6.9 Hz), 7.24 (s, 5H, Ph). MS, *m*/*z*: 371 (M^+). Found (%): C, 58.53; H, 5.18; N, 18.96. Calc. for $C_{18}H_{19}N_5O_4$ (%): C, 58.66; H, 5.20; N, 18.86.