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SYNTHESIS OF THIENOIMIDAZO[4,5-*b*]PYRIDINES AND THENYLIDENOIMIDAZOLINONES

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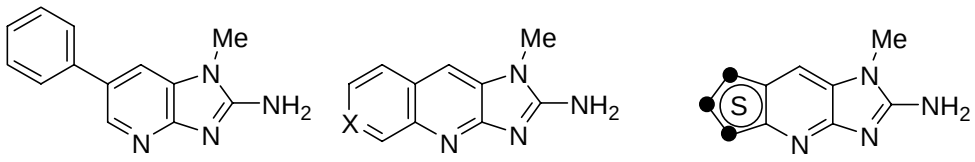
Abstract – The two isomers 2-amino-1-methylimidazo[4,5-*b*]thieno[3,2-*e*]pyridine (**3**) and 2-amino-1-methylimidazo[4,5-*b*]thieno[2,3-*e*]pyridine (**4**) were synthesized by the Friedländer reaction starting from creatinine and the appropriate aminothiophenecarbaldehydes (**11** and **13**). Creatinine was also condensed with 2-nitro-3-thiophenecarbaldehyde (**10**) in ethylene glycol to yield the 2-amino-1-methyl-5-[2-(2-nitro-3-thenylidene)]-2-imidazolin-4-one (**7a**), with 3-amino-2-thiophenecarbaldehyde (**13**) under Perkin conditions to yield 2-acetamido-5-[2-(3-acetamido-2-thenylidene)]-1-methyl-2-imidazolin-4-one (**8**), and with 4-azido-3-thiophenecarbaldehyde (**17**) in acetic acid to yield 2-amino-5-[2-(4-azido-3-thenylidene)]-1-methyl-2-imidazolin-4-one (**9**). The thenylidenoimidazolinone (**8**) was converted into compound (**4**).

INTRODUCTION

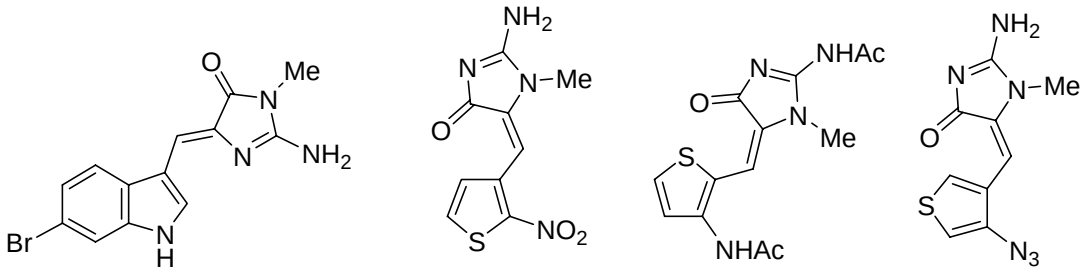
There has been evidence that some mutagenic heterocyclic amines are formed during cooking of foods by reaction between creatine, amino acids and sugars.[1] One of these heterocyclic amines is 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (**PhIP**, Figure 1), and apart from its mutagenic/carcinogenic properties it has also similarities to the linear imidazo[4,5-*b*]pyridines (**1** and **2**). Compounds (**1** and **2**) are part of our synthetic programme towards structure-activity relationships[2] and are also the parent compounds to **3**–**5**. Several imidazo[4,5-*b*]pyridines, -quinolines, -quinoxalines and -naphthyridines have been synthesized by our group[3-7] and others.[8] The substitution of –CH= for –N= (benzene-pyridine) or –CH=CH– for –S– (benzene-thiophene) in aromatic rings is an application of classical bioisosterism.[9] In this paper we present the synthesis towards analogues (**3**) and (**4**), which are related to **1** using bioisosterism.



PhIP **1** X=CH, **2** X=N **3-5**

Figure 1

Heteroarylmethyleneimidazolinones have been described frequently in the last decades. Compound (**6**,[10] Figure 2) has been isolated from natural sources, and shows specific cytotoxicity for cancer cells.[11] Similar compounds have been used in medicinal chemistry; for example, arylideneimidazol-4-one amino acids, which have been tested in structure-activity studies of glycine receptor ligands.[12] Previously, the benzene and furan analogues of these compounds have been described by our group[7,13] and therefore it was natural for us to choose these intermediate thenylideneimidazolinones (**7a**, **8** and **9**) providing similar features to natural products in the synthesis of our targets (**3**–**5**).



6 **(*E*)-7a** **(*E*)-8** **(*E*)-9**

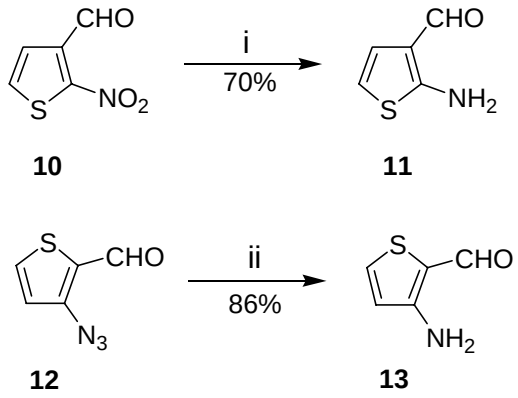
Figure 2

RESULTS AND DISCUSSION

The title compounds (**3**–**5**) are imidazo[4,5-*b*]pyridines, and there is a possibility to synthesize them *via* either of two condensation pathways; namely, the direct Friedländer condensation (Scheme 3) or the stepwise condensation (Scheme 4 and 5) where the starting material has an amine equivalent rather than the amine required for the direct condensation.

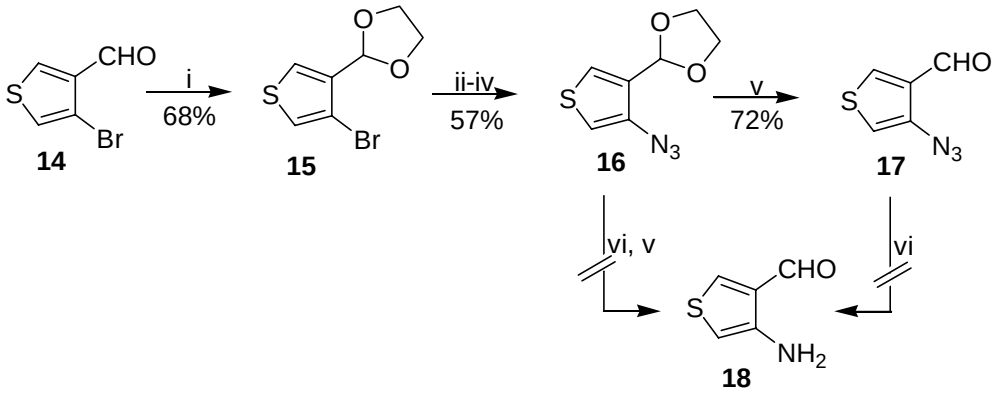
Traditionally, the Friedländer reaction[14] has been used in quinoline synthesis, reacting an *ortho*-aminocarbaldehyde with a carbonyl compound having an active methylene group. Recently some studies on the mechanism of this reaction has been published.[15] Often the Friedländer reaction is catalyzed with an acid or base, but the neutral conditions are used since creatinine is sensitive to mineral acids.[16] In the stepwise condensation, compounds such as **7a** were synthesized at first, and after reduction of the nitro group, the compounds should be cyclizable to the desired compounds.

The starting materials (**10**, **11** and **13**, Scheme 1) and (**17**, Scheme 2) for these reactions were synthesized according to the literature with a few modifications. Compound (**10**) was synthesized according to Mąkosza.[17] Vicarious nucleophilic substitution (VNS) on 2-nitrothiophene yielded 3-dichloromethyl-2-nitrothiophene[17-19] which was hydrolyzed in an aqueous solution of formic acid to afford the carbaldehyde (**10**) in 80% yield.



Scheme 1. i. Fe/AcOH, 75 ºC, 30 min; ii. NH_4SH, MeOH, rt, 10 min.

2-Amino-3-thiophenecarbaldehyde (**11**) has been described to be obtained *via* substitution of the nitro to azide and then reduction to amino group in 20% yield from **10**.[20] However, the desired amine was obtained in 70% yield by warming the nitro compound (**10**) with iron at 75 ˚C in acetic acid. Compound (**13**) was prepared from 3-bromothiophene *via* 3-bromo-2-thiophenecarbaldehyde[21,22] (organometallic formylation) and 3-azido-2-thiophenecarbaldehyde (**12**).[23,24] The azide was reduced with NH_4SH in methanol[25] to provide the amine (**13**) in 86% yield.



Scheme 2. i. Ethylene glycol, toluene, *p*-toluenesulfonic acid, Dean and Stark overnight; ii. n-BuLi, ether, –78 ˚C, 30 min.; iii, Tosyl azide, –78 ˚C, 5 h; iv. $Na_4P_2O_7/H_2O$, rt, overnight; v. 2M HCl, rt, overnight; vi. 40% NH_4SH, MeOH, rt, 45 min.

To obtain 3-amino-4-thiophenecarbaldehyde (**18**, Scheme 2), the route we used was in analogy with that of compound (**13**). The aldehyde (**14**) was obtained from 3,4-dibromothiophene *via* organometallic formylation[26] and protected as an acetal to give **15**.[27] The second organometallic reaction was performed

by quenching with tosyl azide to give **16**.[28] The ^{1}H-NMR showed, apart from the expected coupling between H-2 and H-5, also a long range coupling between H-2 and H-2' explained by the favourable zig-zag arrangement of these protons. Hydrolysis of **16** gave **17**[28] but the reduction of the azide (**17**) to the amine (**18**) was unsuccessful. In addition, the reduction of the protected **16** gave the amine, 3-amino-4-thiophenecarbaldehyde ethylene acetal, but the hydrolysis of the acetal failed to give the desired product (**18**).

We have previously investigated the reaction of the four possible isomers of the vicinal aminopyridinecarbaldehyde with creatinine (**19**, Figure 3) and its isomer, 2-amino-1-methyl-2-imidazolin-5-one (isocreatinine, **20**) in ethylene glycol[4,7] and also 2-aminobenzaldehyde with creatinine in ethylene glycol.[5]

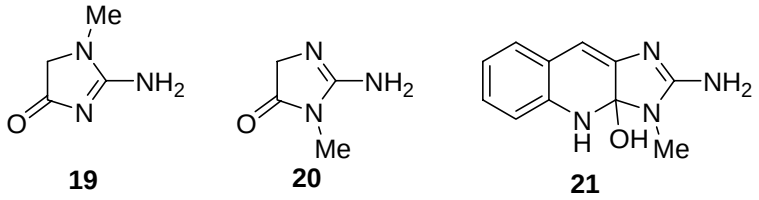
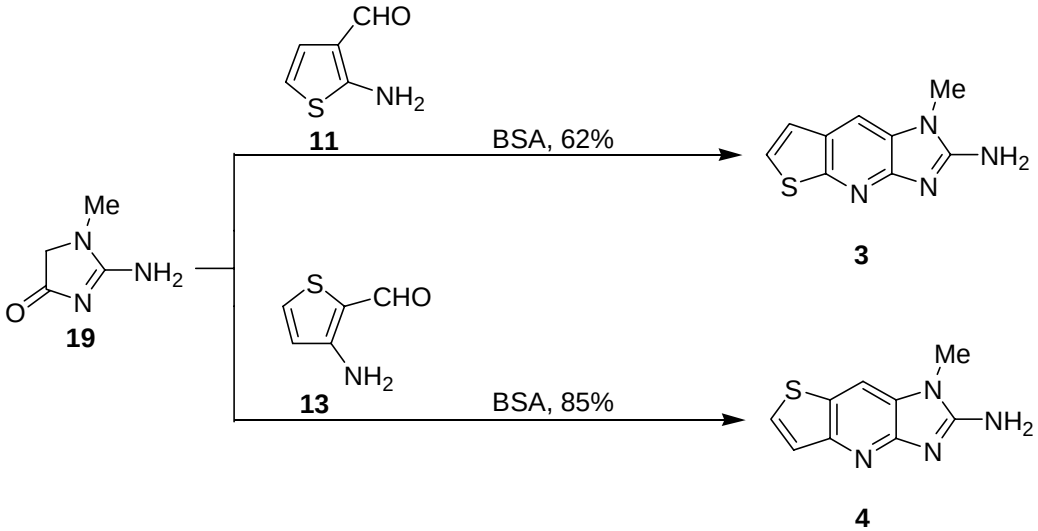


Figure 3

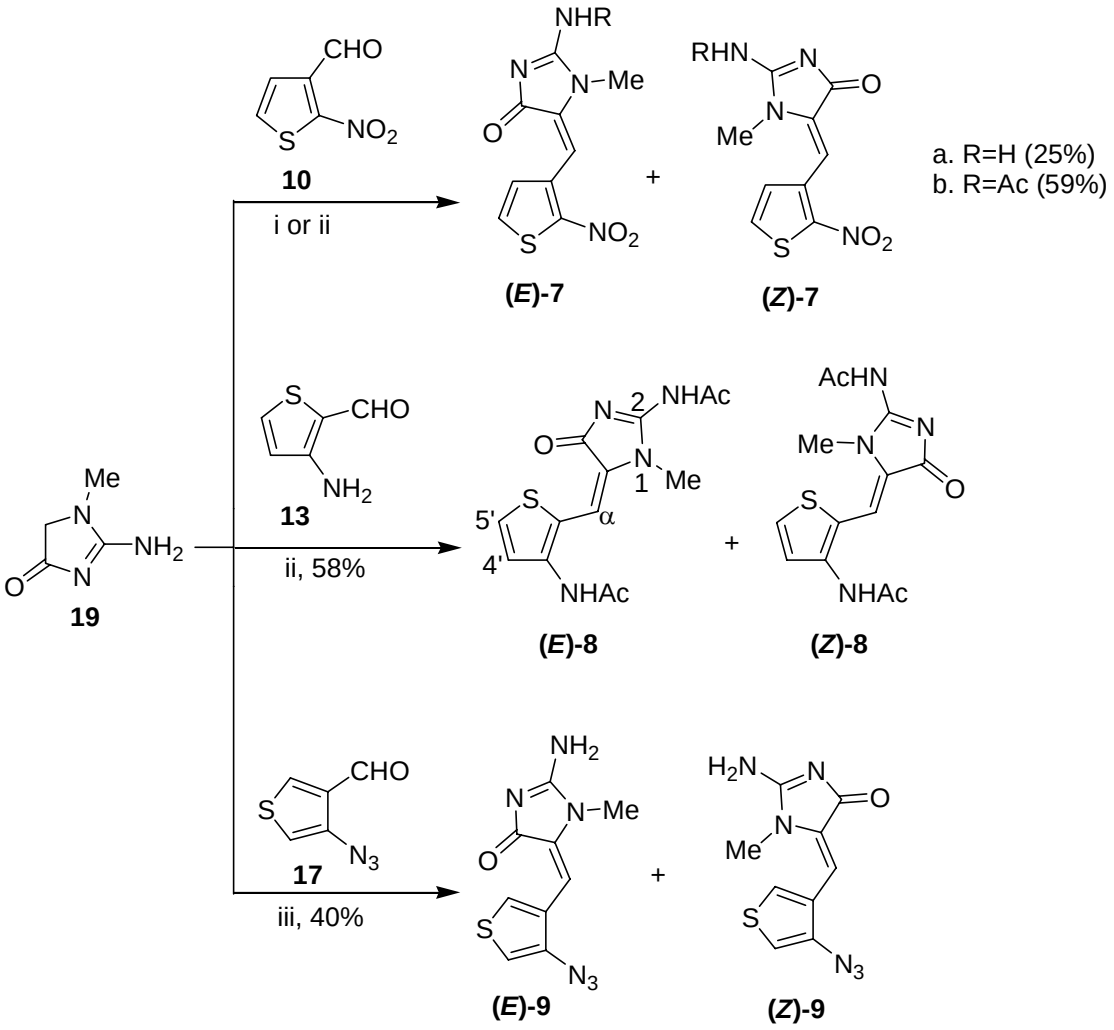
By using the two compounds (**19** and **20**), the isomers with the *N*-methyl groups pointing in opposite directions, could be obtained exclusively. The 2-aminobenzaldehyde afforded only the alcohol (**21**) when treated with isocreatinine in the Friedländer reaction but the π-excessive thiophene compound gave a complex mixture of products.



Scheme 3. Heated at 140 ºC for 2 h.

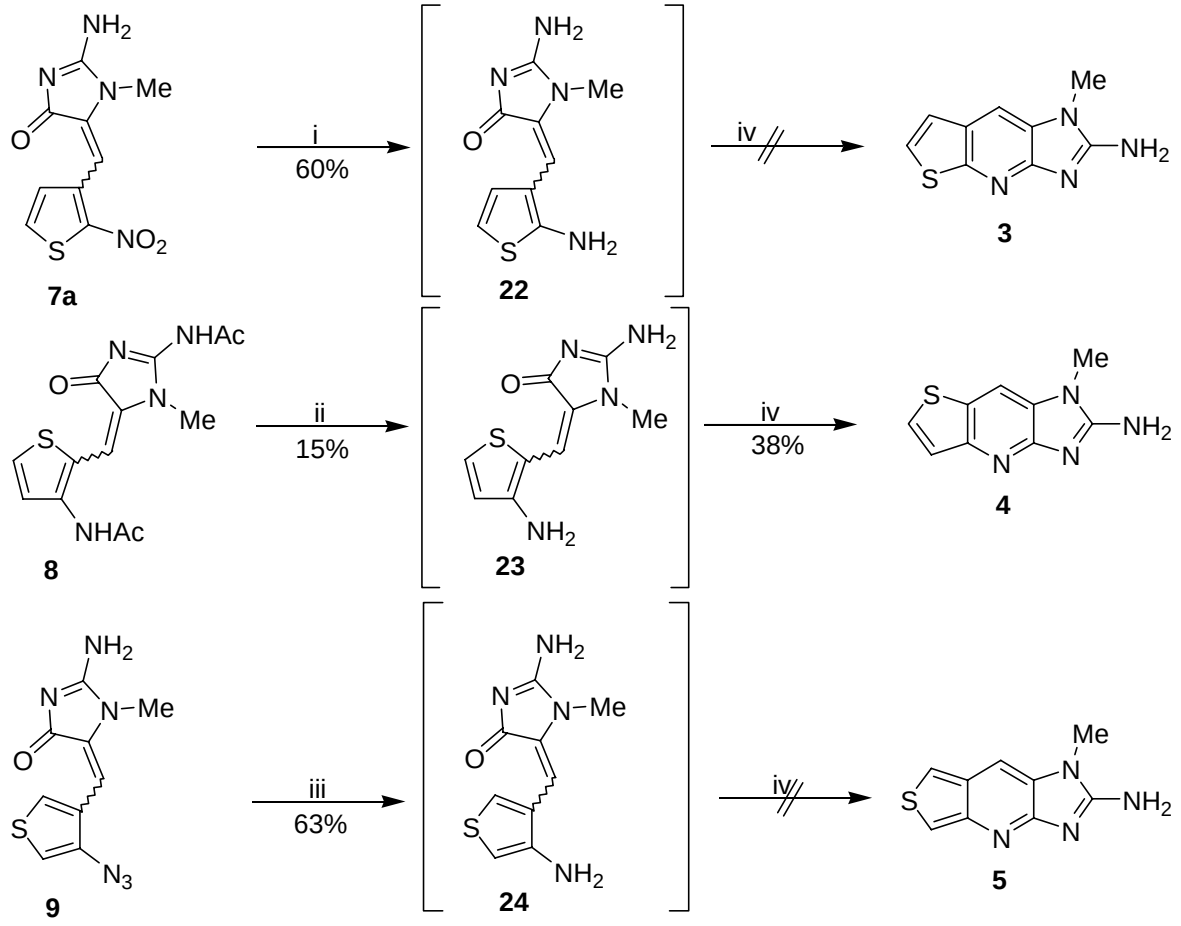
Attempts to use ethylene glycol or DMF in the Friedländer reaction did not give the desired compounds for either of the aminothiophenecarbaldehyde (**11** or **13**). However, by using bis(trimethylsilyl)acetamide (BSA) as solvent, previously used in our group to synthesize **PhIP**,[6] creatinine was forced into its enol

form and the desired compounds (**3**) and (**4**) were obtained in 62 and 85% yields, respectively (Scheme 3). The 2-nitro-3-thiophenecarbaldehyde (**10**)[17-19] was treated with **19** in ethylene glycol and the condensation reaction resulted in the (*E*) isomer (25% yield, Scheme 4). Other solvents such as methanol or DMF did not improve the yield to any extent. When other conditions were applied to **10** (such as the Perkin conditions,[29] sodium acetate in a mixture of acetic anhydride and acetic acid) the acetylated (*E*)-isomer [(***E***)-**7b**] was obtained in a somewhat higher yield (59%). When these conditions were used on 3-amino-2-thiophenecarbaldehyde, the diacetylated product [(***E***)-**8**] was obtained. When stored in DMSO at room temperature for one week, the acetylated products ((***E***)-**7b** and (***E***)-**8**) were isomerized to a ratio of 90/10 and 75/25 (*E*/*Z*) respectively. To condense the azide (**17**) with creatinine, acetic acid was used at a lower temperature (65 ˚C due to the sensitivity of the azide) and the compound obtained was again the *E*-isomer. To be able to diffrentiate between the (*E*)- and the (*Z*)-isomers NOE diff. nmr experiments were performed and it was obvious from the NOE coupling between the N-methyl and the α-H that the isomer obtained was the *E*-isomer.



Scheme 4. i. Ethylene glycol, 140 ºC for 1.5 h; ii. NaOAc, AcOH, Ac_2O, 140 ºC for 20 min; iii. AcOH, 65 ºC, overnight

The reduction of the nitro group in **7a** proceeded smoothly in ethanol with 10% Pd/C under H_2 at 50 psi, without reducing the double bond to give **22**[30] (Scheme 5), and the azide in **9** was reduced similarly at ambient pressure to afford **24**.[31] The diacetyl compound (**8**) was deacetylated completely giving **23**[32] in concentrated H_2SO_4 at 50 ˚C and attempts were made to cyclize these three compounds. Cyclisation in methanol, ethylene glycol with molecular sieves, or in *ortho*-xylene with a Dean and Stark trap did not give the desired cyclized product. Cyclisation of **23** to **4** was successful in refluxing acetic acid but neither **3** nor **5** could be obtained from cyclisation of **22** and **24**.



Scheme 5. i. EtOH, Pd/C (10%), H_2, 3.4 atm, overnight; ii. conc. H_2SO_4, 50 ºC, 30 min.; iii. EtOH, Pd/C (10%), H_2, 1 atm, rt, overnight; iv. AcOH, mol. sieves, reflux overnight

In conclusion, three new thenylideneimidazolinone (**7–9**) were synthesized and attempts were made to cyclize these to the corresponding imidazo[4,5-*b*]pyridines (**3**–**5**), but only **4** was obtained. Compounds (**3** and **4**) are new compounds and **3** has a new ring system. These (**3** and **4**) were obtained in good yields by treating the *ortho*-aminocarbaldehydes (**11** and **13**) with the enolic silyl ether of creatinine.

EXPERIMENTAL

All chemicals and solvents were of analytical grade and used as purchased. Evaporations were performed at reduced pressure below 40 °C. The reactions and purifications were monitored by TLC (UV detection)

on aluminium sheets coated with silica gel 60 F254 (Merck). Flash chromatography (FC) was performed on silica gel (63–200 μ, J.T. Baker). Melting points were taken using a Büchi Melting Point B-545 instrument and are uncorrected. IR spectra (neat) were recorded on an Avatar 330 FT-IR Termo Nicolet. NMR spectra were recorded on a Bruker DPX 300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz) at 25 °C, unless otherwise stated, and referenced to the solvent [DMSO-d_6 2.50, 39.5 and $CDCl_3$ 7.26, 77.0]. The coupling constants are reported in Hz. HMBC, HMQC, NOE diff. and decoupled ^{13}C-NMR spectra were used for the assignments. In assigning **7a**, **7b**, **8**, **9** the numbering in Scheme 4 is used. MS spectra were obtained on a Micromass Platform instrument using EI ionization (direct insertion at 70 eV). For compounds containing bromine the ^{81}Br peak is reported. 3-Bromothiophene and 3,4-dibromothiophene were commercially available. 2-Nitro-3-thiophenecarbaldehyde **(10)**[17-19,33] was prepared from 3-dichloromethyl-2-nitrothiophene (4.0 g, 18.9 mmol) as described[18] in 80% yield. 3-Bromo-2-thiophenecarbaldehyde[21,22] was prepared from 3-bromothiophene (6.0 g, 36.8 mmol) as described[21] in 70% yield.

The condensation reaction in bis(trimethylsilyl)acetamide - general procedure

Creatinine (1.3 g, 12.0 mmol) and the appropriate aminocarbaldehyde (4.0 mmol) were heated in bis(trimethylsilyl)acetamide (BSA) (3.0 mL, 12 mmol) at 140 °C for 2 h. After cooling, 1M HCl (20 mL) was added. The mixture was stirred for 30 min and then the pH was adjusted to 11 with 2M NaOH. The reaction mixture was poured into water and the precipitate was filtered off.

2-Amino-1-methylimidazo[4,5-*b*]thieno[3,2-*e*] pyridine (3)

This compound was obtained from 2-amino-3-thiophenecarbaldehyde (**11**), using the above method to yield **3** (0.5 g, 62%). mp 299–302 ºC (MeCN); IR ν 3271, 3091, 1670, 1653, 1578, 1540, 1465, 1445, 1420, 1399, 1249, 1111 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 7.83 (1H, s, H-8), 7.42 (1H, d, 6.0, H-6), 7.31 (1H, d, 6.0, H-7), 7.1 (2H, br s, NH_2), 3.55 (3H, s, 1-Me); ^{13}C-NMR (DMSO-d_6) δ 158.8 (C-2), 156.3 (C-3a), 153.9 (C-4a), 127.0 (C-8a), 124.5 (C-7a), 122.0 (C-7), 121.1 (C-6), 107.9 (C-8), 28.5 (1-Me); MS *m/z* 204 (M, 100%), 203 (53), 188 (7), 176 (20); *Anal.* Calcd for $C_9H_8N_4S$: C, 52.92; H, 3.95; N, 27.43. Found: C, 53.10; H, 3.86; N, 27.33.

2-Amino-1-methylimidazo[4,5-*b*]thieno[2,3-*e*] pyridine (4)

Method 1: This compound was obtained from 3-amino-2-thiophenecarbaldehyde (**13**), using the above method to yield **4** (0.7 g, 85%).

Method 2: Compound (**4**) was also obtained by refluxing **23** (20 mg, 0.09 mmol) in AcOH (3 mL) overnight in the presence of molecular sieves (7 mg, 38%).

mp 298–301 ºC (MeCN); IR ν 3270, 3087, 3069, 1668, 1580, 1538, 1465, 1420, 1407, 1255 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 8.01 (1H, s, H-8), 7.71 (1H, d, 5.5, H-5), 7.35 (1H, d, 5.5, H-6), 7.1 (2H, br s, NH_2),

3.55 (3H, s, 1-Me); ^{13}C-NMR (DMSO-d_6) δ 158.8 (C-2), 156.4 (C-3a), 149.6 (C-4a), 126.8 (C-8a), 126.0 (C-5), 124.1 (C-6), 123.8 (C-7a), 107.1 (C-8), 28.5 (1-Me); MS *m/z* 204 (M, 100%), 203 (58), 188 (6), 176 (17); *Anal.* Calcd for $C_9H_8N_4S$: C, 52.92; H, 3.95; N, 27.43. Found: C, 53.06; H, 4.05; N, 27.28.

2-Amino-1-methyl-5-[2-(2-nitro-3-thenylidene)]-2-imidazolin-4-one (*E*-7a)

Compound (**10**) (330 mg, 2.1 mmol) and **19** (0.3 g, 2.6 mmol) were heated in ethylene glycol (2 mL) at 140 °C for 1.5 h. The reaction mixture was poured on ice water and the precipitate was filtered off and recrystallized from DMA/2-PrOH to yield ***E*-7a** (132 mg, 25%); mp 232–235 ºC (decomp); IR ν 3015, 1664, 1634, 1565, 1476, 1350, 1311, 1211, 1067 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 8.6 (2H, br s, NH_2), 8.10 (1H, d, 5.6, H-4'), 7.86 (1H, d, 5.6, H-5'), 6.76 (1H, s, α-H), 3.21 (3H, s, 1-Me); ^{13}C-NMR (DMSO-d_6) δ 173.9 (C-4), 167.2 (C-2), 146.1 (C-2'), 139.0 (C-5), 136.8 (C-3'), 131.5 (C-4'), 130.8 (C-5'), 101.6 (C-α), 28.0 (1-Me); MS, *m/z* 252 (M, 28%), 206 (52), 109 (100); *Anal.* Calcd for $C_9H_8N_4O_3S$: C, 42.85; H, 3.20; N, 22.21. Found: C, 42.77; H, 3.28; N, 22.11.

The condensation reaction under Perkin conditions – General procedure

Creatinine (95 mg, 0.84 mmol) and the appropriate thiophenecarbaldehyde (0.79 mmol) were heated together with NaOAc (0.31 g, 3.7 mmol) in AcOH (1.0 mL) and Ac_2O (0.3 mL) for 20 min to precipitate an orange solid. After pouring the reaction mixture into water, the orange solid was filtered off.

2-Acetamido-1-methyl-5-[2-(2-nitro-3-thenylidene)]-2-imidazolin-4-one (7b)

This compound was obtained from 2-nitro-3-thiophenecarbaldehyde (**10**) using the above method to yield (***E*)-7b** (137 mg, 59%). mp 267–268 ºC (MeCN); IR ν 3283, 3151, 3112, 3074, 1739, 1630, 1568, 1353, 1309, 1261, 1123, 1070, 999 cm^{-1}; ^{1}H-NMR (DMSO-d_6 at 80 ºC) δ 11.3 (1H, br s, NH), 7.88 (1H, d, 5.5, H-5'), 7.75 (1H, d, 5.5, H-4'), 6.94 (1H, s, α-H), 3.26 (3H, s, 1-Me), 2.15 (3H, s, 2-Me); ^{13}C-NMR (DMSO-d_6 at 80 ºC) δ 181.4 (2-CO), 162.3 (C-4), 150.5 (C-2), 147.4 (C-2'), 134.8 (C-3'), 132.5 (C-5), 130.7 (C-4' or C-5'), 130.6 (C-5' or C-4'), 105.4 (C-α), 27.2 (1-Me), 27.1 (2-Me); MS *m/z* 294 (M, 15%), 279 (4), 248 (45), 235 (61), 206 (89), 153 (41), 109 (100); When stored in DMSO for one week the product isomerised to a ratio of 90/10 (*E*/*Z*). (***Z*)-7b** ^{1}H-NMR (DMSO-d_6 at 80 ºC) δ 11.3 (1H, br s, NH), 8.03 (1H, d, 5.5), 7.32 (1H, d, 5.6), 6.85 (1H, s, α-H), 2.97 (3H, s, 1-Me), 2.14 (3H, s, 2-Me); *Anal.* Calcd for $C_{11}H_{10}N_4O_4S$: C, 44.90; H, 3.43; N, 19.04. Found: C, 44.73; H, 3.35; N, 19.10.

2-Acetamido-5-[2-(3-acetamido-2-thenylidene)]-1-methyl-2-imidazolin-4-one (8)

This compound was obtained from 3-amino-2-thiophenecarbaldehyde (**13**), using the above method to yield (***E*)-8** (140 mg, 58%); mp 291–292 ºC (decomp) (MeCN); IR ν 3160, 3084, 1731, 1650, 1623, 1577, 1353, 1331, 1275, 1234, 1113, 1071, 1016, 983 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 11.4 (1H, br s, NH), 10.0 (1H, s, NH'), 7.63 (1H, d, 5.5, H-5'), 7.42 (1H, d, 5.5, H-4'), 6.79 (1H, s, α-H), 3.30 (3H, s, 1-Me), 2.11 (3H, s, 3'-Me), 2.10 (3H, s, 2-Me); ^{13}C-NMR (DMSO-d_6) δ 181.1 (2-CO), 168.2 (3'-CO), 161.9 (C-4),

151.2 (C-2), 140.0 (C-3'), 128.6 (C-5'), 124.0 (C-5), 123.9 (C-4'), 120.7 (C-2'), 109.0 (C-α), 27.7 (2- or 1-Me), 27.4 (1- or 2-Me), 23.4 (3'-Me); MS *m/z* 306 (M, 100%), 291 (4), 264 (42), 247 (86), 205 (82); When stored in DMSO for one week the product isomerised to a ratio of 75/25 (*E*/*Z*). (***Z***)-**8** ^{1}H-NMR (DMSO-d_6) δ 11.4 (1H, br s, NH), 9.8 (1H, s, NH'), 7.67 (1H, d, 5.4), 7.49 (1H, d, 5.4), 6.75 (1H, s, α-H), 3.15 (3H, s, 1-Me), 2.10 (3H, s, Ac), 2.05 (3H, s, Ac); *Anal.* Calcd for $C_{13}H_{14}N_4O_3S$: C, 50.97; H, 4.61; N, 18.29. Found: C, 51.12; H, 4.81; N, 18.07.

2-Amino-5-[2-(4-azido-3-thenylidene)]-1-methyl-2-imidazolin-4-one (*E*-9)

Compound (**17**) (100 mg, 0.65 mmol) and **19** (220 mg, 2.0 mmol) were dissolved in AcOH (3 mL) and the solution was heated at 65 ºC and left overnight. Evaporation *in vacuo* and FC ($CHCl_3$ to $CHCl_3$-MeOH 4:1) yielded a yellow solid (64 mg, 40 %); mp 178 ºC (decomp) ($CHCl_3$/MeOH); IR ν 3315, 3106, 2969, 2116, 2093, 1693, 1668, 1631, 1548, 1501, 1355, 1258, 1233 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 9.14 (1H, d, 3.2, H-2'), 7.9 (2H, br s, NH_2), 7.40 (1H, d, 3.2, H-5'), 5.86 (1H, s, α-H), 3.15 (3H, s, 1-Me); ^{13}C-NMR (DMSO-d_6) δ 174.9 (C-4), 166.2 (C-2), 136.2 (C-3'), 135.5 (C-5), 127.0 (C-2'), 126.5 (C-4'), 110.1 (C-5'), 101.2 (C-α), 21.1 (1-Me); MS (ES+) *m/z* 249 (M+H, 97), 221 (100), 206 (51). *Anal.* Calcd for $C_9H_8N_6OS$: C, 43.54; H, 3.25; N, 33.85. Found: C, 43.37; H, 3.18; N, 33.95.

2-Amino-3-thiophenecarbaldehyde (11)[20]

A mixture of **10** (1.1 g, 7.0 mmol) and 1.4 g of iron powder in AcOH (700 mL) was heated at 75 ºC for 30 min. After cooling, the solvent was evaporated and the residue partitioned between EtOAc and sat. $NaHCO_3$. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through a plug of silica and gave a dark red oil (620 mg, 70%). ^{1}H-NMR (DMSO-d_6) δ 9.58 (1H, CHO), 8.0 (2H, br s, NH_2), 6.89 (1H, d, 5.8, H-4), 6.28 (1H, d, 5.8, H-5); ^{13}C-NMR (DMSO-d_6) δ 183.5 (CHO), 165.6 (C-2), 125.7 (C-4), 116.1 (C-3), 107.5 (C-5).

3-Azido-2-thiophenecarbaldehyde (12)[23,24,28,34]

3-Bromo-2-thiophenecarbaldehyde (4.0 g, 21.0 mmol) was dissolved in DMPU (50 mL), and NaN_3 (5.5 g, 84.0 mmol) was added portionwise under argon at ambient temperature. The reaction was warmed at 35 °C for 24 h, poured onto ice water and extracted with ether. The organic layer was washed with brine and dried ($MgSO_4$). Evaporation *in vacuo* and FC ($CHCl_3$) of the residue gave **12** (2.6 g, 81%); mp 56–58 ºC (MeOH) (lit.,[23] 56.6–57.2 ºC (MeOH), lit.,[24] 57–58 ºC, lit.,[28] 57–58 ºC, lit.,[34] 55 ºC) IR ν 3275, 3103, 3075, 2110, 1640, 1525, 1428, 1388, 1356, 1279, 1226 cm^{-1}; ^{1}H-NMR was in agreement with published data.[23] ^{13}C-NMR ($CDCl_3$) δ 180.2 (CHO), 144.9 (C-3), 135.2 (C-5), 127.6 (C-2), 120.6 (C-4); MS *m/z* 153 (M, 12%), 125 (58), 97 (87), 70 (100).

3-Amino-2-thiophenecarbaldehyde (13)[23,35]

Compound (**12**) (3.25 g, 21.0 mmol) was dissolved in MeOH (150 mL) and 40% NH_4SH (3.3 mL, 26.0 mmol) was added dropwise. TLC ($CHCl_3$/MeOH, 8:1) showed completion of the reaction after 10 min at rt while the gas evolution had ceased. The reaction mixture was evaporated *in vacuo* and FC ($CHCl_3$) of the residue provided **13** (2.3 g, 86%). mp 66–68 ºC (EtOH/H_2O), (lit.,[23] 68–70 ºC (EtOH/H_2O), lit.,[35] 67 ºC (petroleum ether)) IR ν 3398, 3252, 3171, 2835, 1606, 1499, 1455, 1420, 1385, 1298, 1238, 1081 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.53 (1H, d, 0.6, CHO), 7.44 (1H, d, 5.3, H-5), 6.51 (1H, dd, 5.3, 0.6, H-4), 6.1 (2H, br s, NH_2); ^{13}C-NMR ($CDCl_3$) δ 182.4 (CHO), 154.3 (C-3), 136.2 (C-5), 119.6 (C-4), 113.2 (C-2); MS *m/z* 127 (M, 100%), 126 (21), 99 (39), 98 (21), 72 (28).

3-Bromo-4-thiophenecarbaldehyde (14)[26,36]

This compound was prepared from 3,4-dibromothiophene (4.0 g, 16.5 mmol) as described[26] to yield **14** (1.85 g, 59%). IR ν 3103, 2853, 2792, 1681, 1490, 1408, 1154, 1002, 803, 746 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.94 (1H, s, CHO), 8.15 (1H, d, 3.5, H-2), 7.36 (1H, d, 3.5, H-5); ^{13}C-NMR ($CDCl_3$) δ 184.6 (CHO), 137.5 (C-3), 134.6 (C-2), 125.0 (C-5), 111.3 (C-4); MS, *m/z* 192 (M, 88%), 191 (100), 163 (7).

3-Bromo-4-thiophenecarbaldehyde ethylene acetal (15)[27]

This compound was prepared from **14** (1.55 g, 8.1 mmol) as described[27] to yield **15** (1.3 g, 68%). IR ν 3108, 2953, 2885, 1528, 1326, 1094, 1000, 962, 937, 804 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.47 (1H, d, 3.5, H-2), 7.28 (1H, d, 3.5, H-5), 5.90 (1H, s, H-2'), 3.94 (4H, m, H-4' and H-5'); ^{13}C-NMR ($CDCl_3$) δ 137.8 (C-3), 124.9 (C-2), 124.2 (C-5), 109.6 (C-4), 99.8 (C-2'), 65.2 (C-4' and C-5'); MS, *m/z* 236 (M, 93%), 235 (100).

3-Azido-4-thiophenecarbaldehyde ethylene acetal (16)[28]

This compound was prepared from **15** (1.0 g, 4.3 mmol) as described[28] to yield **16** (480 mg, 57%); IR ν 3096, 2946, 2886, 2112, 1687, 1519, 1435, 1365, 1257, 1108 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.42 (1H, dd, 3.4, 0.6, H-2), 6.86 (1H, d, 3.4, H-5) 5.78 (1H, d, 0.6, H-2') 4.05 (4H, m, H-4' and H-5'); ^{13}C-NMR ($CDCl_3$) δ 136.0 (C-4), 132.1 (C-3), 125.1 (C-2), 110.8 (C-5), 98.5 (C-2'), 65.1 (C-4' and C-5').

3-Azido-4-thiophenecarbaldehyde (17)[28]

This compound was prepared from **16** (480 mg, 2.4 mmol) as described[28] to yield **17** (264 mg, 72%); mp: 45–47 ºC (MeOH) (lit.,[28] 50–52 ºC); IR ν 3085, 2120, 1674, 1508, 1431, 1422, 1370, 1260, 1163, 825, 709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.82 (1H, s, CHO), 8.09 (1H, d, 3.4, H-2), 6.93 (1H, d, 3.4, H-5); ^{13}C-NMR ($CDCl_3$) δ 183.3 (CHO), 138.2 (C-4), 135.5 (C-2), 133.3 (C-3), 111.6 (C-5).

REFERENCES

1. S. Grivas, T. Nyhammar, K. Olsson, and M. Jägerstad, *Food Chem.*, 1986, **20**, 127.

2. R. Vikse, A. Knapstad, L. Klungsøyr, and S. Grivas, *Mutat. Res.*, 1993, **298**, 207; R. Vikse, L. Klungsøyr, and S. Grivas, *Mutat. Res.*, 1993, **319**, 273; S. Grivas, N. Russo, and M. Toscano, 'Topics in Molecular Organization and Engeneering,' Vol. 11, ed. by N. Russo, J. Anastassopoulou and G. Barone, Kluwer Academic publishers, Dordrecht, 1994, pp. 243–247; R. Vikse, F. T. Hatch, N. W. Winter, M. G. Knize, S. Grivas, and J. S. Felton, *Environ. Mol. Mutagen.*, 1995, **26**, 79; F. T. Hatch and M. E. Colvin, *Mutat. Res.*, 1997, **376**, 87.
3. S. Lindström, T. Ahmad, and S. Grivas, *Heterocycles*, 1994, **38**, 529; S. Lindström, M. Eriksson, and S. Grivas, *Acta Chem. Scand.*, 1993, **47**, 805; S. Grivas, W. Tian, E. Ronne, S. Lindström, and K. Olsson, *Acta Chem. Scand.*, 1993, **47**, 521.
4. S. Grivas and E. Ronne, *J. Chem. Res. (S)*, 1994, 268.
5. E. Ronne, K. Olsson, and S. Grivas, *Synth. Commun.*, 1994, **24**, 1363.
6. S. Lindström, *Acta Chem. Scand.*, 1995, **49**, 361.
7. S. Grivas and P. Schuisky, *Heterocycles*, 1998, **48**, 1575.
8. C. J. Collins, J. E. Bupp, and M. J. Tanga, *Arkivoc*, 2002, **3**, 90; M. J. Tanga, W. W. Bradford, J. E. Bupp, and J. A. Kozocas, *J. Heterocycl. Chem.*, 2003, **40**, 569.
9. R. B. Silverman, 'The Organic Chemistry of Drug Design and Drug Action,' Academic Press, San Diego, 1992, pp. 19–23.
10. G. Guella, I. Mancini, H. Zibrowius, and F. Pietra, *Helv. Chim. Acta*, 1989, **72**, 1444.
11. K. H. Hollenbeak and F. J. Schmitz, *Lloydia*, 1977, **40**, 479.
12. J. Karolak-Wojciechowska, A. Mrozek, K. Kieć-Kononowicz, and J. Handzlik, *J. Mol. Struct.*, 2003, **649**, 25.
13. P. Schuisky, W. Twistel, and S. Grivas, *Heterocycles*, 1998, **48**, 1431.
14. C.-C. Cheng and S.-J. Yan, *Org. Reactions*, 1982, **28**, 37.
15. J. M. Muchowski and M. L. Maddox, *Can. J. Chem.*, 2004, **82**, 461.
16. G. L. Kenyon and G. L. Rowley, *J. Am. Chem. Soc.*, 1971, **93**, 5552.
17. M. Mąkosza and Z. Owczarczyk, *Tetrahedron Lett.*, 1987, **28**, 3021.
18. M. Mąkosza and Z. Owczarczyk, *J. Org. Chem.*, 1989, **54**, 5094.
19. K. Görlitzer and P.-M. Dobberkau, *Pharmazie*, 1996, **51**, 386.
20. A. Capperucci, A. Degl'Innocenti, M. Funicello, G. Mauriello, P. Scafato, and P. Spagnolo, *J. Org. Chem.*, 1995, **60**, 2254.
21. L. S. Fuller, B. Iddon, and K. A. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3465.
22. J. D. Prugh, G. D. Hartman, P. J. Mallorga, B. M. McKeever, S. R. Michelson, M. A. Murcko, H. Schwam, R. L. Smith, J. M. Sondey, J. P. Springer, and M. F. Sugrue, *J. Med. Chem.*, 1991, **34**, 1805.
23. S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand.*, 1975, **B29**, 224.
24. C. J. Moody, C. W. Rees, and S. C. Tsoi, *J. Chem. Soc., Perkin Trans. 1*, 1984, 915.
25. T. J. Collins, R. D. Powell, C. Slebodnick, and E. S. Uffelman, *J. Am. Chem. Soc.*, 1991, **113**, 8419.
26. D. W. Hawkins, B. Iddon, D. S. Longthorne, and P. J. Rosyk, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2735.
27. S. Gronowitz, A. Biezais, and B. Mathiasson, *Ark. Kemi*, 1963, **21**, 265.
28. P. Spagnolo and P. Zanirato, *J. Org. Chem.*, 1978, **43**, 3539.
29. J. R. Johnson, *Org. Reactions*, 1942, **1**, 210.
30. Compound (**22**): ^{1}H-NMR (DMSO-d_6) δ 7.6 (2H, br s, NH_2), 7.22 (1H, d, *J*=5.5, H-4'), 6.52 (1H, d, *J*=5.5, H-5'), 6.38 (1H, s, α-H), 5.7 (2H, br s, NH_2), 3.18 (3H, s, 1-Me).
31. Compound (**24**): ^{1}H-NMR (DMSO-d_6) δ 8.87 (1H, d, *J*=3.3), 7.9 (2H, br s, NH_2), 6.05 (1H, d, *J*=3.3), 6.03 (1H, s), 5.0 (2H, br s, NH_2), 3.20 (3H, s).
32. Compound (**23**): ^{1}H-NMR (DMSO-d_6) δ 7.47 (1H, d, *J*=5.4), 6.90 (1H, s), 6.57 (1H, d, *J*=5.4), 6.4 (2H, br s, NH_2), 3.29 (3H, s).
33. V. M. Colburn, B. Iddon, H. Suschitzky, and P. T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1337; S. Ostrowski, *Heterocycles*, 1996, **43**, 389.
34. C. Paulmier, *Compt. Rend.*, 1975, **281**, 317.

35. G. Ah-Kow, C. Paulmier, and P. Pastour, *Bull. Soc. Chim. Fr.*, 1976, 151.
36. S. Gronowitz, P. Moses, A.-B. Hörnfeldt, and R. Håkansson, *Ark. Kemi*, 1961, **17**, 165; R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, 1960, **16**, 563; P. Fournari, R. Guilard, and M. Person, *Bull. Soc. Chim. Fr.*, 1967, 4115.