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Azoles. Part 12.[1] Synthesis of Thieno-Extended Purines: First Example of the Imidazo[4′,5′:4,5]thieno[3,2-*d*]pyrimidine Ring System

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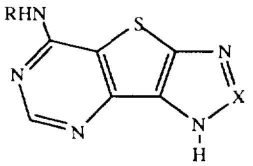
Dedicated to Emeritus Professor Hans Suschitzky on the occasion of his 80th birthday (December 14th, 1995)

Abstract: 1-Benzyl-4-bromoimidazole-5-carbonitriles were synthesised by several methods and shown to be surprisingly resistant to nucleophilic displacement of the bromine atom (e.g. by sulfanylacetamide under various conditions). 1-Benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile underwent Br → Li exchange with butyllithium (THF/-100 °C) and the resulting 4-lithiated imidazole was treated successively with elemental sulfur and chloroacetamide, to give 2-[1-benzyl-5-cyano-2-(methylsulfanyl)-imidazol-4-ylthio]acetamide. With sodium ethoxide in ethanol this cyclised, to give 6-amino-1-benzyl-2-(methylsulfanyl)thieno[2,3-*d*]imidazole-5-carboxamide which gave the first reported derivative of the title compound on treatment with triethyl orthoformate in acetic anhydride. 1-Benzyl-4-bromoimidazole-5-carbaldehyde was synthesised from 1-benzyl-2,4,5-tribromoimidazole by its initial conversion into a 2-TBDMS-protected derivative followed by introduction of the 5-formyl group *via* Br → Li exchange and an *N*-formylpiperidine quench of the resulting 5-lithiated imidazole and, finally, removal of the 2-TBDMS-group (Bu_4NF/THF).

The purine ring system is undoubtedly one of the most ubiquitous heterocyclic ring systems.[2-4] It occurs naturally, e.g. as uric acid and caffeine and in the cytokinins (plant hormones that appear to promote cell division and inhibit senescence[5-13]), in DNA and RNA, in the various nucleosides and nucleotides acting as hormones and neurotransmitters, is present in some co-enzymes, and the metabolic interconversion of nucleoside phosphate esters provides energy transfer. Its many synthetic derivatives often exhibit biological activity, particularly antimetabolic, antiviral and antitumour activity, e.g. acyclovir, 6-mercaptopurine and azothioprine (an immunosuppressive agent). The importance of purine chemistry has prompted the synthesis of a plethora of related heterocyclic ring systems as potentially biologically active compounds.[e.g. 14-16]

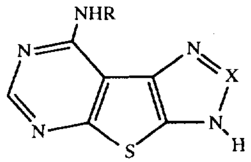
Several years ago our attention was drawn to the work of Leonard and his coworkers who synthesised a number of "extended" (or "stretched") purines with a "spacer unit" separating the imidazole and pyrimidine rings and employed these as dimensional probes of enzyme-co-enzyme binding sites.[17-19] Schneller's group[19-23] and others[24,25] have carried out parallel studies with purines, pteridines and related systems. *lin*-Extended purines in which the "spacer unit" is a benzene ring (fusion of the heterocyclic rings to the 1,2-and 4,5-faces) are biologically active but those in which it is a naphthalene ring are not, whilst fusion of the heterocyclic rings to the benzene ring in an angular manner (i.e. to the 1,2- and either 3,4- or 5,6-faces) results in a loss of activity.

Of all the possible heterocyclic rings that could be inserted as "spacer units" in "extended" purines only the "π-deficient" pyridine[26,27] and pyrazine[28-31] rings appear to have been used. Leonard[17] considered systems in which the "spacer unit" is a "π-excessive" thiophene ring to be "good candidates for an analysis of deaminase and oxidase activities". Consequently, in the 1970's, we planned to synthesise molecules with the general structures **1**-**4**, particularly with a view to synthesising some cytokinin analogues which we hoped may exhibit interesting plant growth regulating properties. Unlike the systems synthesised by Leonard, Schneller and others these systems are neither completely linear nor fully angular but are "bent" due to the "kite"-shaped structure of the thiophene ring. Previously we have gained some experience through constructing several thiophene[32] (**5**-**7**) and thiazole[33] (**8**) analogues.



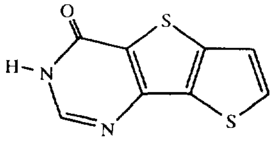
1; X = CH

2; X = N



3; X = CH

4; X = N



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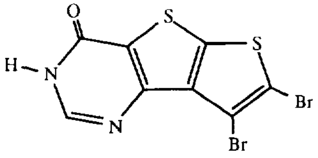

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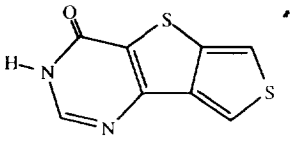

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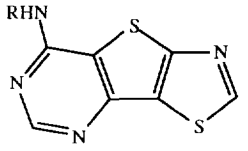

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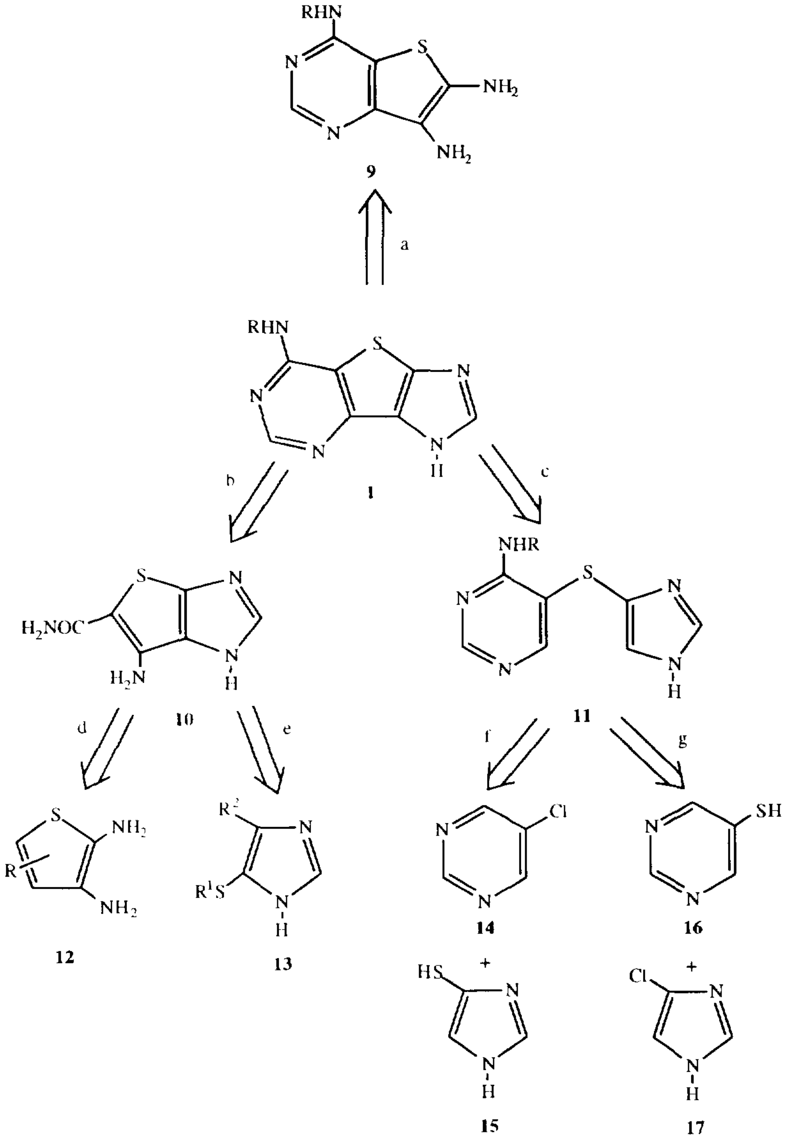
A retrosynthetic analysis for target molecules **1** is shown in Scheme 1. 2,3-Diaminothiophenes **12** and annelated analogues such as **9** are notoriously unstable and difficult to prepare,[34,35] which excludes routes a and b/d from further consideration. Whilst 5-chloropyrimidine **14** is susceptible to nucleophilic substitution[36] imidazole-4(5)-thiols such as **15** are unknown and 4(5)-chloroimidazole **17** would be extremely resistant to attack by nucleophiles such as thiol **16**,[37] which excludes routes c/f and c/g involving construction of sulfide **11**. Consequently our chosen route was b/e (Scheme 1) which requires multiply functionalized imidazoles **13** to synthesise thienoimidazoles **10**.

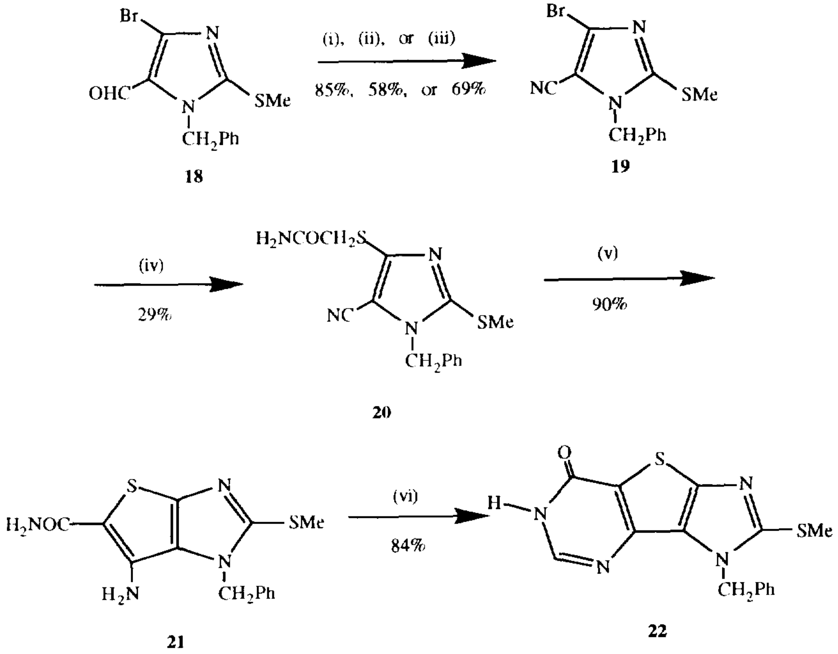
Previously[1] we have reported extensively on the synthesis of multiply substituted imidazoles, particularly 1-protected 4-bromoimidazole-5-carbaldehydes which can be used to obtain thieno[2,3-*d*]imidazoles.[35,38,39] We now report an extension of this work which has allowed us to synthesise the first example of the target ring system **1**. We also highlight some remaining problems with our methodology in the hope that our results will



SCHEME 1

stimulate further work in this area. Other groups[40-51] have adopted the "thiophene approach" (route b/d; Scheme 1) to thieno[2,3-*d*]imidazoles, which is less successful and less versatile than the "imidazole route" (b/e; Scheme 1) in our opinion. Derivatives of thieno[2,3-*d*]imidazole have been of interest as anthelminthic agents,[40] antiviral agents (e.g. the thiophene analogue of enviroxime[43]), omeprazole-like H^+/K^+-ATPase inhibitors[44,45,47] and angiotensin II antagonists.[48-51]

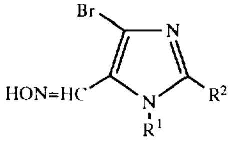
We chose as our starting material 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbaldehyde **18** (Scheme 2).[52] Previously[35] the 2-(phenylsulfanyl)-analogue of this compound has been converted successfully into 1-benzyl-2-(phenylsulfanyl)-1*H*-thieno[2,3-*d*]imidazole-5-carboxylate through its reaction with ethyl 2-sulfanylacetate (ethyl 2-mercaptoacetate) in ethanol in the presence of sodium ethoxide. Our model chemistry was conducted with a compound carrying a 2-protecting group in order to avoid problems with transmetallation reactions (5-Li → 2-Li).[1] In any case cytokinins substituted by a methylsulfanyl group in the imidazole ring exhibit enhanced biological activity.[53] Our successful synthesis of the first example **22** of the title ring system is summarised in Scheme 2.



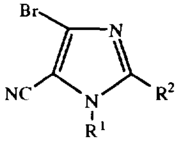
Reagents: (i) H_2NOH followed by Ac_2O on oxime; (ii) For **18** CHO = Br, BuLi/THF/-78 °C, then TosCN; (iii) For **18** CHO = Br, BuLi/THF/-78 °C, ZnI_2, then TosCN; (iv) BuLi/THF/-78 °C, S_8, then $ClCH_2CONH_2$; (v) NaOEt/EtOH; (vi) $HC(OEt)_3/Ac_2O$.

Scheme 2

Nitriles **19** (85% yield) and **26** (76%) were available through dehydration of the oximes, **23** and **24**, respectively, of the corresponding carbaldehydes (e.g. **18**)[52,54] with acetic anhydride. An attempt to dehydrate oxime **25** to nitrile **27** with phosphorus oxychloride[35] failed, giving only an intractable black tar. Imidazole-2-carbonitriles have been synthesised by cyanation of 2-lithiated imidazoles with tosyl cyanide.[55,56] Nitriles **19** (58% yield) and **26** (38%) were prepared similarly from the corresponding 5-lithiated imidazoles.[52,54] Transmetallation of 1-benzyl-4-bromo-2-(methylsulfanyl)imidazol-5-yllithium with zinc(II) iodide and subsequent treatment of the resulting organozinc derivative with tosyl cyanide[57] gave nitrile **19** in 69% yield.

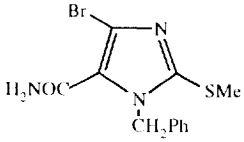


23; $R^1 = CH_2Ph$, $R^2 = SMe$
24; $R^1 = CH_2Ph$, $R^2 = SPh$
25; $R^1 = CH_2C_6H_3(OMe)_2$-3,4, $R^2 = SMe$



19: $R^1 = CH_2Ph$, $R^2 = SMe$
26: $R^1 = CH_2Ph$, $R^2 = SPh$
27: $R^1 = CH_2C_6H_3(OMe)_2$-3,4, $R^2 = SMe$

Unfortunately the bromine atom in nitrile **19** (Scheme 2) proved surprisingly resistant to displacement by sulfur nucleophiles. A similar observation has been made by us previously with 1-benzyl-4-bromoimidazole-5-carbonitrile.[35] Thus, when nitrile **19** was treated with ethyl 2-sulfanylacetate, either in refluxing ethanol containing sodium ethoxide (5 h) or as the pregenerated sodium salt ($HSCH_2CO_2Et/NaOEt/EtOH$) in dimethyl sulfoxide (DMSO) at ambient temperature (4 h), it gave starting material (56% recovery) and an intractable black tar or a complicated mixture [by thin layer chromatography (TLC)] from which no attempt was made to separate products, respectively. Nitriles **19** and **26** failed to react with freshly prepared sulfanylacetamide (2-mercapto-acetamide) in *N,N*-dimethylformamide (DMF) containing potassium carbonate either for prolonged periods at ambient temperature or under reflux. At ambient temperature no change could be detected by TLC whilst prolonged heating caused decomposition. With sulfanylacetamide in refluxing ethanol containing sodium ethoxide nitrile **19** gave mainly starting material (43% recovery) together with a small amount (9%) of the amide **28**. Addition of copper(II) sulfate[58] to a similar reaction gave only an inseparable multicomponent mixture (TLC). Finally, we attempted a Pd(O)-catalysed coupling reaction between nitrile **19** and an organotin derivative of sulfanylacetamide in refluxing toluene;[59] after 4 h starting material had been consumed and TLC analysis of the product showed that it consisted of three products which did not correspond either with the sulfide **20** or thieno[2,3-*d*]imidazole **21** (both prepared as described later) and this mixture was not examined further.



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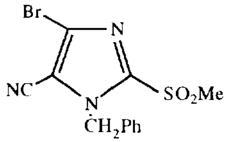

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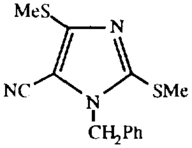
Next we decided to synthesise the sulfone **29** in the hope that its bromine atom would be more susceptible to nucleophilic displacement than that in its precursor **19**. Oxidation of the 2-methylsulfanyl compound **19** with hydrogen peroxide in acetic acid gave an excellent yield (80%) of the sulfone **29** but there was evidence of displacement of both the bromine atom and the 2-methylsulfonyl group when it was reacted with sodium benzenethiolate.

Imidazole-carbonitriles have been converted at low temperatures into lithiated derivatives.[56,60,61] Therefore, we considered that sulfur functionality could be introduced into compound **19** *via* Br → Li exchange followed by quenching with a sulfur reagent. 1-Benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile **19** was treated first with butyllithium (THF/-100 °C), then with dimethyl disulfide, which gave a good yield (58%)

of 1-benzyl-2,4-bis(methylsulfanyl)imidazole-5-carbonitrile **30**. At higher temperatures (-78 °C) yields of this product were lower, presumably due to competing side-reactions. When this reaction was repeated using the disulfide obtained from sulfanylacetamide (through its oxidation with iodine in ethanol) in place of the dimethyl disulfide, none of the desired compound **20** (Scheme 2) was obtained, only the product **31** of debromination. A similar failure has been reported previously.[35] Unfortunately, in this case the disulfide had a low solubility in tetrahydrofuran (THF).



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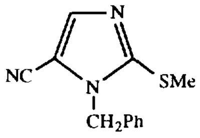

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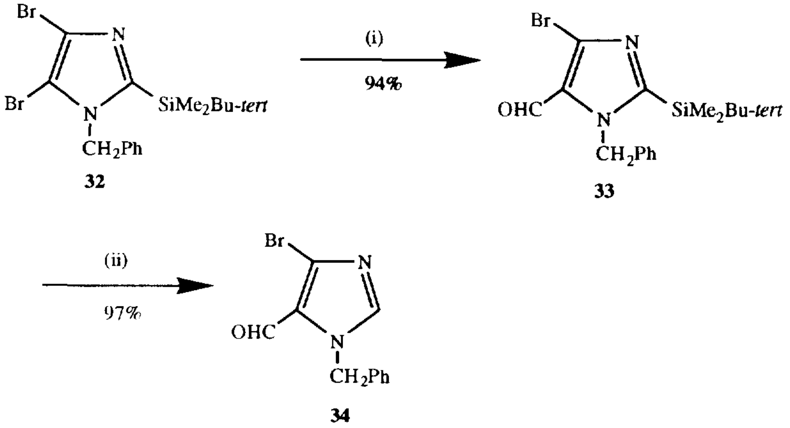
Compound **20** (Scheme 2) was obtained, however, in moderate yield (29%) when the 4-lithiated imidazole obtained from nitrile **19** was quenched with an excess of elemental sulfur followed by addition of chloroacetamide to the resulting lithiated thiol. Cyclisation of compound **20** with sodium ethoxide in ethanol gave the thieno[2,3-*d*]imidazole **21** in excellent yield (90%). Treatment of this thienoimidazole with triethyl orthoformate in acetic anhydride gave a good yield (84%) of 1-benzyl-2-(methylsulfanyl)imidazo[4′,5′;4,5]-thieno[3,2-*d*]pyrimidin-5(6*H*)-one **22** (Scheme 2), which is the first example of this thieno-extended purine ring system.

The synthesis summarised in Scheme 2 suffers from several disadvantages. Ideally we would like to accomplish this procedure without the need to protect C-2. Furthermore a benzyl group is not the ideal *N*-protecting group. The conversion of our multiply functionalised imidazoles into thieno[2,3-*d*]imidazoles carrying substituents which allow annelation of the pyrimidine ring is also problematic. The resistance of compounds such as **19** and **26** to nucleophilic displacement of the bromine atoms is also surprising, especially in view of the fact that similar thiazoles react without difficulty.[33] Currently we are working to solve all these difficulties.

Previously we[54] have synthesised 1-benzyl-4-bromoimidazole-5-carbaldehyde **34** (Scheme 3) from 1-benzyl-4,5-dibromoimidazole *via* Br → Li exchange at C-5 followed by quenching the resulting 5-lithiated imidazole with DMF. Recently[1] we have reported that this Br → Li exchange reaction is not as straightforward as previously reported due to 5-Li → 2-Li transmetallation. Therefore, we have examined briefly an alternative route to carbaldehyde **34**. 1-Benzyl-2,4,5-tribromoimidazole[37] was reacted successively with methyllithium (Et_2O/-78 °C) and *tert*-butyldimethylsilyl chloride (TBDMSCl), to give the 2-TBDMS-protected imidazole **32** (Scheme 3) but in poor yield (31%). Coupling between the 2-lithiated imidazole and the TBDMSCl was shown (by following the reaction using TLC) to be slow, even at ambient temperature (~ 1 h to go to completion) and side reactions are probably responsible for the low yield. Generating the 2-lithiated imidazole from 1-benzyl-4,5-dibromoimidazole and LDA failed to improve the yield. However, compound **32** could be converted into carbaldehyde **33** in excellent yield (94%) *via* its successive treatment with butyllithium and *N*-formylpiperidine. Removal of the 2-TBDMS protecting group was accomplished in the usual way (with Bu_4NF), to give 1-benzyl-4-bromoimidazole-5-carbaldehyde **34** (Scheme 3) in 97% yield.



Reagents: (i) BuLi/Et$_2$O/-78 °C, then *N*-formylpiperidine; (ii) Bu$_4$NF/THF.

SCHEME 3

EXPERIMENTAL

The instruments used and general experimental conditions were the same as those described previously.[32] The neutral alumina used for column chromatography was Type H from BDH Ltd.

The following compounds were prepared by literature methods: 2,4,5-tribromoimidazole (64%), m.p. 223 °C (from aqueous ethanol) (lit.,[62] 71% and m.p. 221-222 °C) (see **CAUTION** given in Part 11[1] regarding the neurotoxicity of polybrominated imidazoles!); 1-benzyl-2,4,5-tribromoimidazole (77%), m.p. 60-62 °C (from ethanol) (lit.,[37] 90% and m.p. 67-68 °C); 2,4,5-tribromo-1-(3,4-dimethoxybenzyl)imidazole (63%), m.p. 123-125 °C (from ethyl acetate) (lit.,[37] 60% and m.p. 122-124 °C); 1-benzyl-4,5-dibromo-2-(methylsulfanyl)-imidazole (98%), m.p. 67-69 °C (flash chromatographed on silica[52]) (lit.,[52] 72% as a pale-yellow oil); 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbaldehyde **18** (39%), m.p. 79-81 °C (from light petroleum) (lit.,[52] 60% and m.p. 76-78 °C); and sulfanylacetamide (2-mercaptoacetamide) (77%), m.p. 55 °C (from butanol) (lit.,[63] m.p. 54-55 °C).

4-Bromo-1-(3,4-dimethoxybenzyl)-2-(methylsulfanyl)imidazole-5-carbaldehyde

(a) 1.4 mol dm^{-3} Methyllithium in ether (5.5 cm^3, 7.7 mmol) was added dropwise to a stirred solution of 2,4,5-tribromo-1-(3,4-dimethoxybenzyl)imidazole (3.20 g, 7.03 mmol) in tetrahydrofuran (THF) (50 cm^3) at -78 °C and the resulting mixture was stirred for a further 15 min at this temperature. Dimethyl disulfide (2.59 g, 2.48 cm^3, 27.5 mmol) was added dropwise, then the mixture was allowed to warm up to ambient temperature. Work-up in the usual way[1] (extraction of the product with trichloromethane) gave a crude product which was flash chromatographed on silica. Ethyl acetate-light petroleum (20:80) gave 4,5-dibromo-1-(3,4-dimethoxybenzyl)-2-(methylsulfanyl)imidazole (1.90 g, 64%), m.p. 90-92 °C, which was used without further purification in the next step (b); δ_H (90 MHz; CDCl$_3$) 2.52 (3 H, s, SMe), 3.82 (6 H, s, 2 x OMe), 5.06 (2 H, s, CH$_2$) and 6.76 (3 H, m, ArH).

(b) 1.5 mol dm^{-3} Butyllithium in hexane (4.9 cm^3, 7.35 mmol) was added to a stirred solution of 4,5-dibromo-1-(3,4-dimethoxybenzyl)-2-(methylsulfanyl)imidazole (2.82 g, 6.68 mmol), prepared as described in (a), in THF (50 cm^3) at -78 °C and the mixture was stirred at this temperature for a further 30 min prior to addition of anhydrous *N,N*-dimethylformamide (DMF) (0.54 g, 0.57 cm^3, 7.35 mmol). Then the resulting mixture was allowed to warm up to ambient temperature when it was worked up in the usual manner (crude product extracted with trichloromethane), to give 4-bromo-1-(3,4-dimethoxybenzyl)-2-(methylsulfanyl)-imidazole-5-carbaldehyde (1.34 g, 54%), m.p. 145-147 °C (from hexane), ν_{max} cm^{-1} 1664 (CO); δ_H (300 MHz; $CDCl_3$) 2.69 (3 H, s, SMe), 3.83 (6 H, s, 2 x OMe), 5.39 (2 H, s, CH_2), 6.75-6.87 (3 H, m, ArH) and 9.60 (1 H, s, C*H*O) (Found: C, 45.0; H, 4.1; N, 7.4%; M$^+$ + 1, 371. $C_{14}H_{15}BrN_2O_3S$ requires C, 45.3; H, 4.1; N, 7.6%; M + 1, 371).

1-Benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbaldehyde oxime 23

1-Benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbaldehyde **18** (2.00 g, 6.43 mmol) in ethanol (60 cm^3) was added to a stirred solution of hydroxylamine hydrochloride (3.13 g, 45.0 mmol) and sodium hydrogen carbonate (3.78 g, 45.0 mmol) in water (10 cm^3) and the resulting solution was stirred overnight at ambient temperature. The ethanol was distilled off and water (50 cm^3) added to the residue. Extraction with ethyl acetate gave the **product 23** (1.97 g, 94% crude), m.p. 185-187 °C (from ethanol), ν_{max} cm^{-1} 1620 (C=N) and 3135-3185 br (OH); δ_H (90 MHz; [$^2H_6$]-Me_2CO) 2.58 (3 H, s, SMe), 5.54 (2 H, s, CH_2), 7.10-7.40 (6H, m, CH and ArH) and 7.99 (1 H, br s, exchangeable, OH), which was used without further purification as described later.

The following oximes were prepared similarly: 1-benzyl-4-bromo-2-(phenylsulfanyl)imidazole-5-carbaldehyde oxime **24** (98%), m.p. 168 °C (from ethanol), ν_{max} cm^{-1} 1626 (C=N) and 3126 br (OH); δ_H (300 MHz; [$^2H_6$]-Me_2CO) 5.74 (2 H, s, CH_2), 7.66-7.34 (10 H, m, ArH), 8.07 (1 H, s, CH) and 10.75 (1 H, br s, exchangeable, OH) (Found: C, 52.8; H, 3.4; N, 10.6%; M$^+$ + 1, 388. $C_{17}H_{14}BrN_3OS$ requires C, 52.6; H, 3.6; N, 10.8%; M + 1, 388); and 4-bromo-1-(3,4-dimethoxylbenzyl)-2-(methylsulfanyl)imidazole-5-carbaldehyde oxime **25** (79%), m.p. 200-201 °C (from ethyl acetate); δ_H (300 MHz; $CDCl_3$) 2.62 (3 H, s, SMe), 3.81 (3 H, s, OMe), 3.83 (3 H, s, OMe), 5.40 (2 H, s, CH_2), 6.65-6.78 (4 H, m, CH and ArH) and 8.07 (1 H, s, exchangeable, OH) (Found: M$^+$ + 1, 386. $C_{14}H_{16}BrN_3O_3S$ requires M + 1, 386).

1-Benzyl-4-bromo-2-(methyl- and phenyl-sulfanyl)imidazole-5-carbonitriles 19 and 26

(a) **By dehydration of oximes 23 and 24**. A solution of oxime **23** (4.00 g, 12.3 mmol) in acetic anhydride (60 cm^3) was heated under reflux for 1 h, then the excess of reagent was distilled off under reduced pressure, to give a red-brown oil which was flash chromatographed on silica. Ethyl acetate-hexane (20:80) eluted the carbonitrile **19** (3.21 g, 85%), m.p. 81-83 °C (from hexane-ethyl acetate), ν_{max} cm^{-1} 2222 (CN); δ_H (300 MHz; [$^2H_6$]-Me_2CO) 2.68 (3 H, s, SMe), 5.28 (2 H, s, CH_2) and 7.20-7.50 (5 H, m, ArH) (Found: C, 46.7; H, 3.4; N, 13.5%; M$^+$ + 1, 307.9832. $C_{12}H_{10}BrN_3S$ requires C, 46.8; H, 3.3; N, 13.6%; M + 1, 307.9858).

1-Benzyl-4-bromo-2-(phenylsulfanyl)imidazole-5-carbonitrile **26** (76%) was prepared similarly and had m.p. 85 °C (from flash chromatography column), ν_{max} cm^{-1} 2225 (CN); δ_H (300 MHz; $CDCl_3$) 5.29 (2 H, s, CH_2) and 7.18-7.37 (10 H, m, ArH) (Found: C, 55.5; H, 3.25; N, 11.15%; M$^+$ + 1, 370. $C_{17}H_{12}BrN_3S$ requires C, 55.3; H, 3.3; N, 11.4%; M + 1, 370).

(b) **By cyanation of the 5-lithiated imidazole.** 1.5 mol dm^{-3} Butyllithium in hexane (1.93 cm^3, 2.90 mmol) was added to a stirred solution of 1-benzyl-4,5-dibromo-2-(methylsulfanyl)imidazole (1.00 g, 2.76 mmol) in THF (15 cm^3) at -78 °C at such a rate that the temperature did not exceed -60 °C, then the mixture was stirred for a further 2 min prior to addition of a solution of tosyl cyanide (0.53 g, 2.92 mmol) in THF (15 cm^3). The resulting mixture was allowed to warm up to ambient temperature when it was quenched with water (15 cm^3). Work-up in the usual way gave an oil which was flash chromatographed on silica. Ethyl acetate-hexane (10:90) eluted 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile **19** (0.494 g, 58%), identical in all respects with the sample prepared as described in (a).

1-Benzyl-4-bromo-2-(phenylsulfanyl)imidazole-5-carbonitrile **26** (38%) was prepared similarly and had identical properties to the sample prepared as described in (a).

(c) **By cyanation of the organozinc derivative** 1.54 mol dm^{-3} Butyllithium in hexane (5.3 cm^3, 8.16 mmol) was added to a stirred solution of 1-benzyl-4,5-dibromo-2-(methylsulfanyl)imidazole (2.95 g, 8.15 mmol) in THF (60 cm^3) at -78 °C, then the mixture was stirred for a further 2 min prior to addition of a solution of zinc(II) iodide (2.60 g, 8.15 mmol) in THF (10 cm^3). Then the resulting mixture was allowed to warm up to ambient temperature during 20 min. It was cooled again to -78 °C and a solution of tosyl cyanide (1.20 g, 6.63 mmol) in THF (10 cm^3) was added. Again the mixture was allowed to warm up to ambient temperature at which temperature it was stirred for 24 h. Work-up in the usual way gave the nitrile **19** (1.40 g, 69% - based on TosCN), identical in all respects with the samples prepared as described in (a) and (b).

Reactions of 1-Benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile 19

(a) **With sulfanylacetamide** (i) Sodium (0.15 g, 6.52 mmol) was added cautiously to ethanol (15 cm^3) followed by freshly prepared sulfanylacetamide (0.30 g, 3.30 mmol) and the mixture was stirred at ambient temperature for 30 min. Then a solution of 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile **19** (1.00 g, 3.25 mmol) in ethanol (70 cm^3) was added and the resulting mixture was stirred overnight, then heated under reflux for 6 h. The ethanol was distilled off under reduced pressure and water (30 cm^3) was added to the residue. The resulting precipitate was filtered off and flash chromatographed on silica. Ethyl acetate-hexane (30:70) eluted starting material **19** (0.43 g, 43% recovery) followed by 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carboxamide **28** (0.095 g, 9%), m.p. 167-169 °C (from ethanol), ν_{max} (KBr) cm^{-1} 1634 (CO) and 3179 and 3322 (NH_2); δ_H (300 MHz; [$^2H_6$]-DMSO) 2.54 (3 H, s, SMe), 5.41 (2 H, s, CH_2), 7.04-7.38 (5 H, m, ArH), 7.45 (1 H, br s, exchangeable, NH) and 7.76 (1 H, br s, exchangeable, NH) (Found: M^+ + 1, 325.9941. $C_{12}H_{12}BrN_3OS$ requires M + 1, 325.9963).

(ii) Tributyltin chloride (8.95 cm^3, 10.74 g, 33.0 mmol) was added to a stirred solution of sulfanylacetamide (3.00 g, 33.0 mmol) and triethylamine (4.7 cm^3, 3.40 g, 33.6 mmol) in tetrachloromethane (80 cm^3). After 1 h the mixture was filtered through Celite and distillation of the solvent under reduced pressure gave tributylstannanesulfanylacetamide as a pale yellow oil which was used without purification as follows. The organotin compound (1.36 g, 3.58 mmol) was added to 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile **19** (1.00 g, 3.24 mmol) in anhydrous toluene (70 cm^3) containing tetrakis(triphenylphosphine)palladium(0) (0.38 g, 0.33 mmol) under argon and the resulting mixture was heated under reflux for 4 h when TLC analysis revealed absence of starting material and the presence of three products none of which were the desired thieno[2,3-*d*]imidazole **21** or its precursor **20** (Scheme 2). No attempt was made to separate and identify these products.

1-Benzyl-4-bromo-2-(methylsulfonyl)imidazole-5-carbonitrile 29

Hydrogen peroxide (13 cm^3 30% *w/v*, an excess) was added dropwise to a stirred solution of 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile **19** (1.00 g, 3.25 mmol) in acetic acid (20 cm^3), then the resulting mixture was heated under reflux for 1.5 h, cooled and poured into water (40 cm^3). Ether extracted the sulfone **29** (0.88 g, 80%), m.p. 106-108 °C (from ethanol), ν_{max} (KBr) cm^{-1} 2226 (CN); δ_H (300 MHz; CDCl$_3$) 3.27 (3 H, s, SO$_2$Me), 5.59 (2 H, s, CH$_2$) and 7.34 (5 H, m, ArH) (Found: C, 42.8; H, 2.9; N, 12.7%; M$^+$ + 18, 357.0025. $C_{12}H_{10}BrN_3O_2S$ requires C, 42.5; H, 3.0; N, 12.4%; M + 18, 357.0022).

1-Benzyl-2,4-bis(methylsulfanyl)imidazole-5-carbonitrile 30

1.54 mol dm^{-3} Butyllithium in hexane (0.53 cm^3, 0.82 mmol) was added to an efficiently stirred solution of 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile **19** (0.25 g, 0.81 mmol) in THF (15 cm^3) at -100 °C (liquid N$_2$-MeOH slush bath) followed, after 3 min, by addition of dimethyl disulfide (0.88 g, 0.084 cm^3, 0.89 mmol). Then the mixture was allowed to warm up to 10 °C when water (8 cm^3) was added cautiously. The product was extracted with ethyl acetate and flash chromatographed on silica. Ethyl acetate-hexane (10:90) eluted the product **30** (0.13 g, 58%), m.p. 74 °C (from hexane-ethyl acetate), ν_{max} cm^{-1} 2211 (CN); δ_H (300 MHz; CDCl$_3$) 2.57 (3 H, s, SMe), 2.66 (3 H, s, SMe), 5.06 (2 H, s, CH$_2$) and 7.24-7.35 (5 H, m, ArH) (Found: C, 56.3; H, 4.7; N, 14.9%; M$^+$ + 1, 276.0615. $C_{13}H_{13}N_3S_2$ requires C, 56.7; H, 4.8; N, 15.3%; M + 1, 276.0629).

2-[1-Benzyl-5-cyano-2-(methylsulfanyl)imidazol-4-ylthio]acetamide 20

1.5 mol dm^{-3} Butyllithium in hexane (1.08 cm^3, 1.62 mmol) was added to a stirred solution of 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbonitrile **19** (0.50 g, 1.62 mmol) in THF (15 cm^3) at -100 °C (liquid N$_2$-MeOH slush bath) followed, after 3 min, by addition of elemental sulfur (0.10 g, 3.13 mmol). The resulting mixture was allowed to warm up to -80 °C when it was stirred at this temperature for a further 10 min before being cooled down again to -100 °C. A solution of 2-chloroacetamide (0.30 g, 3.25 mmol) in THF (20 cm^3) was added and the mixture was allowed to warm up slowly to approximately 10 °C when water (30 cm^3) was added cautiously. The organic layer was separated and the aqueous layer was extracted several times with ethyl acetate. The organic layer and extracts were combined, dried and the solvents were distilled off under reduced pressure. The crude product was flash chromatographed on silica (ethyl acetate as eluent), to give various unidentified products (in small amounts) followed by 2-[1-benzyl-5-cyano-2-(methylsulfanyl)imidazol-4-ylthio)acetamide **20** (0.15 g, 29%), m.p. 153-155 °C (from ethanol), ν_{max} cm^{-1} 1661 (CO), 2208 (CN) and 3191 and 3371 (NH$_2$); δ_H (300 MHz; [^{2}H$_6$]-DMSO) 2.65 (3 H, s, SMe), 3.76 (2 H, s, SCH$_2$), 5.18 (2 H, s, C*H*$_2$Ph), 7.18-7.43 (6 H, m, NH and ArH) and 7.56 (2 H, br s, exchangeable, NH$_2$) [Found (FAB): M$^+$ + 1, 319. $C_{14}H_{14}N_4OS_2$ requires M + 1, 319] characterised by conversion into compound **21**.

6-Amino-1-benzyl-2-(methylsulfanyl)thieno[2,3-*d*]imidazole-5-carboxamide 21

Sodium (4.0 mg, 0.17 mmol) was added to ethanol (15 cm^3) followed by 2-[1-benzyl-5-cyano-2-(methylsulfanyl)imidazol-4-ylthio]acetamide **20** (0.5 g, 1.57 mmol) and the resulting mixture was heated under reflux for 1 h, then cooled in an ice bath. The product **21** (0.45 g, 90%) which crystallised out was filtered off and dried, m.p. 214-215 °C (from ethanol), ν_{max} cm^{-1} 1650 (CO) and 3150-3458 (multiple bands, NH_2 and $CONH_2$); δ_H (300 MHz; [$^2H_6$]-DMSO) 2.60 (3 H, s, SMe), 5.49 (2 H, s, CH_2), 6.77 (2 H, s, exchangeable, NH_2 or $CONH_2$), 6.85 (2 H, s, exchangeable, NH_2 or $CONH_2$) and 7.18-7.37 (5 H, m, ArH) (Found: M^+ + 1, 319.0679. $C_{14}H_{14}N_4OS_2$ requires M + 1, 319.0687.

1-Benzyl-2-(methylsulfanyl)imidazo[4′,5′:4,5]thieno[3,2-*d*]pyrimidin-5(6*H*)-one 22
A mixture of 6-amino-1-benzyl-2-(methylsulfanyl)thieno[2,3-*d*]imidazole-5-carboxamide **21** (0.248 g, 0.78 mmol), acetic anhydride (3 cm^3) and triethyl orthoformate (3 cm^3) was heated under reflux for 2.5 h, then poured into water. The product was extracted with ethyl acetate and flash chromatographed on silica. Ethyl acetate eluted the thienopyrimidinone **22** (0.216 g, 84%), m.p. 279-281 °C (from acetonitrile - DMSO), ν_{max} cm^{-1} 1676 (CO); δ_H (300 MHz; [$^2H_6$]-DMSO) 2.68 (3 H, s, SMe), 5.53 (2 H, s, CH_2), 7.28-7.35 (5 H, m, ArH) and 8.26 (1 H, br s, exchangeable, NH) (Found: C, 54.2; H, 3.6; N, 16.9%; M^+ + 1, 329.0527. $C_{15}H_{12}N_4OS_2$ requires C, 54.85; H, 3.7; N, 17.05%; M + 1, 329.0531).

1-Benzyl-4-bromo-2-(*tert*-butyldimethylsilyl)imidazole-5-carbaldehyde 33
(a) 1.5 mol dm^{-3} Methyllithium in ether (9.3 cm^3, 14.0 mmol) was added dropwise to a stirred solution of 1-benzyl-2,4,5-tribromoimidazole (5.00 g, 12.7 mmol) in ether (125 cm^3) at -78 °C and the resulting mixture was stirred for a further 2 min before a solution of *tert*-butyldimethylsilyl chloride (2.10 g, 14.0 mmol) in ether (15 cm^3) was added, then the mixture was allowed to warm up to ambient temperature when it was stirred for a further 6 h prior to quenching with 20% aqueous ammonium chloride (50 cm^3). Work-up in the usual way gave a residue which was chromatographed on neutral alumina. Ethyl acetate-hexane (5:95) eluted 1-benzyl-4,5-dibromo-2-(*tert*-butyldimethylsilyl)imidazole **32** (1.67 g, 31%), m.p. 68-70 °C; δ_H (300 MHz; $CDCl_3$) 0.22 (6 H, s, 2 x Me), 0.90 (9 H, s, CMe_3), 5.28 (2 H, s, CH_2) and 6.84-7.31 (5 H, m, ArH) (Found: M + 1, 429. $C_{16}H_{22}Br_2N_2Si$ requires M^+ + 1, 429).

(b) 1.7 mol dm^{-3} Butyllithium in hexane (2.3 cm^3, 3.91 mmol) was added dropwise to a stirred solution of 1-benzyl-4,5-dibromo-2-(*tert*-butyldimethylsilyl)imidazole **32** (1.53 g, 3.56 mmol) in ether (40 cm^3) at -78 °C and the resulting mixture was stirred for 10 min further prior to addition of *N*-formylpiperidine (0.44 g, 0.43 cm^3, 3.89 mmol). Then the mixture was allowed to warm up slowly to ambient temperature. Work-up in the usual way (extraction of the product with ether) gave a residue which was chromatographed on neutral alumina. Ethyl acetate-hexane (5:95) eluted 1-benzyl-4-bromo-2-(*tert*-butyldimethylsilyl)imidazole-5-carbaldehyde **33** (1.27 g, 94%), m.p. 63-65 °C (from hexane), ν_{max} cm^{-1} 1678 (CO); δ_H (300 MHz; $CDCl_3$) 0.28 (6 H, s, 2 x Me), 0.92 (9 H, s, CMe_3), 5.61 (2 H, s, CH_2), 6.83-7.27 (5 H, m, ArH) and 9.65 (1 H, s, C*H*O) (Found: C, 54.2; H, 6.0; N, 7.4%; M^+ + 1, 379.0835. $C_{17}H_{23}BrN_2OSi$ requires C, 53.8; H, 6.1; N, 7.4%; M + 1, 379.0842).

1-Benzyl-4-bromoimidazole-5-carbaldehyde 34
1.0 mol dm^{-3} Tetrabutylammonium fluoride in THF (0.69 cm^3, 0.69 mmol) was added to a stirred solution of the aldehyde **33** (0.200 g, 0.53 mmol) in THF (5 cm^3) and the resulting mixture was stirred at ambient temperature for 5 min. Water (5 cm^3) was added, the mixture was stirred for a further 10 min, then the organic

layer was separated and the aqueous layer extracted with ether. The organic layer and ethereal extracts were combined, dried ($MgSO_4$) and the solvents were distilled off under reduced pressure, to give a residue which was chromatographed on neutral alumina. Ethyl acetate-hexane (10:90) eluted 1-benzyl-4-bromoimidazole-5-carbaldehyde **34** (0.136 g, 97%), m.p. 66-68 °C! (lit.,[54] 59-60 °C).

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REFERENCES

1. Part 11: Iddon, B.; Petersen, A.K.; Becher, J.; Christensen, N.J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1475.
2. Lister, J.H. *Chem. Heterocycl. Compds.* Vol 24; *"Fused Pyrimidines. Part II, The Purines"*; Brown, D.J., Ed.; Wiley-Interscience, New York; 1971.
3. Hurst, D.T. *"An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines, and Pteridines"*; Wiley, Chichester; 1980.
4. Shaw, G. in *"Comprehensive Heterocyclic Chemistry"*; Katritzky, A.R.; Rees, C.W., Series Eds.; Potts, K.T., Vol. Ed.; Pergamon Press, Oxford; Vol. 5, Ch. 4.09; p. 499, and references cited therein.
5. *"Cytokinins: Chemistry, Activity and Function"*; Mok, D.W.S.; Mok, M.C., Eds.; CRS Press, Florida; 1994.
6. Matsubara, S. *Crit. Rev. Plant Sci.* **1990**, *9*, 17.
7. Letham, D.S.; Palni, L.M.S. *Ann. Rev. Plant Physiol.* **1983**, *34*, 163.
8. Matsubara, S. *Phytochem.* **1980**, *19*, 2239.
9. Koshimizu, K.; Iwamura, H. *Nippon Nogeikagaku Kaishi* **1978**, *52*, R49.
10. Haidoune, M.; Pethe, C.; Laloue, M.; Mornet, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3009.
11. Fujii, T.; Ohba, M.; Kawamura, H.; Nakashio, Y.; Honda, K.; Matsubara, S. *Chem. Pharm. Bull Jpn.* **1994**, *42*, 1045.
12. Iwamura, H.; Murakami, S.; Koshimizu, K.; Matsubara, S. *J. Med. Chem.* **1985**, *28*, 577.
13. Gregson, S.; Shaw, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 187, and references cited therein.
14. Jacobsen, K.A.; van Galen, P.J.M.; Williams, M. *J. Med. Chem.* **1992**, *35*, 407.
15. Montgomery, J.A.; Secrist, J.A. in *"Comprehensive Heterocyclic Chemistry"*; Katritzky, A.R.; Rees, C.W., Series Eds.; Potts, K.T., Vol. Ed.; Pergamon Press, Oxford; Vol. 5, Ch. 4.10, p. 607, and references cited therein.
16. Longthorne, D.S. Ph.D. Thesis, University of Salford, 1994.
17. Leonard, N.J.; Hiremath, S.P. *Tetrahedron* **1986**, *42*, 1917, and references cited therein.
18. Leonard, N.J. *Acc. Chem. Res.* **1982**, *15*, 128.
19. Schneller, S.W.; Christ, W.J. *J. Heterocycl. Chem.* **1982**, *6*, S-139.
20. Schneller, S.W.; Ibay, A.C.; Martinson, E.A.; Wells, J.N. *J. Med. Chem.* **1986**, *29*, 972.
21. Schneller, S.W.; Ibay, A.C.; Christ, W.J. *J. Heterocycl. Chem.* **1984**, *21*, 791.

22. Schneller, S.W.; Christ, W.J. *J. Org. Chem.* **1981**, *46*, 1699.
23. Schneller, S.W.; Christ, W.J. *J. Heterocycl. Chem.* **1981**, *18*, 539.
24. Pendergast, W.; Chan, J.H. in "*Chemistry and Biology of Pteridines*"; Blair, J.A., Ed.; Walter de Gruyter and Co., Berlin; 1983.
25. Dempcy, R.O.; Skibo, E.B. *J. Org. Chem.* **1991**, *56*, 776.
26. Humphries, M.J.; Ramsden, C.A. *Synlett* **1995**, 203.
27. Al-Shaar, A.H.M.; Chambers, R.K.; Gilmour, D.W.; Lythgoe, D.J.; McClenaghan, I.; Ramsden, C.A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2789.
28. Rodgers, G.R.; Neish, W.J.P. *Monatsh. Chem.* **1986**, *117*, 879.
29. Taylor, E.C.; Inbasekaran, M. *Heterocycles* **1978**, *10*, 45.
30. Pachter, I.J.; Nemeth, P.E. *J. Org. Chem.* **1963**, *28*, 1203.
31. Taylor, E.C.; Sherman, W.R. *J. Am. Chem. Soc.* **1959**, *81*, 2464.
32. Hawkins, D.W.; Iddon, B.; Longthorne, D.S.; Rosyk, P.J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2735.
33. Athmani, S.; Iddon, B. *Tetrahedron* **1992**, *48*, 7689.
34. Norris, R.K. in *Chem. Heterocycl. Compds.* Vol. 44; "*Thiophene and its Derivatives, Part II*"; Gronowitz, S., Ed.; Wiley-Interscience, New York; 1986, Ch. V, p. 631 (see especially p. 665).
35. Iddon, B.; Khan, N.; Lim, B.L. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1457.
36. Brown, D.J. in *Chem. Heterocycl. Compds.* Vol 16; "*The Pyrimidines*"; Wiley-Interscience, New York; 1962, Ch. VI, p. 162 (see especially p. 211): Brown, D.J. in *Chem. Heterocycl. Compds.;* Vol. 16 "*The Pyrimidines; Supplement I*"; Wiley-Interscience, New York; 1970, Ch. VI, p. 110 (see especially p. 158).
37. Iddon, B.; Khan, N.; Lim, B.L. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1437, and references cited therein.
38. Iddon, B.; "*Studies in Organic Chemistry 35; Chemistry of Heterocyclic Compounds*"; Kovác, J.; Zálupsky, Eds.; Elsevier, Amsterdam; 1988, p. 24.
39. Khozeeva, R.V.; Kvitko, I. Ya.; Baranov, E.L.; El'tsov, A.V. *J. Org. Chem. U.S.S.R. (Engl. Transl.)* **1977**, *13*, 215 (the use of 5-chloro-1-phenylimidazole-4-carbaldehyde is described in this paper).
40. Hoff, D.R.; Peterson, L.H. S. Afr. Pat. 68 00,904/1969 (*Chem. Abstr.* **1970**, *72*, 100702).
41. Binder, D.; Noe, C.R.; Hillebrand, F. *Arch. Pharm.* **1979**, *312*, 845.
42. Binder, D.; Hillebrand, F.; Noe, C.R. *J. Chem. Res. (S)* **1979**, 96.
43. Binder, D.; Noe, C.R.; Kollmann, H.; Rosenwirth, B. *Arch. Pharm.* **1985**, *318*, 40.
44. Binder, D.; Rovenszky, F. Europ. Pat. EP 201,094/1986 (*Chem. Abstr.* **1987**, *106*, 102287).
45. Binder, D.; Rovenszky, F.; Ferber, H. Europ. Pat. EP 261,478/1988 (*Chem. Abstr.* **1988**, *109*, 149534).
46. Guerrera, F.; Siracusa, M.A.; Tornetta, B.; Bousquet, E.; Agozzino, P.; LaMartina, L. *J. Heterocycl. Chem.* **1984**, *21*, 587.
47. Weidmann, K.; Herling, A.W.; Lang, H.-J.; Scheunemann, K.-H.; Rippel, R.; Nimmesgem, H.; Scholl, T.; Bickel, M.; Metzger, H. *J. Med. Chem.* **1992**, *35*, 438.
48. Kuhnke, J.; Schoellkopf, K.; Beckmann, R.; Graf, H. Ger. Offen. DE 4,032,522/1992 (*Chem. Abstr.* **1992**, *117*, 48557).

49. Kuhnke, J., Schoellkopf, K.; Beckmann, R.; Graf, H. Ger. Offen. DE 4,034, 728/1992 (*Chem. Abstr.* **1992**, *117*, 90286).
50. Fortin, M.; Frechet, D.; Hamon, G.; Jouquey, S.; Vevert, J.P. Europ. Pat. EP 461,040/1991 (*Chem. Abstr.* **1992**, *116*, 151760).
51. Naka, T.; Inada, Y. Europ. Pat. EP 483,683/1992 (*Chem. Abstr.* **1992**, *117*, 131198).
52. Iddon, B.; Khan, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1453.
53. Dammann, L.G.; Leonard, N.J.; Schmitz, R.Y.; Skoog, F. *Phytochem.* **1974**, *13*, 329.
54. Iddon, B.; Khan, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1445.
55. Dudfield, P.J.; Ekwuru, C.T.; Hamilton, K.; Osbourn, C.E.; Simpson, D.J. *Synlett* **1990**, 277.
56. Iddon, B.; Ngochindo, R.I. *Heterocycles* **1994**, *38*, 2487.
57. Klement, I.; Lennick, K.; Tucker, C.E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623.
58. Whittle, C.P. *Austral. J. Chem.* **1980**, *33*, 1545.
59. Dickens, M.J.; Gilday, J.P.; Mowlem, T.J.; Widdowson, D.A. *Tetrahedron* **1991**, *47*, 8621.
60. Apen, P.G.; Rasmussen, P.G. *J. Am. Chem. Soc.* **1991**, *113*, 6178.
61. Apen, P.G.; Rasmussen, P.G. *J. Heterocycl. Chem.* **1992**, *29*, 1091.
62. Stensiö, K.-E.; Wahlberg, K.; Wahren, R. *Acta Chem. Scand.* **1973**, *27*, 2179.
63. Atkinson, E.R.; Handrick, G.R.; Bruni, R.J.; Granchelli, F.E. *J. Med. Chem.* **1965**, *8*, 29.

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