Synthesis of Novel 2-Aminoimidazo[4,5-b]pyridines, Including the Thieno Analogue of the Cooked-food Mutagen IFP
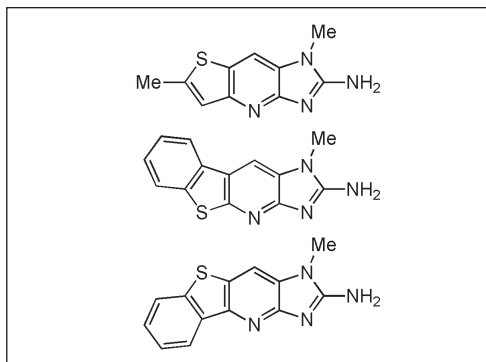
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Eight new compounds, including three new ring systems obtained *via* the Friedländer condensation of *ortho*-aminothiophenecarbaldehydes 11, 21 and 24 with creatinine (8), are reported. The condensation afforded 1, which is the thieno analogue of the cooked-food mutagen IFP (2-amino-1,6-dimethylfuro[2,3-*e*]imidazo[4,5-*b*]pyridine), and the benzothieno[2,3-*e*]- and benzothieno[3,2-*e*]imidazo[4,5-*b*]pyridines 2 and 3. Attempts to condense 11 with isocreatinine (12) were unsuccesful. Desulfurization of 3 gave the known cooked-food carcinogen PhIP. The 2-nitro (4) and 2-hydroxy (5) derivatives of 3 are reported. The related 2-amino-1-methyl-imidazo[4,5-*b*]benzothiophene (25) was synthesized by a different route. Fully assigned ^{1}H and ^{13}C nmr data of all new compounds are reported.

Introduction.

The imidazo[4,5-*b*]pyridine scaffold, which is a bioisosteric analogue of purine, appears to be important in molecules with pharmacological activities such as angiotensin II receptor antagonist [1], thromboxane A$_2$/prostaglandin H$_2$ receptor antagonist [2], tuberculostatic [3], inhibitors of leukotriene A$_4$ hydrolase [4] and anti HIV-1 [5]. The 2-aminoimidazole moiety is found in molecules isolated from natural products such as marine sponges and exhibit, for example, histamine receptor antagonist activity [6], antimicrobial [7] and anticancer activities [8]. Interestingly, several 2-aminoimidazo[4,5-*b*]pyridines have been shown to be highly mutagenic and carcinogenic and some of these are formed together with other heterocyclic amines during the cooking of foods [9]. In connection with our previous studies [10,11], and for the ongoing studies on the quantitative structure activity relationships (QSAR) additional compounds containing the imidazopyridine core were needed. Based on our model reaction systems where creatinine, reducing sugars and amino acids were heated together in order to form such 2-aminoimidazoheterocycles [12], **IFP** (Figure 1) was recently isolated by heating such a reaction system [13]. The mutagenic **IFP** was first isolated in cooked meats [14].
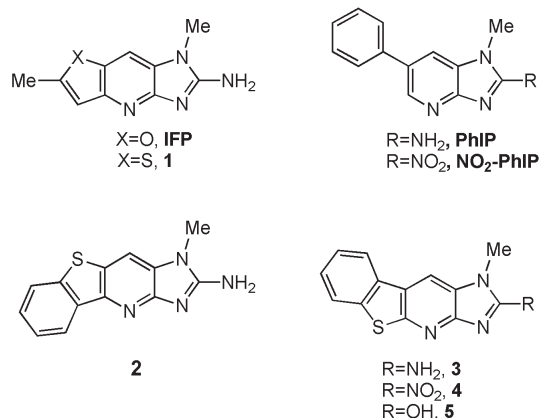

Figure 1

Several other 2-aminoimidazo-heterocyclic amines related to the cooked-food mutagens have been described by our group [15–18] and others [19–21]. These heterocyclic amines are promutagenic and the species responsible for their mutagenicity is believed to be the nitrenium ion due to its high reactivity [22].

In the present article we report the sulfur analogue of **IFP**, 2-amino-1,6-dimethylthieno[2,3-*e*]imidazo[4,5-*b*]-pyridine (**1**, Figure 1) and the related substances **2**-**5**. We

envisioned that, in addition to the direct interest for compound **3**, it could also serve as precursor of **PhIP** after removal of the sulfur atom and thus provide a new straightforward synthesis to **PhIP**.

Results and Discussion.

The Friedländer reaction [23], studies on the mechanism of which were recently reported [24], have previously been used by our group to obtain the related imidazo-quinoline [18] **6** (Figure 2) and -naphthyridines such as **7a-c** [17,25] that are analogous to the **IFP** sulfur analogue **1**, by simply heating creatinine (**8**, Scheme 2) or isocreatinine (**12**, Scheme 2) with an appropriate *ortho*-aminocarbaldehyde in ethylene glycol instead of using typical Friedländer conditions.
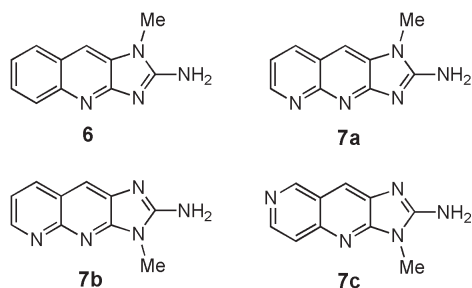
Figure 2

Several other procedures have been described [23] for the Friedländer reaction, including bismuth triflates catalysis [26], solid state synthesis [27], tin chloride/zinc chloride conditions on the *ortho*-nitrocarbaldehyde [28] and microwave conditions [29]. In analogy with previous work [30], we found that it was necessary to transform creatinine to its enolic silyl ether with bis(trimethylsilyl)acetamide (BSA) for our condensation with the thiophene *ortho*-aminocarbaldehyde **11** (Scheme 1) and the benzothiophene analogues **21** and **24** (Scheme 4) used in this work. The required **11**, **21** and **24** for our Friedländer reactions were obtained according to reported procedures with some modifications. The synthesis of the novel compounds 3-azido-5-methyl-2-thiophenecarbaldehyde (**10**) and 3-amino-5-methyl-2-thiophene-carbaldehyde (**11**) from 2-bromo-5-methylthiophene is presented in Scheme 1. The first step, a halogen dance [31], required pure and dry starting materials to give the product **9** [31–33] in good yields. The bromine of **9** was then substituted for an azide by treatment with sodium azide (NaN$_3$) to give **10**. Hexamethylphosphoramide (HMPA) [34] or dimethylsulfoxide (DMSO) [35] have previously been used for the formation of 3-azido-2-thiophenecarbaldehyde from the corresponding 3-bromo compound. In our hands, treatment of **9** with NaN$_3$ in DMSO gave a complex mixture of products. However, in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) lower temperatures could be employed and a single product was obtained.

Scheme 1
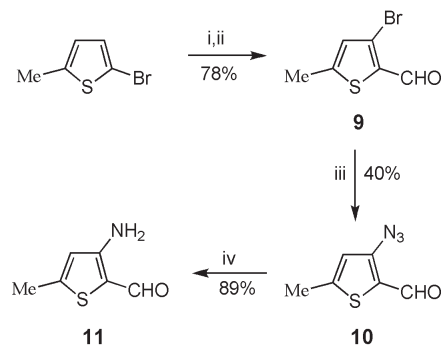
Reagents and Conditions: i. *n*-BuLi, THF, –78 ºC ii. DMF iii. NaN$_3$, DMPU, 35 ºC, overnight iv. 40% NH$_4$SH, MeOH, r.t., 10 min.

For the reduction of the azide **10** to amine **11** we found the use of commercial 40% ammonium sulfide (NH$_4$SH) [36] advantageous compared to the highly poisonous hydrogen sulfide (H$_2$S) gas [35] or the expensive bis(trimethylsilyl)sulfide [37]. For compound **11** we report the NMR-data obtained at 60 ºC in order to reduce the effect of the strong intramolecular hydrogen bonding, due to which both the formyl and the amino group gave two very broad signals each. Similarly, strong hydrogen bonding was also present in the benzothiophene analogue **24** (Scheme 4) described later. The amine **11** was treated with creatinine (**8**, Scheme 2) in BSA to yield **1** in 45% yield. Heating **11** with isocreatinine [38] (**12**, Scheme 2) did not afford the expected **13** but a complex reaction mixture. Several solvents (ethylene glycol, dimethylformamide,

Scheme 2
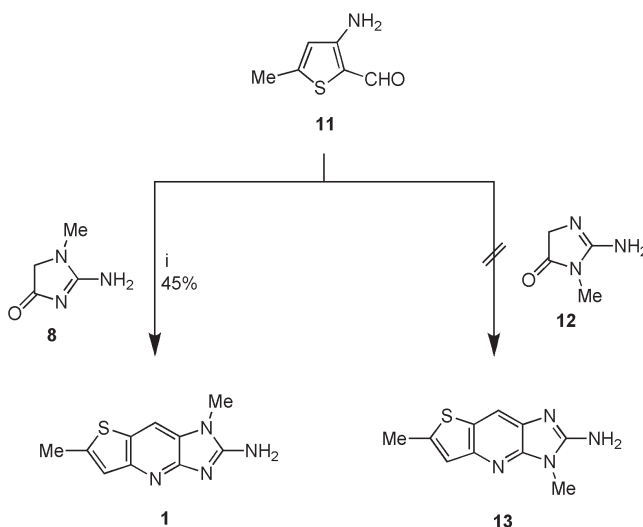
Reagents and Conditions: i. CH$_3$C[=NSi(CH$_3$)$_3$]OSi(CH$_3$)$_3$, 140 °C for 2 hours

acetic acid, methanol, 1-butanol) and drying reagents (molecular sieves, acetic anhydride, magnesium sulfate) were used but the reaction tended to give a complex mixture of products under all of these conditions.

Previously, we have treated *ortho*-aminopyridinecarbaldehydes with creatinine and isocreatinine in the same fashion to yield the expected imidazonaphthyridines [17,25] (*e.g.* **7a-c**, Figure 2). The condensation with isocreatinine was less efficient compared to that with creatinine. The analogous *ortho*-aminobenzaldehyde could easily condense with creatinine to give the corresponding imidazoquinoline **6** [18] (Figure 2). However, the isomer **16** (Scheme 3) was synthesized stepwise *via* the condensation of isocreatinine with *ortho*-nitrobenzaldehyde (**14**) and subsequent reduction and cyclization of the formed benzylidene-2-imidazolinone **15** by boiling in methanol with molecular sieves [17, 25]. In the present work, *ortho*-aminobenzaldehyde (**17** [39]) was treated with isocreatinine (**12**) in ethylene glycol at 80 ºC to produce **16** but led to an incomplete reaction with the major product formed being the alcohol **18** (Scheme 3) as indicated by low resolution ms where both the formula mass and the fragmentation fitted well, by hrms, by ir and by nmr experiments [40]. Higher reaction temperatures gave complex mixtures of products. Alcohol **18** could however dehydrate to **16** under the harsh conditions employed during its EI mass spectrometric analysis. The results of the condensation with isocreatinine in the *ortho*-aminocarbaldehyde series of pyridine, benzene and thiophene obtained here seem to

follow a reasonable pattern. The pyridine derivative being the least electron-rich condensed with isocreatinine giving the expected imidazonaphthyridines [25] *e.g.*, **7b** and **7c** (Figure 2), the benzene analogue **17** formed alcohol **18** (Scheme 3) while the π-excessive thiophene derivative **11** (Scheme 2) gave a complex mixture of products.

The N-H HMBC experiment gave ^3J correlations between the N-4 and H-5 and between the N-1 and H-9. The ^{1}H-NMR spectra of the alcohol **18** and the expected **16** [25] showed mainly two differences. The shifting of the methyl signal of **18** to higher fields by 1.1 ppm and of the H-5 of **18** by 0.6 ppm. The C-9 of **18** at 135.2 ppm could only be observed when the experiment was run at 50 ºC.

The synthesis of the benzothiophene analogues, **2** and **3** (Figure 1) started in both cases with bromination of benzothiophene. 2-Bromobenzothiophene [41–44] was synthesized *via* organometallic bromination [44] and 3-bromobenzothiophene by electrophilic substitution [45]. 2-Bromobenzothiophene was treated according to the literature [46] to introduce the formyl group at C-3 yielding 2-bromo-3-benzothiophenecarbaldehyde (**19**, Scheme 4) [46–49] in 98% yield, in contrast to the reported [46] 34% yield. Its 3-bromo isomer **22** [50] was obtained by lithiation of 2,3-dibromobenzothiophene and subsequent treatment of the lithio derivative with dimethylformamide *in situ* [51]. The two isomeric bromoaldehydes **19** and **22** were then treated with NaN$_3$ in DMSO [52] to give the corresponding azides **20** [52,53] and **23** [52,53]. The method has been published [52] for **23** where the substitution of a nitro group for the azide was compared to the substitution of the bromine for the azide. The substitution of the bromine was more efficient and hence it was our method of choice. By applying the same method on **19**, amine **21** [37,53] was obtained in 91% overall yield *via* azide **20** [53].

Scheme 3
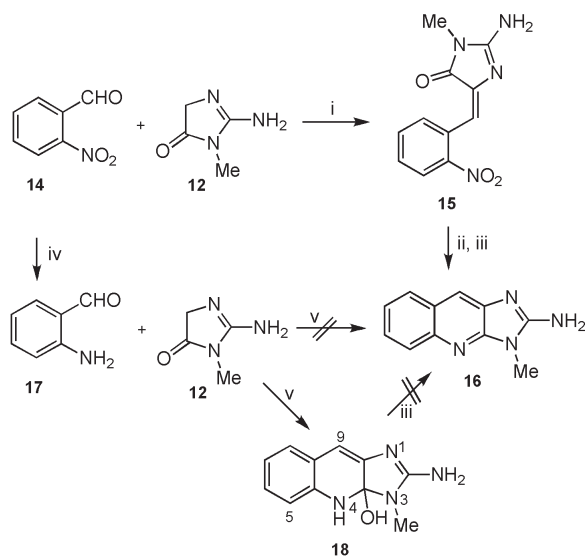
Scheme 4

Reagents and Conditions: i. AcOH, 100 ºC, 1 hour [25] ii. MeOH/EtOAc, Raney nickel, H$_2$, ambient conditions, 15 min. iii. MeOH, molecular sieves (3Å), reflux overnight iv. Water, FeSO$_4$, HCl, NH$_3$ v. ethylene glycol, 80 ºC, 2 hours
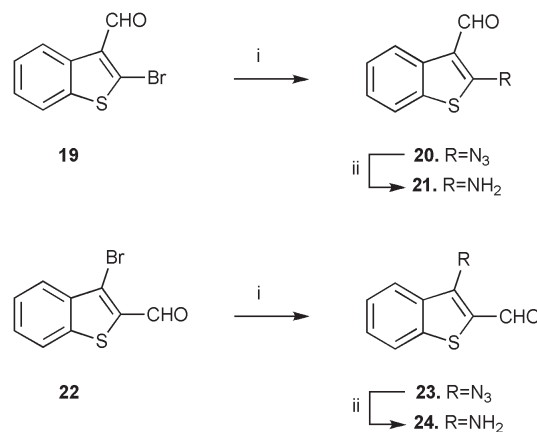
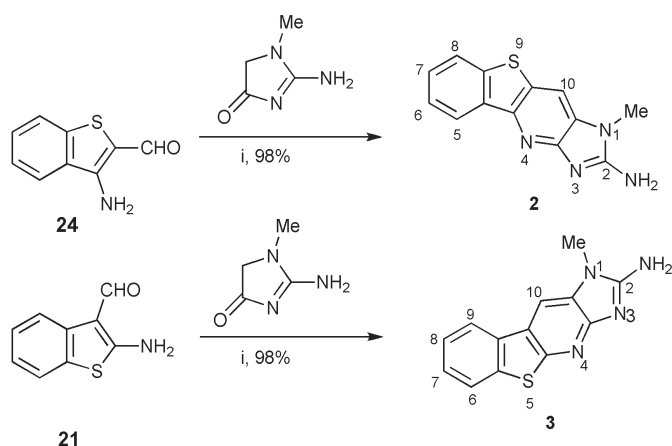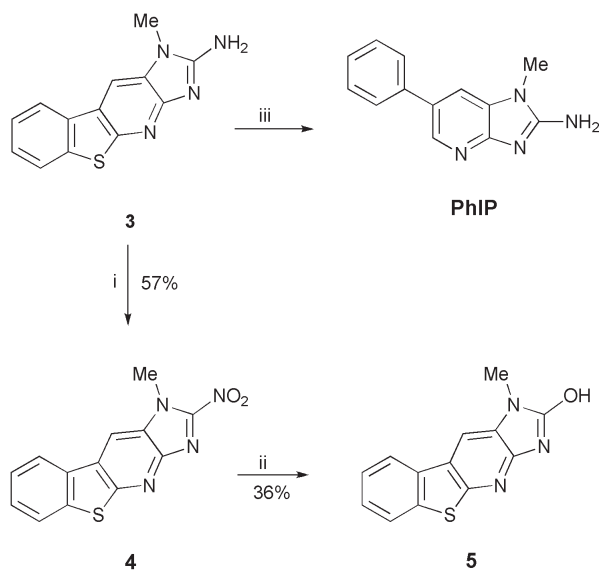Reagents and Conditions: i. NaN$_3$, DMSO, r.t., 45 min. ii. 40% NH$_4$SH, MeOH, r.t. 10 min. 91% (two steps)

The azide **20** is isolable but light sensitive and thus preferable to suspend it in methanol immediately and treat it with 40% NH_4SH [36] to form amine **21** [37,53]. The same procedure was used for the conversion of the 3-azido isomer **23** [52,53] to amine **24** [37,53] which was obtained in 92% overall yield from **22** [30]. The two *ortho*-aminobenzothiophenecarbaldehydes **21** and **24** were treated with creatinine in BSA [30] to give **2** and **3** in almost quantitative yields (Scheme 5).

Scheme 5

Reagents and Conditions: i. $CH_3C[=NSi(CH_3)_3]OSi(CH_3)_3$, 140 °C for 2 hours

Scheme 6

Reagents and Conditions: i. $NaNO_2/AcOH/H_2O$, r.t. ii. DMF/H_2O, 100 ºC, 10 min. iii. EtOH-dioxane, reflux, Raney Ni catalyst or Al-Ni alloy with 0.2 M NaOH present

The synthesis of the cooked-food carcinogen **PhIP**, its precursors, labelled analogues and possible metabolites has been, and still is, the object of extensive research for analytical and biomedical studies carried out by our group [16,30,54] and others [19,55–57]. A number of various synthetic approaches towards **PhIP** have been reported [21,58]. Some of these include Suzuki coupling of bromopyridines with boronic acids [16,19], thermal electrocyclic ring closure of an isocyanate [56], a photochemical transformation [59], and the Friedländer condensation between 3-amino-2-phenylacrolein and the *in situ* formed enolic silyl ether of creatinine [30]. In yet another way to **PhIP** we envisioned the efficiently obtained **3** as a possible starting material. Indeed, reductive desulfurization of **3** by Raney nickel catalyst in refluxing ethanol-dioxane (1:1) or Raney nickel alloy (50:50 Al-Ni)[60] in refluxing dioxane-ethanol-0.2 *M* NaOH (1:1:0.5) afforded **PhIP** in the modest yields of 25–35% (Scheme 6). Further, crucial for the reproducibility of this desulfurization to **PhIP** was the use of excess *fresh* Raney nickel. Removal of sulfur from **3** by alternative reagents [61], will be the subject of a future report.

The synthesis of the 2-nitro analogue **NO₂-PhIP** (Figure 1) from **PhIP** itself has been described previously [57,62] and it has been found useful for metabolic and adduct formation studies with biomolecules [62,63]. In connection to that we treated compound **3** with sodium nitrite in acetic acid-water according to the published procedure [64] to yield the nitro derivative **4** in moderate yields (Scheme 6). A short reaction time yielded **4** as the major product while longer reaction times gave us 2-hydroxy-1-methylbenzothieno[3,2-*e*]imidazo[4,5-*b*]pyridine (**5**) which is an interesting isoster of **3**. Compound **5** could also be obtained by heating **4** in dimethylformamide and water where **5** precipitated from the reaction mixture in 36% yield.

Finally, in this series of the compounds reported here it was also of interest to prepare 2-aminoimidazo-benzothiophene **25** (Scheme 7), which is related to **6** and **7** and to its bioisoster **26** previously synthesized [65] and tested [11]. Nitration of 3-bromobenzothiophene [66], gave 3-bromo-2-nitrobenzothiophene [45,67,68] (**27**, Scheme 7) which when treated with methylamine [69] in ethanol, resulted in the desired precursor **28** [69]. The choice of solvent in the reduction towards the diamine **29** proved to be of importance. Pd/C and H_2 in acetic acid [69] did not give us a pure product, which in the next step gave low yields of the target molecule **25**. However, by using a 1:1 mixture of ethanol and ethyl acetate instead of acetic acid the reduction to **29** was cleaner and subsequent treatment with cyanogen bromide [70] gave **25** in moderate yields. Only a few 2-substituted imidazo[4,5-*b*]benzothiophenes have been previously reported, including 2-amino derivatives as potential H_1-antihistaminic agents [71], but these do not include compound **25**.

Scheme 7
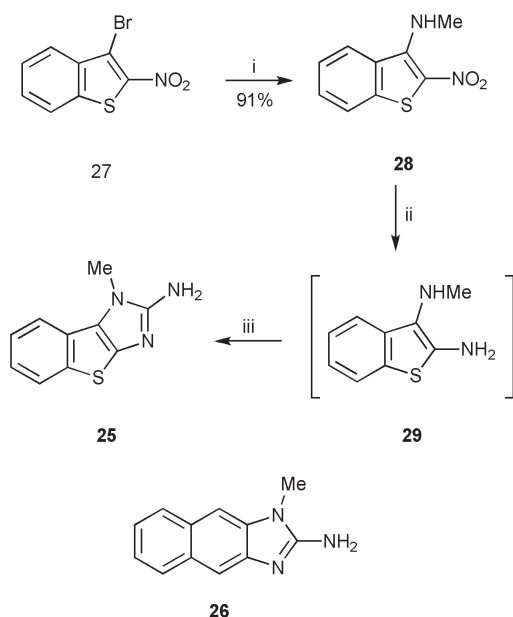
Reagents and Conditions: i. MeNH$_2$, EtOH, reflux, 2 h ii. Pd/C, H$_2$, EtOH/EtOAc 1:1, 200 psi, r.t., 2 h iii. BrCN, MeOH, r.t., overnight, 33% (two steps)

Concluding Remarks.

The three *ortho*-aminocarbaldehydes **11**, **21** and **24** were treated with the enolic silyl ether of creatinine to give **1**, and two additional new ring systems, **2** and **3**. Compound **3** was desulfurized to **PhIP** and also diazotized and converted into the nitro derivative **4**, which in turn could be transformed to the isosteric 2-hydroxy derivative of **3**. Selective reduction of the nitro group in **28** made it possible to obtain the novel imidazobenzothiophene **25**.

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: 75MHz) at 25 °C unless otherwise stated and referenced to the solvent [(CD$_3$)$_2$SO 2.50, 39.5, CDCl$_3$ 7.26, 77.0 and CD$_3$OD 3.31, 49.0]. The coupling constants are reported in Hz. HMBC, HMQC and ^{15}N-HMBC experiments were used for the assignments. Mass spectra were obtained on a Micromass Platform instrument using electron inpact ionisation (direct insertion at 70 eV, unless otherwise stated). For compounds containing bromine the [81]Br is reported.

General Procedure for the Friedländer Reaction [30] of *ortho*-Aminocarbaldehydes **11**, **21** and **24** with Creatinine (**8**).

Creatinine (1.3 g, 11.5 mmol) and the appropriate *ortho*-aminocarbaldehyde (4 mmol) were heated in BSA (2.4 g, 12 mmol) at 140 °C for 2 h. After cooling 1 *M* HCl (20 mL) was added. The mixture was stirred for 30 minutes and the *p*H was adjusted to ~11 with 2 *M* NaOH. The reaction mixture was poured in water and the precipitate was collected by filtration to give **1**, **2** and **3** in 45, 98 and 98% yield respectively.

2-Amino-1,6-dimethylimidazo[4,5-*b*]thieno[2,3-*e*]pyridine (**1**).

This compound was obtained as beige needles (ethanol/water), mp 324–326 ºC; ir: 3279, 3053, 1663, 2911, 2848, 1579, 1556, 1527, 1473, 1409, 1314, 1239, 1090, 818 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 7.91 (1H, s, H-8), 7.1 (2H, br s, NH$_2$), 7.05 (1H, s, H-5), 3.52 (3H, s, 1-Me), 2.55 (3H, s, 6-Me); ^{13}C nmr ((CD$_3$)$_2$SO): δ 158.3 (C-2), 155.8 (C-3a), 149.9 (C-4a), 139.4 (C-7a), 126.0 (C-8a), 123.6 (C-6), 122.1 (C-5), 107.1 (C-8), 28.5 (1-Me), 16.3 (6-Me); ms: *m/z* 218 (M, 100%), 217 (70), 203 (7), 190 (10), 176 (5), 161 (6), 109 (12).

Anal. Calcd. for C$_{10}$H$_{10}$N$_4$S: C, 55.0; H, 4.6; N, 25.7. Found: C, 54.9; H, 4.6; N, 25.6.

2-Amino-1-methylbenzothieno[2,3-*e*]imidazo[4,5-*b*]pyridine (**2**).

This compound was obtained as beige prisms (sublimation), mp 348–350 ºC; ir: 3462, 3306, 3056, 1653, 1534, 1469, 1416, 1303, 757, 726 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 8.29 (1H, m, H-5), 8.09 (1H, s, H-10), 7.96 (1H, m, H-8), 7.48 (2H, m, H-6, H-7), 7.2 (2H, br s, NH$_2$), 3.59 (3H, s, Me); ^{13}C nmr ((CD$_3$)$_2$SO): δ 158.7 (C-2), 156.0 (C-3a), 143.9 (C-4a), 137.7 (C-8a), 135.2 (C-4b), 128.2 (C-10a), 126.3 (C-7), 124.4 (C-6), 123.5 (C-9a), 123.1 (C-8), 121.4 (C-5), 107.7 (C-10), 28.6 (Me); ms: *m/z* 254 (M, 100%), 239 (5), 212 (7), 197 (4), 185 (4), 170 (5).

Anal. Calcd. for C$_{13}$H$_{10}$N$_4$S: C, 61.4; H, 4.0; N, 22.0. Found: C, 61.3; H, 3.9; N, 21.9.

2-Amino-1-methylbenzothieno[3,2-*e*]imidazo[4,5-*b*]pyridine (**3**).

This compound was obtained as beige prisms (sublimation), mp 346–348 ºC; ir: 3297, 3045, 1650, 1624, 1530, 1470, 1433, 1406, 1316, 1112, 940, 776, 720 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 8.37 (1H, s, H-10), 8.22 (1H, d, H-9, 7.1), 7.92 (1H, d, H-6, 7.4), 7.46–7.36 (2H, m, H-7 and H-8), 7.2 (2H, br s, NH$_2$), 3.63 (3H, s, Me); ^{13}C nmr ((CD$_3$)$_2$SO): δ 158.9 (C-2), 157.6 (C-3a or C-4a), 153.0 (C-4a or C-3a), 135.2 (C-5a), 134.3 (C-9a), 126.9 (C-10a), 125.2 (C-7), 124.5 (C-8), 122.9 (C-6), 120.7 (C-9), 119.9 (C-9b), 107.1 (C-10), 28.7 (Me); ms: *m/z* 254 (M, 100%), 253 (48), 239 (7), 226 (12), 212 (6), 197 (6), 185 (3).

Anal. Calcd. for C$_{13}$H$_{10}$N$_4$S: C, 61.4; H, 4.0; N, 22.0. Found: C, 61.5; H, 3.8; N, 22.2.

1-Methyl-2-nitrobenzothieno[3,2-*e*]imidazo[4,5-*b*]pyridine (**4**).

Compound **3** (0.19 g, 0.75 mmol) was treated with sodium nitrite in aqueous acetic acid as reported for analogous 2-aminoimidazoquinoxalines [64] to afford **4**, which was crystallized from dimethylacetamide/2-propanol to yield 0.13 g (57%), mp 254–255 ºC; ir: 3037, 2948, 1693, 1546, 1503, 1483, 1447, 1404, 1324, 1290, 1243, 881, 779, 768 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 9.40 (1H, s, H-10), 8.49 (1H, m, H-9), 8.09 (1H, m, H-6), 7.63 (2H, m, H-7 and H-8), 4.28 (3H, s, Me); ^{13}C nmr

((CD$_3$)$_2$SO): δ 159.7 (C-3a or C-4a), 149.9 (C-2), 149.1 (C-4a or C-3a), 136.8 (C-5a), 132.3 (C-9a), 128.5 (C-7), 128.4 (C-9b), 127.6 (C-10a), 125.5 (C-8), 123.4 (C-6), 122.8 (C-9), 115.0 (C-10), 34.1 (Me); ms: m/z 284 (M, 70%), 269 (51), 268 (5), 255 (100), 254 (26), 238 (12), 226 (39); hrms: calcd. for C$_{13}$H$_9$N$_4$O$_2$S (M+H)$^+$ 285.0447, found 285.0454.

2-Hydroxy-1-methylbenzothieno[3,2-e]imidazo[4,5-b]pyridine (**5**).

Compound **4** (150 mg, 0.5 mmol) was boiled in dimethylformamide (3 mL) and water (0.5 mL) for 10 min. The crystals formed after cooling to room temperature were pure **5**, 48 mg (37%), mp >410 °C; ir: 3024, 2937, 2741, 1692, 1626, 1586, 1464, 1438, 1418, 1224, 1170, 1112, 1057, 719, 703, 691, 609 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 11.8 (1H, br s, OH), 8.37 (1H, s, H-10), 8.29 (1H, d, H-9, J 7.4), 7.97 (1H, d, H-6, J 7.6), 7.53–7.43 (2H, m, H-8 and H-7), 3.40 (3H, s, Me); ^{13}C nmr ((CD$_3$)$_2$SO): δ 154.0 (C-2), 151.3 (C-4a), 144.1 (C-3a), 135.4 (C-5a), 133.6 (C-9a), 126.0 (C-7), 124.8 (C-8), 124.0 (C-10a), 123.0 (C-6), 122.6 (C-9b), 121.4 (C-9), 107.7 (C-10), 26.6 (Me); ms: m/z 256 (48), 255 (M, 100%), 240 (21), 226 (33), 213 (29).

Anal. Calcd. for C$_{13}$H$_9$N$_3$OS: C, 61.2; H, 3.5; N, 16.5. Found: C, 61.2; H, 3.5; N, 16.4.

3-Bromo-5-methyl-2-thiophenecarbaldehyde [31-33] (**9**).

This compound was prepared from 2-bromo-5-methylthiophene [72] (1.0 g, 5.6 mmol) as described [31]. FC (hexane to hexane/ethyl acetate, 8:1) of the crude product yielded **9**, which was recrystallized from hexane to yield 0.9 g (78%), mp 50–51 °C (lit. [31] 45–47 °C, lit. [32] 30–32 °C); ir: 3080, 2845, 1650, 1512, 1445, 1364, 1325, 1221, 1178, 855, 839, 698, 688 cm^{-1}; ms: m/z 206 (65), 205 (M, 100%), 177 (11), 167 (5), 96 (25). The ^{1}H- and ^{13}C-NMR data were in good agreement with those published [31,32].

3-Azido-5-methyl-2-thiophenecarbaldehyde (**10**).

Compound **9** (1.65 g, 8.0 mmol) was dissolved in DMPU (20 mL), sodium azide (2.1 g, 32.3 mmol) was added in portions under argon at ambient temperature. The reaction was warmed to 35 °C for 24 hours, poured onto ice-water and extracted with diethyl ether. The organic layer was washed with brine and dried (magnesium sulfate). Evaporation *in vacuo* and FC (chloroform) of the residue gave **10**, which was recrystallized from hexane to yield 530 mg (39%), mp 70–72 °C; ir: 3054, 2857, 2110, 1649, 1539, 1462, 1379, 1367, 1260, 1236, 814, 695 cm^{-1}; ^{1}H nmr (CDCl$_3$): δ 9.82 (1H, s, CHO), 6.75 (1H, d, H-4, J 0.7) and 2.53 (3H, d, Me, J 0.7); ^{13}C nmr (CDCl$_3$): δ 179.7 (CHO), 151.5 (C-5), 144.9 (C-3), 126.0 (C-2), 119.1(C-4) and 16.8 (Me); ms: m/z 167 (M, 31%), 139 (100), 111 (69), 110 (49), 84 (94).

Anal. Calcd. for C$_6$H$_5$N$_3$OS: C, 43.1; H, 3.0; N, 25.1. Found: C, 43.1; H, 3.0; N, 25.1.

3-Amino-5-methyl-2-thiophenecarbaldehyde (**11**).

Compound **10** (530 mg, 3.2 mmol) was dissolved in methanol (25 mL) and 40% ammonium sulfide (0.5 mL, 4.0 mmol) was added dropwise. Tlc (chloroform-methanol, 8:1) showed completion of the reaction after 10 min at room temperature while the gas evolution had ceased. The reaction mixture was evaporated *in vacuo* and FC (chloroform) of the residue gave **11**, which was recrystallized from hexane-diethyl ether to yield 400 mg (89%), mp 65–66 °C; ir: 3416, 3281, 3165, 2794, 2744, 1620, 1586, 1467, 1384, 828, 696 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO, 60 °C): δ 9.53 (1H, s, CHO), 6.9 (2H, br s, NH$_2$), 6.37 (1H, s, H-4), 2.37 (3H, d,

Me, J 0.6); ^{13}C nmr ((CD$_3$)$_2$SO, 60 °C): δ 179.0 (CHO), 156.0 (C-3), 150.7 (C-5), 119.2 (C-4), 110.3 (C-2), 15.9 (Me); ms: m/z 141 (M, 100%), 140 (21), 124 (7), 113 (17), 112 (40).

Anal. Calcd. for C$_6$H$_7$NOS: C, 51.0; H, 5.0; N, 9.9. Found: C, 51.1; H, 4.9; N, 9.9.

2-Bromobenzothiophene [41-43].

2-Bromobenzothiophene was synthesized from benzothiophene as published [44] mp 38–40 °C (distillation) (lit. [42] 41–42 °C, lit. [43] 46–47 °C); ir: 3082, 3056, 1502, 1455, 1422, 1174, 1152, 944, 829, 819, 747, 724, 706 cm^{-1}; ms: m/z 214 (M, 39%), 133 (30), 106 (13), 93 (23), 89 (100). The ^{1}H- and ^{13}C-nmr data were in good agreement with those reported [41].

2-Bromo-3-benzothiophenecarbaldehyde [46–49] (**19**).

This compound was synthesized from 2-bromobenzothiophene as described [46] and crystallisation from hexane yielded **19**, mp 73–74 °C (lit. [46] 70 °C; lit. [47] 73 °C; lit. [49] 74–76 °C); ir: 3083, 2835, 2736, 1667, 1495, 1460, 1421, 1379, 1345, 1104, 1044, 749, 729 cm^{-1}; ^{13}C nmr (CDCl$_3$): δ 185.9 (CHO), 138.7 (C-7a), 135.5 (C-3a), 133.4 (C-2), 131.3 (C-3), 126.4 (C-5 or C-6), 126.1 (C-6 or C-5), 123.8 (C-4), 121.2 (C-7). The ^{1}H nmr [47] and ms [48] data were in agreement with those published.

2-Azido-3-benzothiophenecarbaldehyde [52,53] (**20**).

A solution of **19** (2.1 g, 8.7 mmol) in dimethylsulfoxide (20 mL) was treated with sodium azide (2.3 g, 35.4 mmol) under argon at room temperature. Tlc (chloroform-methanol, 8:1) showed completion of the reaction after 2 h. The reaction mixture was poured in water, the precipitate was filtered, and washed with a small aliquot of cold methanol to give **20**, 1.7 g (97%), mp 95–96 °C (dec.) (lit. [52] 90–93 °C, lit. [53] 91–94 °C (dec.)); ir: 2833, 2748, 2350, 2122, 1800, 1657, 1507, 1461, 1428, 1389, 1364, 1296, 1138, 1046, 751 cm^{-1}; ^{1}H nmr (CDCl$_3$): δ 10.17 (1H, s, CHO), 8.55 (1H, d, H-4, J 7.8), 7.69 (1H, d, H-7, J 8.0), 7.49 (1H, t, H-5, J 7.2), 7.38 (1H, t, H-6, J 7.7); ^{13}C nmr (CDCl$_3$): δ 182.6 (CHO), 156.4 (C-2), 135.4 (C-3a), 132.6 (C-7a), 126.7 (C-5 or C-6), 125.7 (C-6 or C-5), 124.5 (C-4), 121.8 (C-3), 121.7 (C-7); ms (20 eV): m/z 203 (M, 7%), 177 (36), 175 (45) 147 (76), 120 (100).

2-Amino-3-benzothiophenecarbaldehyde [37, 53] (**21**).

Compound **20** (1.7 g, 8.5 mmol) was suspended in methanol (100 mL) and 40% ammonium sulfide (2.2 mL, 17.6 mmol) was added dropwise. Tlc (chloroform-methanol, 8:1) showed completion of the reaction after 15 min at room temperature while the gas evolution had ceased. The reaction mixture was evaporated *in vacuo* and FC (chloroform) of the residue gave **21**, which after sublimation yielded 1.4 g (94%), mp 142–144 °C (lit. [53] 73–77 °C); ir: 3337, 3230, 3117, 2807, 1610, 1574, 1474, 1459, 1432, 1359, 1203, 1066, 742, 720 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 10.02 (1H, s, CHO), 8.6 (2H, br s, NH$_2$), 7.92 (1H, d, H-4, J 7.7), 7.63 (1H, d, H-7, J 7.9), 7.25 (1H, dt, H-5, J 7.4, 0.9), 7.10 (1H, dt, H-6, J 7.6, 0.9); ^{13}C nmr ((CD$_3$)$_2$SO): δ 182.0 (CHO), 167.5 (C-2), 137.4 (C-3a), 128.4 (C-7a), 125.4 (C-5), 122.3 (C-7 or C-6), 121.9 (C-6 or C-7), 117.7 (C-4), 107.8 (C-3); ms: m/z 177 (M, 71%), 160 (21), 149 (28), 148 (10), 121 (100).

3-Bromo-2-benzothiophenecarbaldehyde [50] (**22**).

A 1.6 M solution of buthyl lithium (8.0 mL, 12.8 mmol) in hexane was added dropwise at −78 °C to a solution of 2,3-dibro-

mobenzothiophene [73] (3.3 g, 11.3 mmol) in diethylether (35 mL). The mixture was stirred for 1 h before dimethylformamide (0.9 mL, 11.5 mmol) was added, keeping the temperature below –65 ºC. When the reaction had reached ambient temperature saturated ammonium chloride (20 mL) was added and the mixture was extracted with diethylether (3 x 20 mL), washed with brine, dried (sodium sulfate) and evaporated *in vacuo*. FC (hexane to hexane-ethyl acetate, 4:1) of the residue yielded **22**, which was recrystallized from acetone to yield 2.5 g (92%), mp 118–119 ºC (lit. [50] 118–118.5 ºC); ir: 3260, 2825, 1661, 1500, 1304, 1248, 1195, 1158, 919, 808, 760 cm^{-1}; ^{1}H nmr (CDCl$_3$): δ 10.29 (1H, s, CHO), 8.02 (1H, dd, H-4, *J* 7.2, 1.9), 7.88 (1H, dd, H-7, *J* 6.9, 1.3), 7.55 (2H, m, H-5 and H-6); ^{13}H nmr (CDCl$_3$): δ 184.7 (CHO), 140.5 (C-7a), 138.0 (C-3a), 136.5 (C-2), 129.3 (C-7), 126.0 (C-4), 125.0 (C-5 or C-6), 123.4 (C-6 or C-5), 118.8 (C-3); ms: *m/z* 242 (M, 5%), 214 (4), 213 (4), 133 (20), 132 (51), 93 (70), 89 (100).

3-Azido-2-benzothiophenecarbaldehyde [52, 53] (**23**).

A solution of **22** (2.1 g, 8.7 mmol) in dimethylsulfoxide (20 mL) was treated with sodium azide (2.3 g, 35.4 mmol) under argon at room temperature. Tlc (chloroform-methanol, 8:1) showed that the reaction was complete after 45 min. The reaction mixture was poured in water and the precipitate was filtered and washed with a small aliquot of cold methanol to yield **23**, 1.6 g (93%), mp 87–88 ºC (lit. [52] 84–86 ºC, lit. [53] 88–90 ºC (dec.)); ir: 2848, 2243, 2105, 1649, 1595, 1513, 1382, 1358, 1235, 1207, 748, 725 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 10.18 (1H, s, CHO), 8.07 (1H, d, H-7, *J* 8.2), 8.01 (1H, d, H-4, *J* 8.2), 7.64 (1H, t, H-6, *J* 7.2), 7.54 (1H, t, H-5, *J* 8.1); ^{13}C nmr ((CD$_3$)$_2$SO): δ 182.4 (CHO), 139.5 (C-7a), 137.3 (C-3), 133.2 (C-3a), 129.3 (C-6), 127.8 (C-2), 125.7 (C-5), 124.2 (C-7), 123.0 (C-4); ms: *m/z* 203 (M, 3%), 175 (47), 146 (100), 103 (68).

3-Amino-2-benzothiophenecarbaldehyde [37,53] (**24**).

Compound **23** (1.6 g, 8.0 mmol) was suspended in methanol (100 mL) and 40% ammonium sulfide (2.2 mL, 17.6 mmol) was added dropwise. Tlc (chloroform-methanol, 8:1) showed completion of the reaction after 45 min at room temperature while the gas evolution had ceased. The reaction mixture was evaporated *in vacuo* and FC (chloroform) of the residue gave **24**, which after sublimation yielded 1.3 g (91%), mp 127–130 ºC (lit. [53] 118–120 ºC); ir: 3368, 3339, 3205, 1655, 1578, 1554, 1516, 1472, 1432, 1371, 1317, 1238, 765, 724 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 10.03 (1H, s, CHO), 8.16 (1H, d, *J* 8.1), 7.83 (1H, d, *J* 8.1), 7.7 (2H, br s), 7.53 (1H, t, *J* 7.2), 7.39 (1H, t, *J* 7.2); ^{1}H nmr (CD$_3$OD): δ 9.7 (1H, br s, CHO), 8.02 (1H, d, H-4, *J* 8.2), 7.75 (1H, d, H-7, *J* 8.2), 7.53 (1H, dt, H-6, *J* 7.7, 1.0), 7.39 (1H, dt, H-5, *J* 8.1, 0.8); ^{13}C nmr (CD$_3$OD): δ 184.6 (CHO), 153.1 (C-3), 144.1 (C-7a), 132.9 (C-3a), 130.6 (C-6), 125.3 (C-5), 124.7 (C-7), 124.3 (C-4), 110.8 (C-2); ms (20 eV): *m/z* 177 (M, 100%), 176 (10), 160 (6), 149 (44), 121 (29), 104 (20).

2-Amino-1-methylimidazo[4,5-*b*]benzothiophene (**25**).

Compound **28** (2.5 g, 12.0 mmol) was suspended in a mixture of ethyl acetate (20 mL) and ethanol (20 mL) and 10% Pd/C (0.15 g) was added. The reaction was run overnight under H$_2$ atmosphere at 200 psi in a Parr apparatus, tlc (ethyl acetate). The mixture was filtered through a bed of celite and washed with ethanol (10 mL). Cyanogen bromide (1.3 g, 12.3 mmol) was added to the solution of the diamine **29** [^{1}H nmr ((CD$_3$)$_2$SO): δ

7.54 (1H, d, *J* 7.7), 7.39 (1H, d, *J* 7.7), 7.19 (1H, t, *J* 7.4), 6.98 (1H, t, *J* 7.3), 5.2 (2H, br s), 2.67 (3H, s); ^{13}C nmr ((CD$_3$)$_2$SO): δ 139.5 (C), 136.9 (C), 128.9 (C), 124.0 (CH), 121.9 (CH), 120.4 (CH), 118.3 (C), 117.7 (CH), 34.9 (CH$_3$)] and the mixture was left over night under argon at ambient temperature. The *p*H of the mixture was adjusted to ~10 with 28% ammonia solution and was evaporated *in vacuo*. FC (chloroform to chloroform-methanol, 8:1) of the residue gave **25**, which was recrystallized from ethanol-water to yield 1.0 g (43 %), mp 267–271 ºC; ir: 3430, 3291, 3113, 3043, 1638, 1539, 1512, 1452, 1421, 1282, 745, 717 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 7.79 (2H, m, H-5, H-8), 7.31 (1H, app t, H-7, *J* 7.6), 7.10 (1H, app t, H-6, *J* 7.6), 6.2 (2H, br s, NH$_2$), 3.75 (3H, s, Me); ^{13}C nmr ((CD$_3$)$_2$SO): δ 155.2 (C-2), 139.6 (C-3a), 136.4 (C-4a), 126.1 (C-8a), 124.5 (C-8b), 124.3 (C-5), 124.2 (C-7), 120.6 (C-6), 116.2 (C-8) and 30.7 (Me); ms: *m/z* 203 (M, 100%), 188 (13), 175 (9), 161 (33), 148 (12), 134 (32).

Anal. Calcd. for C$_{10}$H$_9$N$_3$S: C, 59.1; H, 4.5; N, 20.7. Found: C, 59.1; H, 4.8; N, 20.7.

3-Bromo-2-nitrobenzothiophene [45,66–68] (**27**).

Compound **27** was prepared from 3-bromobenzothiophene as described [66]. Recrystallisation from ethanol yielded **27**, mp 160–162 ºC (lit. [45] 160–161 ºC, lit. [66] 164–165 ºC, lit. [67] 162–162.8 ºC); ir: 1590, 1551, 1515, 1482, 1419, 1301, 1331, 1241, 1114, 916, 868, 759, 726 cm^{-1}; ms: *m/z* 259 (M, 36%), 229 (5), 213 (11), 201 (36), 132 (100), 93 (39). The ^{1}H- and ^{13}C-nmr data were in agreement with those published [68].

3-Methylamino-2-nitrobenzothiophene [69] (**28**).

Compound **27** (3.4 g, 13.2 mmol) was suspended in ethanol (65 mL) and heated to reflux with 40% aqueous methylamine (4.5 mL, 58.0 mmol) being added in portions under the surface of the reaction mixture. After heating for a total of 2.5 h the mixture was concentrated to ~35 mL and was allowed to cool. The precipitate was filtered and washed with cold ethanol to afford **28**, which after recrystallisation from ethanol yielded 2.5 g (91%), mp 205–206 ºC (lit. [69] 200–202 ºC); ir: 3247, 1607, 1587, 1554, 1503, 1442, 1393, 1339, 1285, 1252, 1174, 1129, 998, 726 cm^{-1}; ^{1}H nmr ((CD$_3$)$_2$SO): δ 9.6 (1H, br s, NH), 8.45 (1H, d, H-4, *J* 8.4), 7.92 (1H, d, H-7, *J* 8.1), 7.68 (1H, dt, H-6, *J* 8.1, 0.9), 7.46 (1H, dt, H-5, *J* 8.3, 0.9), 3.57 (3H, d, Me, *J* 5.5); ^{13}C nmr ((CD$_3$)$_2$SO): δ 149.0 (C-3), 138.3 (C-7a), 131.4 (C-6), 128.9 (C-3a), 128.2 (C-4), 125.0 (C-5), 123.8 (C-7), 118.7 (C-2), 33.1 (Me); ms: *m/z* 208 (M, 46%), 193 (1), 191 (1), 179 (6), 134 (100).

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