Efficient regioselective synthesis of triheterocyclic compounds: imidazo[2,1-*b*]benzothiazoles, pyrimido[2,1-*b*]benzothiazolones and pyrimido[2,1-*b*]benzothiazoles

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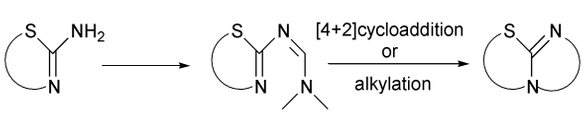
The preparation and characterisation of triheterocyclic compounds, *via* annulation reactions, are described. Amidines **1** reacted with substituted bromomethyl compounds, acid chlorides, and acrylic dienophiles to afford the corresponding imidazo[2,1-*b*]benzothiazoles **2** and pyrimido[2,1-*b*]benzothiazoles **3** or **4**.

Introduction

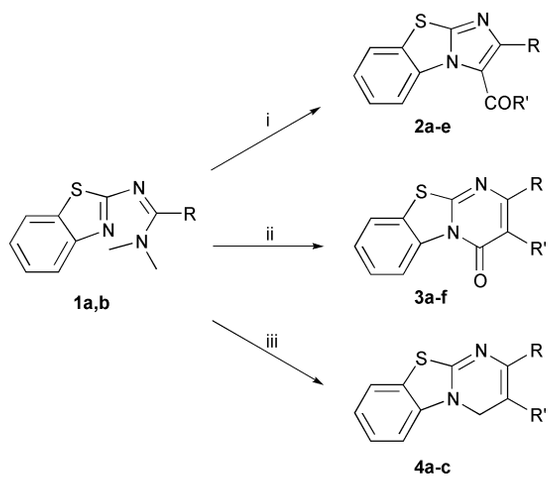
In recent years, polyheterocycles have received increasing attention due to their potential biological properties, and considerable efforts have been undertaken to exploit synthetic routes to these compounds. In particular, imidazo[2,1-*b*]benzothiazoles were tested *in vivo* for anti-inflammatory and analgesic activities together with low ulcerogenic properties.[1,2] Substituted compounds have been shown to be fungicidal agents,[3] while tetrahydro derivatives were tested in cancer chemotherapy.[4] Imidazo- and pyrimido[2,1-*b*]benzothiazoles were evaluated for their affinity at the central benzodiazepine receptor.[5] Trapani and co-workers have explored the widespread activities of these compounds displaying anxiolytic, anticonvulsant, muscle relaxant and sedative properties.[6–8] Moreover, pyrimidobenzothiazolone derivatives have been shown to be useful for the prophylactic treatment of the allergic disease state.[9,10] Therefore, it would be important to search for new, versatile and regioselective methods to synthesise such polyheterocyclic ring systems.

In the course of our studies directed towards the synthesis of heterocyclic compounds based on the use of neutral or cationic 1,3-diazadienes,[11–13] we have recently developed annulation protocols for the preparation of fused thiazines or thiazoles with pyrimidines or imidazoles (Scheme 1).



Scheme 1

In this context, we have reported a new and efficient method for the synthesis of 2,3-dihydroimidazo[2,1-*b*]thiazole and 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine derivatives from amidines of 2-amino-Δ^2-thiazoline.[14] In the same manner, 7*H*-imidazo[2,1-*b*][1,3]thiazines and 2*H*,6*H*-pyrimido[2,1-*b*]-[1,3]thiazines were easily obtained.[15] In order to increase the scope of this strategy to more conjugated polyheterocycles, we focused our research by the use of the same procedure to develop a regioselective synthesis of imidazo[2,1-*b*]benzothiazoles **2a**–**e**, pyrimido[2,1-*b*]benzothiazolones **3a**–**f** or pyrimido[2,1-*b*]benzothiazoles **4a**–**c** by reaction of amidines **1a**,**b** derived from an aromatic amine with α-bromo ketones, acid chlorides or acrylic dienophiles, respectively (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) α-halogeno ketones, base; (ii) acid chlorides, base; (iii) acrylic dienophiles.

Results and discussion

Our first target compounds were *N′*-(benzothiazol-2-yl)-*N,N*-dimethylamidines **1a** and **1b** containing a diazadiene chain. The preparation of these compounds was accomplished according to a procedure developed in the literature by the condensation of *N,N*-dimethylformamide dimethyl acetal (R = H, **1a**) or *N,N*-dimethylacetamide dimethyl acetal (R = CH_3, **1b**) with 2-aminobenzothiazole in boiling dichloromethane.[16] With the aim of investigating the reactivity of these amidines **1a**,**b** we have first realised their alkylation using α-bromo ketones or ethyl bromoacetate (Scheme 3).

Alkylation of the heterocyclic nitrogen atom provided the *N*-alkyl amidinium bromides **5**. These salts were stable enough to be isolated and were dehydrohalogenated using an ethanolic solution of potassium hydroxide giving rise to imidazo[2,1-*b*]-benzothiazoles **2a**–**e**. In this reaction, it was postulated that under the basic medium an enolate anion is formed which is involved in an intramolecular cyclisation with the iminium group, followed by loss of dimethylamine. As expected, the ring closure of compounds **5** occurred in higher yields when the bromomethyl reagent was substituted with a stronger electron-withdrawing group. Thus, by this method we obtained five imidazobenzothiazoles **2a**–**e**, as presented in Table 1.

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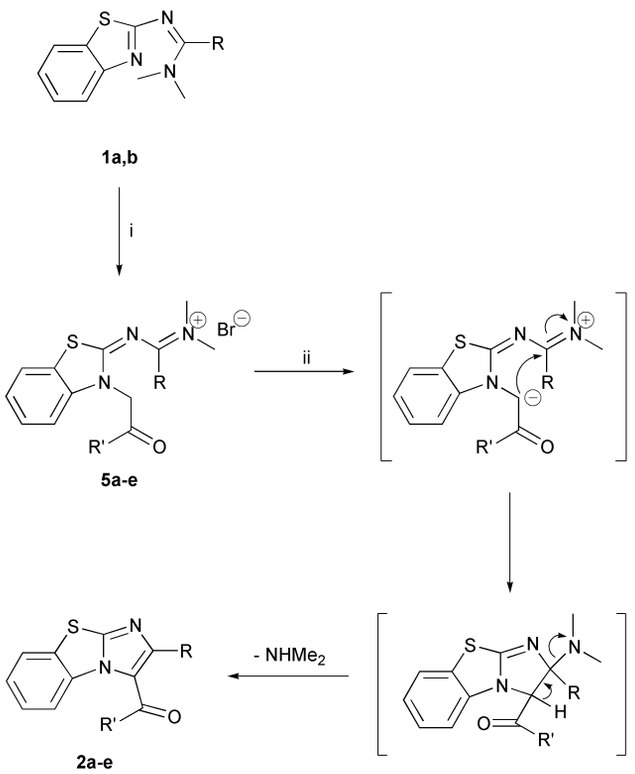
Table 1 Yields of amidinium bromides **5** and imidazo[2,1-*b*]benzothiazoles **2**

R	R′	Product	Yield (%)	Product	Yield (%)
H	C_2H_5O	**5a**	92	**2a**[17]	36
H	*p*-BrC_6H_4	**5b**	96	**2b**	84
H	*p*-ClC_6H_4	**5c**	90	**2c**	72
H	*p*-$CH_3C_6H_4$	**5d**	85	**2d**	77
CH_3	*p*-ClC_6H_4	**5e**	78	**2e**	68



Scheme 3 *Reagents and conditions*: (i) R′$COCH_2Br$, THF, 66 °C, 20 h; (ii) KOH, EtOH, 78 °C, 18 h.

The structure of compounds **2** was confirmed by a single-crystal X-ray analysis of **2a** (Fig. 1).[18] The X-ray structure shows a fused triheterocycle with an almost planar shape obeying the necessary aromatic form.

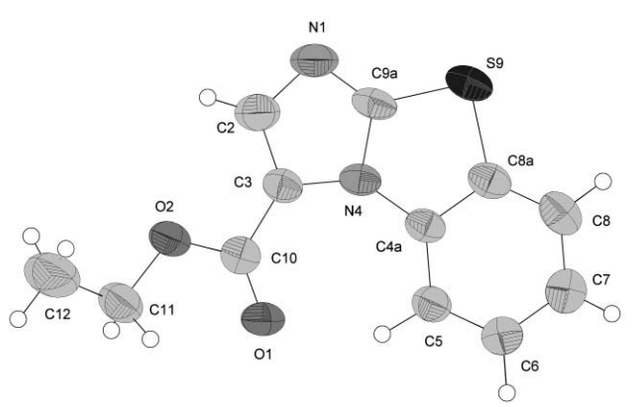


Fig. 1 ORTEP representation of compound **2a** with crystallographic numbering scheme.

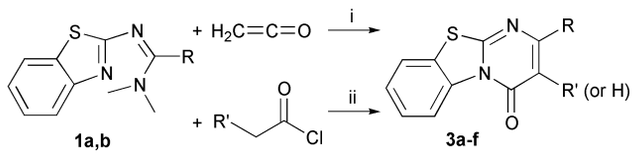
By a similar synthetic strategy, when amidines **1a**,**b** reacted with acid chlorides the 4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones **3a**–**d** were formed (Scheme 4). The heterocyclic nitrogen atom was affected by acylation but intermediary salts could not be isolated. Subsequent treatment using triethylamine afforded cycloadducts leading to the desired compounds after deamination. The most successful conditions found were to perform the reaction at room temperature in dichloromethane, yielding compounds **3a**–**d** in 30–50% yield. When 1,3-diazadienes **1a**,**b** were exposed to ketene, produced by cracking of acetone,[19] [4 + 2] cycloaddition reactions took place, furnishing pyrimidobenzothiazolones **3e**,**f** in good yield after loss of dimethylamine (Scheme 4, Table 2). The ^1H NMR deshielding effect

Table 2 Yields of 4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones **3a**–**f**

R	R′	Product	Yield (%)
H	$COOCH_3$	**3a**[8,20]	28
H	$COOC_2H_5$	**3b**[8,10,20]	35
CH_3	$COOC_2H_5$	**3c**	44
H	C_6H_5	**3d**	35
H	H	**3e**[10]	51
CH_3	H	**3f**	87

Table 3 Yields of 4*H*-pyrimido[2,1-*b*]benzothiazoles **4a**–**c**

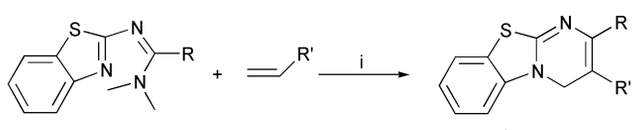
R	R′	Product	Yield (%)
H	CHO	**4a**	43
H	$COCH_3$	**4b**	52
CH_3	$COCH_3$	**4c**	48



Scheme 4 *Reagents and conditions*: (i) CH_2Cl_2, rt, 2 h; (ii) CH_2Cl_2, rt, 6 h; then 0 °C, Et_3N, 16 h.

observed for the 6-methine group signal is attributed to the proximity of the 4-carbonyl function.

According to the latter results, *N*′-(benzothiazol-2-yl)-*N*,*N*-dimethylamidines **1a**,**b** behaved like heterodienes in the presence of acrylic dienophiles (Scheme 5, Table 3). These [4 + 2]



Scheme 5 *Reagents and conditions*: (i) $CHCl_3$, 3 days, rt for **4a** or reflux for **4b**,**c**.

cycloaddition reactions occurred in a regiocontrolled manner and the intermediary cycloadducts underwent spontaneous deamination, affording 4*H*-pyrimido[2,1-*b*]benzothiazoles **4a**–**c** in modest yields.

In summary, alkylation of 1,3-diazadienes **1** by arylacyl bromides occurred smoothly, and subsequent annulation reactions proceeded in good yields, affording imidazo[2,1-*b*]-benzothiazoles **2** while acylation using acid chlorides gave rise to 4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones **3** in lower yields. It is noteworthy that aromaticity of benzothiazole precursors did not prevent the course of the [4 + 2] cycloaddition reactions and only moderate decrease of yields was observed in comparison with less conjugated heterocyclic starting materials such as amidines derived from 2-amino-Δ^2-thiazoline or 2-amino-1,3-thiazine. The latter reaction is an easy method for the preparation of new 3-functionalised 4*H*-pyrimido[2,1-*b*]-benzothiazoles. These represent a class of compounds that could be used as precursors for the synthesis of new derivatives with useful biological activity. Further work dealing with the construction of other related heterocycles is currently under investigation.

Experimental

All reagents were purchased from Acros Organics and Aldrich. All chemicals were reagent grade and used without further purification, and all solvents were freshly distilled before use. The CNRS Analysis Laboratory (Vernaison) performed the elemental analyses. Column chromatography was conducted over silica gel 60 (40–63 μm), available from E. Merck. Thin-layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60 F-254). Melting points, measured using a Reichert microscope were uncorrected. The ^{13}C and ^{1}H NMR spectra were recorded at room temperature using a Bruker AC200, operating at 50 and 200 MHz, respectively. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Hewlett-Packard 5989 spectrometer. The IR spectra were obtained using a Bruker Vector 22 spectrometer.

Amidines 1: general procedure

A suspension of 2-aminobenzothiazole (10 mmol) and *N,N*-dimethylformamide dimethyl acetal (11 mmol, for **1a**) or *N,N*-dimethylacetamide dimethyl acetal (13 mmol, for **1b**) in dichloromethane (10 mL) was refluxed for 16 h. After removal of the solvent, the residue was chromatographed using as eluent dichloromethane–ethyl acetate (5 : 1). Compounds **1** were crystallised from diethyl ether.

***N′*-(Benzothiazol-2-yl)-*N,N*-dimethylformamidine 1a**[16]**.** Yield 83%; white crystals; mp 99 °C (Found: C, 58.63; H, 5.37; N, 20.60. $C_{10}H_{11}N_3S$ requires C, 58.51; H, 5.40; N, 20.47%); ^{1}H NMR ($CDCl_3$) δ 3.12 and 3.13 (2s, 6H, N(CH_3)$_2$), 7.13–7.70 (m, 4H, C*H*ar), 8.37 (s, 1H, NC*H*); ^{13}C NMR ($CDCl_3$) δ 35.1 and 40.9 (2C, N(*C*H$_3$)$_2$), 120.6, 121.2, 122.8 and 125.7 (4*C*Har), 133.3, 152.1 (2*C*ar), 156.5 (N*C*H), 173.6 (S*C*N); MS, *m*/*z* (%) 205 (100, M^+), 190 (43), 189 (48), 163 (35), 135 (45); IR (KBr) ν_{max}/cm^{-1} 1619 (s), 1490 (s), 1439 (w), 1405 (m), 1339 (m), 1097 (m), 757 (m).

***N′*-(Benzothiazol-2-yl)-*N,N*-dimethylacetamidine 1b.** Yield 82%; white crystals; mp 86 °C (Found: C, 60.37; H, 5.89; N, 19.01. $C_{11}H_{13}N_3S$ requires C, 60.25; H, 5.97; N, 19.16%); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 3.12 (s, 6H, N(CH_3)$_2$), 7.12–7.74 (m, 4H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 16.4 (C*C*H$_3$), 38.3 (2C, N(*C*H$_3$)$_2$), 120.6, 120.9, 122.6 and 125.4 (4*C*Har), 134.5, 152.5 (2*C*ar), 161.7 (C*C*H$_3$), 172.4 (S*C*N); MS, *m*/*z* (%) 219 (100, M^+), 178 (24), 175 (24), 163 (30), 135 (40); IR (KBr) ν_{max}/cm^{-1} 1578 (s), 1539 (m), 1397 (s), 1158 (m), 953 (m), 774 (m).

N-Alkyl amidinium bromides 5; general procedure

To a solution of an amidine **1** (2 mmol) in tetrahydrofuran (10 mL) was added ethyl bromoacetate (2.2 mmol, for **5a**) or an α-bromo ketone (2.2 mmol, *p*-bromophenacyl bromide for **5b**, *p*-chlorophenacyl bromide for **5c** and **5e**, *p*-methylphenacyl bromide for **5d**). The reaction mixture was refluxed for 20 h and cooled to room temperature. The solvent was evaporated off and the residue was crystallised from diethyl ether. ^{13}C spectra of compounds **5b**,**e** could not be recorded due to their low solubilities.

Amidinium bromide 5a. Yield 92%; white crystals; mp 109 °C; ^{1}H NMR (DMSO-d_6) δ 1.22 (t, 3H, *J* 7.2 Hz, CH$_2$CH_3), 3.26, 3.42 (2s, 6H, N(CH_3)$_2$), 4.21 (q, 2H, *J* 7.2 Hz, OCH_2), 5.38 (s, 2H, NCH_2), 7.47–8.18 (m, 4H, C*H*ar), 8.77 (s, 1H, NC*H*); ^{13}C NMR (DMSO-d_6) δ 14.0 (CH$_2$*C*H$_3$), 36.6, 42.2 (N(*C*H$_3$)$_2$), 46.8 (N*C*H$_2$), 61.7 (O*C*H$_2$), 114.0, 122.9, 124.0, 125.9, 128.2, 137.8 (2*C*ar, 4*C*Har), 161.2 (N*C*H), 166.4 (*C*O), 172.3 (S*C*N); MS, *m*/*z* (%) 291 (43), 219 (58), 174 (100); IR (KBr) ν_{max}/cm^{-1} 1739 (s), 1653 (s), 1470 (m), 1409 (m), 1224 (m), 1142 (m), 765 (m).

Amidinium bromide 5b. Yield 96%; white crystals; mp 207 °C; ^{1}H NMR (DMSO-d_6) δ 3.09, 3.35 (2s, 6H, N(CH_3)$_2$), 6.20 (s, 2H, NCH_2), 7.46–8.19 (m, 8H, C*H*ar), 8.74 (s, 1H, NC*H*); MS, *m*/*z* (%) 403/401 (35/35), 357 (69), 185/183 (96/100); IR (KBr) ν_{max}/cm^{-1} 1693 (s), 1653 (s), 1517 (s), 1473 (m), 1416 (m), 1402 (m), 1130 (m), 981 (m).

Amidinium bromide 5c. Yield 90%; white crystals; mp 209 °C; ^{1}H NMR (DMSO-d_6) δ 3.09, 3.35 (2s, 6H, N(CH_3)$_2$), 6.21 (s, 2H, NCH_2), 7.47–8.19 (m, 8H, C*H*ar), 8.73 (s, 1H, NC*H*); ^{13}C NMR (DMSO-d_6) δ 36.4, 42.1 (N(*C*H$_3$)$_2$), 52.2 (N*C*H$_2$), 114.2, 123.9, 125.9, 128.2, 129.2 (2), 130.4 (2) (8*C*Har), 123.0, 132.8, 138.2, 139.5 (4*C*ar), 161.2 (N*C*H), 172.3 (S*C*N), 190.5 (*C*O); MS, *m*/*z* (%) 359/357 (14/36), 312 (74), 201 (61), 139 (100); IR (KBr) ν_{max}/cm^{-1} 1695 (m), 1666 (m), 1521 (s), 1415 (m), 1401 (m), 1229 (w), 1133 (w), 767 (w).

Amidinium bromide 5d. Yield 85%; white crystals; mp 215 °C; ^{1}H NMR (DMSO-d_6) δ 2.43 (s, 3H, CH_3), 3.07, 3.35 (2s, 6H, N(CH_3)$_2$), 6.18 (s, 2H, NCH_2), 7.42–8.19 (m, 8H, C*H*ar), 8.75 (s, 1H, NC*H*); ^{13}C NMR (DMSO-d_6) δ 21.3 (*C*H$_3$), 36.4, 42.0 (N(*C*H$_3$)$_2$), 52.2 (N*C*H$_2$), 114.2, 124.0, 125.8, 128.2, 128.5 (2), 129.5 (2) (8*C*Har), 123.0, 131.6, 138.3, 145.2 (4*C*ar), 161.1 (N*C*H), 172.2 (S*C*N), 190.7 (*C*O); MS, *m*/*z* (%) 337 (35), 292 (82), 201 (35), 119 (100), 91 (69); IR (KBr) ν_{max}/cm^{-1} 1688 (m), 1648 (m), 1521 (s), 1418 (w), 1403 (w), 1233 (w), 1183 (w).

Amidinium bromide 5e. Yield 78%; white crystals; mp 170 °C; ^{1}H NMR (DMSO-d_6) δ 2.57 (s, 3H, CH_3), 3.09, 3.29 (2s, 6H, N(CH_3)$_2$), 6.10 (s, 2H, NCH_2), 7.42–8.19 (m, 8H, C*H*ar); MS, *m*/*z* (%) 328/326 (35/100), 291 (35), 215 (32), 146 (29), 111 (66); IR (KBr) ν_{max}/cm^{-1} 1699 (m), 1549 (s), 1430 (w), 1408 (m), 1227 (m), 1000 (w), 833 (m), 755 (w).

Imidazo[2,1-*b*][benzothiazoles 2; general procedure

A solution of an amidinium bromide **5** (1.5 mmol) and potassium hydroxide (3 mmol) in ethanol (20 mL) was refluxed for 18 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (100 mL) and washed with water (100 mL). The aqueous phase was extracted with dichloromethane (3 × 70 mL). The combined organic layers were washed with water (3 × 70 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by chromatography using dichloromethane-ethyl acetate (9 : 1) as eluent to furnish the corresponding compound **2** which were crystallised from diethyl ether.

3-(Ethoxycarbonyl)imidazo[2,1-*b*]benzothiazole 2a.[17] Yield 36%; white crystals; mp 138 °C (Found: C, 58.57; H, 4.15; N, 11.49. $C_{12}H_{10}N_2O_2S$ requires C, 58.52; H, 4.09; N, 11.37%); ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3H, *J* 7.2 Hz, CH$_2$CH_3), 4.42 (q, 2H, *J* 7.2 Hz, OCH_2), 7.34–7.73 (m, 3H, C*H*ar), 8.05 (s, 1H, NC*H*), 9.06–9.11 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH$_2$*C*H$_3$), 61.0 (O*C*H$_3$), 117.9, 123.7, 125.5, 126.5 (4*C*Har), 130.1, 133.3, 138.1 (2*C*ar, *C*CO), 143.5 (N*C*H), 153.3 (S*C*N), 159.9 (*C*O); MS, *m*/*z* (%) 246 (100, M^+), 218 (41), 201 (79), 174 (73), 146 (39); IR (KBr) ν_{max}/cm^{-1} 1717 (s), 1472 (s), 1387 (m), 1313 (m), 1160 (m), 1128 (m), 753 (w).

3-(*p*-Bromobenzoyl)imidazo[2,1-*b*]benzothiazole 2b. Yield 84%; white crystals; mp 231 °C (Found: C, 53.94; H, 2.46; N, 7.74. $C_{16}H_9BrN_2OS$ requires C, 53.80; H, 2.54; N, 7.84%); ^{1}H NMR ($CDCl_3$) δ 7.40–7.84 (m, 7H, C*H*ar), 7.83 (s, 1H, NC*H*), 8.90–8.96 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 118.4, 123.9, 126.0, 126.8, 130.9 (2), 132.1 (2) (8*C*Har), 127.7, 129.7, 130.4, 133.7, 137.5 (4*C*ar, *C*CO), 147.2 (N*C*H), 155.8 (S*C*N), 182.3 (*C*O); MS, *m*/*z* (%) 358/356 (100/99, M^+), 277 (14), 201 (97), 157/155 (20/18), 146 (37); IR (KBr) ν_{max}/cm^{-1} 1636 (s), 1466 (s), 1417 (m), 1363 (m), 1192 (w), 896 (m), 752 (s).

3-(*p*-Chlorobenzoyl)imidazo[2,1-*b*]benzothiazole 2c. Yield 72%; white crystals; mp 227 °C (Found: C, 61.36; H, 2.94; N, 9.07. $C_{16}H_9ClN_2OS$ requires C, 61.44; H, 2.90; N, 8.96%); ^{1}H NMR ($CDCl_3$) δ 7.40–7.92 (m, 7H, C*H*ar), 7.83 (s, 1H, NC*H*), 8.89–8.95 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 118.2, 123.7, 125.8, 126.6, 128.9 (2), 130.7 (2) (8*C*Har), 129.6, 130.2, 133.5, 136.9, 139.0 (4*C*ar, *C*CO), 147.1 (N*C*H), 155.4 (S*C*N), 182.1 (*C*O); MS, *m*/*z* (%) 314/312 (38/100, M^+), 277 (9), 201 (73), 173 (13), 146 (31); IR (KBr) ν_{max}/cm^{-1} 1638 (s), 1466 (s), 1417 (m), 1366 (m), 1190 (w), 897 (m), 752 (s).

3-(*p*-Toluoyl)imidazo[2,1-*b*]benzothiazole 2d. Yield 77%; white crystals; mp 168 °C (Found: C, 69.64; H, 4.20; N, 9.76. $C_{17}H_{12}N_2OS$ requires C, 69.84; H, 4.14; N, 9.58%); ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 7.26–7.89 (m, 7H, C*H*ar), 7.84 (s, 1H, NC*H*), 8.89–8.94 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 21.7 (*C*H$_3$), 118.3, 123.7, 125.7, 126.5, 129.3 (2), 129.6 (2) (8*C*Har), 130.0, 130.3, 133.6, 135.9, 143.5 (4*C*ar, *C*CO), 146.7 (N*C*H), 154.9 (S*C*N), 183.3 (*C*O); MS, *m*/*z* (%) 292 (100, M^+), 146 (38), 119 (30), 91 (60); IR (KBr) ν_{max}/cm^{-1} 1634 (s), 1467 (s), 1417 (m), 1369 (m), 1176 (w), 899 (m), 746 (s).

3-*p*-Chlorobenzoyl-2-methylimidazo[2,1-*b*]benzothiazole 2e. Yield 68%; white crystals; mp 165 °C (Found: C, 62.37; H, 3.49; N, 8.68. $C_{17}H_{11}ClN_2OS$ requires C, 62.48; H, 3.39; N, 8.57%); ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, CH_3), 7.33–7.86 (m, 7H, C*H*ar), 8.25–8.31 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 17.1 (C*C*H$_3$), 117.4, 124.2, 125.7, 126.8, 129.6 (2), 131.3 (2) (8*C*Har), 126.7, 130.4, 134.0, 138.1, 139.9 (4*C*ar, *C*CO), 153.8, 154.3 (S*C*N, *C*CH$_3$), 185.3 (*C*O); MS, *m*/*z* (%) 328/326 (35/100, M^+), 291 (36), 290 (35), 215 (26), 187 (14), 146 (16); IR (KBr) ν_{max}/cm^{-1} 1626 (s), 1476 (s), 1367 (m), 1133 (s), 1089 (w), 935 (s), 748 (s).

4*H*-Pyrimido[2,1-*b*][benzothiazol-4-ones 3; general procedure. Method A

A solution of an amidine **1** (2 mmol) and an acid chloride (2.4 mmol) [methyl (chloroformyl)acetate for **3a**, ethyl (chloroformyl)acetate for **3b**,**c** or phenylacetyl chloride for **3d**] in dichloromethane (10 mL) was stirred for 4 h at room temperature. After cooling of the mixture to 0 °C, triethylamine (4.8 mmol) was added and stirring was continued for 16 h at room temperature. The solvent was evaporated off and the residue was purified by chromatography over silica, using as eluent dichloromethane–ethyl acetate (9 : 1). Compounds **3a**–**d** were crystallised from diethyl ether.

3-Methoxycarbonyl-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one 3a.[8,20] Yield 28%; white crystals; mp 192 °C (Found: C, 55.25; H, 3.17; N, 10.89. $C_{12}H_8N_2O_3S$ requires C, 55.38; H, 3.10; N, 10.76%); ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H, OCH_3), 7.51–7.77 (m, 3H, C*H*ar), 8.72 (s, 1H, NC*H*), 9.08–9.14 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 52.3 (O*C*H$_3$), 110.4 (*C*CO), 120.6, 121.9, 127.5, 127.6 (4*C*Har), 124.4, 136.1 (2*C*ar), 157.4 (S*C*N), 157.5 (N*C*H), 164.4, 166.3 (2*C*O); MS, *m*/*z* (%) 260 (57, M^+), 229 (100), 202 (16), 201 (13), 161 (35), 134 (19); IR (KBr) ν_{max}/cm^{-1} 1739 (s), 1669 (m), 1489 (s), 1304 (m), 1262 (w), 1125 (m), 796 (w), 755 (w).

3-Ethoxycarbonyl-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one 3b.[8,10,20] Yield 35%; white crystals; mp 142 °C (Found: C, 56.79; H, 3.55; N, 10.24. $C_{13}H_{10}N_2O_3S$ requires C, 56.93; H, 3.67; N, 10.21%); ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H, *J* 7.0 Hz, CH_2CH_3), 4.43 (q, 2H, *J* 7.0 Hz, OCH_2), 7.54–7.78 (m, 3H, C*H*ar), 8.75 (s, 1H, NC*H*), 9.17–9.23 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_2CH_3), 61.3 (OCH_2), 110.9 (*C*CO), 120.7, 122.0, 127.6, 127.7 (4*C*Har), 124.5, 136.2 (2*C*ar), 157.4 (S*C*N), 157.6 (N*C*H), 163.9, 166.3 (2*C*O); MS, *m*/*z* (%) 274 (68, M^+), 229 (100), 202 (97), 161 (45), 134 (26); IR (KBr) ν_{max}/cm^{-1} 1717 (s), 1688 (s), 1487 (s), 1356 (m), 1254 (m), 1126 (m), 791 (w), 768 (w).

3-Ethoxycarbonyl-2-methyl-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one 3c. Yield 44%; white crystals; mp 134 °C (Found: C, 58.45; H, 4.29; N, 9.61. $C_{14}H_{12}N_2O_3S$ requires C, 58.32; H, 4.19; N, 9.72%); ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H, *J* 7.2 Hz, CH_2CH_3), 2.50 (s, 3H, CH_3), 4.45 (q, 2H, *J* 7.2 Hz, OCH_2), 7.47–7.73 (m, 3H, C*H*ar), 9.05–9.11 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_2CH_3), 22.9 (C*C*H$_3$), 61.8 (O*C*H$_2$), 113.7 (*C*CO), 120.2, 122.0, 127.5, 127.6 (4*C*Har), 124.1, 136.0 (2*C*ar), 158.3 (S*C*N), 162.5, 162.7, 165.7 (*C*CH$_3$, 2*C*O); MS, *m*/*z* (%) 288 (78, M^+), 243 (100), 242 (57), 216 (79), 175 (53), 134 (28); IR (KBr) ν_{max}/cm^{-1} 1725 (s), 1669 (s), 1507 (s), 1230 (m), 1161 (m), 1039 (w), 776 (w).

3-Phenyl-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one 3d. Yield 35%; white crystals; mp 174 °C (Found: C, 69.17; H, 3.73; N, 10.19. $C_{16}H_{10}N_2OS$ requires C, 69.05; H, 3.62; N, 10.06%); ^{1}H NMR ($CDCl_3$) δ 7.42–7.72 (m, 8H, C*H*ar), 8.12 (s, 1H, NC*H*), 9.13–9.19 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 120.5, 122.0, 127.1, 127.4, 128.2, 128.6 (2), 128.9 (2) (9*C*Har), 121.9, 124.8, 133.3, 136.4 (4*C*ar), 149.9 (S*C*N), 160.5, 160.9 (N*C*H, *C*O); MS, *m*/*z* (%) 278 (100, M^+), 250 (52), 116 (23), 89 (17); IR (KBr) ν_{max}/cm^{-1} 1675 (s), 1507 (s), 1455 (m), 1356 (m), 1248 (m), 996 (w), 780 (m), 692 (m).

Method B

Ketene (**CAUTION**), produced by cracking of acetone,[19] was bubbled into a solution of an amidine **1** (4 mmol) in dichloromethane (150 mL) until complete consumption of the starting material, as monitored by TLC (approximately 1 h). After evaporation of the mixture, the residue was dissolved in a small amount of dichloromethane and subjected to flash chromatography [dichloromethane–ethyl acetate (9 : 1 for **3e** and 1 : 1 for **3f**)]. Compounds **3e**,**f** were crystallised from diethyl ether.

4*H*-Pyrimido[2,1-*b*]benzothiazol-4-one 3e.[10] Yield 51%; white crystals; mp 173 °C (Found: C, 59.52; H, 3.13; N, 13.71. $C_{10}H_6N_2OS$ requires C, 59.39; H, 2.99; N, 13.85%); ^{1}H NMR ($CDCl_3$) δ 6.42 (d, 1H, *J* 6.5 Hz, C*H*CO), 7.46–7.73 (m, 3H, C*H*ar), 7.95 (d, 1H, *J* 6.5 Hz, NC*H*), 9.08–9.13 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 109.4 (*C*HCO), 120.2, 121.7, 126.9, 127.2 (4*C*Har), 124.2, 136.0 (2*C*ar), 151.8 (N*C*H), 161.0 (*C*O), 162.3 (S*C*N); MS, *m*/*z* (%) 202 (100, M^+), 174 (70), 146 (10), 134 (10); IR (KBr) ν_{max}/cm^{-1} 1681 (s), 1490 (s), 1450 (m), 1246 (m), 993 (w), 814 (w), 760 (w).

2-Methyl-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one 3f. Yield 87%; white crystals; mp 205 °C (Found: C, 61.22; H, 3.84; N, 12.74. $C_{11}H_8N_2OS$ requires C, 61.09; H, 3.73; N, 12.95%); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H, CH_3), 6.26 (s, 1H, C*H*CO), 7.26–7.71 (m, 3H, C*H*ar), 9.05–9.10 (m, 1H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 23.8 (C*C*H$_3$), 107.2 (*C*HCO), 120.0, 121.7, 126.9, 127.0 (4*C*Har), 124.1, 136.0 (2*C*ar), 161.1, 161.4, 162.9 (*C*O, S*C*N, *C*CH$_3$); MS, *m*/*z* (%) 216 (100, M^+), 188 (64), 187 (56), 149 (13); IR (KBr) ν_{max}/cm^{-1} 1675 (s), 1505 (s), 1396 (m), 1240 (m), 1163 (w), 980 (w), 768 (w).

4*H*-Pyrimido[2,1-*b*]benzothiazoles 4; general procedure

A mixture of an amidine **1** (4 mmol) and a dienophile [acrolein (10 mmol) in chloroform (10 mL) for **4a** or methyl vinyl ketone (5 mL) for **4b**,**c**] was stirred for 20 h at room temperature (**4a**) or at reflux (**4b**,**c**) for 3 days. The resulting solution was concentrated under reduced pressure and the residue was purified by chromatography over silica, using dichloromethane–ethyl acetate (1 : 1 for **4a** and 7 : 3 for **4b**,**c**). Compounds **4** were crystallised from diethyl ether.

3-Formyl-4*H*-pyrimido[2,1-*b*]benzothiazole 4a. Yield 43%; yellow crystals; mp 185 °C (Found: C, 61.28; H, 3.94; N, 12.79. $C_{11}H_8N_2OS$ requires C, 61.09; H, 3.73; N, 12.95%); ^{1}H NMR ($CDCl_3$) δ 4.86 (s, 2H, CH_2), 7.14–7.61 (m, 4H, C*H*ar), 7.38 (s, 1H, NC*H*), 9.46 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$) δ 43.0 (*C*H$_2$), 111.2, 122.3, 125.0, 127.6 (4 *C*Har), 113.5 (*C*CO), 123.8, 135.1 (2*C*ar), 154.9 (N*C*H), 167.9 (S*C*N), 188.7 (*C*HO); MS, *m*/*z* (%) 216 (100, M$^+$), 215 (86), 187 (43), 160 (11), 134 (19); IR (KBr) ν_{max}/cm^{-1} 1638 (s), 1490 (s), 1476 (s), 1363 (m), 1264 (m), 1166 (m), 749 (m).

3-Acetyl-4*H*-pyrimido[2,1-*b*]benzothiazole 4b. Yield 52%; yellow crystals; mp 222 °C (Found: C, 62.68; H, 4.47; N, 12.24. $C_{12}H_{10}N_2OS$ requires C, 62.59; H, 4.38; N, 12.16%); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H, COCH_3), 4.81 (s, 2H, CH_2), 7.13–7.53 (m, 4H, C*H*ar), 7.57 (s, 1H, NC*H*); ^{13}C NMR ($CDCl_3$) δ 24.5 (CO*C*H$_3$), 43.6 (*C*H$_2$), 110.8, 122.0, 124.4, 127.2 (4*C*Har), 123.7, 139.2 (2*C*ar), 111.9 (*C*CO), 147.5 (N*C*H), 166.3 (S*C*N), 195.1 (*C*O); MS, *m*/*z* (%) 230 (94, M$^+$), 229 (100), 215 (86), 187 (43), 160 (11), 134 (19); IR (KBr) ν_{max}/cm^{-1} 1628 (m), 1612 (m), 1506 (s), 1365 (m), 1283 (m), 1168 (m), 735 (m).

3-Acetyl-2-methyl-4*H*-pyrimido[2,1-*b*]benzothiazole 4c. Yield 48%; yellow crystals; mp 197 °C (Found: C, 63.80; H, 4.85; N, 11.35. $C_{13}H_{12}N_2OS$ requires C, 63.91; H, 4.95; N, 11.47%); ^{1}H NMR ($CDCl_3$) δ 2.41, 2.47 (2s, 6H, COCH_3, CH_3), 4.75 (s, 2H, CH_2), 7.11–7.54 (m, 4H, C*H*ar); ^{13}C NMR ($CDCl_3$) δ 25.0 (CO*C*H$_3$), 31.6 (C*C*H$_3$), 44.6 (*C*H$_2$), 108.5 (*C*CO), 110.9, 122.0, 124.2, 127.1 (4*C*Har), 123.6, 139.1 (2*C*ar), 155.5 (*C*CH$_3$), 164.3 (S*C*N), 195.6 (*C*O); MS, *m*/*z* (%) 244 (100, M$^+$), 243 (78), 229 (69), 201 (34), 175 (22), 134 (24); IR (KBr) ν_{max}/cm^{-1} 1616 (m), 1512 (s), 1363 (m), 1272 (m), 1209 (m), 955 (w), 750 (m).

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