Synthesis of Ethyl 2-Arylaminoimidazo[2,1-b]benzothiazole-3-carboxylates

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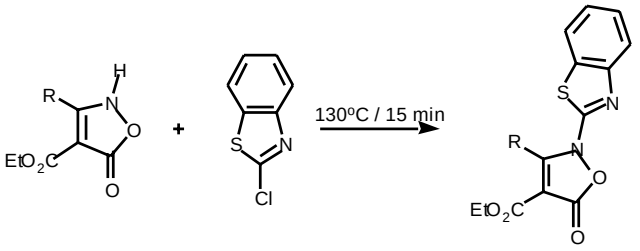
3-Arylamino-4-ethoxycarbonylisoxazol-5(2H)-ones, substituted on nitrogen with a benzothiazole group, reacts with triethylamine in ethanol under reflux conditions to provide a convenient synthesis of ethyl 2-arylaminoimidazo[2,1-b]benzothiazole-3-carboxylates.

Keywords: Isoxazolones; 2-Chlorobenzothiazole; Imidazobenzothiazoles; Base induced rearrangement; Triethylamine.

INTRODUCTION

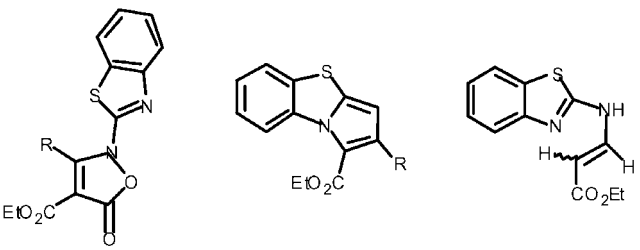
The synthesis of isoxazol-5(2H)-one with benzothiazole substituted on nitrogen **1a** has been reported by Prager and co-workers[1] as shown in Scheme I.

Scheme I



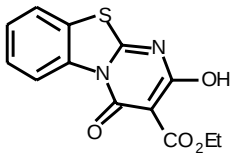
1a R=H

It has been reported[2] that the 2-benzothiazol-2-yl isoxazolones **1a** and **2b** gave the corresponding imidazobenzothiazoles **2a** and **2b** respectively on photolysis in ethyl acetate/trifluoroacetic acid, and the acrylate **3** was obtained from the photolysis of **1a** in methanol.



1b R=Me **2a R=H** **2b R= Me** **3**

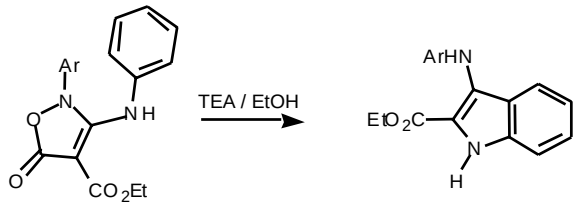
Base-catalysed rearrangement of isoxazolinyl heterocycle **1a** using a solution of sublimed potassium t-butoxide in dry tetrahydrofuran at 40 °C gave ethyl 2-hydroxy-4-oxo-4H-pyrimido[2,1-b]benzothiazole-3-carboxylate **4**.[3]



4

We have recently reported[4] that the reaction of certain 2-aryl-3-arylaminoisoxazolones **5** with triethylamine leads to the formation of indoles **6** and carbon dioxide, an outcome that is formally the same as that achieved by photolysis or pyrolysis[5] (Scheme II).

Scheme II



5 **6**

We have also reported[6] that 3-(4-substituted phenyl)-aminoisoxazol-5(2H)-ones, substituted on nitrogen with a nitropyridine group, react with triethylamine to give imidazo[1,2-a]pyridines and indoles. With 4-bromophenyl and

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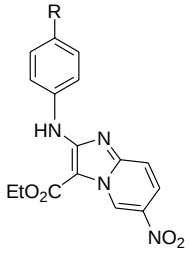
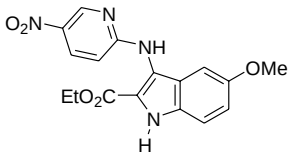
4-methylphenyl group substituents only imidazopyridines **7a-b** are formed, but the 4-methoxyphenyl derivative gave a 3:1 mixture of corresponding imidazo[2,1-a]pyridine **7c** and 2-pyridylaminoindole **8**, respectively.



7a R=Br
7b R=Me
7c R=OMe



8

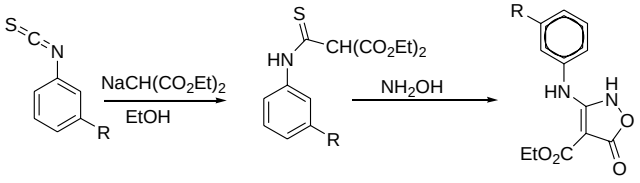
Here we describe the synthesis of new N-substituted derivatives of *m*-substituted 3-(phenyl)aminoisoxazol-5(2H)-ones **11** with a benzothiazole group substituted on N-2 **12**, and their rearrangement in the presence of triethylamine to produce ethyl 2-arylaminoimidazo[2,1-b]benzothiazole-3-carboxylate **13**, as shown in Scheme IV.

RESULTS AND DISCUSSION

The required isoxazolones **12** were synthesized by reaction of 2-chlorobenzothiazole with 2H-isoxazolones **11**, which in turn were made by a modification of the procedure of Worrall.[7,8] Thus, the reaction of the sodium salt of diethyl malonate in ethanol with arylisothiocyanates **9** gave the thiocarbamates **10** in high yield, and these were converted to the corresponding isoxazolone **11** by reaction with 2 equiv of hydroxylamine (Scheme III).

N-arylation of **11** with 2-chlorobenzothiazole in chloroform or toluene under reflux conditions gave the corresponding N-substituted isoxazolones **12** in fair yield.

Scheme III



9 **10** **11**

R=H,Br,Me

The rearrangement of **12**, as shown in Scheme IV, proceeded in 45-62% yield in refluxing ethanol for 24 h in the presence of triethylamine. The reaction pathway leading to the imidazobenzothiazole is consistent with our earlier suggestion for the formation of imidazopyridines, which is consistent with the electronic requirements of the reaction, as shown in Scheme V, or with the alternative pathway suggested by Prager and co-workers.[9]

CONCLUSION

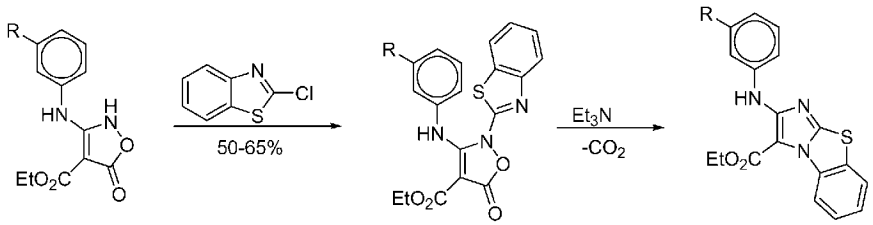
The base catalysed rearrangements of 3-arylaminoisoxazolones substituted on nitrogen with a benzothiazole group appears to be generally applicable to the synthesis of imidazobenzothiazoles, which are clearly suitable synthetic intermediates for a series of new planar polycyclic heterocycles that could be expected to intercalate with DNA.[10,11]

EXPERIMENTAL

General procedures

Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perrin and Amareg.[12] ^{1}H (400 MHz) and ^{13}C (75 MHz) NMR measure-

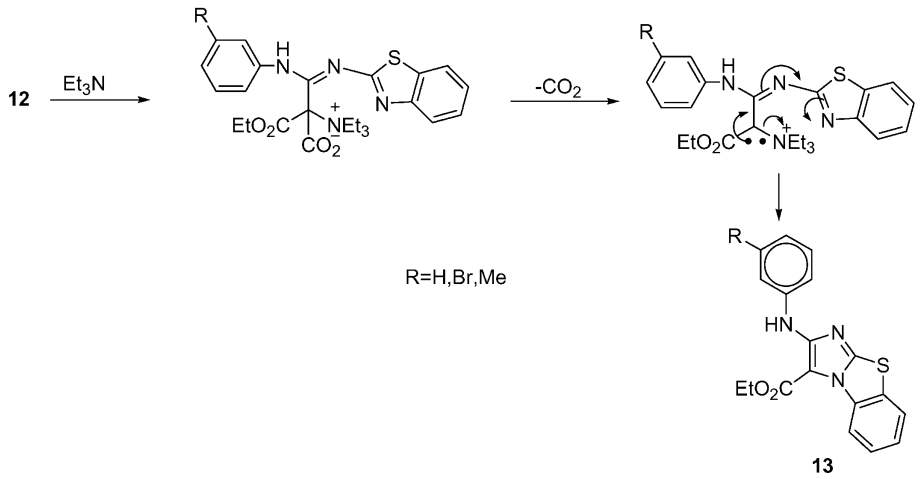
Scheme IV



11 **12** **13**

R=H,*m*-Me,*m*-Br

Scheme V



ments were recorded on a Brucker 400 spectrometer in deuteriochloroform with tetramethylsilane as internal standard, unless otherwise stated. Infrared spectra were recorded on a Thermonicolet (Nexus670) FT-infrared spectrometer, using sodium chloride cells, measured as Nujol mulls or films. Mass spectra were recorded on a Varian Matt 311 spectrometer and relative abundance of fragments are quoted in parentheses after the *m/z* values. Melting points were determined on a Philip Harris C4954718 apparatus and are uncorrected. Microanalyses were performed on a Carlo-Erba Analyzer 1104 at the University of Giessen, Germany.

Diethyl (3-bromophenyl)thiocarbamoylmalonate (10, R=Br)

In a 100 mL round-bottomed flask, absolute ethanol (50 mL) was reacted with sodium (2.9 g, 0.126 mol) and after cooling to room temperature diethyl malonate (20 g, 18.95 mL, 0.126 mol) was added. The reaction mixture was stirred at room temperature for 15 min; 3-bromophenyl isothiocyanate (26.96 g, 0.126 mol) was added and the stirring was continued for a further 6 h, during which a yellowish white precipitate of sodium diethyl (3-bromophenyl)thiocarbamoylmalonate salt was formed. The salt was collected and washed with light petroleum ether (b.p. 30-60 ºC) (3 × 50 mL) to give yellow crystals m.p. 157-158 ºC (34.22 g, 70%). The pure salt was dissolved in water (40-50 mL) and neutralized with dropwise addition of HCl (10%) to maintain the pH at 7. The product was extracted with chloroform and the extract was washed with water (3 × 50 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave (10, R=Br) as a yellow oil (25.5 g, 68%). ^{1}H NMR δ 1.292 (t, 3H, *J* = 7.1 Hz), 1.295 (t, 3H, *J* = 7.1 Hz), 2.70 (q, 2H, *J* = 7.1 Hz), 4.272 (q, 2H, *J* = 7.1 Hz), 5.061 (s, 1H), 7.224 (t, 1H, *J* = 8.06 Hz), 7.361 (bd, 1H, *J* = 7.95 Hz), 8.668 (bd, 1H, *J* = 8.06 Hz), 8.057 (t, 1H, *J* = 1.9 Hz), 10.833 (bs, NH). FT-IR υ_{max} 3296, 1747, 1590, 1541, 1476, 1394, 1168, 1023, 680, 784 cm^{-1}.

Diethyl (3-methylphenyl)thiocarbamoylmalonate (10, R=Me)

This compound was prepared as described above, using 3-methylphenyl isothiocyanate (1.3 g, 8.7 mmol) and stirring for a further 1 h after addition of 3-methylphenyl isothiocyanate to the diethyl malonate salt to give diethyl (3-methylphenyl)thiocarbamoyl malonate (1.924, 71.25%) as pale yellow solid, m.p. 53-54 ºC. ^{1}H NMR δ 1.33 (t, 6H, *J* = 7.2 Hz), 2.38 (s, 3H), 4.29 (q, 2H, *J* = 7.2 Hz), 4.30 (q, 2H, *J* = 7.2 Hz), 5.09 (s, 1H), 7.09 (t, 1H, *J* = 7.8 Hz), 7.55 (bs, 1H), 7.61 (bd, 1H, *J* = 8 Hz), 10.75 (s, exchanged by D_2O addition, 1H, NH). FT-IR υ_{max} 3252, 1752, 1731, 1592, 1556, 1422, 1296, 1148, 1027, 858, 798, 717 cm^{-1}.

Ethyl 3-(3-bromophenyl)amino-5-oxo-2,5-dihydroisoxazol-4-carboxylate (11, R=Br)

To a solution of hydroxylamine hydrochloride (2 g, 28.8 mmol) in water (8 mL), potassium bicarbonate (2.8 g, 28 mmol) was added slowly. Ethanol (32 mL) was added and the resulting potassium chloride was filtered off.

Diethyl (3-bromophenyl) thiocarbamoylmalonate (3.4 g, 9 mmol) was added to the filtrate and the mixture refluxed for 24 h. The reaction mixture was acidified with dilute hydrochloric acid and the white precipitate was collected by vacuum filtration. The white solid was recrystallized from

ethanol to give the desired product (2.51 g, 85%) as colourless crystals m.p. 100-102 ºC. Anal. Calc for $C_{12}H_{11}BrN_2O_4.H_2S$: C, 41.73; H, 3.19; N, 8.11%; found: C, 41.87; H, 3.22; N, 8.18%. ^{1}H NMR (D_6-DMSO+$CDCl_3$) δ 1.38 (t, 3H, *J* = 7.1 Hz), 4.37 (q, 2H, *J* = 7.1 Hz), 6.15 (bs, 1H, NH), 7.23 (dt, 1H, J_1 = 8.2 Hz, J_2 = 1.8 Hz), 7.28 (t, 1H, *J* = 7.8 Hz), 7.33 (dt, 1H, J_1 = 7.8 Hz, J_2 = 1.6 Hz), 7.51 (t, 1H, *J* = 1.8 Hz), 9.38 (bs, 1H, NH),^{13}C NMR(D_6-DMSO+$CDCl_3$) δ 14.49, 60.26, 75.21, 119.80, 122.92, 123.82, 128.24, 130.95, 137.58, 162.85, 165.37, 166.72. FT-IR υ_{max} 3512, 3297, 1710, 1701, 1590, 1478, 1413, 1323, 1203, 1116, 1011, 794, 734 cm^{-1}; MS *m/z* (%) 328 (M^+, 66%), 326 (M^+, 68%), 282 (81), 280 (70), 201 (26), 197 (16), 171 (26), 157 (36), 91 (31), 90 (32), 76 (21), 63 (24), 45 (19), 44 (100), 40 (47), 36 (23) and HRMS *m/z* 325.99021 ($C_{12}H_{11}BrN_2O_4$ requires 325.99022).

Ethyl 3-(3-methylphenyl)amino-5-oxo-2,5-dihydroiso-xazol-4-carboxylate (11, R=Me)

The compound was prepared as described above using diethyl (3-methylphenyl)thiocarbamoylmalonate (1.1 g, 3.5 mmol) and refluxing for 24 h to give the desired product as colourless crystals (0.7 g,75%), m.p. 109-111 ºC. ^{1}H NMR (D_6-DMSO+$CDCl_3$) δ 1.38 (t, 3H, *J* = 7.1 Hz), 2.37 (s, 3H), 4.35 (q, 2H, *J* = 7.1 Hz), 7.02 (bd, 1H, *J* = 7.6 Hz), 7.07 (bd, 1H, *J* = 7.9 Hz), 7.1 (bs, 1H), 7.27 (t, 1H, *J* = 7.8 Hz), 9.31 (s, 1H, NH). ^{13}C NMR (D_6-DMSO+$CDCl_3$) δ 14.53, 21.34, 60.17, 74.82, 118.19, 121.82, 126.42, 129.47, 135.90, 139.75, 163.35, 165.64, 166.66. FT-IR υ_{max} 3519, 3316, 1710, 1678, 1578, 1324, 1226, 1169, 1113, 1000, 795, 725 cm^{-1}.

Ethyl 2-(benzothiazol-2-yl)-3-(3-bromophenyl)amino-5-oxo-2,5-dihydro-4-carboxylate (12, R=Br)

Ethyl 3-(3-bromophenyl)amino-5-oxo-2,5-dihydroiso-xazol-4-carboxylate (100 mg, 0.3 mmol) and 2-chlorobenzo-thiazole (51 mg, 0.3 mmol) were refluxed in chloroform or toluene (5 mL) for 48 h. The solvent was removed under re-duced pressure. On addition of n-hexane (10 mL) to the resi-due (colourless oil) a white precipitate was formed. The pre-cipitate was filtered and recrystallized from ethanol to give ethyl 2-(benzothiazol-2-yl)-3-(3-bromophenyl)amino-5-oxo-2,5-dihydro-4-carboxylate as white prisms (84.4 mg, 60%) m.p. 153-155 ºC. Anal. Calc for $C_{19}H_{14}BrN_3O_4S$: C, 49.56, H, 3.04, N, 9.13%; found: C, 49.56; H, 2.71; N, 9.02%. ^{1}H NMR δ 1.32 (t, 3H, *J* = 7.1 Hz), 4.30 (q, 2H, *J* = 7.1 Hz), 7.08 (t, 1H, *J* = 7.9 Hz), 7.14 (dt, 1H, J_1 = 8.65 Hz, J_2 = 1.59 Hz), 7.20 (dt, 1H, J_1 = 7.79 Hz, J_2 = 1.55 Hz), 7.38 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.34 Hz), 7.39 (t, 1H, *J* = 1.92 Hz), 7.44 (td, 1H, J_1 = 7.64 Hz, J_2 = 1.29 Hz), 7.69 (dd, 1H, J_1 = 8.15 Hz, J_2 = 0.96 Hz), 7.79 (dt, 1H, J_1 = 7.8 Hz, J_2 = 0.97 Hz), 10.17 (s, 1H, NH). ^{13}C NMR δ 14.31, 61.17, 79.20, 121.03, 121.63, 122.63, 122.99, 125.74, 126.04, 127.10, 129.51, 130.38, 133.35, 138.02, 149.10, 157.07, 161.23, 163.02, 163.81. FT-IR υ_{max} 3206, 1775, 1712, 1572, 1475, 1441, 1381, 1227, 1178, 1051, 956, 766 cm^{-1}; MS *m/z* (%) 461 (M^+, 12%), 459 (M^+, 11%), 417 (82), 415 (71), 371 (48), 369 (40), 334 (25), 294 (28), 291 (27), 290 (100), 262 (30), 224 (27), 177 (33), 161 (34), 150 (40), 135 (26), 134 (33), 108 (29), 44 (65) and HRMS *m/z* 458.98883 ($C_{19}H_{14}BrN_3O_4S$ requires 458.98884).

Ethyl 2-(benzothiazol-2-yl)-3-(3-methylphenyl)amino-5-oxo-2,5-dihydro-4-carboxylate (12, R=Me)

This compound was prepared as described above, using the corresponding isoxazolone (11, R=Me) (70 mg, 0.27 mmol) and 2-chlorobenzothiazole (45.8 mg, 0.27 mmol) to give the desired product as white prisms (50 mg, 50%) after recrystalization from ethanol, m.p. 159-161 ºC. Anal. Calc for $C_{20}H_{17}N_3O_4S$: C, 60.74, H, 4.33, N, 10.62%; found: C, 60.49; H, 4.14; N, 10.93%. ^{1}H NMR δ 1.3 (t, 3H, *J* = 7.1 Hz), 2.19 (s, 3H), 4.28 (q, 2H, *J* = 7.1 Hz), 6.85 (bd, 1H, *J* = 7.47 Hz), 6.98 (bd, 1H, *J* = 8.1 Hz), 7.00 (bs, 1H), 7.08 (t, 1H, *J* = 7.6 Hz), 7.36 (td, 1H, J_1 = 8.1 Hz, J_2 = 0.94 Hz), 7.42 (td, 1H, J_1 = 7.6 Hz, J_2 = 0.85 Hz), 7.69 (bd, 1H, *J* = 8 Hz), 7.77 (dd, 1H, J_1 = 7.9 Hz, J_2 = 0.65 Hz), 10.07 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR δ 14.31, 21.11, 60.95, 78.64, 119.63, 121.57, 123.09, 123.23, 125.97, 126.94, 127.33, 129.01, 133.67, 136.44, 139.30, 149.18, 157.33, 161.87, 163.49. FT-IR υ_{max} 3204, 1774, 1705, 1576, 1514, 1443, 1382,1232, 958, 767 cm^{-1}.

Ethyl 2-(benzothiazol-2-yl)-3-(phenyl)amino-5-oxo-2,5-dihydro-4-carboxylate (12, R=H)

This compound was prepared as described above, using the corresponding isoxazolone (11, R=H)[7] (100 mg, 0.4 mmol) and 2-chlorobenzothiazole (67.85 mg, 0.4 mmol) to give the desired product as white prisms (100 mg, 65%) after recrystalization from ethanol, m.p. 141-142 ºC. Anal. Calc for $C_{19}H_{15}N_3O_4S$: C, 59.83, H, 3.96, N, 11.02%; found: C, 60.00; H, 3.72; N, 11.05%. ^{1}H NMR δ 1.29 (t, 3H, *J* = 7.1 Hz), 4.27 (q, 2H, *J* = 7.1 Hz), 7.04-7.08 (m, 1H), 7.18-7.23 (m, 4H), 7.35 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 7.40 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 7.65 (dd, 1H, J_1 = 7.9 Hz, J_2 = 0.88 Hz), 7.76 (dd, 1H, J_1 = 7.75 Hz, J_2 = 1 Hz), 10.15 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR δ 14.30, 60.97, 78.72,

121.56, 122.48, 123.01, 125.92, 126.54, 126.93, 129.20, 133.47, 136.72, 149.12, 157.23, 161.68, 163.35, 163.99. FT-IR υ_{max} 3190, 1782, 1686, 1569, 1497, 1456, 1442, 1378, 1282, 1224, 1177, 950, 765 cm^{-1}.

Ethyl 2-(3-bromophenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate (13, R=Br)

The isoxazolone (12, R=Br) (100 mg, 0.217 mmol) and triethylamine (0.13 mL) were refluxed in ethanol (10 mL) for 24 h. The reaction mixture was left to cool to rt, and the resulting precipitate was collected to give ethyl 2-(3-bromophenyl)amino imidazo[2,1-b]benzothiazole-3-carboxylate (13, R=Br) as yellow needles (50 mg, 55%), m.p. 158-160 ºC. Anal. Calc for $C_{18}H_{14}BrN_3O_2S$: C, 51.92; H, 3.36; N, 10.06%; found: C, 51.87; H, 2.99; N, 10.09%. ^{1}H NMR δ 1.54 (t, 3H, *J* = 7.1 Hz), 4.52 (q, 2H, *J* = 7.1 Hz), 7.11 (ddd, 1H, J_1 = 7.88 Hz, J_2 = 1.7 Hz, J_3 = 1 Hz), 7.18 (t, 1H, *J* = 7.95 Hz), 7.34 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.14 Hz), 7.46 (td, 1H, J_1 = 7.9 Hz, J_2 = 1.3 Hz), 7.50 (ddd, 1H, J_1 = 8 Hz, J_2 = 2.1 Hz, J_3 = 1 Hz), 7.69 (dd, 1H, J_1 = 7.95 Hz, J_2 = 0.88 Hz), 7.95 (t, 1H, *J* = 7.95 Hz), 8.62 (bs, 1H, NH), 8.84 (bd, 1H, *J* = 8.35 Hz). ^{13}C NMR δ 14.71, 60.72, 116.69, 116.89, 120.83, 122.89, 123.62, 124.59, 124.63, 126.48, 128.79, 130.33, 134.34, 141.52, 141.60, 151.77, 160.28. FT-IR υ_{max} 3296, 1641, 1607, 1593, 1556, 1457, 1412, 1375, 1292, 1174, 1085, 1062, 753 cm^{-1}; MS *m/z* (%) 417 (M^+, 70%), 415 (M^+, 62%), 317 (11), 369 (9), 290 (100), 289 (23), 263 (15), 262 (21), 161 (15), 160 (12), 134 (13), 130 (12), 102 (10), 40 (18) and HRMS *m/z* 414.99900 ($C_{18}H_{14}BrN_3O_2S$ requires 414.99901).

Ethyl 2-(3-methylphenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate (13, R=Me)

The isoxazolone (12, R=Me) (100 mg, 0.253 mmol) and triethylamine (0.13 mL) were refluxed in ethanol (10 mL) for 24 h.The reaction mixture was left to cool to rt, and the resulting precipitate was collected to give ethyl 2-(3-methylphenyl)aminoimidazo[2,1-b]benzothiazole-3-carbox ylate (13, R=Me) as yellow needles (0.04 g, 45%), m.p. 123-125 ºC. ^{1}H NMR δ 1.53 (t, 3H, *J* = 7.1 Hz), 2.38 (s, 3H), 4.51 (q, 2H, *J* = 7.1 Hz), 6.83 (bd, 1H, *J* = 7.6 Hz), 7.23 (t, 1H, *J* = 7.6 Hz), 7.33 (bt, 1H, *J* = 7.5 Hz), 7.42-7.48 (m, 3H), 7.67 (bd, 1H, *J* = 7.8 Hz), 8.52 (bs, exchanged by D_2O addition, 1H, NH), 8.86 (bd, 1H, *J* = 7.3 Hz). ^{13}C NMR δ 14.73, 21.67, 60.48, 115.54, 116.84, 119.01, 123.53, 123.60, 123.72, 124.36, 126.40, 126.52, 128.98, 134.51, 138.98, 140.23, 152.06, 160.39. FT-IR υ_{max} 3308, 1644, 1613, 1577, 1462, 1417, 1374, 1281, 1167, 1156, 1087, 752 cm^{-1}.

Ethyl 2-(phenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate (13, R=H)

The isoxazolone (12, R=H) (100 mg, 0.2624 mmol) and triethylamine (0.13 mL) were refluxed in ethanol (10 mL) for 24 h. The reaction mixture was left to cool to rt, and the resulting precipitate was collected to give ethyl 2-(3-methylphenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate (13, R=H) as cream crystals (55 mg, 62%), m.p. 157-159 ºC. Anal. Calc for $C_{18}H_{15}N_3O_2S$: C, 64.08; H, 4.48; N, 12.45%; found: C, 63.79; H, 4.48; N, 12.50%. ^{1}H NMR δ 1.53 (t, 3H, *J* = 7.1 Hz), 4.50 (q, 2H, *J* = 7.1 Hz,), 7.00 (bt, 1H, *J* = 7.4 Hz), 7.25-7.369 (m, 2H), 7.31 (td, 1H, J_1 = 7.3 Hz, J_2 = 1 Hz), 7.65 (dd, 1H, J_1 = 7.2 Hz, J_2 = 0.75 Hz), 7.63 (bd, 2H, *J* = 7.7 Hz), 7.43 (td, 1H, J_1 = 7.3 Hz, J_2 = 1.2 Hz), 8.56 (bs, exchanged by D_2O addition 1H, NH), 8.83 (bd, 1H, *J* = 6.6 Hz). ^{13}C NMR δ 14.69, 60.50, 116.81, 118.32, 121.85, 123.50, 124.37, 126.38, 128.67, 129.11, 134.46, 140.32, 151.99, 160.34. FT-IR υ_{max} 3309, 1644, 1601, 1569, 1494, 1463, 1422, 1370, 1273, 1171, 1087, 1065, 742 cm^1.

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