SHORT PAPER

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Carbanion induced synthesis of pyrido[2,1-b] benzothiazoles through ring transformation reactions†

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3-Aryl-1-[(*E*)-cyanomethylidene]-1*H*-pyrido[2,1-*b*]benzothiazole-4-carbonitriles (**3**) and the polysubstituted pyrido[2,1-b]benzothiazoles (**8, 9**) have been prepared from the reaction of 2-benzothiazoleacetonitrile (**2**) with 6-aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitrile (**1**) and the ketenedithioacetals (**6 ,7**), respectively.

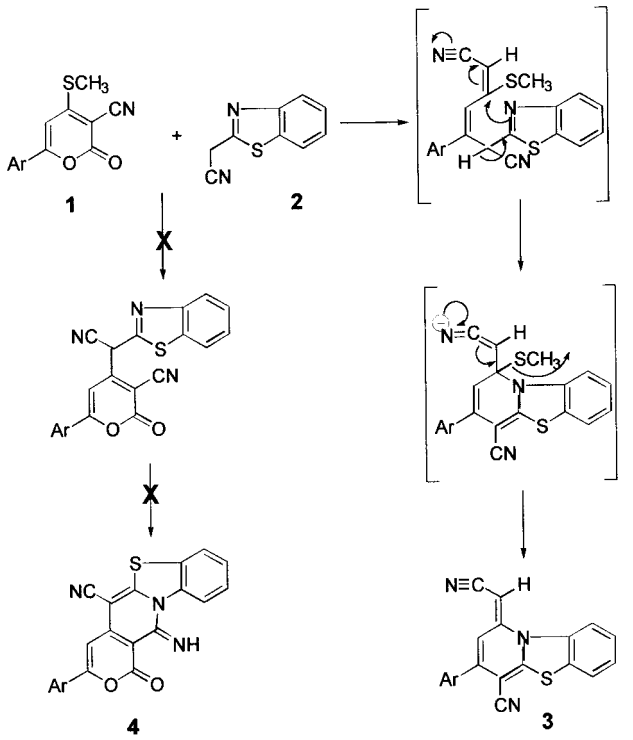
Keywords: 2-pyrones, benzothiazoles, fused pyridines, ketene dithioacetals

Benzothiazoles are isosteres of the pharmacologically important benzimidazoles, differing in the substitution of a nitrogen atom by sulfur. They frequently display novel biodynamic properties. Fusion of a benzothiazole ring with pyridine results in a class of bridgehead N,S heterocycles, the pyrido[2,1-*b*]benzothiazoles, structurally analogous to the naturally occurring alkaloid harmaline. Suitably functionalised compounds of this ring system have been reported to display significant antiviral[1] and antiinflammatory activity.[2] The therapeutic importance of this nucleus inspired us to develop a highly efficient, simple and elegant route for the synthesis of this class of compound.

Numerous synthetic approaches are described in the literature but highly useful and important are those through the Diels–Alder reaction of ethyl (*E*)-3-(1,3-benzothiazol-2-yl)-3-cyanopropenoate as a 1-aza-1,3-butadiene with ethoxyethylene,[3,4] and the Michael addition of cyanoacetamide or 2-benzothiazoleacetonitrile (**2**) to arylidene benzothiazole, acetylenic esters or ketones separately followed by cyclisation.[5,6] They are also obtained by cyclocondensation of 2-benzothiazoleacetamide with aldehyde and malononitrile.[7] A cyclocondensation of 2-(methylamino)benzothiazole with malonate followed by cycloaddition to symmetrical ethynes and subsequent elimination of isocyanate led to the formation of pyrido[2,1-*b*]benzothiazole.[8] It has also been obtained by 1,4-dipolar cycloaddition reactions of pyridiniumolates with ynamines.[9]

Our approach to pyrido[2,1-*b*]benzothiazoles[10] here is a single-step carbanion-induced ring transformation reaction involving 6-aryl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile[11] (**1**) and 2-benzothiazoleacetonitrile (**2**). The electronic topography of lactone (**1**) shows the presence of three electrophilic centres C_2, C_4 and C_6 of which the last is the most susceptible to nucleophilic attack, followed by C_4 and C_2.

The reaction of **1** with 2-benzthiazoleacetonitrile (**2**) in the presence of alkali in dry DMF yielded regioselectively the pyrido[2,1-*b*]benzothiazole (**3**) in high yield. The possible product **4**, obtainable by attack of carbanion at C_4 followed by cyclisation involving the nitrile function, was not observed, presumably due to poor susceptibility of C_4 towards the nucleophile. The formation of **3** is initiated by attack of carbanion generated *in situ* from **2** at C_6 in **1** with ring opening followed by decarboxylation and cyclisation with concomitant elimination of methyl mercaptan. A plausible mechanism is shown in Scheme 1.



3	Ar
a)	3-ClC$_6$H$_4$
b)	4-ClC$_6$H$_4$
c)	4-FC$_6$H$_4$
d)	4-MeOC$_6$H$_4$
e)	2-Thienyl
f)	2-Furyl

Scheme 1

The IR spectrum of **3b** showed characteristic CN stretching frequency at ν 2191 cm^{-1}. The ^{1}H NMR spectrum showed two singlets due to cyanomethylene (δ 5.65) and 2-H protons (δ 6.76). In addition, a multiplet at δ 7.58–7.67 for 6 protons was assigned for 7-H, 8-H and four aromatic protons. The two multiplets at δ 8.15–8.34 were attributed to 9-H and 6-H protons respectively. Extensive efforts to prove further the assigned structure by X-ray diffraction failed because of the non-diffractive nature of the crystals. The stereochemistry of the exomethylene unit was assigned by ^{1}H–^{1}H NOE experiments. Irradiation of cyanomethylene (δ 5.65) and 2-H (δ

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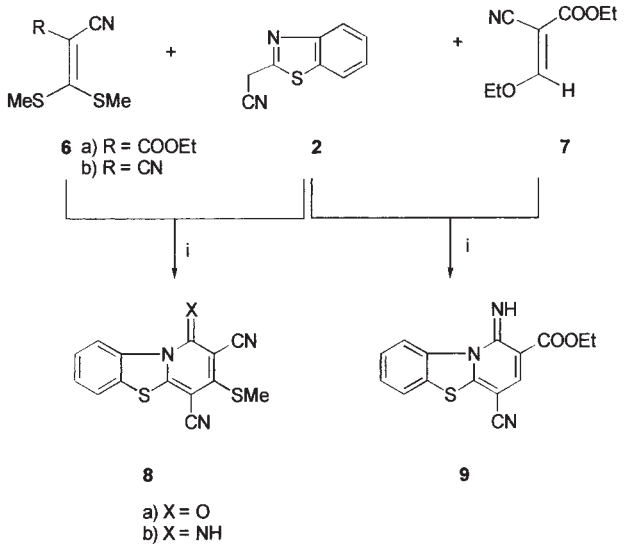
6.76) peaks separately in **3b** did not enhance the signal intensity either of their counterpart or of the 9-H proton, strongly indicating the *E* configuration of the isolated compound. Further, a reaction of 2-benzthiazoleacetonitrile (**2**) with ketene dithioacetals (**6a,b**) separately led to the highly functionalised pyrido[2,1-*b*]benzothiazoles (**8a,b**) while compound **9** was obtained from the reaction of **2** and ethyl ethoxymethylenecyanoacetate (**7**) (Scheme 2). In this reaction the initial step is the Michael addition of carbanion to the ketene (**6a,b**) followed by a condensation-cyclisation reaction with elimination of methyl mercaptan.



Scheme 2

All the synthesised compounds were characterised spectroscopically and their C, H and N analyses were in agreement with the proposed constitutions.

Experimental

M.p.s were determined in open capillary with a Büchi 530 melting point apparatus. ^{1}HNMR spectra were recorded on a Bruker WM (400 MHz) spectrometer using TMS as reference. IR spectra were obtained in KBr disc on a Perkin-Elmer AC-1 spectrophotometer. EI mass spectra were obtained at 70eV using a Jeol JMS-D 300 spectrometer. Elemental analyses (C, H, N) were carried out on a Carlo Erba 1108 elemental analyzer. TLC was performed on 7 × 3 cm thin layer analytical plates (SRL). Silica gel used for column chromatography was 60–120 mesh.

3-Aryl-1-[(E)-cyanomethylidene]-1H-pyrido[2,1-b]benzothiazole-4-carbonitrile (**3a-f**)

General procedure: A mixture of 6-aryl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile (**1**, 1 mmol), 2-benzothiazoleacetonitrile (**2**, 174 mg, 1 mmol) and KOH (56 mg, 1 mmol) in dry DMF (40 ml) was stirred at room temperature for 48 hours. After completion the reaction mixture was poured in 100 ml of distilled water and acidified with 10% HCl. The solid thus obtained was filtered off and crystallised from DMSO.

3-(3-Chlorophenyl)-1-[(E)-cyanomethylidene]-1H-pyrido[2,1-b]benzothiazole-4-carbonitrile (**3a**): yield 69.6%, m.p. > 260 °C; δ_H (DMSO-d_6) 5.54 (s, 1 H, CHCN), 6.78 (s,1 H, 2-H), 7.54–7.62 (m, 5 H, ArH, 7-H, 8-H), 7.72 (s, 1 H, ArH), 8.16–8.18 (m, 1 H, 9-H), 8.35–8.40 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 2191 (CN); *m/z* 359 (M$^+$), 332, 323, 298 (Found: C, 66.51; H, 2.43; N, 11.35. $C_{20}H_{10}ClN_3S$ requires C, 66.75; H, 2.80; N, 11.68%).

3-(4-Chlorophenyl)-1-[(E)-cyanomethyidene]-1H-pyrido[2,1-b]benzothiazole-4-carbonitrile (**3b**): yield 75%, m.p. > 260 °C; δ_H (DMSO-d_6) 5.65 (s, 1 H, CHCN), 6.76 (s, 1 H, 2-H), 7.58–7.67 (m, 6 H, ArH, 7-H, 8-H), 8.15–8.19 (m, 1 H, 9-H), 8.34–8.39 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 2190 (CN); *m/z* 359 (M$^+$), 333, 323 (Found: C, 66.39; H, 2.59; N, 11.41. $C_{20}H_{10}ClN_3S$ requires C, 66.75; H, 2.80; N, 11.68%).

3-(4-Fluorophenyl)-1-[(E)-cyanomethylidene]-1H-pyrido[2,1-b]benzothiazole-4-carbonitrile (**3c**): yield 73%, m.p. >260 °C; δ_H (DMSO-d_6) 5.67 (s, 1 H, CHCN), 6.74 (s, 1 H, 2-H), 7.47 (t, 2 H, *J* 8.56 Hz, ArH), 7.58–7.74 (m, 4 H, ArH, 7-H, 8-H), 8.14–8.16 (m, 1 H, 9-H), 8.33–8.36 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 2192 (CN); *m/z* 343 (M$^+$), 316, 151 (Found: C, 69.53; H, 2.65; N, 12.09. $C_{20}H_{10}FN_3S$ requires C, 69.95; H, 2.93; N, 12.24%).

1-[(E)-Cyanomethylidene]-3-(4-methoxyphenyl)-1H-pyrido[2,1-b]benzothiazole-4-carbonitrile (**3d**): yield 75%, m.p. > 260 °C; δ_H (DMSO-d_6) 3.86 (s, 3 H, OCH_3), 5.59 (s, 1 H, CHCN), 6.70 (s, 1 H, 2-H), 7.08 (d, 2 H, *J* 7.8 Hz, ArH), 7.54 (d, 2 H, *J* 7.8 Hz, ArH), 7.58–7.62 (m, 2 H, 7-H, 8-H), 8.14–8.16 (m, 1 H, 9-H), 8.31–8.34 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 2194 (CN); *m/z* 355 (M$^+$), 341, 279, 247, 220 (Found: C, 70.70; H, 3.31; N, 11.68. $C_{21}H_{13}N_3OS$ requires C, 70.96; H, 3.68; N, 11.82%).

1-[(E)-Cyanomethylidene]-3-(2-thienyl)-1H-pyrido[2,1-b]benzothiazole-4-carbonitrile (**3e**): yield 83%, m.p. > 260 °C; δ_H (DMSO-d_6) 5.48 (s, 1 H, CHCN), 7.09 (s, 1 H, 2-H), 7.16 (t, 1 H, *J* 3.78 Hz, 4'-H), 7.46–7.52 (m, 3 H, 7-H, 8-H, 3′-H), 7.72–7.73 (m, 2 H, 5′-H, 9-H), 8.12–8.20 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 2185 (CN); *m/z* 331 (M$^+$), 329, 269, 219 (Found: C,65.16; H, 2.59; N, 12.29 $C_{18}H_9N_3S_2$ requires C, 65.23; H, 2.74; N, 12.68%).

1-[(E)-Cyanomethylidene]-3-(2-furyl)-1H-pyrido[2,1-b]benzothiazole-4-carbonitrile (3f): yield 82%, m.p. > 260 °C; δ_H (DMSO-d_6) 5.66 (s, 1 H, CHCN), 6.88 (s, 1 H, 2-H), 7.30 (t, 1 H, *J* 4.8 Hz, 4′-H), 7.58–7.62 (m, 2 H, 7-H, 8-H), 7.73 (d, 1 H, *J* 3.4 Hz, 5′-H), 7.85 (d, 1 H, *J* 5.1 Hz, 3′-H), 8.14–8.16 (m, 1 H, 9-H), 8.31–8.40 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 2214 (CN); *m/z* 315 (M$^+$), 297, 264 , 254 (Found: C, 68.31; H, 2.51; N, 13.09. $C_{18}H_9N_3OS$ requires C, 68.56; H, 2.87; N, 13.32%).

Synthesis of 3-methylthio-1-oxo-1H-pyrido[2,1-b]benzothiazole-2,4-dicarbonitrile (**8a**): A mixture of (benzothiazol-2-yl)acetonitrile (2, 174 mg, 1 mmol), ethyl 2-cyano-3,3-dimethylthioacrylate (6a, 217 mg, 1 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in dry DMF (10 ml) was heated at 140 °C for 1 hour. After completion, the reaction was cooled and poured into ice-cooled water (100 ml) and the resulted solution was acidified with 10% HCl. Solid thus obtained was filtered and crystallised from DMSO. yield 81%, m.p. >260 °C; δ_H (DMSO-d_6) 2.65 (s, 3 H, SCH_3), 7.64–7.72 (m, 2 H, 7-H, 8-H), 8.24 (d, 1 H, *J* 7.6 Hz, 9-H), 8.98 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 1650 (CO), 2214 (CN); *m/z* 297 (M$^+$), 284, 271, 256, 238 (Found: C, 56.39; H, 2.14; N, 14.02. $C_{14}H_7N_3OS_2$ requires C, 56.54; H, 2.37; N, 14.13%).

Synthesis of 1-imino-3-methylthio-1H-pyrido[2,1-b]benzothiazole-2,4-dicarbonitrile (**8b**): A mixture of 2-benzothiazoleacetonitrile (2, 174 mg, 1 mmol), ethyl 2-cyano-3,3-di(methylthio)acrylonitrile (**6b**, 170 mg, 1 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in dry DMF (10 ml) was heated at 140 °C for 1 hour. After completion, the reaction was cooled and poured into ice-cooled water (100 ml) and the resulted solution was acidified with 10% HCl. Solid thus obtained was filtered and crystallised from DMSO, yield 77.7%, m.p. >260 °C; δ_H (DMSO-d_6) 2.78 (s, 3 H, SCH_3), 7.58–7.68 (m, 2 H, 7-H, 8-H), 8.16 (d, 1 H, *J* 7.6 Hz, 9-H), 9.46 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 2214 (CN), 3423 (NH); *m/z* 296 (M$^+$), 283, 271, 251 (Found: C, 56.52; H, 2.49; N, 18.56. $C_{14}H_8N_4S_2$ requires C, 56.73; H, 2.72; N, 18.91%).

Synthesis of ethyl 4-cyano-1-imino-1H-pyrido[2,1-b]benzothiazole-2-carboxylate (9): A mixture of 2 (174 mg, 1 mmol), ethyl ethoxymethylenecyanoacetate (7, 170 mg, 1 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in dry DMF (10 ml) was heated at 140 °C for 1 hour. After completion, the reaction was cooled and poured into ice-cooled water (100 ml) and the resulted solution was acidified with 10% HCl. Solid thus obtained was filtered and crystallized from DMSO. yield 85%, m.p. >260 °C; δ_H (DMSO-d_6) 1.45 (t, 3 H, *J* 6.2 Hz, CH_3), 4.38–4.46 (q, 2 H, OCH_2), 7.61–7.76 (m, 2 H, 7-H, 8-H), 8.08 (m, 1 H, 9-H), 8.41 (s, 1 H, 3-H), 9.44 (m, 1 H, 6-H); ν_{max}/ cm^{-1} 1697 (CO), 2210 (CN), 3415 (NH); *m/z* 297 (M$^+$), 269, 252 (Found: C, 60.49; H, 3.58; N, 14.48. $C_{15}H_{11}N_3O_2S$ requires C, 60.59; H, 3.73; N, 14.13%).

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